Multidisciplinary Management of Breast Cancer
10-13 September 2017
Dublin, Ireland

Course director:

- Philip Poortmans

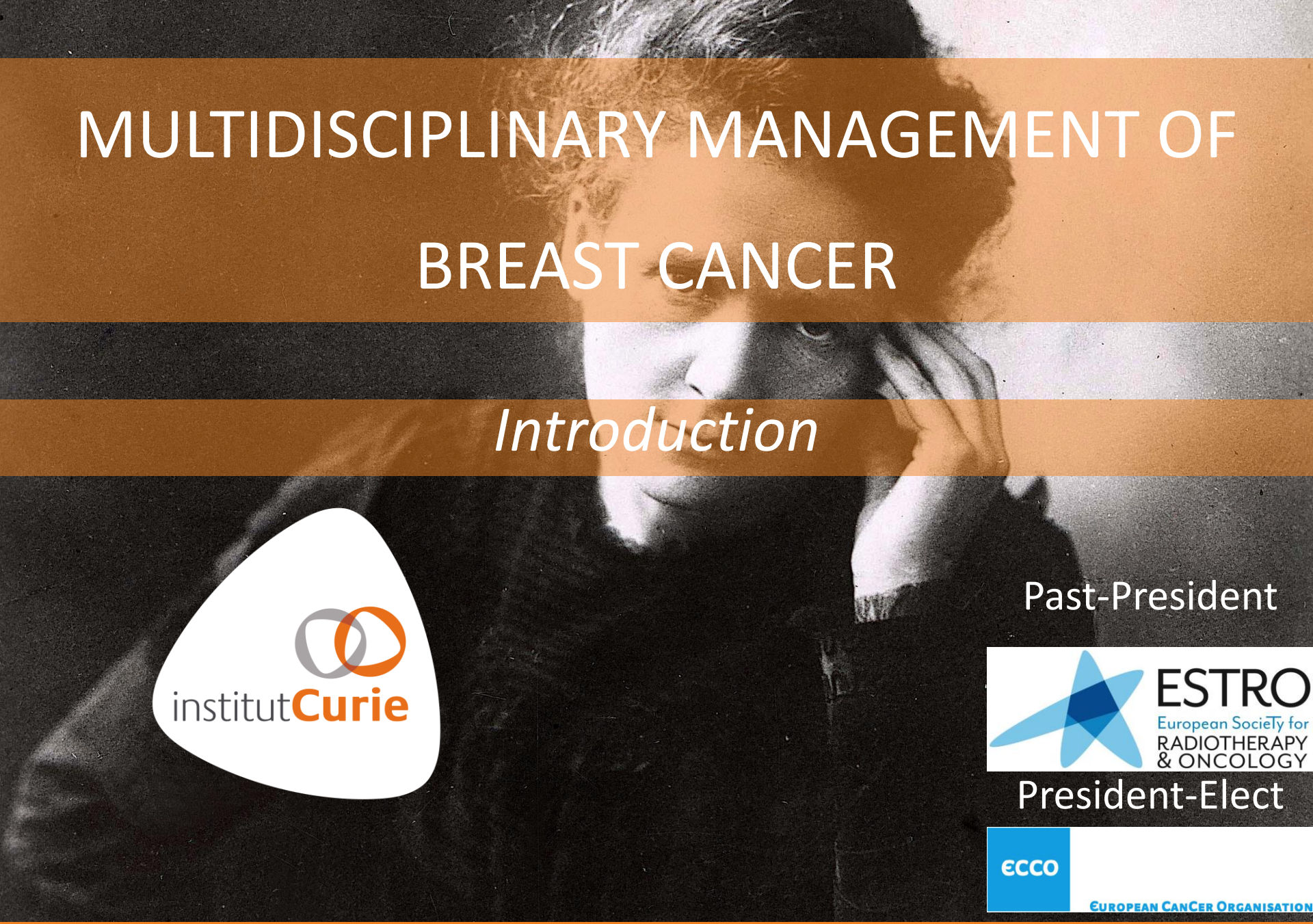
Faculty:

- Marianne Aznar
- Liesbeth Boersma
- Sarah Darby
- Youlia Kirova
- Thorsten Kuehn
- Birgit Vriens
- Birgitte Vrou Offersen
- Lynda Wyld
- Sandra Hol

ESTRO School

MULTIDISCIPLINARY MANAGEMENT OF BREAST CANCER

Introduction



institutCurie

Past-President

ESTRO
European Society for RADIOTHERAPY & ONCOLOGY

President-Elect

ECCO
EUROPEAN CANCER ORGANISATION

Philip Poortmans, MD, PhD

None of the teachers and others involved have a conflict of interest.

Multidisciplinary Breast Cancer Course

Course director: Philip Poortmans, *Paris (F)*

Local organiser: Elizabeth Forde*, Dublin (IE)*

Teachers:

Thorsten Kühn, *Esslingen (D);* Lynda Wyld*, Sheffield (UK)*

Liesbeth Boersma, *Maastricht (NL)*; Youlia Kirova, *Paris (F)*; Birgitte Offersen, *Aarhus (DK)*

Marianne Aznar, *Copenhagen (DK)*

Sarah Darby, *Oxford (UK)*

Ronan McDermott, *Dublin (IE);* Barbara Dunne*, Dublin (IE)*

Contouring administrator: Sandra Hol, *Tilburg (NL)*

ESTRO representative: Elena Giusti

ESTRO School

Multidisciplinary Breast Cancer Course

Course aim:

- promoting an **integrated approach** to the management of breast cancer
- **individualise treatment** approach based on tumour and patient-related factors
- **improving delivery of radiotherapy**, starting from optimal target volume definition
- **interactive** through the integration of lectures, clinical case discussions and volume delineations
- **multidisciplinary** from evidence based medicine to the on-going research

ESTRO School

Multidisciplinary Breast Cancer Course

European School of Oncology
Learning to care

EUSOMA
European Society of Breast Cancer Specialists

EUROPA DONNA
The European Breast Cancer Coalition

esso
The European Society of Surgical Oncology

ESTRO School

Thank you all for your active contribution!

- Local organiser, Elisabeth Forde and her team
- Teachers
- Contouring administrator
- ESTRO staff
- Participants

institutCurie

Epidemiology of Breast Cancer: Trends in Incidence and Mortality

Sarah Darby
Nuffield Department of Population Health
University of Oxford
United Kingdom

CANCER RESEARCH UK

UNIVERSITY OF OXFORD

Plan of talk

- Incidence of breast cancer
- Mortality from breast cancer

Note: This talk is mainly about how to think about these concepts, rather than about facts.

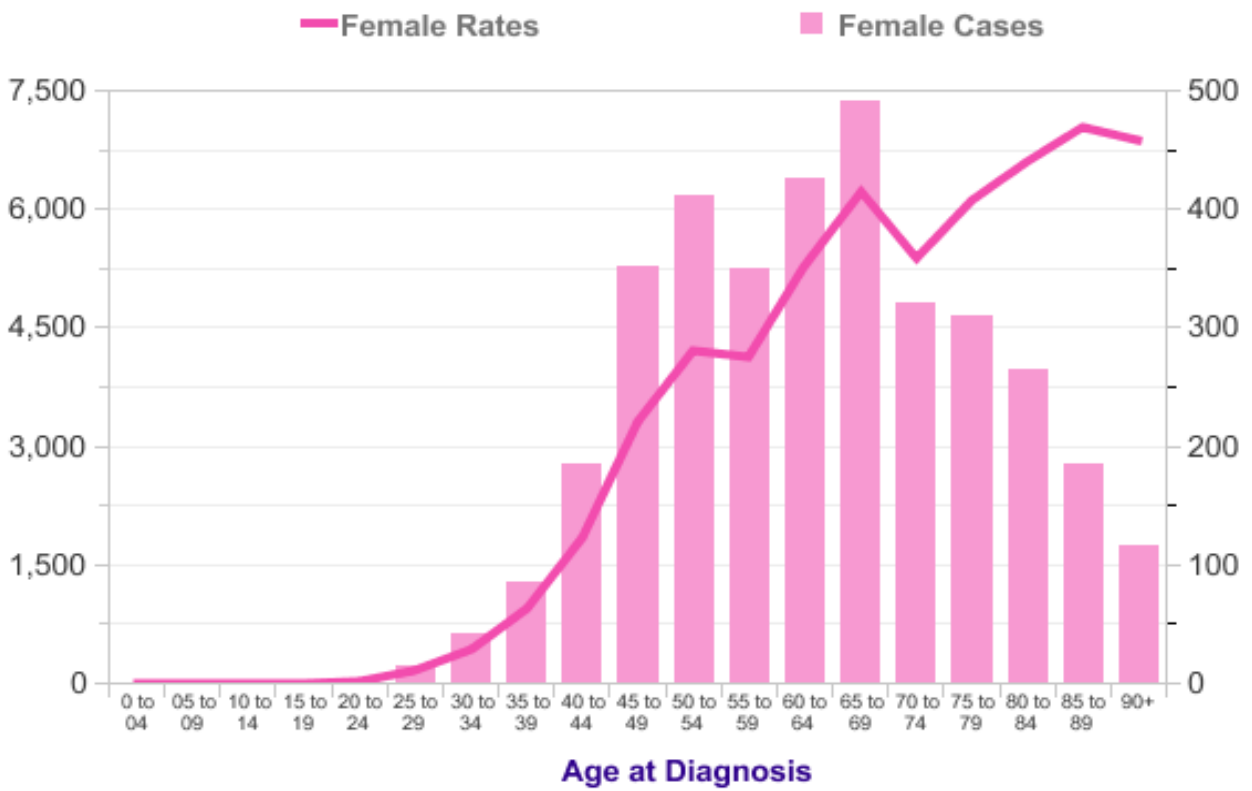
What is incidence?

- **Incidence:** number of *new* cases arising in a given time period in a specified population. Collected routinely by cancer registries.
- Distinguish from **prevalence**: number of persons in a specified population who have been diagnosed with a disease, and who are *still alive on a particular date*, eg cancer survivors
- **Incidence rate**: eg number of cases diagnosed per 100,000 persons per year.

Difference between Incidence and Incidence Rate

Female Breast Cancer (C50): 2012-2014, UK

Annual incidence, ie number of new cases per year



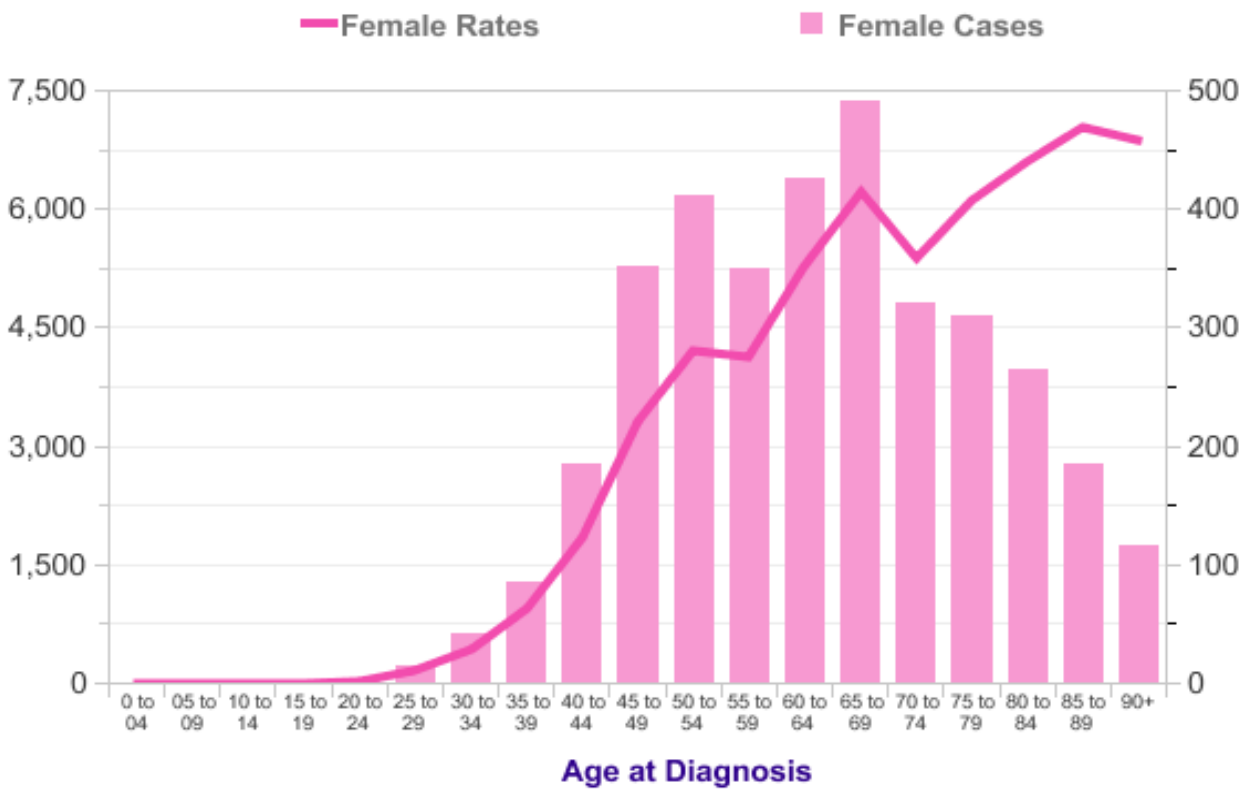
Annual incidence rate, ie number of new cases per 100,000 population peryear

Source: cruk.org/cancerstats

Difference between Incidence and Incidence Rate

Female Breast Cancer (C50): 2012-2014, UK

Annual incidence, ie number of new cases per year

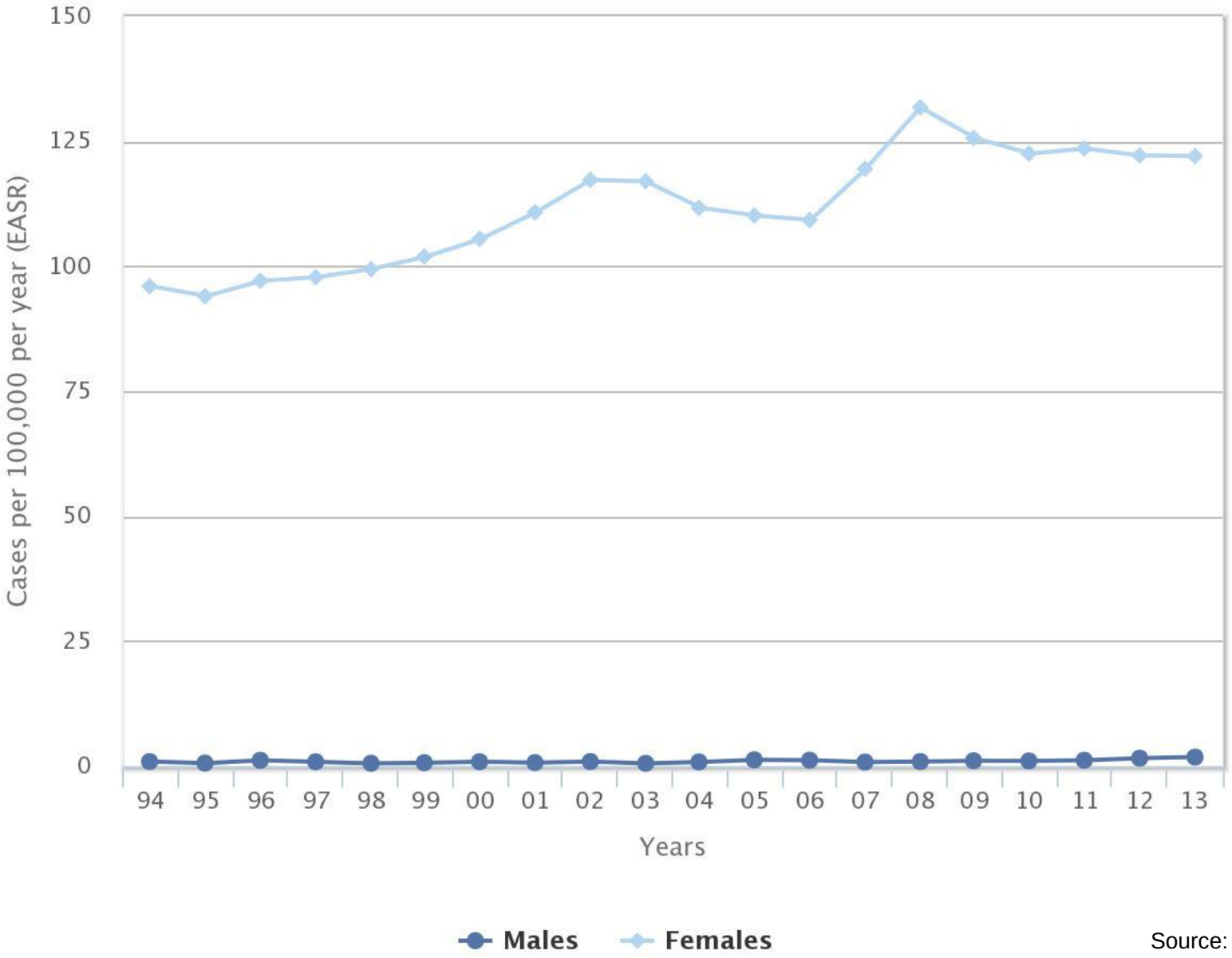


Annual incidence rate, ie number of new cases per 100,000 population peryear

Confusion: Often figures for incidence rates are just labelled incidence

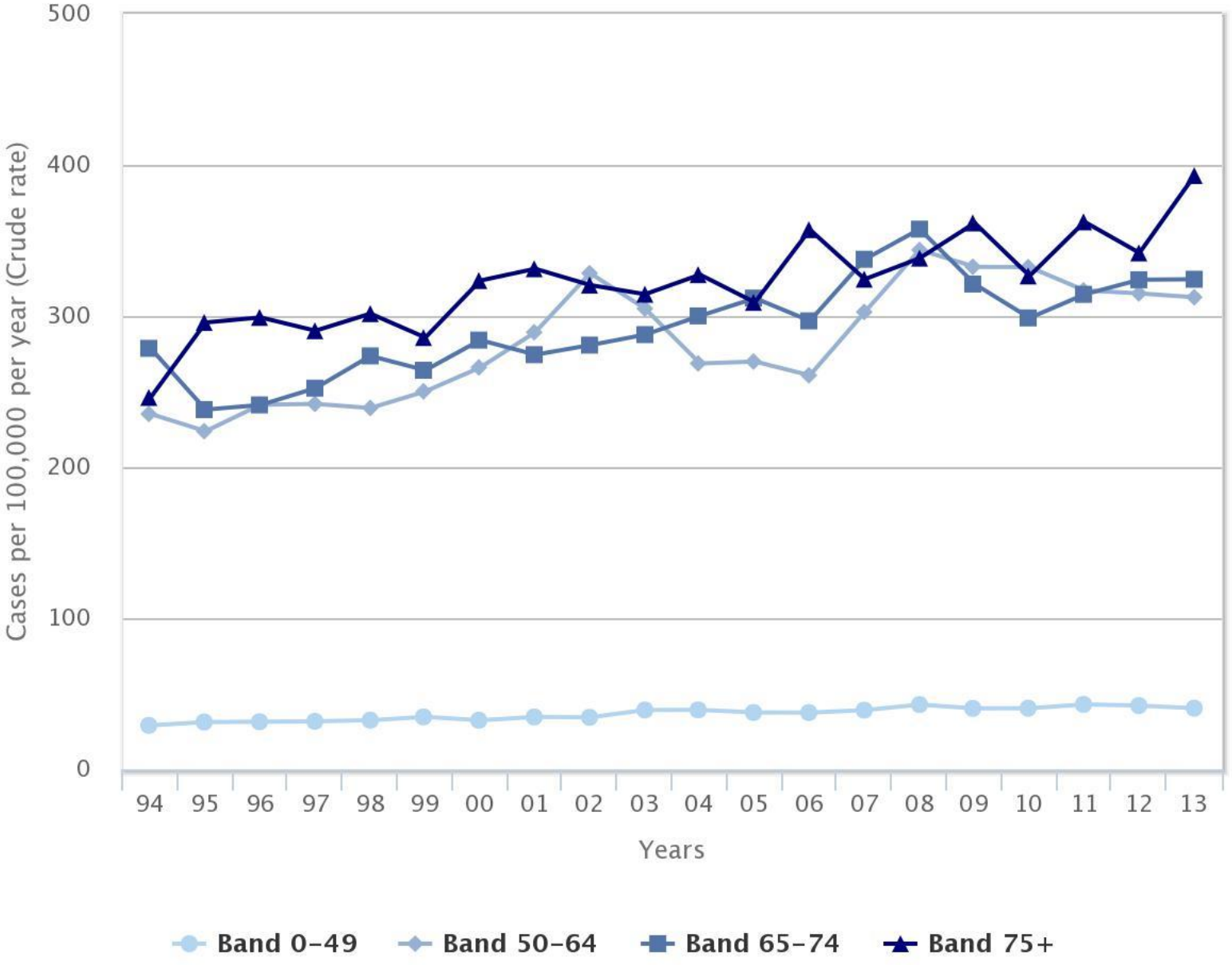
Source: cruk.org/cancerstats

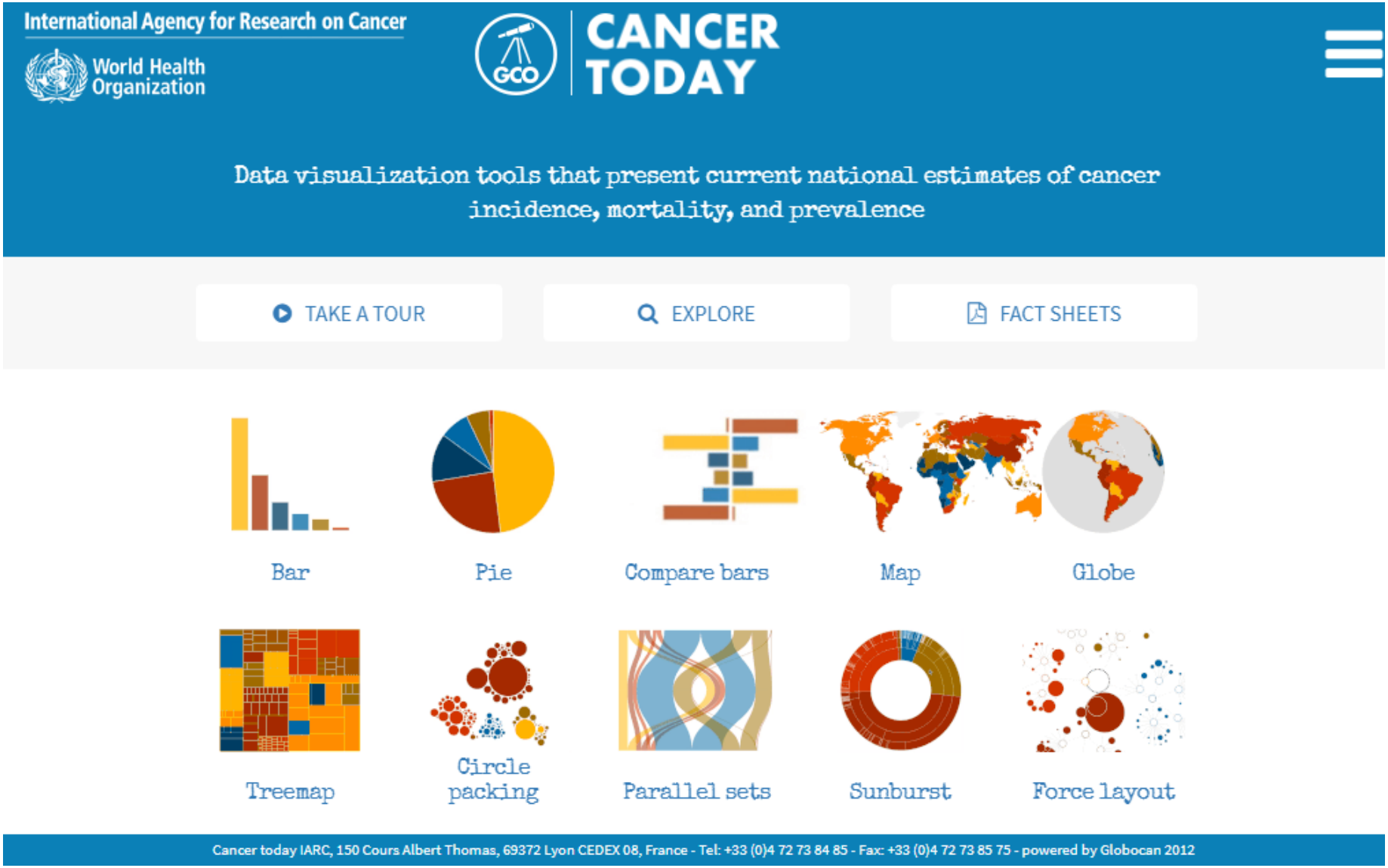
Breast Cancer Incidence Rates in Ireland, 1994-2013 by Sex



Source: www.ncri.ie

Female Breast Cancer Incidence Rates in Ireland, 1994-2003, by Age

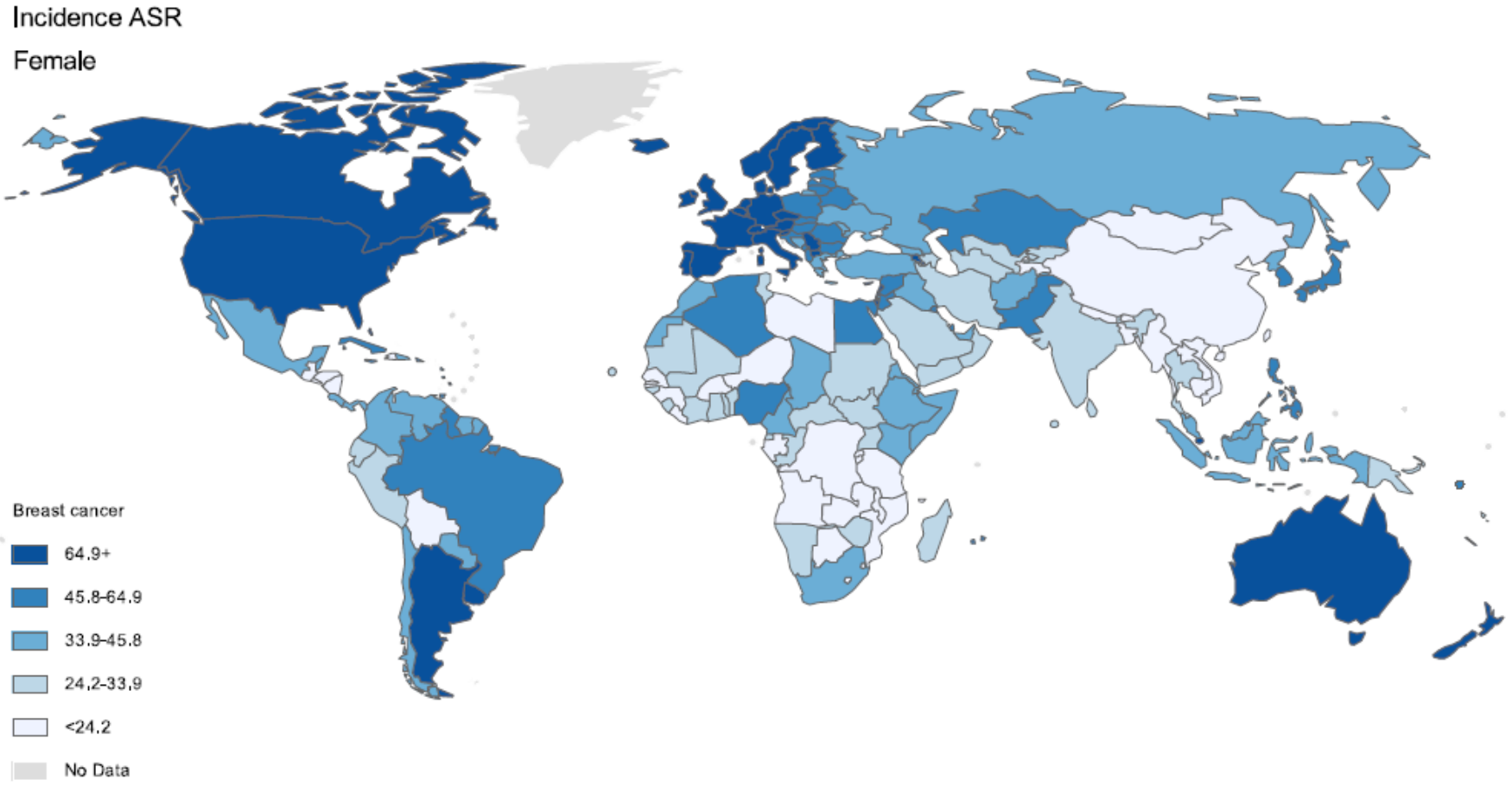




Source: gco.iarc.fr/today

Incidence Rates of Female Breast Cancer, 2012

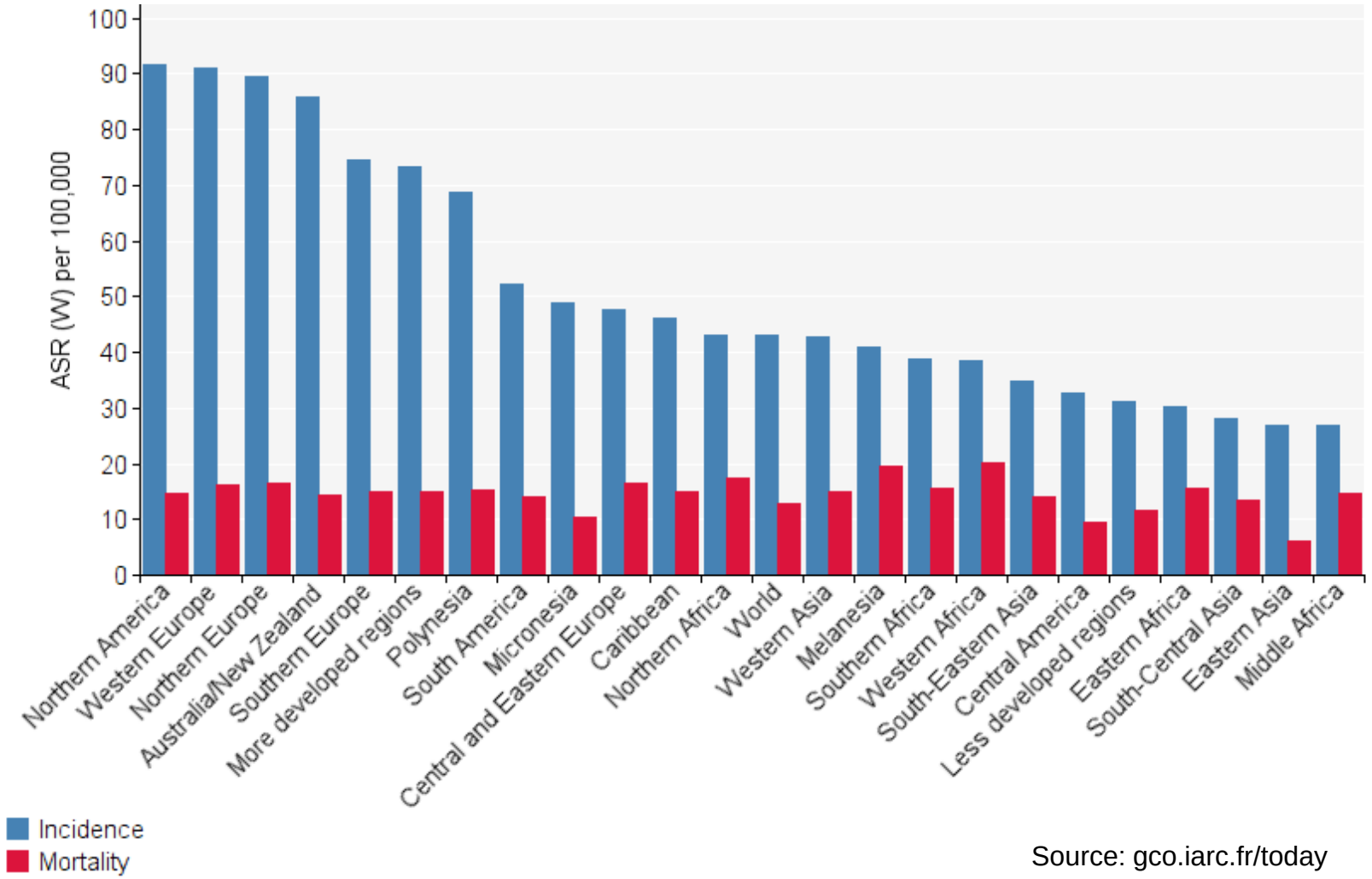
per 100,000 per year



Source: gco.iarc.fr/today

Female Breast Cancer Rates, 2012

per 100,000 per year



Source: gco.iarc.fr/today

Age standardisation

- **Age has a powerful influence on cancer risk, so age standardisation is necessary when comparing several populations with different age structures**

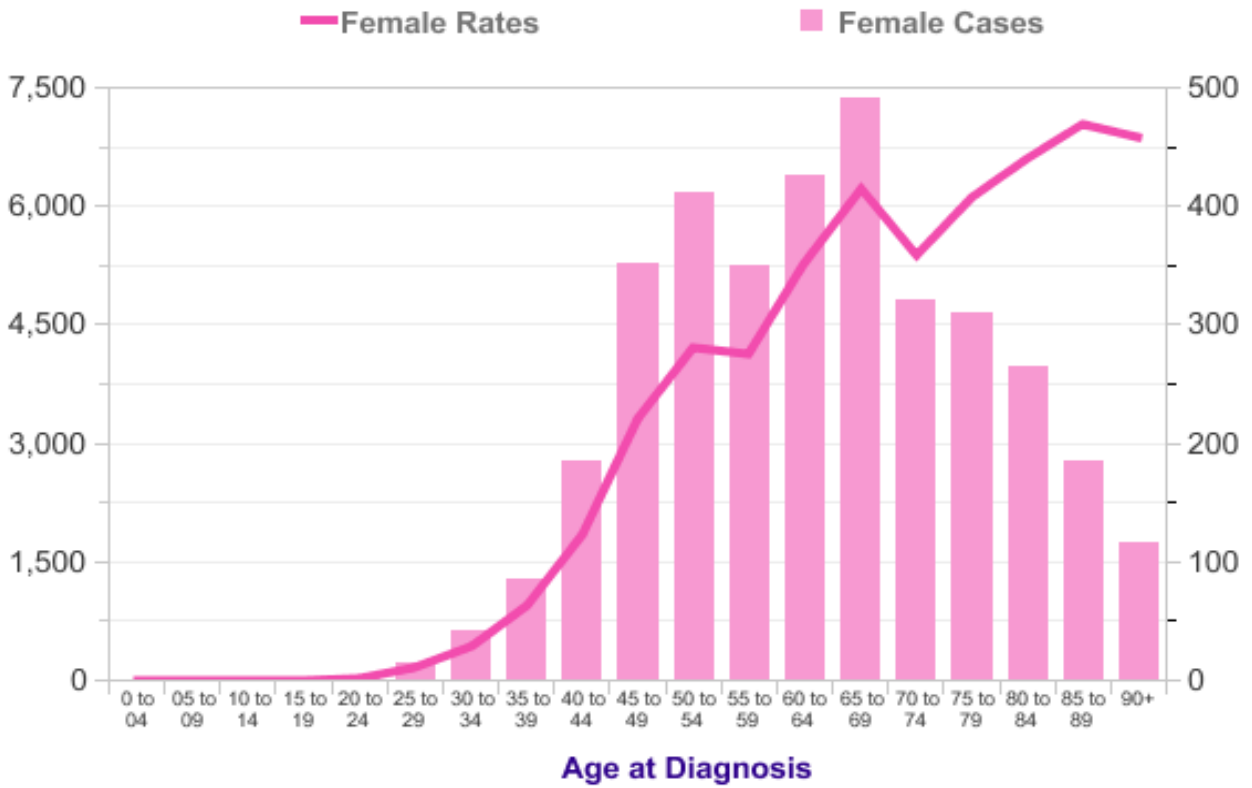
- **An age-standardised rate (ASR) is the rate that a population would have if it had a standard age structure, eg WHO World Standard Population**

WHO World Standard Population Distribution (%)	
Age group	**% of population**
0-4	8.86
5-9	8.69
10-14	8.60
15-19	8.47
20-24	8.22
25-29	7.93
30-34	7.61
35-39	7.15
40-44	6.59
45-49	6.04
50-54	5.37
55-59	4.55
60-64	3.72
65-69	2.96
70-74	2.21
75-79	1.52
80-84	0.91
85-89	0.44
90-94	0.15
95-99	0.04
100+	0.005
Total	100

Difference between Incidence and Incidence Rate

Female Breast Cancer (C50): 2012-2014, UK

Annual incidence, ie number of new cases per year

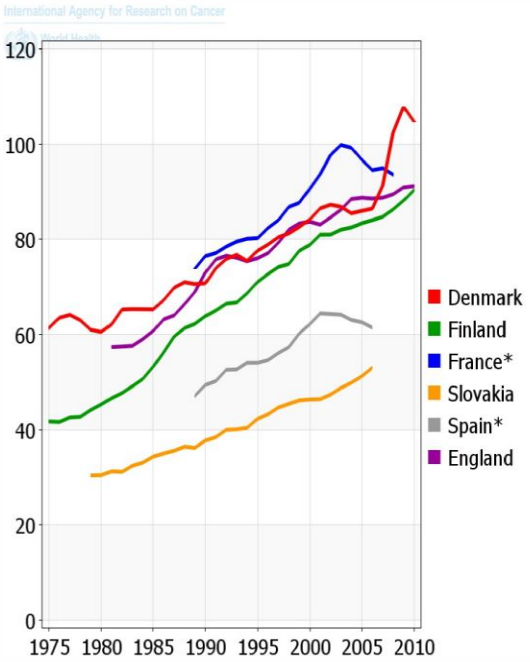


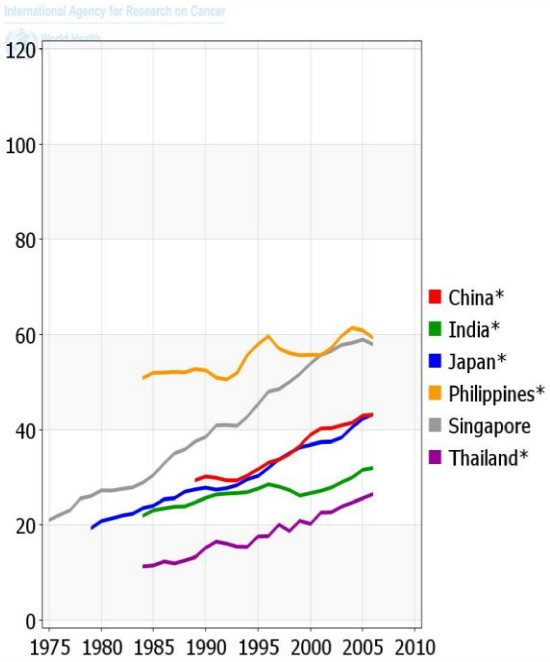
Annual incidence rate, ie number of new cases per 100,000 population peryear

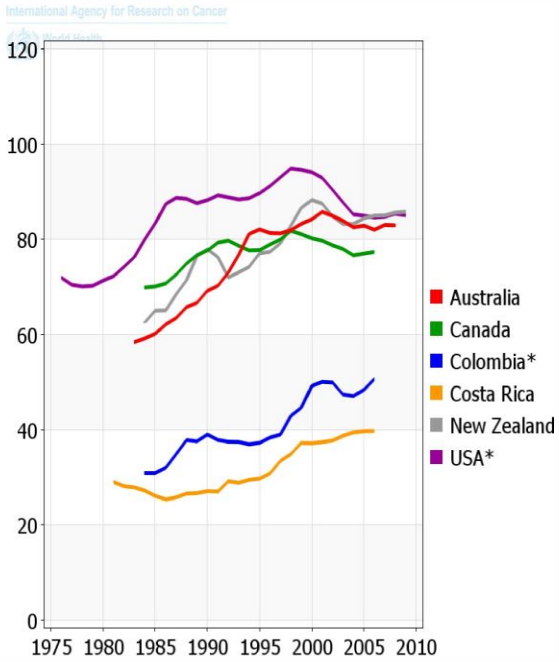
Age-standardised rates can be compared between different countries and over different time-periods

Source: cruk.org/cancerstats

Incidence Rates of Female Breast Cancer, 2012, by country







Rates are age-standardised using WHO World Standard

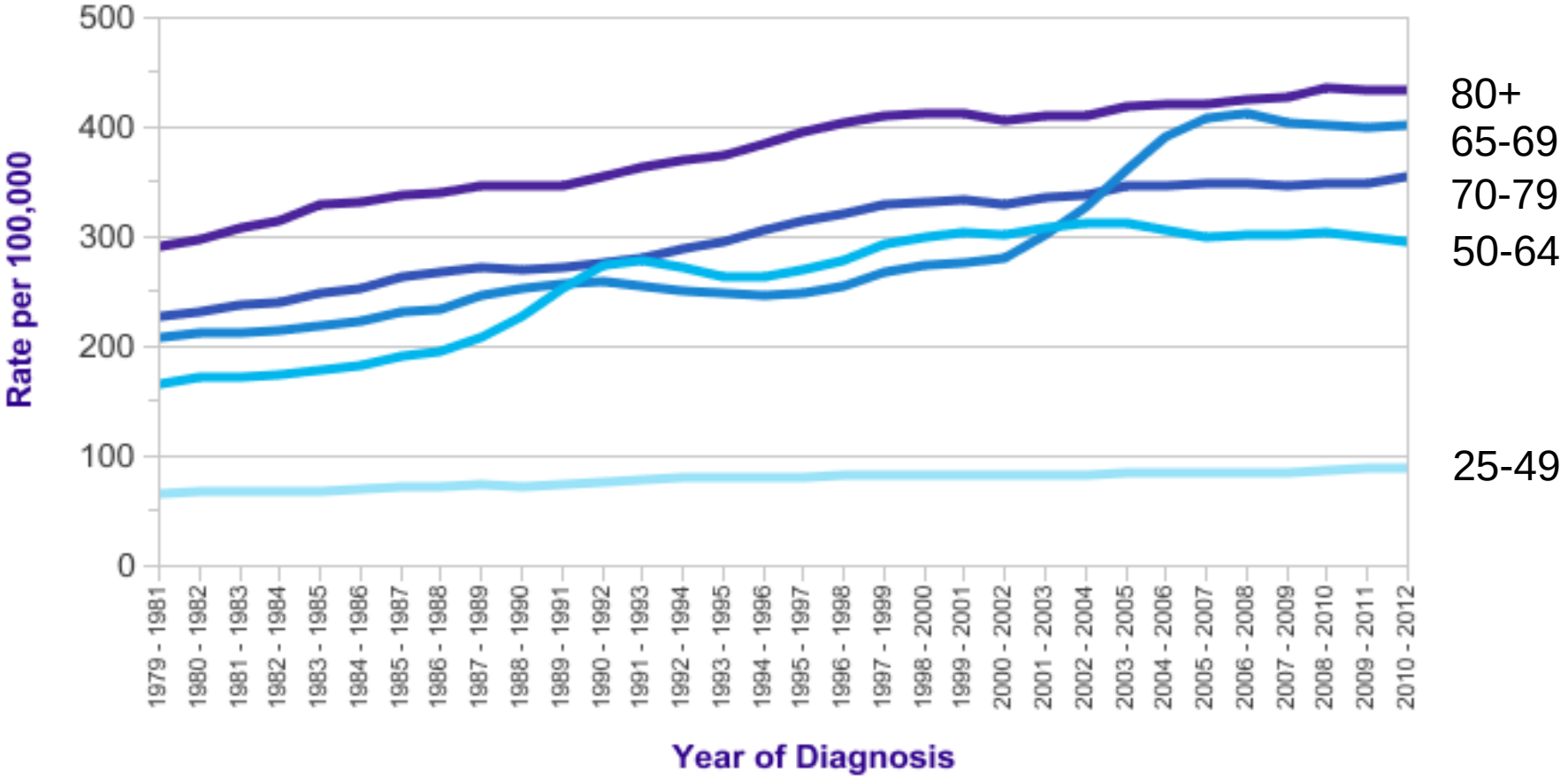
* Rate based on regional registry data, rather than entire country

Source: gco.iarc.fr/today

Factors Influencing Cancer Rates

- **Incidence**:
  - Underlying disease rate
  - Earlier diagnosis via screening
  - Earlier diagnosis outside formal screening programme

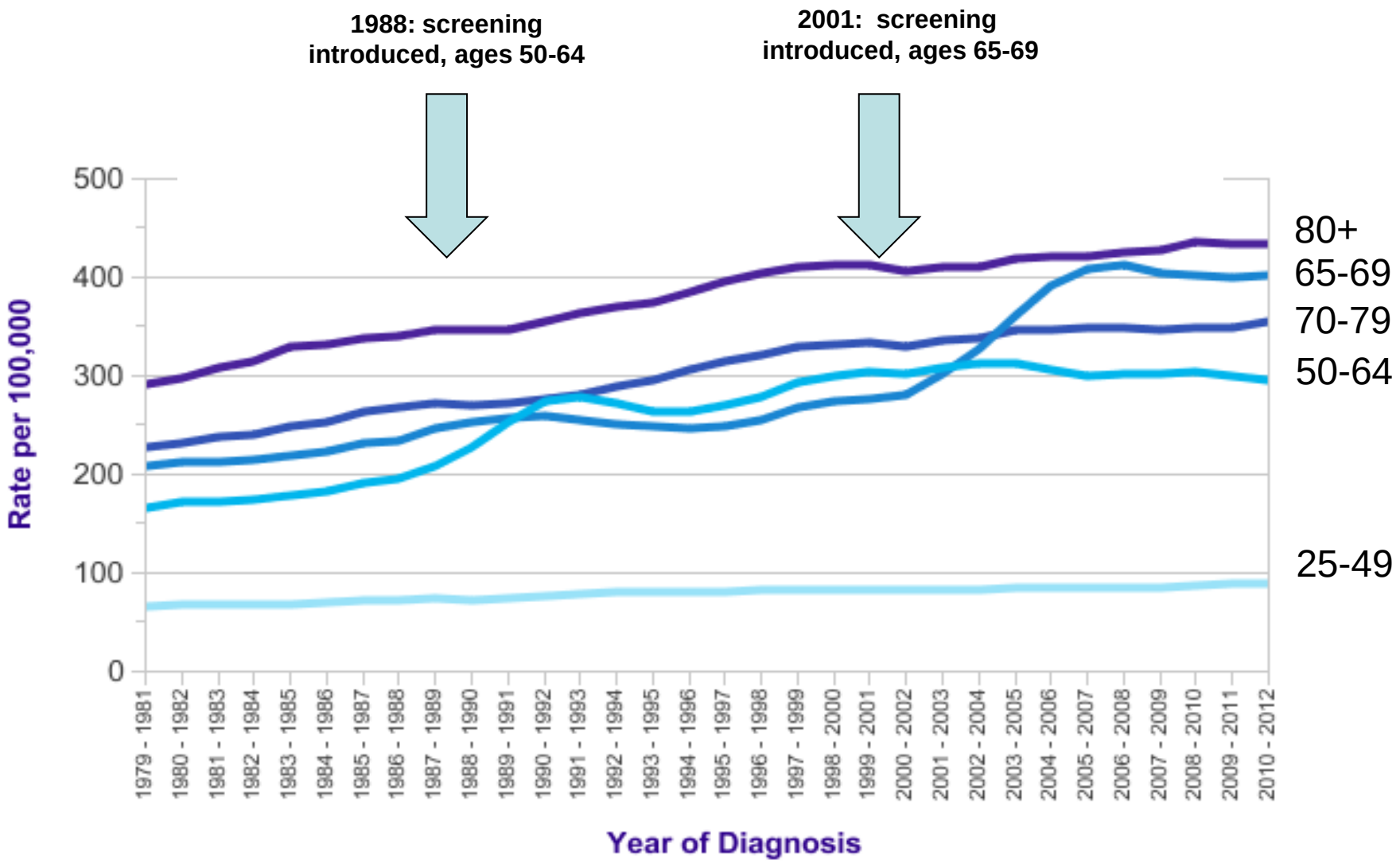
Incidence Rate of Breast Cancer UK, 1979-2012, by Age



European Age-Standardised Rate.

Source: cruk.org/cancerstats

Incidence Rate of Breast Cancer UK, 1979-2012, by Age

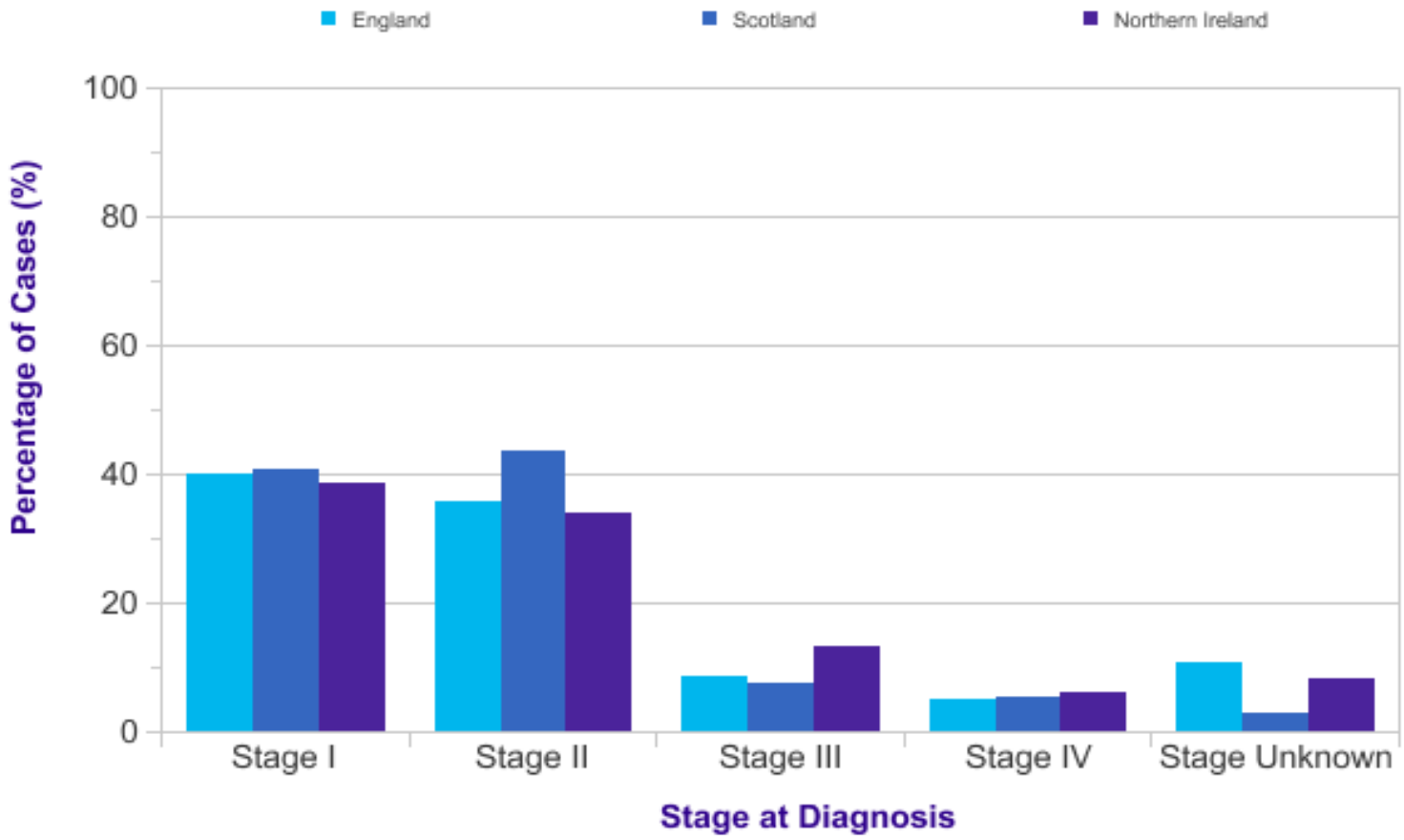


Source: cruk.org/cancerstats

European Age-Standardised Rate.

Invasive Breast Cancer (C50)

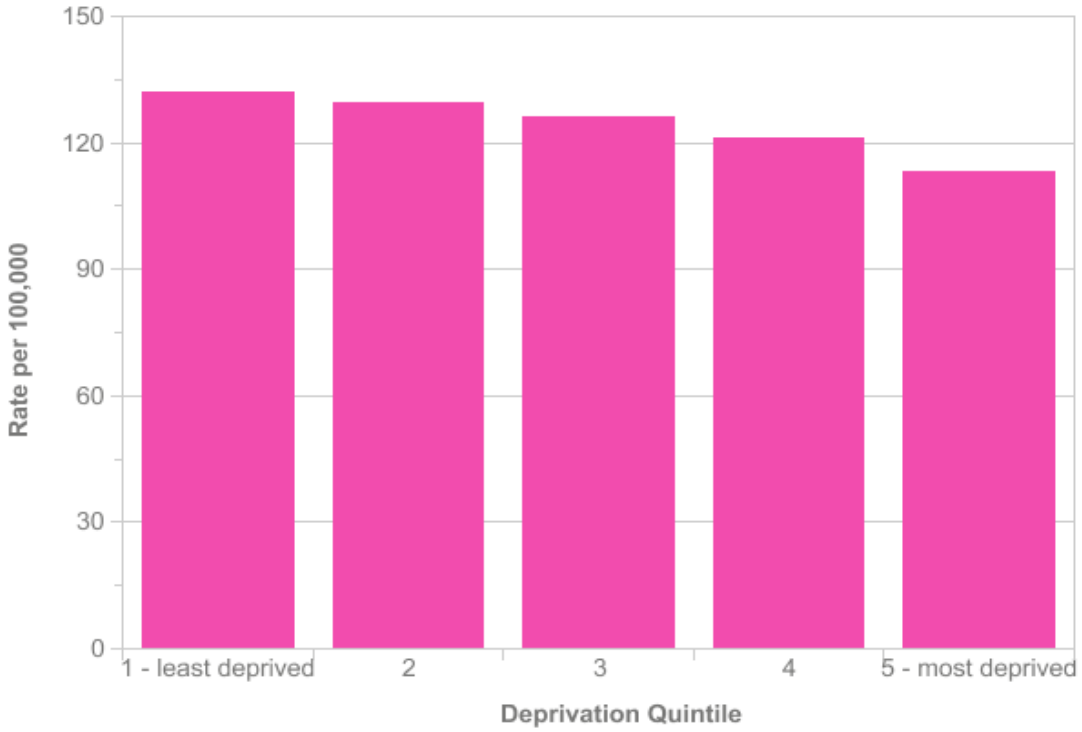
Proportion of Cases Diagnosed at Each Stage, England, All Ages, 2014



Source: cruk.org/cancerstats

Invasive Breast Cancer (C50)

Incidence Rates by Deprivation Quintile, England, 2006-2010



Rates age-standardised using WHO European Standard

Source: cruk.org/cancerstats

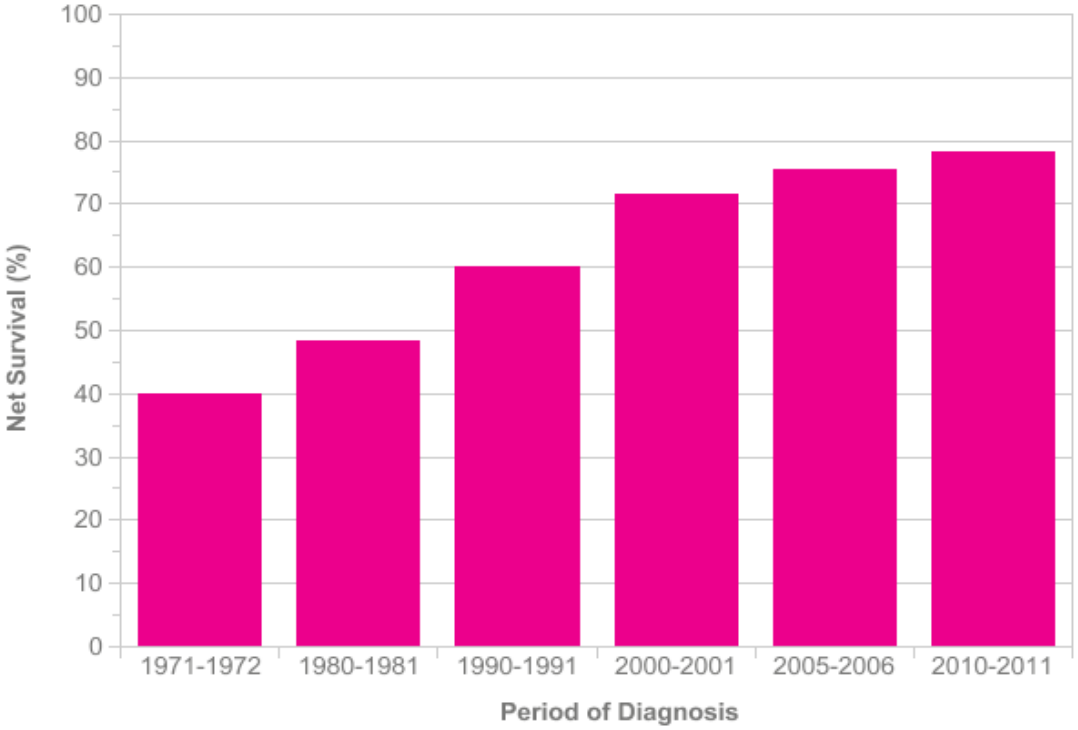
Factors Influencing Cancer Rates

- **Incidence**:
  - Underlying disease rate
  - Earlier diagnosis via screening
  - Earlier diagnosis outside formal screening programme

- **Survival**
  - Efficacy, availability, and uptake of treatment
  - Earlier diagnosis via screening
  - Earlier diagnosis outside formal screening programme

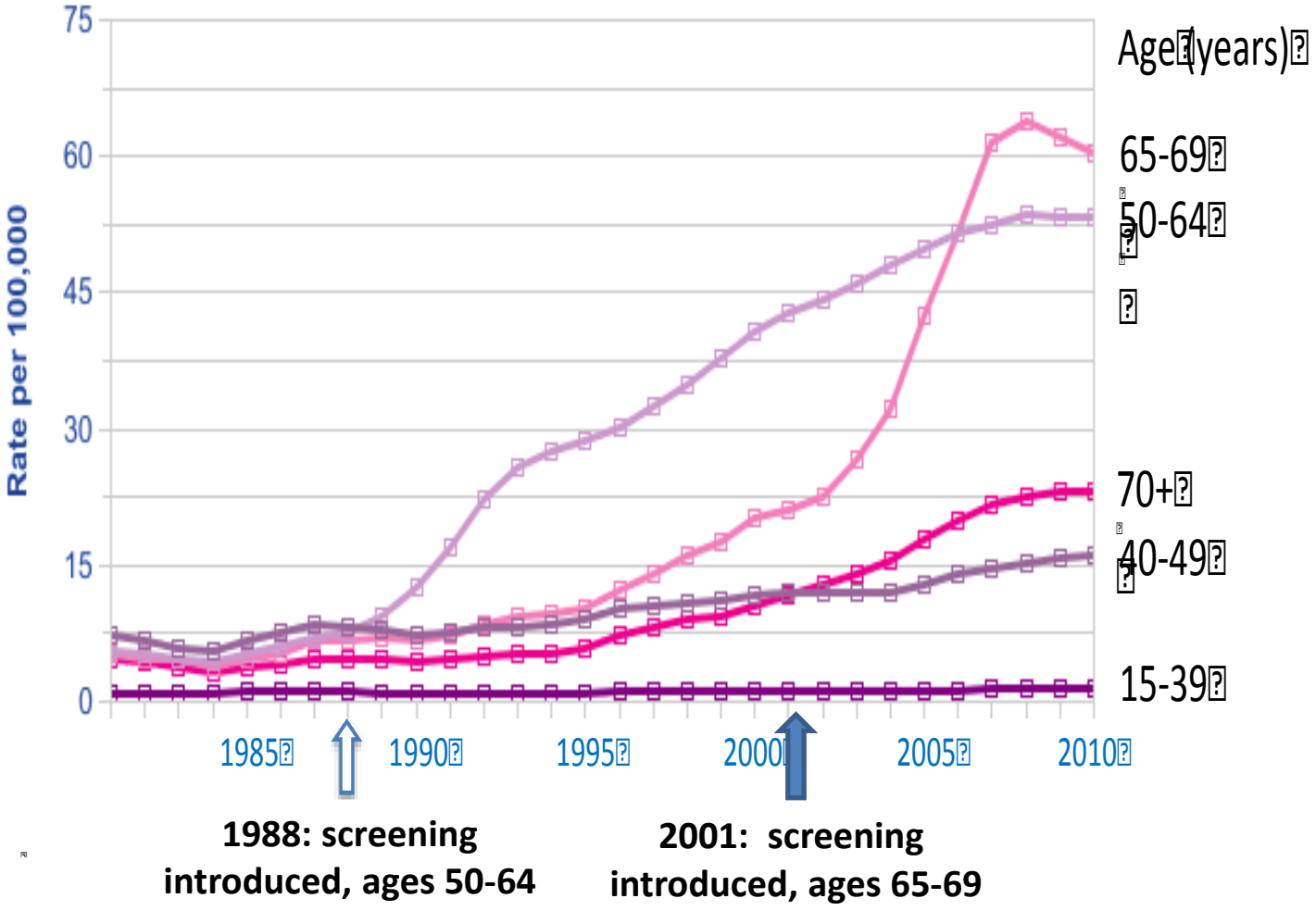
Breast Cancer (C50): 1971-2011

Age-Standardised Ten-Year Net Survival, England and Wales



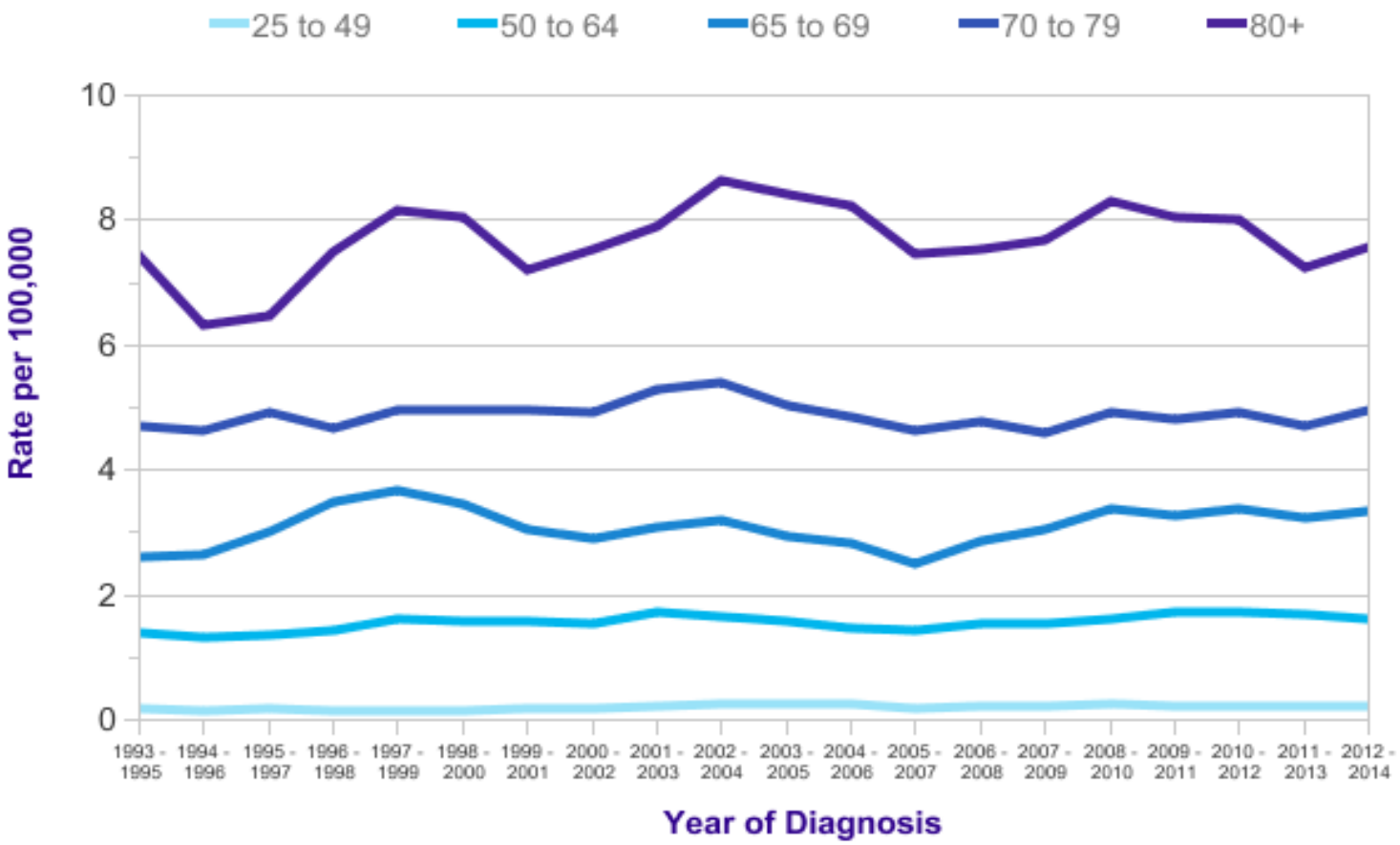
Source: cruk.org/cancerstats

Incidence Rate of *in Situ* Breast Cancer, UK, 1979-20102



Source: cruk.org/cancerstats

Breast Cancer (C50): 1993-2014
European Age-Standardised Incidence Rates per 100,000 Population, by Age, Males, UK



Source: cruk.org/cancerstats

Conclusions for Breast Cancer Incidence

- Female breast cancer incidence rates have been increasing in recent years in most countries
- Some of this increase might be avoided in the future by changes in lifestyle
- But some of the increase is due to formal screening programmes, and some may be due to earlier diagnosis outside formal screening programmes
- This makes trends and comparisons of breast cancer incidence rates and survival hard to interpret

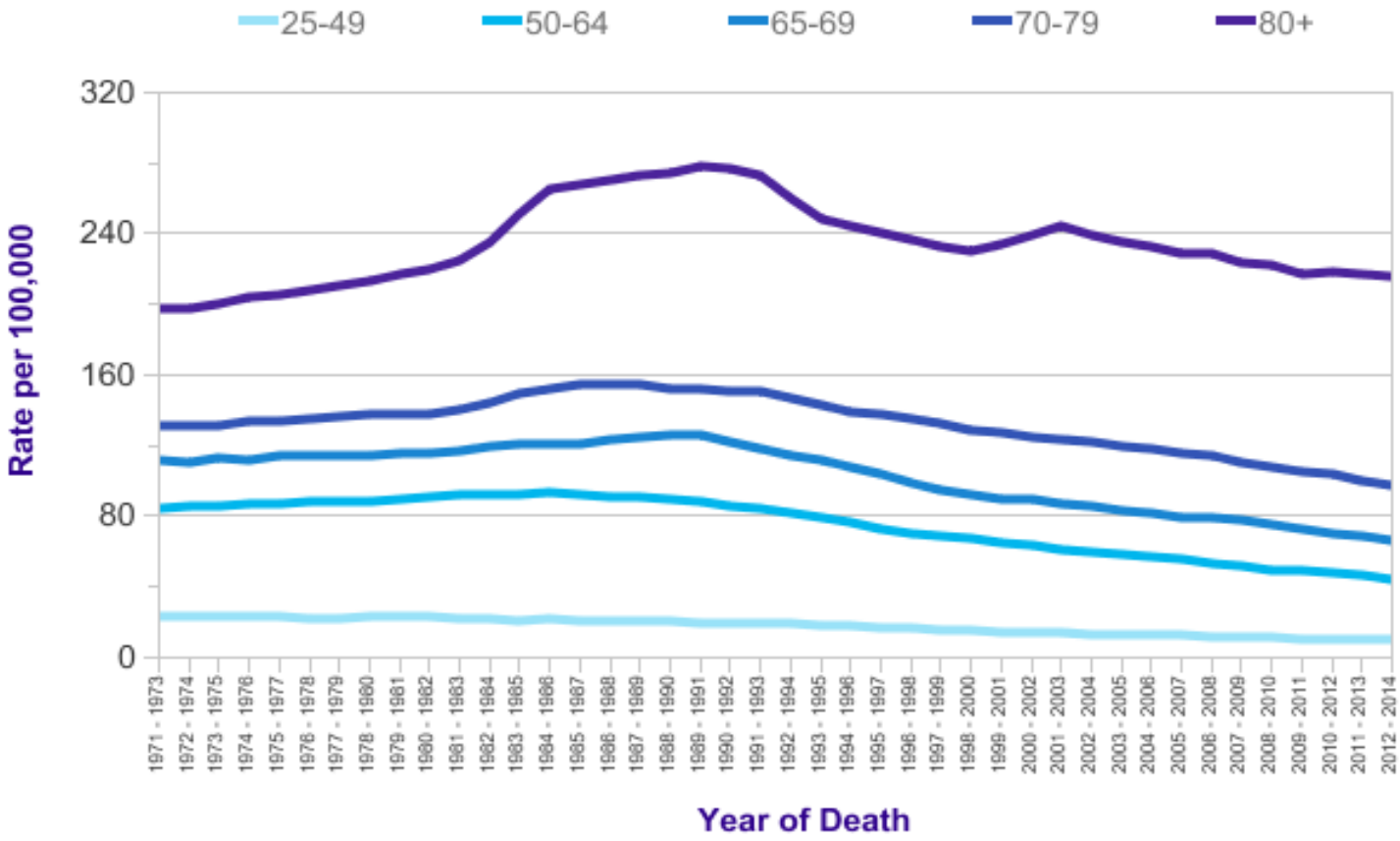
Mortality from Breast Cancer

Mortality from Breast Cancer

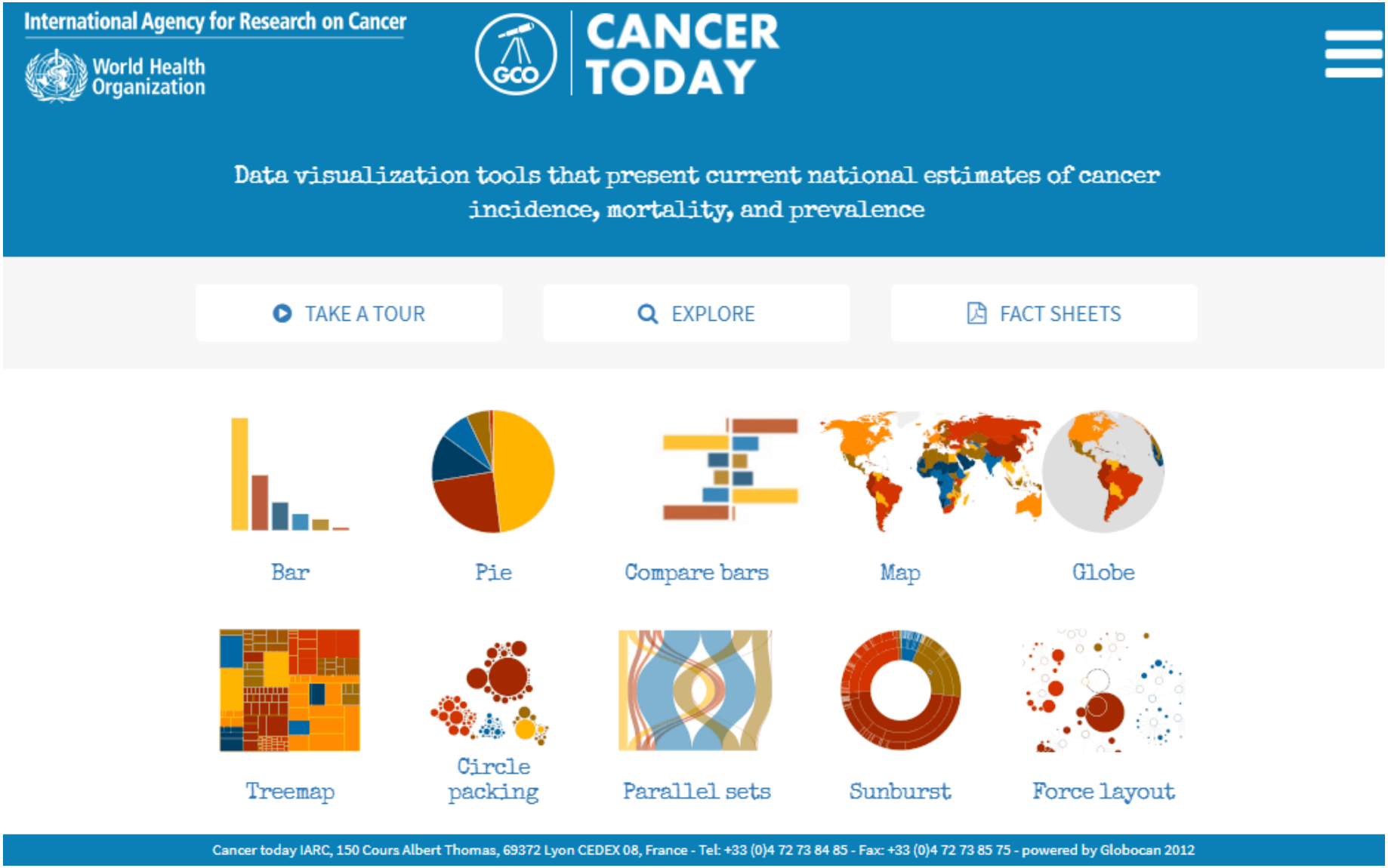
- Unlike comparisons of survival, comparisons of mortality rates are not distorted by variations screening programmes and earlier diagnosis.

- Trends and comparisons of breast cancer mortality rates are therefore easier to interpret than incidence rates
- They will reflect:
  - Underlying disease rates
  - Biological impact of early diagnosis, without distortion
  - Efficacy, availability, and uptake of treatment

Breast Cancer (C50): 1971-2014
Mortality Rates per 100,000 Population, by Age, Females, UK



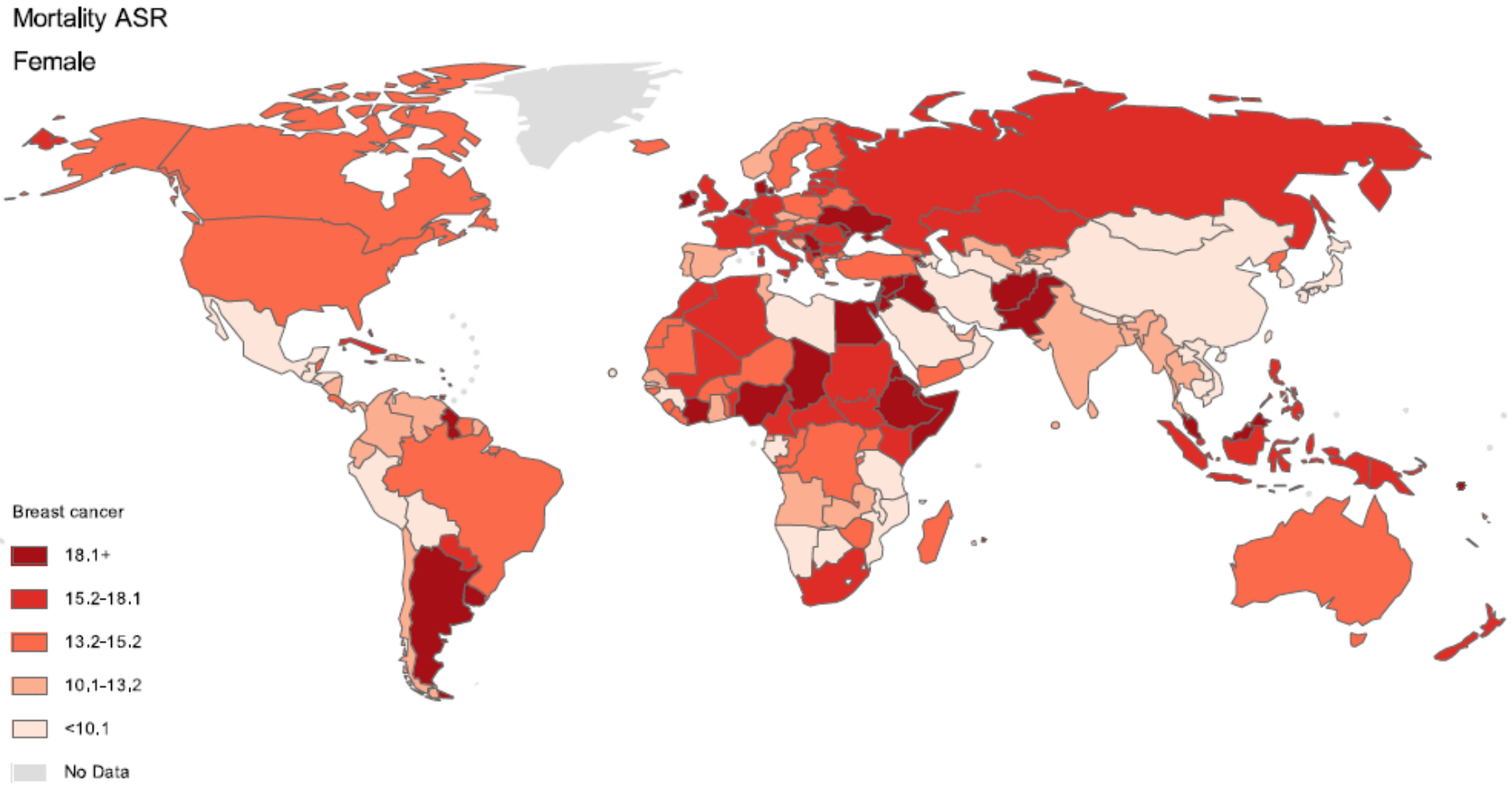
Source: cruk.org/cancerstats



Source: gco.iarc.fr/today

Mortality Rates for Female Breast Cancer, 2012

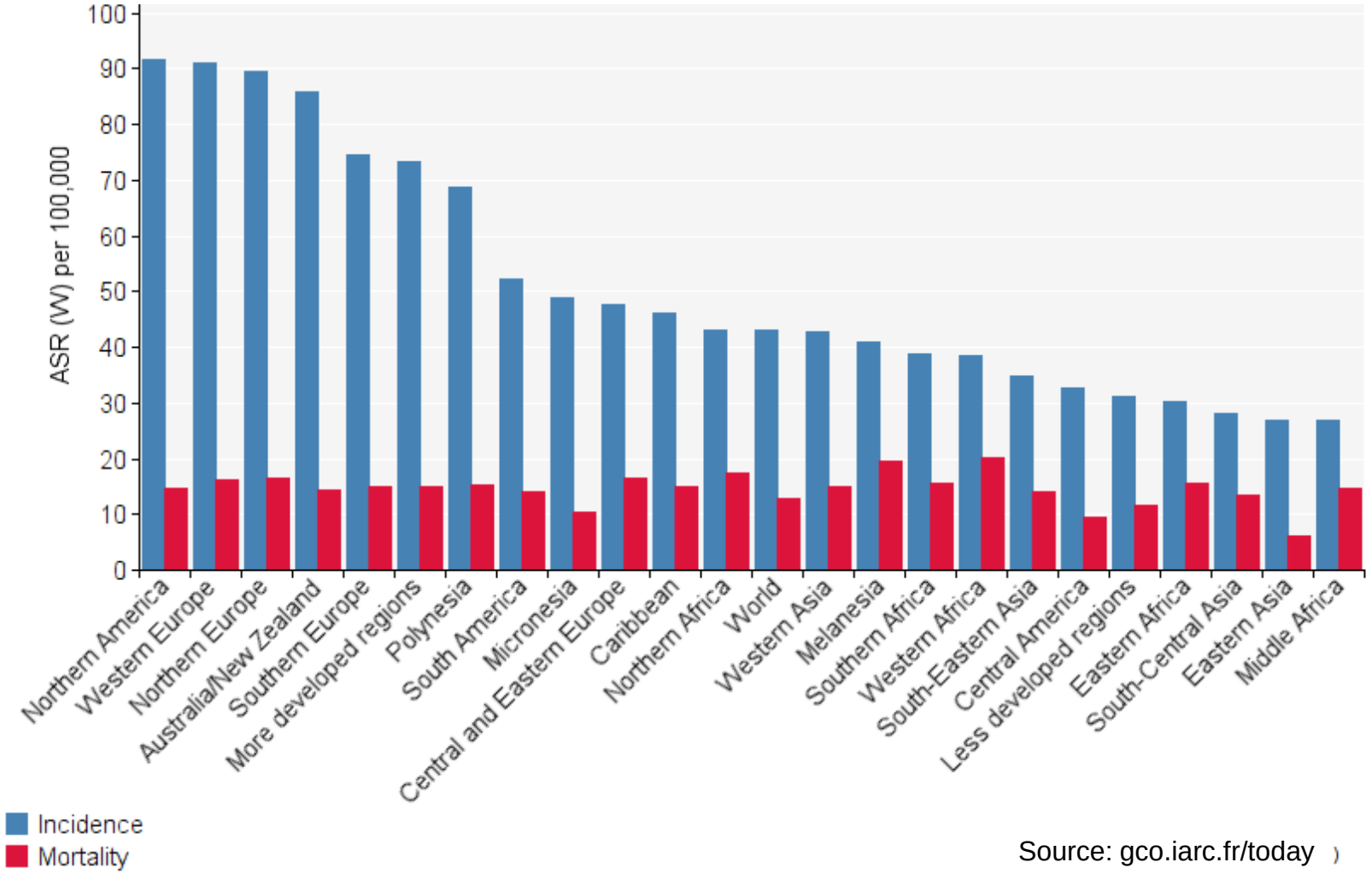
per 100,000 per year



Source: gco.iarc.fr/today

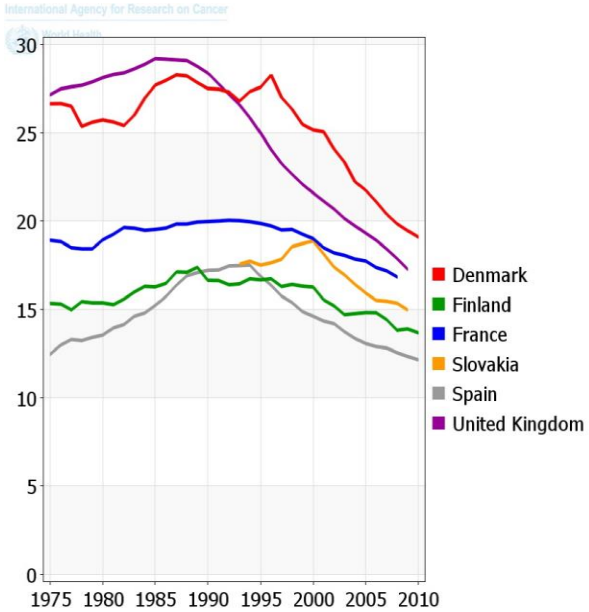
Female Breast Cancer Rates, 2012

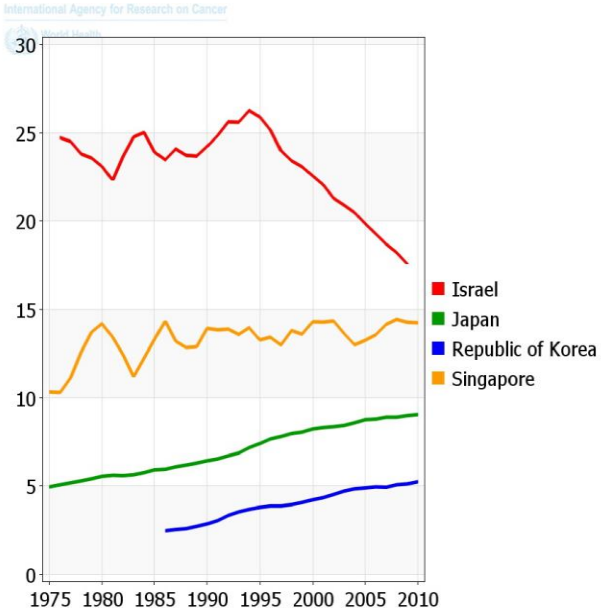
per 100,000 per year

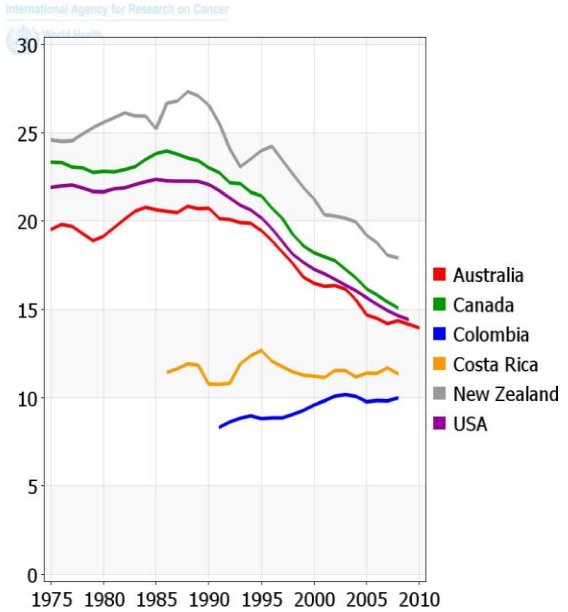


Source: gco.iarc.fr/today

Mortality Rates for Female Breast Cancer, 2012, by Country







Rates are age-standardised using WHO World Standard

Source: gco.iarc.fr/today

Conclusions for Breast Cancer Mortality

- Breast cancer mortality rates have been decreasing in Western Europe, USA, and Australia for about 20 years.
- More recently they started to decrease in countries of the former Eastern Europe (eg Slovakia) and Israel
- These decreases are attributed partly to earlier diagnosis, but mainly to more effective treatment

- In some countries, including Singapore and Costa Rica, breast cancer mortality rates have remained stable and in some, including Japan, South Korea they are still increasing.
- This suggests that changes in lifestyle are more important in these countries than earlier diagnosis and more effective treatment

and now for some facts

… see part 2

Trends in Mortality from Breast Cancer for each Country for the Students on the Course

(except Turkey and Morocco)

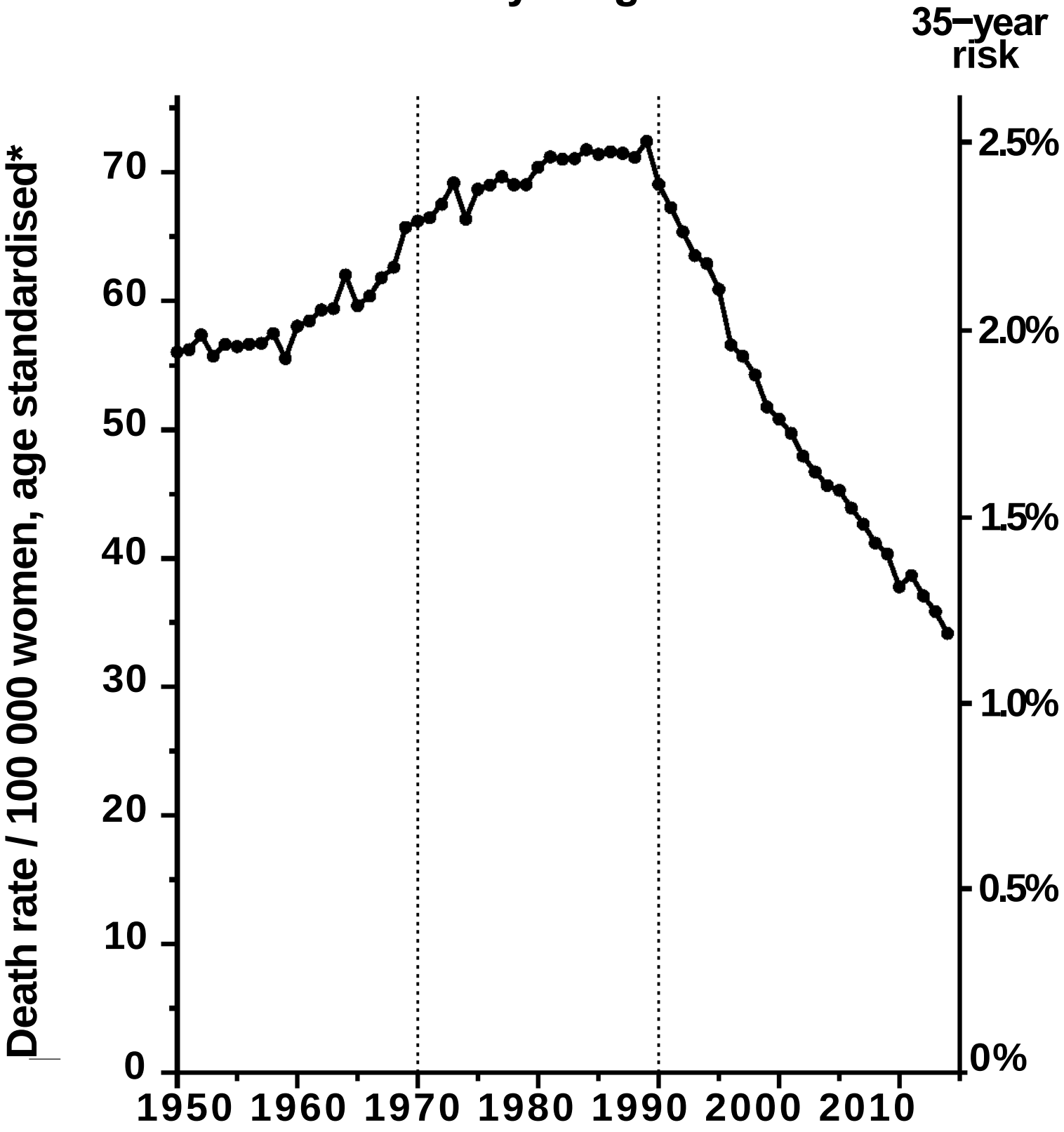
Each of the following graphs shows the trend over time in the breast cancer death rate

- left axis: age-standardised death rate
- right axis: cumulative 35 year risk
- bottom axis: calendar year

The vertical axes are the same on each graph

So graphs are all comparable with each other

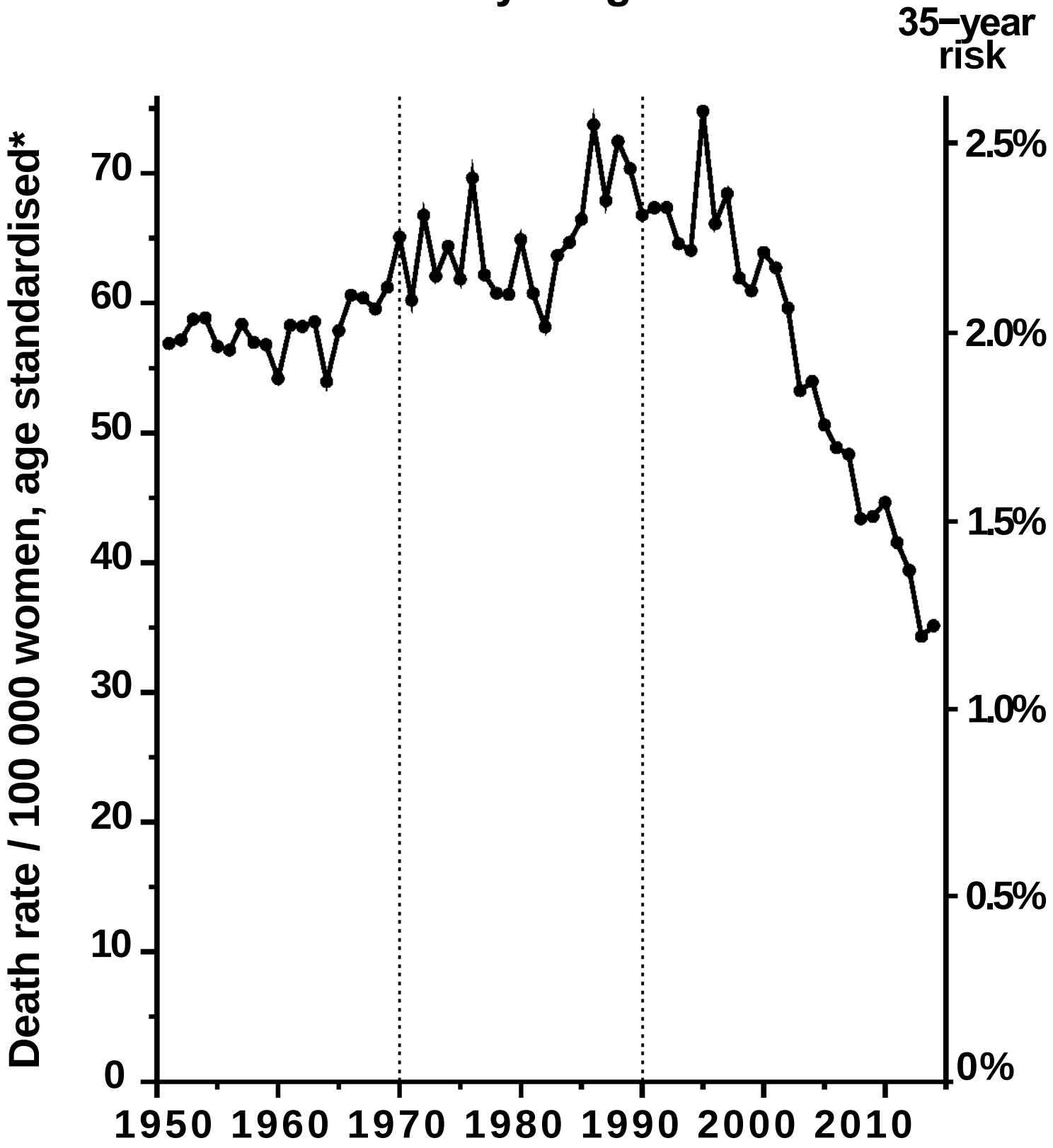
UNITED KINGDOM 1950−2014:
Breast cancer mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

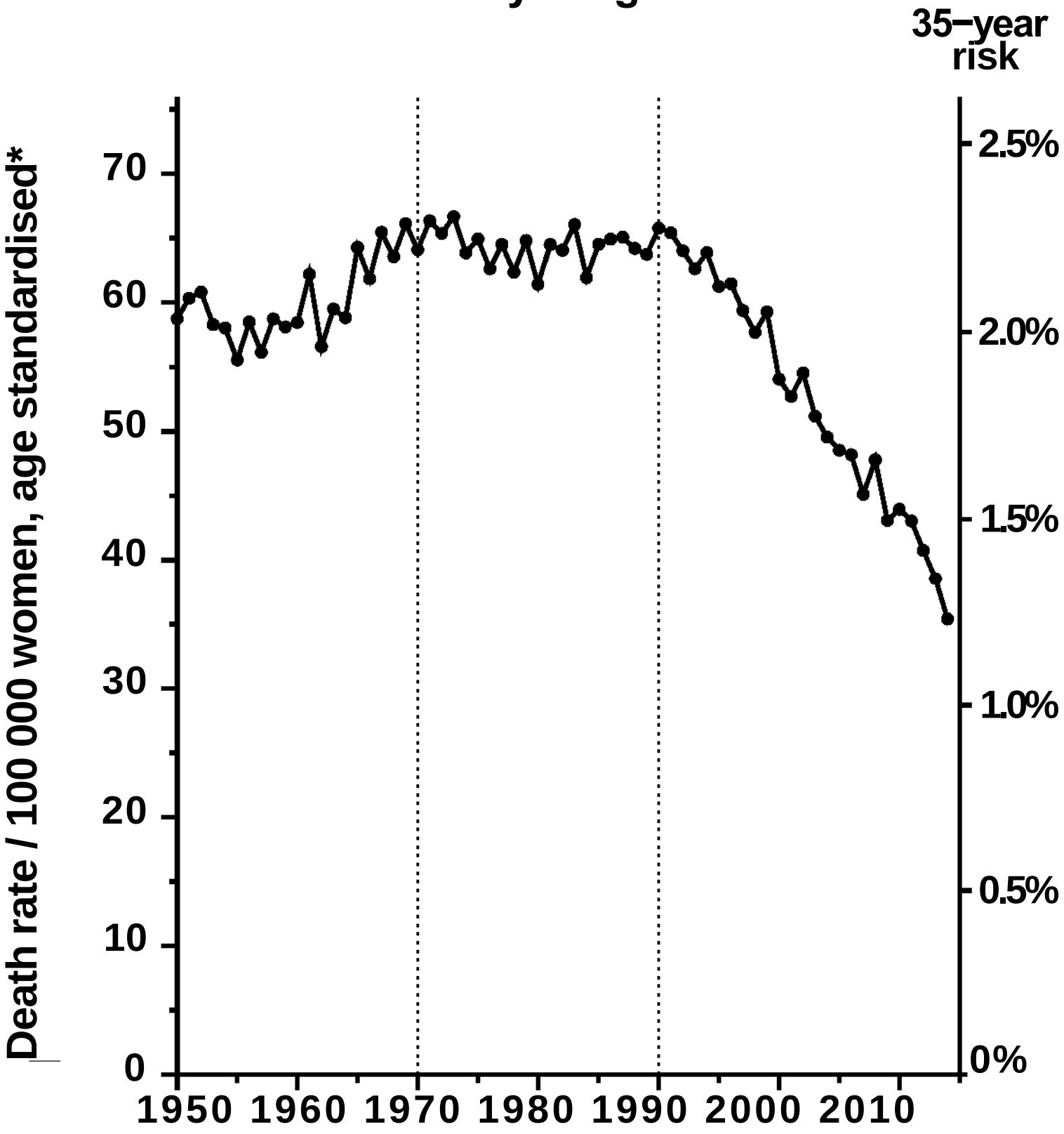
DENMARK 1951−2014:
Breast cancer mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

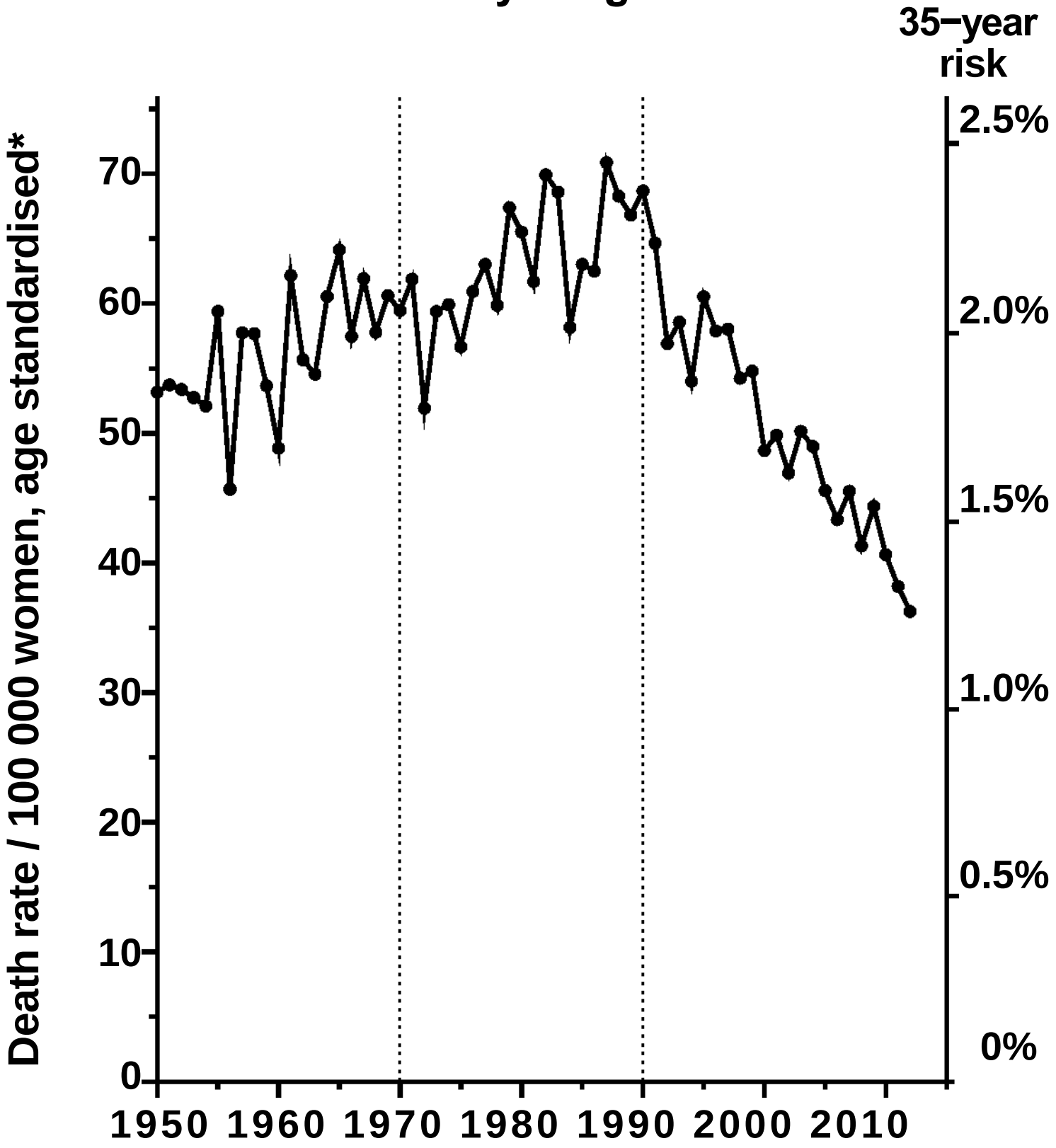
NETHERLANDS 1950–2014:
Breast cancer mortality at ages 35–69



*Mean of annual rates in the seven component 5–year age groups

Source: WHO mortality & UN population estimates

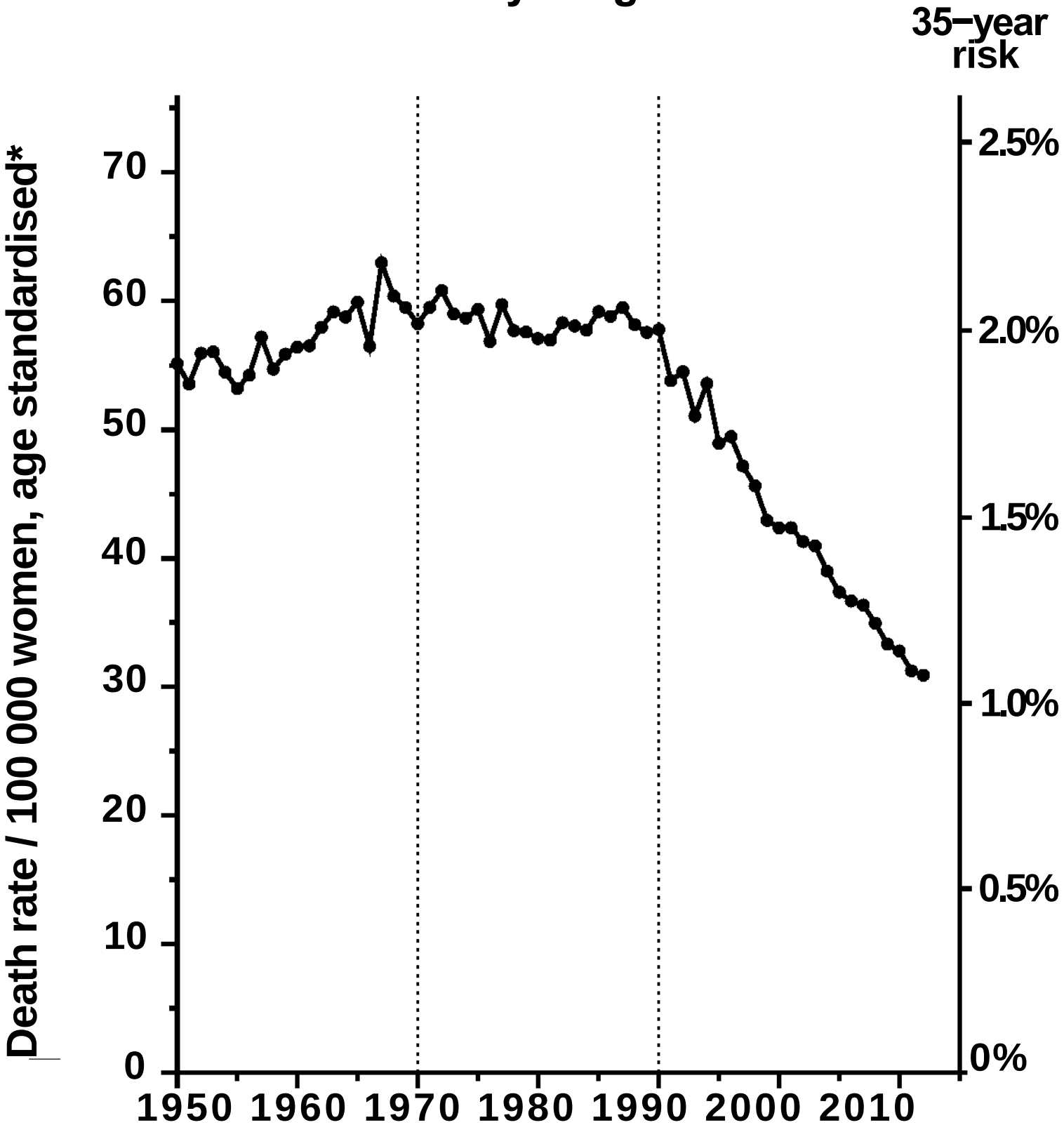
NEW ZEALAND 1950−2012:
Breast cancer mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

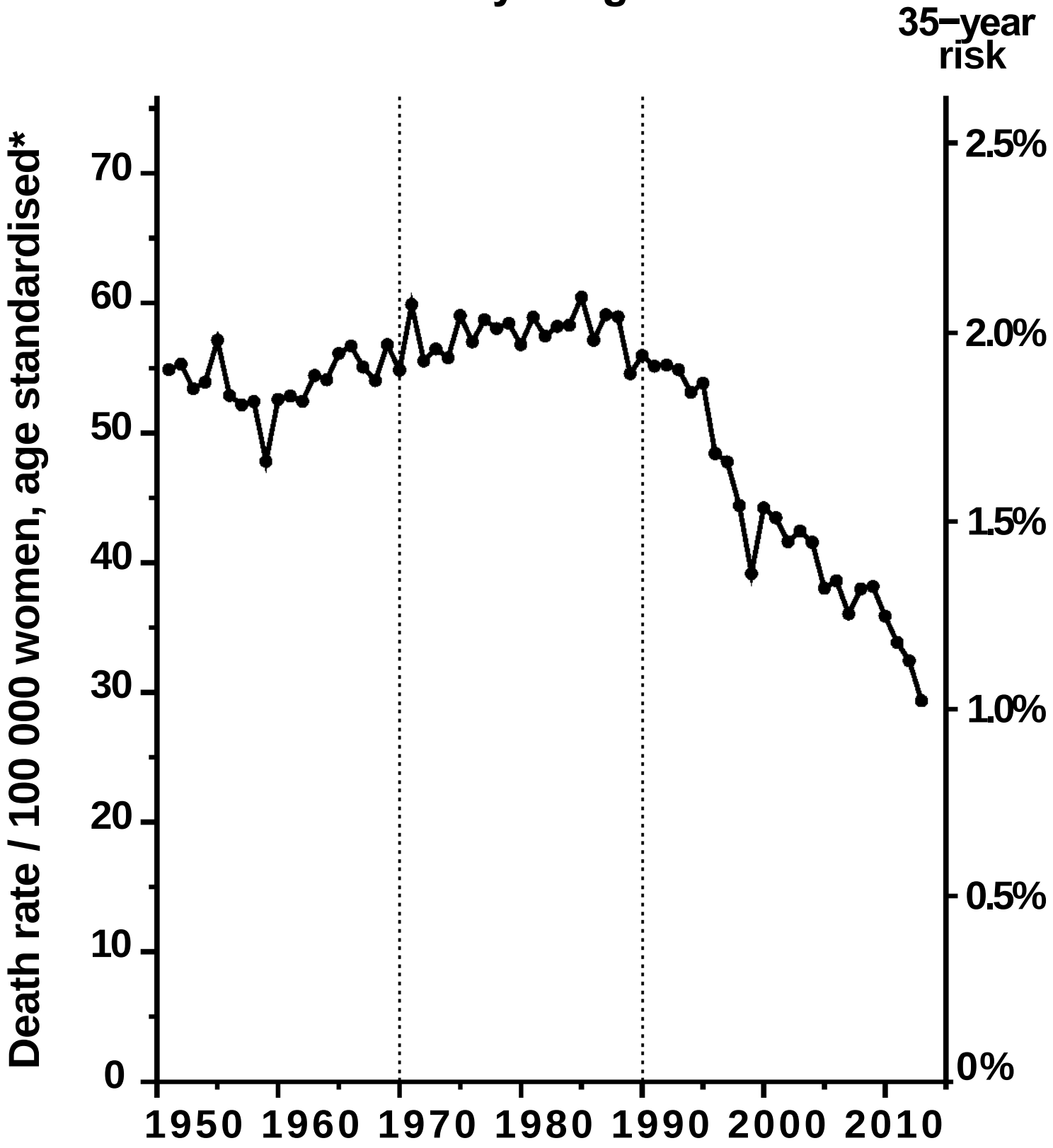
CANADA 1950−2012:
Breast cancer mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

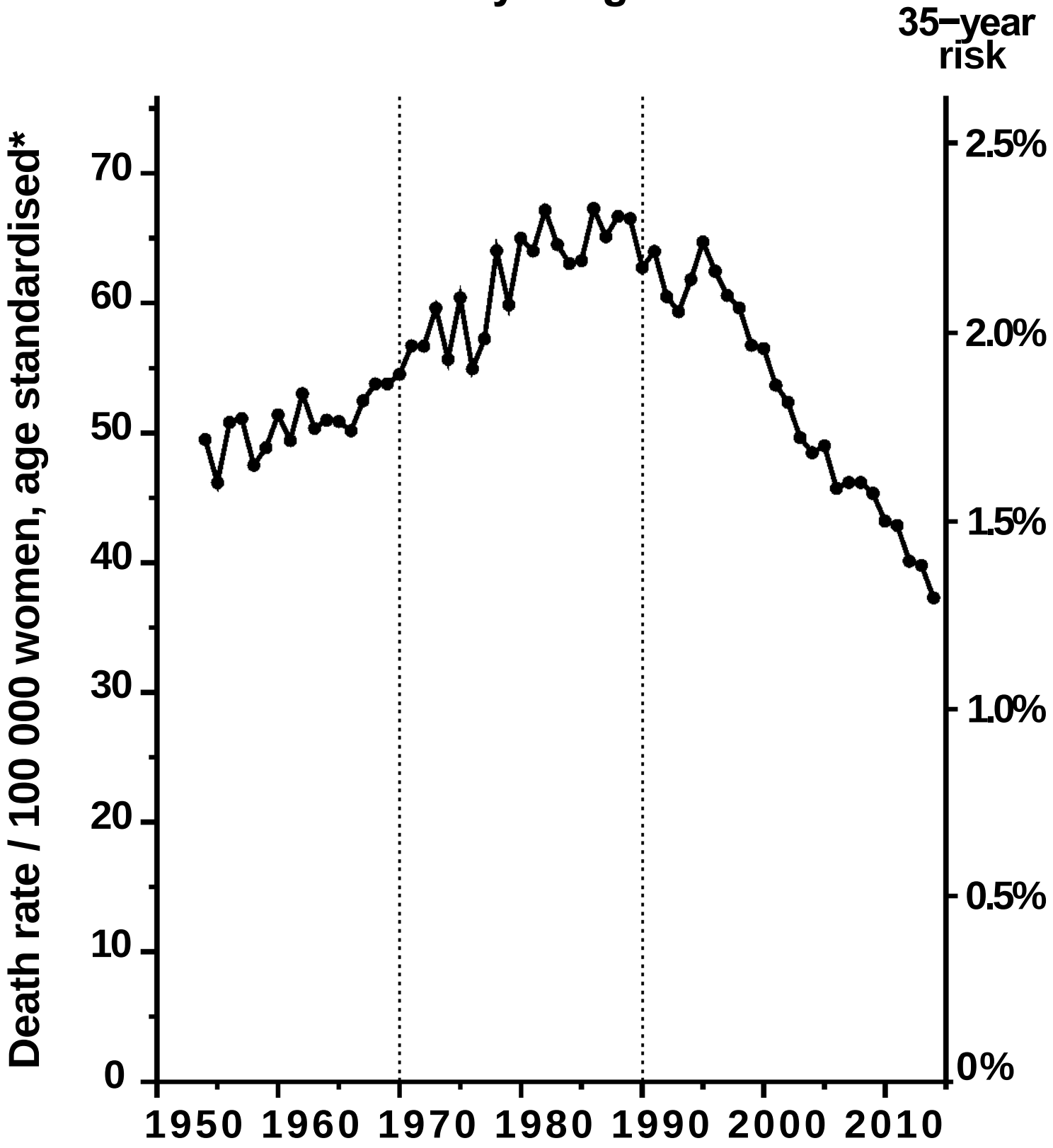
SWITZERLAND 1951−2013:
Breast cancer mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

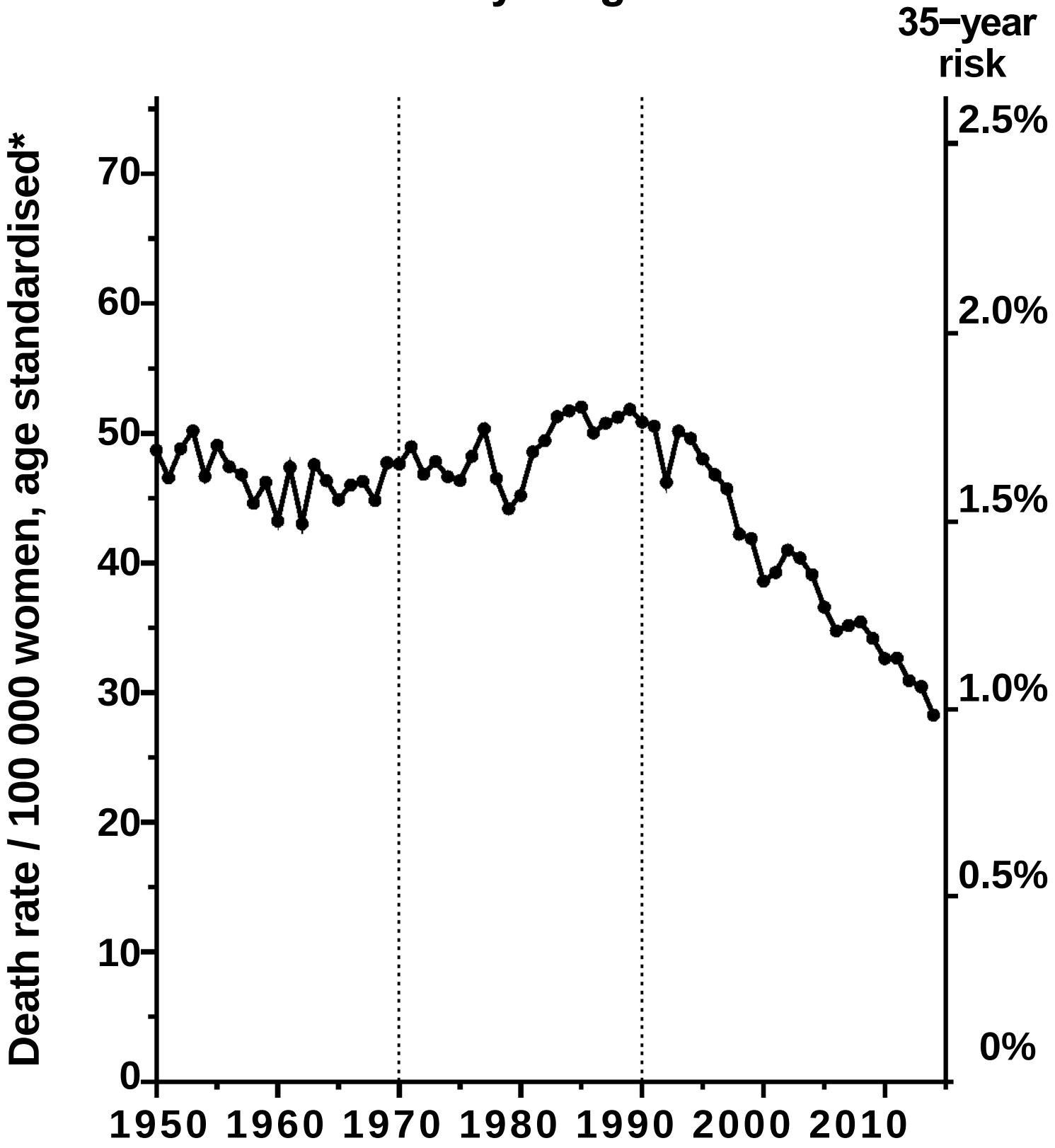
BELGIUM 1954−2014:
Breast cancer mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

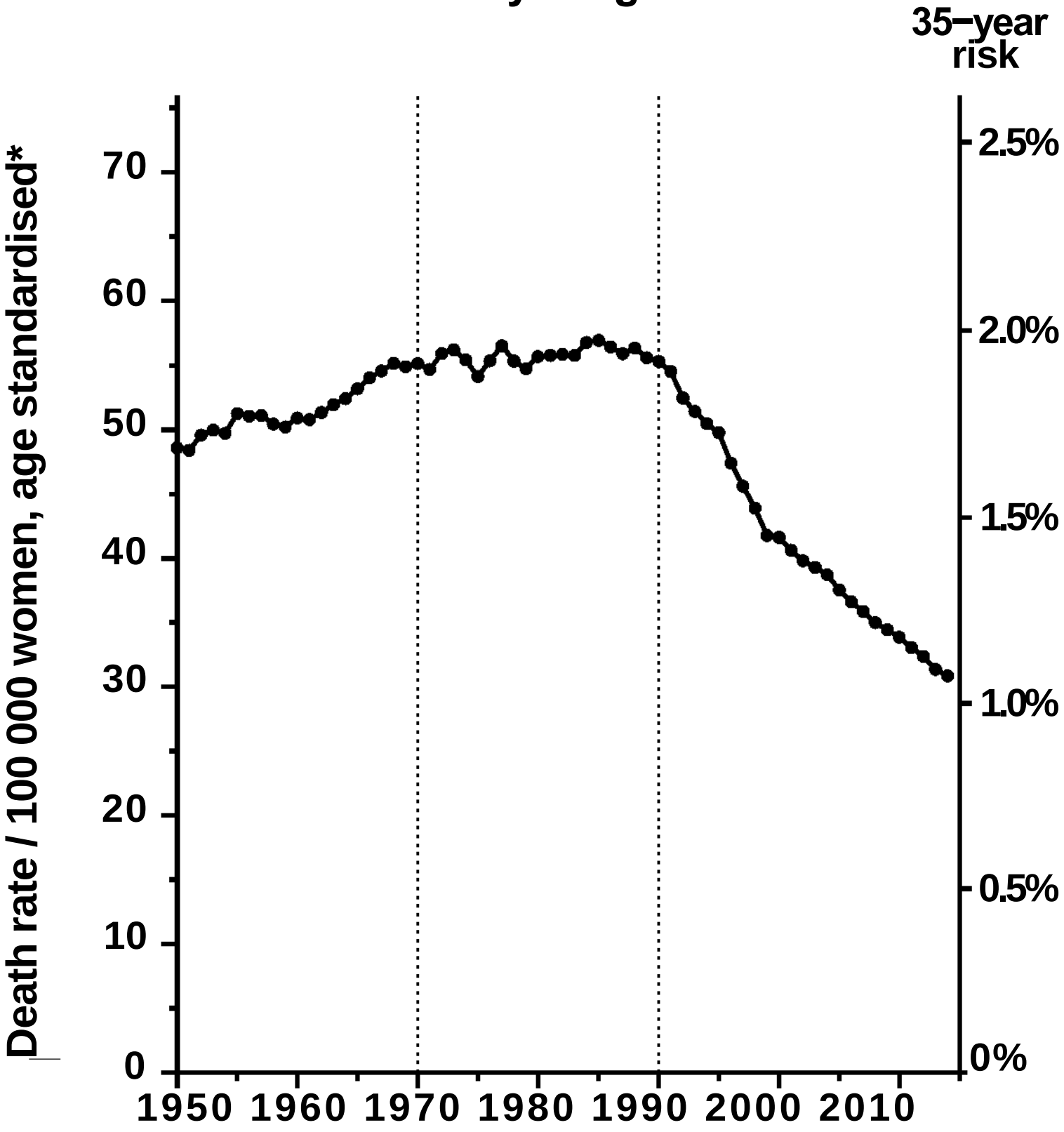
AUSTRALIA 1950−2014:
Breast cancer mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

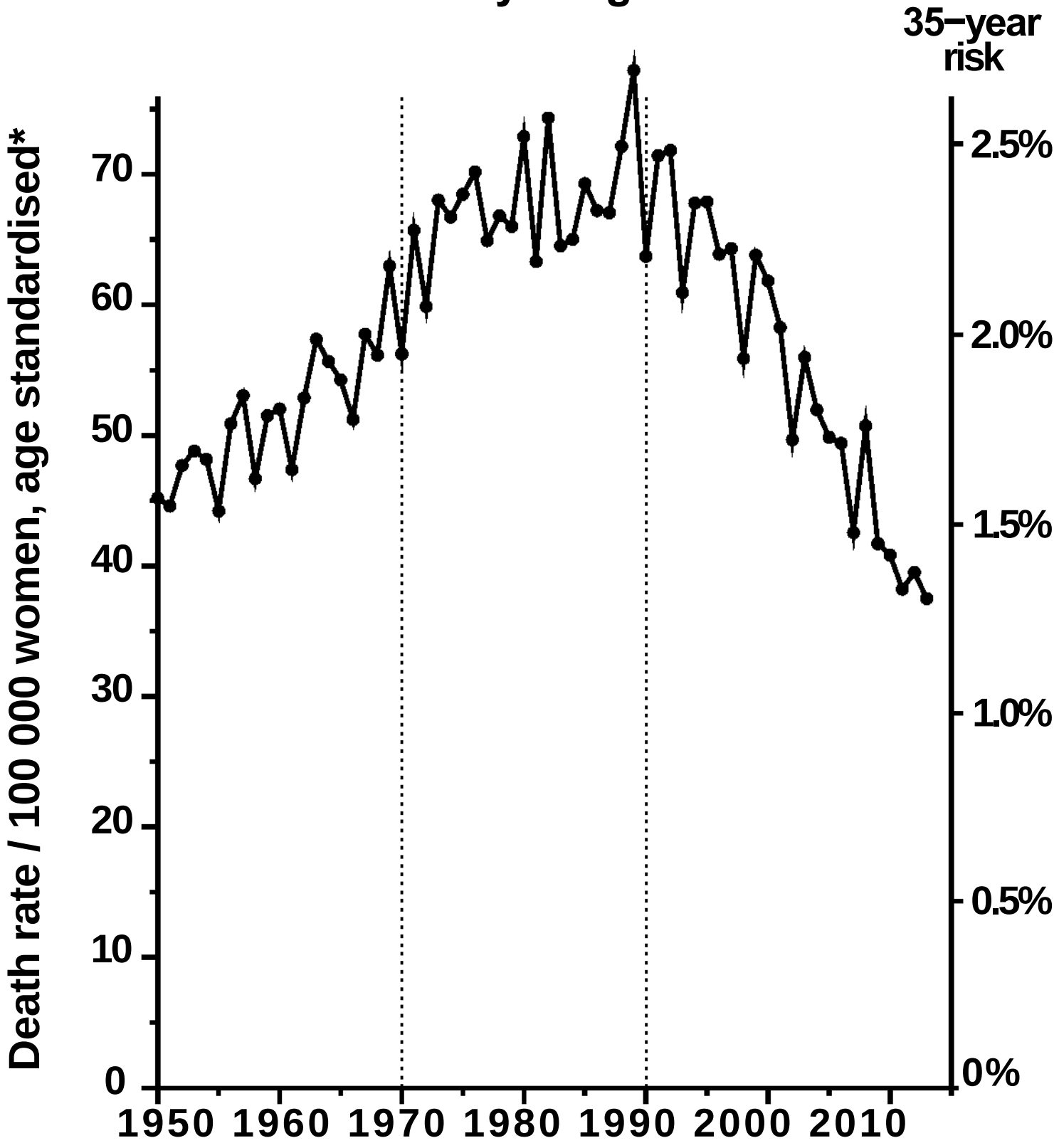
UNITED STATES 1950−2014:
Breast cancer mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

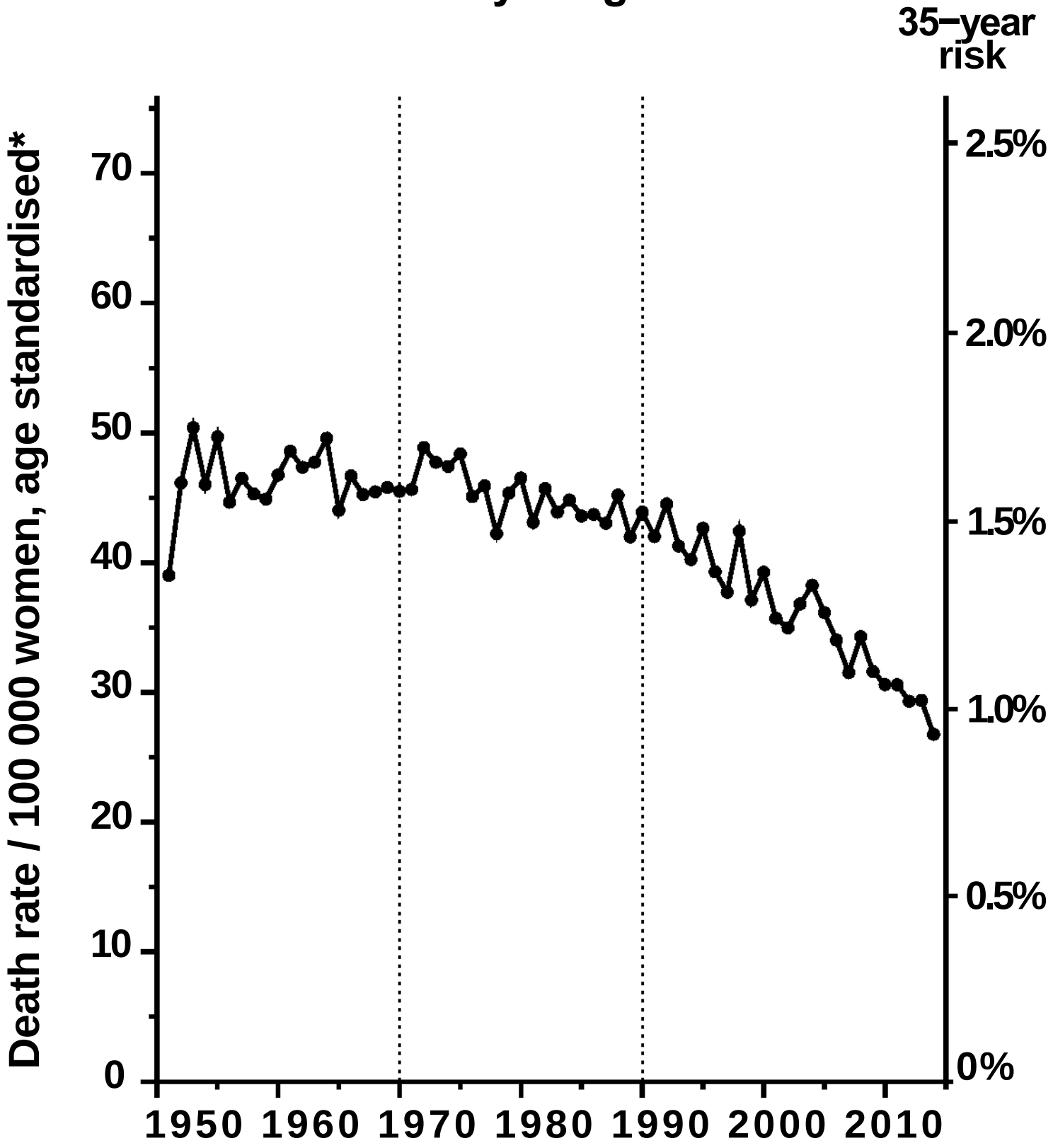
IRELAND 1950−2013:
Breast cancer mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

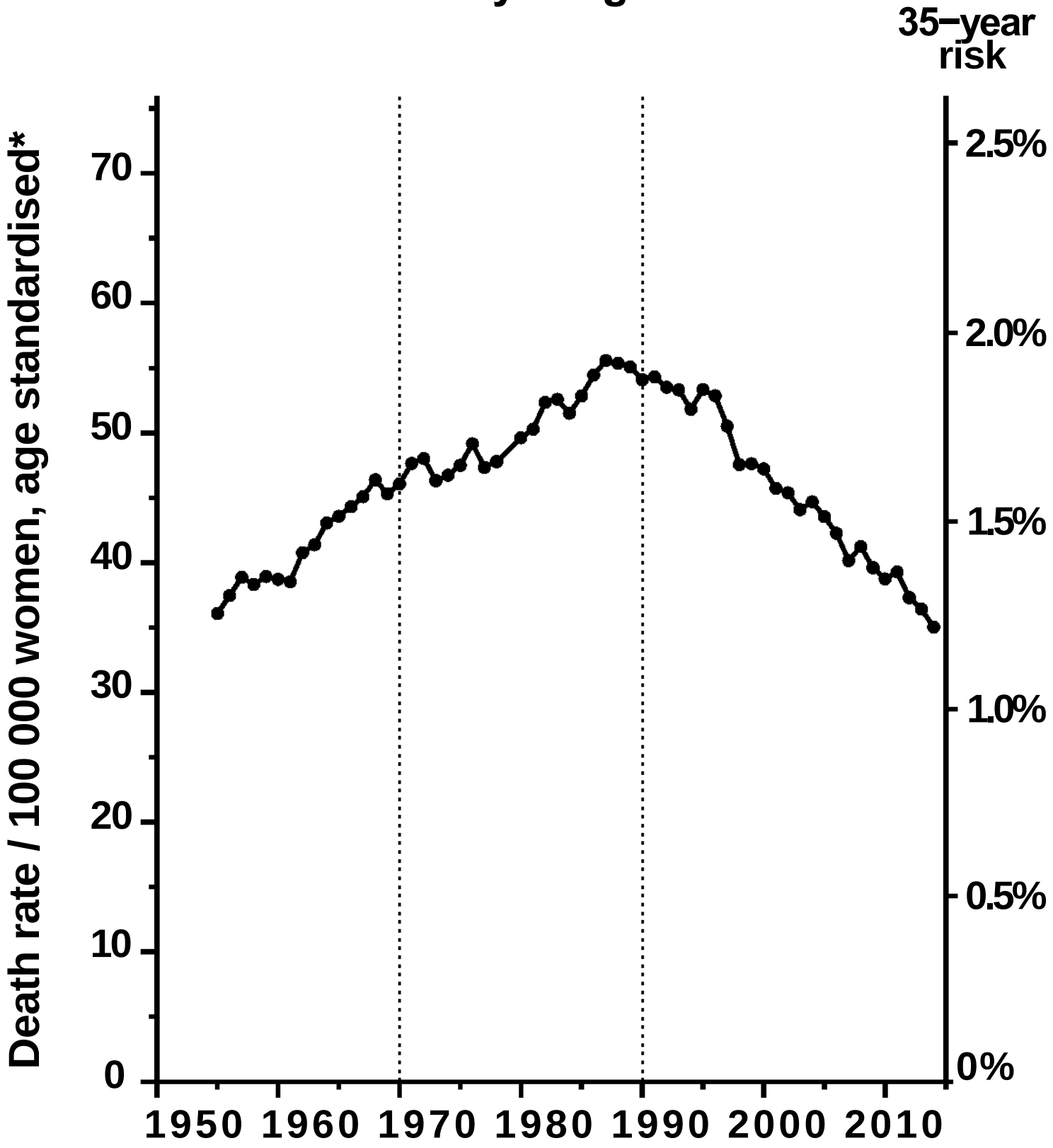
SWEDEN 1951−2014:
Breast cancer mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

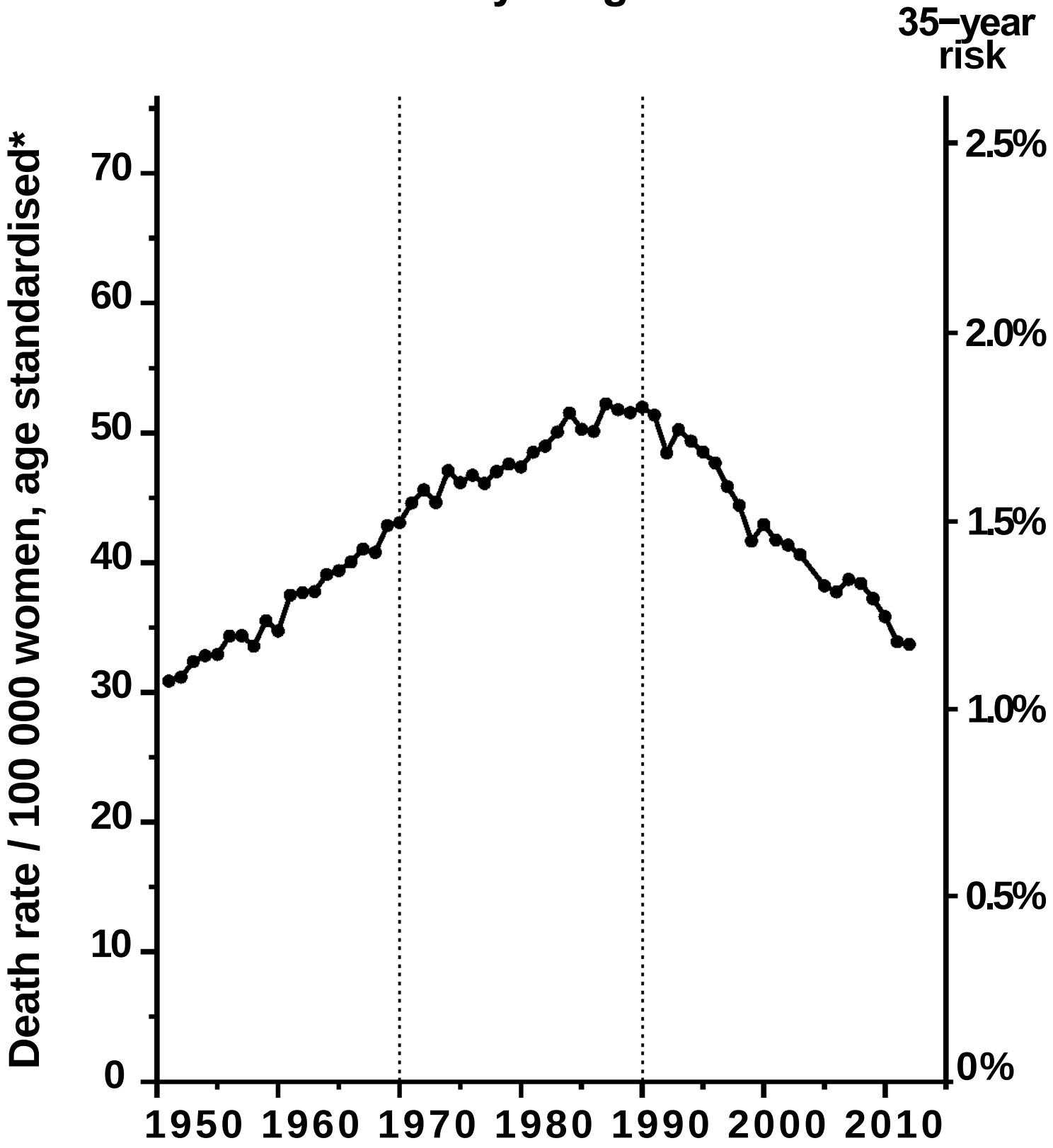
GERMANY 1955−2014:
Breast cancer mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

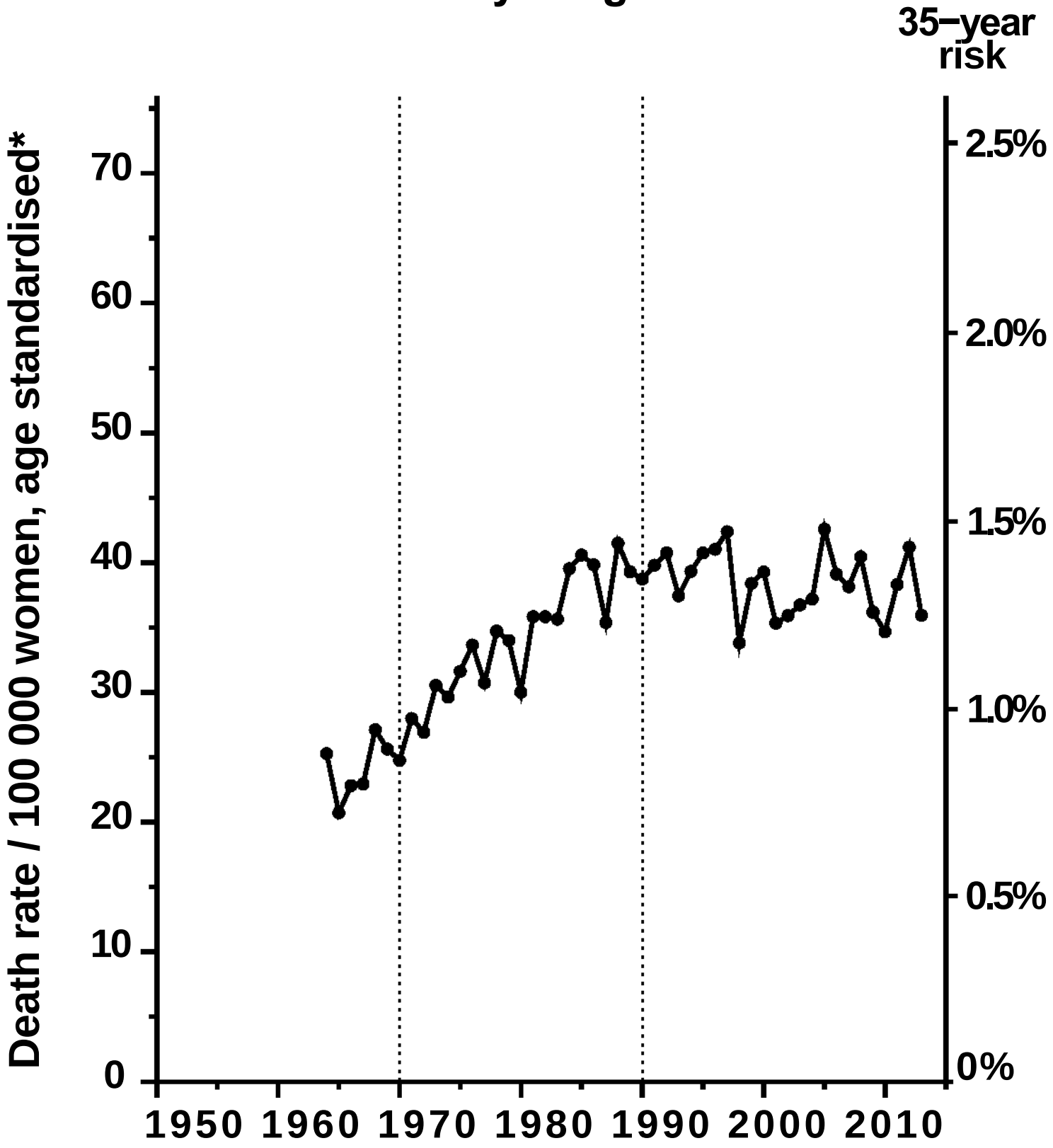
ITALY 1951−2012:
Breast cancer mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

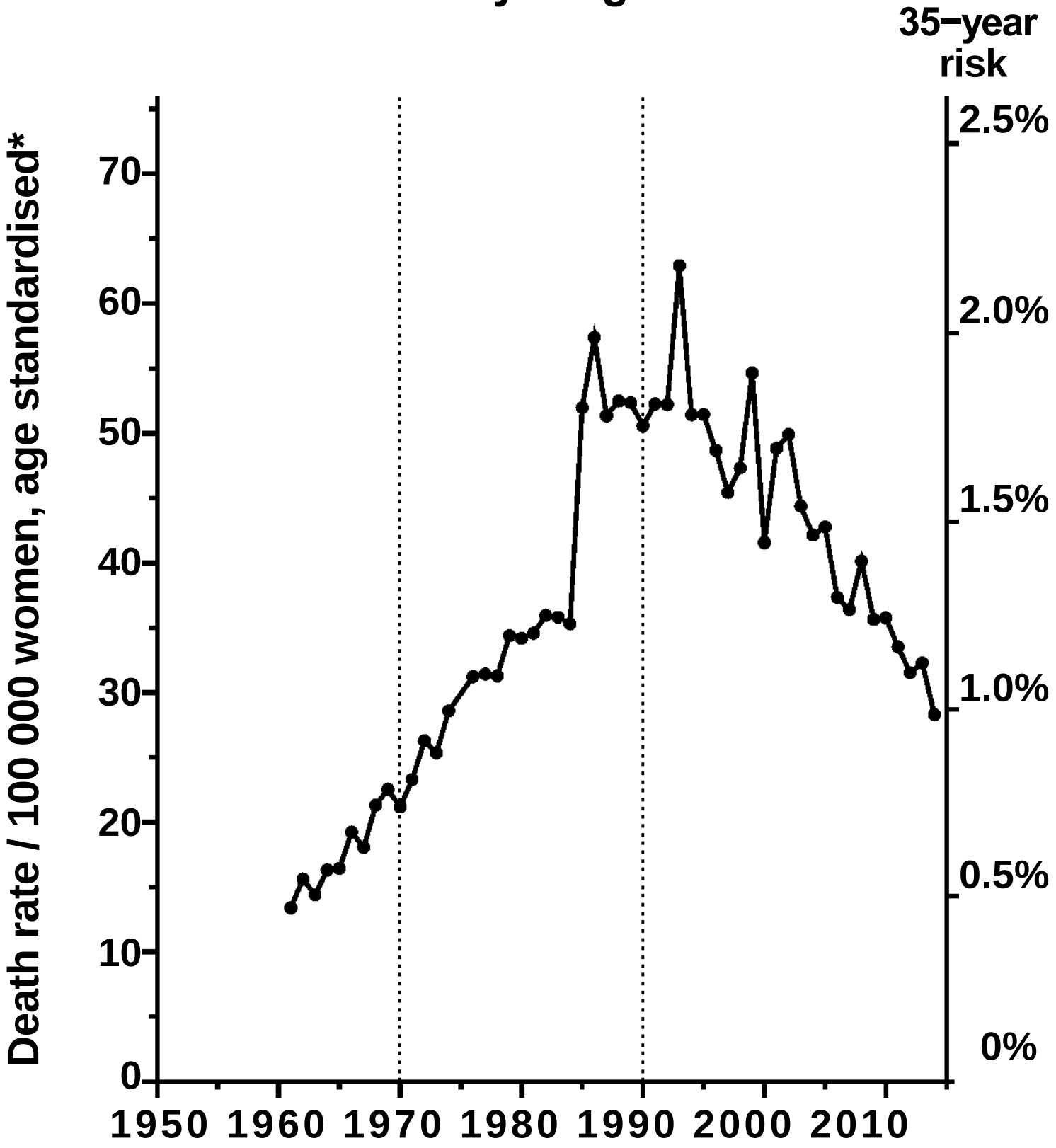
BULGARIA 1964−2013:
Breast cancer mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

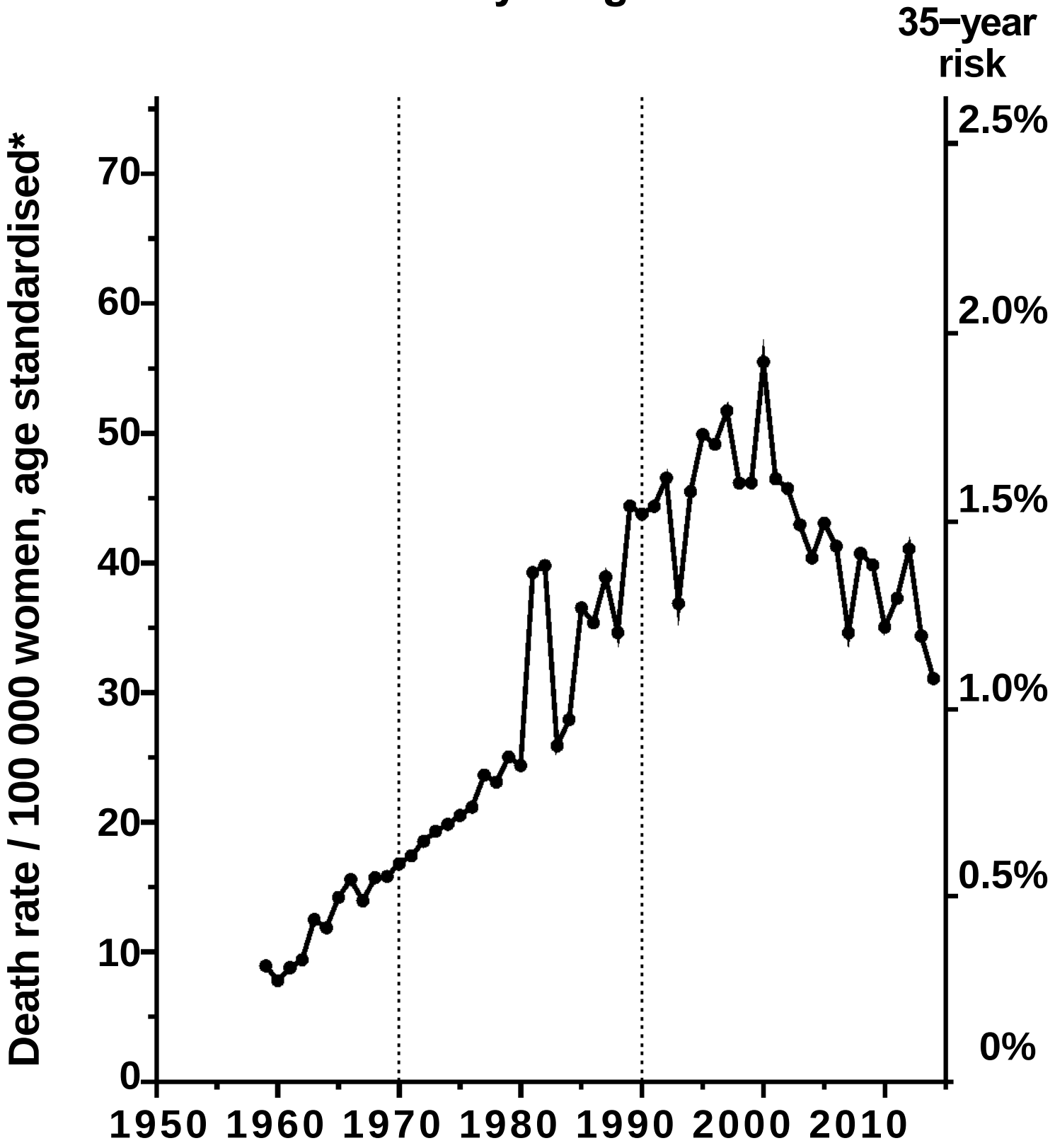
SLOVENIA 1960−2014:
Breast cancer mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

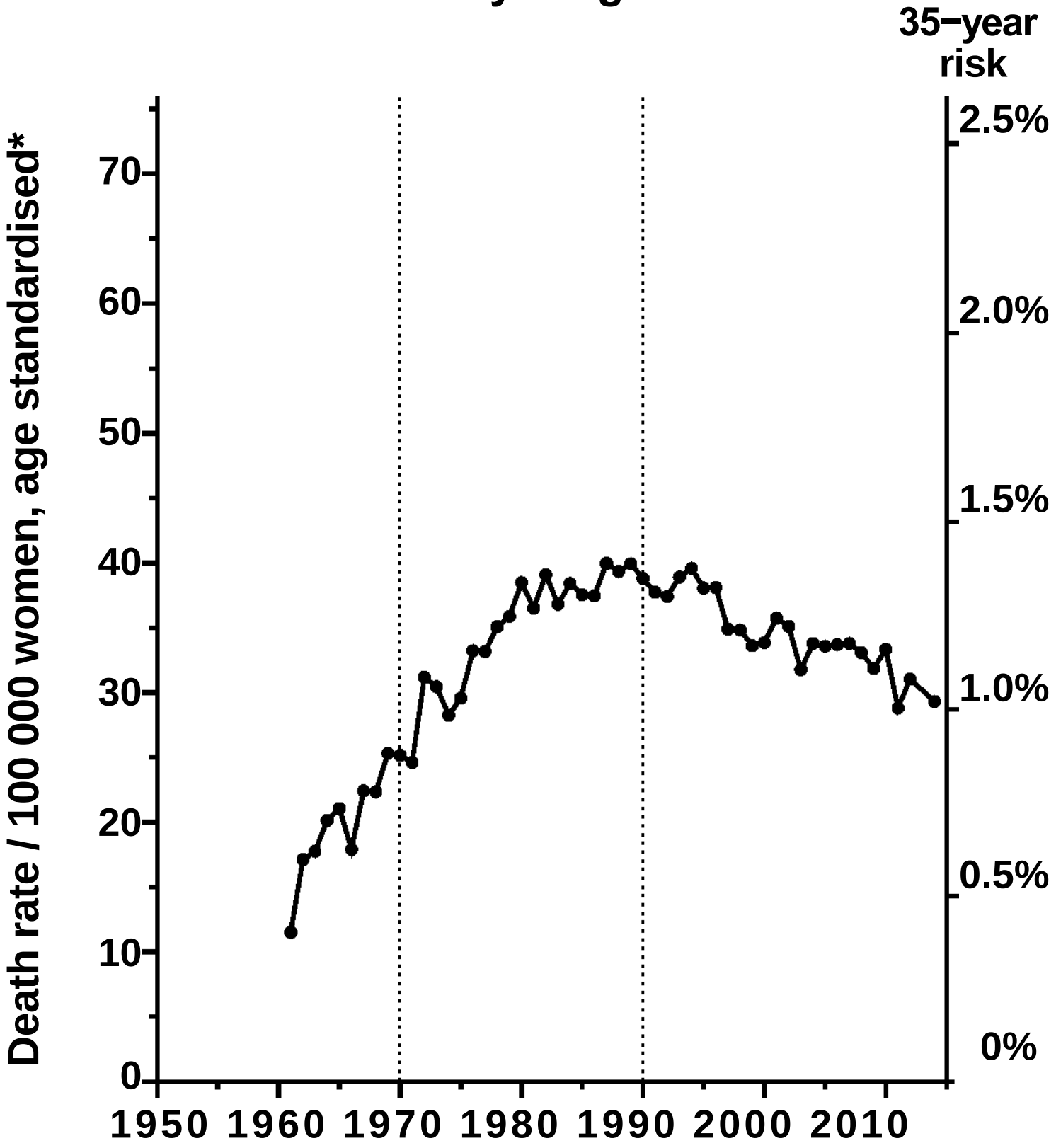
ESTONIA 1959−2014:
Breast cancer mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

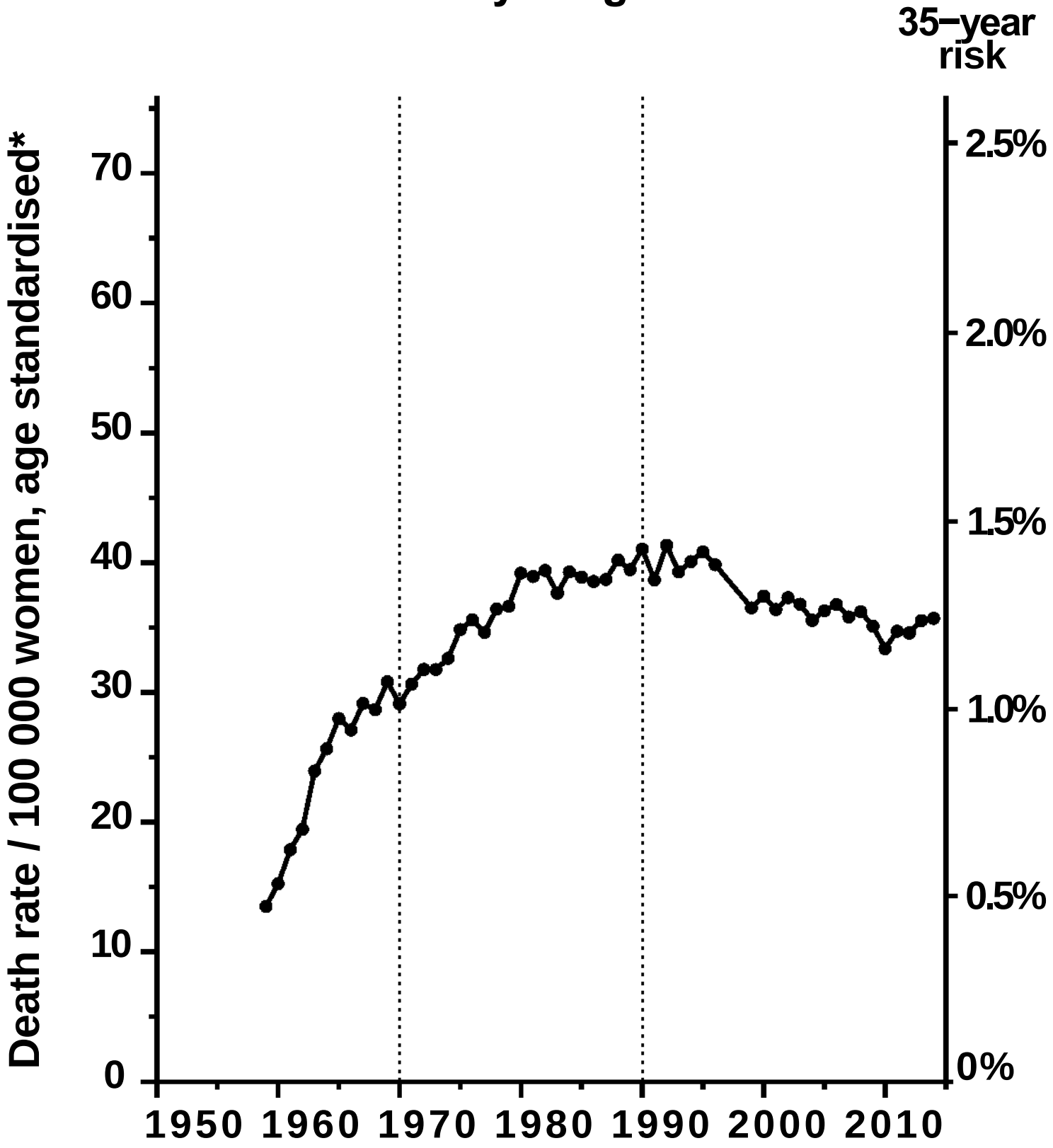
GREECE 1955−2014:
Breast cancer mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

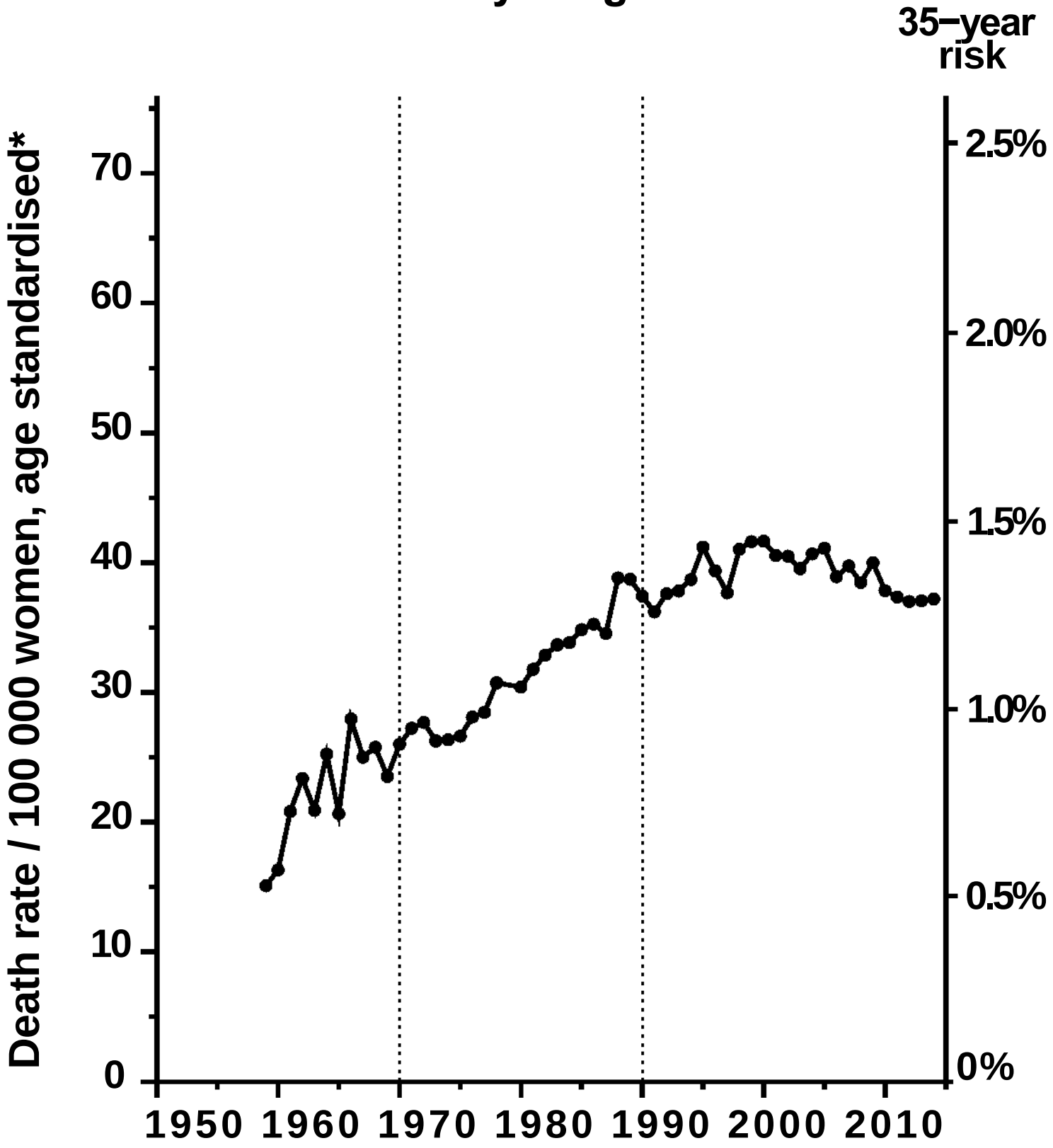
POLAND 1959−2014:
Breast cancer mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

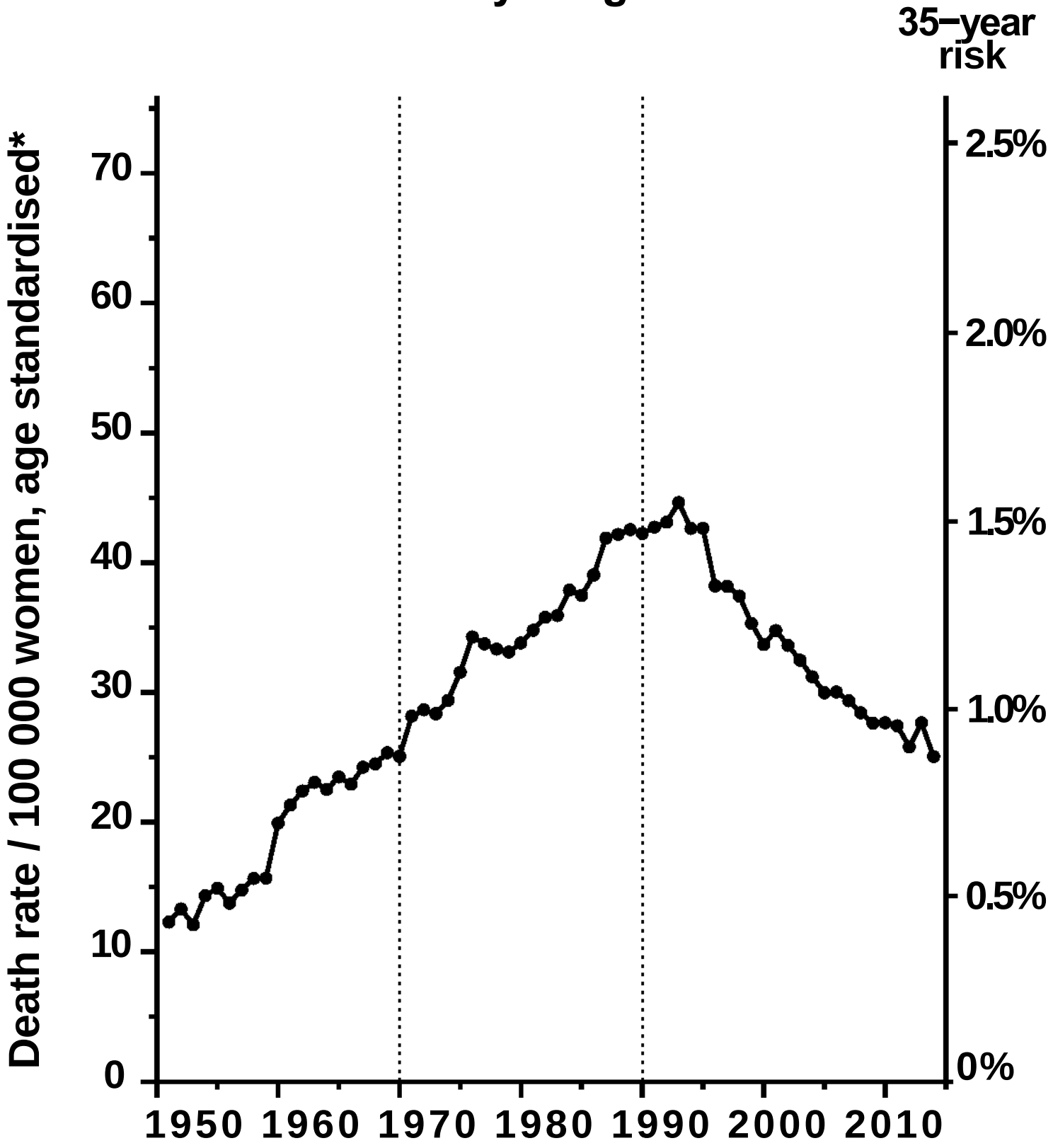
ROMANIA 1959−2014:
Breast cancer mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

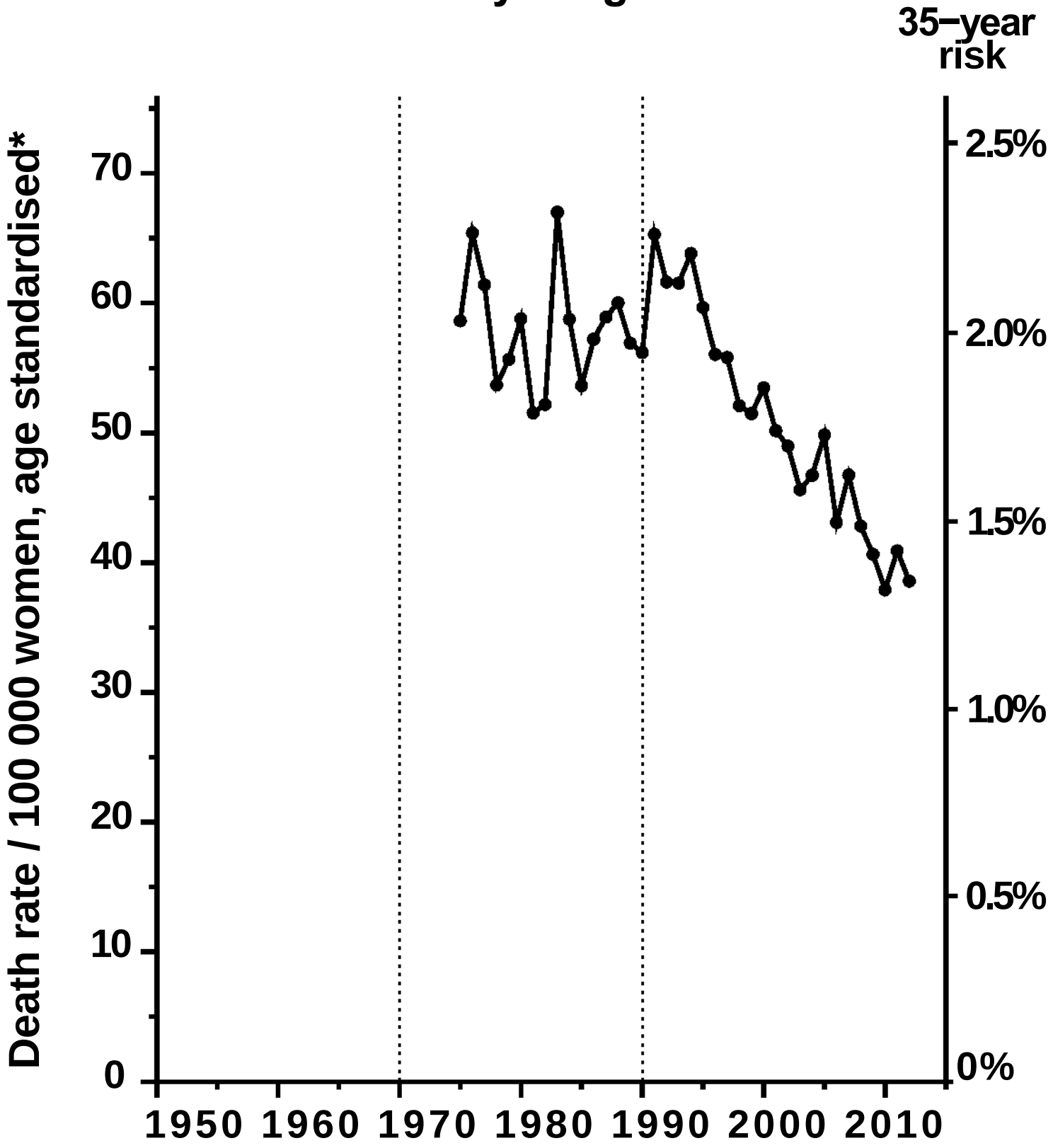
SPAIN 1951−2014:
Breast cancer mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

ISRAEL 1975−2012:
Breast cancer mortality at ages 35−69



*Mean of annual rates in the seven component 5−year age groups

Source: WHO mortality & UN population estimates

The end

Randomized Trials of Radiotherapy after Breast-conserving Surgery

Sarah Darby
Nuffield Department of Population Health
University of Oxford
United Kingdom

CANCER RESEARCH UK

UNIVERSITY OF OXFORD

Plan of talk

- Introduction
- EBCTCG Meta-analysis of radiotherapy after breast-conserving surgery
- Analyses of any, local and distant recurrence

Why do we need randomized trials?

- In clinical practice, the patients who receive a treatment differ in many respects from those who do not
- So, if we compare outcomes in patients who did/did not receive a treatment, there will be many factors that differ between the two groups
- The ***only*** way to obtain reliable comparisons of the effects of medical treatments is to randomize

Why do we need meta-analyses? -1

- Trials that have extreme results will tend to receive more attention than trials with moderate results

- So meta-analyses putting together the information from all the relevant trials are needed to gain a ***balanced view of the evidence***

Why do we need meta-analyses? -2

- As breast cancer is common, even small improvements in survival avoid many deaths
- Individual trials are often not big enough to detect small differences in survival reliably
- Meta-analyses bring together information on large numbers of women so that **small differences that would save many lives can be detected reliably**

Plan of talk

- Introduction
- EBCTCG Meta-analysis of radiotherapy after breast-conserving surgery
- Analyses of any, local and distant recurrence

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

So as not to miss any MODERATE differences in long-term survival, the world's trialists have shared their individual patient data every 5 years since 1985

1985, 1990, 1995, 2000, 2005, 2010

EBCTCG Collaborating Trialists

ACETBC, Tokyo, Japan—O Abe, R Abe, K Enomoto, K Kikuchi, H Koyama, H Masuda, Y Nomura, K Sakai, K Sugimachi, T Tominaga, J Uchino, M Yoshida. Addenbrooke's Hospital, Cambridge, UK—J L Haybittle. ATLAS Trial Collaborative Study Group, Oxford, UK—V Collett, C Davies, J Sayer. Auckland Breast Cancer Study Group, New Zealand—V J Harvey, TM Holdaway, R G Kay, B H Mason. Australian-New Zealand Breast Cancer Trials Group, Sydney, Australia—J F Forbes, N Wilcken. Austrian Breast Cancer Study Group, Vienna, Austria—P Dubsky, H Fohler, M Fidrik, M Gnant, R Greil, R Jakesz, W Krasny, E Kubista, A Lang, C Marth, C Menzel, M Mittlboeck, B Mlineritsch, S Poestlberger, R Poetter, E Ruecklinger, H Samonigg, W Schippinger, G Steger, M Stierer, S Taucher, J Thaler, J Tschmelitsch, W Wohlmuth. Beatson Oncology Centre, Glasgow, UK—P Canney, H M A Yosef. Belgian Adjuvant Breast Cancer Project, Liège, Belgium—C Focan. Berlin-Buch Akademie der Wissenschaften, Germany—U Peek. Birmingham General Hospital, UK—G D Oates, J Powell. Bordeaux Institut Bergonié, France—M Durand, L Mauriac. Bordet Institute, Brussels, Belgium—A Di Leo, S Dolci, M J Piccart. Bradford Royal Infirmary, UK—M B Masood, D Parker, J J Price. Breast Cancer Study Group of the Comprehensive Cancer Centre, Limburg, Netherlands—P S G J Hupperets. British Columbia Cancer Agency, Vancouver, Canada—S Jackson, J Ragaz. Cancer and Leukemia Group B, Washington, DC, USA—D Berry, G Broadwater, C Cirrincione, H Muss, L Norton, R B Weiss. Cancer Care Ontario, Canada—H T Abu-Zahra. Cancer Research Centre of the Russian Academy of Medical Sciences, Moscow, Russia—S M Portnoj. Cancer Research UK, London, UK—M Baum, J Cuzick, M Dowsett, J Houghton, D Riley. Cardiff Trialists Group, UK—R E Mansel. Case Western Reserve University, Cleveland, OH, USA—N H Gordon. Central Oncology Group, Milwaukee, WI, USA—H L Davis. Centre Claudius Regaud, Toulouse, France—A Beatrice, J Mihura, A Naja. Centre Léon-Bérard, Lyon, France—Y Lehingue, P Romestaing. Centre Paul Lamarque, Montpellier, France—J B Dubois. Centre Regional François Baclesse, Caen, France—T Delozier, J Mace Lesec'h. Centre René Huguenin, Paris, St Cloud, France—P Rambert. Charles University, Prague, Czech Republic—L Petruzelka, O Pribylova. Cheltenham General Hospital, UK—J R Owen. Chemo N0 Trial Group, Germany —N Harbeck, F Jänicke, C Meisner. Chicago University, IL, USA—P Meier. Christie Hospital and Holt Radium Institute, Manchester, UK—A Howell, R Swindell. Clinical Trial Service Unit, Oxford, UK (i.e. EBCTCG Secretariat)—M Clarke, R Collins, C Correa, S Darby, C Davies, P Elphinstone, V Evans, J Godwin, R Gray, C Harwood, D Hermans, C Hicks, S James, E MacKinnon, P McGale, T McHugh, R Peto, J Sayer, C Taylor, Y Wang. Coimbra Instituto de Oncologia, Portugal—J Albano, C F de Oliveira, H Gervásio, J Gordilho. Copenhagen Radium Centre, Denmark—H Johansen, H T Mouridsen. Dana-Farber Cancer Institute, Boston, MA, USA—D Hayes, R S Gelman, J R Harris, I C Henderson, C L Shapiro, E Winer. Danish Breast Cancer Cooperative Group, Copenhagen, Denmark—P Christiansen, B Ejlertsen, M Ewertz Kvistgaard, H T Mouridsen, S Møller, M Overgaard. Danish Cancer Registry, Copenhagen, Denmark—B Carstensen, T Palshof. Düsseldorf University, Germany—H J Trampisch. Dutch Working Party for Autologous Bone Marrow Transplant in Solid Tumours, Groningen, Netherlands—O Dalesio, E G E de Vries, S Rodenhuis, H van Tinteren. Eastern Cooperative Oncology Group, Boston, MA, USA—R L Comis, N E Davidson, R Gray, N Robert, G Sledge, D C Tormey, W Wood. Edinburgh Breast Unit, UK—D Cameron, U Chetty, P Forrest, W Jack. Elim Hospital, Hamburg, Germany—J Rossbach. Erasmus MC/Daniel den Hoed Cancer Center, Rotterdam, Netherlands—J G M Klijn, A D Treurniet-Donker, W L J van Putten. European Institute of Oncology, Milan, Italy—A Costa, U Veronesi, G Viale. European Organization for Research and Treatment of Cancer, Brussels, Belgium—H Bartelink, C Legrand, E Rutgers, R Sylvester, C J H van de Velde, J G H van Nes. Evanston Hospital, IL, USA—M P Cunningham. Fox Chase Cancer Centre, Philadelphia, PA, USA—L J Goldstein. French Adjuvant Study Group (GFEA), Guyancourt, France—J Bonneterre, P Fargeot, P Fumoleau, P Kerbrat, M Namer. German Adjuvant Breast Group (GABG), Frankfurt, Germany—W Jonat, M Kaufmann, M Schumacher, G von Minckwitz. German Breast Cancer Study Group (BMFT), Freiburg, Germany—G Bastert, H Rauschecker, R Sauer, W Sauerbrei, A Schauer, M Schumacher. Ghent University Hospital, Belgium—A de Schryver, L Vakaet. GIVIO Interdisciplinary Group for Cancer Care Evaluation, Chieti, Italy— M Belfiglio, A Nicolucci, F Pellegrini, M Sacco, M Valentini. Glasgow Victoria Infirmary, UK—C S McArdle, D C Smith, S Stallard. Gruppo Oncologico Clinico Cooperativo del Nord Est, Aviano, Italy—E Galligioni. Gruppo Ricerca Ormono Chemio Terapia Adiuvante (GROCTA), Genova, Italy—F Boccardo, A Rubagotti. Groote Schuur Hospital, Cape Town, South Africa—D M Dent, C A Gudgeon, A Hacking, E Murray, E Panieri. Guadalajara Hospital de 20 Noviembre, Mexico—A Erazo, J Y Medina. Gunma University, Japan—M Izuo, Y Morishita, H Takei. Guy's Hospital, London, UK—I S Fentiman, J L Hayward, R D Rubens, D Skilton. Heidelberg University I, Germany—H Scheurlen. Heidelberg University II, Germany—M Kaufmann, H C Sohn. Hellenic Cooperative Oncology Group, Athens, Greece—U Dafni, G Fountzilas. Helsinki Deaconess Medical Centre, Finland—P Klefstrom. Helsinki University, Finland—C Blomqvist, T Saarto. Innsbruck University, Austria—R Margreiter. Institut Curie, Paris, France—B Asselain, R J Salmon, J R Vilcoq. Institut Gustave-Roussy, Paris, France—R Arriagada, C Hill, A Laplanche, M G Lê, M Spielmann. Integraal Kankercentrum, Amsterdam, Netherlands—J Benraadt, M Kooi, A O van de Velde, J A van Dongen, J B Vermorken. International Breast Cancer Study Group (Ludwig), Bern, Switzerland—M Castiglione, F Cavalli, A Coates, J Collins, J Forbes, R D Gelber, A Goldhirsch, J Lindtner, K N Price, V Raina, C M Rudenstam, H J Senn. International Collaborative Cancer Group, Charing Cross Hospital, London, UK—J M Bliss, C E D Chilvers, R C Coombes, E Hall, M Marty. International Drug Development Institute, Louvain-la-Neuve, Belgium—M Buyse. International TABLE Study Group, Berlin, Germany—K Possinger, P Schmid, M Untch, D Wallwiener. Israel NSABC, Tel Aviv, Israel—R Borovik, G Brufman, H Hayat, E Robinson, N Yaal-Hahoshen. Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy—P Bruzzi, E Montanaro, R Rosso, M R Sertoli, M Venturini. Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy—G Bonadonna, T Camerini, G De Palo, M G Di Mauro, F Formelli, P Valagussa. Istituto Oncologico Romagnolo, Forlì, Italy—D Amadori. Italian Cooperative Chemo-Radio-Surgical Group, Bologna, Italy— A Martoni, F Pannuti. Italian Oncology Group for Clinical Research, Parma, Italy— R Camisa, G Cocconi, A Colozza, S Gori. Japan Clinical Oncology Group–Breast Cancer Study Group, Matsuyama, Japan—K Aogi, S Takashima. Japanese Foundation for Multidisciplinary Treatment of Cancer, Tokyo, Japan—O Abe, T Ikeda, K Inokuchi, K Kikuchi, K Sawa. Kawasaki Medical School, Japan—H Sonoo. Krakow Institute of Oncology, Poland—S Korzeniowski, J Skolyszewski. Kumamoto University Group, Japan—M Ogawa, J Yamashita. Leuven Akademisch Ziekenhuis, Gasthuisberg, Belgium—R Christiaens, P Neven, R Paridaens, W Van den Bogaert. Marseille Laboratoire de Cancérologie Biologique APM, France—P Martin, S Romain. Memorial Sloan-Kettering Cancer Center, New York, NY, USA—T Hakes, C A Hudis, L Norton, R Wittes. Metaxas Memorial Cancer Hospital, Athens, Greece—G Giokas, D Kondylis, B Lissaios. Mexican National Medical Centre, Mexico City, Mexico—R de la Huerta, M G Sainz. National Cancer Institute, Bethesda, MD, USA—R Altemus, K Camphausen, K Cowan, D Danforth, A Lichter, M Lippman, J O'Shaughnessy, L J Pierce, S Steinberg, D Venzon, J A Zujewski. National Cancer Institute, Bari, Italy—A Paradiso, M De Lena, F Schittulli. National Cancer Institute of Canada Clinical Trials Group, Kingston, Ontario, Canada—J W Chapman, P E Goss, M N Levine, J D Myles, J L Pater, K I Pritchard, L E Shepherd, D Tu, T Whelan, B Zee. National Kyushu Cancer Center, Japan—Y Nomura. National Surgical Adjuvant Breast and Bowel Project (NSABP), Pittsburgh, PA, USA—S Anderson, G Bass, A Brown, J Bryant (deceased), J Costantino, J Dignam, B Fisher, C Geyer, S Paik, C Redmond, S Wieand, N Wolmark. Nolvadex Adjuvant Trial Organisation, London, UK—M Baum, I M Jackson (deceased), M K Palmer. North Central Cancer Treatment Group, Mayo Clinic, Rochester, MN, USA—E Perez, J N Ingle, V J Suman. North Sweden Breast Cancer Group, Umea, Sweden—N O Bengtsson, H Jonsson, L G Larsson. North-Western British Surgeons, Manchester, UK—J P Lythgoe, R Swindell. Northwick Park Hospital, London, UK—M Kissin. Norwegian Breast Cancer Group, Oslo, Norway—B Erikstein, E Hannisdal, A B Jacobsen, J E Varhaug. Norwegian Radium Hospital, Oslo, Norway—B Erikstein, S Gundersen, M Hauer-Jensen, H Høst, A B Jacobsen, R Nissen-Meyer. Nottingham City Hospital, UK—R W Blamey, A K Mitchell, D A L Morgan, J F R Robertson. Oncofrance, Paris, France—M Di Palma, G Mathé, J L Misset. Ontario Clinical Oncology Group, Hamilton, Canada—R M Clark, M Levine, K I Pritchard, T Whelan. Osaka City University, Japan—K Morimoto. Osaka National Hospital, Japan—K Sawa, Y Takatsuka. Churchill Hospital, Oxford, UK—E Crossley, A Harris, D Talbot, M Taylor. Parma Hospital, Italy—G Cocconi, B di Blasio. Petrov Research Institute of Oncology, St Petersburg, Russia—V Ivanov, V Semiglazov. Piedmont Oncology Association, Winston-Salem, NC, USA—J Brockschmidt, M R Cooper. Prefectural Hospital, Oita, Japan—H Ueo. Pretoria University, South Africa—C I Falkson. Royal Marsden Hospital, Institute of Cancer Research, London, UK—R A'Hern, S Ashley, T J Powles, I E Smith, J R Yarnold. St George's Hospital, London, UK—J C Gazet. St Luke's Hospital, Dublin, Ireland—N Corcoran. Sardinia Oncology Hospital A Businico, Cagliari, Sardinia—N Deshpande, L di Martino. SASIB International Trialists, Cape Town, South Africa—P Douglas, A Hacking, H Høst, A Lindtner, G Notter. Saskatchewan Cancer Foundation, Regina, Canada—A J S Bryant, G H Ewing, L A Firth, J L Krushen-Kosloski. Scandinavian Adjuvant Chemotherapy Study Group, Oslo, Norway—R Nissen-Meyer. Scottish Cancer Therapy Network, Edinburgh, UK—L Foster, W D George, H J Stewart, P Stroner. South Sweden Breast Cancer Group, Lund, Sweden—P Malmström, T R Möller, S Rydén, I Tengrup, L Tennvall-Nittby. South-East Sweden Breast Cancer Group, Linköping, Sweden—J Carstenssen, M Dufmats, T Hatschek, B Nordenskjöld, M Söderberg. South-Eastern Cancer Study Group and Alabama Breast Cancer Project, Birmingham, AL, USA—J T Carpenter. South-West Oncology Group, San Antonio, TX, USA—K Albain, W Barlow, J Crowley, S Green, S Martino, C K Osborne, P M Ravdin. Southampton Oncology Centre, UK—N Murray, G T Royle. Stockholm Breast Cancer Study Group, Sweden—U Glas, U Johansson, L E Rutqvist, T Singnomklao, A Wallgren. Swiss Group for Clinical Cancer Research (SAKK), Bern, and OSAKO, St Gallen, Switzerland—M Castiglione, A Goldhirsch, R Maibach, H J Senn, B Thürlimann. Tel Aviv University, Israel—H Brenner, A Hercbergs. Tokyo Cancer Institute Hospital, Japan—M Yoshimoto. Toronto-Edmonton Breast Cancer Study Group, Canada—G DeBoer, A H G Paterson, K I Pritchard. Toronto Princess Margaret Hospital, Canada—J W Meakin, T Panzarella, K I Pritchard. Tumour Hospital, Chinese Academy of Medical Sciences, Beijing, People's Republic of China (in collaboration with the Oxford CTSU)—Y Shan, Y F Shao, X Wang, D B Zhao (CTSU: ZM Chen, HC Pan). Tunis Institut Salah Azaiz, Tunisia—J Bahi. UK Multicentre Cancer Chemotherapy Study Group, London, UK—M Reid, M Spittle. UK/Asia Collaborative Breast Cancer Group, London, UK—G P Deutsch, F Senanayake, D L W Kwong. University Federico II, Naples, Italy—A Bianco, C Carlomagno, M De Laurentiis, S De Placido. University of Texas MD Anderson Cancer Center, Houston, TX, USA—K Broglio, A U Buzdar. Uppsala-Örebro Breast Cancer Study Group, Sweden—J Bergh, L Holmberg, G Liljegren, J Nilsson. Vienna University Hospital 1st Department of Gynaecology, Austria—M Janauer, M Seifert, P Sevelda, C C Zielinsky. West Midlands Oncology Association, Birmingham, UK—J A Dunn, R K Hills, M Lee, J M Morrison, C Poole, D Rea, D Spooner. West of Scotland Breast Trial Group, Glasgow, UK—A Litton. Western Cancer Study Group, Torrance, CA, USA—R T Chlebowski. Würzburg University, Germany—H Caffier.

“Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials”

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)

Lancet 2011; 378: 1707-60

Trials of Radiotherapy after Breast Conserving Surgery (BCS ± RT)

EBCTCG, Lancet 2011; 378: 1707-60

- **Eligibility**
  - Trials of radiotherapy (RT) versus same surgery but no RT
  - Began before 2000
  - RT to conserved breast
- **Included**
  - 10 801 women in 17 trials
  - Follow-up to 2006 (median 9.5 years per woman)
  - Hormonal therapy in both trials arms for 43% of women
  - RT to regional nodes in some trials

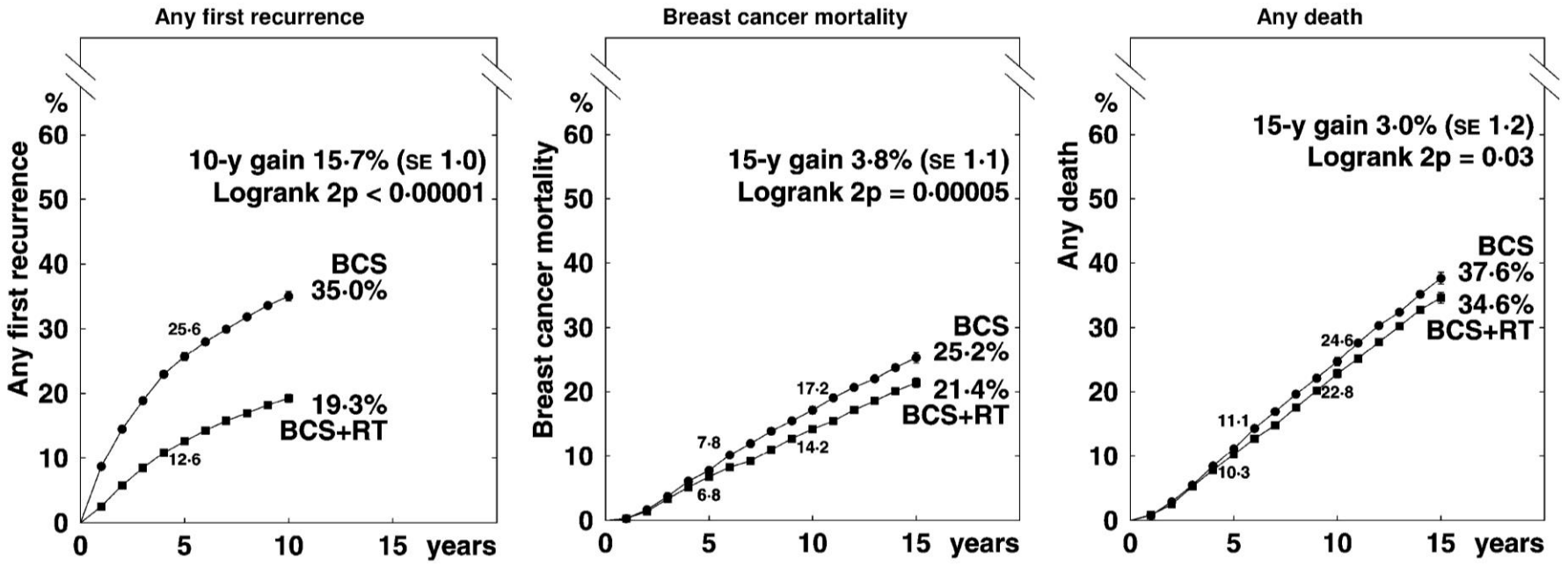
Lancet 2011

Randomised trials of radiotherapy following breast-conserving surgery (BCS ± RT)

Trial category	No of trials started before 2000	Years trials started	No of women	Median follow-up (years)
A. Lump: orig	6	1976-86	4400	12
B. >Lump	4	1981-91	2400	12
C. Lump: low risk	7	1989-96	4000	7
All women	17		10,800	10

Lancet 2011

Effect of RT after BCS on recurrence, breast cancer mortality and all-cause mortality



Data from 10,801 women in 17 trials starting before 2000

Lancet, 2011

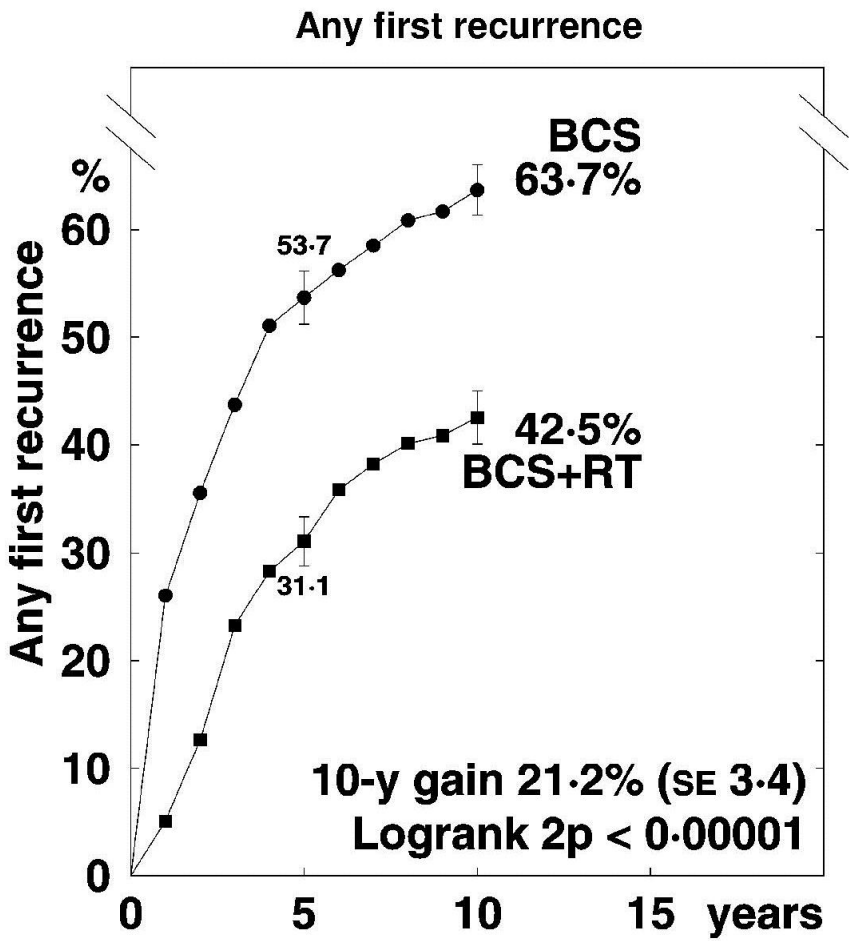
Current questions in RT after BCS

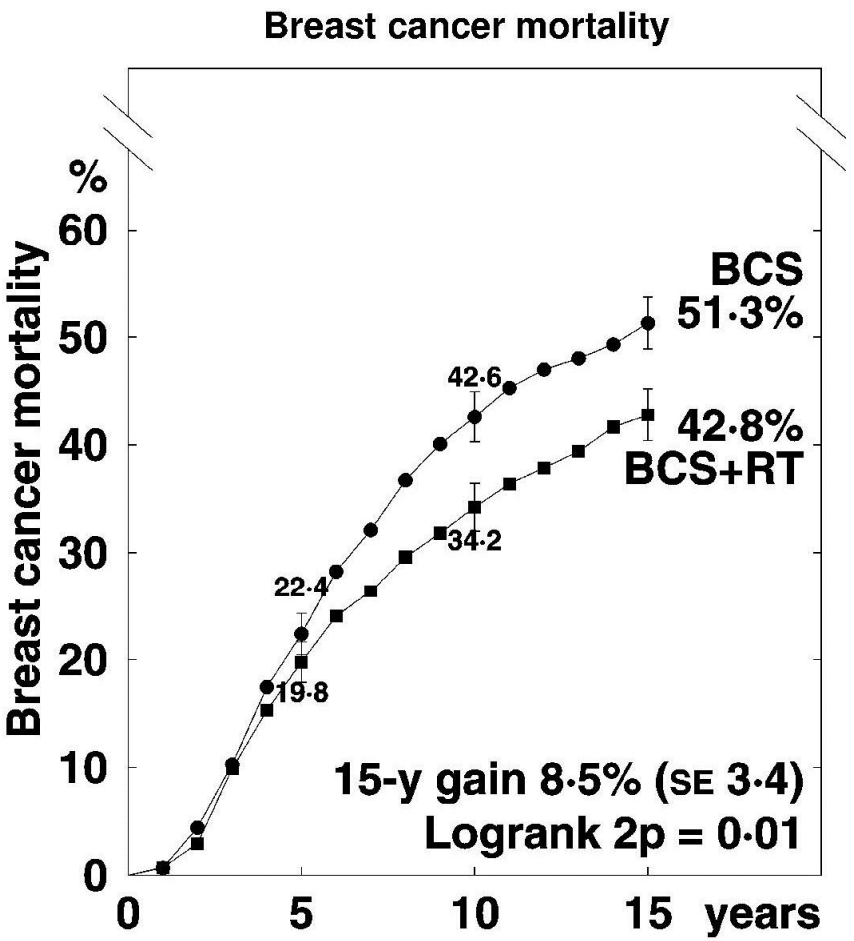
- Is absolute benefit from RT greater for some groups of women than for others?
- Do all women need RT?
- Relationship between effects of RT on recurrence and on breast cancer death?

Lancet, 2011

Effect of RT after BCS on recurrence and breast cancer mortality in pN+ women

1050 pN+ women



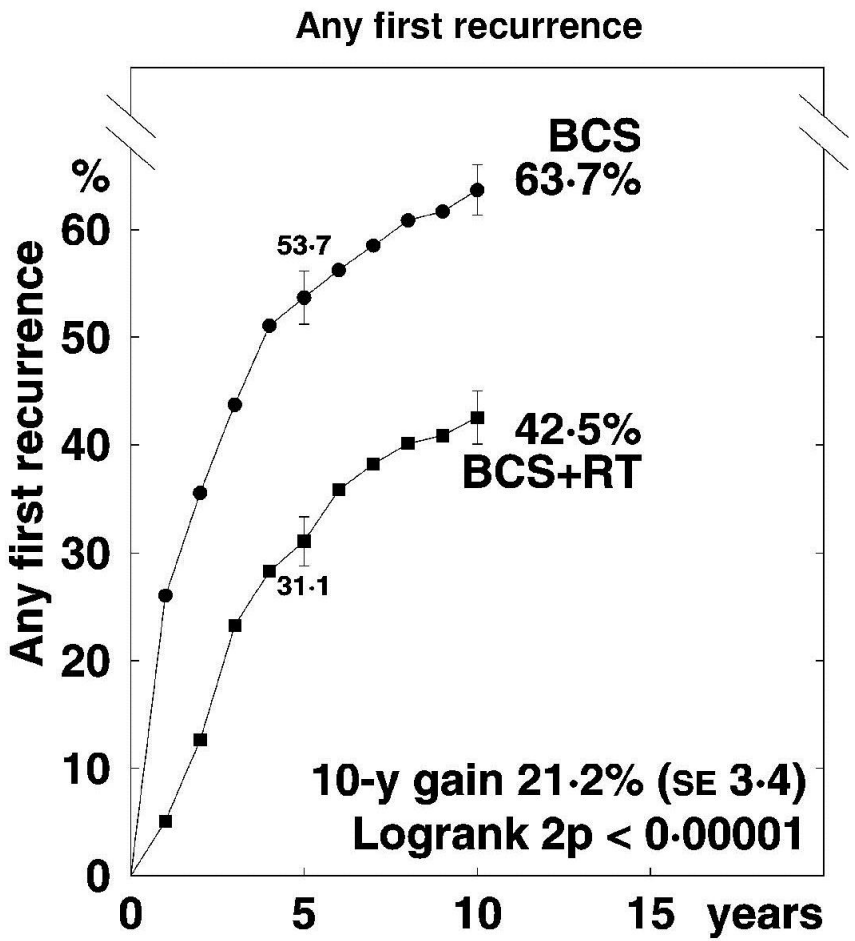


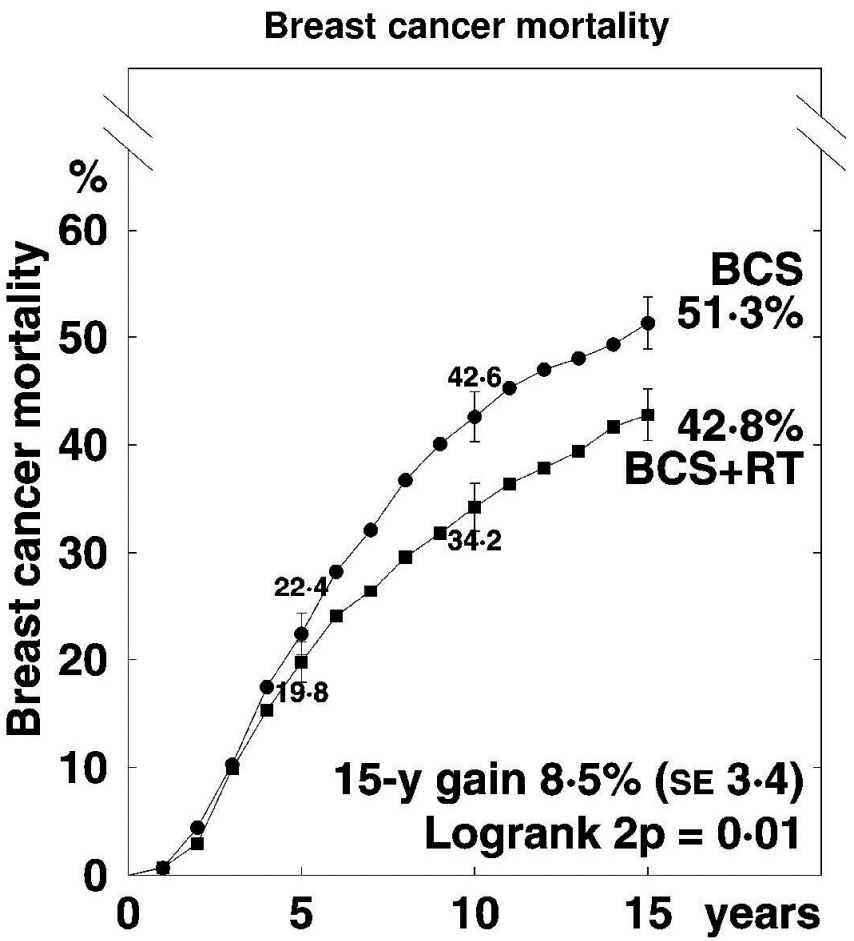
Most trials in pN+ included chemotherapy (usually CMF) in both trial arms

Lancet, 2011

Effect of RT after BCS on recurrence and breast cancer mortality in pN+ women

1050 pN+ women



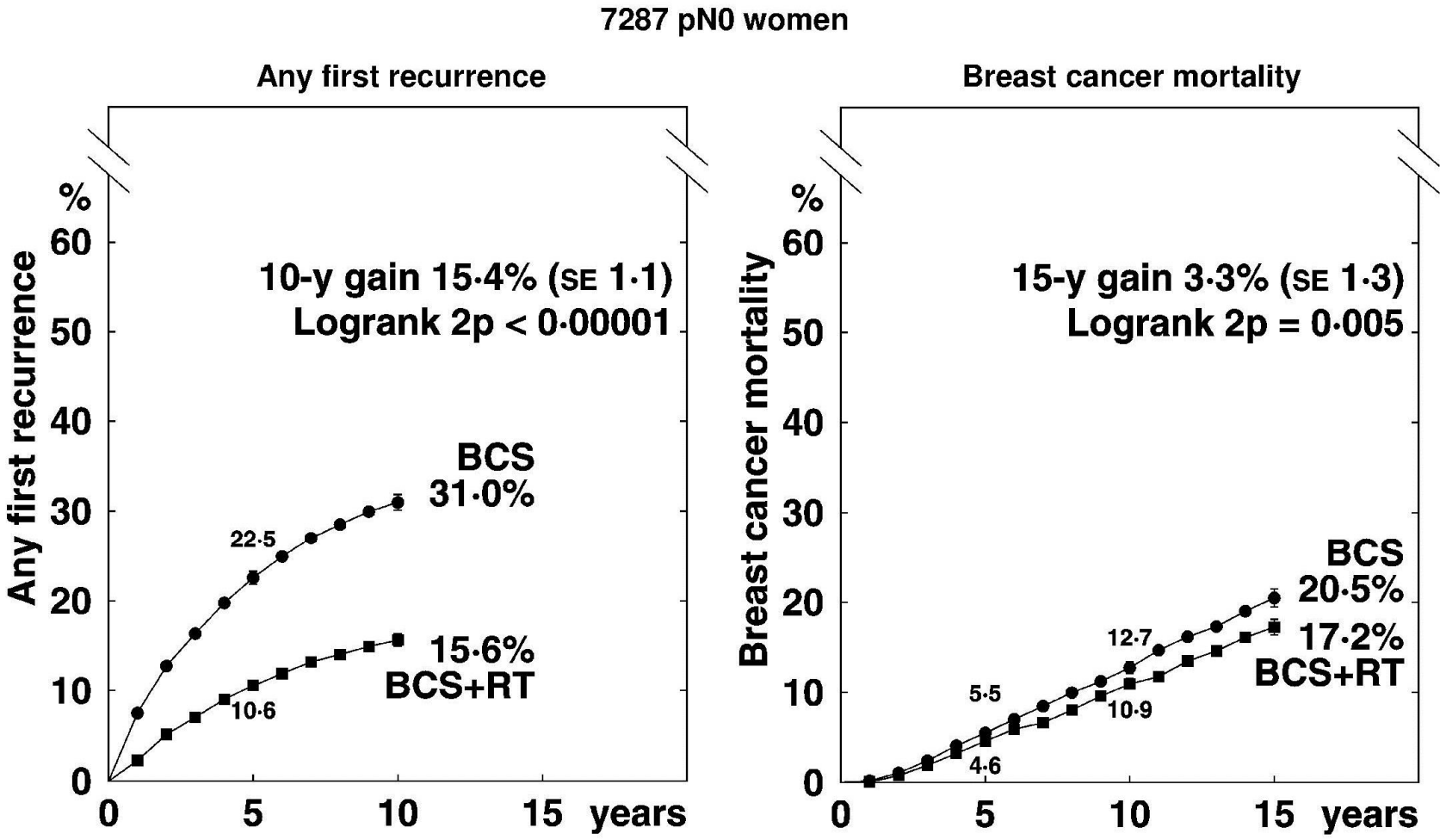


Most trials in pN+ included chemotherapy (usually CMF) in both trial arms

These data suggest that most/all pN+ women need RT after BCS

Lancet, 2011

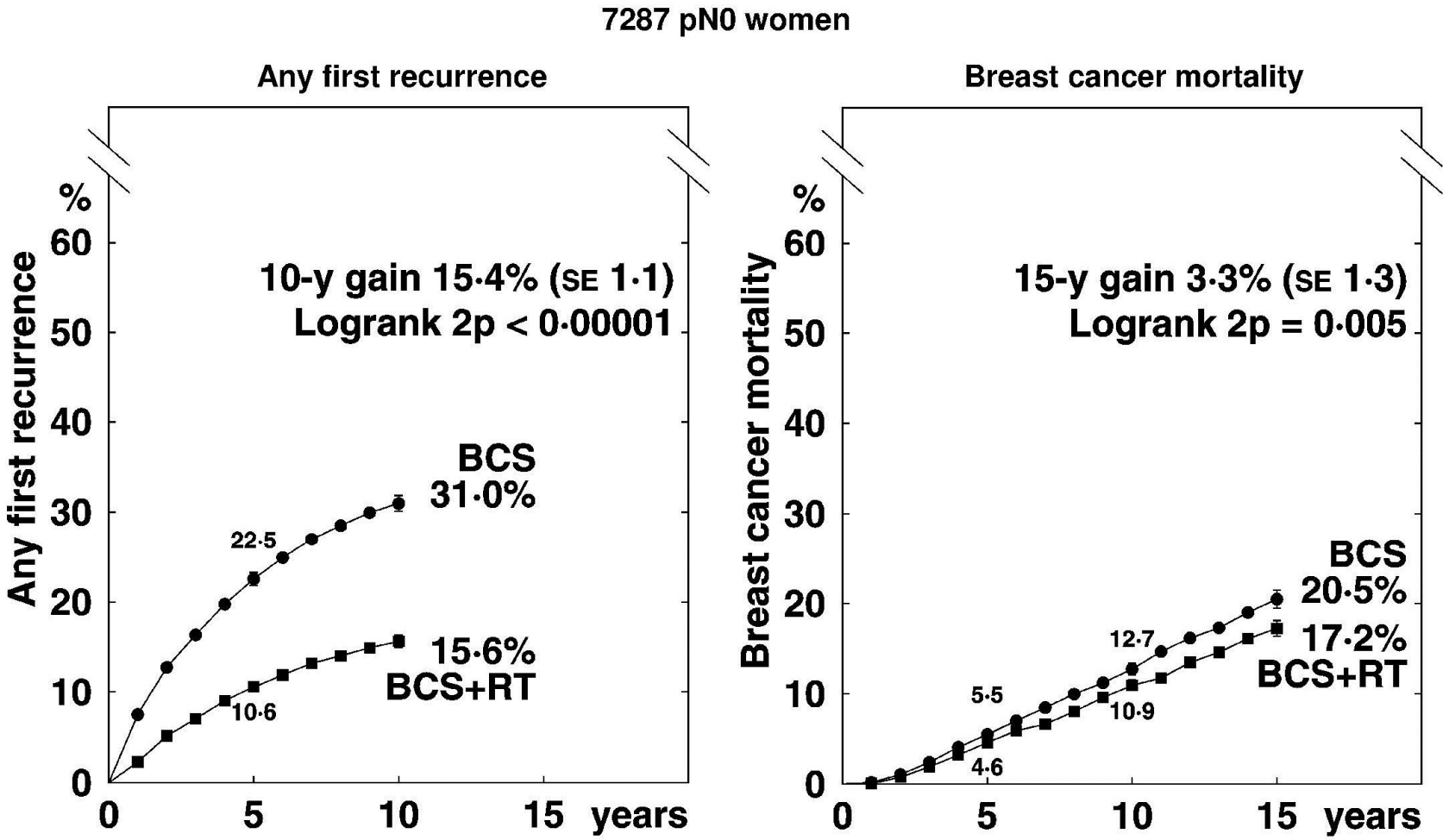
Effect of RT after BCS on recurrence and breast cancer mortality in pN0 women.



Few pN0 women received chemotherapy

Lancet, 2011

Effect of RT after BCS on recurrence and breast cancer mortality in pN0 women.



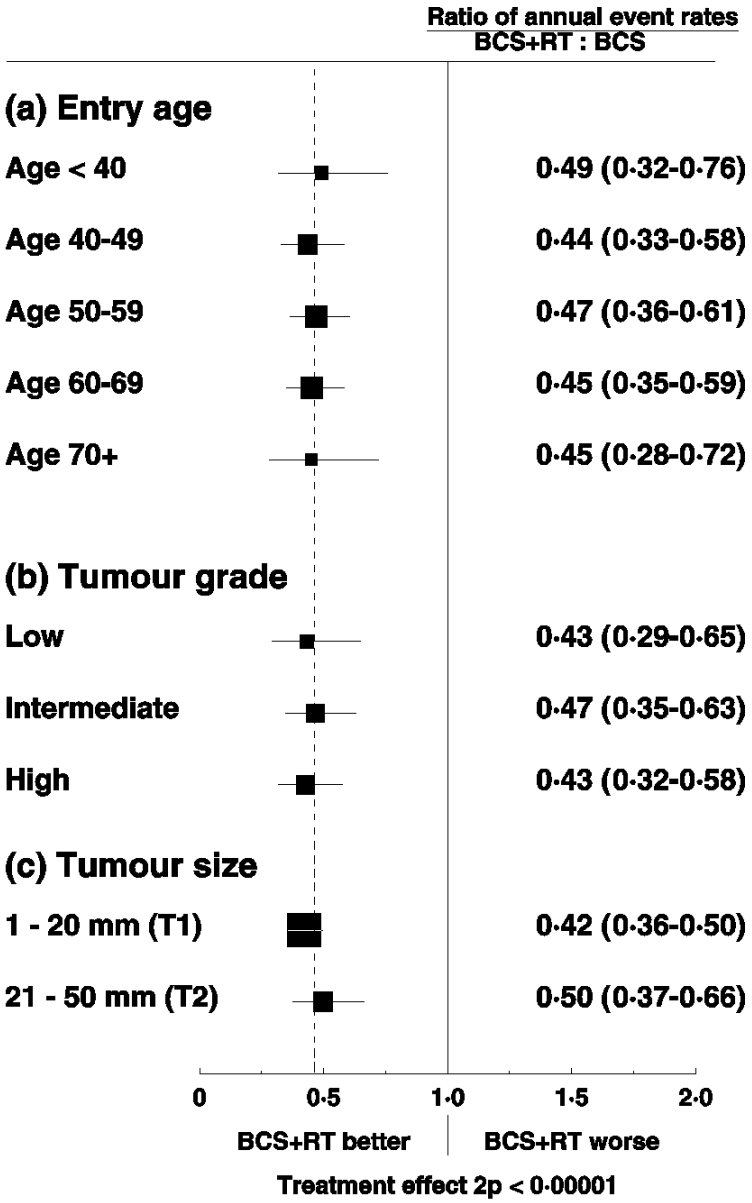
Few pN0 women received chemotherapy

Effect of RT on breast cancer mortality not big enough for analysis of sub-groups

Effect of RT greater for recurrence than mortality (NB uncertainty similar)

Lancet, 2011

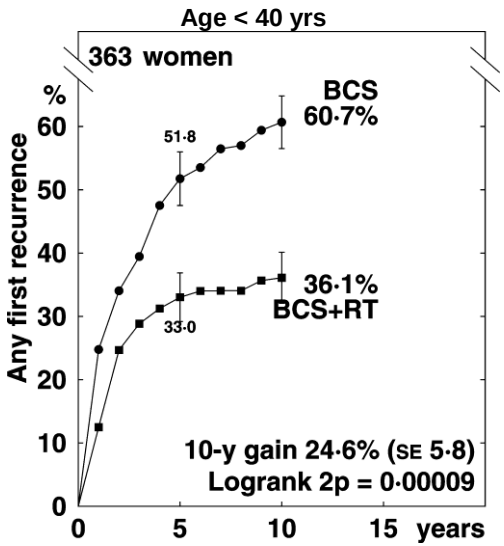
Effect of RT after BCS on recurrence and breast cancer mortality in pN0 women.

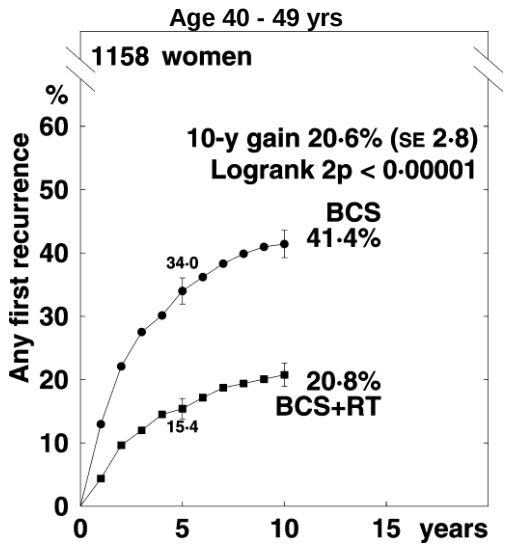


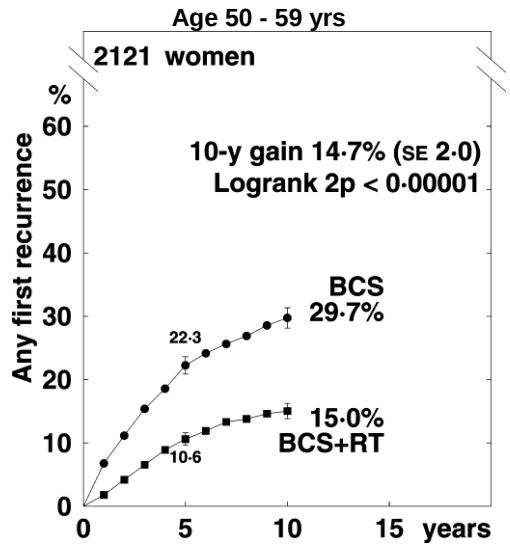
Proportional benefit of RT after BCS similar across categories of age, tumour grade and tumour size.

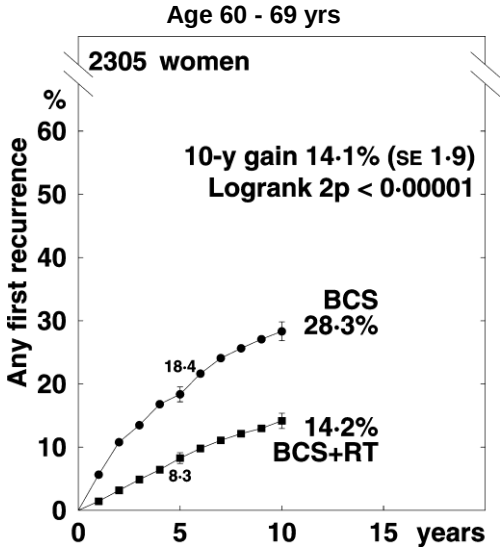
Lancet, 2011

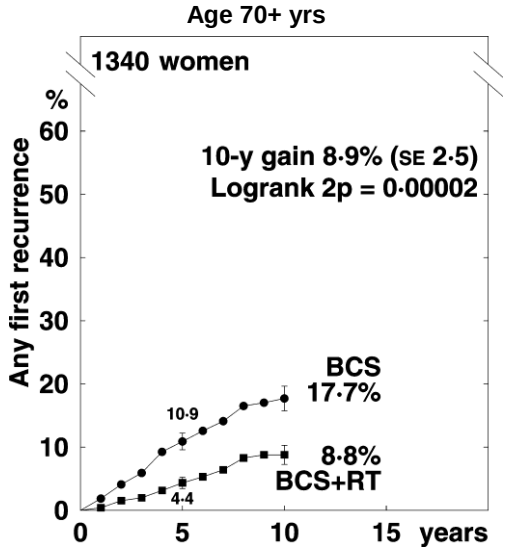
Effect of RT after BCS on recurrence in pN0 women by age at diagnosis











Absolute benefit of RT after BCS varies substantially across categories of age.

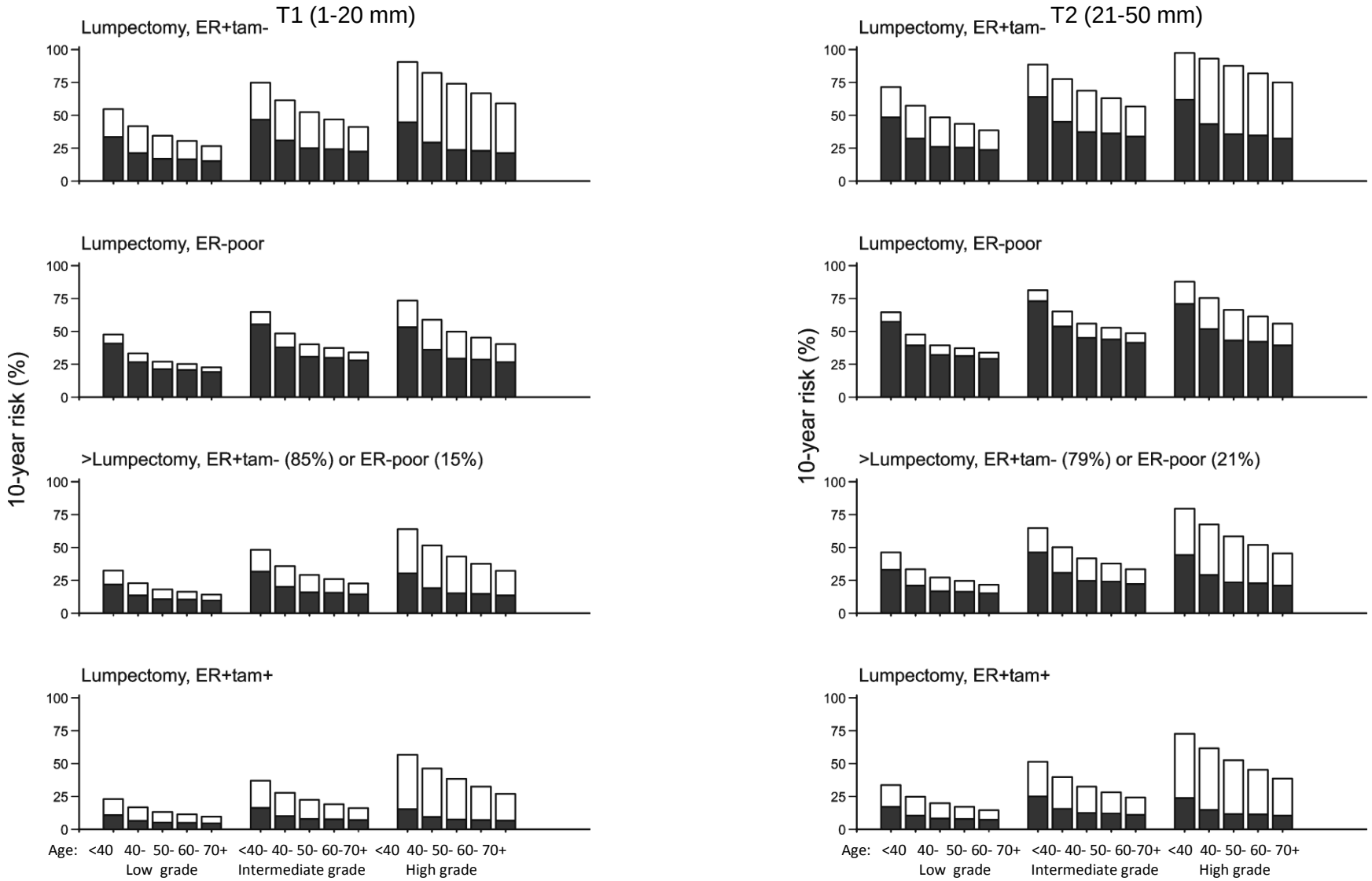
Same goes for other factors, eg grade, tumour size. Need to consider all factors at once.

Lancet, 2011

Absolute 10-year risk (%) of recurrence after BCS in pN0:

dependence on factors suggested by modelling

Black bars: BCS+RT, White bars: absolute gain from RT, Black+white bars: BCS only

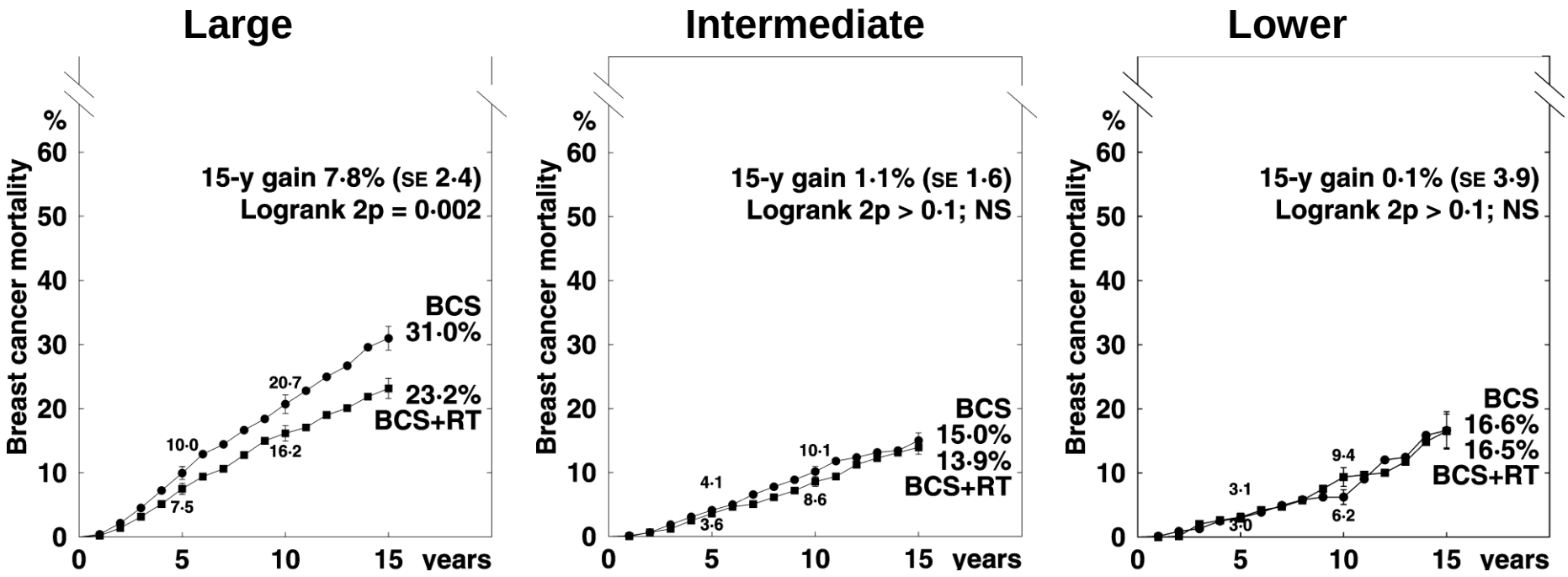


Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Lancet 2011; 378: 1707-60

- We can classify pN0 women into large (≥20%), intermediate (10-19%), and lower (<10%) predicted absolute 10-year recurrence benefit

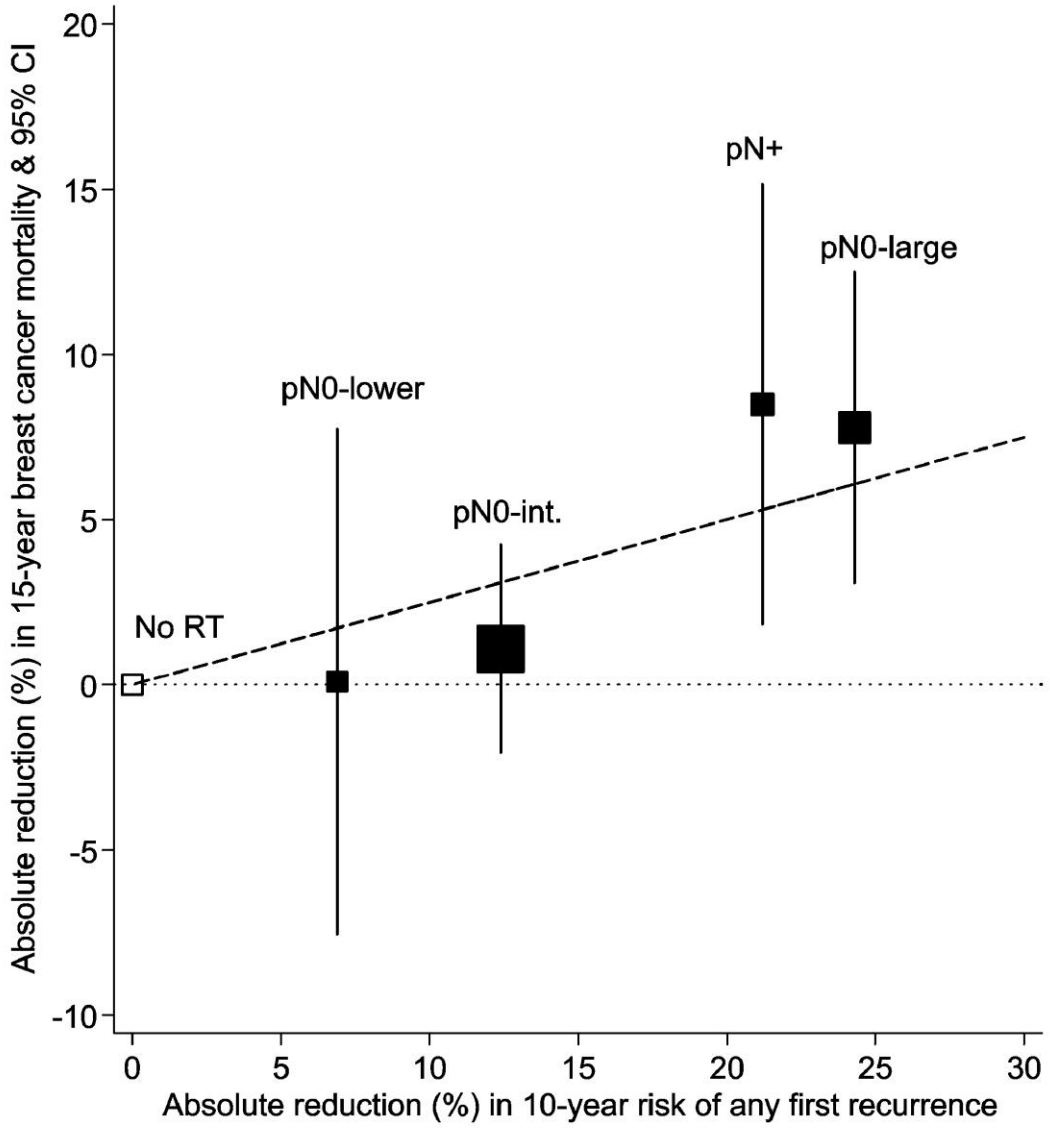
- Then look to see what happens in these three groups in terms of breast cancer mortality

Observed absolute *breast cancer mortality* benefit in pN0 women by size of absolute *recurrence* benefit



Lancet, 2011

Absolute reduction in 15-year breast cancer mortality *versus* 10-year reduction in recurrence



Dashed line is one death avoided for every four recurrences avoided ('one-in-four' rule)

Lancet, 2011

Conclusions for RT after BCS

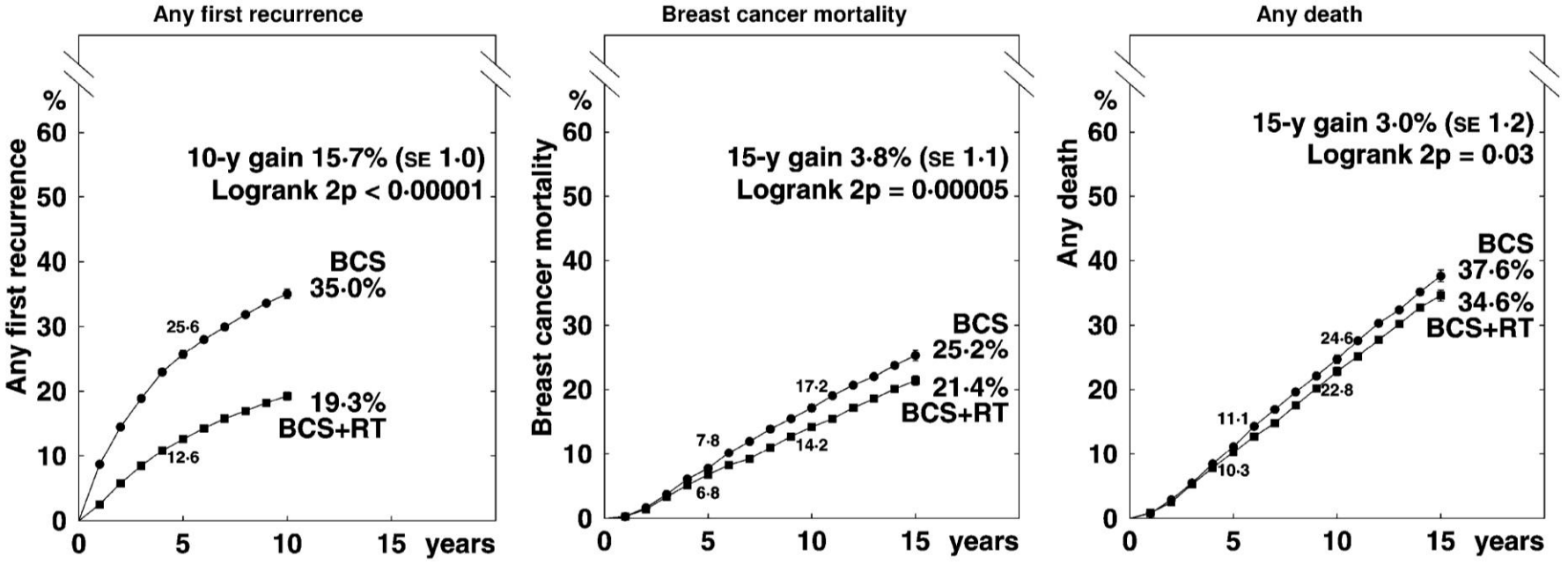
- **Radiotherapy can reduce risks of recurrence and of death from breast cancer**
- **In these trials:**
  - **Big absolute benefit in recurrence and breast cancer mortality for pN+ and high-risk pN0**
  - **Moderate absolute benefit in recurrence and possible small benefit in mortality benefit for other pN0 women**
  - **No significant departure from "One-in-four" rule**

Lancet 2011

Plan of talk

- Introduction
- EBCTCG Meta-analysis of radiotherapy after breast-conserving surgery
- Analyses of any, local and distant recurrence

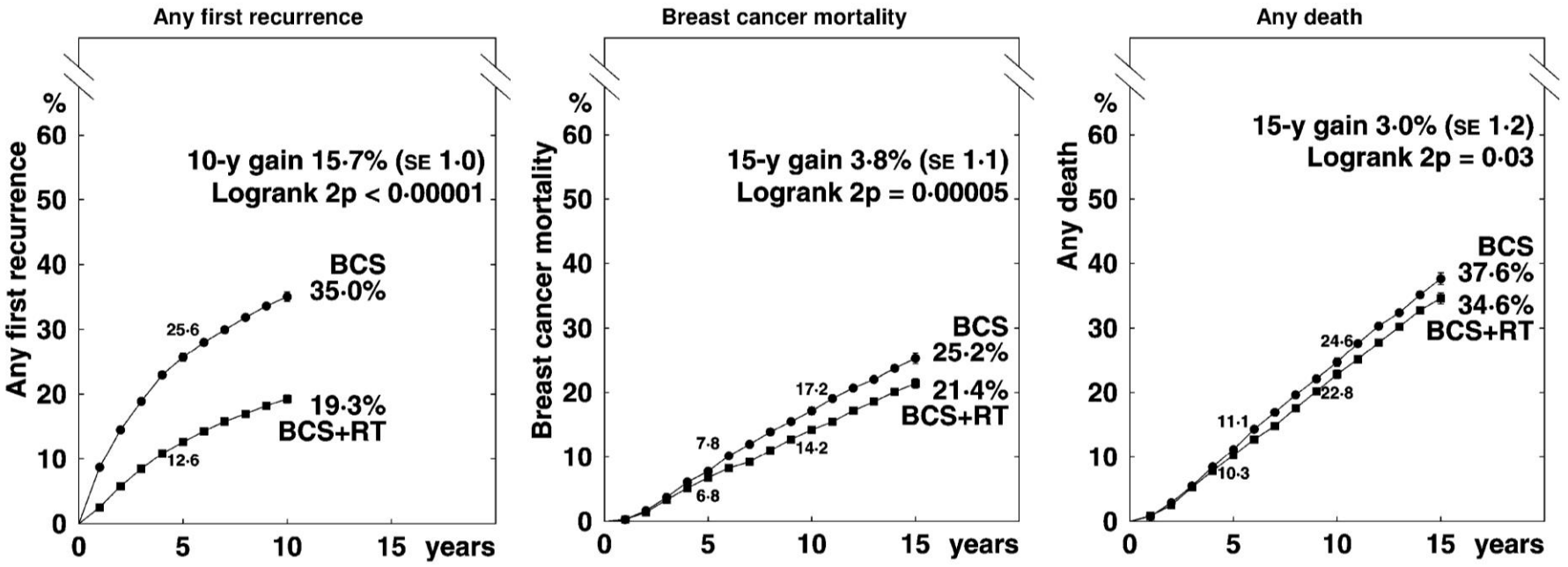
Effect of RT after BCS on recurrence, breast cancer mortality and all-cause mortality



Data from 10,801 women in 17 trials starting before 2000

Lancet, 2011

Effect of RT after BCS on recurrence, breast cancer mortality and all-cause mortality



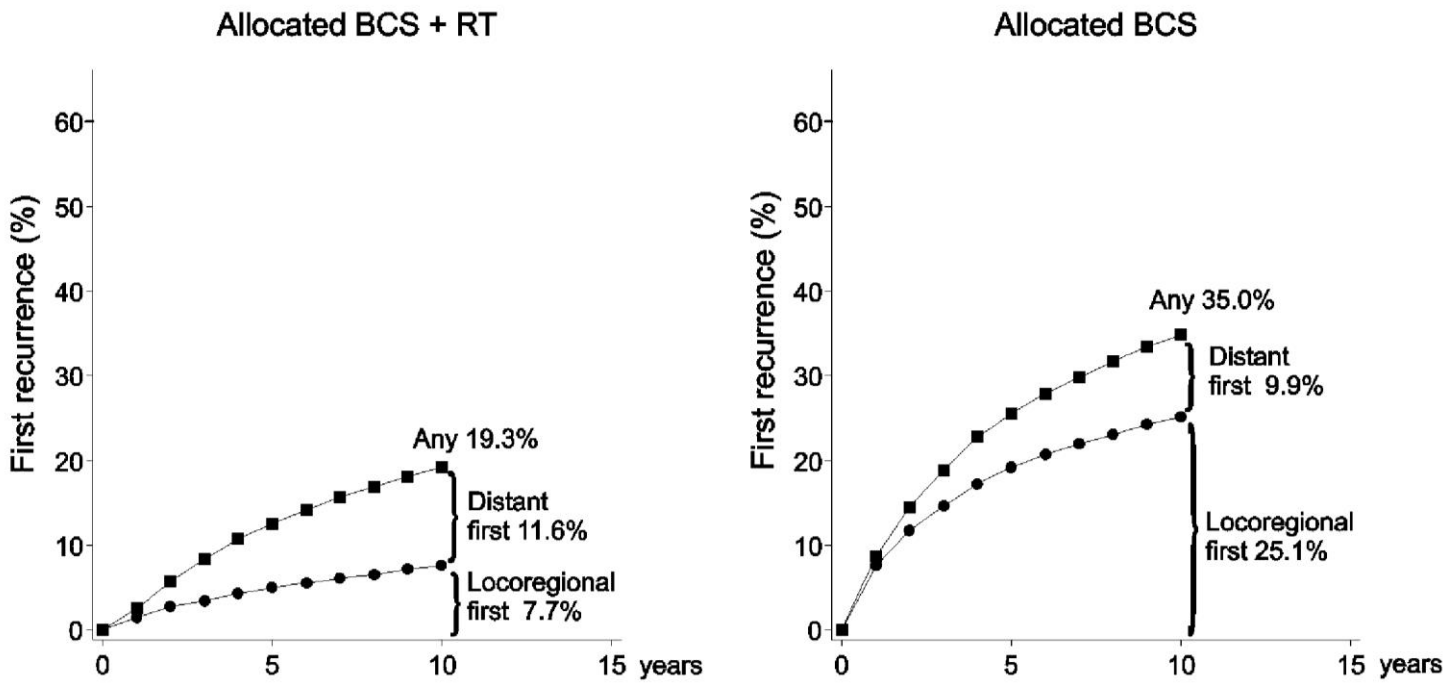
Data from 10,801 women in 17 trials starting before 2000

To reduce breast cancer mortality, RT must be reducing distant recurrence

Lancet, 2011

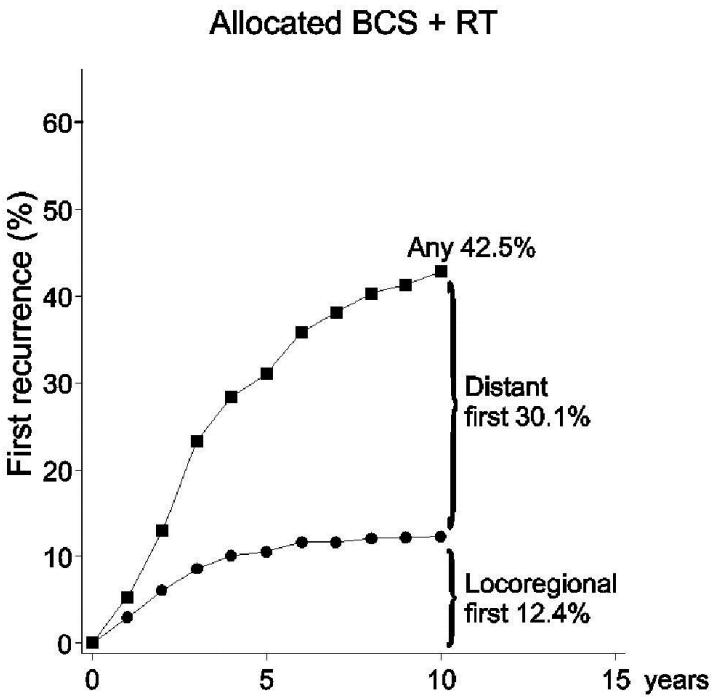
Type of first recurrence after BCS ± RT

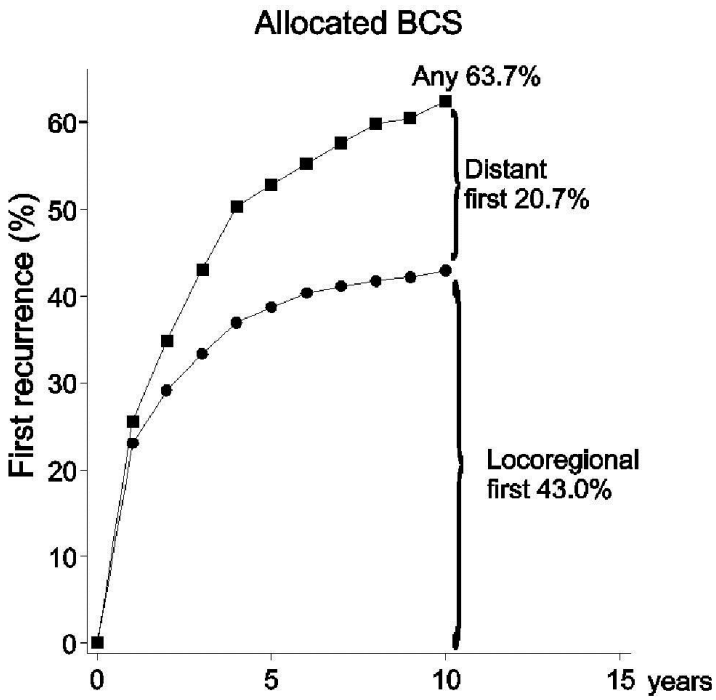
10,801 women in 17 trials



Type of first recurrence after BCS ± RT

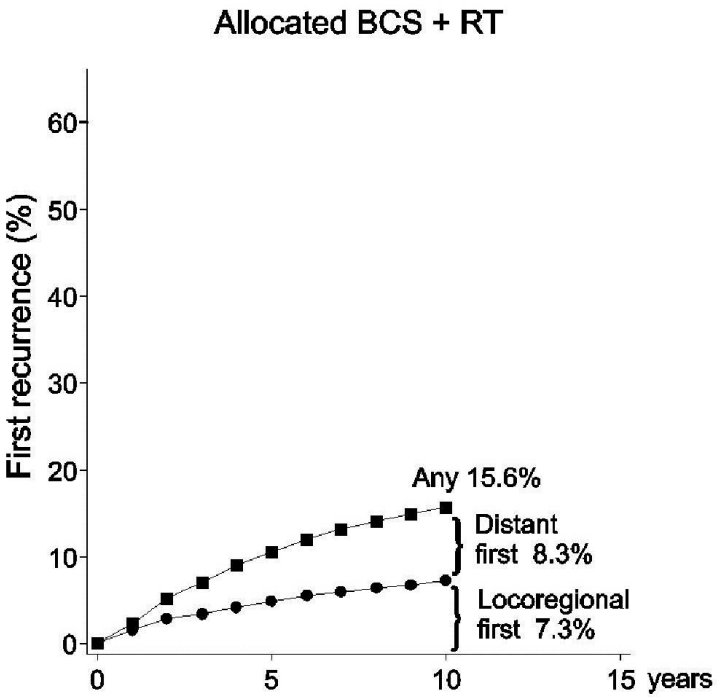
1050 pN+ women

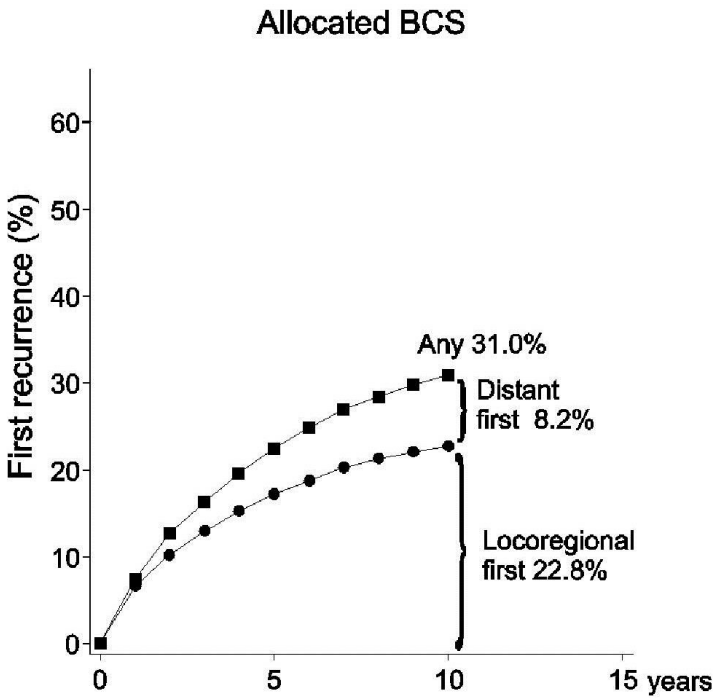




Type of first recurrence after BCS ± RT

7300 pN0 women





Validity of Estimates of Effect of Treatment on Recurrence Rates

- **Valid estimates of the causal effect of radiotherapy on recurrence rates can only be made in terms of any recurrence.**

- **Valid estimates of the effect of radiotherapy on local recurrence rates *cannot be made*** – *although many papers claiming to do so have been published*

- **Valid estimates of the effect of radiotherapy on distant recurrence rates can be made** – *but only if information on distant recurrences occurring after any earlier local recurrence are available, and these will be affected by the treatment given for the local recurrence as well as the initial radiotherapy*

The end

Target Volume delineation:

chest wall, breast

Youlia M. Kirova, M.D.,

Department of Radiation Oncology,

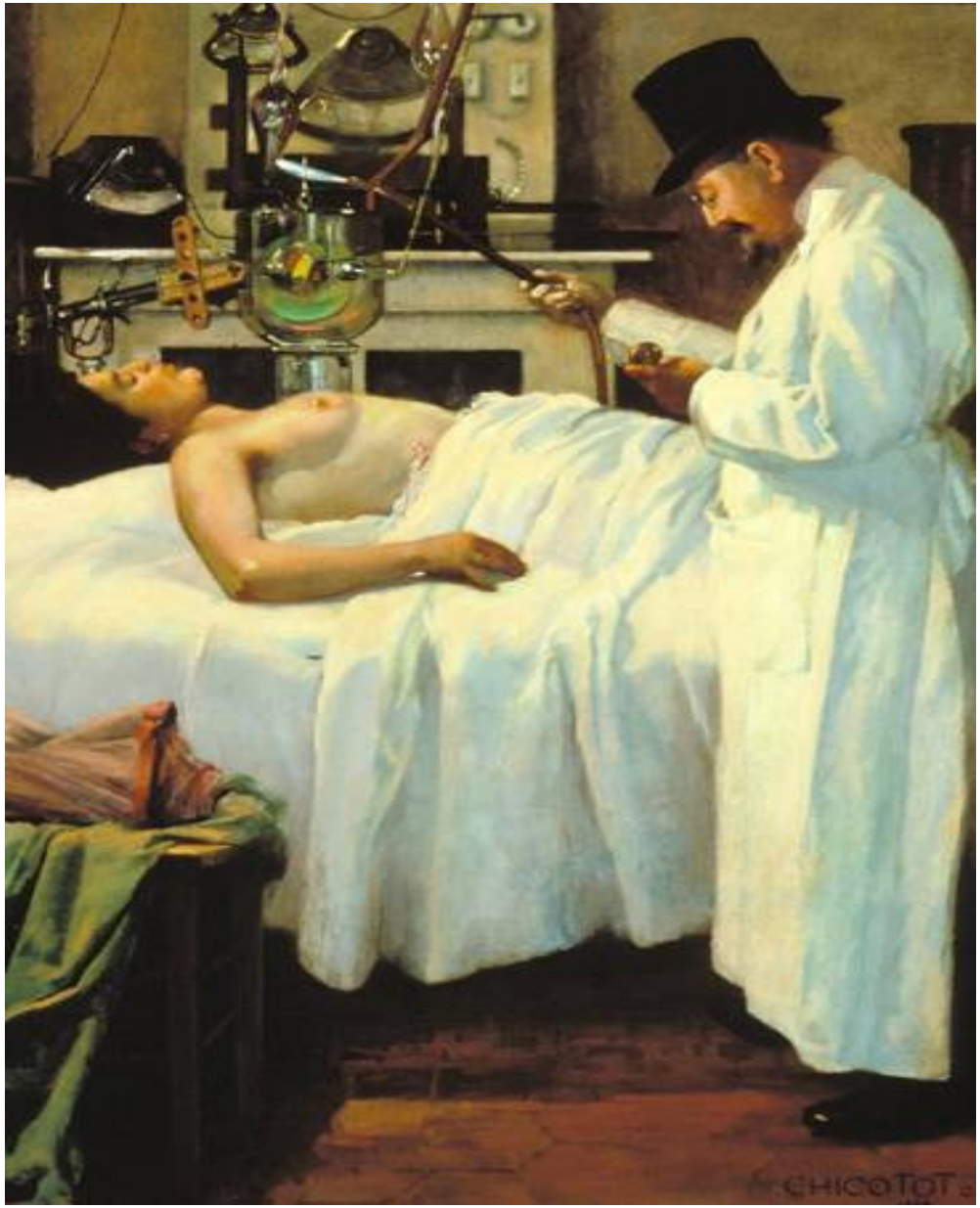
Institit Curie, Paris, France

ESTRO School

institutCurie

youlia.kirova@curie.fr

Evolution of volumes definition in breast cancer treatment



institutCurie
Ensemble, prenons le cancer de vitesse.

ESTRO School

CHEST WALL AFTER MASTECTOMY

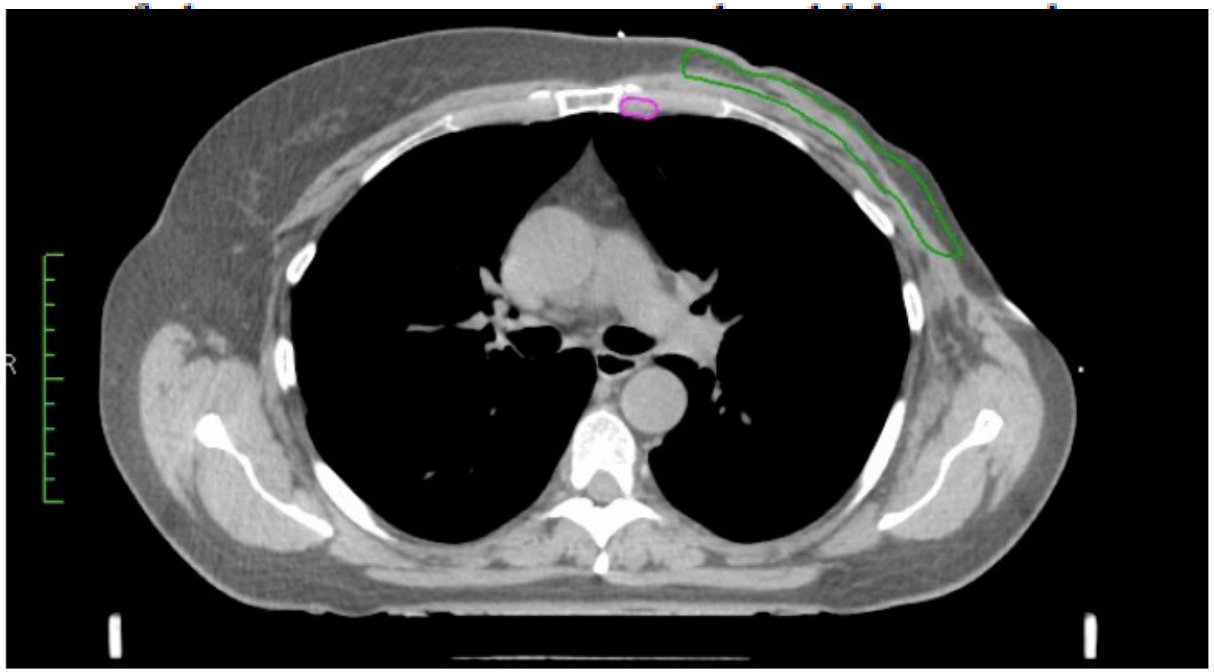
institutCurie
Ensemble, prenons le cancer de vitesse.

ESTRO School

Delineation of the thoracic wall

CTVp_thoracic wall

In mastectomy patients, radio-opaque wires should be positioned around the –imaginary – original site of the breast and also corresponding to the mastectomy scar. While the position of the contra-lateral breast can be helpful for this if both arms are symmetrically elevated, in general the surface of the CTVp_thoracic wall is reduced by the surgical procedure following the pulling on adjacent skin and subcutaneous tissue to close the defect after removal of the breast. Therefore, careful palpation of the thoracic wall while positioning the radio-opaque markers

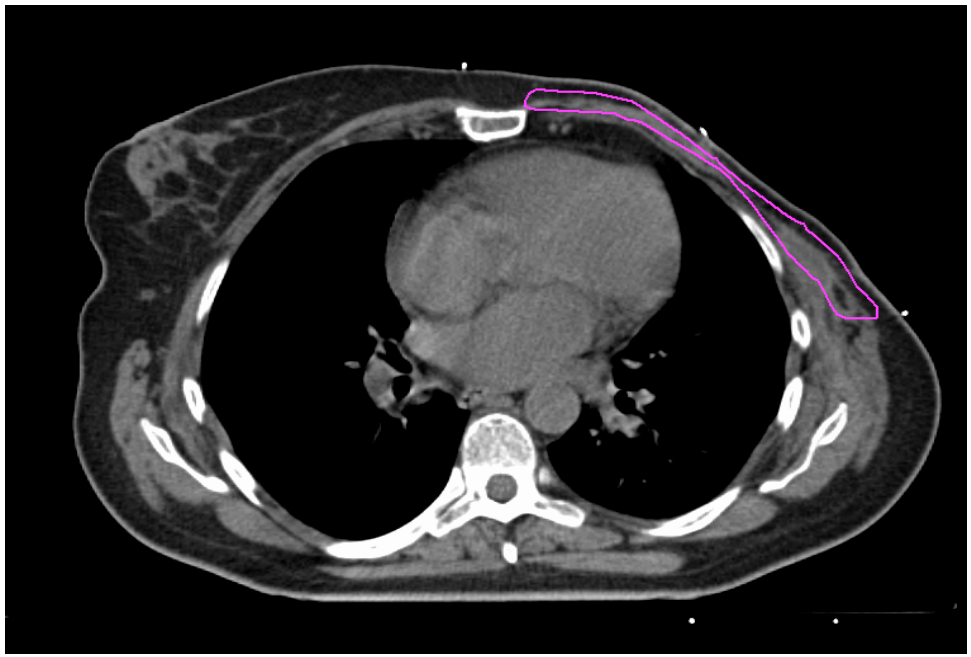


ESTRO Consensus, Radiother Oncol, 2015

ESTRO School

Delineation of the thoracic wall

- **All borders of the CTV thoracic wall are usually considered to be identical to the CTV breast.**
- **In case of an extremely thin thoracic wall, omission of the first 5 mm beneath the skin may result in no CTV at all.**
- **In that case, do extend the CTV into the skin, and consequently use bolus.**

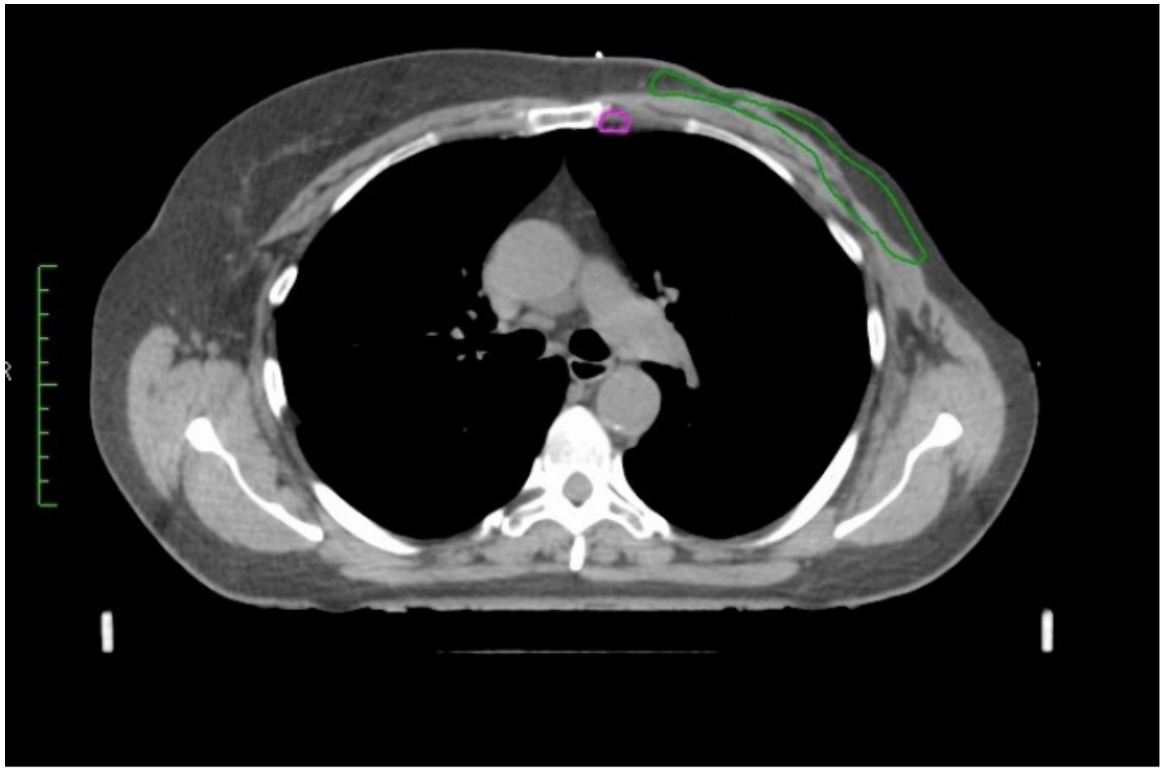


ESTRO Consensus,
Radiother Oncol, 2015

ESTRO School

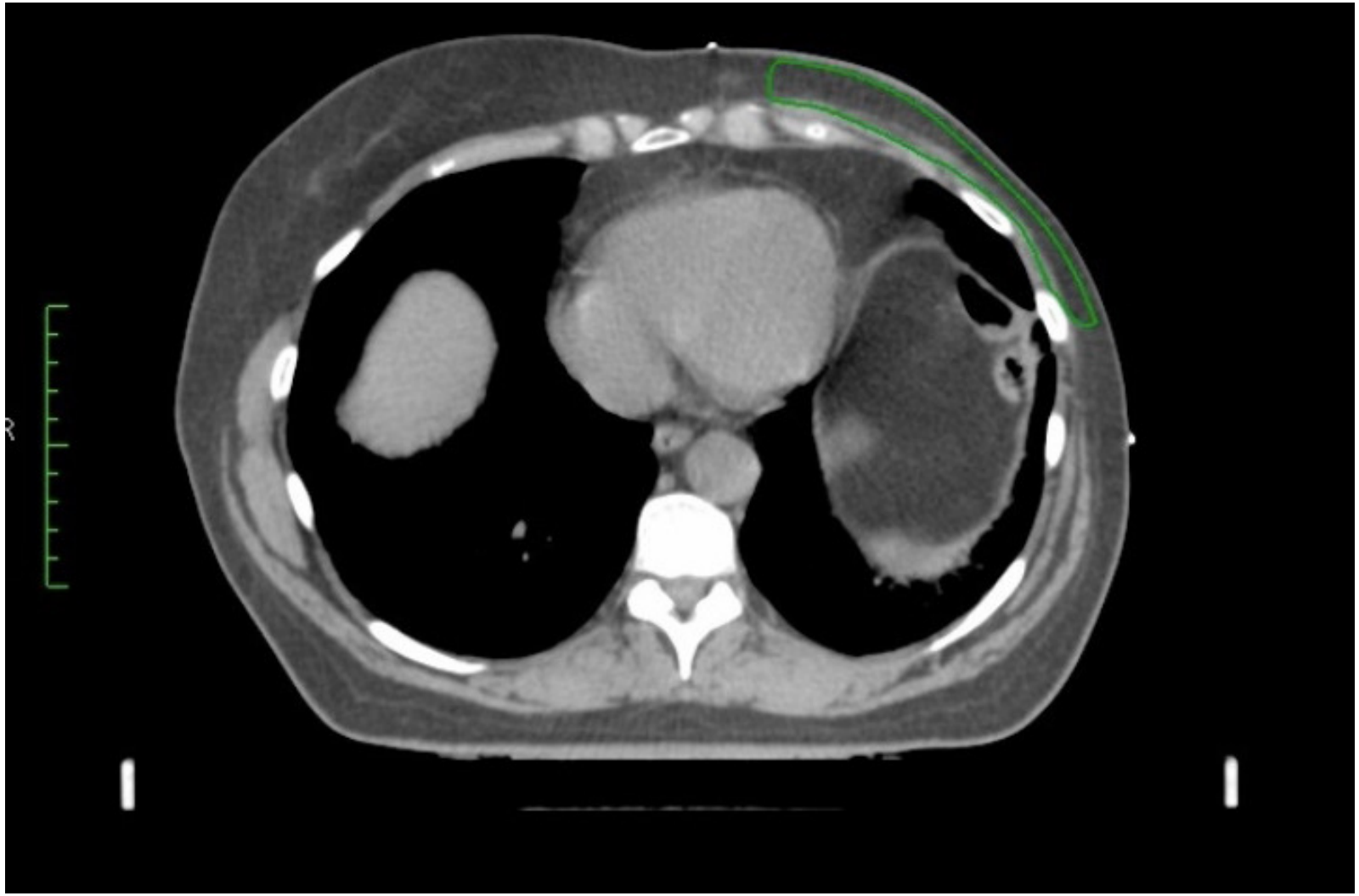
Delineation of the thoracic wall

- **All borders of the CTV thoracic wall are usually considered to be identical to the CTV breast.**
- **In case of an extremely thin thoracic wall, omission of the first 5 mm beneath the skin may result in no CTV at all.**



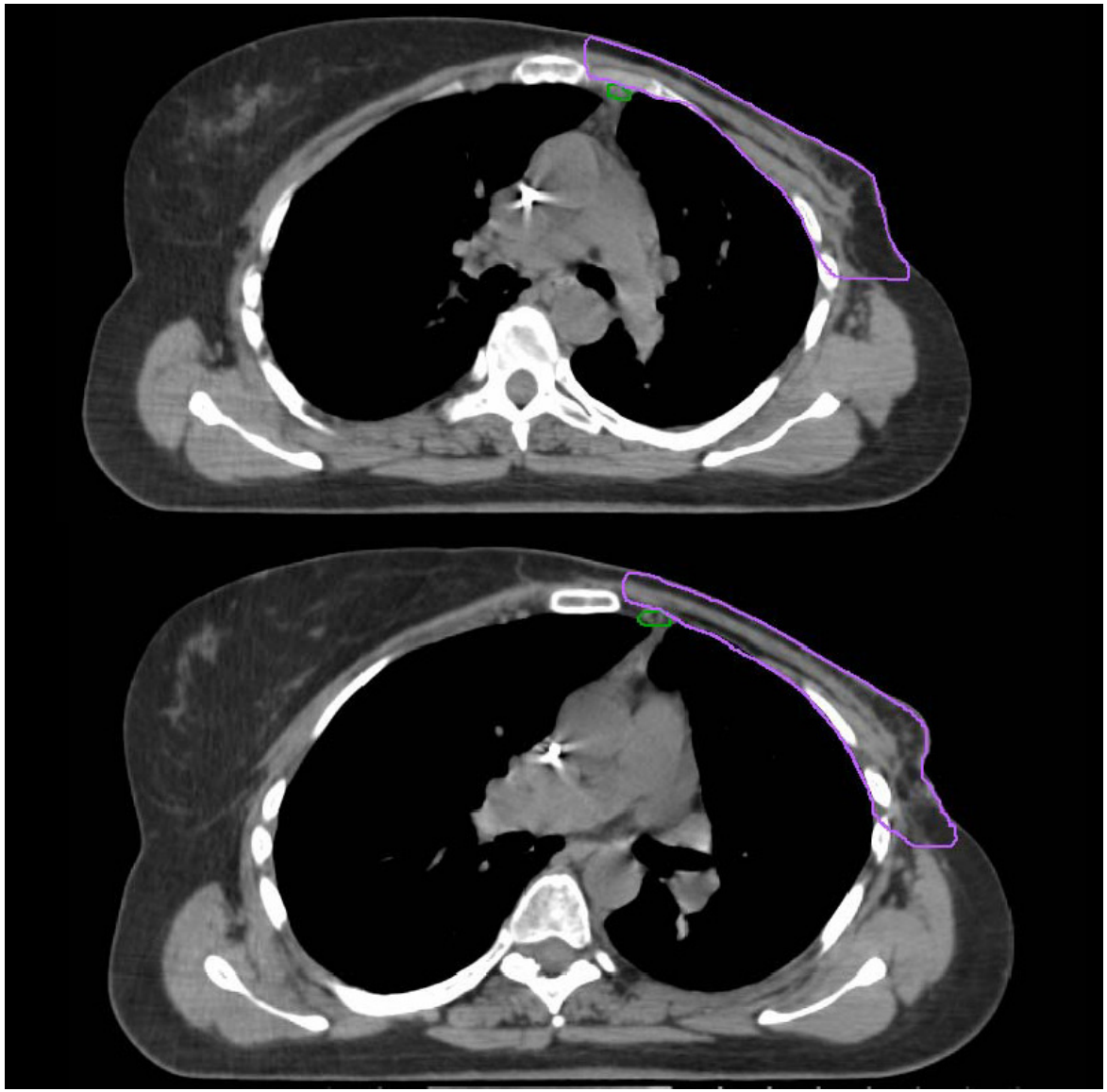
ESTRO Consensus, Radiother Oncol, 2015

ESTRO School



ESTRO School

Delineation of the thoracic wall: RTOG



Discussion:

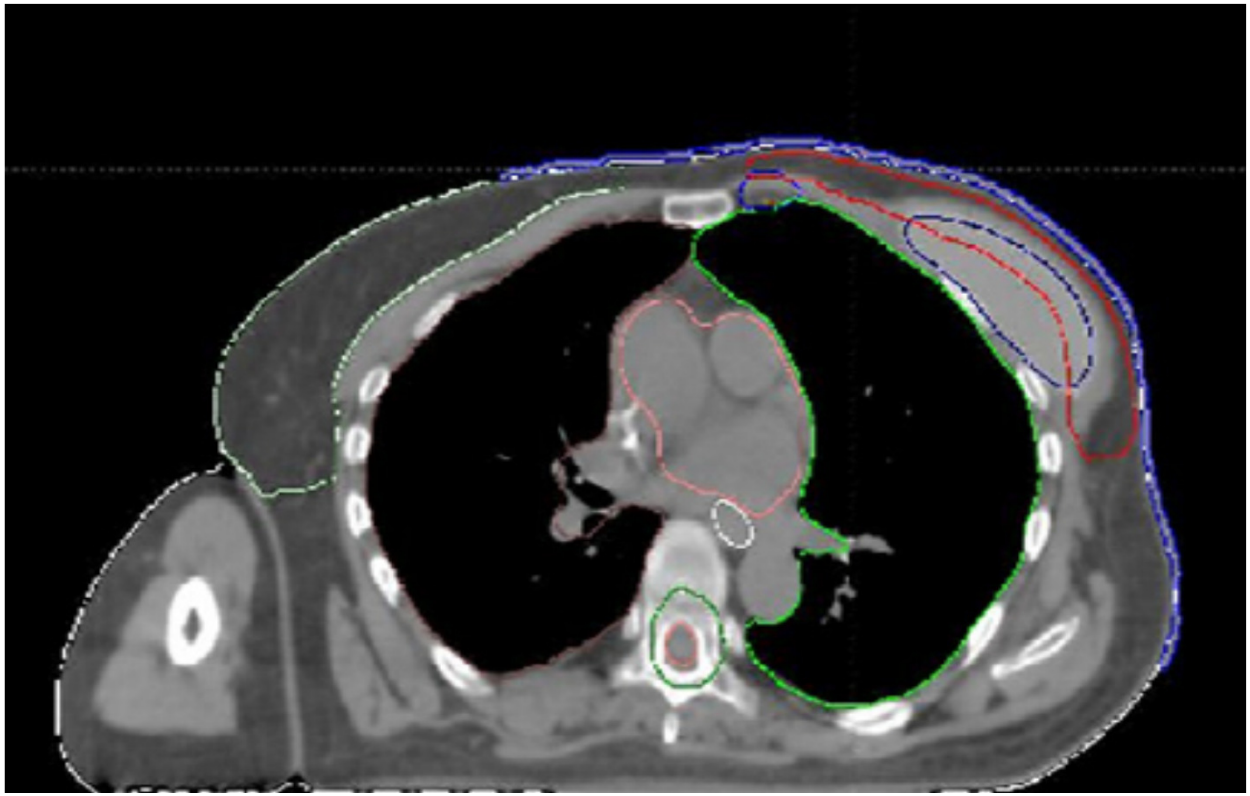
Always include skin and/or thoracic wall in CTV ?

Ref: BreastCancer Atlas RTOG

ESTRO School

Immediate breast reconstruction

The clinical target volume (CTV) was defined as the biologic entity that included the remaining breast tissue at risk of microscopic disease (CTV1),



The volume between skin and implant, the pectoral muscle must be included

Massabeau et al., Med Dosim 2012

institutCurie
Ensemble, prenons le cancer de vitesse.
ESTRO School

Breast

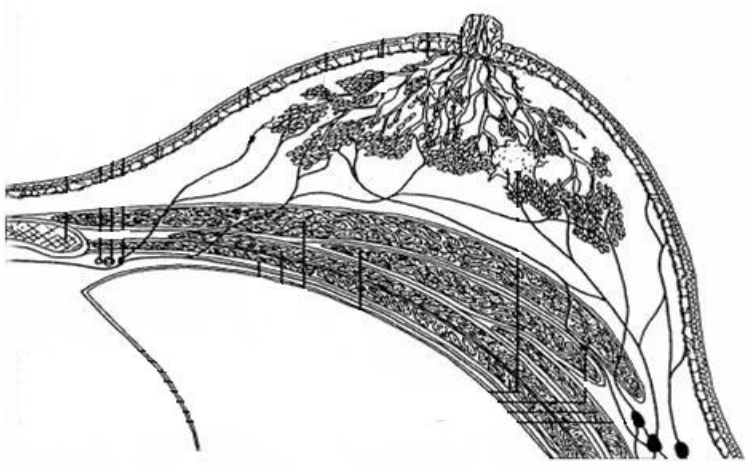
institutCurie
Ensemble, prenons le cancer de vitesse.

ESTRO School

Delineation of the CTV breast using CT:
CTV breast = “whole glandular breast tissue”

This target volume includes the total glandular breast tissue, whose borders are often not clearly visible. To facilitate delineation, radio-opaque markers may be placed around the breast for CT-scanning, keeping in mind that these markers do not necessarily represent the true borders of the CTVp_breast.

ESTRO Consensus, Radiother Oncol, 2015

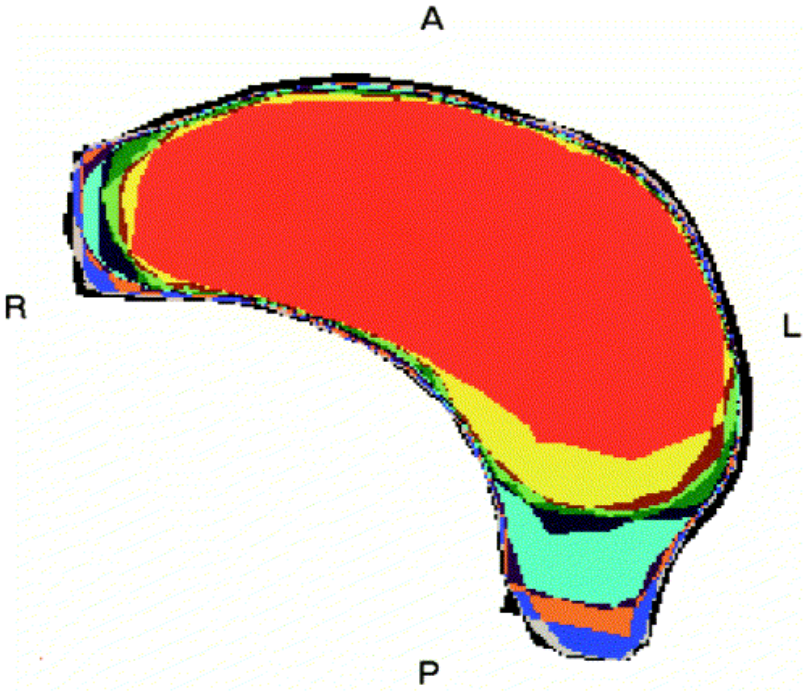


institutCurie
Ensemble, prenons le cancer de vitesse.

ESTRO School

But: Large interobserver variation, especially at cranial, posterior and medial borders- CT scan

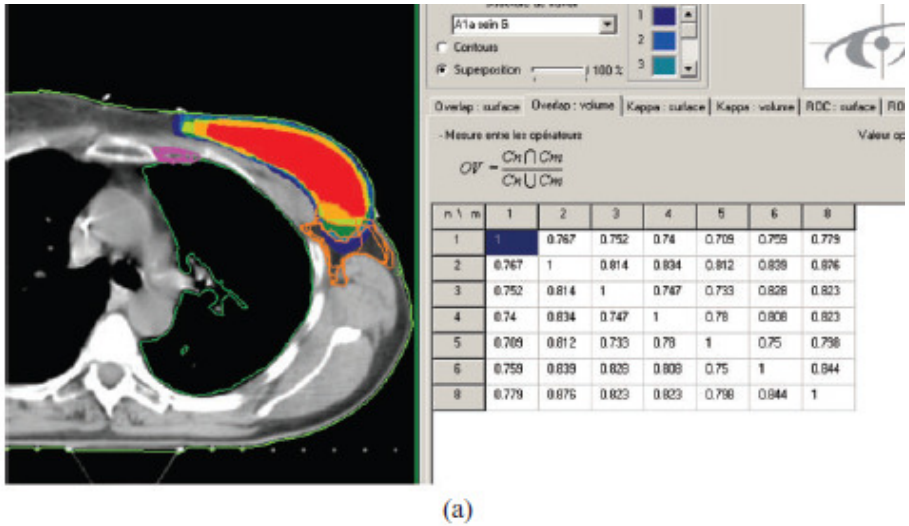
Struikmans et al, R&O 2005



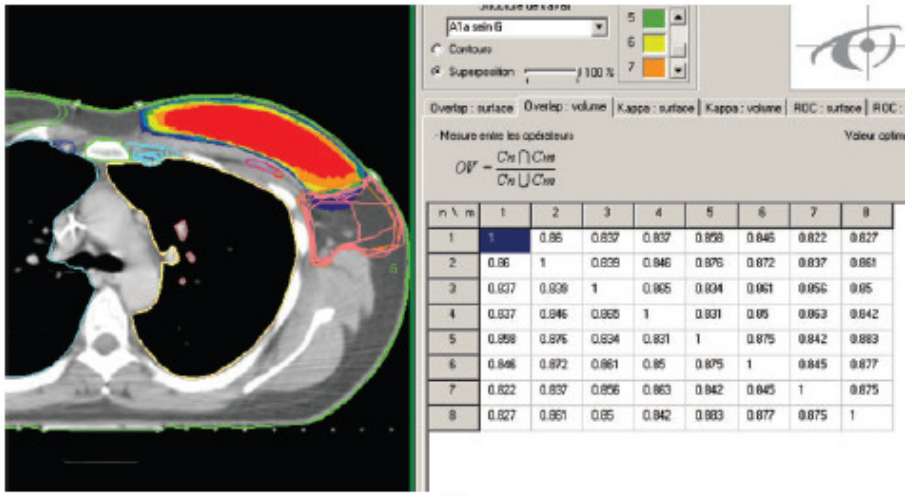
Hurkmans et al, IJROBP 2001

ESTRO School

But: Large interobserver variation in breast and lymph nodes



(a)



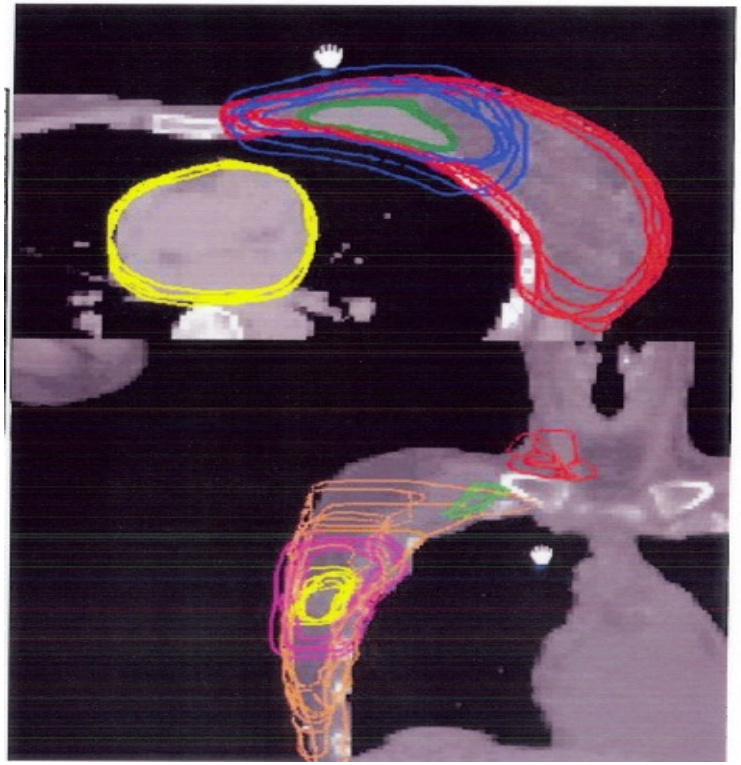
(b)

Castro Pena et al, BJR 2009

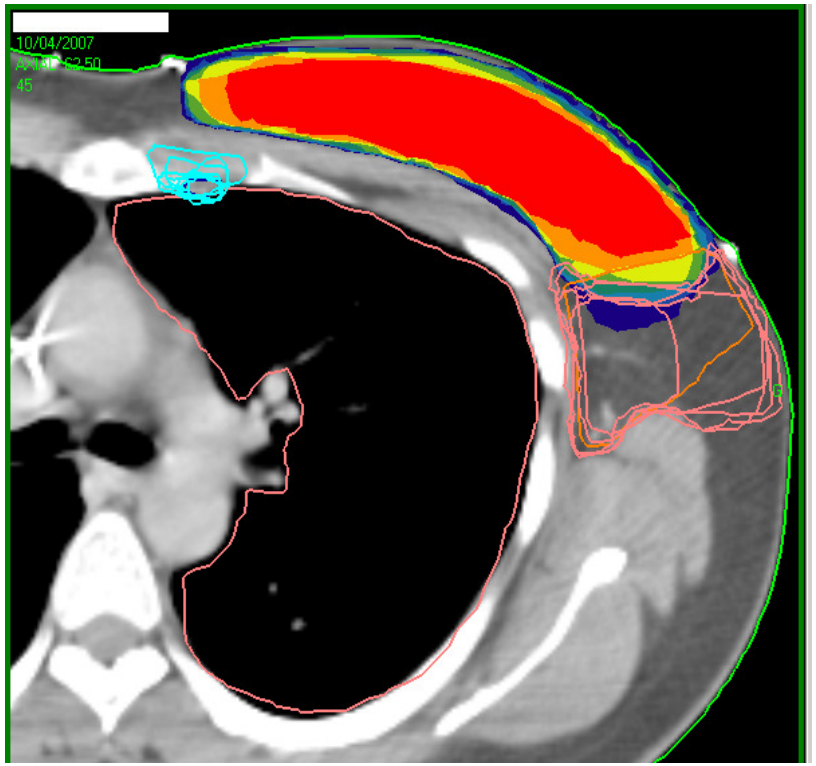
The British Journal of Radiology, July 2009

institutCurie
Ensemble, prenons le cancer de vitesse.

Li et al. IJROBP 2008:
different institutions in USA



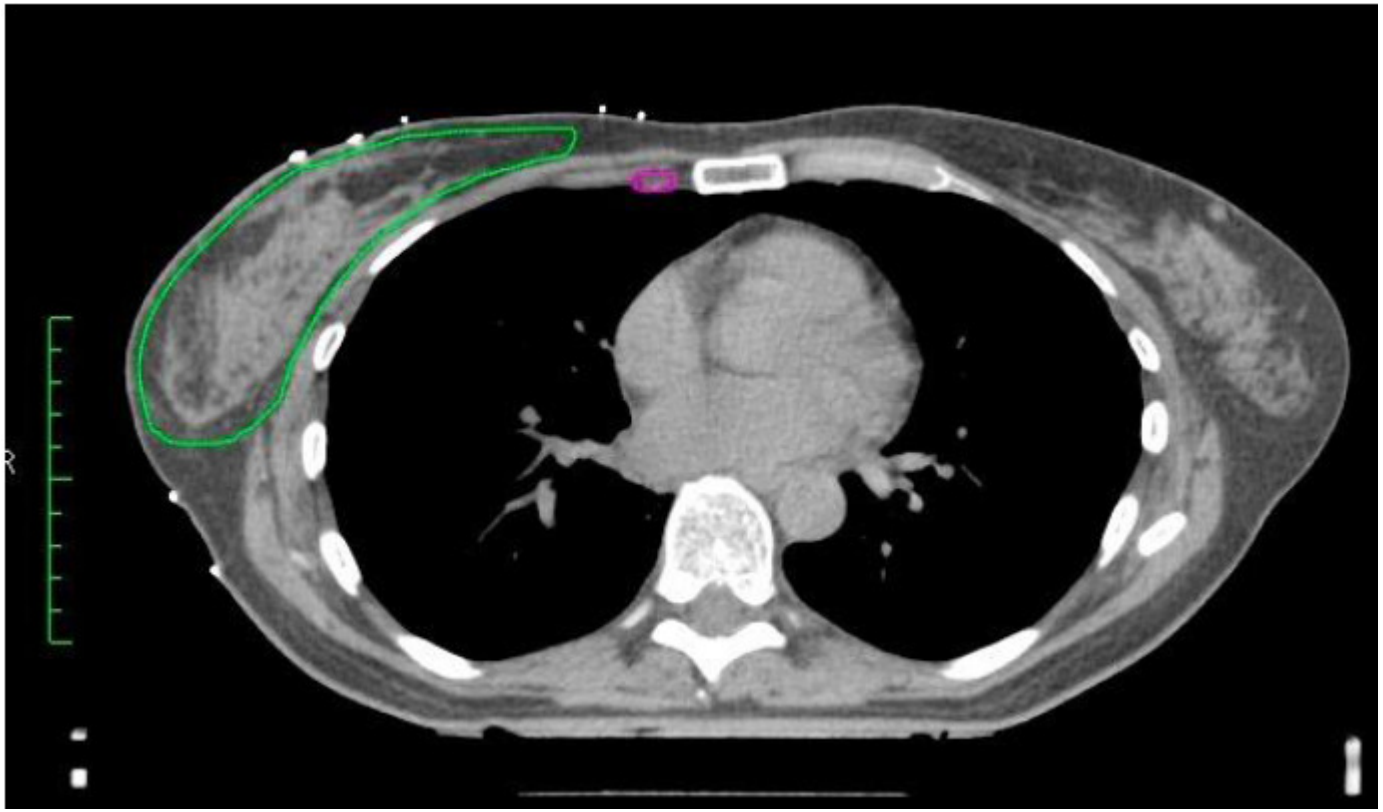
Castro Pena, et al,
Br J Radiol 2009



institutCurie
Ensemble, prenons le cancer de vitesse.

ESTRO School

Breast



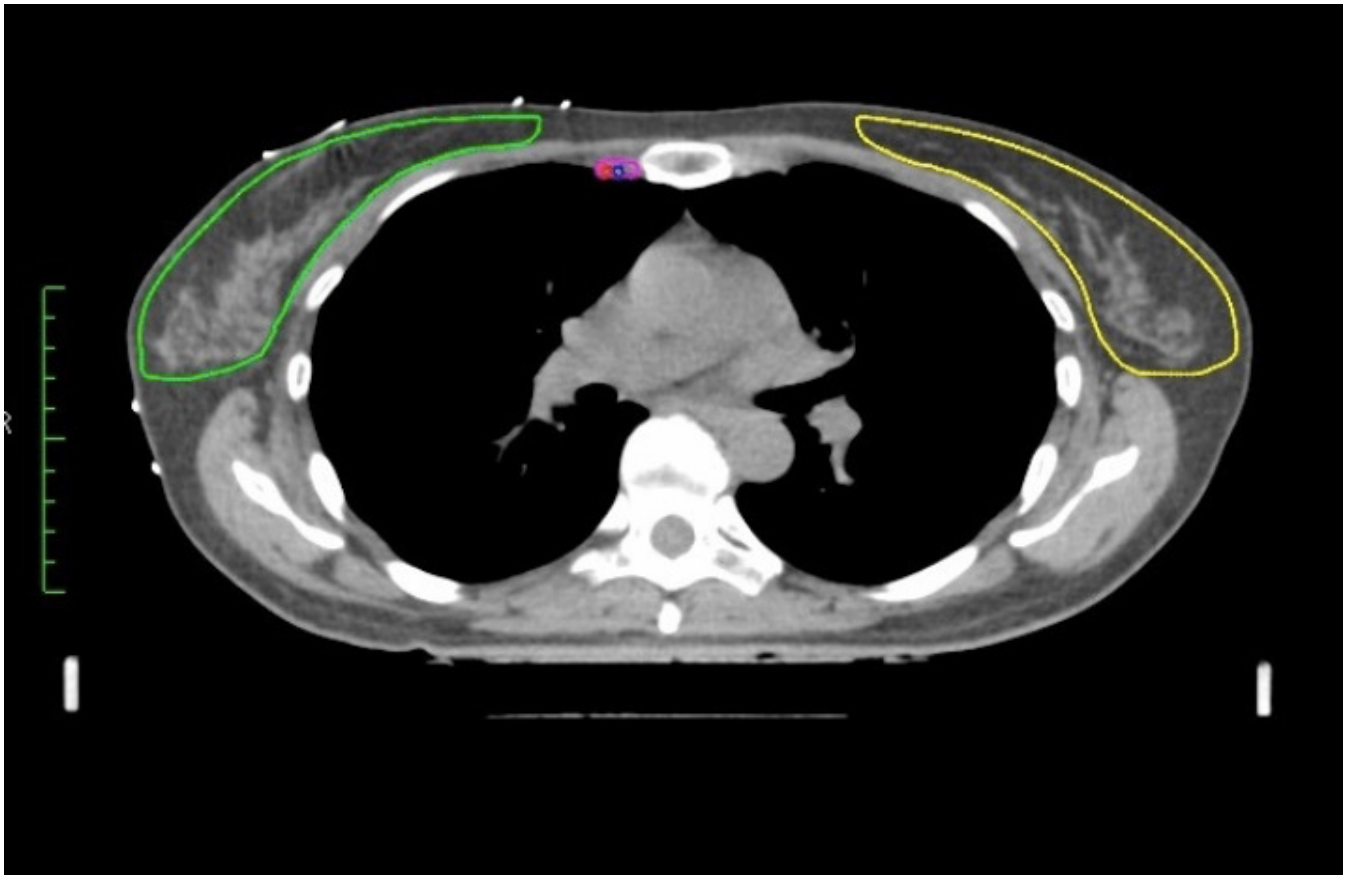
Between Pectoral Muscle and 5 mm below the skin (dosimetric considerations), within the space outlined by skin markers, that showed the limits of the palpable breast tissue.

institutCurie
Ensemble, prenons le cancer de vitesse.

ESTRO Consensus, Radiother Oncol, 2015

ESTRO School

Breast

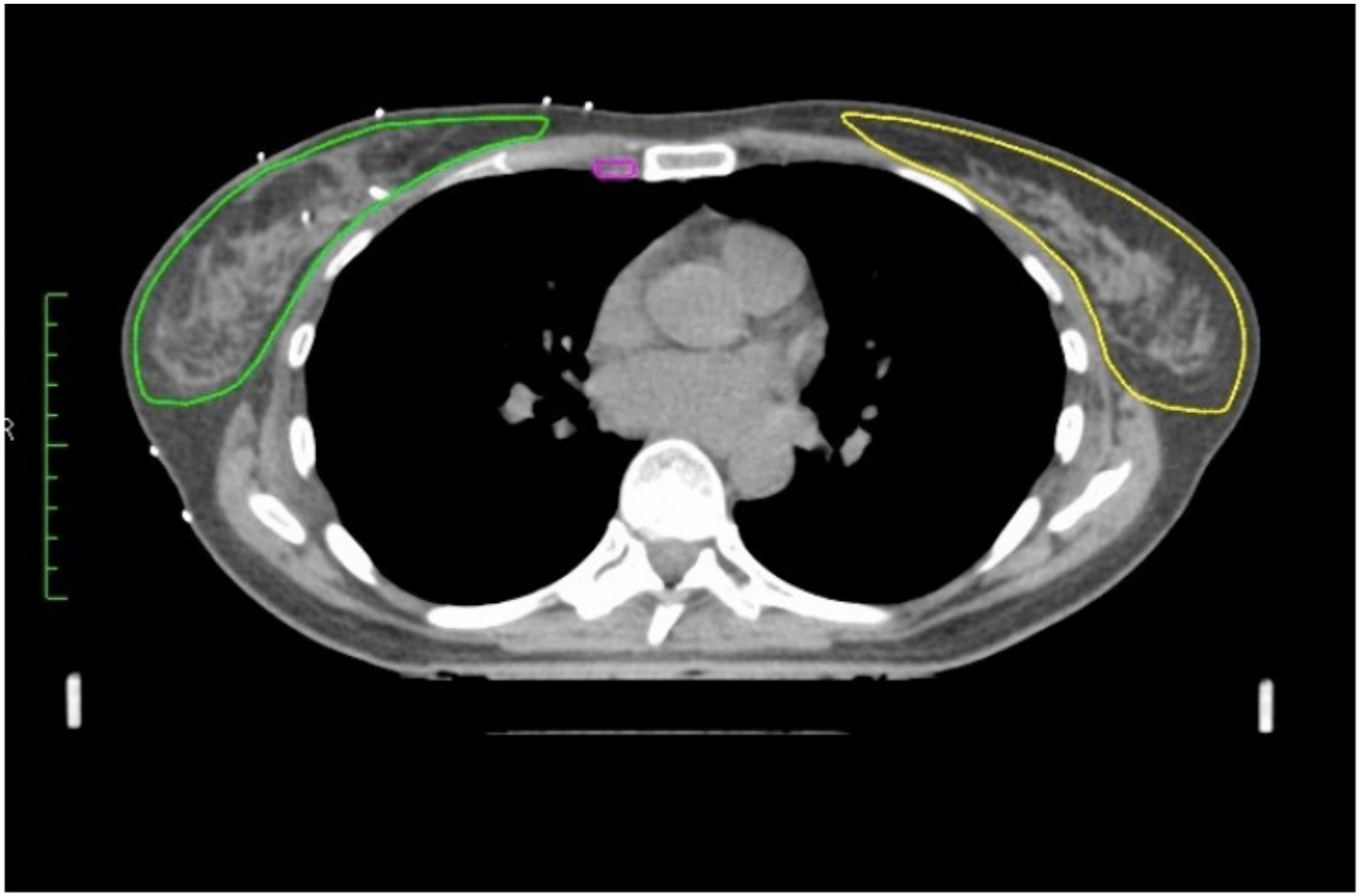


ESTRO Consensus, Radiother Oncol, 2015

institutCurie
Ensemble, prenons le cancer de vitesse.

ESTRO School

Breast



ESTRO Consensus, Radiother Oncol, 2015

institutCurie
Ensemble, prenons le cancer de vitesse.

ESTRO School

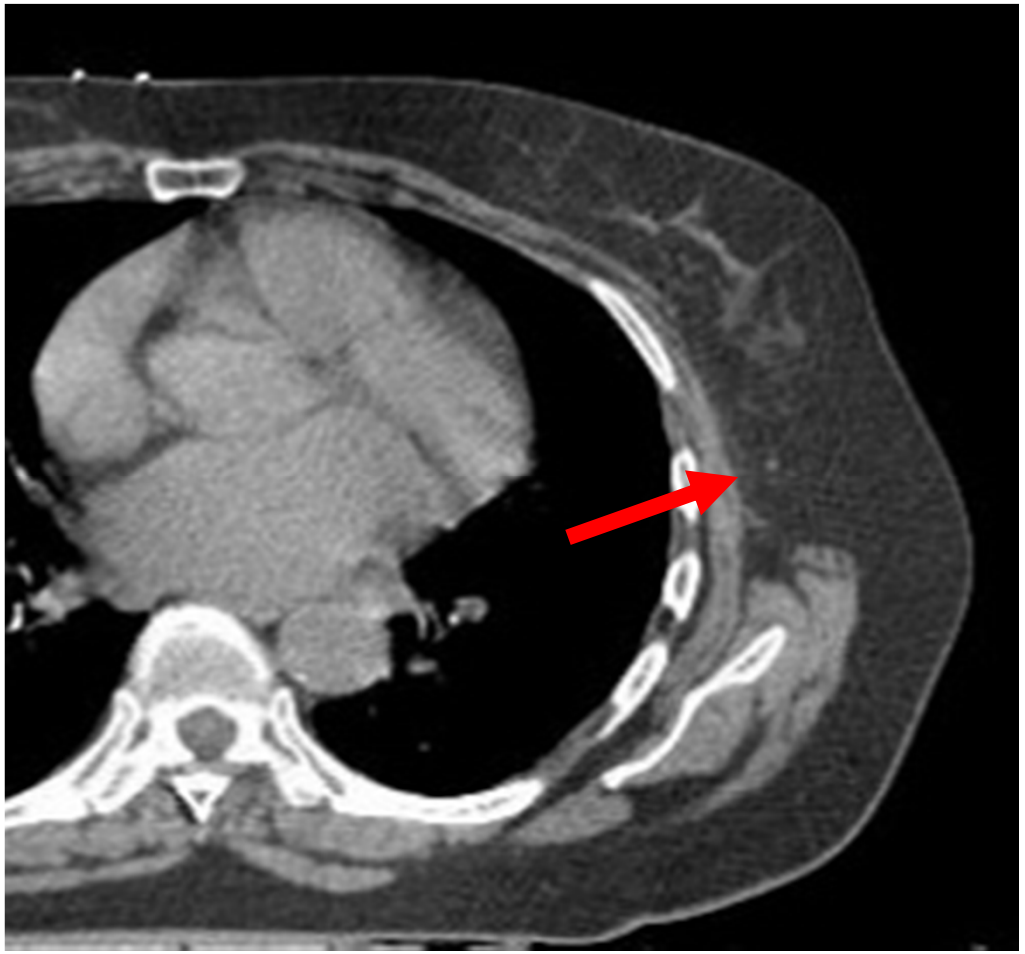
Helpful: Vessels

Medial:
<ipsilateral edge of the sternum

< vessels: rami mammarii (from thoracica int)

Lateral:
< lateral side of the visible breast contour

< vessel: thoracica lateralis



institutCurie
Ensemble, prenons le cancer de vitesse.

ESTRO School

Alternative techniques, volumes definition

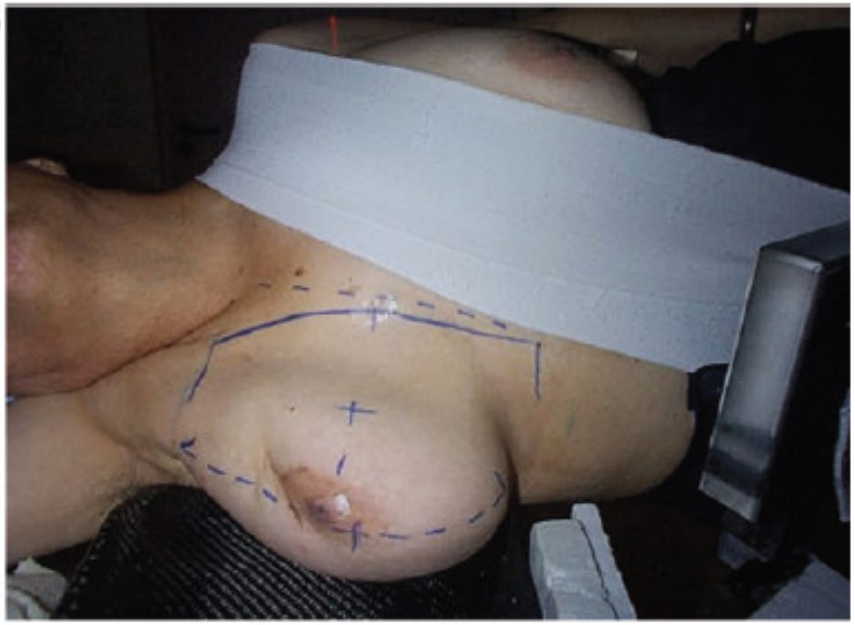
institutCurie
Ensemble, prenons le cancer de vitesse.

…to avoid lung and heart irradiation

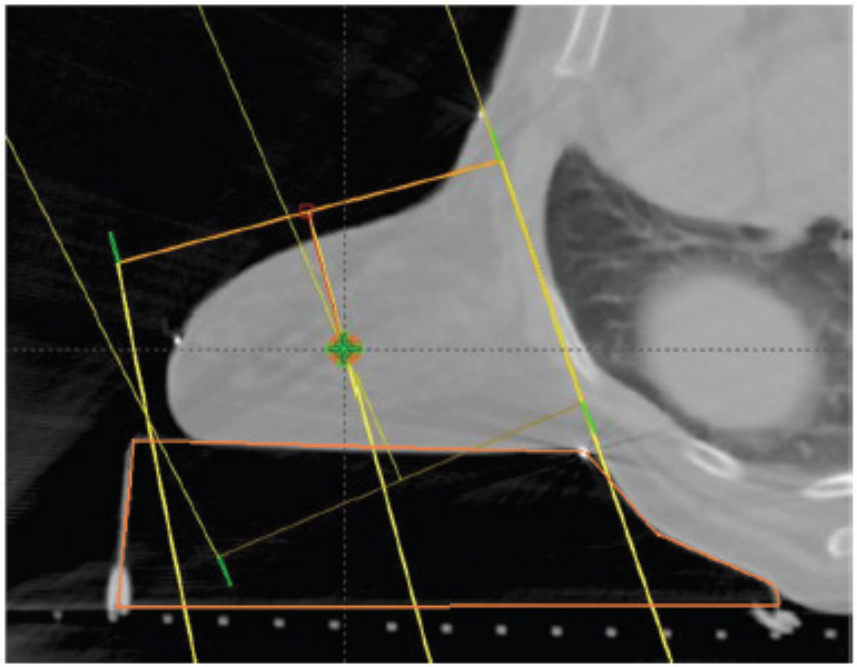
- *Fourquet A et al. Radiother Oncol, 1991*
- *Campana F et al. Int J Radiation Oncology Biol Phys, 2005*
- *Bollet MA et al. Br J Radiol, 2006*
- *Kirova YK et al . Int J Radiation Oncology Biol Phys, 2008*
- *Kirova et al, Radiother Oncol 2014*
- *Bronsart et al, Radiother Oncol, 2017*

institutCurie
Ensemble, prenons le cancer de vitesse.

(A)



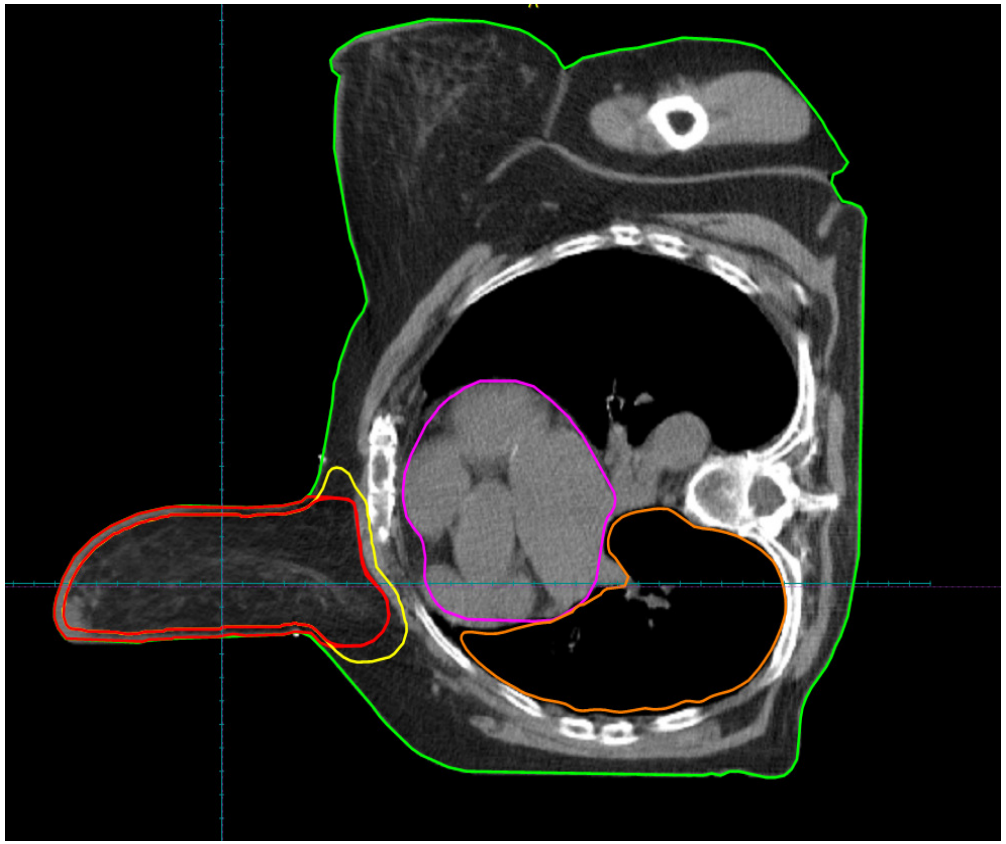
(B)



Volume definition

institutCurie
Ensemble, prenons le cancer de vitesse.

Breast: Delineation in lateral position



Courtesy Dr Castro Pena

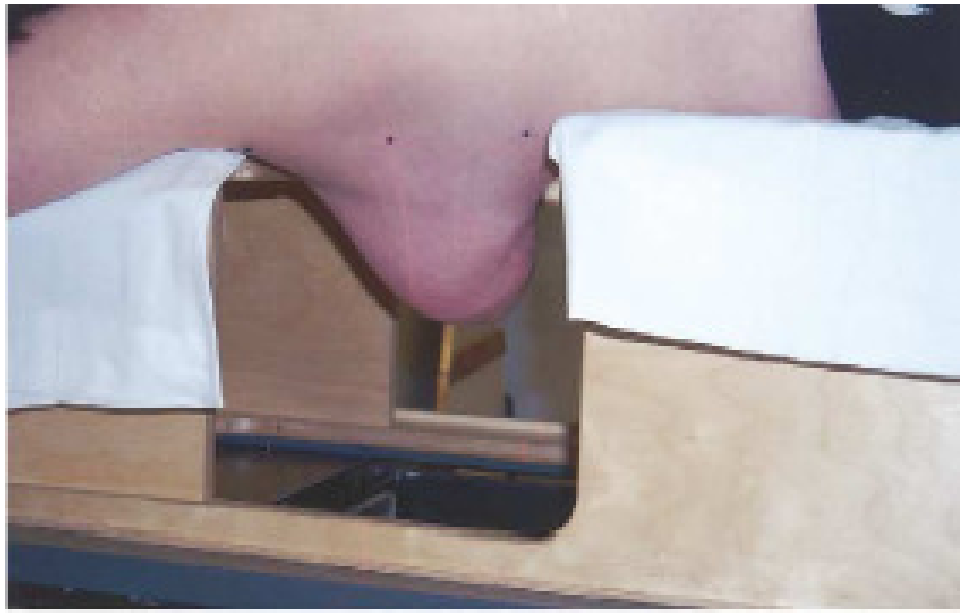
institutCurie
Ensemble, prenons le cancer de vitesse.
ESTRO School

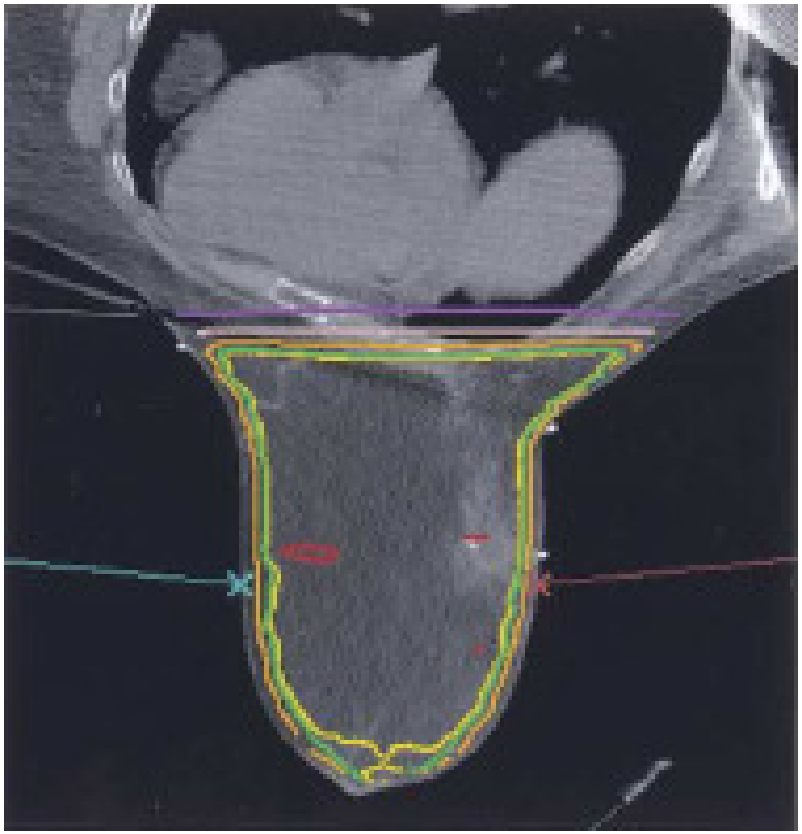
Prone

institutCurie
Ensemble, prenons le cancer de vitesse.

ESTRO School

RT in prone position





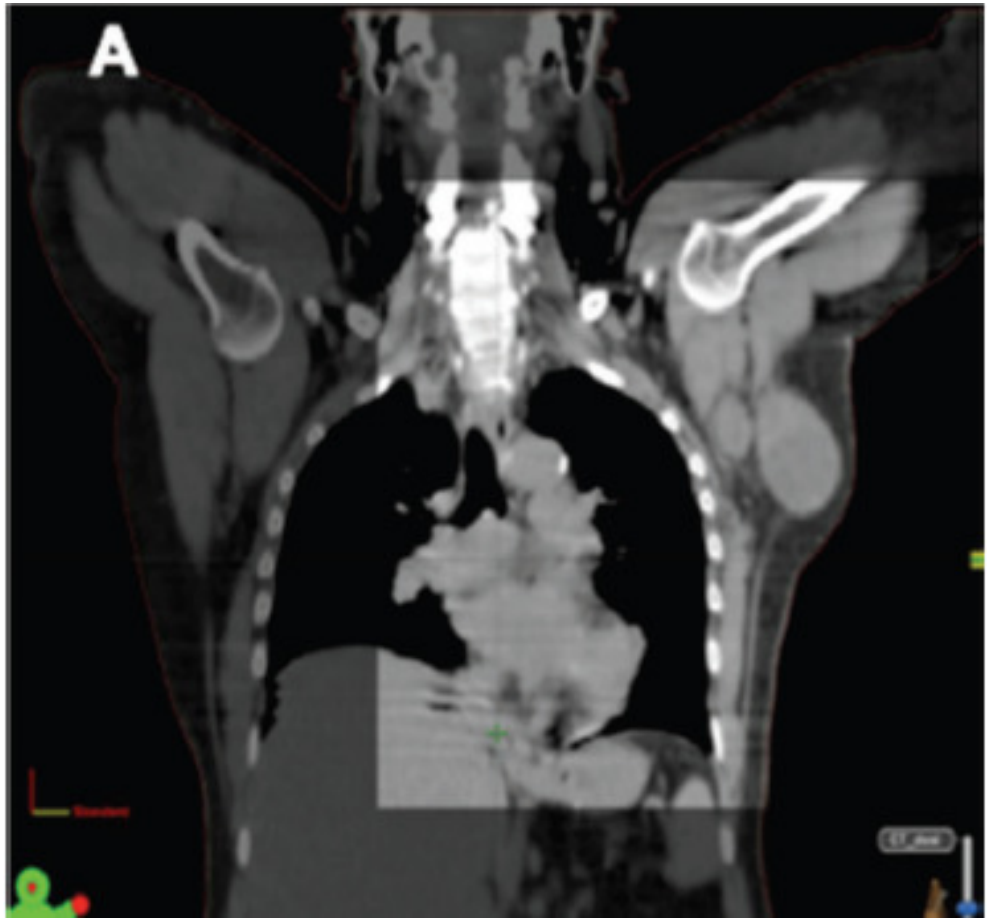
Memorial Sloan-Kettering, New York

Goodman et al *Int J Radiation Oncology Biol Phys* 2004

institutCurie
Ensemble, prenons le cancer de vitesse.

ESTRO School

Advances cases: particular situation, no possible guidelines use, follow the tumour and LN extension



Chira et al, Bio Med 2013

Thank you for your attention

…then homework results and dosimetric considerations…

institutCurie

Local RT: chest wall and whole breast

Marianne Aznar

The Christie/University of Manchester

University of Oxford

Rigshospitalet, Denmark

With thanks to Mirjana Josipovic and Stine Korreman

ESTRO School

The ”planning target volume”

Why do we need to irradiate MORE than our clinical target volume ??

Outline

- Theory/practice

- Dose homogeneity and concept of PTV (Sunday)
- Imaging guidance and surrogates (Monday)
- Dose to OARs, IMRT/VMAT and DIBH (Tuesday)

TREATMENT PLANNING CHALLENGE: COVERAGE AND HOMOGENEITY

What are we trying to achieve ?

Coverage target :

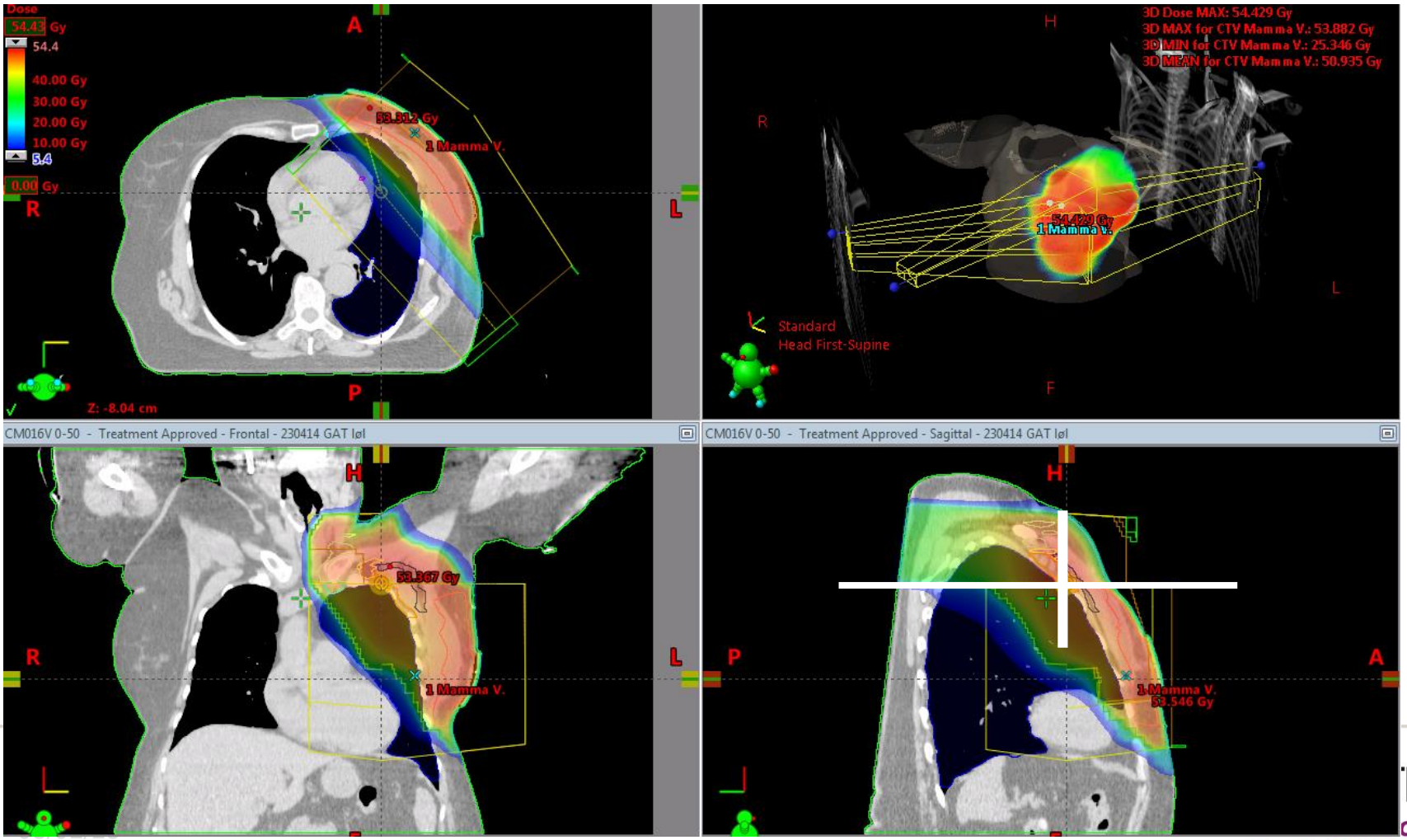
- breast/chest wall
- regional nodes
- IMN ?

Dose homogeneity within the target volume

Max dose to organs at risk (heart, lung, contralateral breast)

Common field arrangements

Isocentric half beam technique



Example of constraints: the DBCG criteria

For 40 Gy /15 fr

Target:
CTV breast/chest wall: $V_{95\%} \geq 98\%$, $V_{107\%} \leq 2\%$, $V_{108\%} = 0$

Heart: $V_{17Gy} \leq 5\%$, $V_{35Gy} \leq 1\%$, max dose ≤ 40 Gy

Ipsilateral lung: mean dose ≤ 16 Gy, $V_{17Gy} \leq 25\%$

Contralateral breast: as little as possible (esp. young patients)

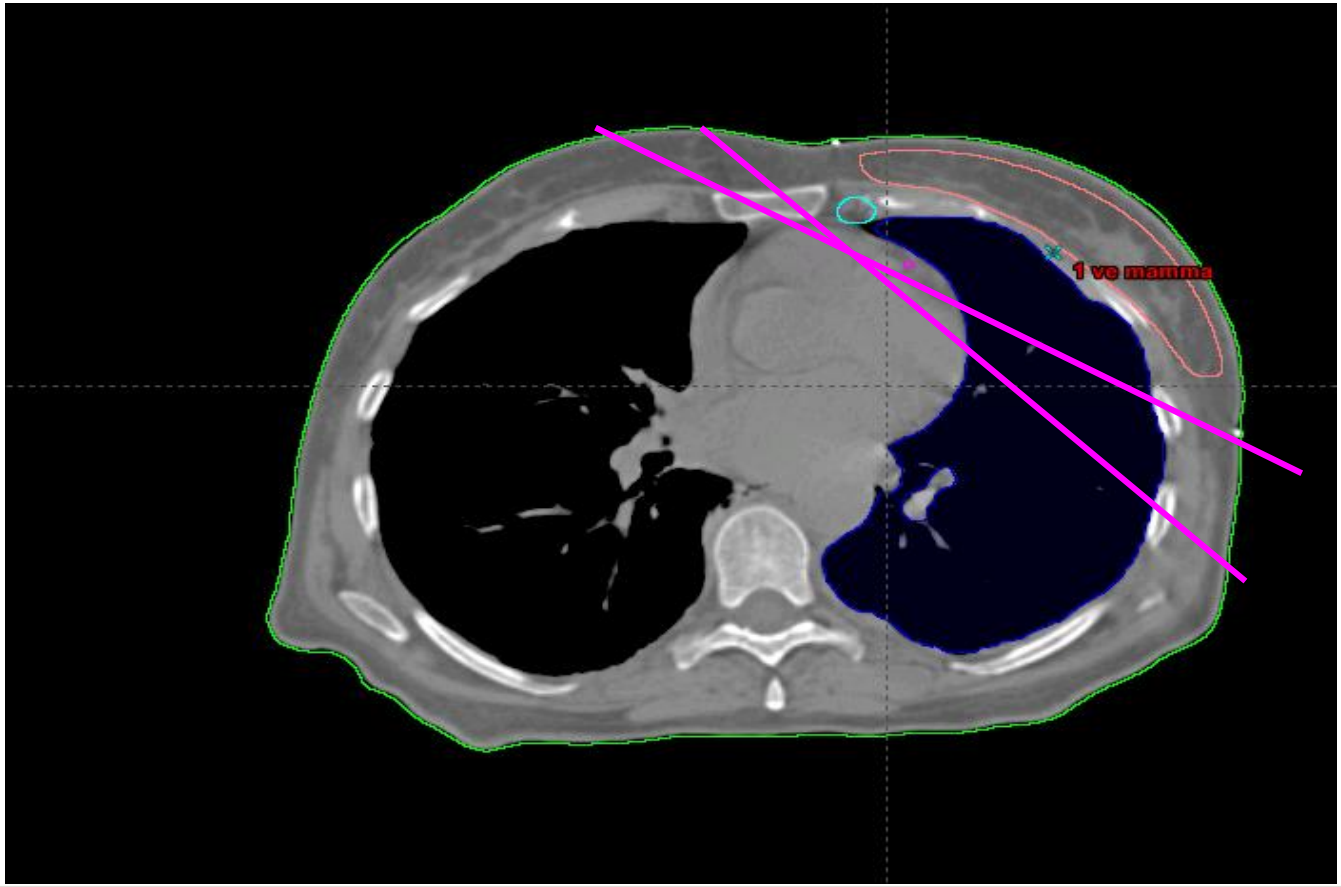
PRIORITIES ??

Common field arrangements

Wide tangents for IMN

Simple

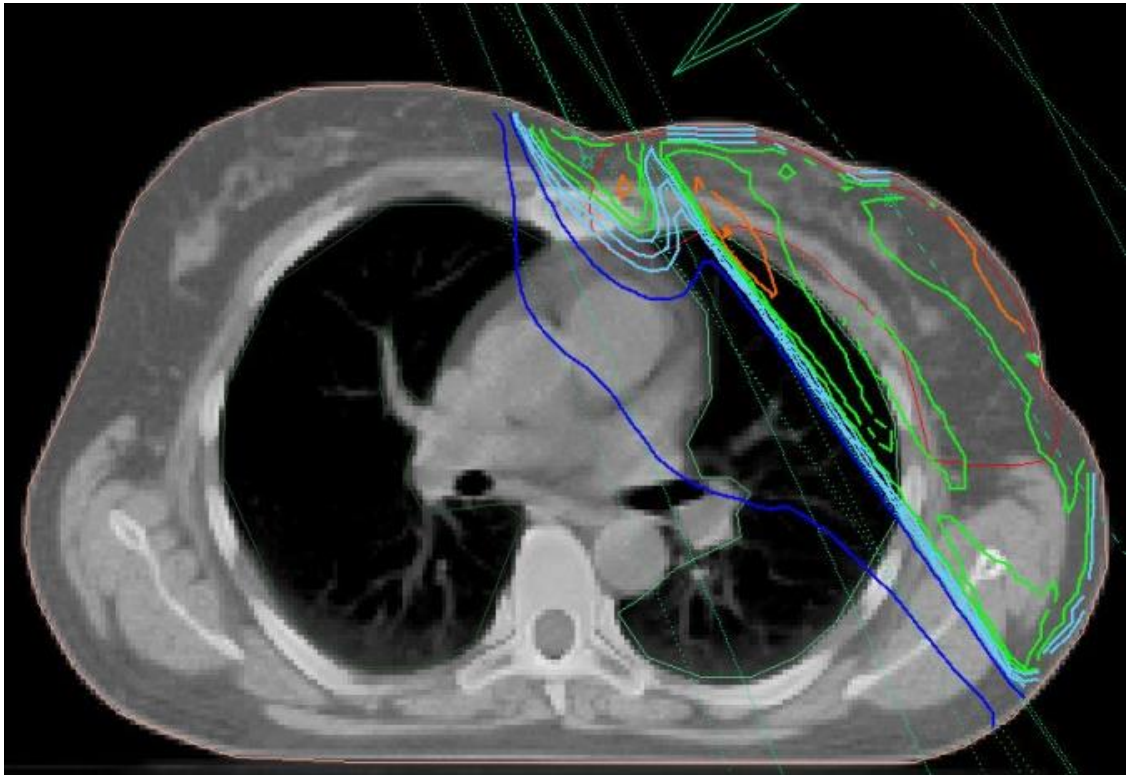
Risk of high dose to OARs (unless…)



Common field arrangements

Field junction for IMN

With electrons + photons

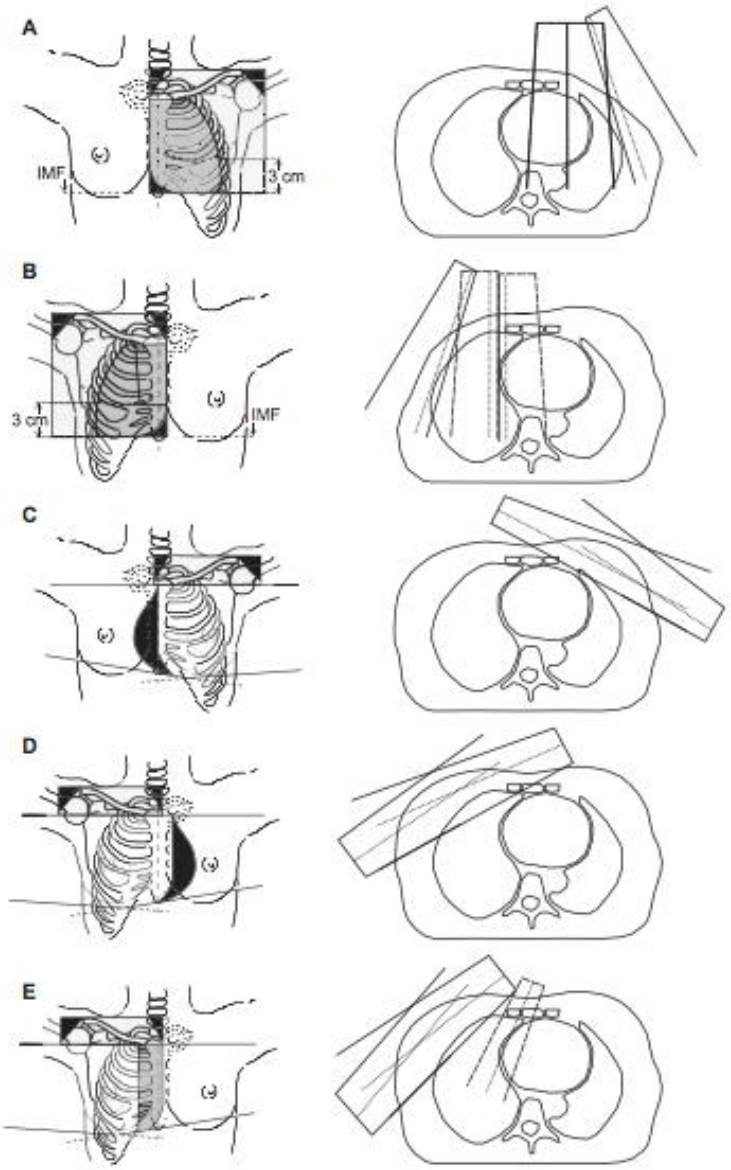


Overlap can be challenging

Higher skin dose

Image guidance?

More references for planning techniques

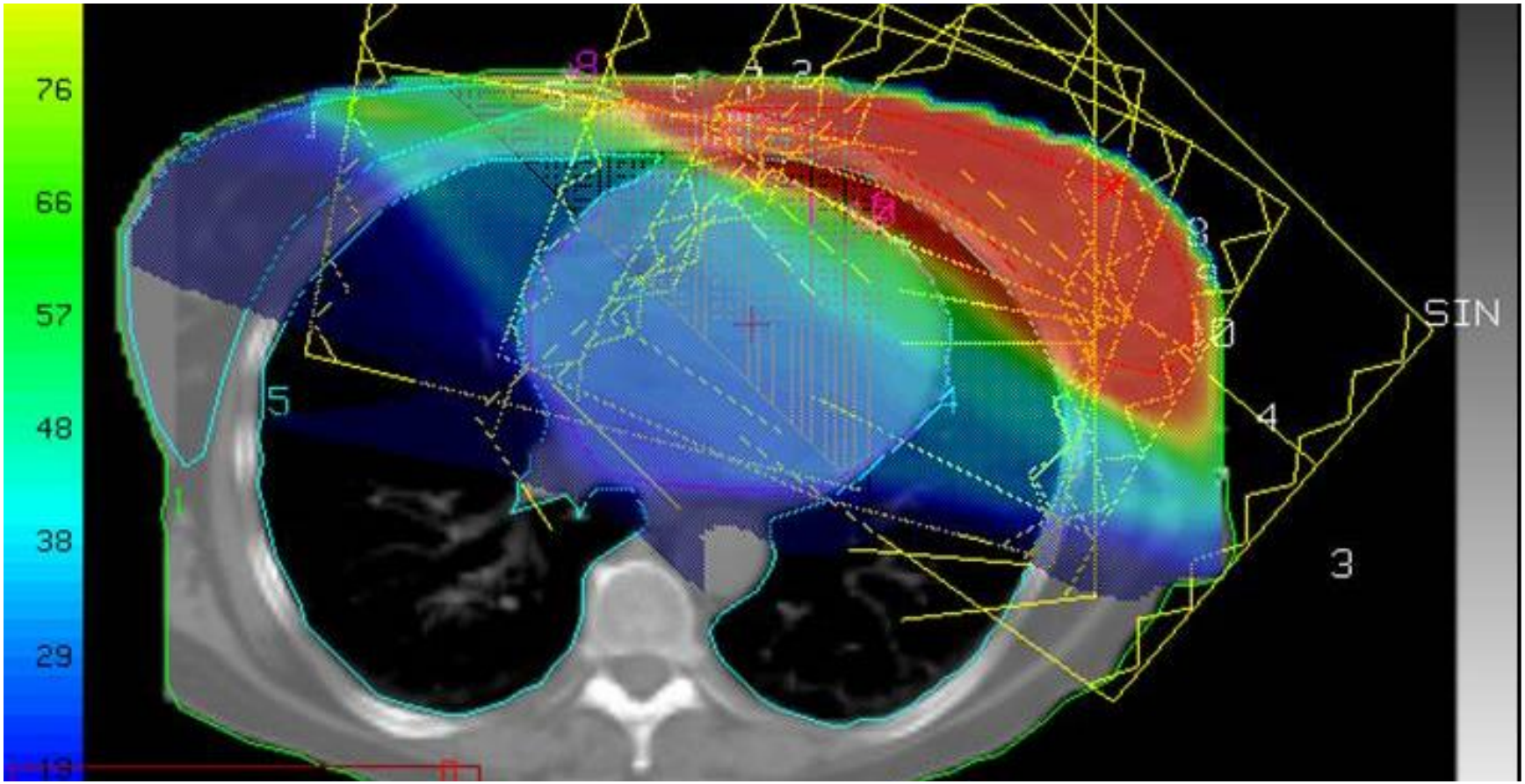


Thorsen et al 2013 Acta Onc
Thorsen et al 2014 Acta Onc
Van der Laan et al 2005 IJROBP

All “open access”

ESTRO School

When all this is not enough…



“a rose, by any other name…”
what IS called IMRT in the literature ?

- Using wedges
- Using small fields to homogenize the dose distribution
- Using inverse-planned MLC motions, but only with tangent beam angles
- Using many field angles and a full computer optimization

What is IMRT ???

Forward IMRT

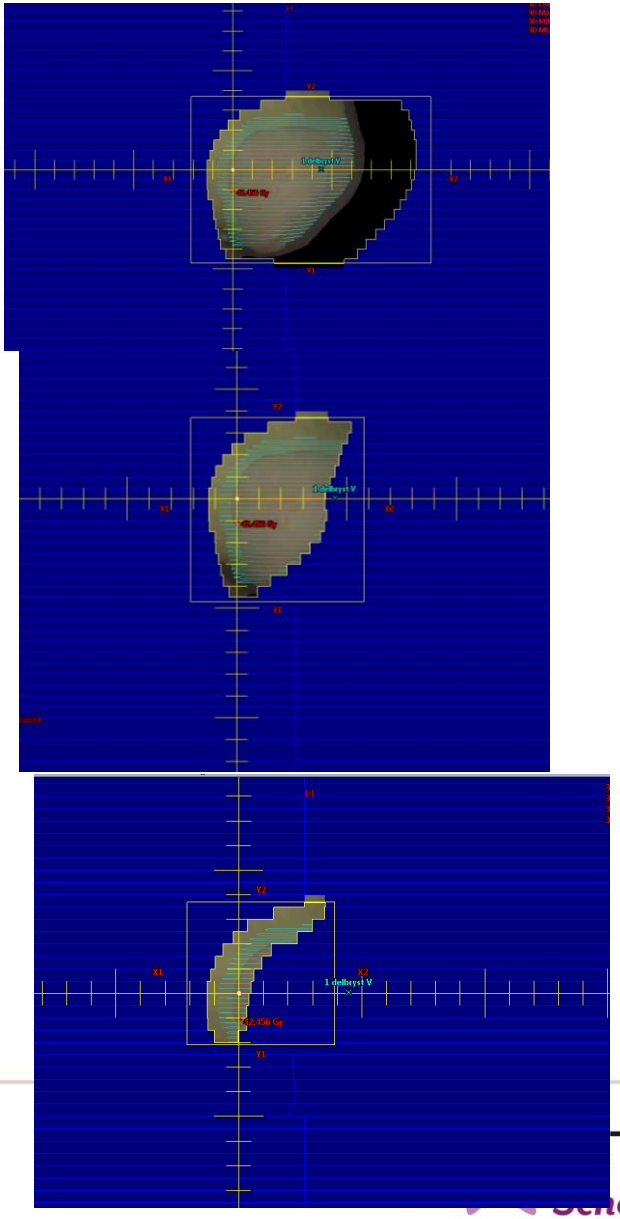
Forward planning for dose homogeneity – field-in-field/electronic compensation

Field arrangement as for standard 3D-CRT (basically tangents)

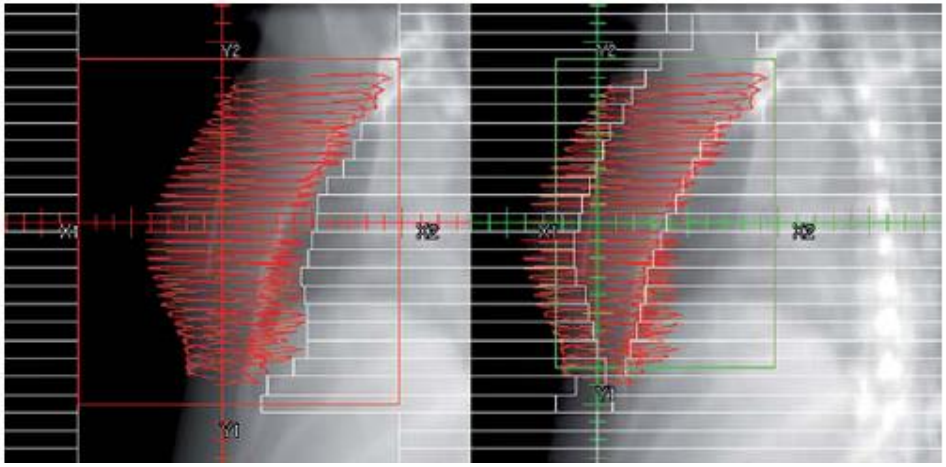
But no wedges !! (decreased scattered radiation)

Forward planning - field-in-field

+



Advantage over good old wedges ?



Comparison of (physical) wedged and f-IMRT tangential fields:

	f-IMRT	Wedged
MU	232	308
Thyroid	1.2cGy	2.8cGy
Contr. breast	5.2	7.9
Mid pelvis	0.2cGy	1.0cGy

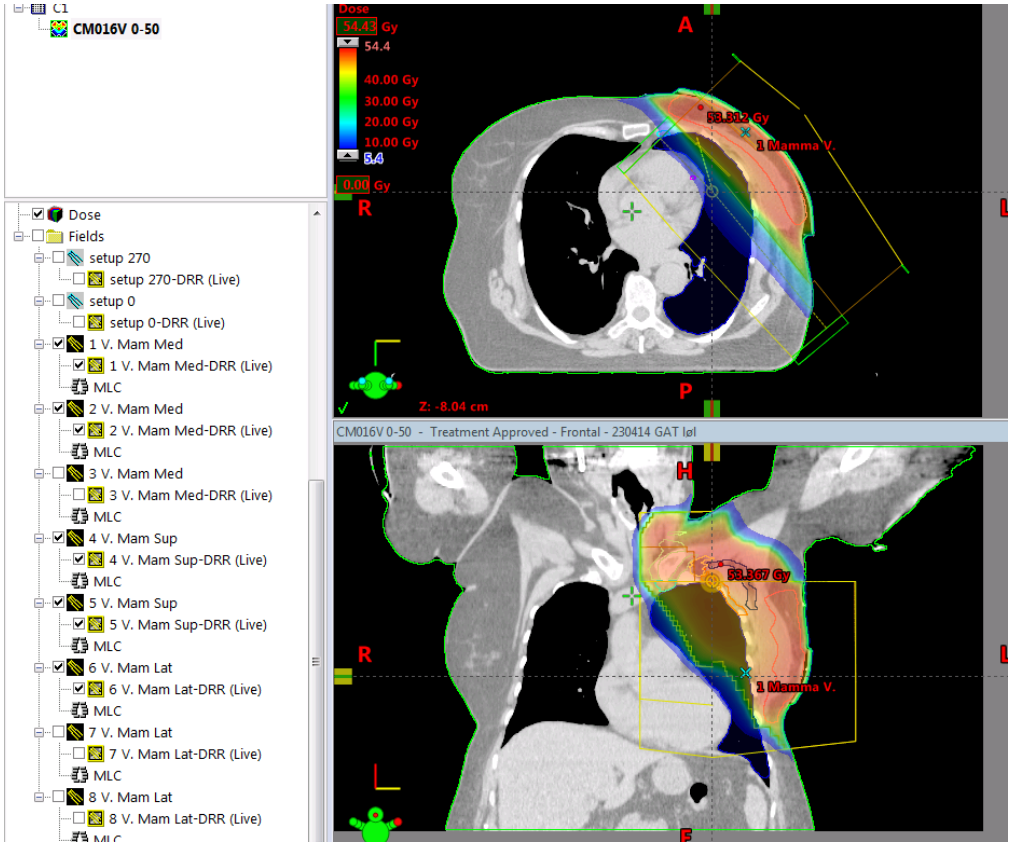
2.5 cGy = approx 16 CBCTs

Ludwig Strahlenther Onkol. 2008

(half that value for dynamic wedges)

ESTRO School

One example from Rigshospitalet



10 fields !!

Including mixed beams(18 MV, but limited to 15 MUs)

Still within a standard treatment slot

ESTRO School

What is IMRT ???

Forward IMRT

Forward planning for dose homogeneity – field-in-field/electronic compensation

Field arrangement as for standard 3D-CRT (basically tangents)

Evidence from clinical trials
(reviews: Staffurth Clin Oncol 2010
McCormick Semin Radiat Oncol 2011)

inverse-planned IMRT

Inverse planning with dosimetric constraints

Extended field arrangement, including non-coplanar fields and non-tangent angles

Take home message for Homogeneity

Dose homogeneity: solid evidence from clinical trials

Remember the distinction between

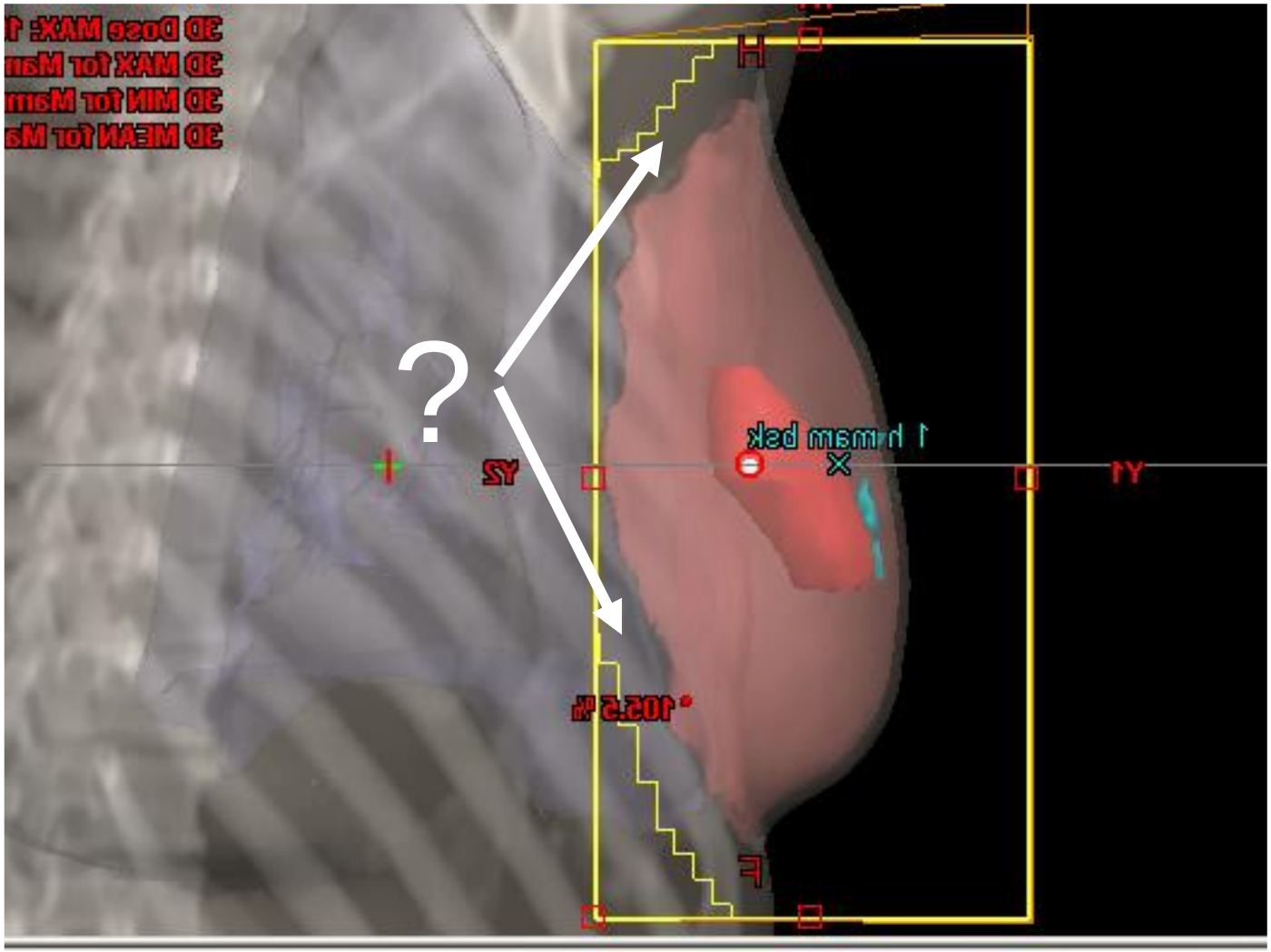
- forward IMRT (use with no restriction ☺)
- inverse planned IMRT /VMAT

Role IMRT / DIBH for dose reduction to OARs (see Tuesday)

UNCERTAINTIES: ROLE AND DEFINITION OF THE PTV

Why are uncertainties important ?

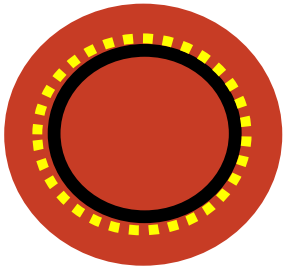
Why do we need to irradiate MORE than our clinical target volume ??



ESTRO School

The ”planning target volume”

CT and treatment plan

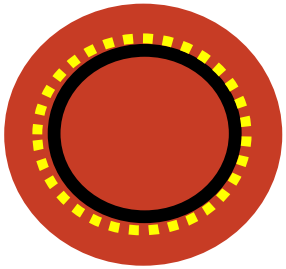


Treatment field

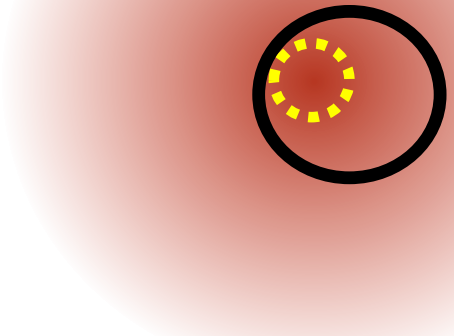
Target

95% isodose

CT and treatment plan

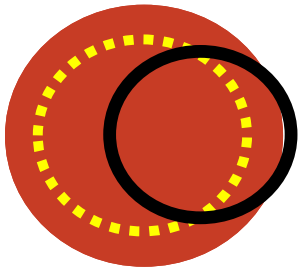


Delivered dose distribution

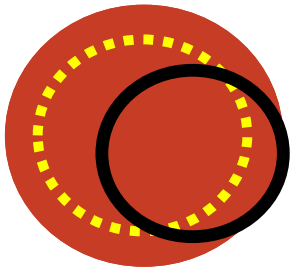


Target’s eye view

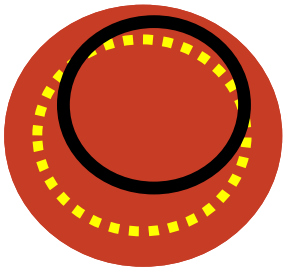
Day 1



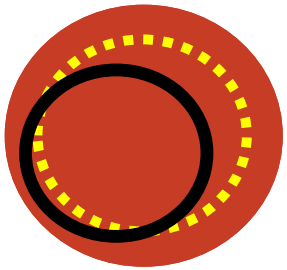
Day 2



Day 3



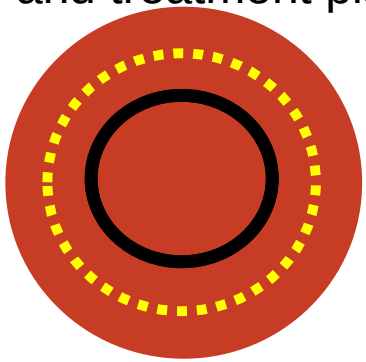
Day 4



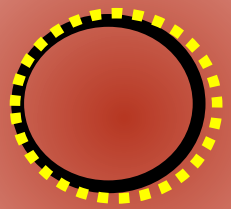
...

Beam’s eye view

CT and treatment plan

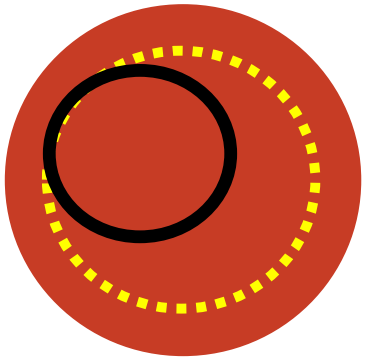


Delivered dose distribution

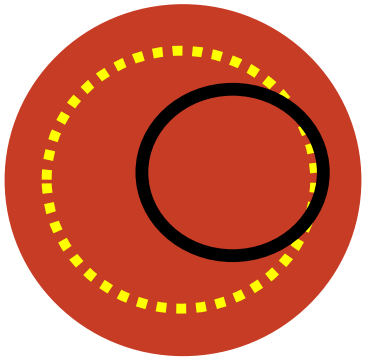


Target’s eye view

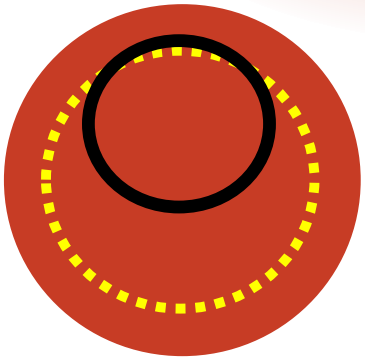
Day 1



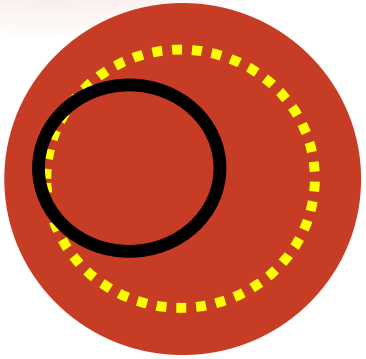
Day 2



Day 3



Day 4

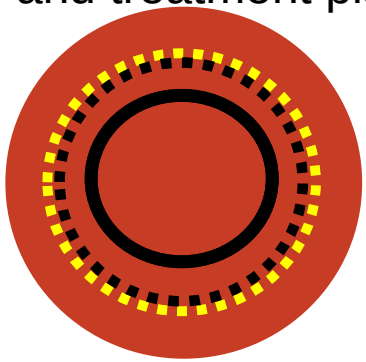


...

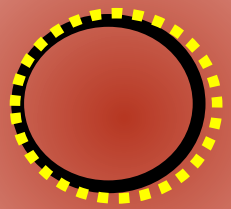
Beam’s eye view

ESTRO School

CT and treatment plan

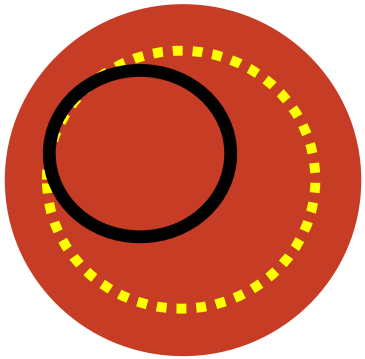


Delivered dose distribution

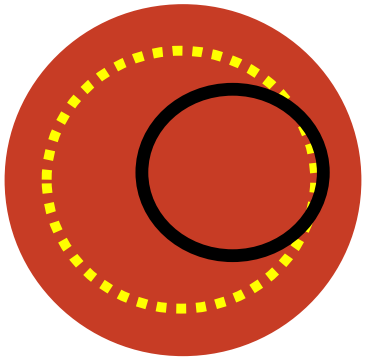


Target’s eye view

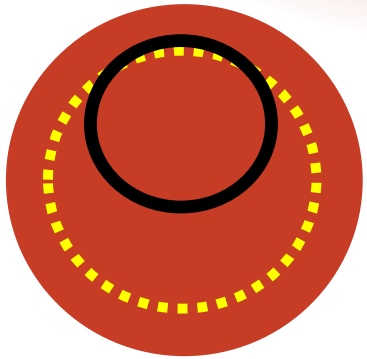
Day 1



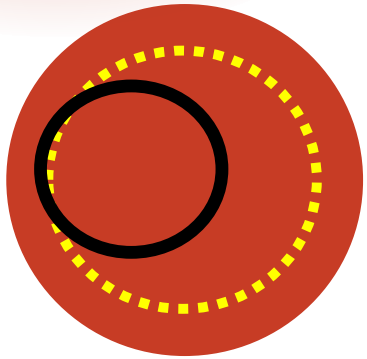
Day 2



Day 3



Day 4

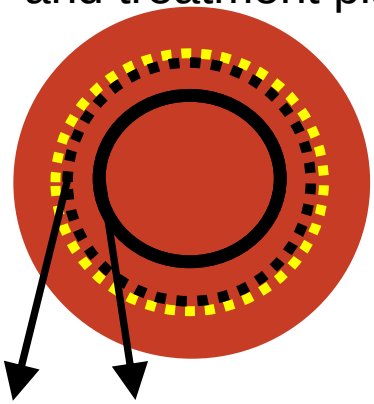


...

Beam’s eye view

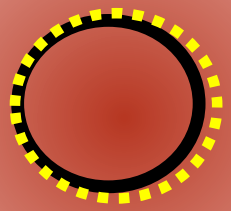
ESTRO School

CT and treatment plan



CTV to PTV margin

Delivered dose distribution

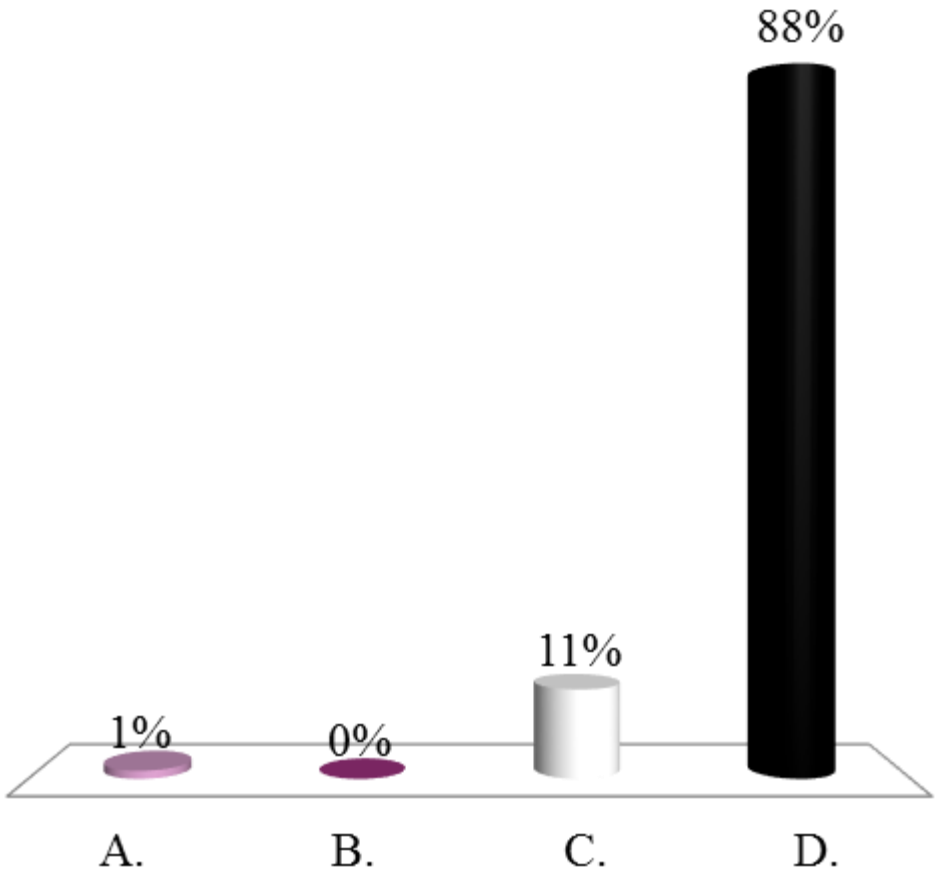


Target’s eye view

$$M = 2.5\ \Sigma_{tot} + 1.64\ (\sigma_{tot}-\sigma_{p})$$

Where do uncertainties arise?

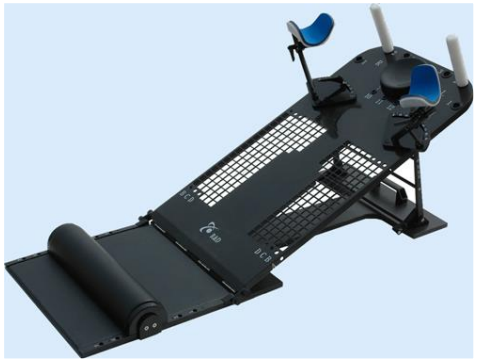
A. During contouring
B. During planning (e.g. dose calculation)
C. During treatment delivery
D. All of the above

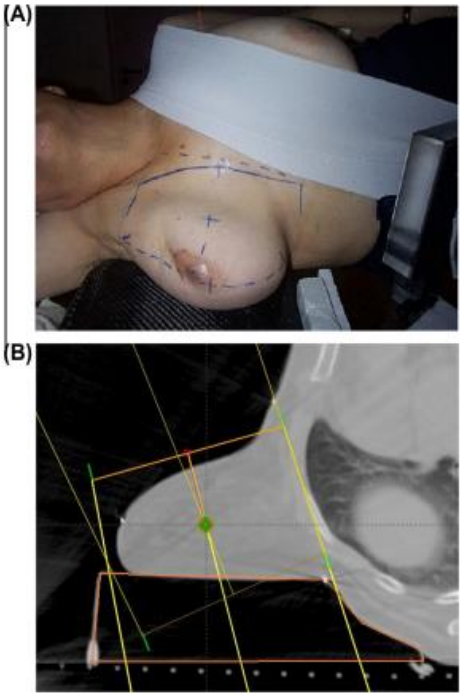


Uncertainties due to delineation

Solution: guidelines !

Uncertainties due to patient positioning





How to assess/correct positioning?

ESTRO School

What can go wrong ???

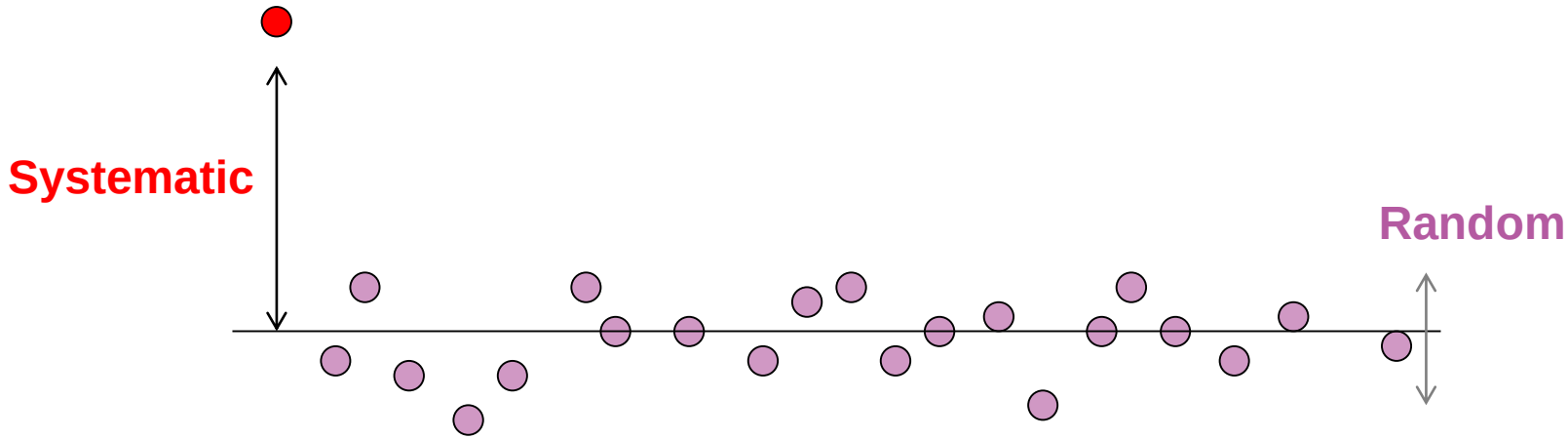
- Breathing motion
- Incorrect patient set-up
- Incorrect target or OAR position
- Changes in breast volume

Random vs systematic uncertainties

Systematic: “preparation error”

Random: “execution error”

$$M = 2.5\,\Sigma_{tot} + 1.64\,(\sigma_{tot}-\sigma_{p})$$



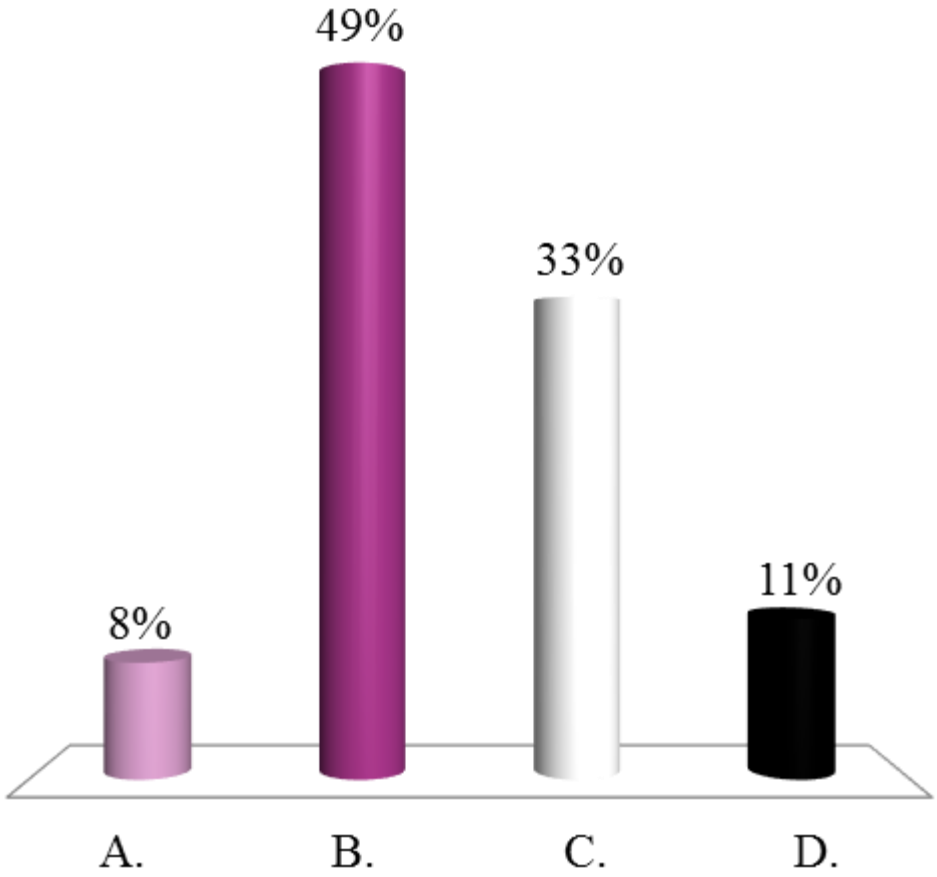
Which one of these is NOT a good example of systematic uncertainty?

A. A junior physician contouring the target volume (might under- or over-estimate the CTV)

B. A patient with a large BMI, who doesn't fit comfortably in the "breast board" fixation

C. A nervous patient, who "tenses up" during simulation

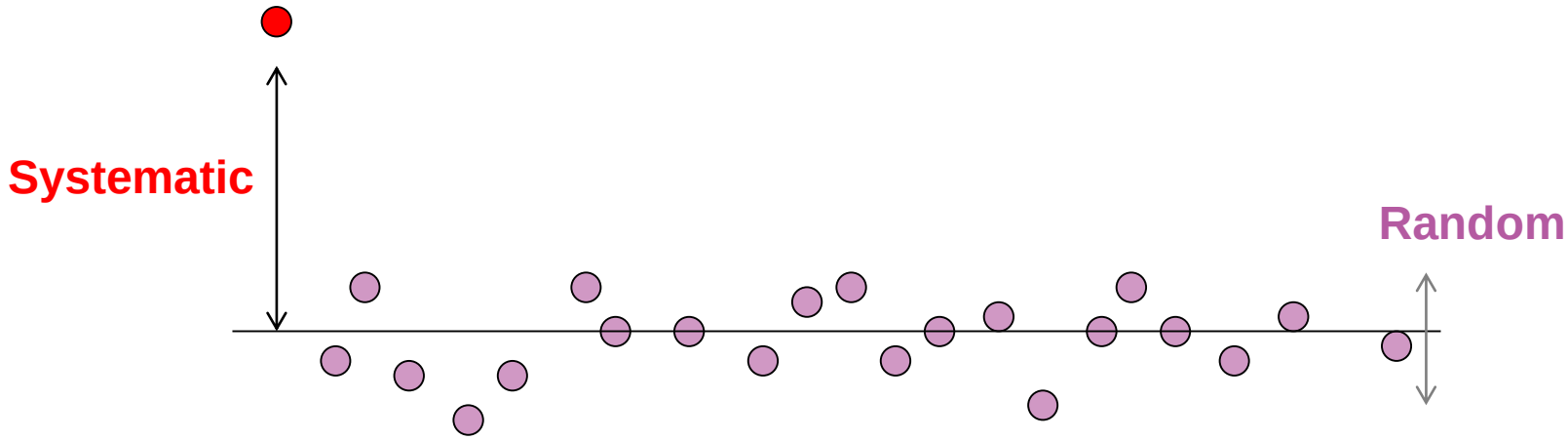
D. An outdated dose calculation algorithm, which will underestimate the dose received by the lung tissue.



Random vs systematic uncertainties

$$M = 2.5\ \Sigma_{tot} + 1.64\ (\sigma_{tot}-\sigma_p)$$

Where $\Sigma_{tot}=\sqrt{(\Sigma_1^2+ \Sigma_2^2+ \Sigma^2_3\ldots)}$



TAKE HOME MESSAGE

What it means (in English, not maths! ☺):

- The systematic uncertainties (between planning and delivery) count more
- The largest uncertainty will greatly dominate over the others
- So… our first goal is to reduce the largest, systematic uncertainties

ESTRO School

What margin for YOUR institution?

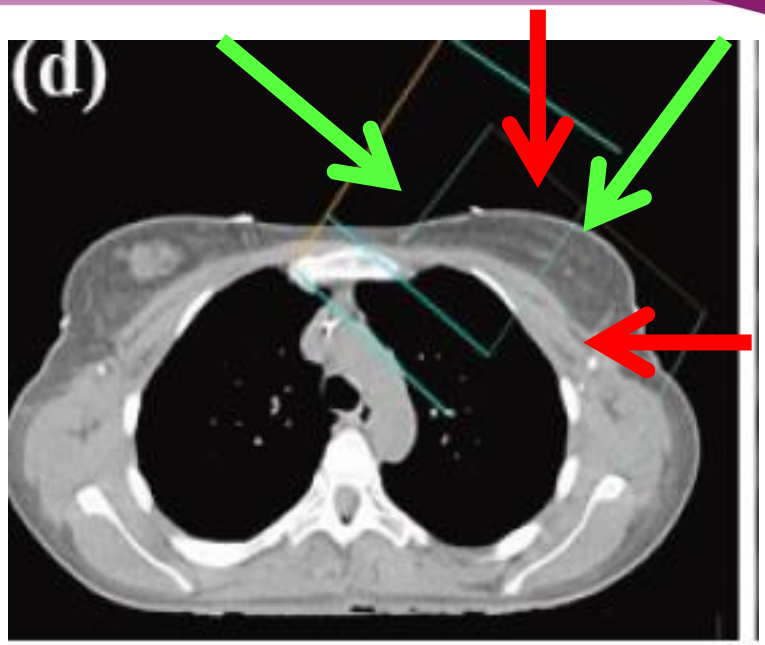
It depends on many parameters:

Immobilization/interfraction motion

Breathing/intrafraction motion

Observer uncertainty (delineation + matching)

Set-up verification (IGRT): type and frequency



And how can we do this ???? With image guidance !

IMAGE GUIDANCE:

WHICH MODALITY?
HOW OFTEN
WHICH STRUCTURE?

3 approaches:

”Guestimate” (least recommended)

Borrow from literature (check similar parameters!!)

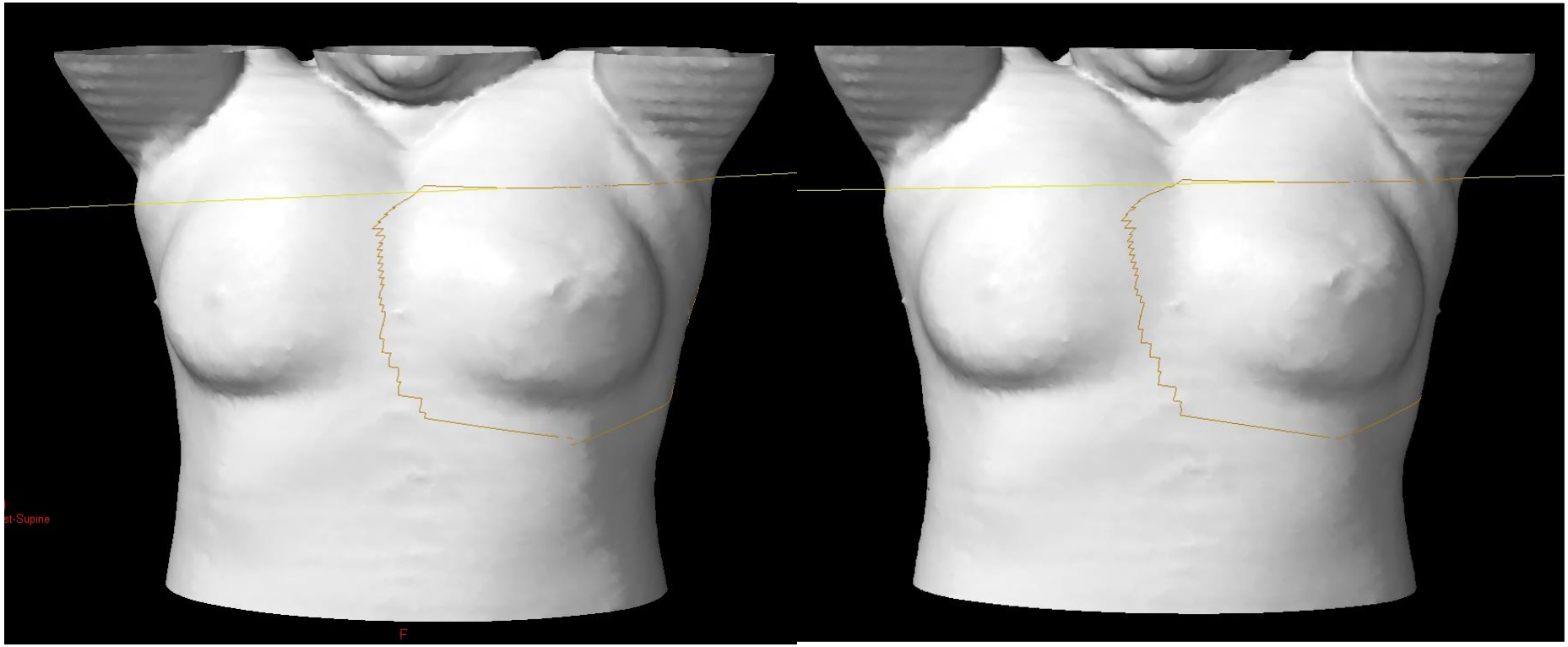
Calculate (or set your physicist to do it ☺): best but time-consuming

Breast

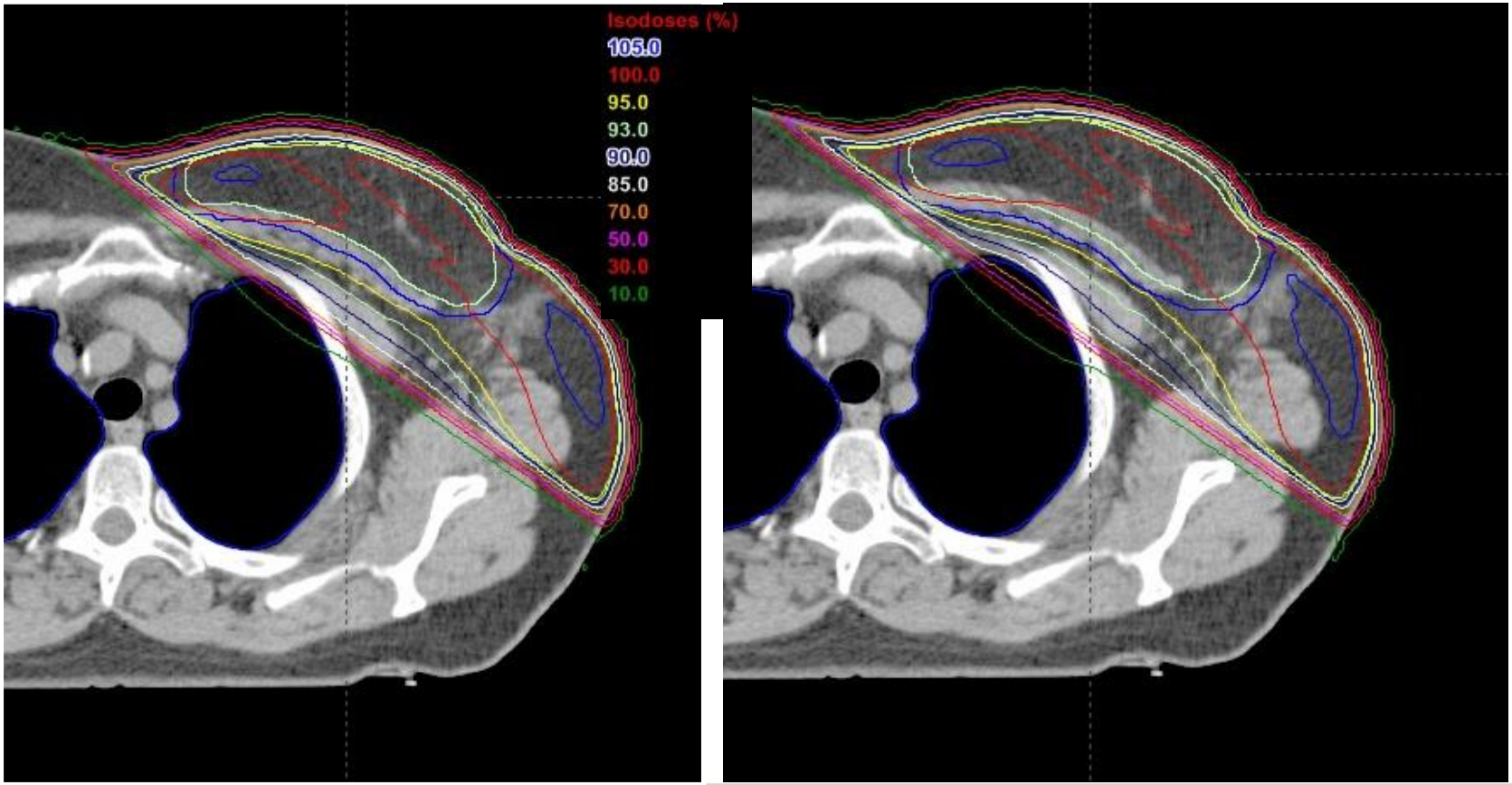
Contouring and different techniques

Contouring

Breast guideline vs 0.5cm more medial

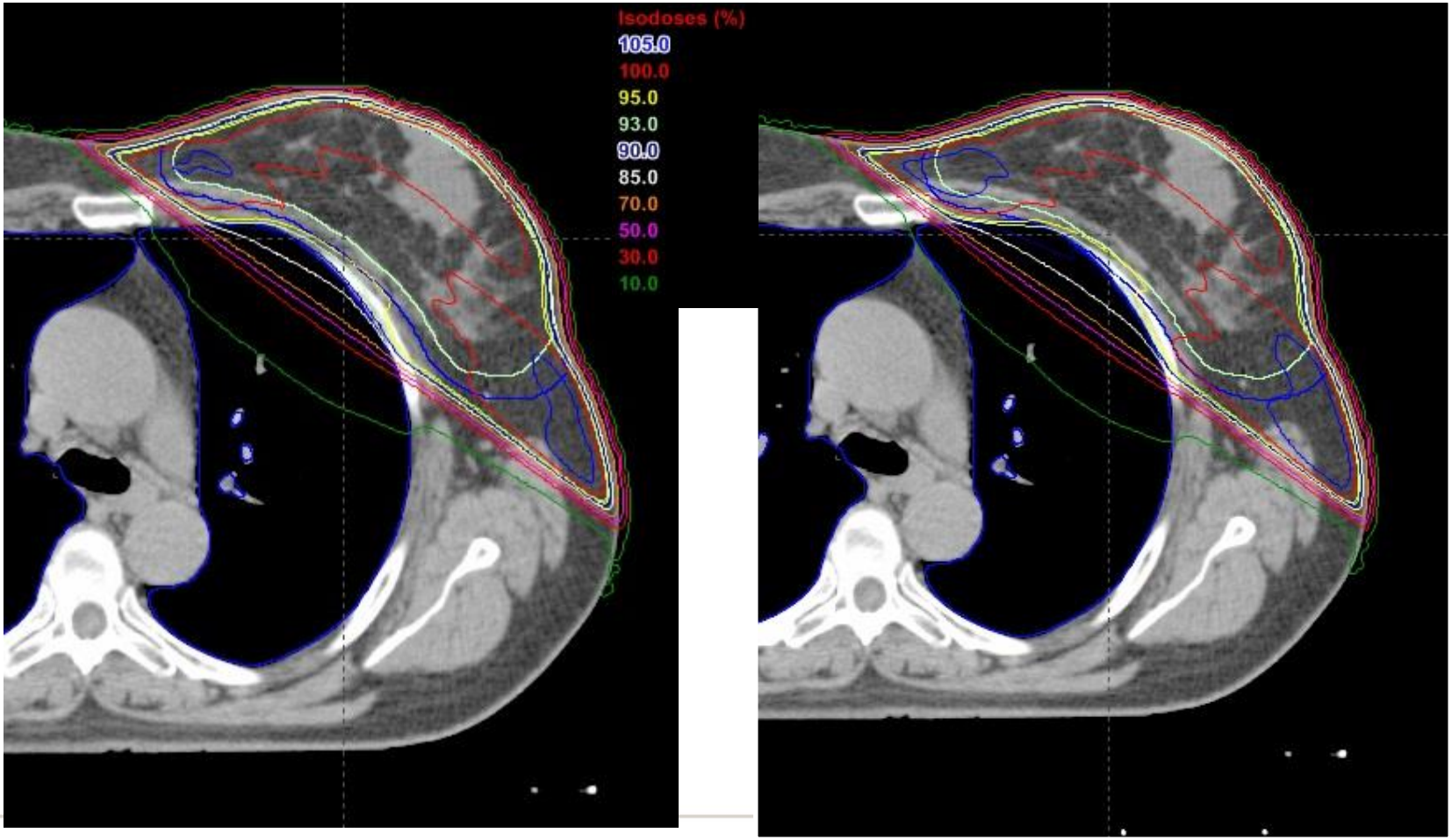


Breast guideline vs 0.5cm more medial



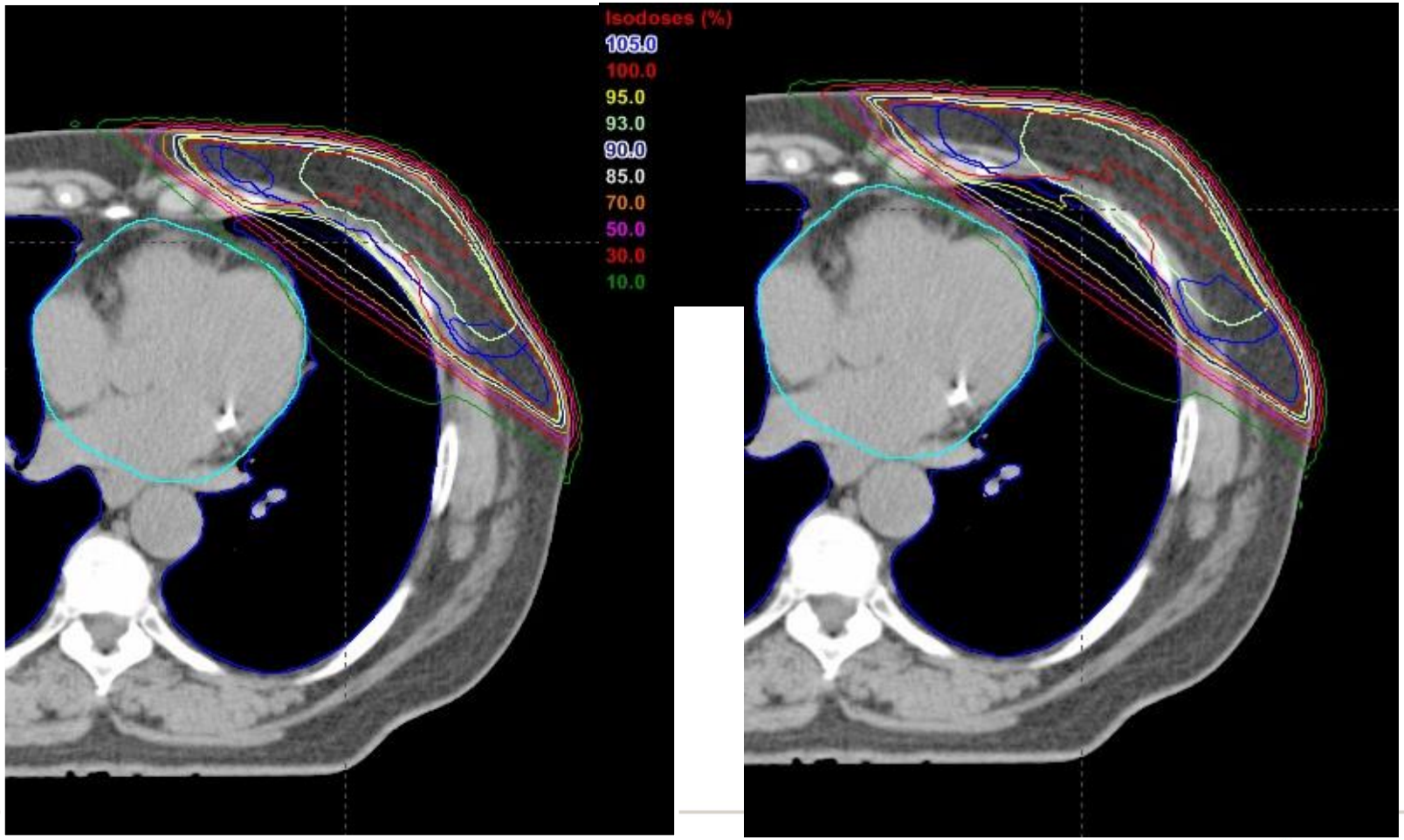
ESTRO School

Breast guideline vs 0.5cm more medial



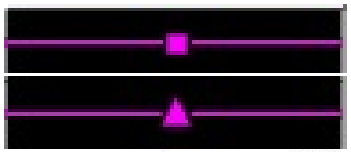
ESTRO School

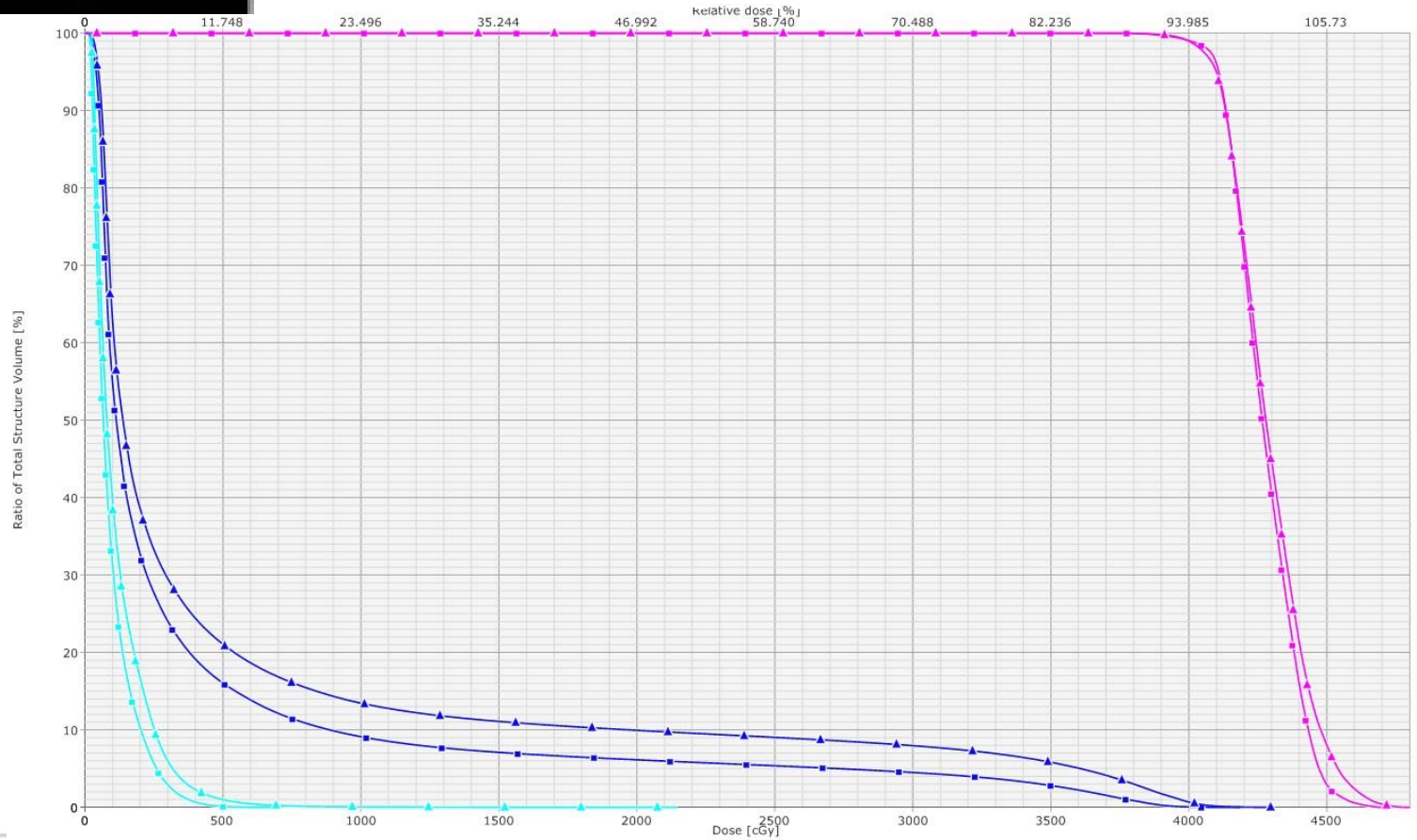
Breast guideline vs 0.5cm more medial



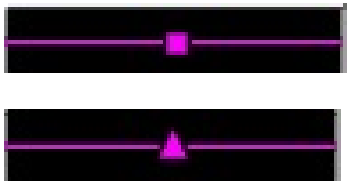
ESTRO School

DVH




Relative dose [%]
0
11.748
23.496
35.244
46.992
58.740
70.488
82.236
93.985
105.73
Ratio of Total Structure Volume [%]
100
90
80
70
60
50
40
30
20
10
0
0
500
1000
1500
2000
2500
3000
3500
4000
4500
Dose [cGy]

Mean dose to lung and heart



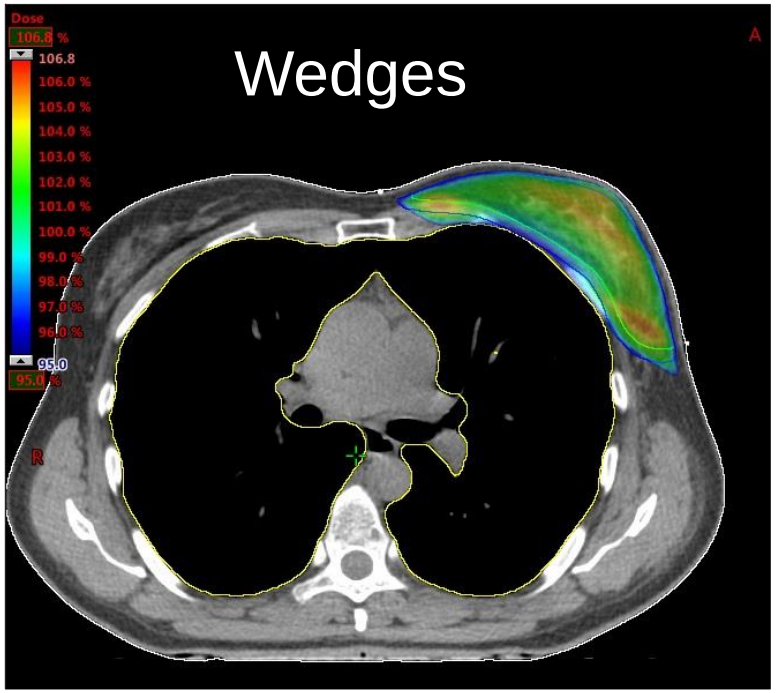
PTVbreast	4275.6
PTVbreast	4293.4
Lung_L	403.5
Lung_L	558.8
Heart	93.2
Heart	117.2

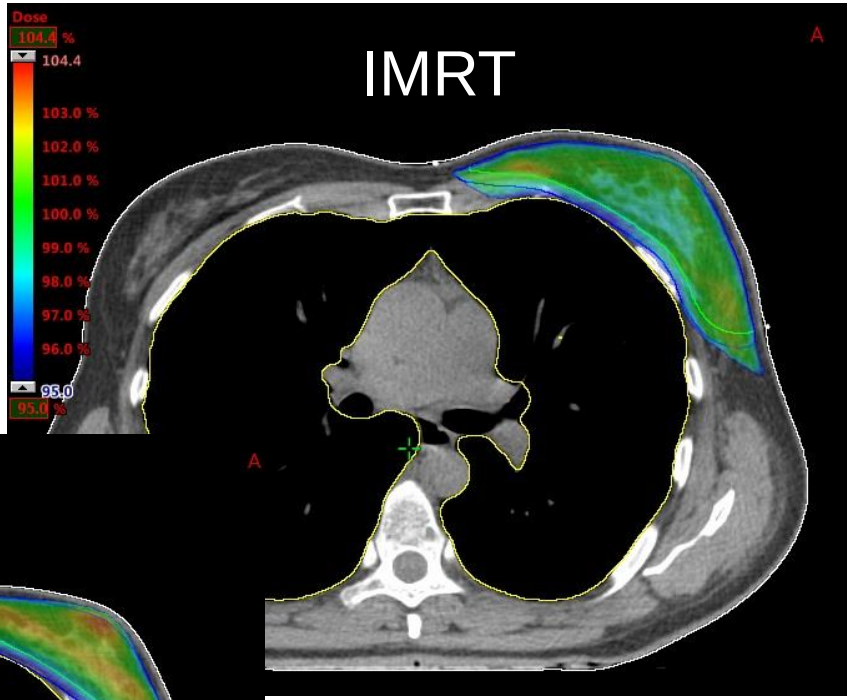
Comparison of different techniques

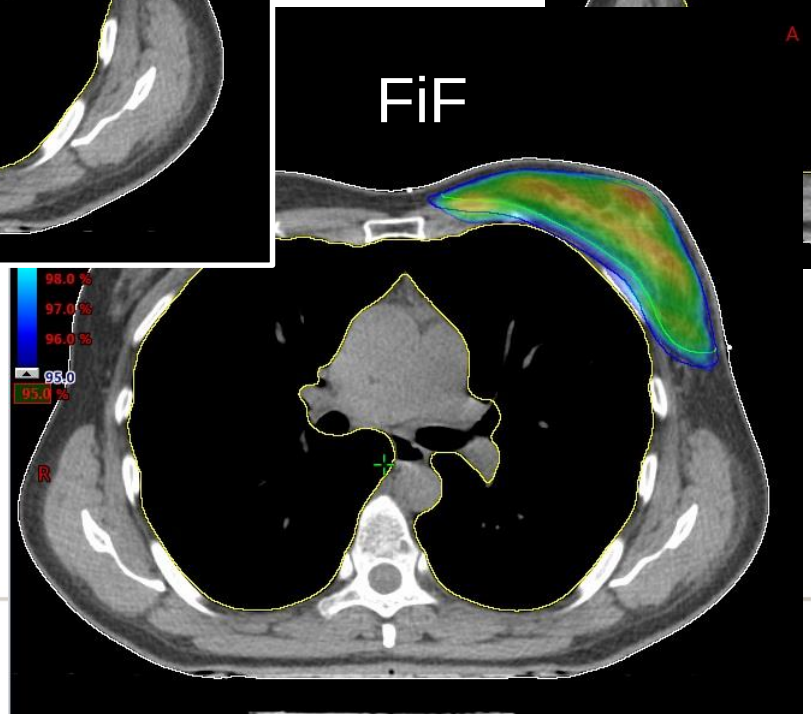
Left Breast

- 16 x 2,66 Gy

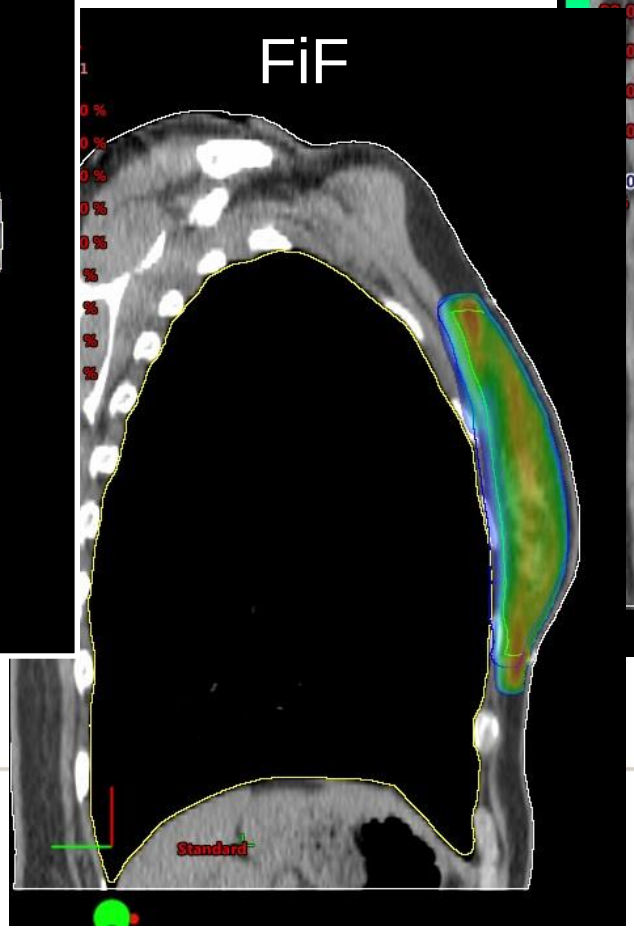
Breast

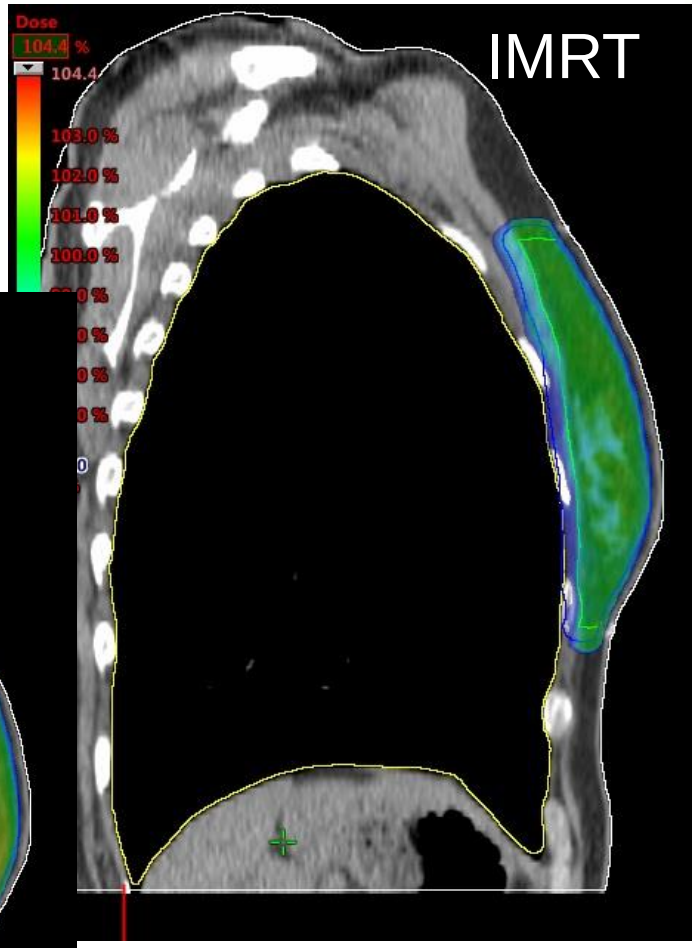






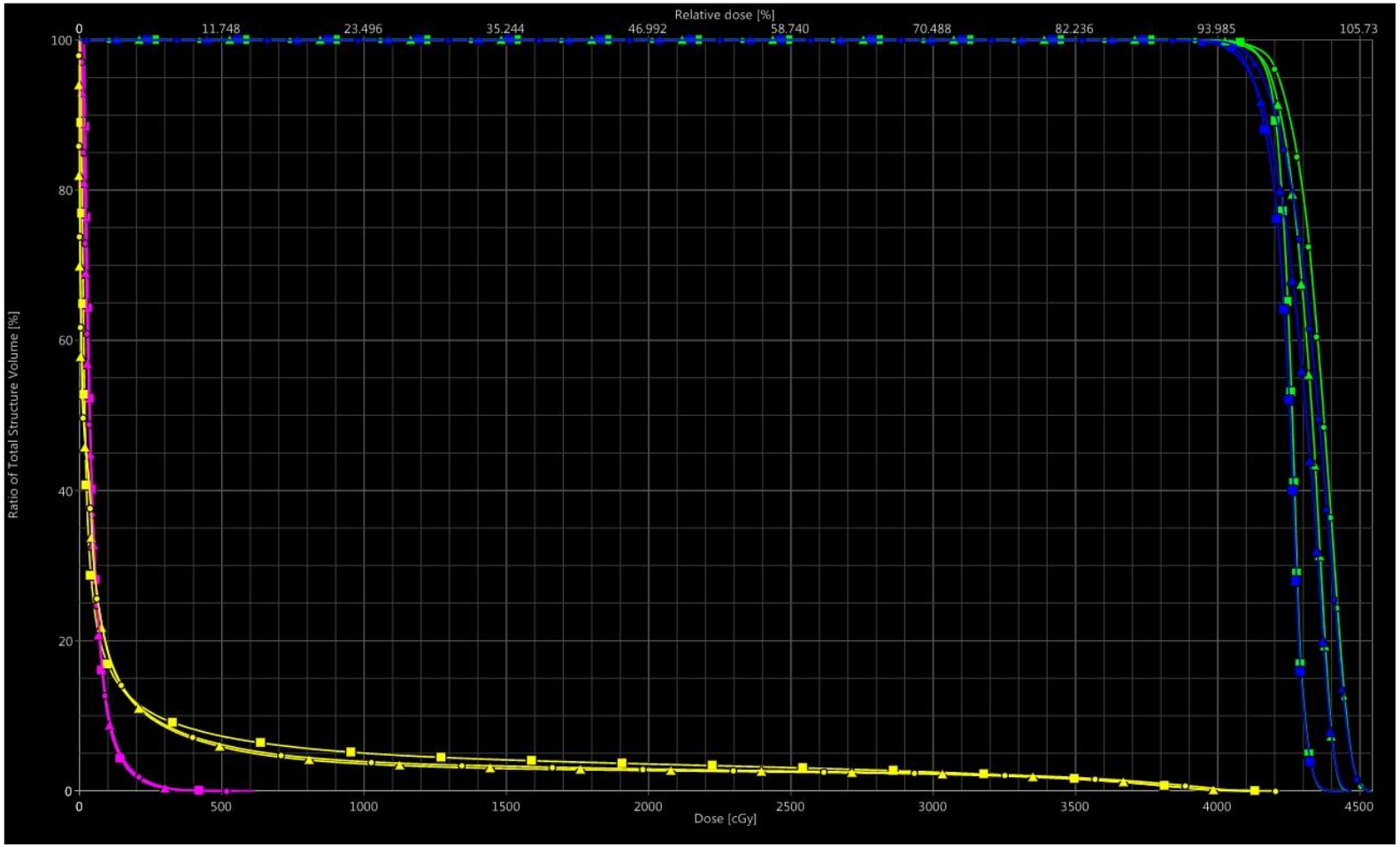
ESTRO School





ESTRO School

DVH



■ IMRT

▲ FiF

● Wedges

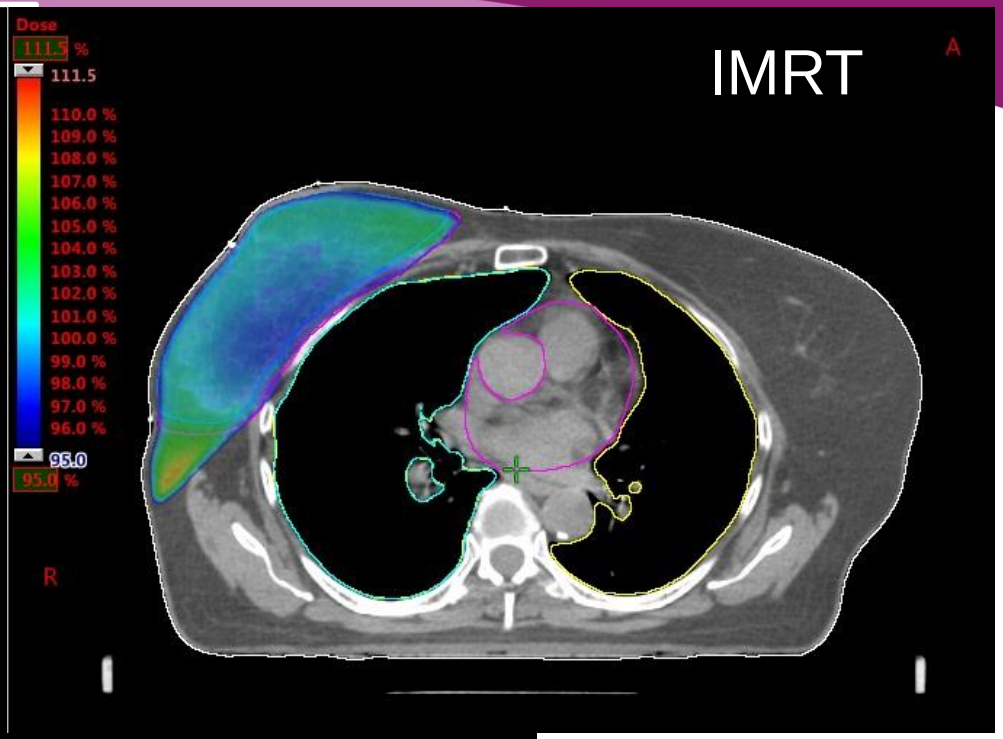
ESTRO School

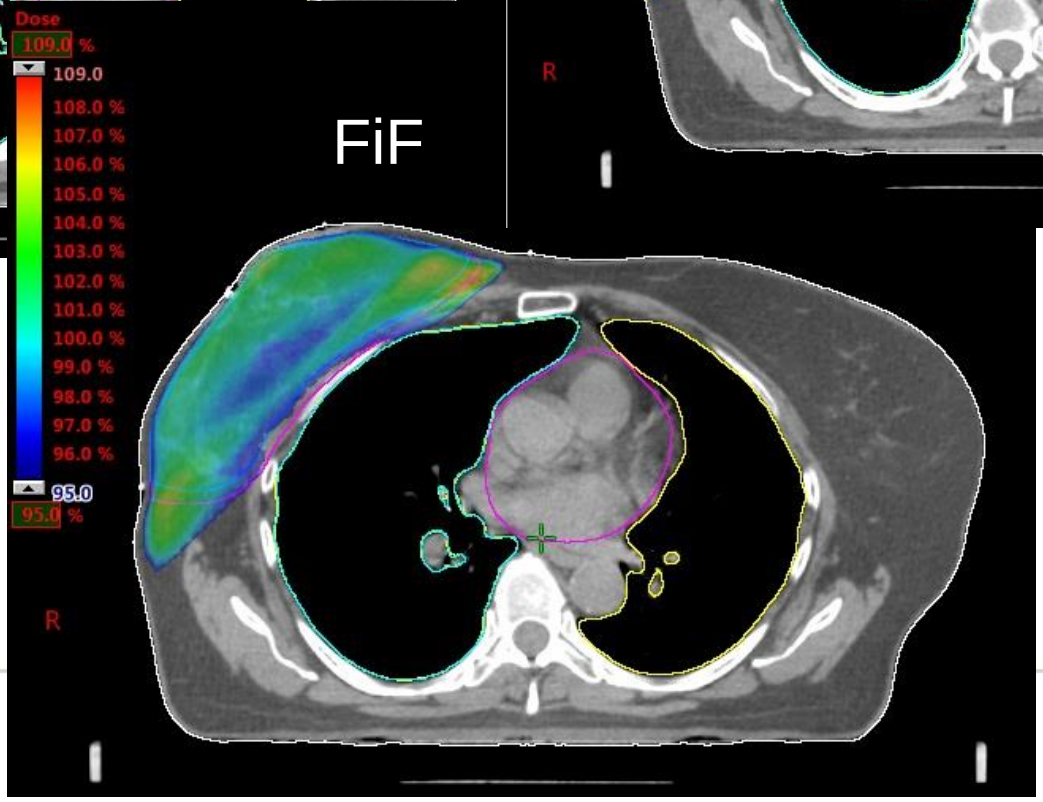
DVH values

	Lungs		Heart			
	V20	MLD	V20	V10	V5	MHD
FiF	2,7	164	0	0	0	49
Wedges	2,9	173	0	0	0	51
IMRT	3,7	198	0	0	0	53

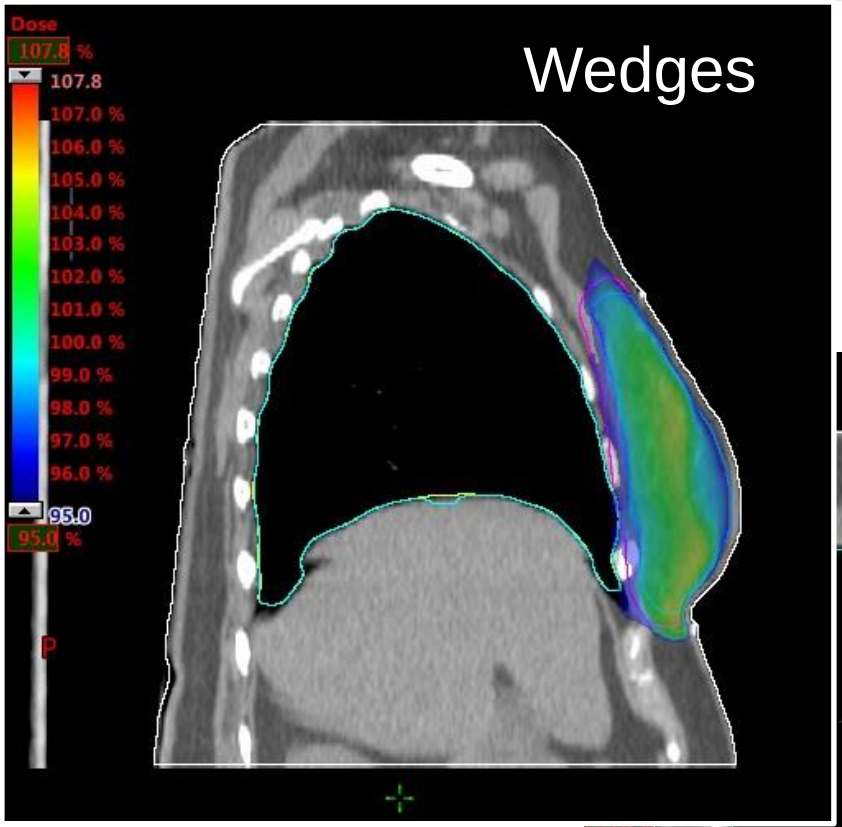
Right Breast

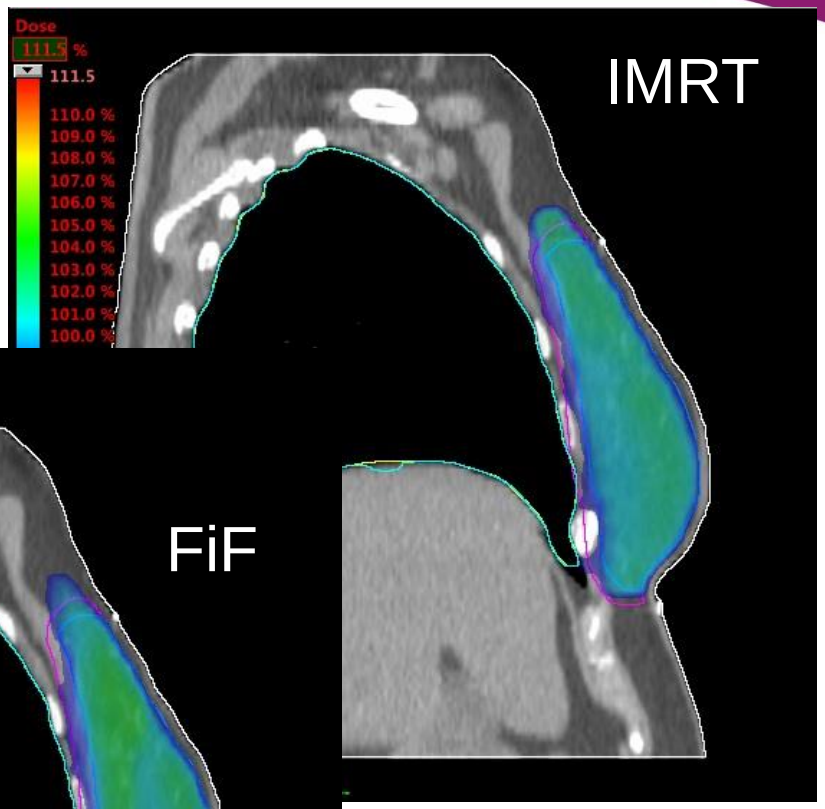
- 16 x 2,66 Gy

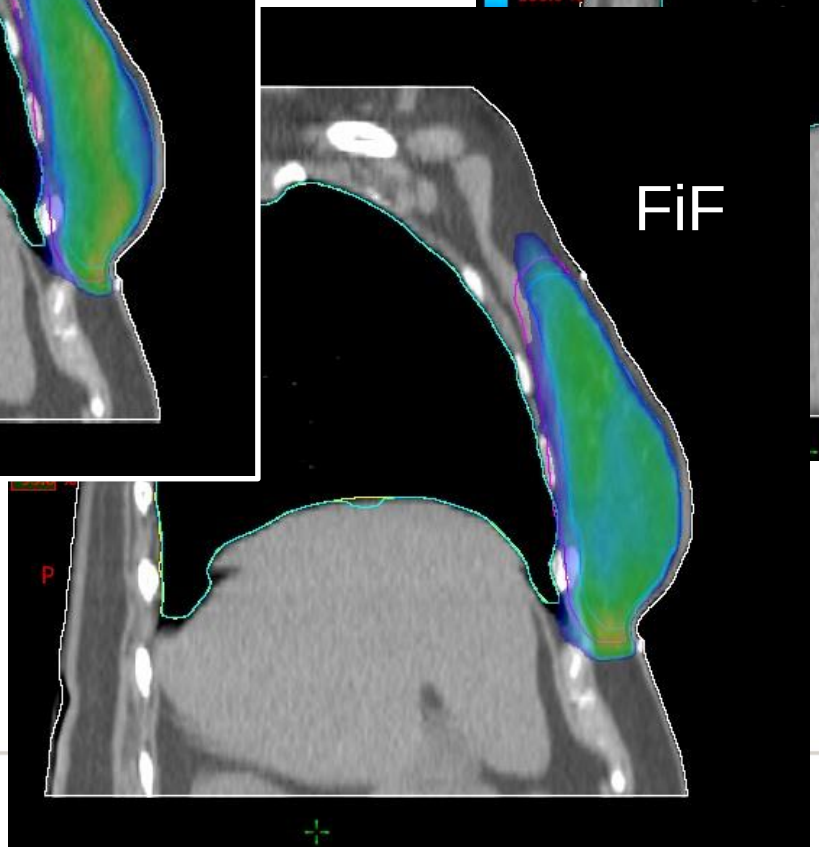




ESTRO School

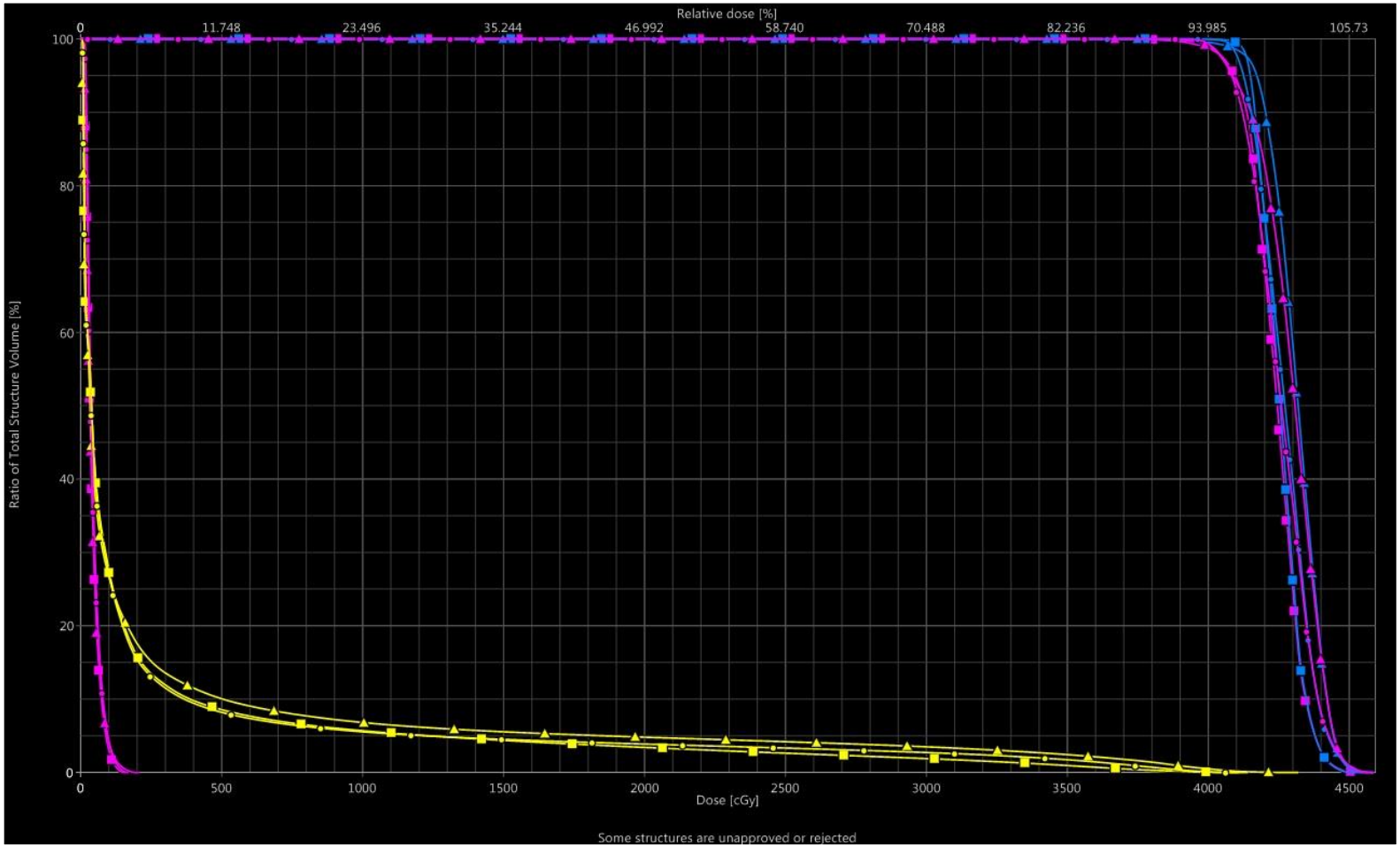






ESTRO School

DVH



- ■ IMRT
- ▲ Wedges
- ● FiF

ESTRO School

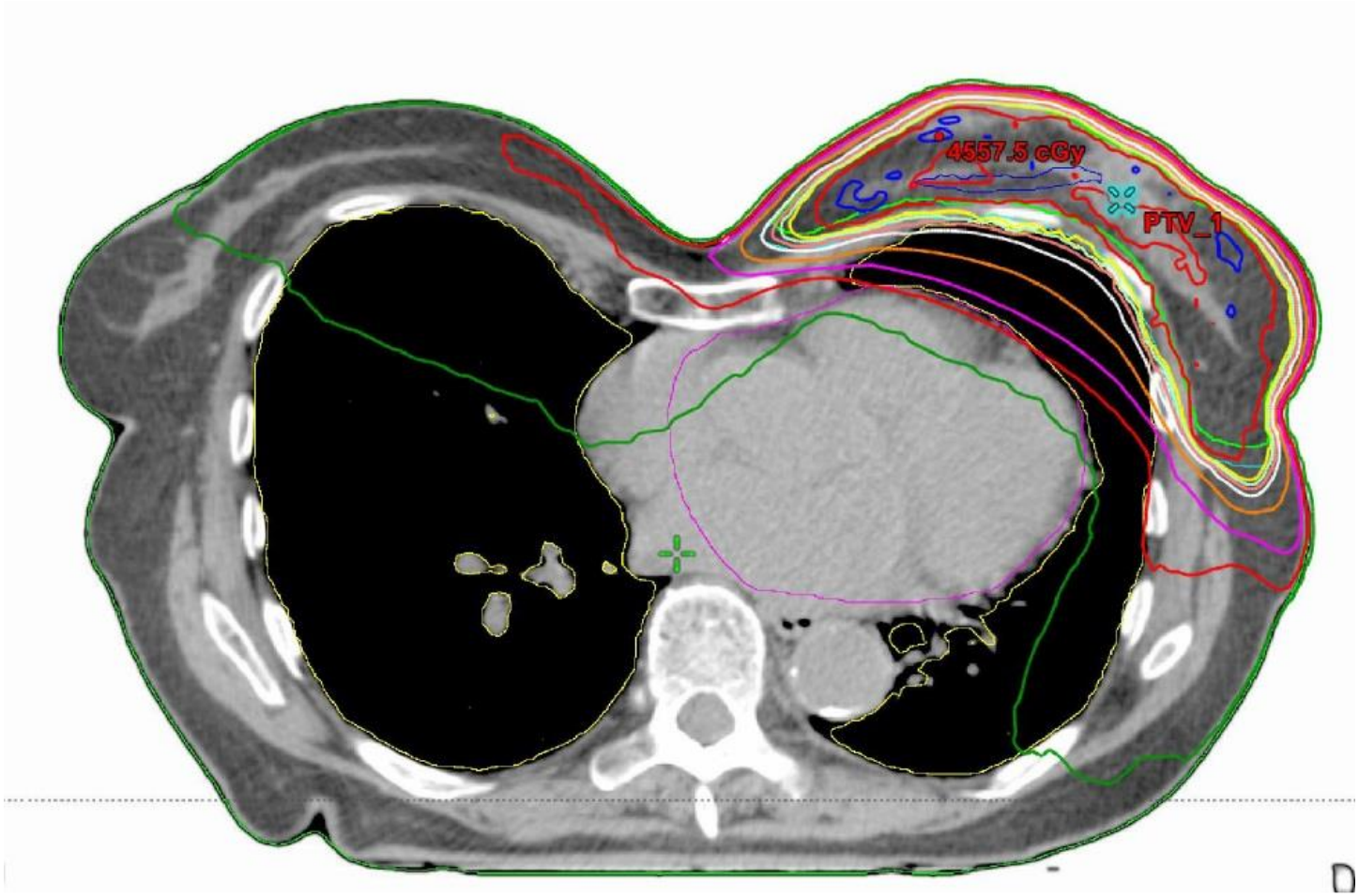
DVH values

	Lungs		Heart			
	V20	MLD	V20	V10	V5	MHD
FiF	3,9	230	0	0	0	44
Wedges	4,8	269	0	0	0	41
IMRT	3,4	218	0	0	0	41

Breast Left RA

- 16 x 2,66 Gy

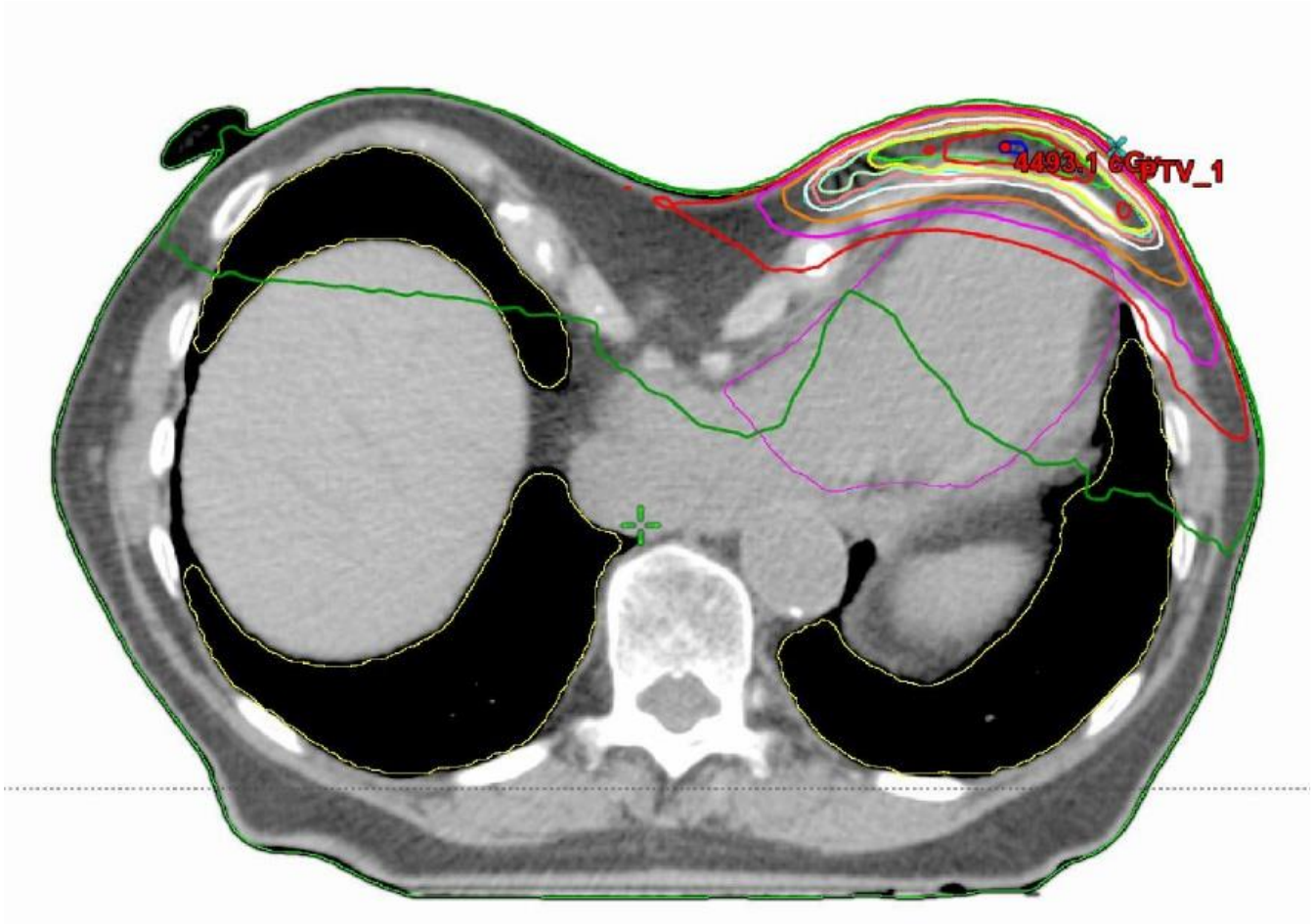
Isodoses

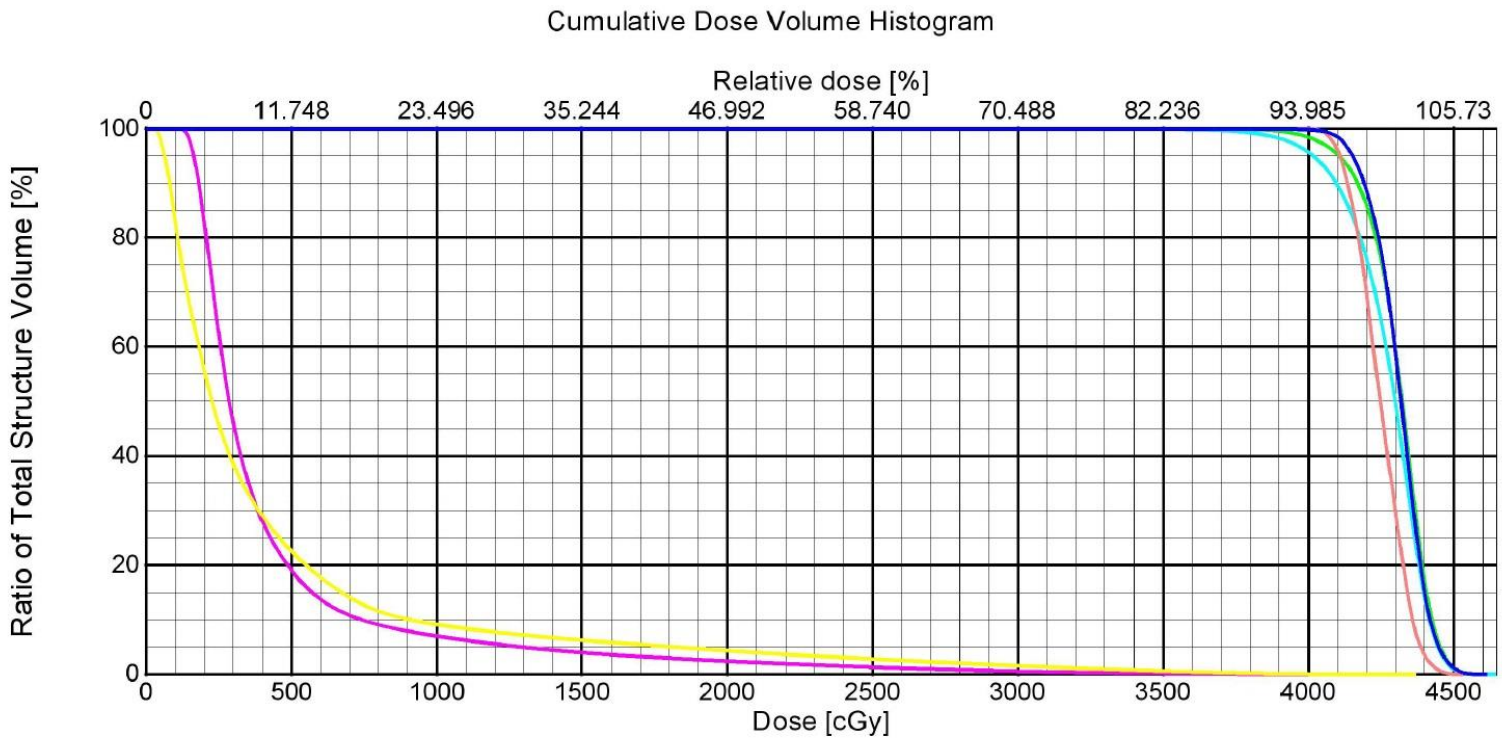


Isodoses

ESTRO School

Isodoses





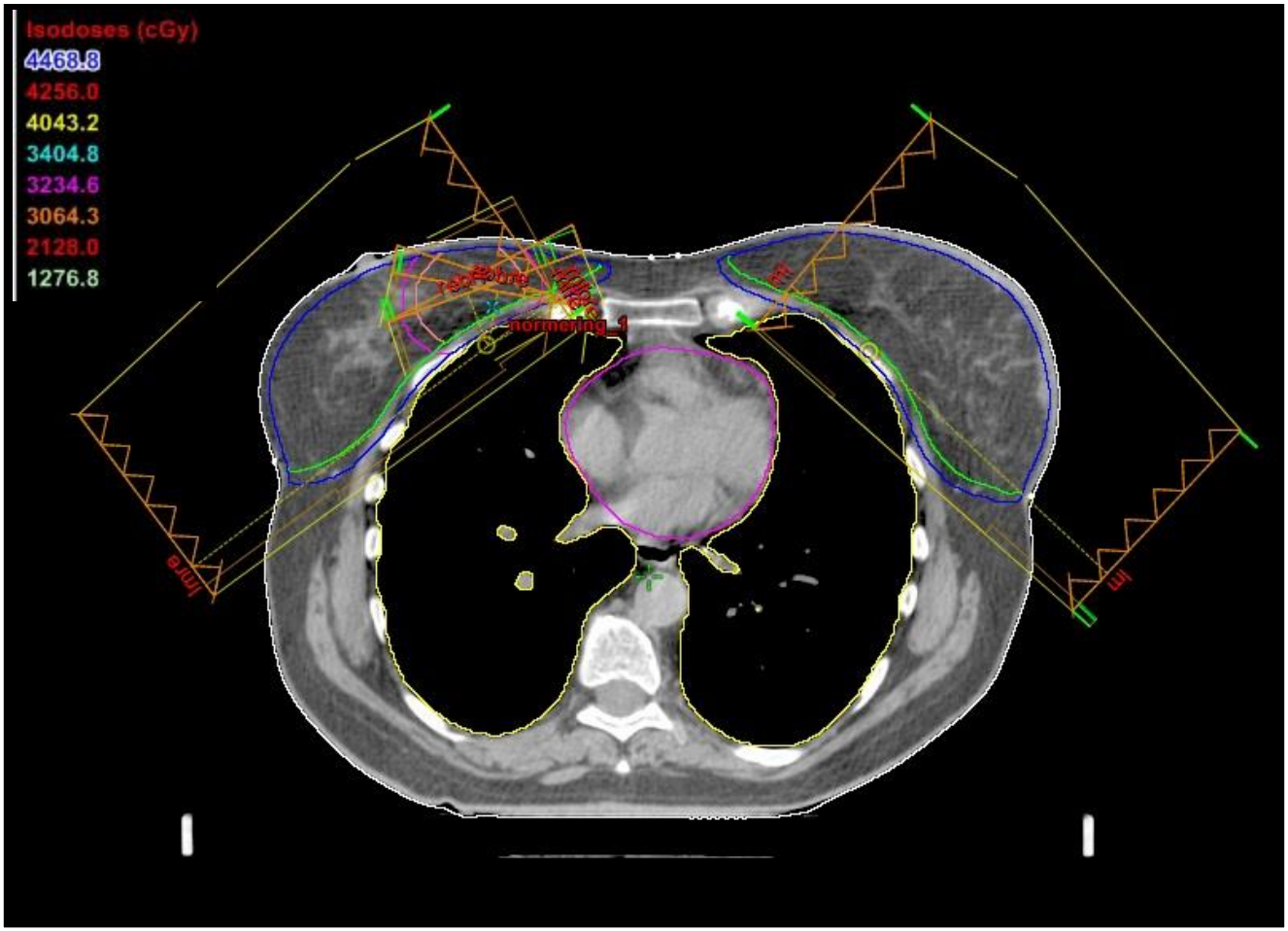
Structure	Structure Status	Coverage [%/%]	Volume	Min Dose	Max Dose	Mean Dose	Modal Dose	Median Dose	Std Dev
CTV_4256	Approved	100.0 / 100.0	456.6 cm³	3678.1 cGy	4648.3 cGy	4307.7 cGy	4353.8 cGy	4322.9 cGy	107.2 cGy
PTV_4256	Approved	100.0 / 100.0	594.0 cm³	3174.2 cGy	4648.3 cGy	4273.5 cGy	4336.7 cGy	4298.9 cGy	135.0 cGy
Heart	Approved	100.0 / 100.0	746.6 cm³	110.1 cGy	4171.5 cGy	430.0 cGy	229.1 cGy	285.6 cGy	452.4 cGy
Lungs	Approved	100.0 / 100.0	3763.9 cm³	28.5 cGy	4372.6 cGy	437.5 cGy	95.2 cGy	226.2 cGy	610.5 cGy
Lump	Approved	100.0 / 100.2	3.5 cm³	3991.0 cGy	4533.5 cGy	4248.6 cGy	4222.6 cGy	4247.7 cGy	86.1 cGy
CTVlump_4256	Approved	100.0 / 99.9	69.7 cm³	3844.5 cGy	4616.7 cGy	4312.8 cGy	4337.0 cGy	4319.3 cGy	89.5 cGy

ESTRO School

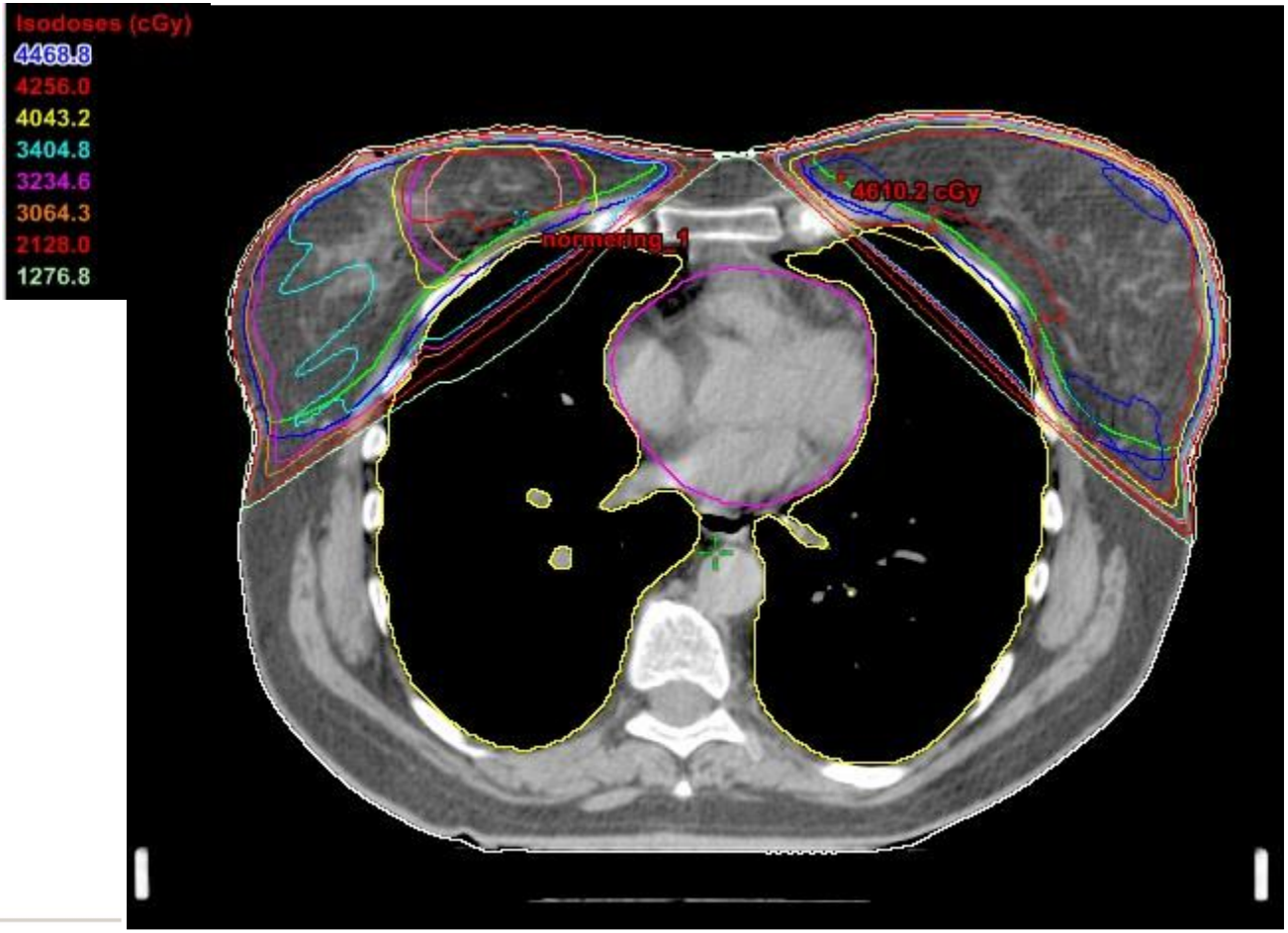
Both Breasts

- Breast left: 16 x 2,66 Gy
- Breast right: 23 x 2,66 Gy on primary tumorbed and 23 x 2,03 Gy on breast

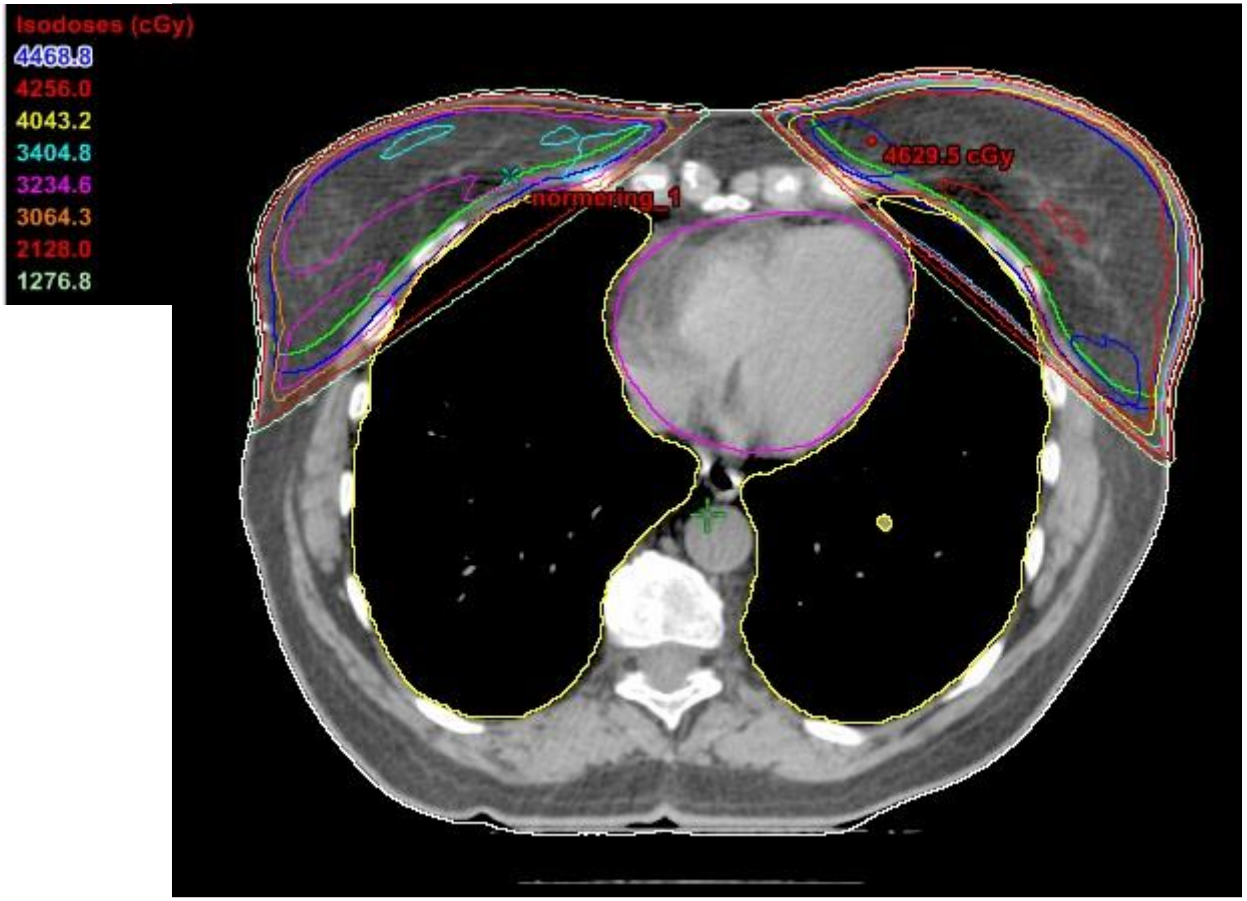
Beams


Isodoses (cGy)
4468.8
4256.0
4043.2
3404.8
3234.6
3064.3
2128.0
1276.8
normering_1

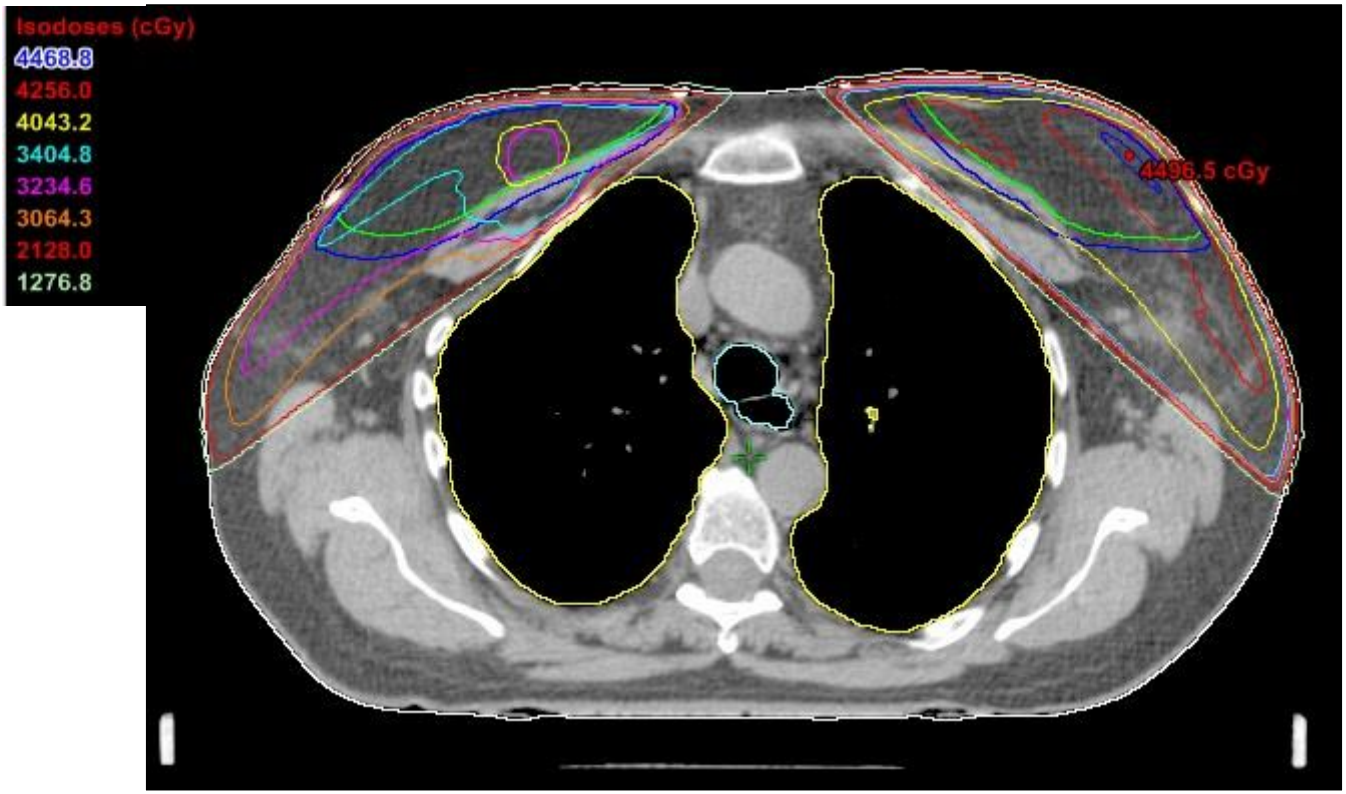
Isodoses


Isodoses (cGy)
4468.8
4256.0
4043.2
3404.8
3234.6
3064.3
2128.0
1276.8
4610.2 cGy
normering_1

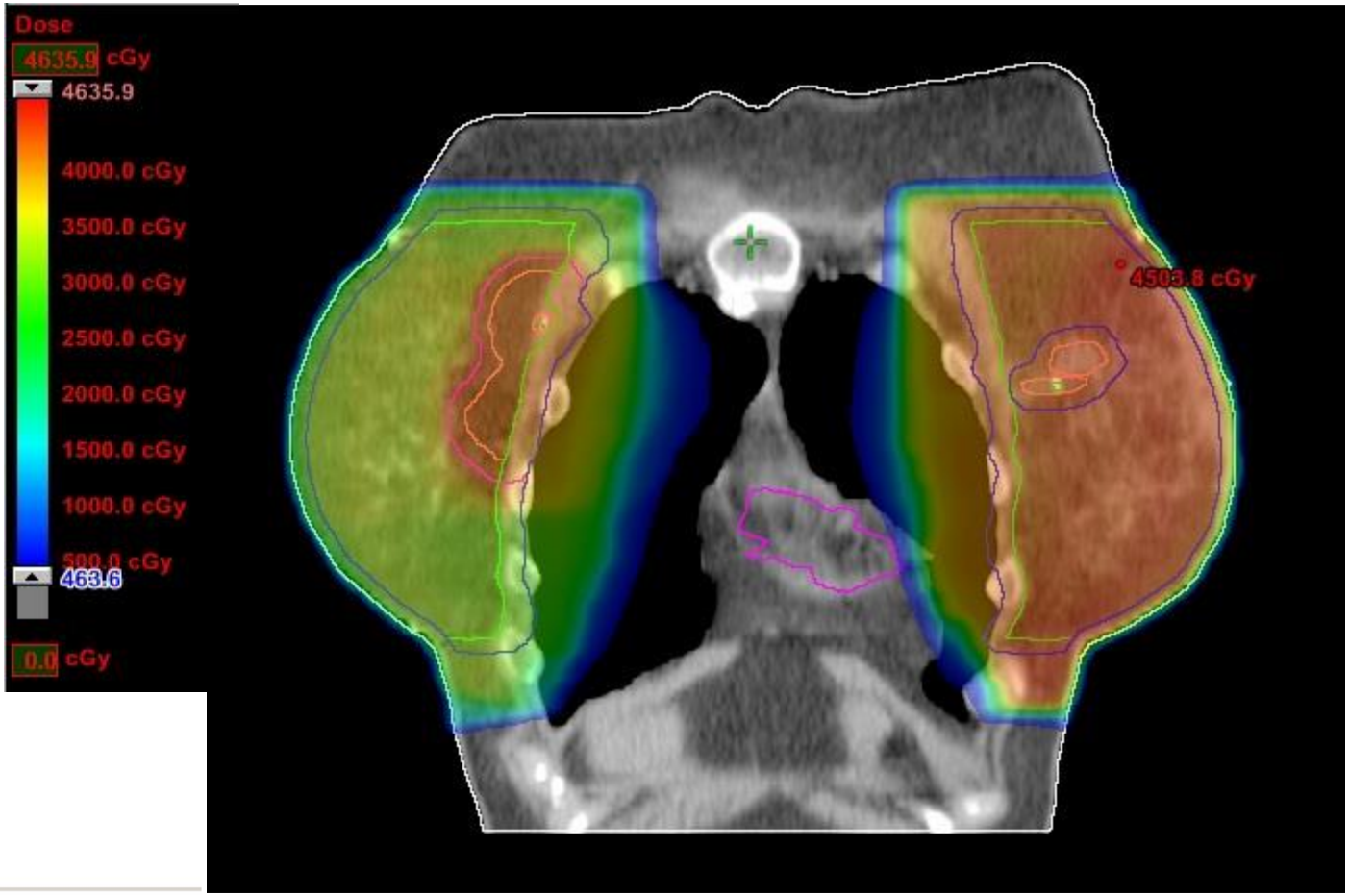
Isodoses


Isodoses (cGy)
4468.8
4256.0
4043.2
3404.8
3234.6
3064.3
2128.0
1276.8
4623.5 cGy

Isodoses


Isodoses (cGy)
4468.8
4256.0
4043.2
3404.8
3234.6
3064.3
2128.0
1276.8
4496.5 cGy

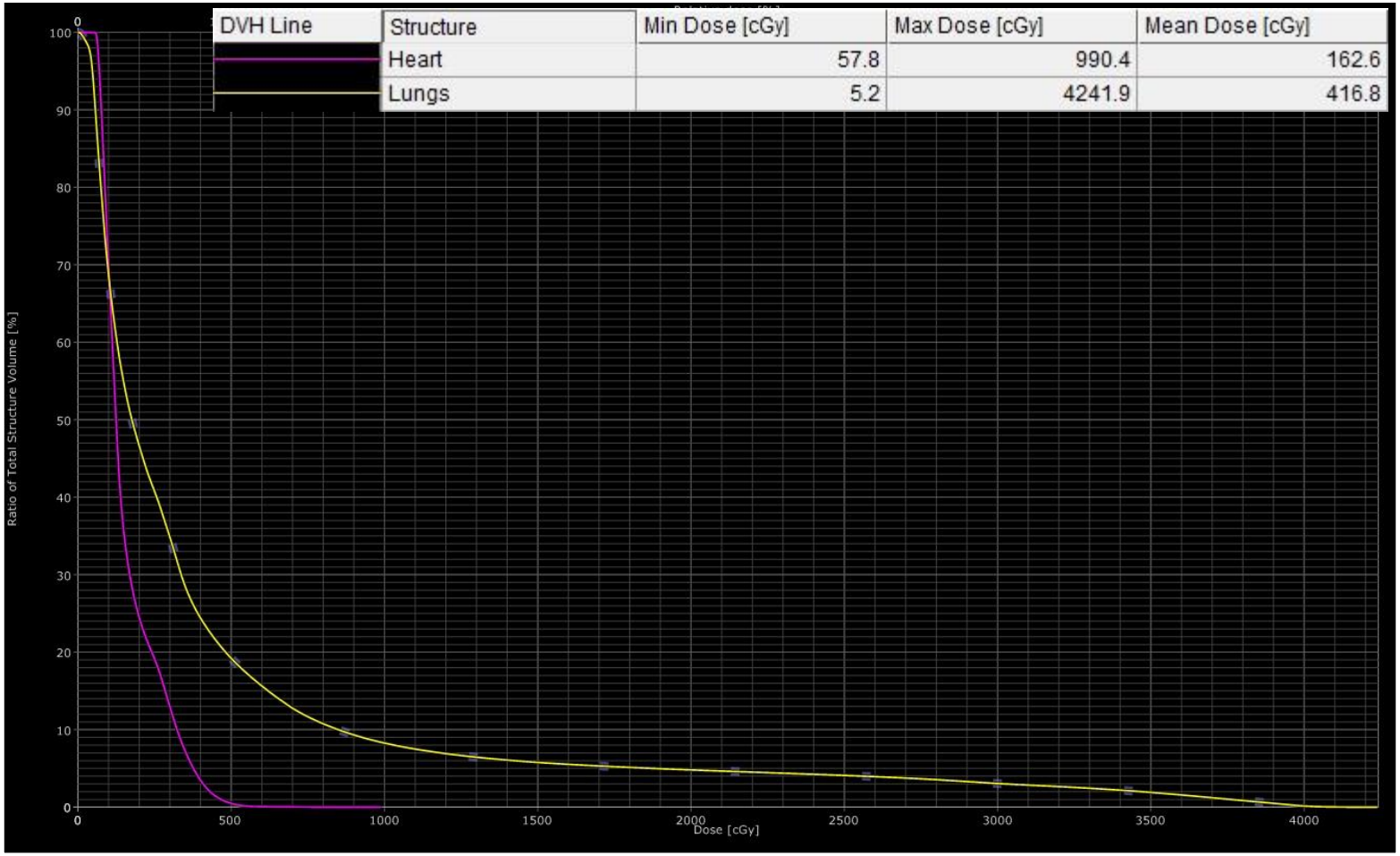
Isodoses


Dose
4635.9 cGy
4635.9
4000.0 cGy
3500.0 cGy
3000.0 cGy
2500.0 cGy
2000.0 cGy
1500.0 cGy
1000.0 cGy
463.6
0.0 cGy
4503.8 cGy

Isodoses

ESTRO School

DVH



ESTRO School

Treatment de-escalation including APBI

Always less, where is the limit?

institutCurie

Past-President

ESTRO
European Society for RADIOTHERAPY & ONCOLOGY

President-Elect

ECCO
European CanCer Organisation

Philip Poortmans, MD, PhD

Conflict of interest:

I am a radiation oncologist …

… so!

Less local treatment: where is the limit?

1. Introduction
2. The role of radiation therapy in BCT
3. The role of PMRT
4. Interaction with systemic treatment
5. Discussion
6. Conclusions

Less local treatment: introduction

± 1970		± 2000		± 2015
Maximal tolerable treatment	→	*Minimal effective treatment*	→ ?	*No treatment any more*

Less local treatment: introduction

But what do we really know to base this on?

Less local treatment: introduction

Evidence is what we need
To fully inform the patient

Poortmans P, et al. Breast. 2017;31:295-302.

ESTRO School

Medical Radiology Diagnostic Imaging

Seymour H. Levitt
James A. Purdy
Carlos A. Perez
Philip Poortmans
Editors

Technical Basis of Radiation Therapy
Practical Clinical Applications
Fifth Edition

This well-received book, now in its fifth edition, is unique in providing a detailed description of the technological basis of radiation therapy. Another novel feature is the collaborative writing of the chapters by North American and European authors. This considerably broadens the book's perspective and increases its applicability in daily practice throughout the world. The book is divided into two sections. The first covers basic concepts in treatment planning, including essential physics and biological principles related to time-dosefractionation, and explains the various technological approaches to radiation therapy, such as intensity-modulated radiation therapy, tomotherapy, stereotactic radiotherapy, and high and low dose rate brachytherapy. Issues relating to quality assurance, technology assessment, and cost-benefit analysis are also reviewed. The second part of the book discusses in depth the practical clinical applications of the different radiation therapy techniques in a wide range of cancer sites. All of the chapters have been written by leaders in the field. This book will serve to instruct and acquaint teachers, students, and practitioners in the various fields of oncology with the basic technological factors and approaches in radiation therapy.

ISSN 0942-5373
ISBN 978-3-642-11571-4

springer.com

Levitt · Purdy · Perez
Poortmans *Eds.*

Technical Basis of Radiation Therapy

5th Ed.

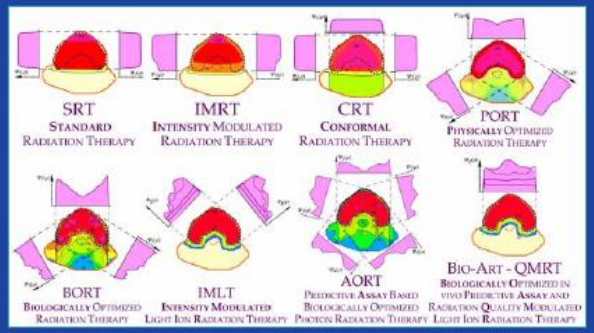
Medical Radiology
Diagnostic Imaging
A.L. Baert
M.F. Reiser
H. Hricak
M. Knauth

Seymour H. Levitt
James A. Purdy
Carlos A. Perez
Philip Poortmans
Editors

Technical Basis of Radiation Therapy

Practical Clinical Applications

5th Edition



Springer

Less local treatment: introduction

Side effects

Radiation therapy:	21st C, only local RT:
- Inconvenience	- 7→5→3→1 weeks
- Skin	- Lowered
- Breast tissue	- No boost ➔ low
- Pulmonary	- Unlikely
- Heart	- Unlikely
- Secondary tumours	- Seldom
- CL breast: more	- Less for older pts/proper techniques

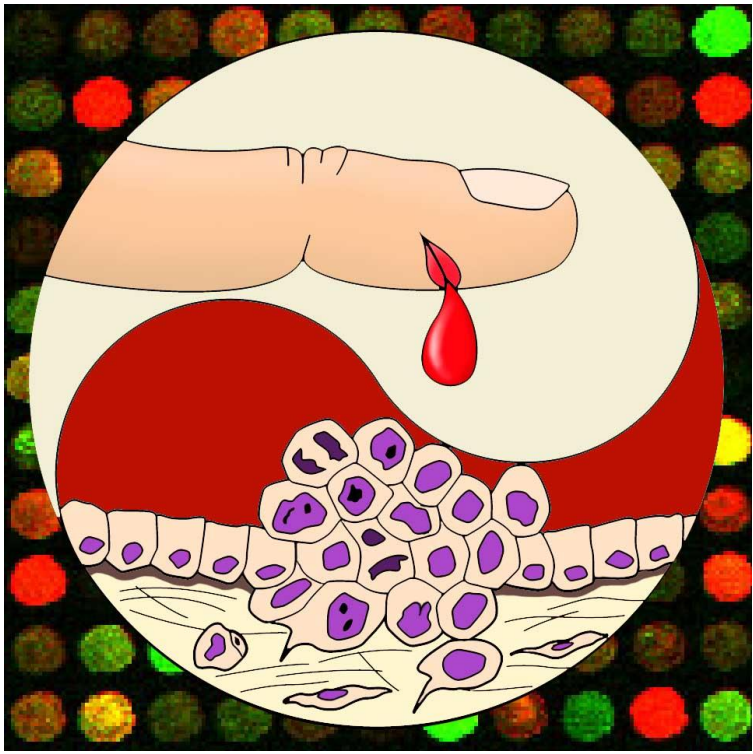
ESTRO School

Wound Response Signature

In vitro Wound Model – 516 genes

Prognostic Significance in

- Breast
- Lung
- Gastric cancer



Less local treatment: where is the limit?

1. Introduction

2. The role of radiation therapy in BCT

3. The role of PMRT

4. Interaction with systemic treatment

5. Discussion

6. Conclusions

ESTRO School

Less local treatment: The role of RT in BCT

Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Lancet 2011; 378: 1707–16

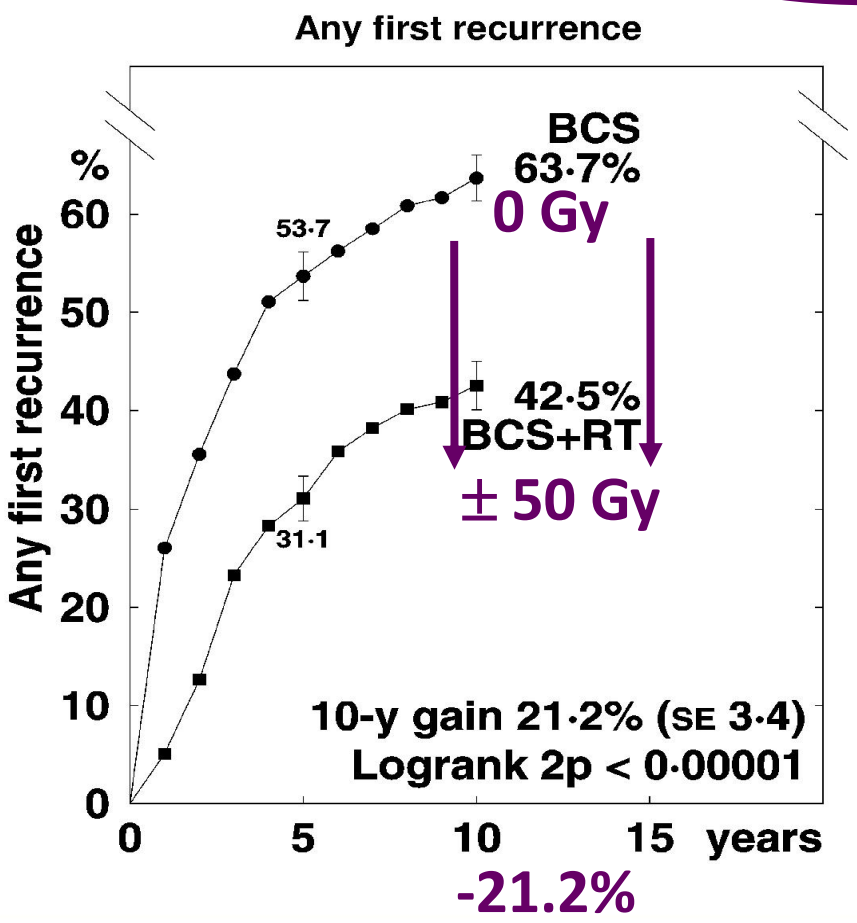
EBCTCG Lancet 2011; 378: 1707–1716

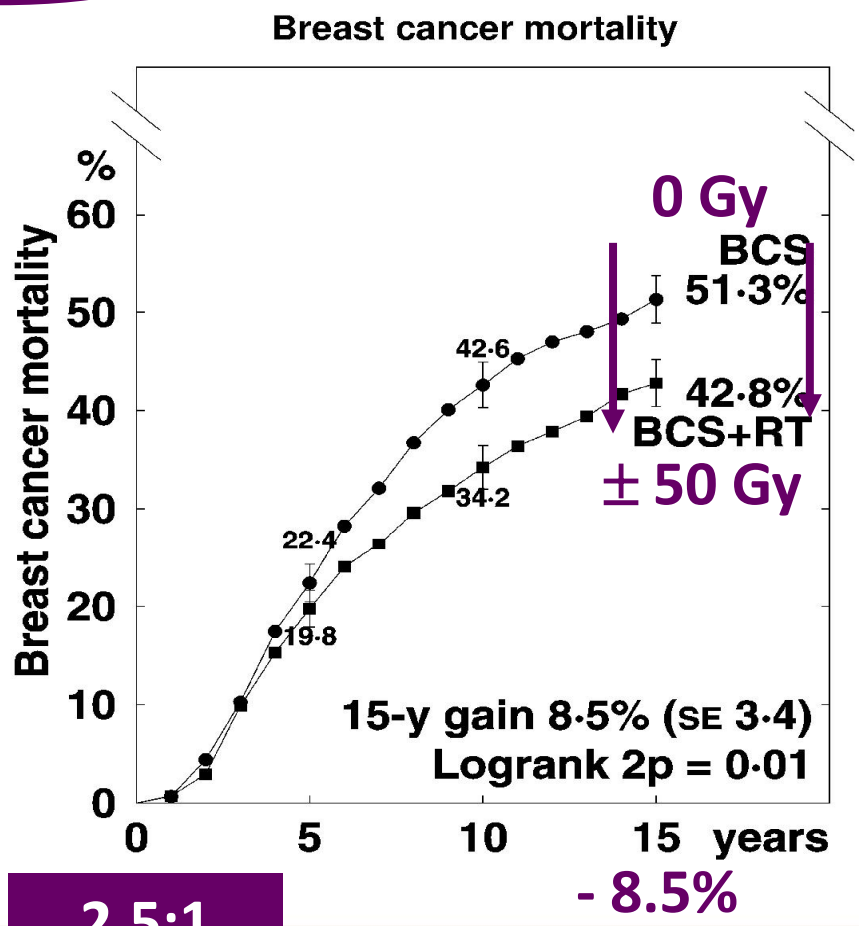
ESTRO School

Less local treatment: The role of RT in BCT

Effect of RT after BCS on recurrence and breast cancer mortality in pN+ women.

1050 pN+ women





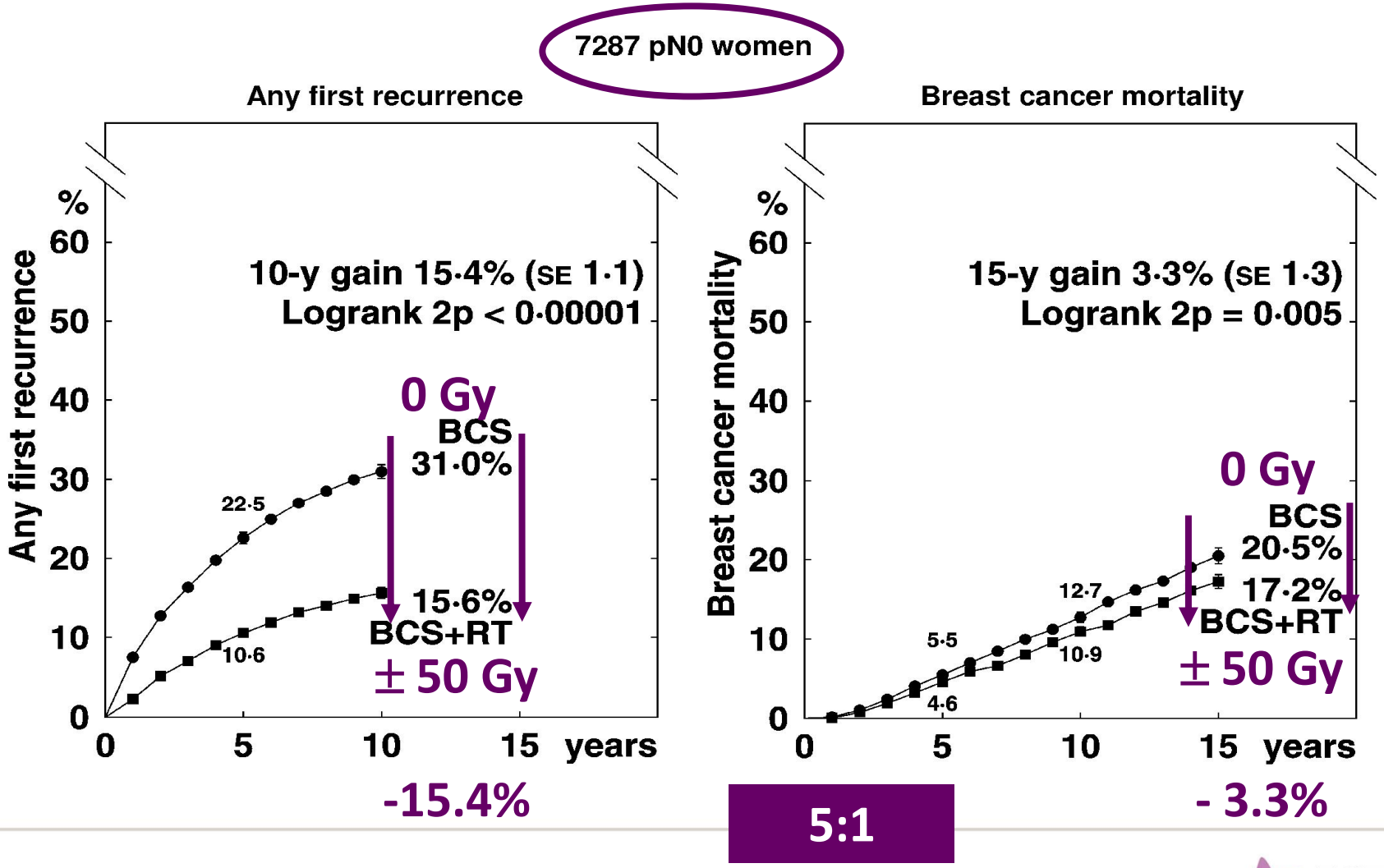
2.5:1

EBCTCG Lancet 2011; 378: 1707–1716

ESTRO School

Less local treatment: The role of RT in BCT

Effect of RT after BCS on recurrence and breast cancer mortality in pN0 women.



EBCTCG Lancet 2011; 378: 1707–1716

ESTRO School

Less local treatment: The role of RT in BCT

RT after lumpectomy - not always necessary?

Less local treatment: The role of RT in BCT

RT after tumorectomy: not always required?

Overview of prospective clinical trials evaluating postoperative radiation therapy omission.

Author, Year	Patients	Study design	Local relapse	DFS	OS	Median FU
Fisher et al., 2002 [11]	1009	TAM vs. placebo + RT vs. TAM + RT	16.5% vs. 9.3% vs. 2.8% ($p = 0.008$; $p < 0.0001$; $p = 0.01$)	–	93% vs. 94% vs. 93% ($p = 0.93$)	87.5 months
Fyles et al., 2004 [7]	769	TAM vs. TAM + RT	7.7% vs. 0.6% at 5 years ($p < 0.001$)	84% vs. 91% at 5 years ($p = 0.004$)	92.8% vs. 93.2% ($p = 0.83$)	67.2 months
Pötter et al., 2007 [9]	869	TAM/AI vs. TAM/AI + RT	5.1% vs. 0.4% ($p = 0.0001$)	HR 3.48 ($p = 0.0021$)	94.5% vs. 97.9% ($p = 0.18$)	53.8 months
Hughes et al., 2013 [10]	636	TAM vs. TAM + RT	9% vs. 2% ($p < 0.001$)	–	66% vs. 67% at 10 years ($p = 0.64$)	151.2 months
Blamey et al., 2013 [12]	1135	- without or with TAM - without or with RT 2 × 2 factorial design	- 13% vs. 4% - 11% vs. 3% Both treatments 0% ($p < 0.001$)	–	96% at 10 years	167 months
Kunkler et al., 2013 [13]	1326	TAM/AI vs. TAM/AI + RT	4.1% vs. 1.3% ($p = 0.0002$)	–	93.9% vs. 93.9% ($p = 0.34$)	60 months

Abbreviations: DFS, disease-free survival; OS, overall survival; FU, follow up; TAM, tamoxifen; AI, aromatase inhibitors; RT, radiation therapy; HR, Hazard Ratio.

Poortmans P, et al. Breast. 2017;31:295-302.

ESTRO School

Less local treatment: The role of RT in BCT

RT after tumorectomy: not always required?

- 0.5% (1% still acceptable?) per year = limit for LRR
- Mind late relapses!
- Role of systemic treatment?
- Website: https://www.tuftsmedicalcenter.org/ibtr/

Less local treatment: The role of RT in BCT

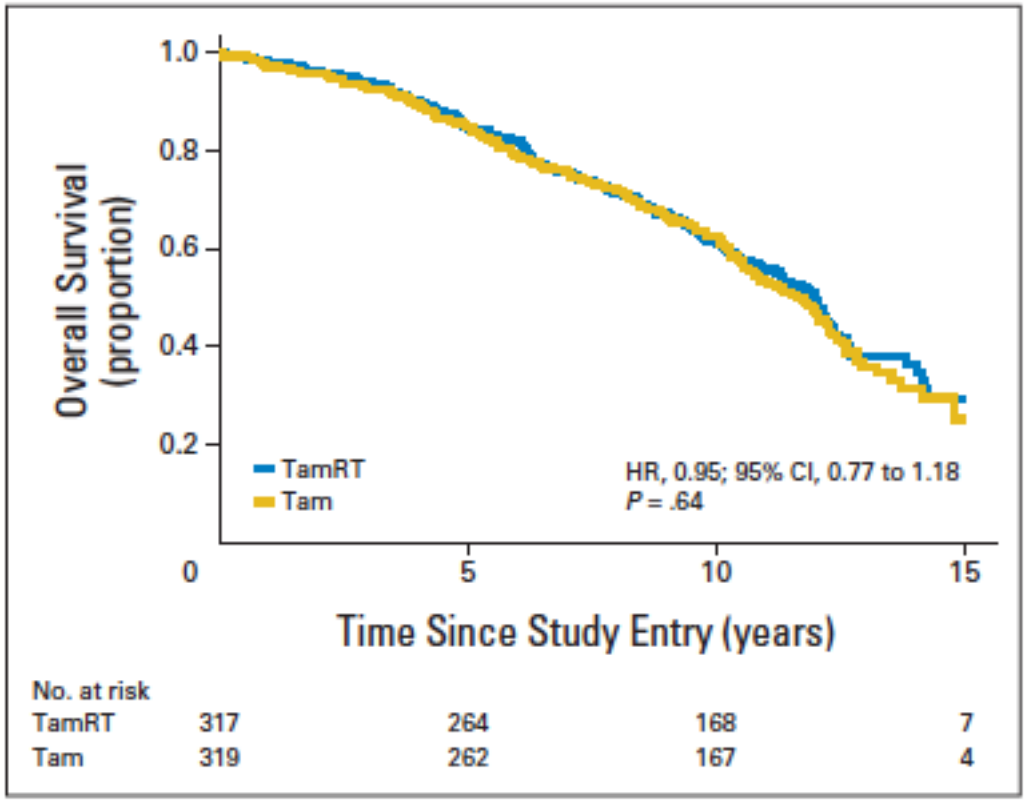
RT after tumorectomy: not always required?

Who decides?

Low risk: ➔ the same in NL, UK, B, It, D, …?

- Countries with 5 y endocrine therapy for ALL ER+
- ←➔ Countries with endocrine therapy starting at intermediate risk *(≥ 5% recurrence or survival benefit)*
- Side effects:
  - Very (too?) well documented and known for RT
  - Emerging knowledge for systemic therapy…

Less local treatment: The role of RT in BCT



- 8% LRR benefit at 10y
- 3% died < breast ca
- 49% died unrelated

Pt selection: EORTC 22922 = 82.3% 10y OS

Hughes KS, et al. JCO 2013;31:2382-7

ESTRO School

Less local treatment: The role of RT in BCT

Ann Surg Oncol (2014) 21:408–415
DOI 10.1245/s10434-013-3233-x

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

Breast-Conservative Surgery With and Without Radiotherapy in Patients Aged 55–75 Years With Early-Stage Breast Cancer: A Prospective, Randomized, Multicenter Trial Analysis After 108 Months of Median Follow-up

C. Tinterri, MD[1], W. Gatzemeier, MD[1], A. Costa, MD[2], M. A. Gentilini, PhD[3], V. Zanini, MD[4], L. Regolo, MD[4], C. Pedrazzoli, MD[5], E. Rondini, MD[5], C. Amanti, MD[6], G. Gentile, MD[7], M. Taffurelli, MD[8], P. Fenaroli, MD[9], C. Tondini, MD[9], G. Sacchetto, MD[10], P. Sismondi, MD[11], R. Murgo, MD[12], M. Orlandi, MD[13], E. Cianchetti, MD[14], and C. Andreoli, MD[1]

Tinterri C, et al. Ann Surg Oncol. 2014;21:408-415.

ESTRO School

Less local treatment: The role of RT in BCT

N = 749

Unifocal; infiltrating; ≤ 25 mm; N0-1a; no EIC; no (L)VI

96.5% adjuvant systemic treatment:

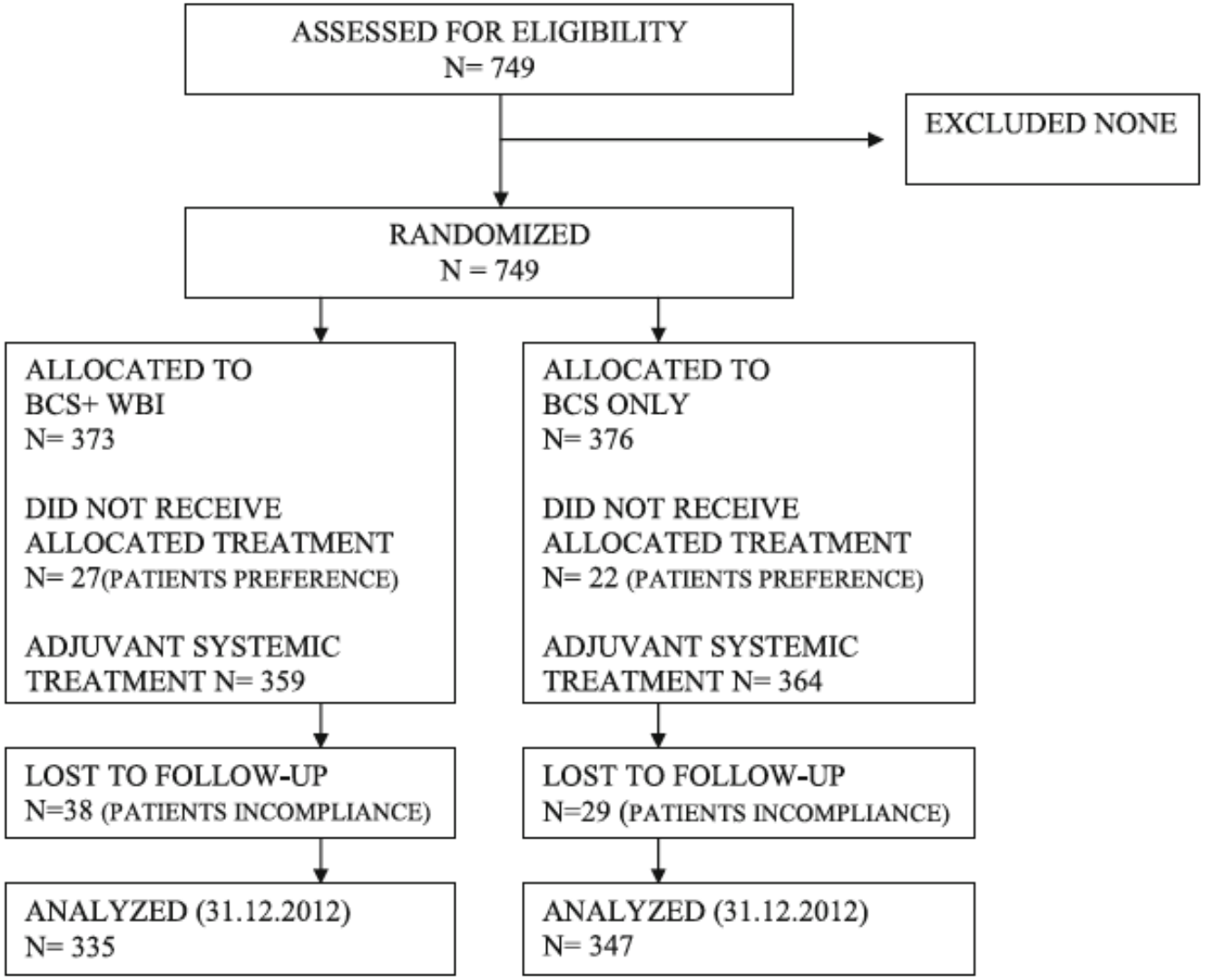
- 81.3% HT
- 9.5% ChT
- 5.7% both

Tinterri C, et al. Ann Surg Oncol. 2014;21:408-415.

ESTRO School

Less local treatment: The role of RT in BCT

STRUCTURE 1 Consort diagram RT 55–75



Tinterri C, et al. Ann Surg Oncol. 2014;21:408-415.

ESTRO School

Less local treatment: The role of RT in BCT

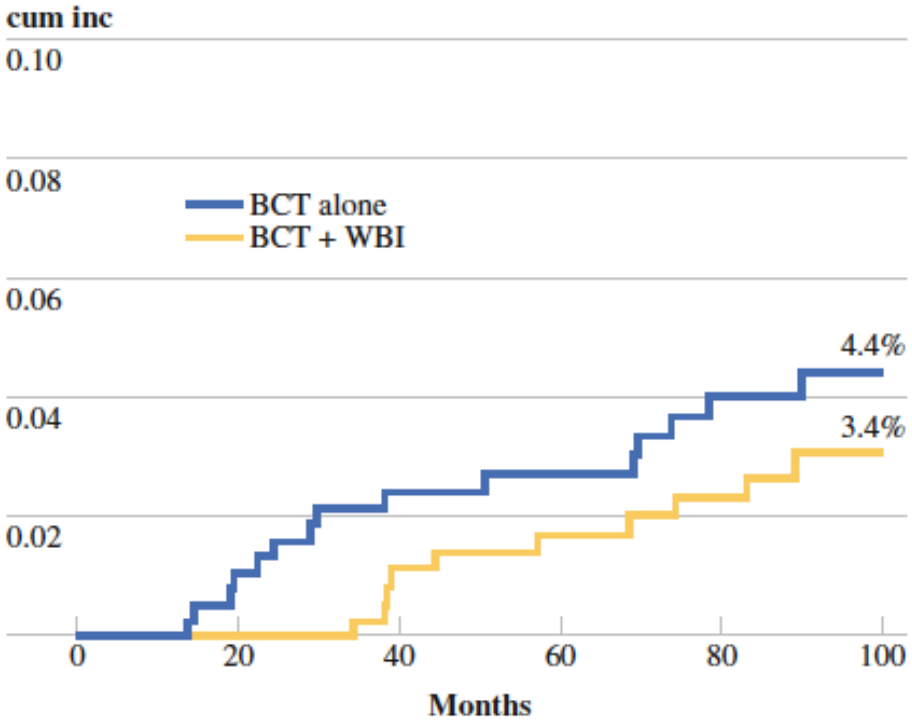


FIG. 1 Nine-year cumulative incidence of in-breast recurrence

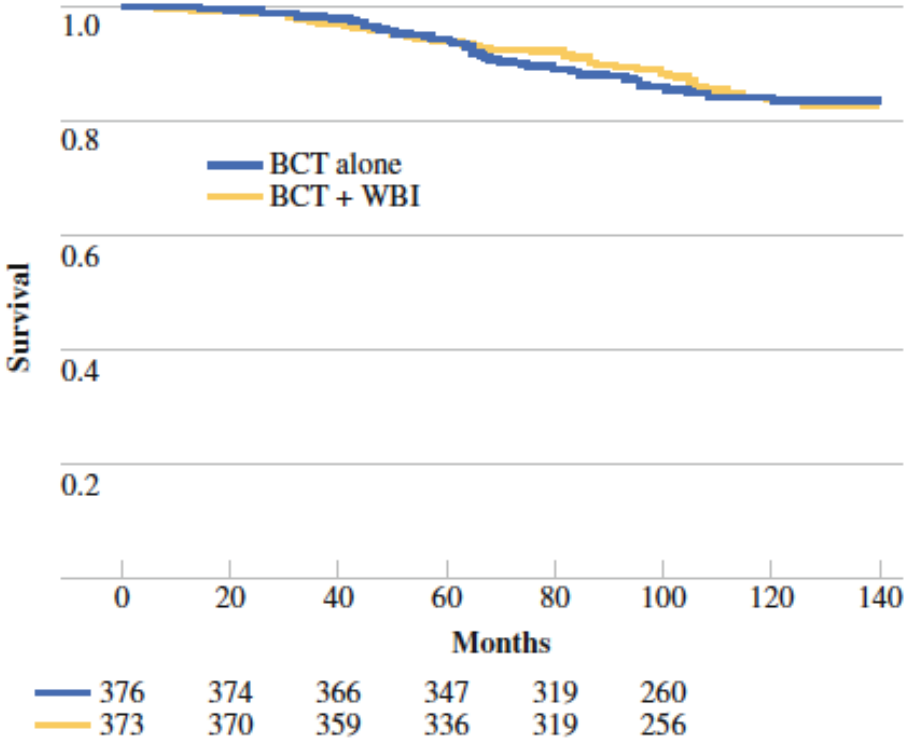


FIG. 2 Overall Survival (108 months)

Tinterri C, et al. Ann Surg Oncol. 2014;21:408-415.

ESTRO School

Less local treatment: The role of RT in BCT

*These data are **promising** and suggest that **WBI after BCS can be omitted in selected** patients with early stage breast cancer without exposing them to an increased risk of local recurrence and death. **Longer follow-up is needed** to further consolidate these results.*

Tinterri C, et al. Ann Surg Oncol. 2014;21:408-415.

Less local treatment: The role of RT in BCT

…***promising*** … ***WBI after BCS can be omitted in selected*** … ***Longer follow-up is needed*** …

Personal notes:

-An estimated ½ of those pts would not get adjuvant systemic treatment according to the Dutch guidelines

-Median FU = 108 months = 9 years

Tinterri C, et al. Ann Surg Oncol. 2014;21:408-415.

ESTRO School

Less local treatment: The role of RT in BCT

ELSEVIER

European Journal of Cancer 40 (2004) 998–1005

European Journal of Cancer

www.ejconline.com

Radiation therapy after breast-conserving surgery: first results of a randomised clinical trial in patients with low risk of recurrence

K.-J. Winzer[a], R. Sauer[b], W. Sauerbrei[c], E. Schneller[d], W. Jaeger[e], M. Braun[f], J. Dunst[g], T. Liersch[h], M. Zedelius[i], K. Brunnert[j], H. Guski[k], C. Schmoor[c], M. Schumacher[c,*] for the German Breast Cancer Study Group (GBSG)

Winzer K-J, et al. Eur J Cancer. 2004;40:998–1005.

ESTRO School

Less local treatment: The role of RT in BCT

N =361 patients (1991-1998); age 45–75 years

pT1pN0M0; GI-II; ER+

Median follow-up of 5.9 years

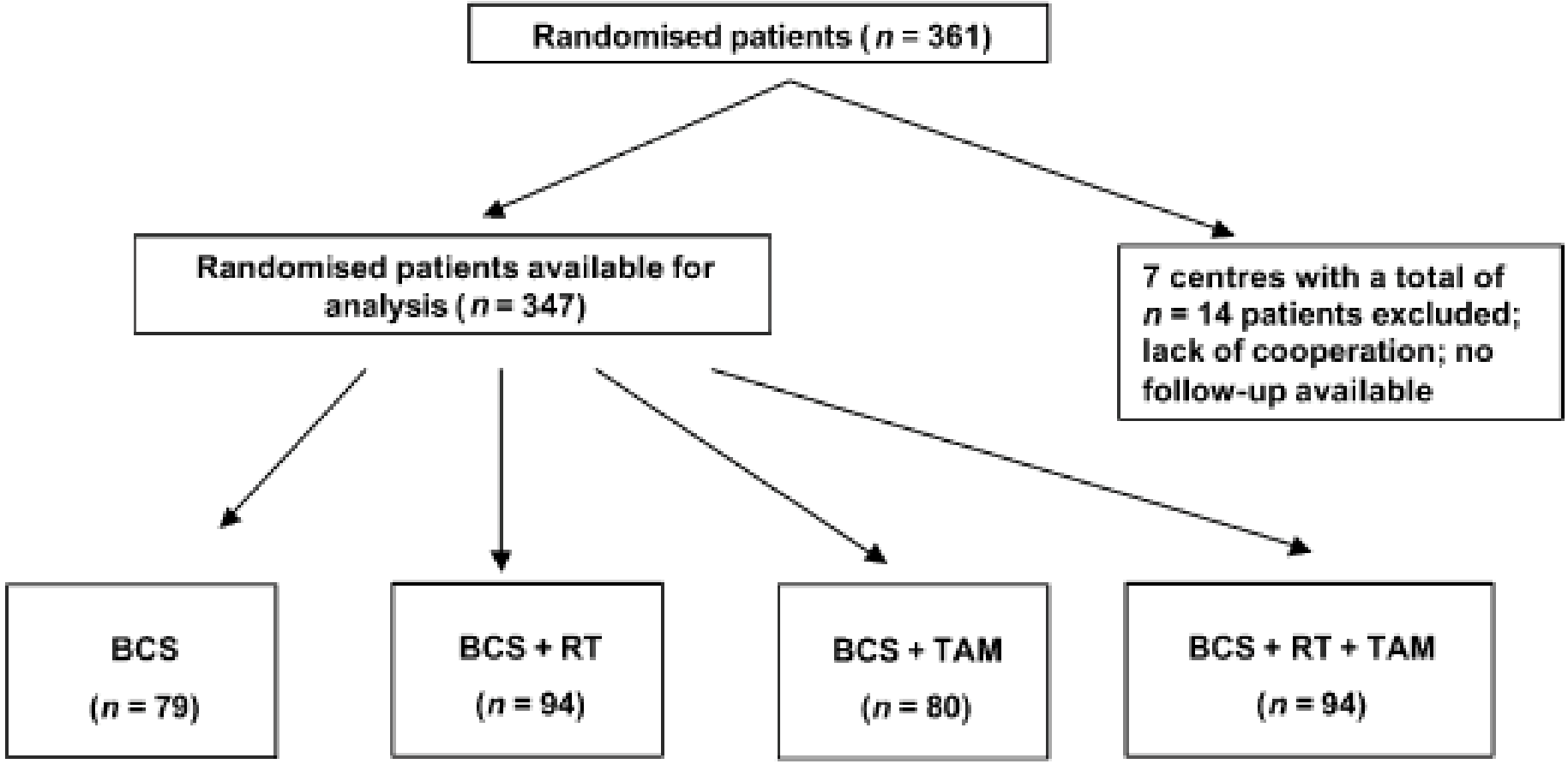
2x2 clinical trial of factorial design:

- +/- radiotherapy &
- +/- tamoxifen (2 years)

Winzer K-J, et al. Eur J Cancer. 2004;40:998–1005.

ESTRO School

Less local treatment: The role of RT in BCT



Winzer K-J, et al. Eur J Cancer. 2004;40:998–1005.

ESTRO School

Less local treatment: The role of RT in BCT

Table 2
Location of first event and number of deaths

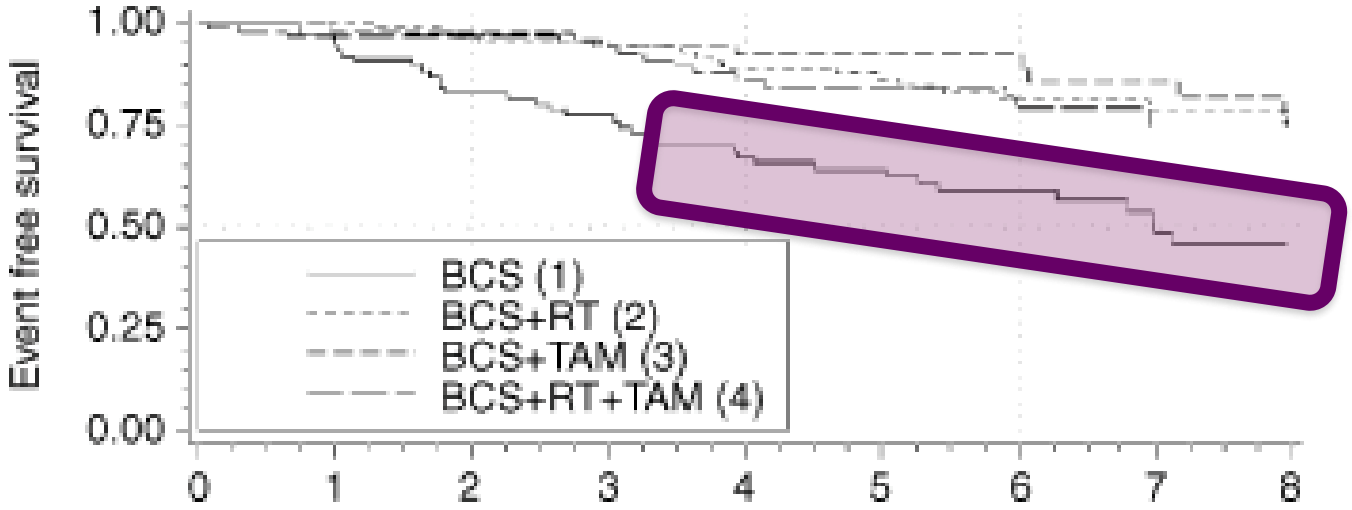
Location of first event	Therapy				
	BCS ($n=79$)	BCS + RT ($n=94$)	BCS + TAM ($n=80$)	BCS + RT + TAM ($n=94$)	Total ($n=347$)
No event	43	76	71	80	270
Ipsilateral breast					
- invasive	22	3	2	3	30
- in situ	1	1	0	0	2
Ipsilateral lymph nodes	0	1	0	0	1
Distant metastases	4	5	2	0	11
Contralateral breast	1	2	0	2	5
Second carcinoma					
non-breast	3	5	3	4	15
Several locations	2	0	1	0	3
Death without recurrence	3	1	1	5	10
Total	36	18	9	14	77
All events (DDFS)	15	14	7	11	48
All deaths	8	4	3	6	21

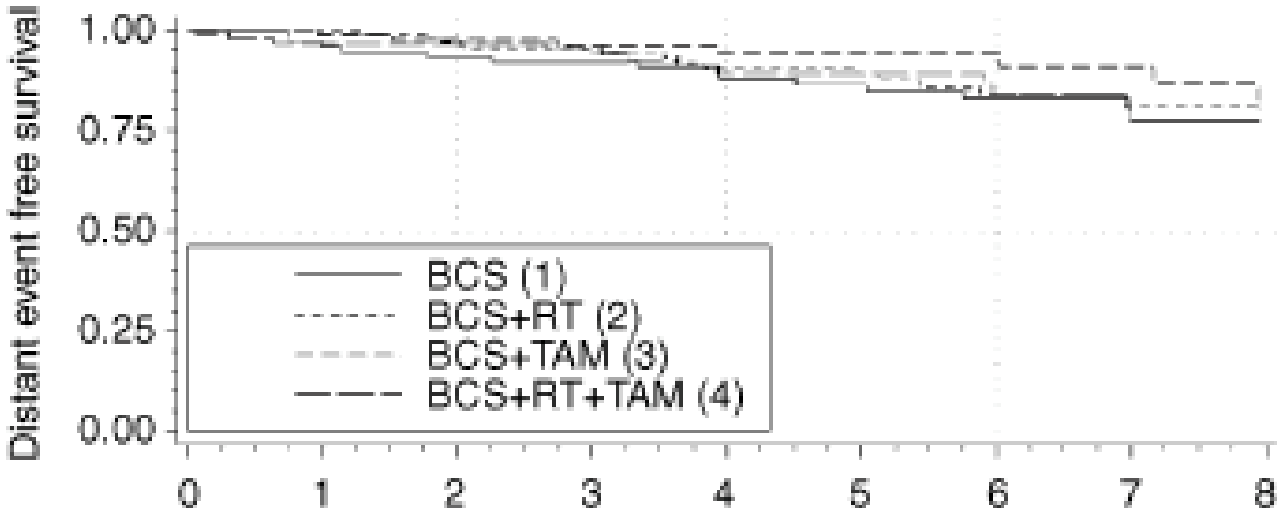
BCS, breast-conserving surgery; RT, radiotherapy; TAM, tamoxifen; DDFS, distant death-free survival

Winzer K-J, et al. Eur J Cancer. 2004;40:998–1005.

ESTRO School

Less local treatment: The role of RT in BCT





Winzer K-J, et al. Eur J Cancer. 2004;40:998–1005.

ESTRO School

Less local treatment: The role of RT in BCT

Mainly due to the presence of local recurrences, the ***event rate was about three times higher in the group with BCS*** *only …*

… even in patients with a favourable prognosis, the ***avoidance of radiotherapy and tamoxifen after BCS increases the rate of local recurrences*** *substantially.*

Winzer K-J, et al. Eur J Cancer. 2004;40:998–1005.

ESTRO School

Less local treatment: The role of RT in BCT

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejcancer.info

Radiotherapy or tamoxifen after conserving surgery for breast cancers of excellent prognosis: British Association of Surgical Oncology (BASO) II trial ☆

R.W. Blamey [a,j], T. Bates [b,*,j], U. Chetty [c,j], S.W. Duffy [d,j], I.O. Ellis [a,j], D. George [e,j], E. Mallon [f,j], M.J. Mitchell [a,j], I. Monypenny [g,j], D.A.L. Morgan [a,j], R.D. Macmillan [a,j], J. Patnick [h,j], S.E. Pinder [i,j]

Blamey RW, et al. Eur J Cancer. 2013;49:2294-302.

ESTRO School

Less local treatment: The role of RT in BCT

N = 1135

Invasive; < 20 mm; N0; G1 or good prognosis subtype

2x2 clinical trial of factorial design:

- +/- radiotherapy &
- +/- tamoxifen

Trial entry was allowed to either comparison or both.

Less local treatment: The role of RT in BCT

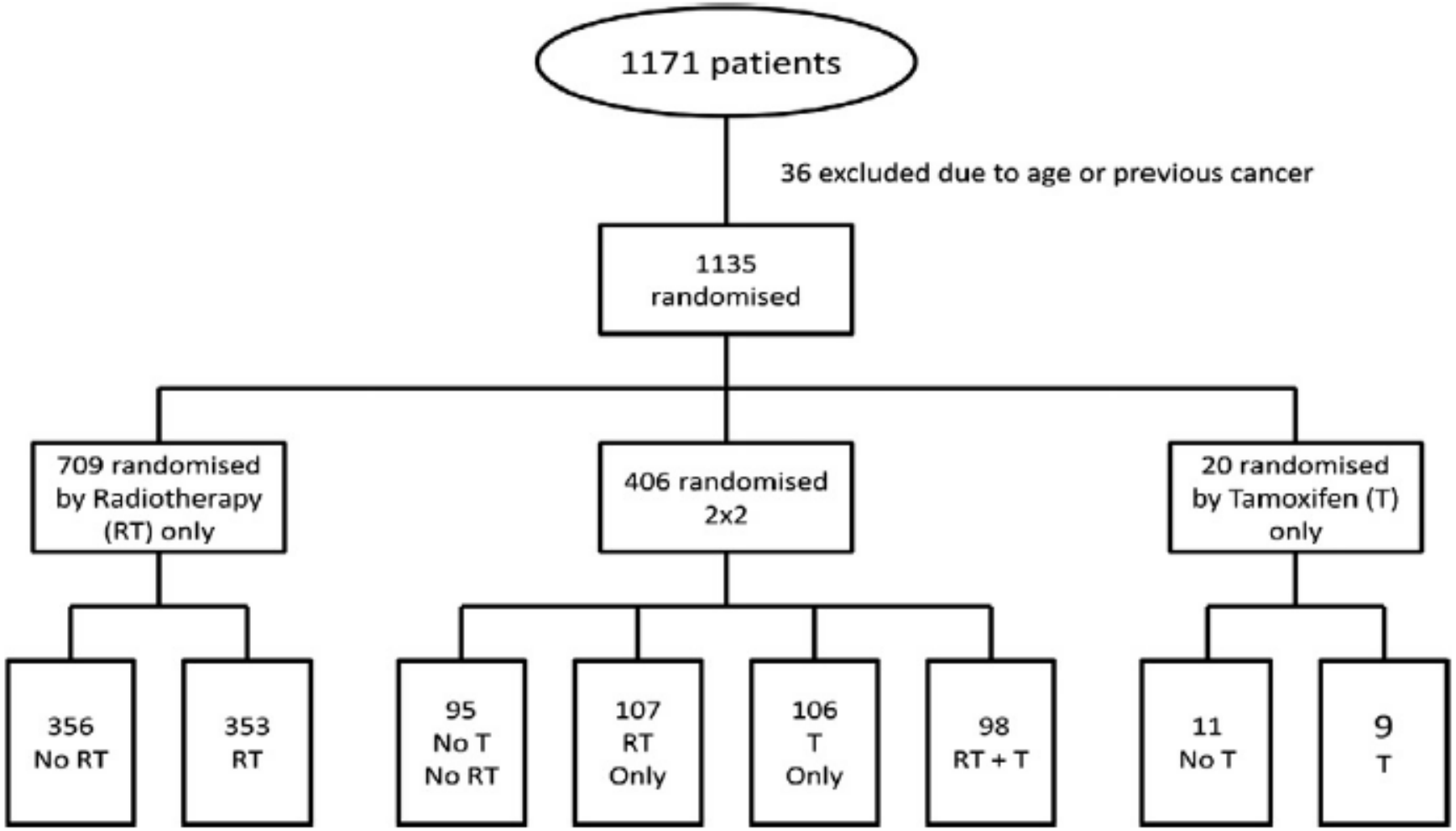


Fig. 1. Design and patient recruitment into British Association of Surgical Oncology (BASO) II trial.

Blamey RW, et al. Eur J Cancer. 2013;49:2294-302.

ESTRO School

Less local treatment: The role of RT in BCT

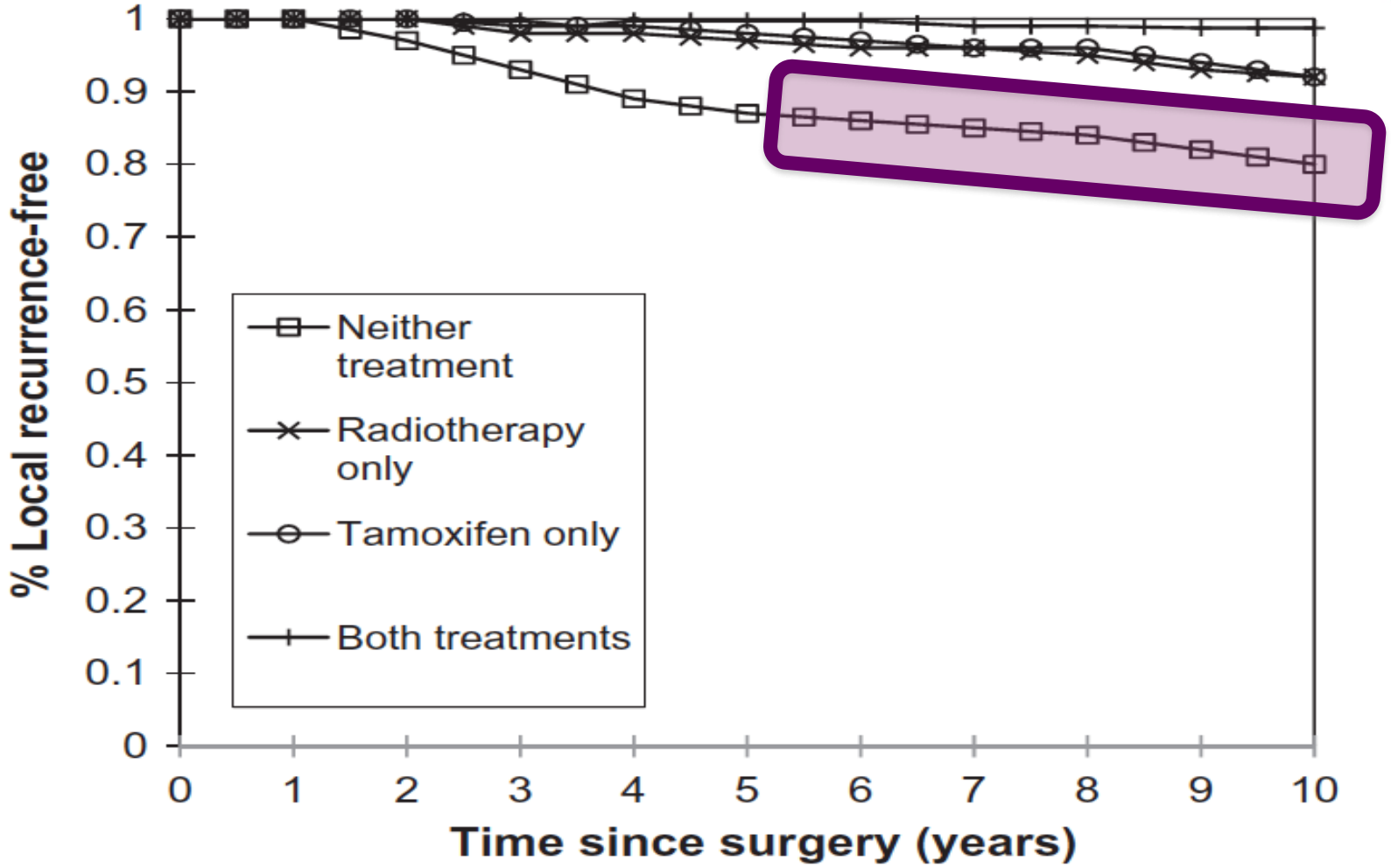


Fig. 2. Survival to first local recurrence by treatment actually received.

Blamey RW, et al. Eur J Cancer. 2013;49:2294-302.

ESTRO School

Less local treatment: The role of RT in BCT

Even in these patients with tumours of excellent prognosis, ***LR after conservative surgery without adjuvant therapy was still very high****. This was reduced to a similar extent by either radiotherapy or tamoxifen but to a greater extent by the receipt of both treatments.*

Blamey RW, et al. Eur J Cancer. 2013;49:2294-302.

ESTRO School

Less local treatment: The role of RT in BCT

… ***LR after conservative surgery without adjuvant therapy was still very high*** …

Personal note:

- Virtually none of those pts would get adjuvant systemic treatment according to the Dutch guidelines

Less local treatment: The role of RT in BCT

Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial

Ian H Kunkler, Linda J Williams, Wilma J L Jack, David A Cameron, J Michael Dixon, on behalf of the PRIME II investigators

Kunkler IH, et al. Lancet Oncol 2015;16:266-73.

ESTRO School

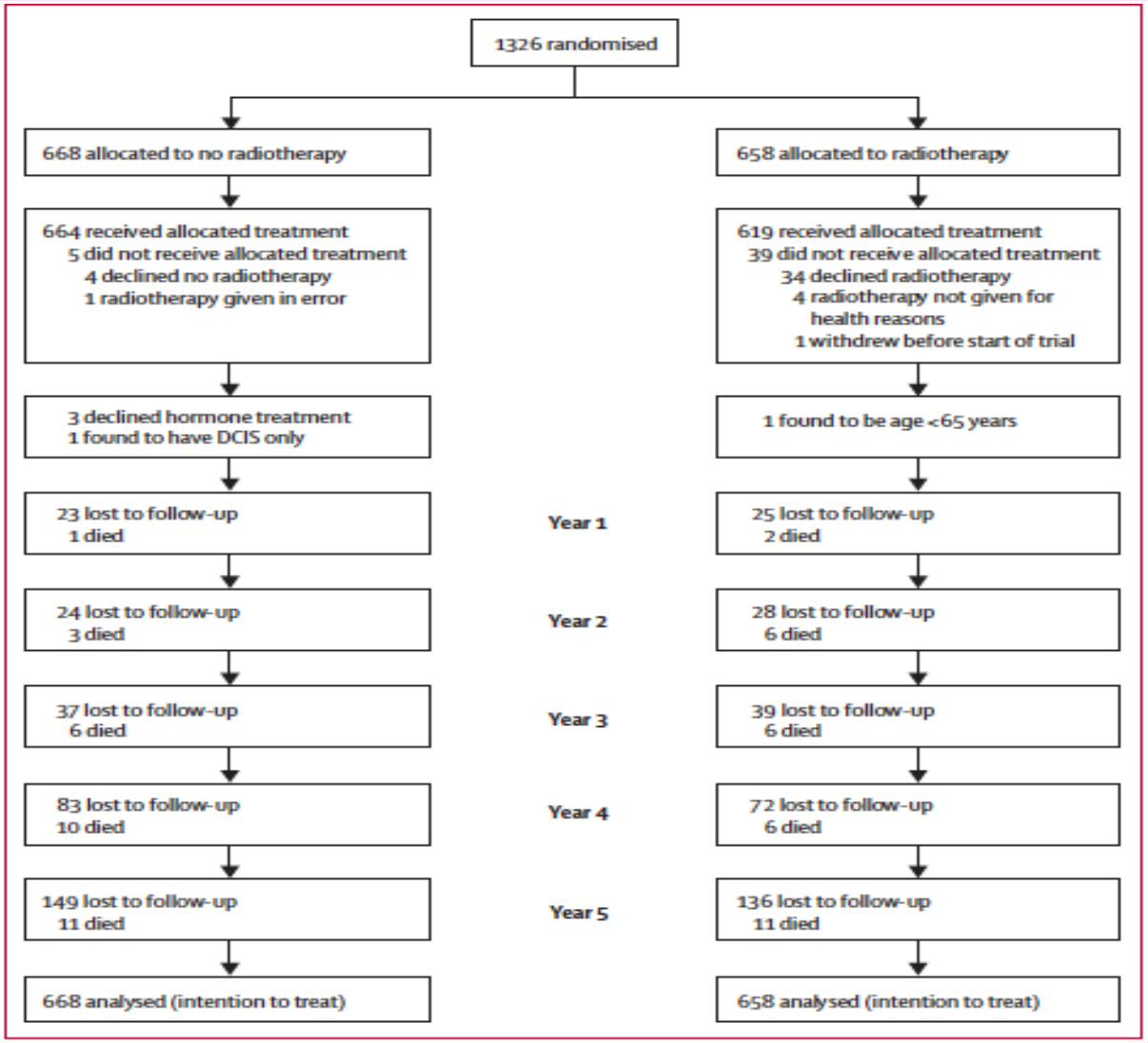
Less local treatment: The role of RT in BCT

N = 1326; age ≥ 65 y

Invasive BC; < 30 mm; N0; ER+; low risk

All had adjuvant endocrine therapy

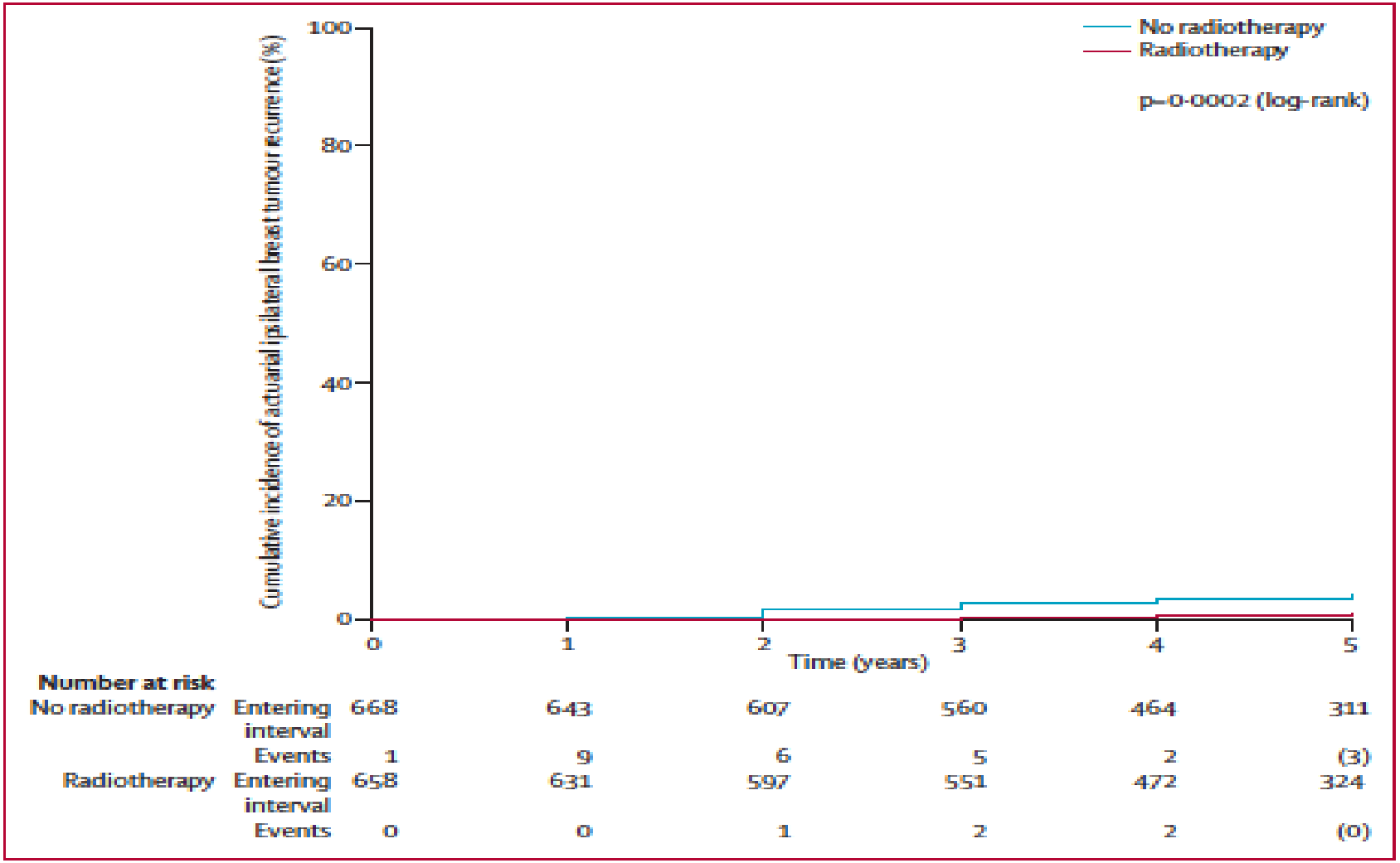
Less local treatment: The role of RT in BCT



Kunkler IH, et al. Lancet Oncol 2015;16:266-73.

ESTRO School

Less local treatment: The role of RT in BCT



Number at risk							
No radiotherapy	Entering interval	668	643	607	560	464	311
	Events	1	9	6	5	2	(3)
Radiotherapy	Entering interval	658	631	597	551	472	324
	Events	0	0	1	2	2	(0)

Figure 2: Time to actuarial ipsilateral breast tumour recurrence

Kunkler IH, et al. Lancet Oncol 2015;16:266-73.

ESTRO School

Less local treatment: The role of RT in BCT

Postoperative WBRT after BCS and adjuvant endocrine treatment resulted in a ***significant but modest reduction in local recurrence*** *for women aged 65 years or older with early breast cancer 5 years after randomisation.*

…probably ***low enough for omission of radiotherapy*** *to be considered for some patients..*

Kunkler IH, et al. Lancet Oncol 2015;16:266-73.

ESTRO School

Less local treatment: The role of RT in BCT

… and adjuvant endocrine treatment …

…probably ***low enough for omission of radiotherapy*** *to be considered for some patients..*

Personal note:

- About half of those pts would not receive adjuvant systemic treatment according to the Dutch guidelines

Kunkler IH, et al. Lancet Oncol 2015;16:266-73.

ESTRO School

Less local treatment: where is the limit?

1. Introduction
2. The role of radiation therapy in BCT
3. The role of PMRT
4. Interaction with systemic treatment
5. Discussion
6. Conclusions

Less local treatment: The role of PMRT

oa
OPEN ACCESS

Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials

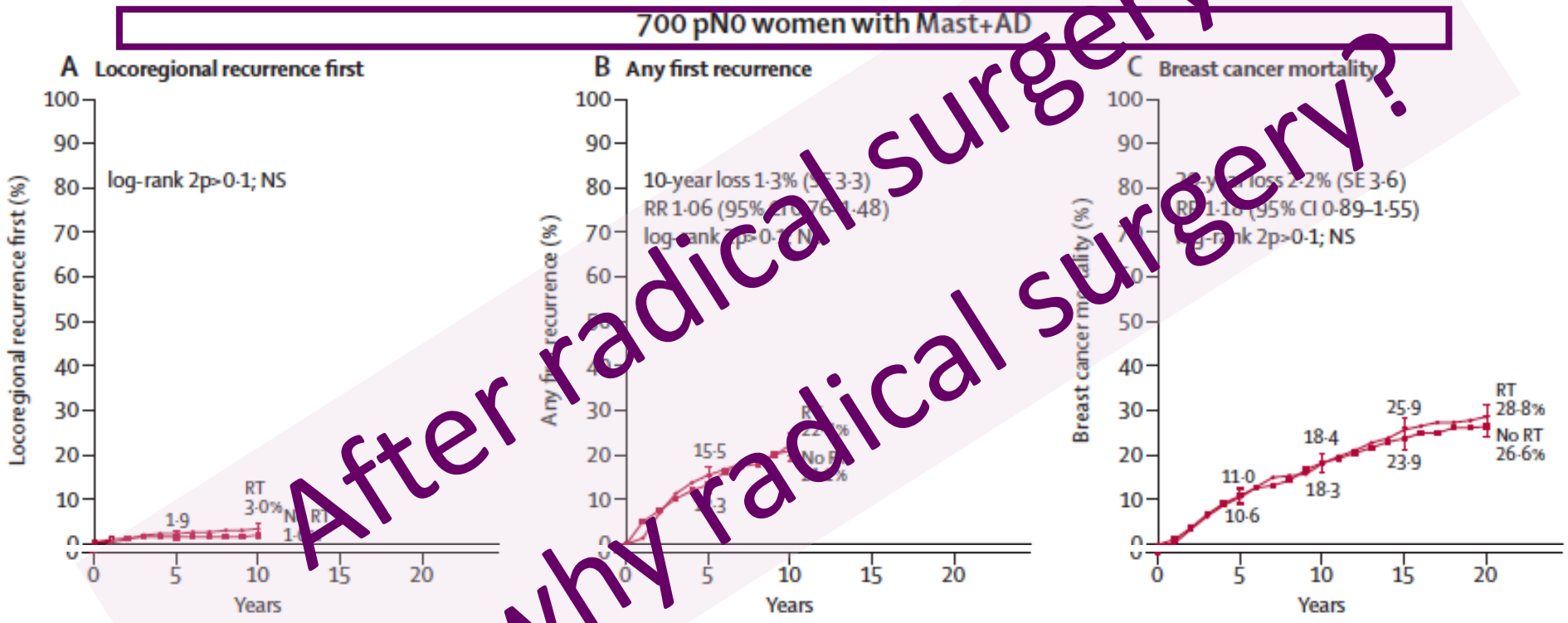
EBCTCG (Early Breast Cancer Trialists' Collaborative Group)*

Lancet 2014; 383: 2127–35

EBCTCG. Lancet. 2014;383:2127-35.

ESTRO School

Less local treatment: The role of PMRT

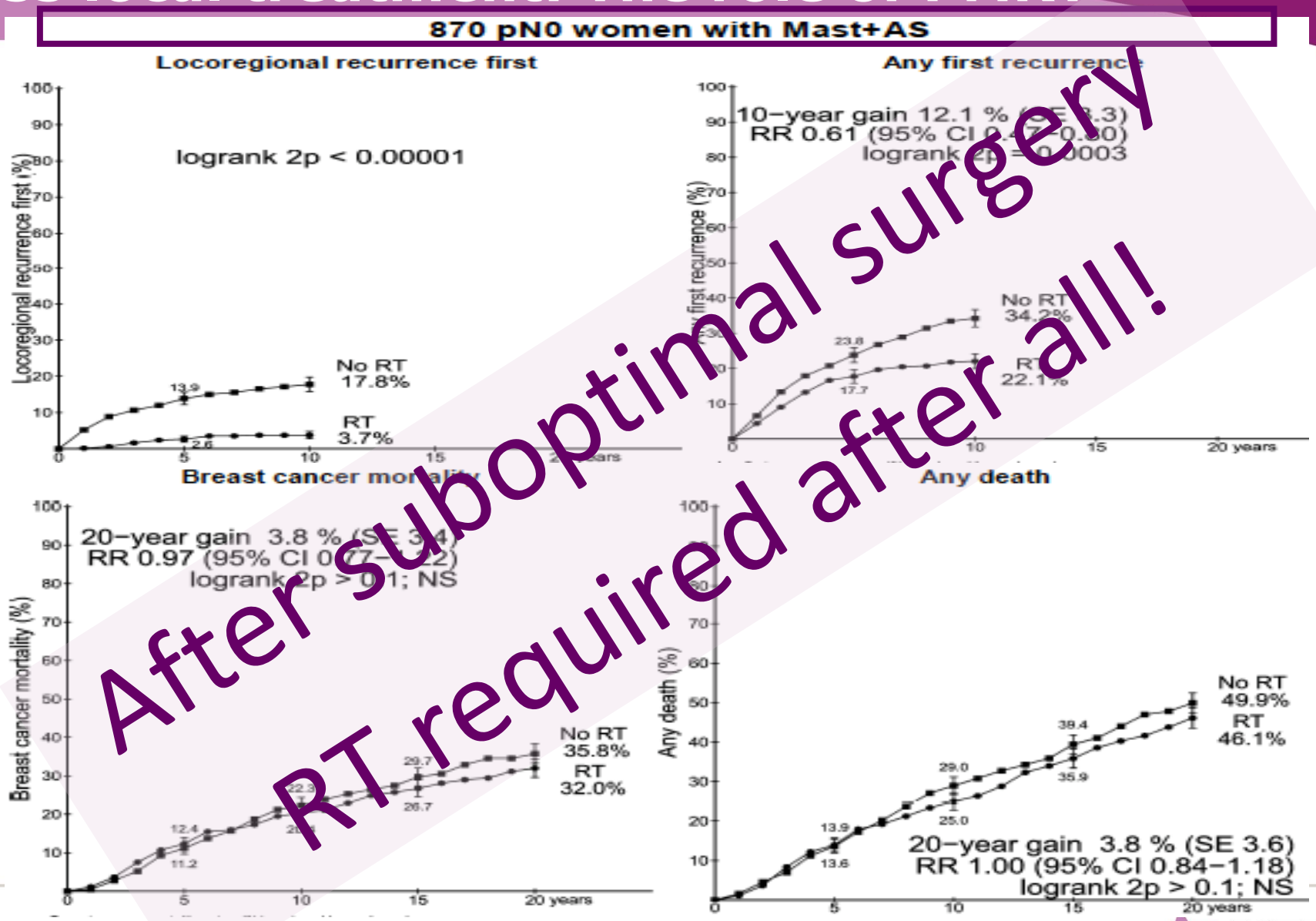


After radical surgery
But why radical surgery?

EBCTCG. Lancet. 2014;383:2127-35.

ESTRO School

Less local treatment: The role of PMRT

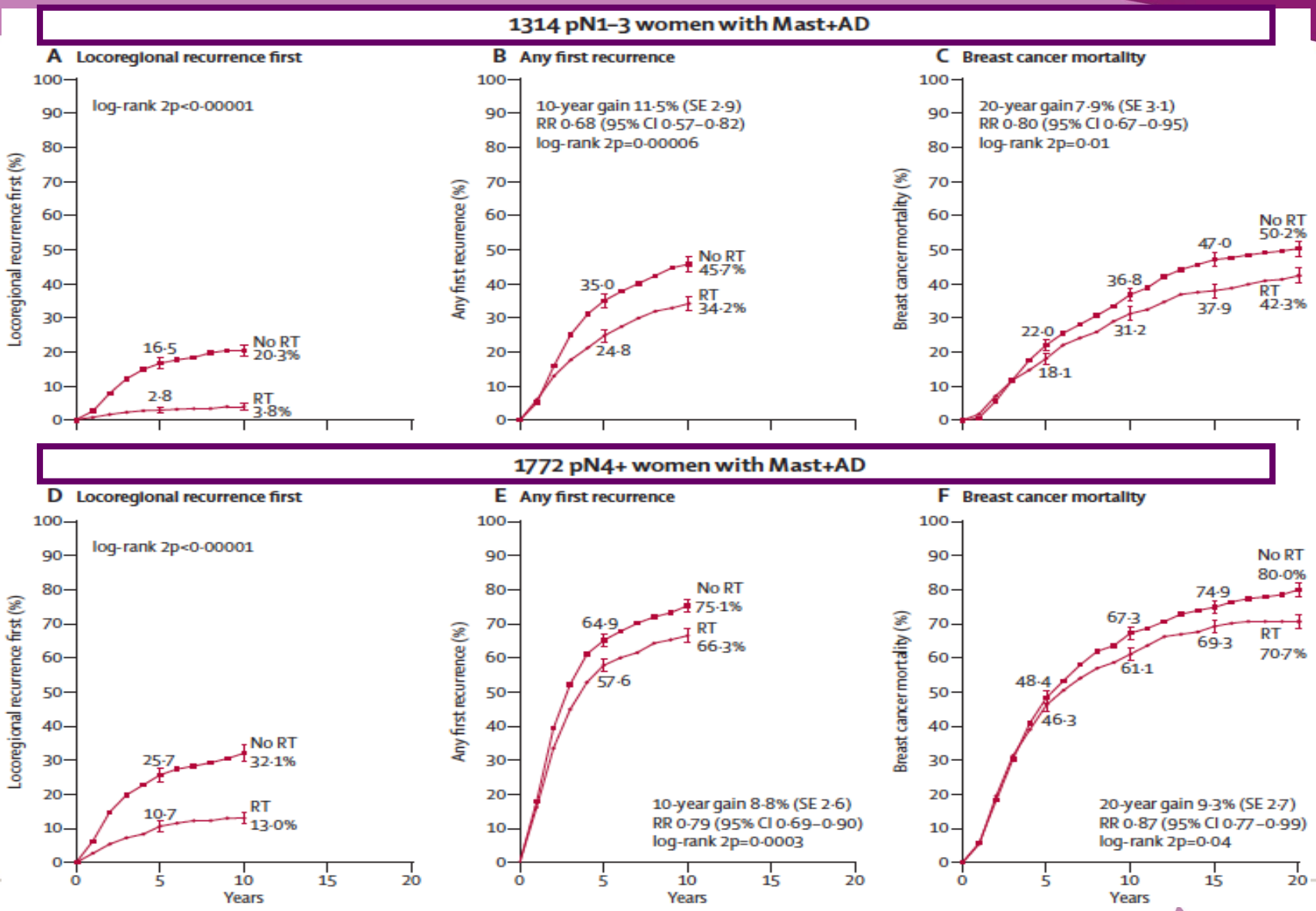


After suboptimal surgery
RT required after all!

EBCTCG. Lancet. 2014;383:2127-35.

ESTRO School

Less local treatment: The role of PMRT



EBCTCG. Lancet. 2014;383:2127-35.

ESTRO School

Less local treatment: The role of PMRT

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2015;373:317-27.

ORIGINAL ARTICLE

Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer

P.M. Poortmans, S. Collette, C. Kirkove, E. Van Limbergen, V. Budach, H. Struikmans, L. Collette, A. Fourquet, P. Maingon, M. Valli, K. De Winter, S. Marnitz, I. Barillot, L. Scandolaro, E. Vonk, C. Rodenhuis, H. Marsiglia, N. Weidner, G. van Tienhoven, C. Glanzmann, A. Kuten, R. Arriagada, H. Bartelink, and W. Van den Bogaert, for the EORTC Radiation Oncology and Breast Cancer Groups*

EBCTCG. Lancet. 2014;383:2127-35.

ESTRO School

Less local treatment: The role of PMRT

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 23, 2015 VOL. 373 NO. 4

Regional Nodal Irradiation in Early-Stage Breast Cancer

Timothy J. Whelan, B.M., B.Ch., Ivo A. Olivotto, M.D., Wendy R. Parulekar, M.D., Ida Ackerman, M.D., Boon H. Chua, M.B., B.S., Ph.D., Abdenour Nabid, M.D., Katherine A. Vallis, M.B., B.S., Ph.D., Julia R. White, M.D., Pierre Rousseau, M.D., Andre Fortin, M.D., Lori J. Pierce, M.D., Lee Manchul, M.D., Susan Chafe, M.D., Maureen C. Nolan, M.D., Peter Craighead, M.D., Julie Bowen, M.D., David R. McCready, M.D., Kathleen I. Pritchard, M.D., Karen Gelmon, M.D., Yvonne Murray, B.Sc., Judy-Anne W. Chapman, Ph.D., Bingshu E. Chen, Ph.D., and Mark N. Levine, M.D., for the MA.20 Study Investigators*

Poortmans P, et al. N Engl J Med 2015;373:317-27.

ESTRO School

Less local treatment: The role of PMRT

Published Ahead of Print on November 23, 2015 as 10.1200/JCO.2015.63.6456
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2015.63.6456

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

DBCG-IMN: A Population-Based Cohort Study on the Effect of Internal Mammary Node Irradiation in Early Node-Positive Breast Cancer

Lise Bech Jellesmark Thorsen, Birgitte Vrou Offersen, Hella Danø, Martin Berg, Ingelise Jensen, Anders Navrsted Pedersen, Sune Jürg Zimmermann, Hans-Jürgen Brodersen, Marie Overgaard, and Jens Overgaard

Whelan T, et al. N Engl J Med 2015;373:307-16.

ESTRO School

Less local treatment: The role of PMRT

Disease-free survival at 10 years:

Improved with regional irradiation

Distant metastases-free survival at 10 years:

Improved with regional irradiation

Overall survival at 10 years:

Overall trend towards improvement with regional irradiation

Breast cancer specific survival at 10 years:

Improved with regional irradiation

Late side effects at 10 years following regional RT:

- Pulmonary and skin
- Limited; most often ≤ grade 2; some transient
- No increased lethal toxicity

Thorsen LB, et al. J Clin Oncol. 2016;34:314-320.

ESTRO School

Less local treatment: The role of PMRT

Disease-free survival at 10 years:

Improved with regional irradiation

Distant metastases-free survival at 10 years:

Improved with regional irradiation

Overall survival at 10 years:

Overall trend towards improvement with regional irradiation

Breast cancer specific survival at 10 years:

Improved with regional irradiation

Late side effects at 10 years following regional RT:

- Pulmonary and skin
- Limited; most often ≤ grade 2; some transient
- No increased lethal toxicity

Thorsen LB, et al. J Clin Oncol. 2016;34:314-320.

ESTRO School

Less local treatment: The role of PMRT

Disease-free survival at 10 years:

Improved with regional irradiation

Distant metastases-free survival at 10 years:

Improved with regional irradiation

Overall survival at 10 years:

Overall trend towards improvement with regional irradiation

Breast cancer specific survival at 10 years:

Improved with regional irradiation

Late side effects at 10 yrs following regional RT:

- Pulmonary and skin
- Limited; most often ≤ grade 2; some transient
- No increased lethal toxicity

Thorsen LB, et al. J Clin Oncol. 2016;34:314-320.

ESTRO School

Less local treatment: where is the limit?

1. Introduction
2. The role of radiation therapy in BCT
3. The role of PMRT
4. Interaction with systemic treatment
5. Discussion
6. Conclusions

Less local treatment: interaction loc-syst T

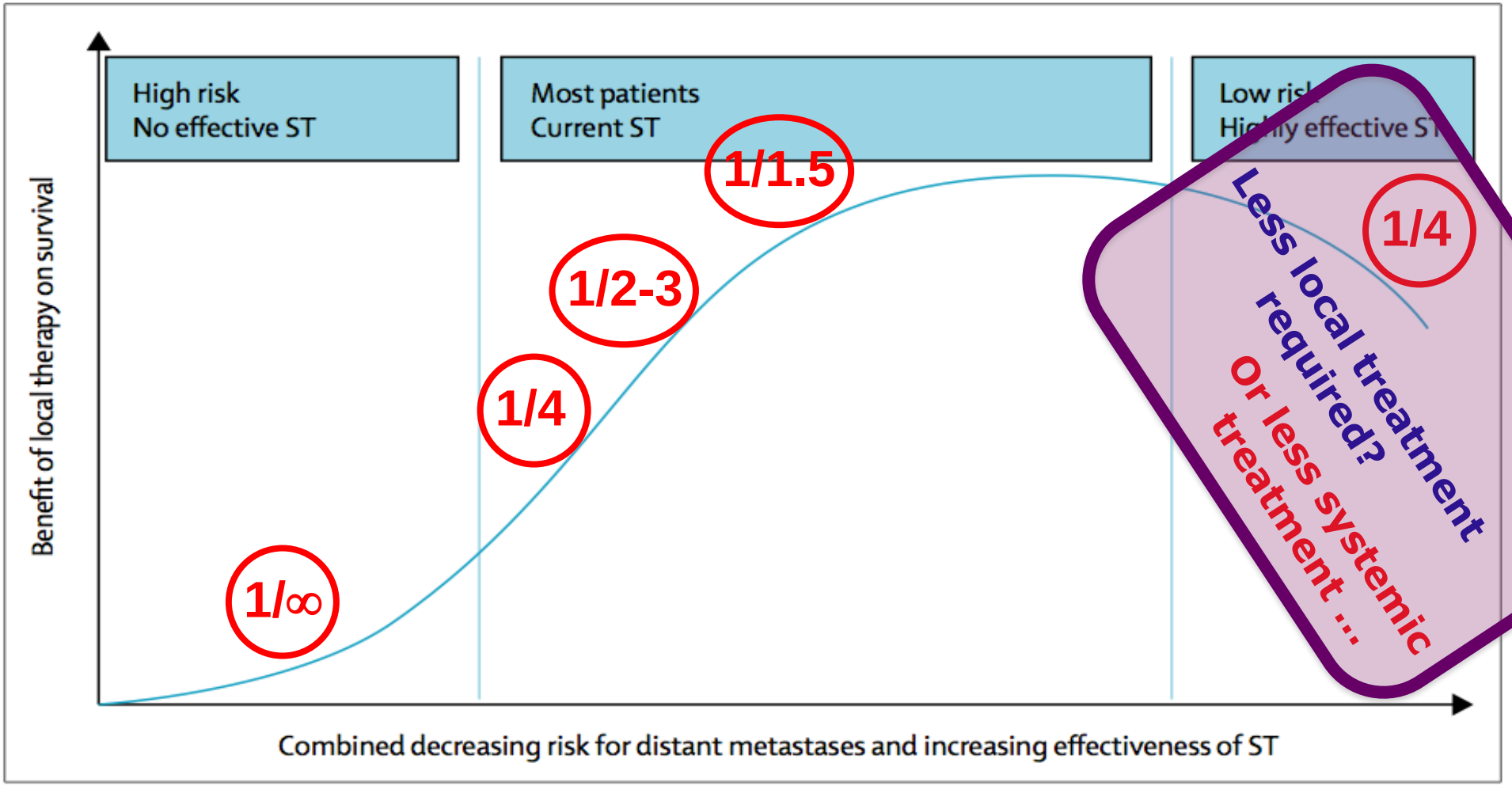


***Figure*: Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour**

Poortmans P. Lancet. 2014 Jun 21;383(9935):2104-6.

ESTRO School

Less local treatment: interaction loc-syst T

RT & survival:

➔ X interaction with surgery and systemic treatment

↓ risk for death < M+ ➔ ↑ importance of LC

➔ earlier stage BC

➔ improved systemic therapy

Less local treatment: interaction loc-syst T

Early stage, low risk *(DCIS; T1G1-2; T2G1)*:

⇒ LC >>> DM: SX/RT

Poortmans P. Lancet. 2014 Jun 21;383(9935):2104-6.

ESTRO School

Less local treatment: interaction loc-syst T

Early stage, high risk *(T1G3; T2G2-3; N1a)*:

⇒ LC: SX/RT effect ↓ by Syst.Th.

⇒ DM: Syst.Th.importance LC ↑: need for SX/RT

Poortmans P. Lancet. 2014 Jun 21;383(9935):2104-6.

ESTRO School

Less local treatment: interaction loc-syst T

Late stage *(T3-4; N2a-3)*:

⇒ DM >>> LC: Syst.Th. ↑ importance of LC SX/RT

Poortmans P. Lancet. 2014 Jun 21;383(9935):2104-6.

ESTRO School

Less local treatment: interaction loc-syst T

Better local treatment adds to the effects of systemic therapy on local recurrence and on breast cancer mortality.

EBCTCG Lancet 2005; 365: 1687-1717; EBCTCG Lancet 2005; 366: 2087–2106

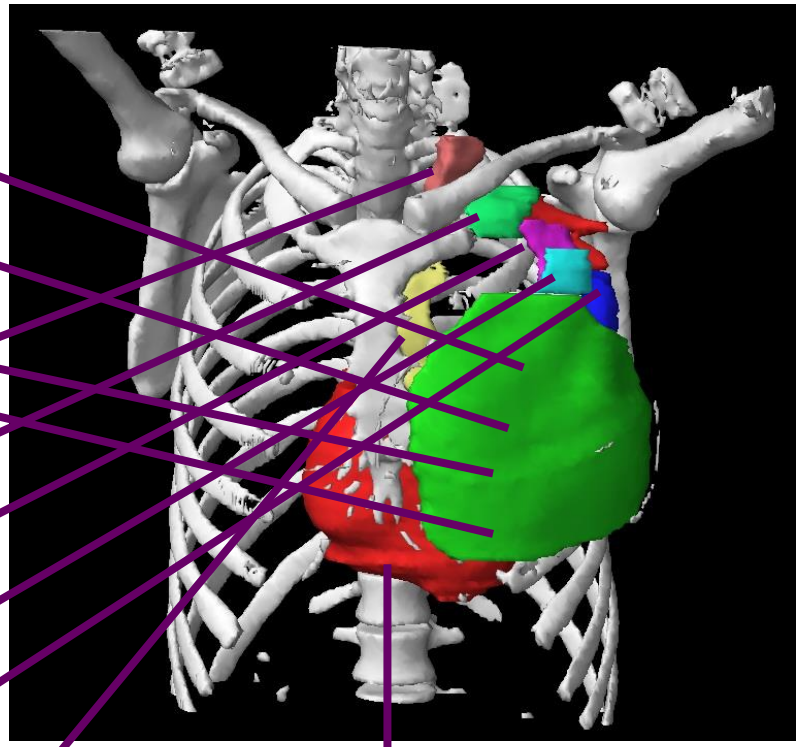
ESTRO School

Less local treatment: where is the limit?

1. Introduction
2. The role of radiation therapy in BCT
3. The role of PMRT
4. Interaction with systemic treatment
5. Discussion
6. Conclusions

Less local treatment: discussion

- Breast
- Boost
- PBI
- Thoracic wall
- LN supraclavicular
- LN axilla level III
- LN axilla level II
- LN axilla Rotter
- LN axilla level I
- LN internal mammary



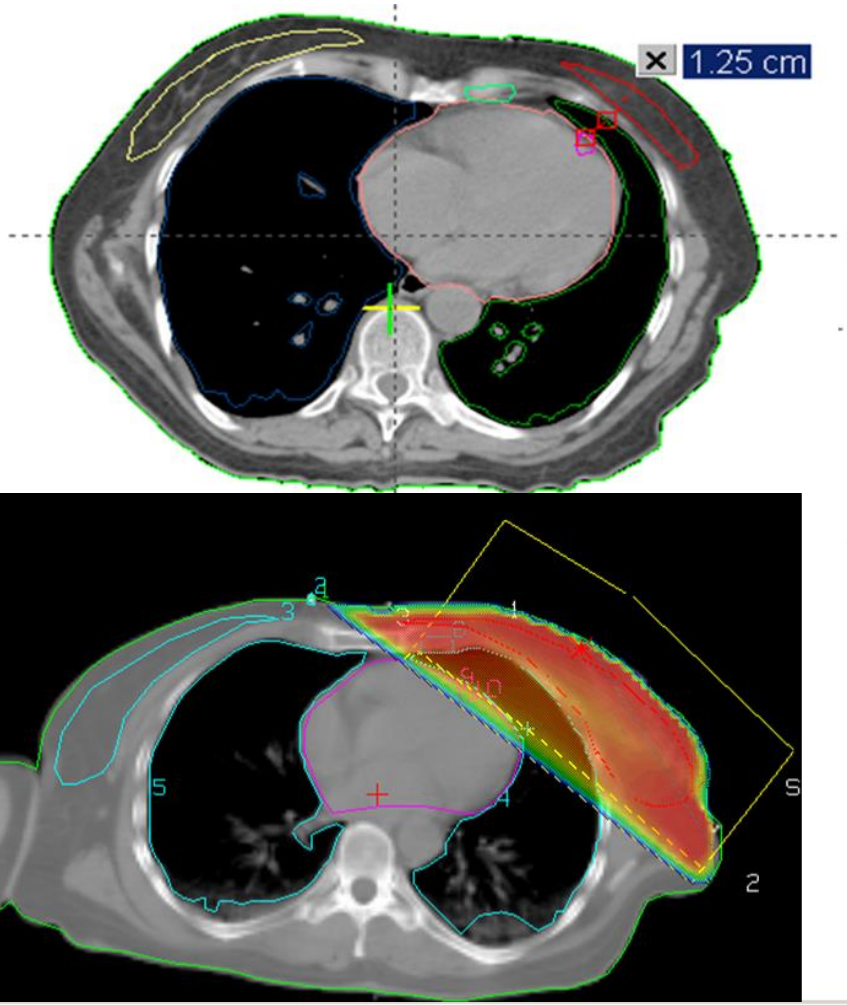
Heart

Offersen BV, et al. Radiother Oncol 2015;114:3-10 & 2016;118:205-8.

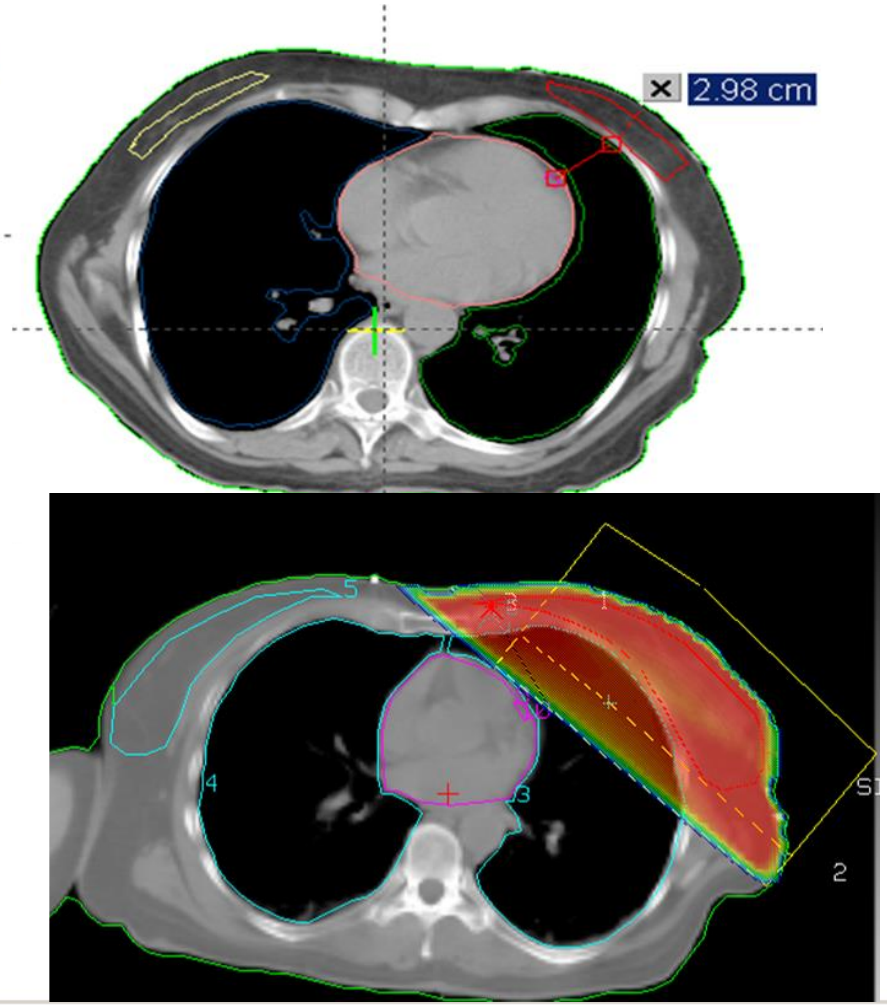
ESTRO School

Less local treatment: discussion

Free respiration



Breath hold



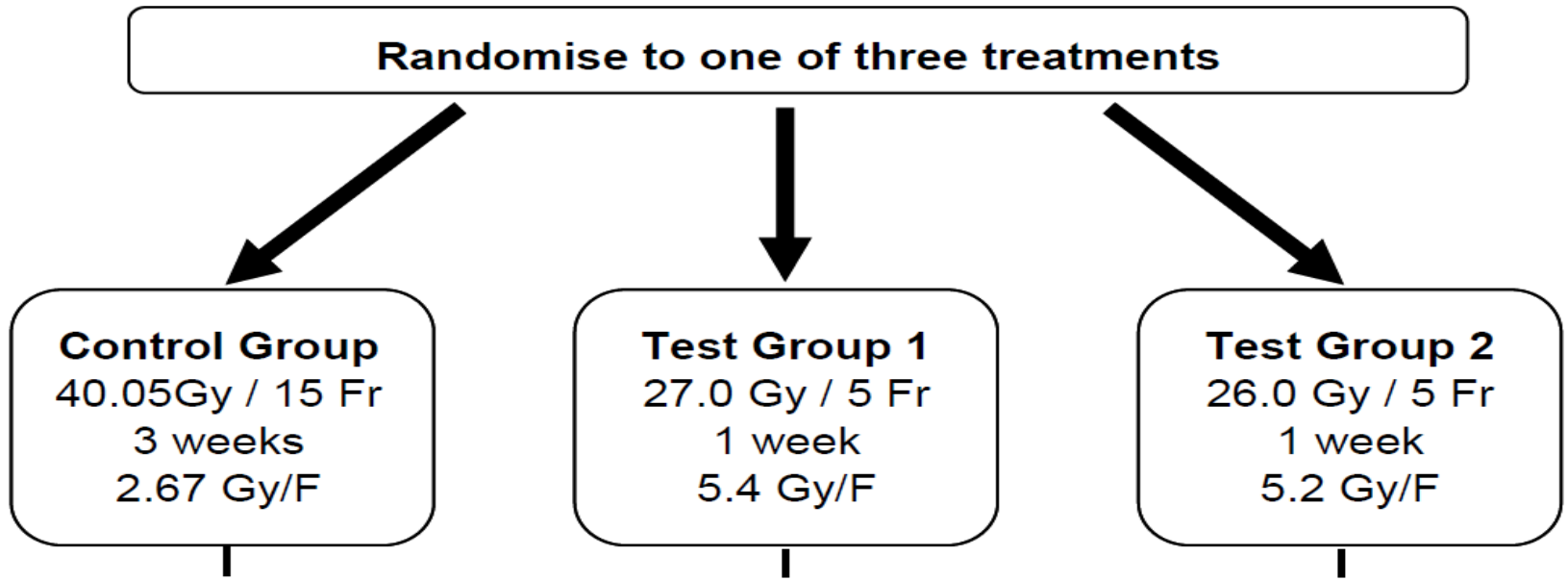
Courtesy of Marianne Aznar, Rigshospitalet, Copenhagen

ESTRO School

Less local treatment: discussion

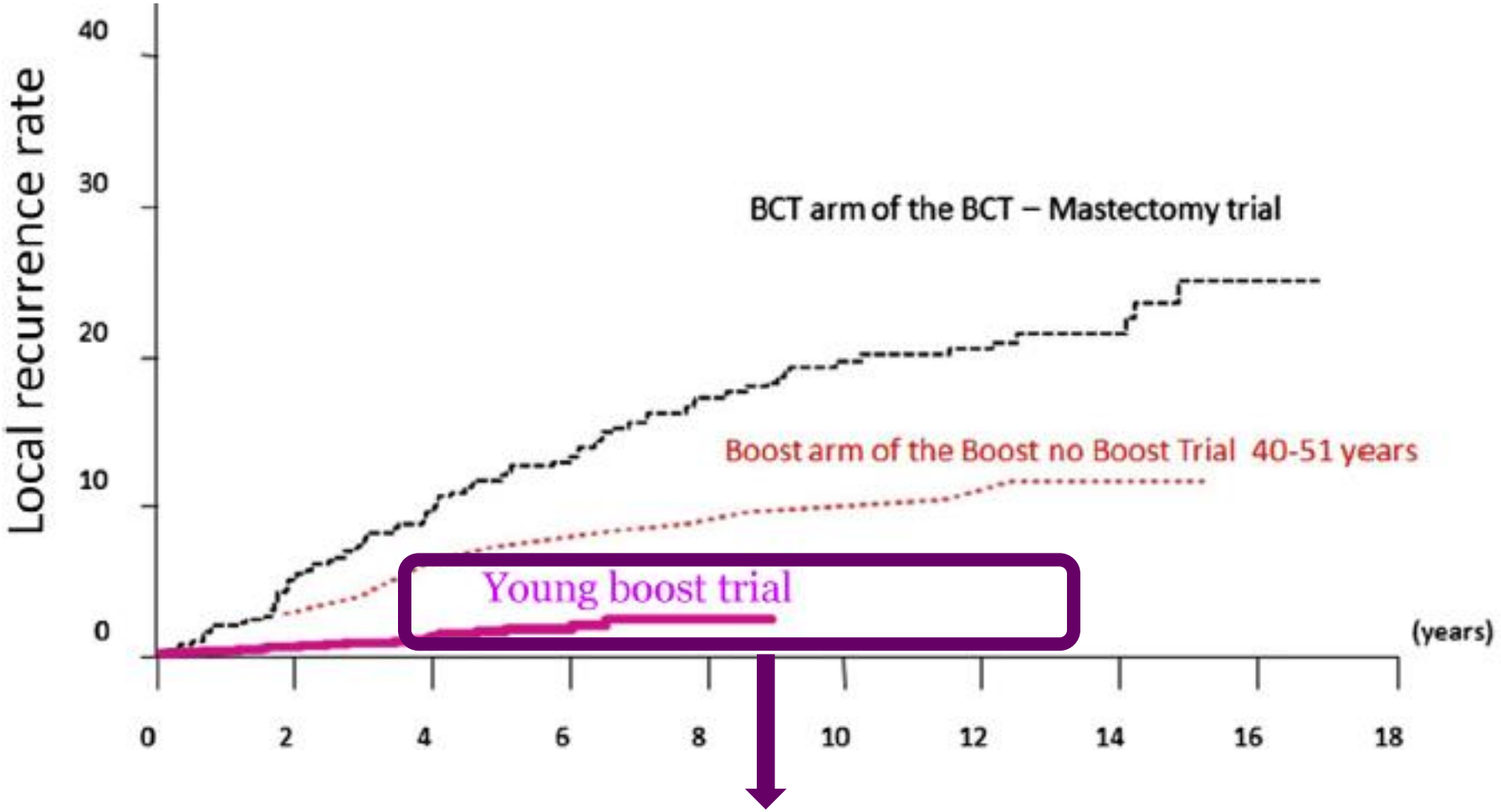
Treatment times are shortening!

FAST-Forward



*16 Gy or 10 Gy in 2 Gy fractions sequential electron or photon boost to the tumour bed is allowed in all 3 treatment arms (boost decision to be declared before randomisation for each individual patient)

Less local treatment: discussion



Update 2016: 1.8% LRR at 9 years !!!

Poortmans P, et al. Breast. 2017;31:295-302.

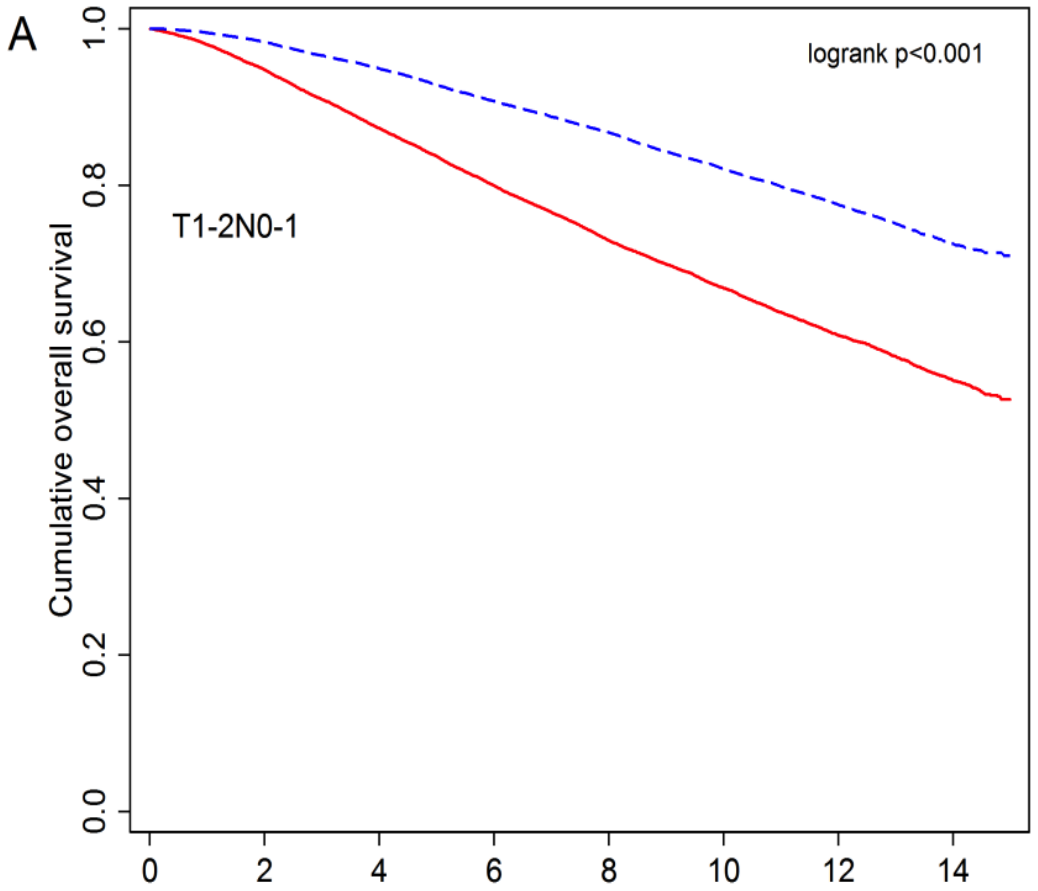
ESTRO School

Less local treatment: where is the limit?

Dutch population based cancer registry

2000-2004 cohort: 37,207 patients

- 58.4% BCT
- 41.6% MRM



van Maaren M, et al. Lancet Oncol. 2016 Aug;17(8):1158-70.

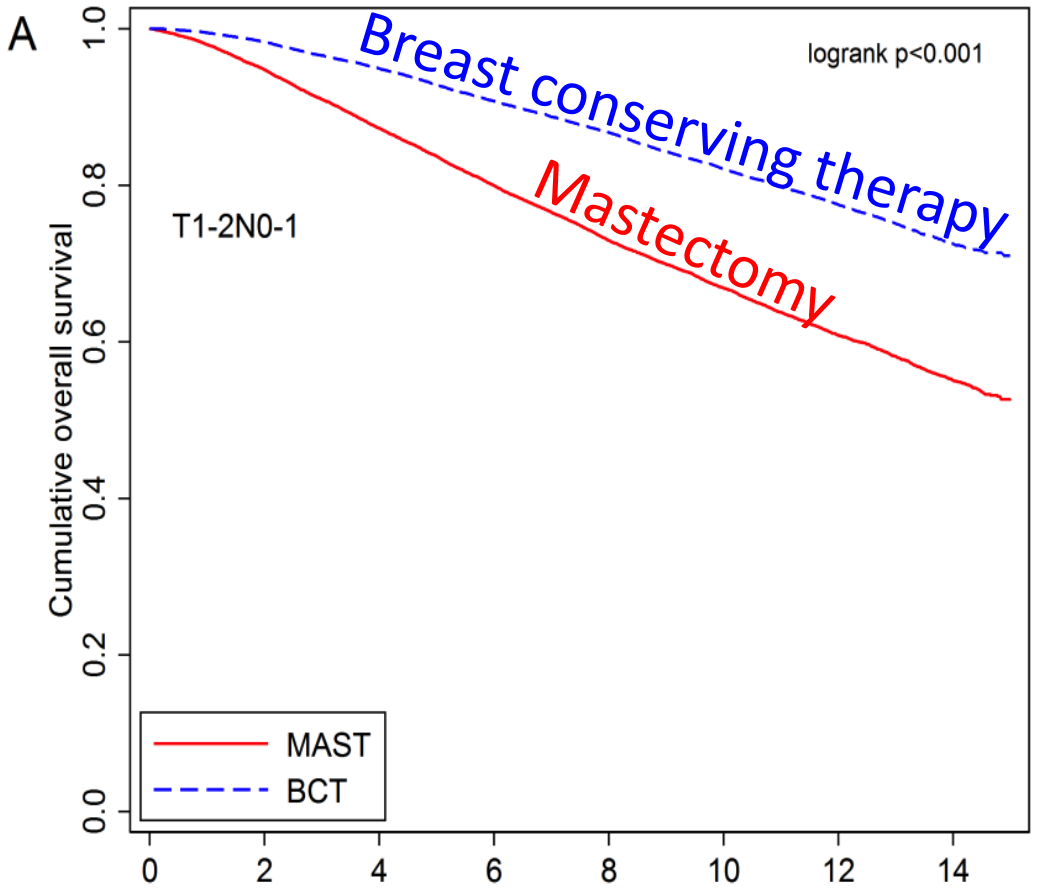
ESTRO School

Less local treatment: where is the limit?

Dutch population based cancer registry

2000-2004 cohort: 37,207 patients

- 58.4% BCT
- 41.6% MRM



van Maaren M, et al. Lancet Oncol. 2016 Aug;17(8):1158-70.

ESTRO School

Interaction between local & systemic treatment

Stage (all 65y;N0;ER+;Her-)	Benefit HT DFS (%)	Benefit HT OS (%)
~~T1a-bG1-3~~	~~4.9-9.5~~	~~0.3-1.4~~
~~T1cG1~~	~~5.7-8.2~~	~~0.9~~
T1cG2	7.8-11.1	2.0
T1cG3	9.6-13.9	3.3
$T2_{<3cm}G1$	8.1-11.6	2.4
$T2_{<3cm}G2$	10.8-15.7	4.3
$T2_{<3cm}G3$	12.7-18.7	5.9

ESTRO School

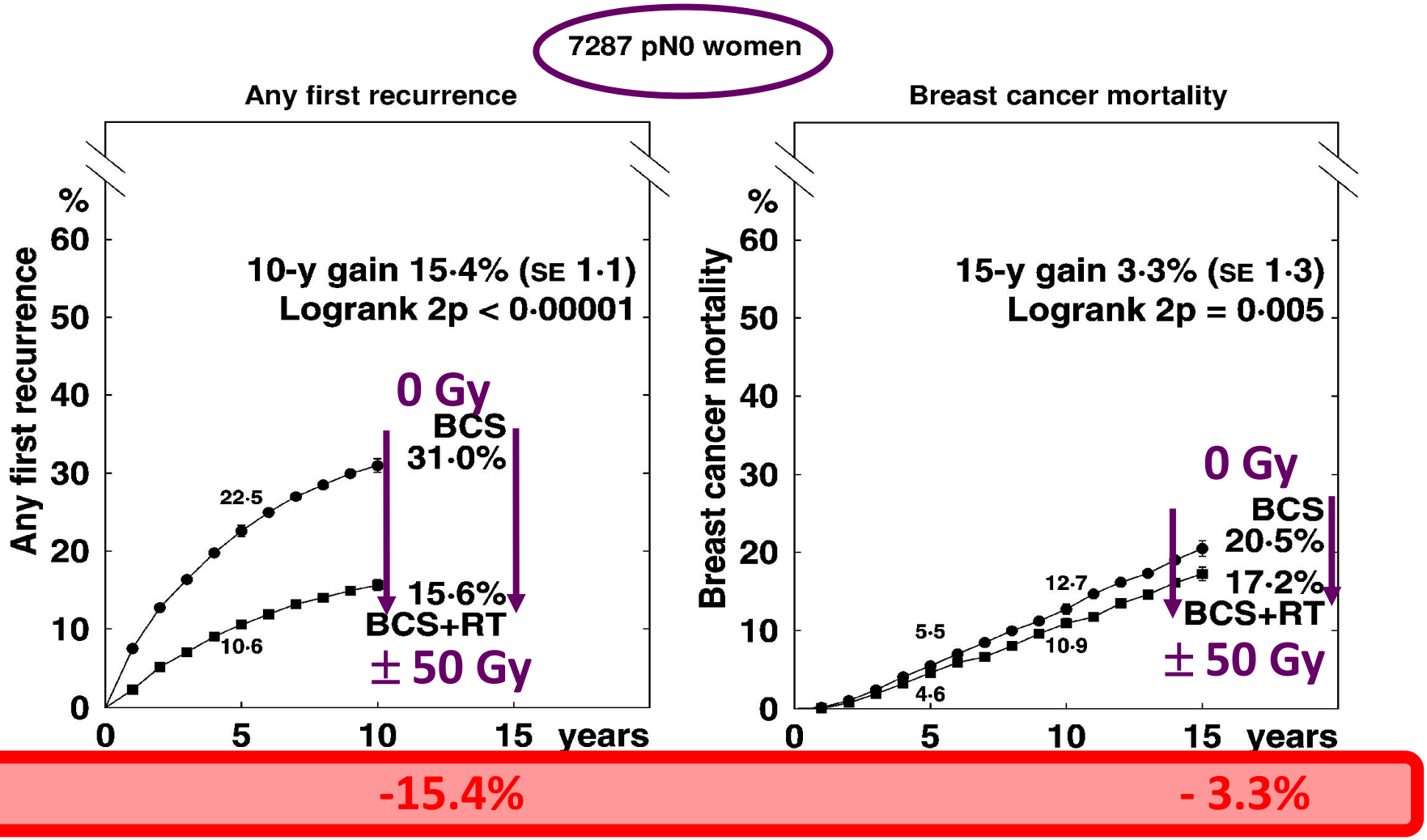
Interaction between local & systemic treatment

Stage (all 65y;N0;ER+;Her-)	Benefit HT DFS (%)	Benefit HT OS (%)
~~T1a-bG1-3~~	~~4.9-9.5~~	~~0.3-1.4~~
~~T1cG1~~	~~5.7-8.2~~	~~0.9~~
T1cG2	7.8-11.1	2.0
T1cG3	9.6-13.9	3.3
$T2_{<3cm}G1$	8.1-11.6	2.4
$T2_{<3cm}G2$	10.8-15.7	4.3
$T2_{<3cm}G3$	12.7-18.7	5.9

ESTRO School

Less local treatment: discussion

Effect of RT after BCS on recurrence and breast cancer mortality in pN0 women.



EBCTCG Lancet 2011; 378: 1707–1716

ESTRO School

Interaction between local & systemic treatment

Stage (all 65y;N0;ER+;Her-)	Benefit HT DFS (%)	Benefit HT OS (%)
~~T1a-bG1-3~~	~~4.9-9.5~~	~~0.3-1.4~~
~~T1cG1~~	~~5.7-8.2~~	~~0.9~~
T1cG2	7.8-11.1	2.0
T1cG3	9.6-13.9	3.3
$T2_{<3cm}G1$	8.1-11.6	2.4
$T2_{<3cm}G2$	10.8-15.7	4.3
$T2_{<3cm}G3$	12.7-18.7	5.9
	-15.4%	**- 3.3%**

EBCTCG Lancet 2011; 378: 1707–1716

ESTRO School

Less local treatment: discussion

Side effects

Hormonal therapy (TAM/AI):

- Hot flushes
- Mood disturbances
- Insomnia
- Joint pain
- Osteoporosis
- Coagulopathy
- Endometrial cancer
- CL breast: less
- Treatments
- Switch to AI
- Switch to TAM
- Big issue
- Prevention/treatment
- Prefer AI if risk
- Switch to AI
- No problem

Less local treatment: discussion

Side effects

Persistence in patients with breast cancer treated with tamoxifen or aromatase inhibitors: a retrospective database analysis

P. Hadji · V. Ziller · J. Kyvernitakis ·
M. Bauer · G. Haas · N. Schmidt · K. Kostev

- ≤ 3 years FU ➔ discontinuation = 52.2% for tamoxifen, 47% for anastrozole, 55.1% for exemestane, and 44.3% for letrozole.
- Switch to: 33% tamoxifen, 20% anastrozole, 22.9% exemestane, and 23% letrozole.

Hadji P, et al. Breast Cancer Res Treat. 2013;138:185–191

ESTRO School

Less local treatment: discussion

Side effects

Persistence in patients with breast cancer treated with tamoxifen or aromatase inhibitors: a retrospective database analysis

P. Hadji · V. Ziller · J. Kyvernitakis · M. Bauer · G. Haas · N. Schmidt · K. Kostev

- The cumulative toxicity of upfront AI may explain the lack of OS benefit despite improvements in DFS.
- Switching from TAM to AI reduces this toxicity and is likely the best balance between efficacy and toxicity.

Hadji P, et al. Breast Cancer Res Treat. 2013;138:185–191

ESTRO School

Less local treatment: discussion

Side effects

Toxicity of Adjuvant Endocrine Therapy in Postmenopausal Breast Cancer Patients: A Systematic Review and Meta-analysis

Eitan Amir, Bostjan Seruga, Saroj Niraula, Lindsay Carlsson, Alberto Ocaña

- Higher discontinuation for: younger pts; comorbidity; Prescription via GP.
- ➔ persistence with all endocrine treatments in women with hormonereceptor-positive BC is low.

Amir E, et al. JNCI 2011;103:1299-1309

ESTRO School

Less local treatment: discussion

Side effects

COMPliance and Arthralgia in Clinical Therapy: the COMPACT trial, assessing the incidence of arthralgia, and compliance within the first year of adjuvant anastrozole therapy

- Arthralgia is important in the clinical management of women with early breast cancer.
- ➔ may contribute to noncompliance and clinical outcomes.

Hadji P, et al. Breast Cancer Res Treat. 2012;134:459–478

ESTRO School

Less local treatment: discussion

Side effects

Adherence to Adjuvant Hormonal Therapy among Breast Cancer Survivors in Clinical Practice: A Systematic Review

- Adherence and persistence to adjuvant hormonal therapy is suboptimal.
- Many of the correlates of adherence and persistence studied to date are not modifiable.
- ➔ critical need for further research on modifiable factors associated with adherence to adjuvant hormonal therapy/behavioral interventions.

Murphy CC, et al. Annals of Oncology 2014;25:372–377

ESTRO School

Less local treatment: discussion

Side effects

Health-related quality of life and psychological distress of breast cancer patients after surgery during a phase III randomized trial comparing continuation of tamoxifen with switching to anastrozole after adjuvant tamoxifen for 1–4 years: N-SAS BC 03

Continuation of tamoxifen treatment after adjuvant tamoxifen for 1–4 years may provide Japanese breast cancer patients with better HRQOL than by switching to anastrozole.

Ohsumi S, et al. Breast Cancer Res Treat. 2011;127:143–152

ESTRO School

Less local treatment: discussion

Side effects

Health-related quality of life, psychological distress, and adverse events in postmenopausal women with breast cancer who receive tamoxifen, exemestane, or anastrozole as adjuvant endocrine therapy: National Surgical Adjuvant Study of Breast Cancer 04 (N-SAS BC 04)

HRQOL was better in Japanese postmenopausal women treated with tamoxifen than those treated with exemestane or anastrozole. HRQOL and AEs were similar with exemestane and anastrozole.

Takei H, et al. Breast Cancer Res Treat. 2012;133:227–236

ESTRO School

Less local treatment: discussion

Side effects

Possible Late Effects of Chemotherapy
Early menopause
Impairment of cognitive function (chemo brain)
Vaginal dryness
Fatigue
Depression
Weight gain
Osteoporosis
Heart disease (CHF)
Neuropathy

Less local treatment: discussion

The eternal quest

"Studies seeking to identify a subgroup of patients who could undergo breast conserving surgery without radiotherapy, based upon clinicopathologic characteristics alone have largely proved unsuccessful"

Jagsi R Ca Cancer J 2014;64:135-162.

ESTRO School

Less local treatment: discussion

➔ *consensus agreements*

Less local treatment: where is the limit?

1. Introduction
2. The role of radiation therapy in BCT
3. The role of PMRT
4. Interaction with systemic treatment
5. Discussion

6.Conclusions

Less local treatment: conclusions

- We know what we know – and that comes from the past ➔ we have to cope with that
- Comparative data on toxicity and QoL of RT vs adjuvant hormonal treatment are lacking
- Our "feelings" on risks and treatment benefits probably need to be adapted
- What's new tomorrow will be challenged again ~ possibly outdated after tomorrow

Less local treatment: conclusions

- Patient selection criteria
- Short (up to 5 (?) years) toxicity
- Long term FU:
  - local control
  - long term toxicity

Less local treatment: conclusions

We did improve BCT rate

Boost only when needed!

Update 2016: 1.8% LRR at 9 years !!!

Poortmans P, et al. Breast. 2017;31:295-302.

ESTRO School

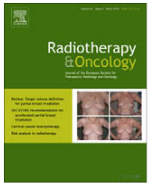
Less local treatment: conclusions

Radiotherapy and Oncology 94 (2010) 264–273

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



GEC-ESTRO Recommendations

Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: Recommendations of the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009)

Csaba Polgár [a,*], Erik Van Limbergen [b], Richard Pötter [c], György Kovács [d], Alfredo Polo [e], Jaroslaw Lyczek [f], Guido Hildebrandt [g], Peter Niehoff [h], Jose Luis Guinot [i], Ferran Guedea [j], Bengt Johansson [k], Oliver J. Ott [l], Tibor Major [a], Vratislav Strnad [l], On behalf of the GEC-ESTRO breast cancer working group

Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 4, pp. 987–1001, 2009
Copyright © 2009 American Society for Radiation Oncology. Published by Elsevier Inc.
Printed in the USA.
0360-3016/09/$–see front matter

doi:10.1016/j.ijrobp.2009.02.031

CONSENSUS STATEMENT

ACCELERATED PARTIAL BREAST IRRADIATION CONSENSUS STATEMENT FROM THE AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO)

BENJAMIN D. SMITH, M.D.,*† DOUGLAS W. ARTHUR, M.D.,‡ THOMAS A. BUCHHOLZ, M.D.,† BRUCE G. HAFFTY, M.D.,§ CAROL A. HAHN, M.D.,‖ PATRICIA H. HARDENBERGH, M.D.,¶ THOMAS B. JULIAN, M.D.,# LAWRENCE B. MARKS, M.D.,** DORIN A. TODOR, PH.D.,‡ FRANK A. VICINI, M.D.,†† TIMOTHY J. WHELAN, M.D.,‡‡ JULIA WHITE, M.D.,§§ JENNIFER Y. WO, M.D.,‖‖ AND JAY R. HARRIS, M.D.¶¶

Less local treatment: conclusions

Prospective clinical trials evaluating (accelerated) partial breast irradiation.

Author, Year	Study design	Number of patients	Local relapse	DFS	OS	Median FU
Dodwell et al., 2005 [27]	Phase II WBI vs. APBI	174	4% vs. 12% (p = 0.05)	–	27% vs. 30% (p = 0.75)	96 months
Chen et al., 2010 [28]	Phase II 3D CRT APBI	94	1.1% at 4 years	95% at 4 years	97% at 4 years	50.4 months
Vicini et al., 2010 [29]	Phase II 3D CRT APBI	52	6% at 4 years	84% at 4 years	96% at 4 years	54 months
Lei et al., 2013 [30]	Phase II IMRT APBI	136	0.7% at 4 years	–	96.8% at 4 years	53.1 months
Veronesi et al., 2013 [32]	Phase III WBI vs. IORT	1305 (654 IORT vs. 651 EBRT)	0.4% vs. 4.4% at 5 years (p < 0.0001)	–	96.8% vs. 96.9% at 5 years (p = 0.59)	69.6 months
Vaidya et al., 2014 [31]	Phase III WBI vs. IORT	3451 (1730 EBRT vs. 1721 IORT)	1.3% vs. 3.3% at 5 years p = 0.042	–	96.1% vs. 94.7% at 5 years (p = 0.099)	29 months
Livi et al., 2015 [33]	Phase III WBI vs. IMRT APBI	520 (260 WBI vs. 260 APBI)	1.4% vs. 1.5% (p = 0.86)	–	96.6% vs. 99.4% at 5 years (p = 0.057)	60 months
Strnad et al., 2016 [34]	Phase III WBI vs. IBT	1184 (551 WBI vs. 633 APBI)	0.92% vs. 1.44% (p = 0.42)	94.45% vs. 95.03% at 5 years (p = 0.79)	95.55% vs. 97.27% at 5 years (p = 0.11)	79.2 months

Poortmans P, et al. Breast. 2017;31:295-302.

ESTRO School

Less local treatment: conclusions

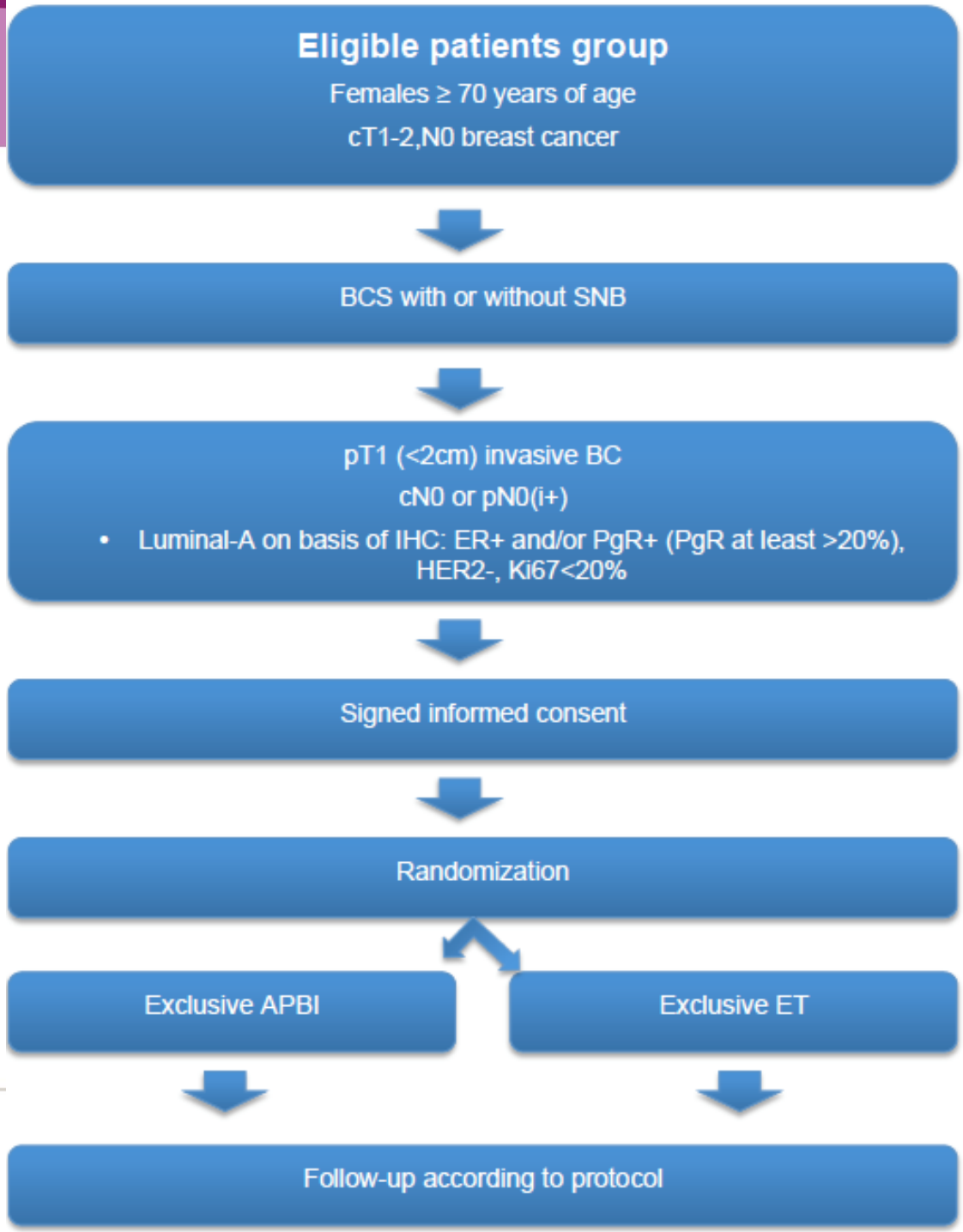
Early stage, low risk

EORTC
The future of cancer therapy

EORTC
Avenue E. Mounier 83/11
1200 Brussels
Belgium
Tel: +32 2 774 1611
Email: eortc@eortc.be
www.eortc.org

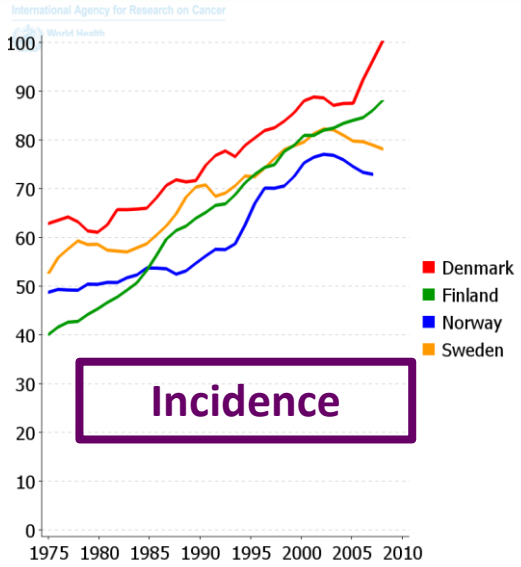
Study information	Outline form		
Title	Partial Breast Irradiation versus Endocrine Therapy for women age ≥70 years with Luminal-A early stage breast cancer: a randomized phase III trial comparing Quality of Life by Patient Reported Outcome Measures		
Short title (max 50 characters)	APBI or ET for elderly with early breast cancer		
Study Number	EORTC-1625 QoL-ROG-ETF-BCG	**Leading Group**	EORTC ROG

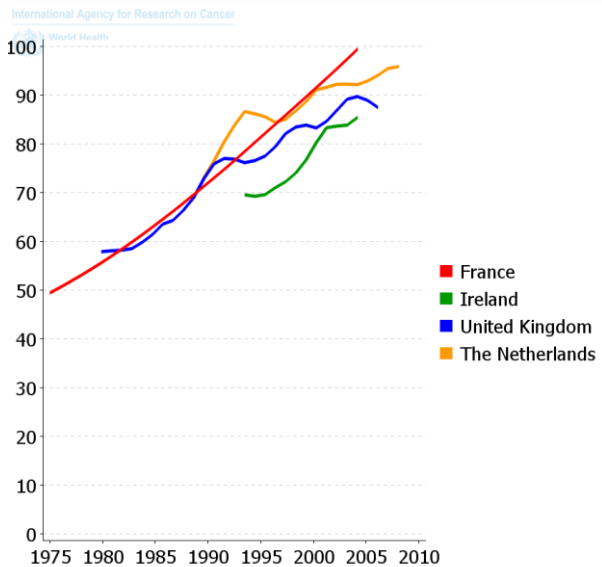
ESTRO School

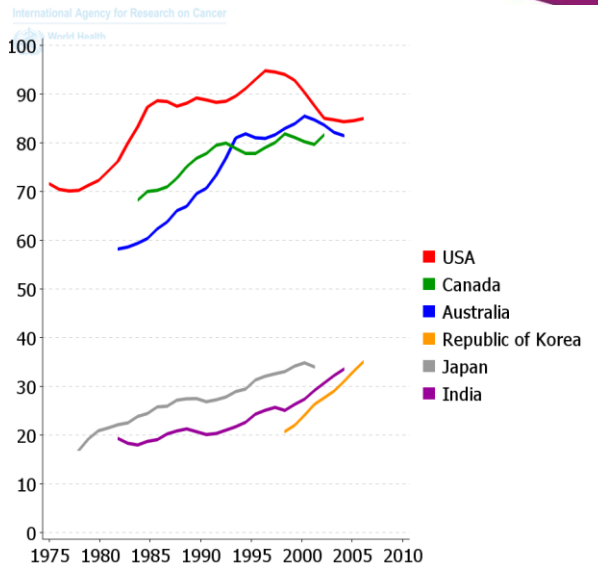


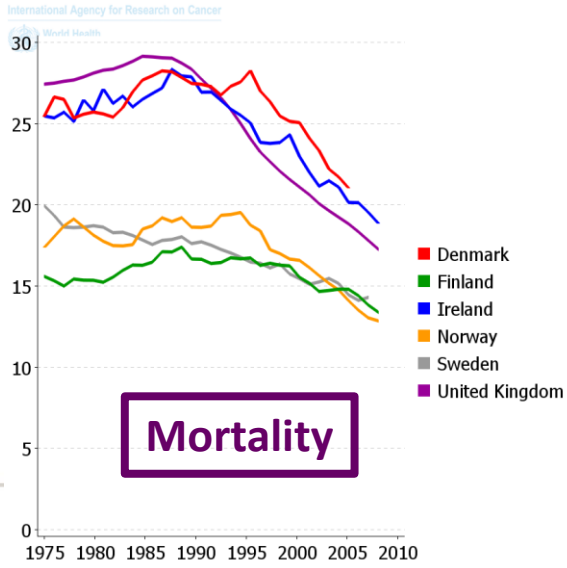
ESTRO School

Less local treatment: conclusions

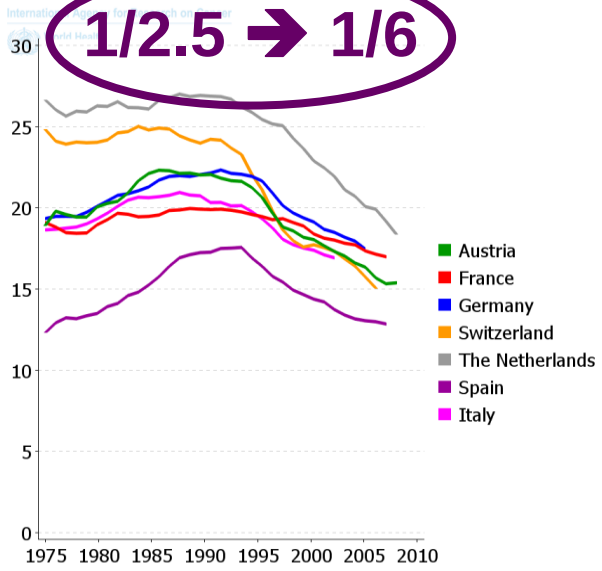


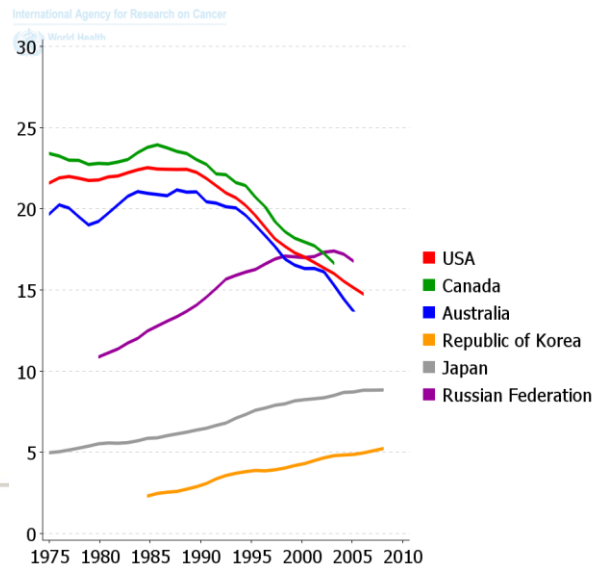






1/2.5 → 1/6





Source: Globocan, 2008. *Rates shown are age-standardised rate per 100,000 using the standard world population.*

Less local treatment: conclusions

Trust comes on foot and leaves on horseback!

Salvador Dalí: Don Quijote de la Mancha

ESTRO School

Suggested further reading

The Breast 35 (2017) 32–33

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Viewpoints and debate

Less is more. Breast conservation might be even better than mastectomy in early breast cancer patients

Oreste D. Gentilini [a, *], Maria-Joao Cardoso [b], Philip Poortmans [c]

[a] San Raffaele University and Research Hospital, Milano, Italy
[b] Breast Unit, Champalimaud Foundation, Lisbon, Portugal
[c] Department of Radiation Oncology, Institut Curie, Paris, France

ARTICLE INFO

Article history:
Received 14 April 2017
Accepted 10 June 2017

ABSTRACT

During the recent years an increase of mastectomy rates in early breast cancer patients has been observed. Nevertheless, several large population-based studies reported a possible improved outcome after breast conserving therapy compared to radical surgery, after all the adjustments. We hereby summarize our opinion on this topic suggesting that these robust and consistent data might challenge the statement that breast conserving therapy is merely *not inferior* to radical surgery.

© 2017 Elsevier Ltd. All rights reserved.

Acknowledgements *(alphabetical):*

- Harry Bartelink
- Laurence Collette
- Sarah Darby
- Birgitte Offersen
- Roberto Orecchia
- Oliver Ott
- John Yarnold
- Icro Meattini
- Meritxell Arenas
- Lorenzo Livi
- And many others!

ESTRO School

institutCurie

Cosmetic results after breast conserving therapy

Liesbeth Boersma, Radiation Oncologist

Maastro Clinic, University Hospital Maastricht, The Netherlands

ESTRO Teaching Course on Breast Cancer, Dublin, Sept. 10-13th 2017

Contents

- How to measure cosmetic results?
- Cosmetic results after BCT and influencing factors
- Tools to improve cosmetic outcome
- Take home messages

How to measure cosmetic results ?

- Subjective measures:
  - Physician
  - Expert panel
  - Patient

- Objective measures, e.g.:
  - BCCT.core
  - BAT
  - …

Subjective measures

- Physicians/Expert panels:
  - Most frequently used is Harris scale: excellent, good, fair, poor

- Patients - Validated questionnaires, e.g.
  - Sneeuw et al: 8 items
  - BCTOS: Breast Cancer Treatment Outcome Scale: 22 items.
  - Breast Q (MSKCC, endorsed by ICHOM): Very extensive questionnaire, several different modules:
    - Breast Conserving Therapy
    - Latissimus Dorsi (LD) Scales
    - Mastectomy +/- reconstruction (including Expectations scales)
    - Reduction/Mastopexy & Augmentation
  - *Breast Q is currently being modified by dr. Young Afat*

Harris et al, 1979; Sneeuw et al, 1992; Pusic et al, 2009; Stanton et al, 2001

Subjective measures: review of PROMs

Table 2 - Psychometric qualities of the instruments included in this study (the + sign indicates that there is evidence that the specific property has been assessed)

	Validity	Reliability (includes internal consistency and test-retest reliability)	Responsiveness to change
BCQ	+	+	+
EORTC QOL-BR23	+	+	No evidence in favour
EORTC QOL C30	+ BR23 module	+	+
FACT-B	+	+	+
FACT-ES	+	+	+
BIBCQ	+	+	No evidence in favour
Polivy BIS		-	No evidence in favour
Hopwood BIS	+	+	No evidence in favour
BCTOS	+	+	No evidence in favour
MAS			No evidence in favour
BREAST-Q	+	+	+
MBROS-S		+	No evidence in favour
MBROS-BI	+	+	+
SLDS-BC		+	No evidence in favour
BCPT		+	No evidence in favour

Included in ICHOM dataset (www.ichom.org)

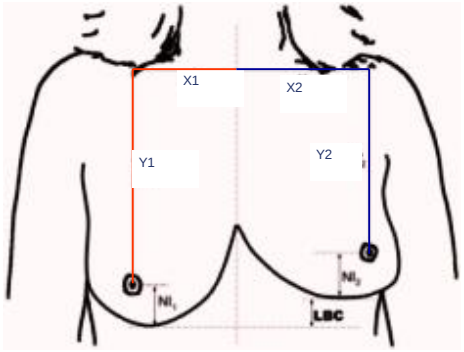
Kanatas et al, 2012

Examples of objective measures

- Using asymmetry features:
  - Photos with manual/ digital measurements (Vrieling et al, 1999; Reddy et al, 2017)
  - BAT – software: Breast Analysing Tool (Fitzal et al, 2007)

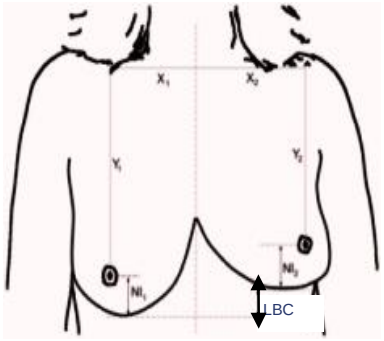
- Using asymmetry, skin colour & scar appearance
  - BCCT.core (Cardoso & Cardoso 2007)
  - 7 asymmetry features
    - pBRA = change in nipple position, pLBC = change in level of lower breast contour, pUNR = change in nipple level, pBCE = change in distance from nipple to inframammary fold, pBCD = change in length of breast contour, pBAD = change in area of the breast, pBOD = change in non overlapping area between left and right breast.

Example of symmetry features in BCCT.core

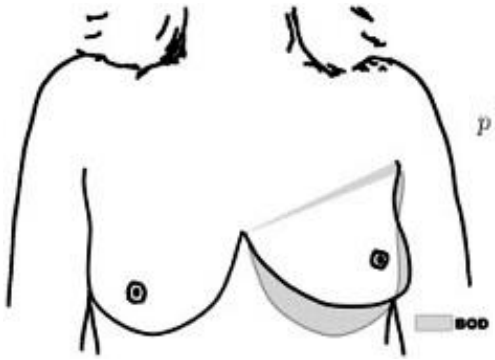


$$BRA = \sqrt{(X_1 - X_2)^2 + (Y_1 - Y_2)^2}$$

$$pBRA = \frac{2 \times BRA}{\sqrt{X_1^2 + Y_1^2} + \sqrt{X_2^2 + Y_2^2}}$$

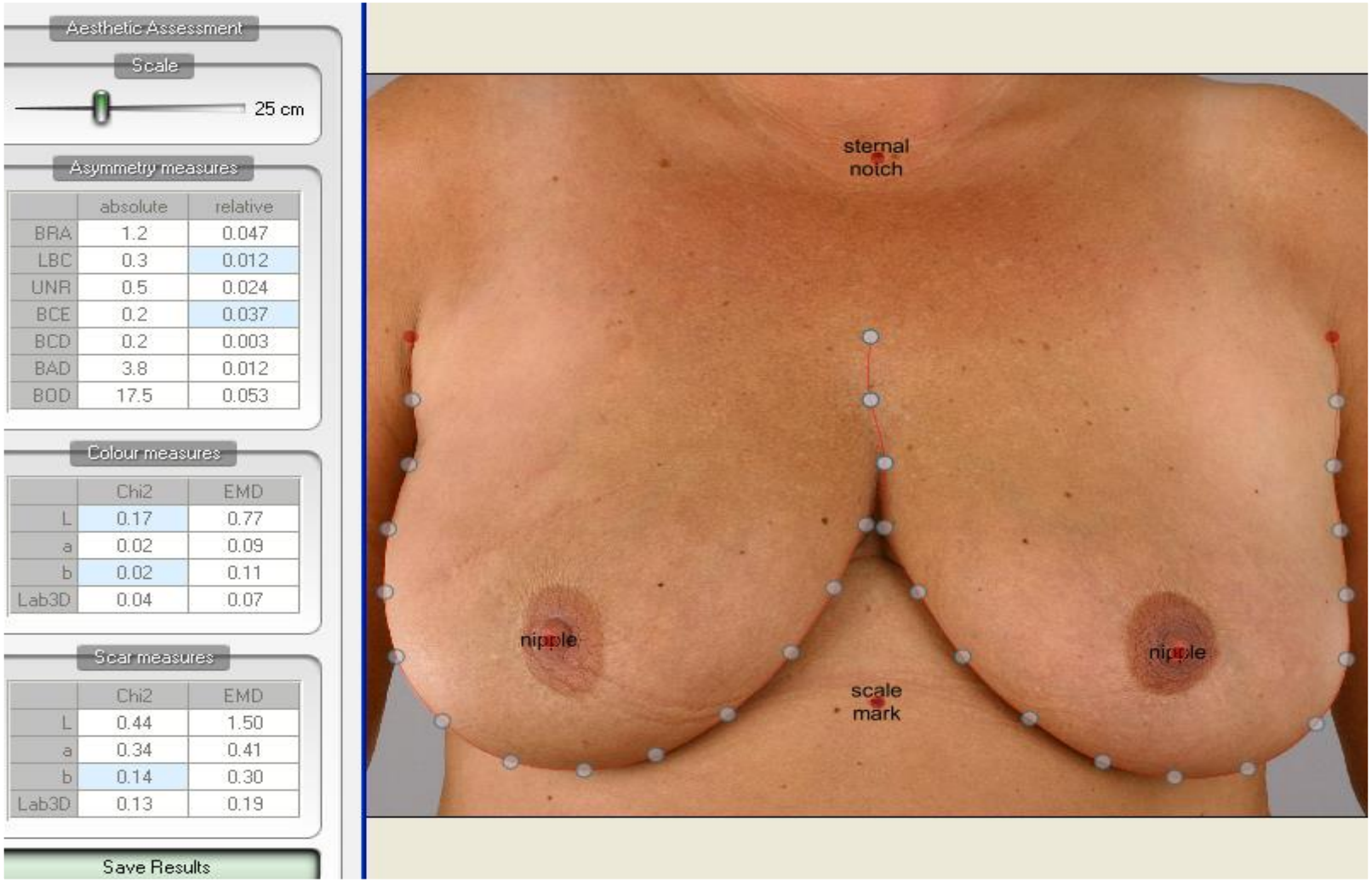


$$pLBC = \frac{2 \times LBC}{(Y_1 + NI_1 + Y_2 + NI_2)}$$



$$pBOD = \frac{2 \times BOD}{(rigth\ area + left\ area)}$$

Example of good cosmetic outcome in BCCT.core



Example of poor cosmetic outcome in BCCT.core

Aesthetic Assessment

Scale

25 cm

Asymmetry measures

	absolute	relative
BRA	2.3	0.095
LBC	2.8	0.118
UNR	1.4	0.065
BCE	1.4	0.674
BCD	5.7	0.157
BAD	49.2	0.272
BOD	49.4	0.274

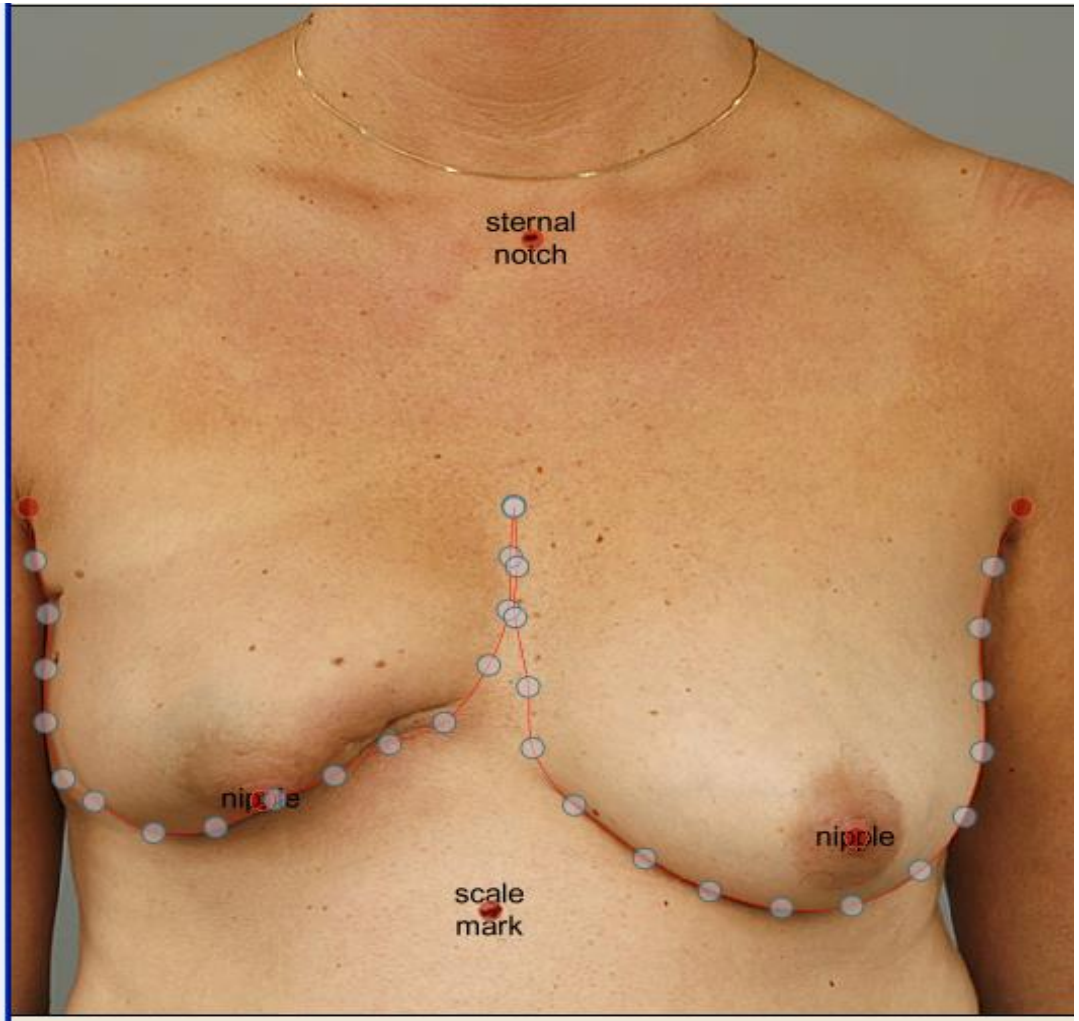
Colour measures

	Chi2	EMD
L	0.20	1.82
a	0.14	0.35
b	0.18	0.57
Lab3D	0.15	0.30

Scar measures

	Chi2	EMD
L	1.50	6.71
a	1.18	1.15
b	1.30	1.95
Lab3D	0.98	0.96

Save Results



MAASTRO CLINIC

ESTRO School

Validity of cosmetic measures

Table 1 Evaluation in four classes: agreement between subjective (expert panel) results and objective (software) results.

	Subjective results		Objective results	
	First-round consensus	Overall	First-round consensus	Overall
Number of patients	17	30	17	30
Number of experts	12	12	10	9
Interobserver agreement (*k*; *wk*)	0.58; 0.73	0.40; 0.57	0.75; 0.83	0.86; 0.90
Expert with highest agreement with consensus (*k*; *wk*)	0.84; 0.91 (2 differences)	0.73; 0.82 (6 differences)		
Expert with lowest agreement with consensus (*k*; *wk*)	0.52; 0.67 (7 differences)	0.37; 0.58 (14 differences)		
Expert with median agreement with consensus (*k*; *wk*)	0.72; 0.83 (4 differences)	0.57; 0.70 (10 differences)		
Agreement between software and consensus (*k*; *wk*)			0.60; 0.73 (5 differences)	0.34; 0.53 (14 differences)

Kappa < 0.2: slight agreement; 0.21-0.4: fair; 0.41- 0.6 moderate; 0.61-0.8: substantial; > 0.81: almost perfect

Cardoso et al, 2007

Validity of cosmetic measures

Table 2 Evaluation in three classes (good and fair merged): agreement between subjective (expert panel) results and objective (software) results.

	Subjective results		Objective results	
	First-round consensus	Overall	First-round consensus	Overall
Number of patients	24	30	24	30
Number of experts	12	12	9	9
Interobserver agreement (*k*; *wk*)	0.61; 0.66	0.51; 0.57	0.82; 0.83	0.87; 0.88
Expert with highest agreement with consensus (*k*; *wk*)	1.00; 1.00 (0 differences)	0.87; 0.88 (2 differences)		
Expert with lowest agreement with consensus (*k*; *wk*)	0.49; 0.56 (7 differences)	0.40; 0.47 (11 differences)		
Expert with median agreement with consensus (*k*; *wk*)	0.77; 0.79 (3 differences)	0.62; 0.66 (6 differences)		
Agreement between software and consensus (*k*; *wk*)			0.72; 0.79 (3 differences)	0.57; 0.61 (6 differences)

Kappa < 0.2: slight agreement; 0.21-0.4: fair; 0.41- 0.6 moderate; 0.61-0.8: substantial; > 0.81: almost perfect

Cardoso et al, 2007

Which factors are most important for the patient ?

Analysis of Young Boost Trial patients (N = 864)

Radiotherapy and Oncology 120 (2016) 107–113

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Phase III randomised trial

Factors associated with patient-reported cosmetic outcome in the Young Boost Breast Trial

Patricia J.A.M. Brouwers [a,*,1], Erik van Werkhoven [b,1], Harry Bartelink [b], Alain Fourquet [c], Claire Lemanski [d], Judith van Loon [a], John H. Maduro [e], Nicola S. Russell [b], Luc J.E.E. Scheijmans [f], Dominic A.X. Schinagl [g], Antonia H. Westenberg [h], Philip Poortmans [f,2], Liesbeth J. Boersma [a,2], on behalf of the Young Boost Trial research group [3]

Brouwers et al, R & O 2016

Which factors are most important for the patient ?

Analysis of Young Boost Trial patients (N = 864)

- Endpoints:
  - BCCT.core, physican and - patient reported

- Tested variables
  - All 7 BCCT.core parameters
  - Ribpain
  - Fibrosis (4 point scale – patient and physician)
  - QoL

Which aspects influence cosmetic score by the patient ?

Analysis of Young Boost Trial patients (N = 864)

- Results – correlation between methods:
  - Correlation patient and physician: kappa 0.42 (moderate)
  - Correlation between patient and BCCT.core: kappa 0.26 (fair)
  - Correlation between physician and BCCT.core: kappa 0.39 (fair)

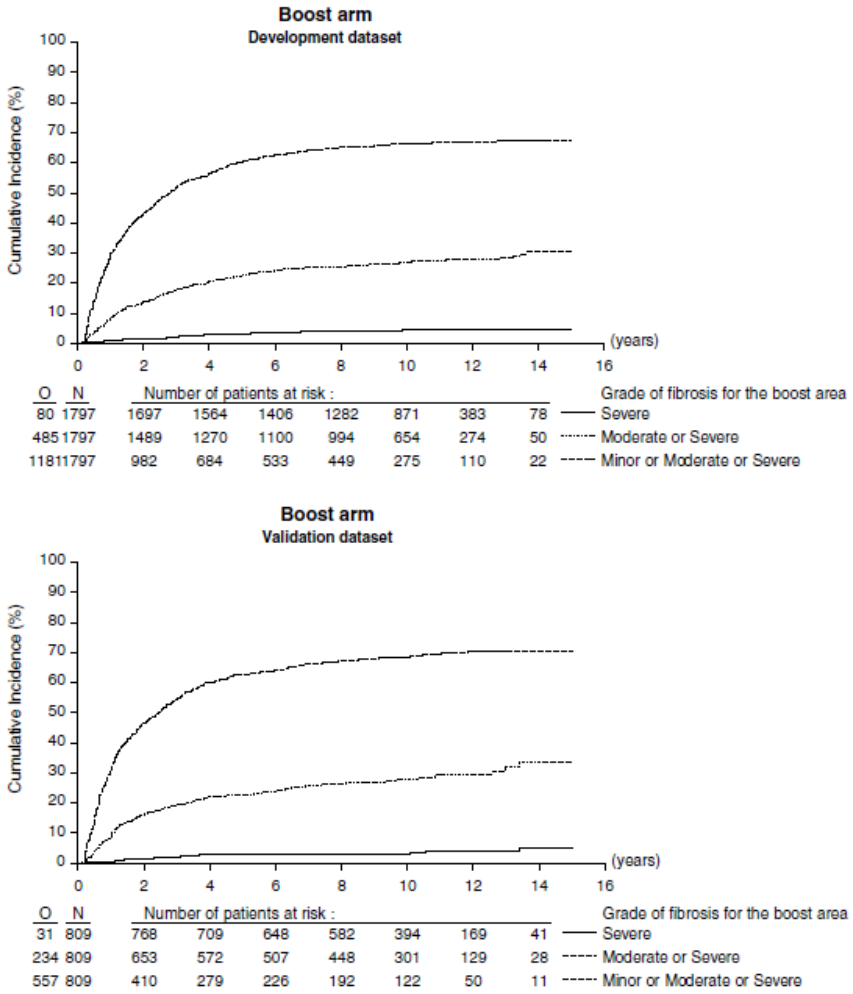
- Results – correlation with patient reported outcome:
  - Significant correlation with patient –reported outcome:
    - pBCE = change in distance from nipple to inframammary fold
    - pBCD = change in length of breast contour
    - Fibrosis *(cause or consequence ?)*
  - Patients with better QoL scored their cosmesis better (also reported by e.g. Hau et al, 2013) *(cause or consequence ?)*

Reported cosmetic results after breast conserving therapy

- Good- excellent outcome / satisfactory results:
  - Reported to vary from 56 % to 92%

  - Many differences between studies:
    - Scored by physician, patient or objective score
    - Time to follow-up
    - Different RT characteristics:
      - Techniques 2D CRT – full IMRT
      - Different dose and fractionation
      - Different target volumes PBI vs WBRT
    - Different surgical techniques
      - Lumpectomy +/- less or more extensive oncoplastic surgery
    - With or without adjuvant systemic treatment

Fibrosis after breast conserving therapy
Change over the years: boost no boost data



Fibrosis:

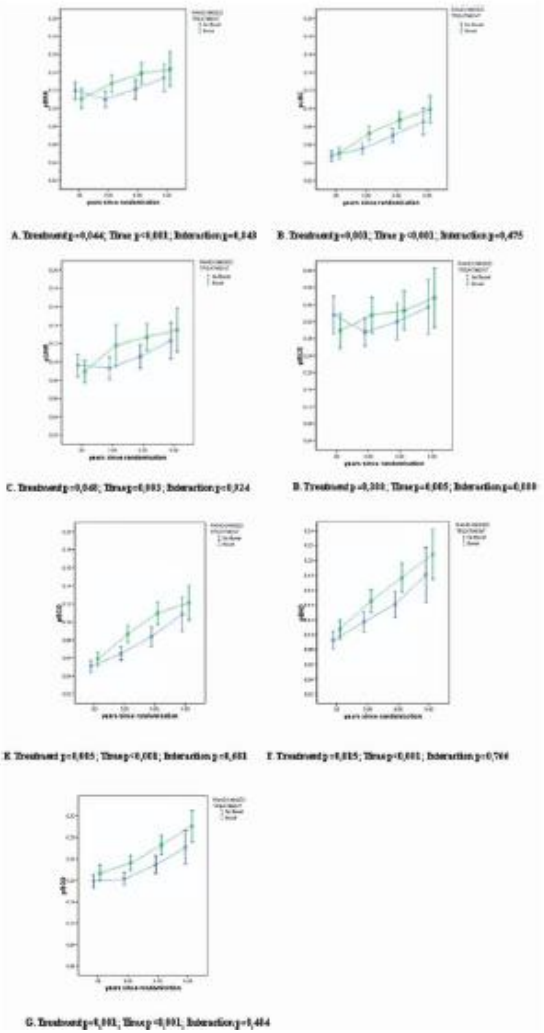
Is most progressive in first 4 years after RT

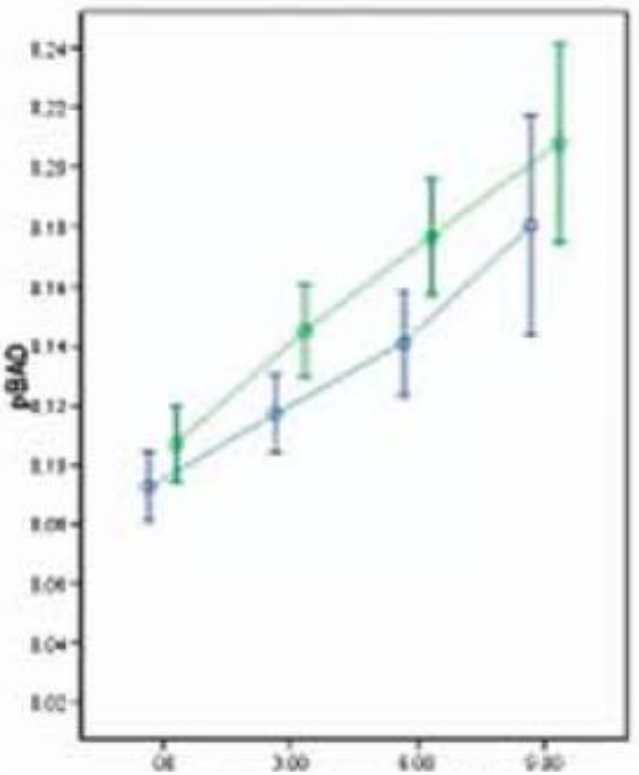
Collette et al 2008

MAASTRO CLINIC

ESTRO School

Cosmetic results after breast conserving therapy
Change over the years; boost no boost data





Years since randomisation

Asymmetry:

progresses over the years

Immink et al, 2012

Which *radiotherapy* related factors play a role ?

- Several RCTs performed to investigate impact on cosmesis of:
  - Hypofractionation (40-42 Gy in 15-16 fx) compared to 25 x 2 Gy
  - Boost vs no boost
  - Low boost vs high boost
  - Prone vs supine
  - IMRT vs 2D-CRT
  - Partial breast RT vs Whole breast RT

Cosmetic results after breast conserving therapy

- Which factors play a role ? Several RCTs to investigate impact of:

Factor studied	Impact on cosmesis	Conclusion
Hypofx	No change in breast appearance	

Hypofx: *Whelan 2008; Haviland 2013;* ***Prone vs supine:*** *Veldeman 2016;* ***2D CRT vs IMRT:*** *Pignol 2016; Mukesh 2014;* ***No vs low boost:*** *Vrieling 1999 & 2000, Hau 2013;* ***Low vs high boost****: Brouwers 2016;* ***PBI vs WBRT:*** *Polgar 2017, Coles 2017, Peterson 2015*

ESTRO School

Cosmetic results after breast conserving therapy

- Which factors play a role ? Several RCTs to investigate impact of:

Factor studied	Impact on cosmesis	Conclusion
Hypofx	No change in breast appearance	
No boost vs low boost	No boost better than boost	

Hypofx: *Whelan 2008; Haviland 2013;* ***Prone vs supine:*** *Veldeman 2016;* ***2D CRT vs IMRT:*** *Pignol 2016; Mukesh 2014;* ***No vs low boost:*** *Vrieling 1999 & 2000, Hau 2013;* ***Low vs high boost****: Brouwers 2016;* ***PBI vs WBRT:*** *Polgar 2017, Coles 2017, Peterson 2015*

ESTRO School

Cosmetic results after breast conserving therapy

- Which factors play a role ? Several RCTs to investigate impact of:

Factor studied	Impact on cosmesis	Conclusion
Hypofx	No change in breast appearance,	
No boost vs low boost	No boost better than boost	
Prone vs Supine	Tendency for better outcome prone than supine	
2D CRT vs IMRT	Only benefit if scored by physician at 5 yr, and if patients are selected	

Hypofx: *Whelan 2008; Haviland 2013;* ***Prone vs supine:*** *Veldeman 2016;* ***2D CRT vs IMRT:*** *Pignol 2016; Mukesh 2014;* ***No vs low boost:*** *Vrieling 1999 & 2000, Hau 2013;* ***Low vs high boost****: Brouwers 2016;* ***PBI vs WBRT:*** *Polgar 2017, Coles 2017, Peterson 2015*

ESTRO School

Cosmetic results after breast conserving therapy

- Which factors play a role ? Several RCTs to investigate impact of:

Factor studied	Impact on cosmesis	Conclusion
Hypofx	No change in breast appearance	
No boost vs low boost	No boost better than boost	
Prone vs Supine	Tendency for better outcome prone than supine	
2D CRT vs IMRT	Only benefit if scored by physician at 5 yr, and if patients are selected	
Partial breast vs WBRT	Results conflicting	

Hypofx: *Whelan 2008; Haviland 2013;* ***Prone vs supine:*** *Veldeman 2016;* ***2D CRT vs IMRT:*** *Pignol 2016; Mukesh 2014;* ***No vs low boost:*** *Vrieling 1999 & 2000, Hau 2013;* ***Low vs high boost****: Brouwers in preparation;* ***PBI vs WBRT:*** *Polgar 2017, Coles 2017, Peterson 2015*

ESTRO School

Cosmetic results after breast conserving therapy

- Which factors play a role ? Several RCTs to investigate impact of:

Factor studied	Impact on cosmesis	Conclusion
Hypofx	No change in breast appearance	Alfa/beta 3.5 Gy →
No boost vs low boost	No boost better than boost	Dose-effect relation present
Prone vs Supine	Tendency for better outcome prone than supine	Due to better dose homogeneity ?
2D CRT vs IMRT	Only benefit if scored by physician at 5 yr, and if patients are selected	
Partial breast vs WBRT	Results conflicting	Probably due to DVH parameters and dose per fraction; not clear

Hypofx: *Whelan 2008; Haviland 2013, Valle 2017;* ***Prone vs supine:*** *Veldeman 2016;* ***2D CRT vs IMRT:*** *Pignol 2016; Mukesh 2014;* ***No vs low boost:*** *Vrieling 1999 & 2000, Hau 2013;* ***Low vs high boost****: Brouwers in preparation;* ***PBI vs WBRT:*** *Polgar 2017, Coles 2017, Peterson 2015*

ESTRO School

Effect of dose ?

- ***Preliminary*** analyses Young Boost Trial (N = 2452)
  - Patients ≤ 50 yrs treated with BCT and 50 Gy WBRT
    - Randomized between boost 16 vs 26 Gy
    - Photos available at baseline and 4 yrs in 684 patients
    - Analyzed using BCCT.core, physicians and patients

Systematic review on oncoplastic surgery in BCT

- Discrimination between :
  - Volume Displacement (VD): mobilizing local glandular flaps
  - Volume Replacement (VR): uses autologous tissue from a remote site

- N = 4170 patients in 41 studies
- 37 studies included VD:
  - 17 of these had PROMs on cosmetics: 70-100% good- excellent
- 11 studies included VR:
  - 6 of these had PROMs on cosmetics: 82-92% good-excellent

Yoon et al, 2016

Effect of oncoplastic surgery ?

Available online at www.sciencedirect.com

ScienceDirect

EJSO 41 (2015) 1411–1416

EJSO
the Journal of Cancer Surgery

www.ejso.com

The influence of simultaneous integrated boost, hypofractionation and oncoplastic surgery on cosmetic outcome and PROMs after breast conserving therapy

J.T.P. Lansu [a,c,*], M. Essers [a], A.C. Voogd [c], E.J.T. Luiten [b], C. Buijs [a], N. Groenendaal [a], P.M.H. Poortmans [a,d]

Effect of oncoplastic surgery ?

- 125 patients treated with BCT 2004-2012
  - 2007: Sequential boost replaced by SIB
  - 2009: Hypofx incrementally introduced
  - 2011: Oncoplastic surgery incrementally introduced

- Evaluation 1 yr after RT
  - PROM:
    - Cosmetic questionnaire Sneeuw et al
    - BCCT.core
    - EORTC QOL C30 and BR23

Lansu et al, 2015

Effect of oncoplastic surgery ?

Score (SD)	Conv fx, SIB, *Lumpectomy* SIB (n = 27)	Conv fx, SIB, *Oncoplastic surgery* OSCF (n = 19)	P-value SIB vs OSCF
BCCT.core score	1.9 (0.6)	2.45 (0.52)	0.02
YBT	27.6 (21.1)	26.94 (15.03)	0.93
C30 Funct. scale	87.1 (18.7)	75.90 (22.57)	0.28
C30 Symptom scale	16.5 (12.9)	17.31 (10.22)	0.57
C30 QOL	82.0 (17.4)	63.45 (35.77)	0.05
BR23 Funct. scale	82.9 (13.0)	70.19 (16.30)	0.06
BR23 Symptom scale	13.7 (9.3)	20.51 (12.35)	0.07
Boost volume	94.65 (57.76)	117.11 (106.20)	0.10

Suggestion that oncoplastic surgery leads to worse outcome!
However, very small figures…
Due to larger boost volumes ??

Lansu et al, 2015

Which factors are related to RT induced fibrosis ?

EUROPEAN JOURNAL OF CANCER 44 (2008) 2587–2599

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

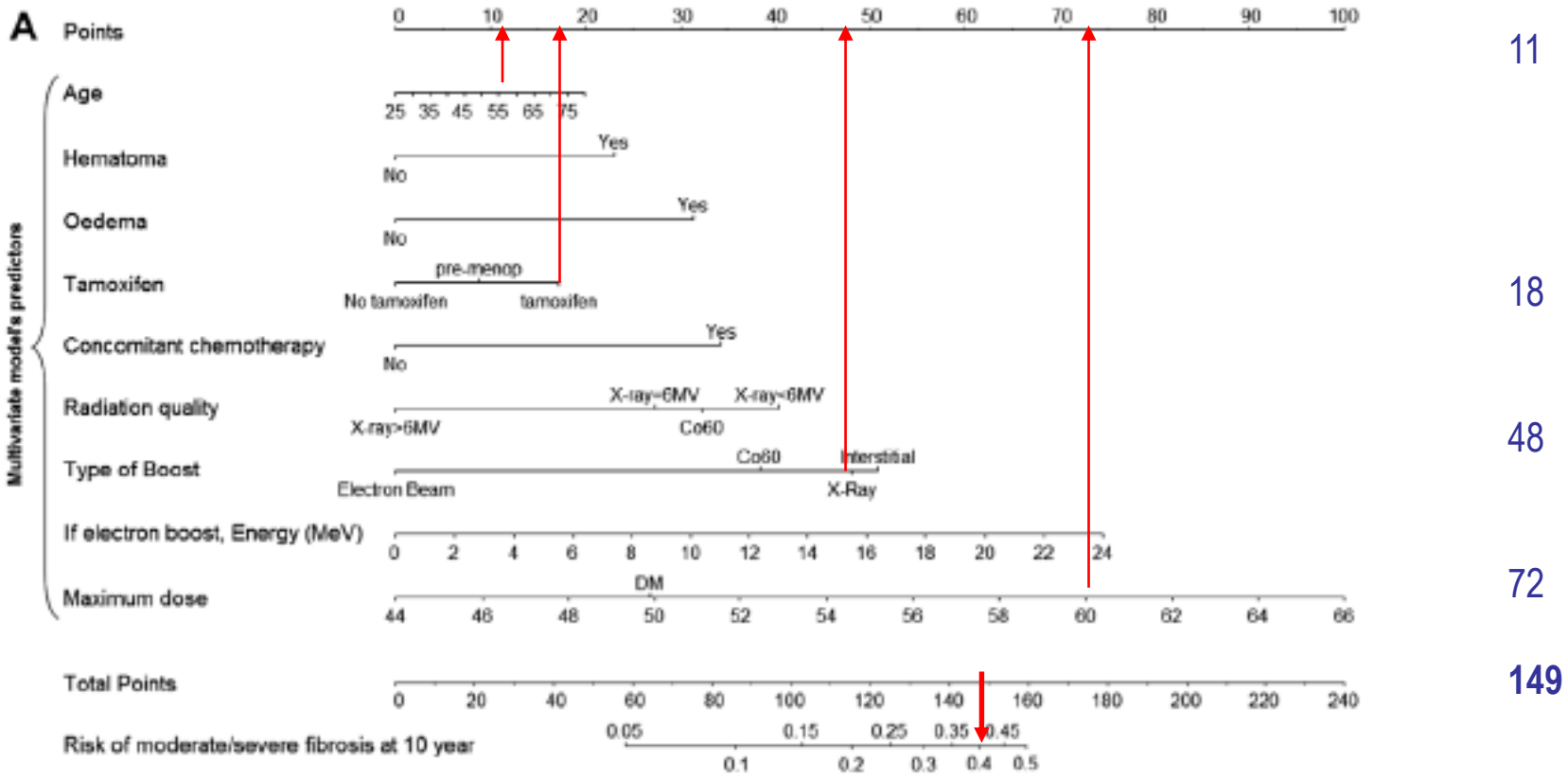
Predictors of the risk of fibrosis at 10 years after breast conserving therapy for early breast cancer – A study based on the EORTC trial 22881–10882 'boost *versus* no boost'

Sandra Collette[a,*], *Laurence Collette*[a], *Tom Budiharto*[a], *Jean-Claude Horiot*[b], *Philip M. Poortmans*[c], *Henk Struikmans*[d], *Walter Van den Bogaert*[e], *Alain Fourquet*[f], *Jos J. Jager*[g], *Willem Hoogenraad*[h], *Rolf-Peter Mueller*[i], *John Kurtz*[j], *David A.L. Morgan*[k], *Jean-Bernard Dubois*[l], *Emile Salamon*[m], *Rene Mirimanoff*[n], *Michel Bolla*[o], *Marleen Van der Hulst*[c], *Carla C. Wárlám-Rodenhuis*[p], *Harry Bartelink*[q], *EORTC Radiation Oncology Group*

Lansu et al, 2015

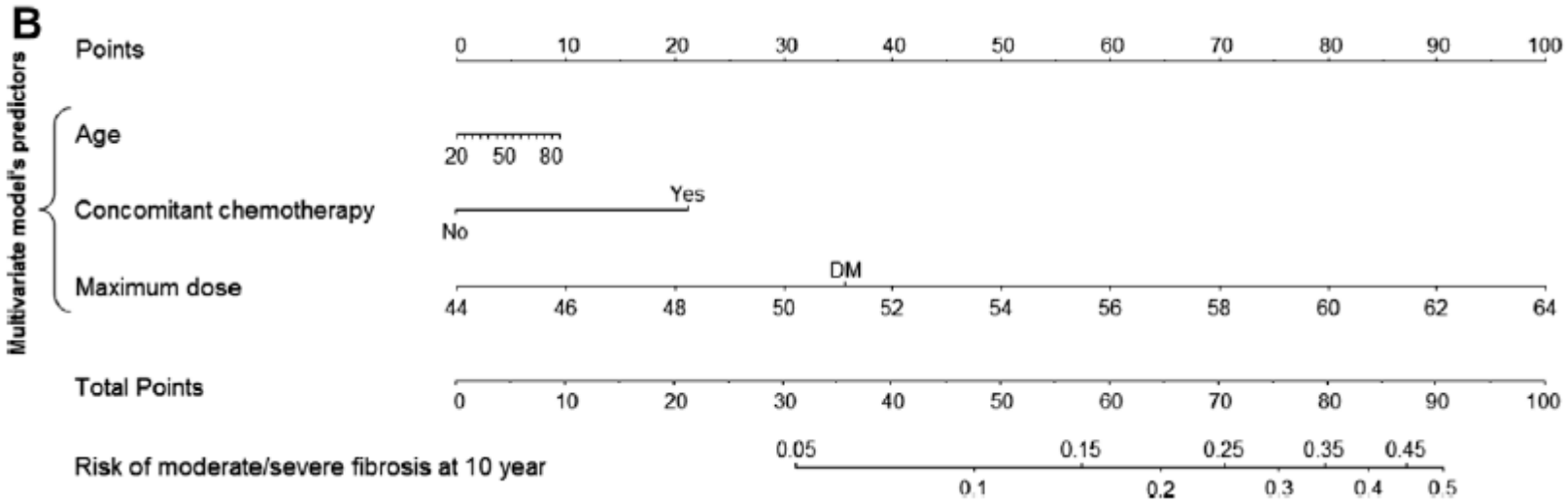
Nomogram for fibrosis after WBRT with boost

56 yr, no hematoma, no edema, with tamoxifen, no chemo, > 6 MV, photon boost, Dmax 60Gy → 40% chance on moderate/severe fibrosis at 10 yr



Collette et al 2008

Nomogram for fibrosis after WBRT <u>without</u> boost



Compared to nomogram with boost:

Hematoma, Edema, Tamoxifen, Rad Quality, Boost/type: NS

Collette et al 2008

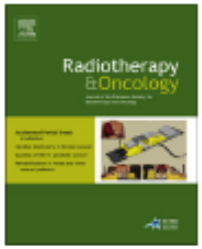
Which RT factors are related to fibrosis ?

Radiotherapy and Oncology 108 (2013) 293–298

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



NTCP for breast fibrosis

Normal tissue complication probability (NTCP) parameters for breast fibrosis: Pooled results from two randomised trials

Mukesh B. Mukesh [a,*], Emma Harris [b], Sandra Collette [c], Charlotte E. Coles [a], Harry Bartelink [d], Jenny Wilkinson [a], Philip M. Evans [e], Peter Graham [f], Jo Haviland [g], Philip Poortmans [h], John Yarnold [i], Raj Jena [a]

NTCP models using individual patient data of 2 large trials

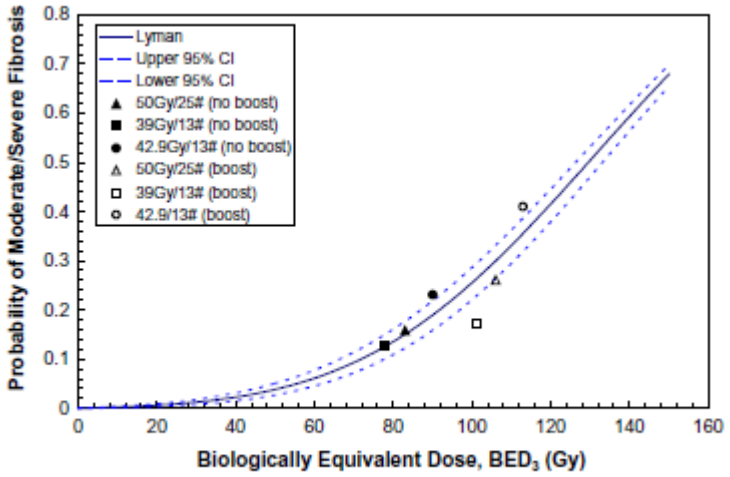


Fig. 1. Lyman Kutcher Burman model – the probability of moderate–severe breast

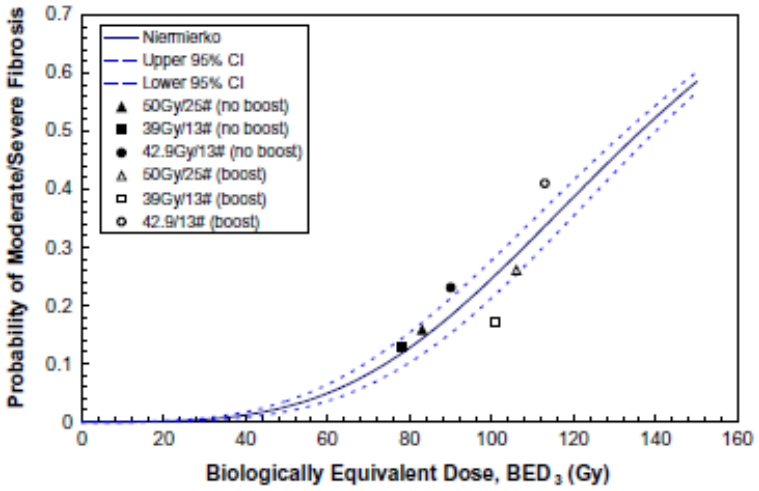


Fig. 2. Niemierko model – the probability of moderate–severe breast fibrosis versus

- Development of model using pooled data of: boost no boost trial & Cambridge IMRT trial
- Validated using the START-pilot trial

- EQD2 for 50% risk on moderate/severe fibrosis: about 80 Gy

Mukesh et al, 2013

Model parameters for fibrosis found in different studies

n = 0: serial organ

n = 1 parallel organ

Table 2
Summarised results of the best fit NTCP parameters for moderate-severe breast fibrosis.

	Number of patients	$BEUD_3(50)$	$\gamma 50$	m	n
Borger et al. [4]	404	NTD_{50} = 72 Gy (α/β = 2 Gy) ($t_{1/2}$ = 1.5 h)			0.16
* Alexander et al.* [6]					
LKB model	1546	104 Gy	–	0.27	0.78
Relative seriality model		104 Gy	1.47		(s = 0.12)
Avanzo et al.* [5]					
With repair correction (($t_{1/2}$ = 4.4 h)	2562	105.8 Gy	–	0.22	0.15
Without repair correction		107.2 Gy		0.22	0.06
Current study					
LKB model	5856	132 Gy		0.35	0.012
Niemierko model		136.4 Gy	0.9		0.011

Conclusions:

- Dose is the most important predictive factor for fibrosis;
- The volume (n) is very small → breast is a serial organ for endpoint fibrosis

* Study of Alexander et al considered to be not representative: also includes mastectomy, techniques outdated, based on studies using different endpoints

Which factors have all been mentioned to influence cosmetic outcome and/or fibrosis ?

- Treatment related factors:
  - Radiotherapy:
    - Boost volume, dose inhomogeneity, V55Gy, Dmax, V107, V110, IMRT, Prone vs supine, boost dose
  - Surgery
    - Post-operative complications like infection, hematoma, seroma
    - Baseline cosmesis after surgery – prior to RT, location of the tumor, time between surgery and radiotherapy
    - Oncoplastic surgery
  - Chemotherapy/ hormonal therapy
    - Yes/no
    - Concurrent/ sequential
- Patient related factors:
    - Age, BMI, smoking, diabetes, breast size, Bra size, pain..

Summary (2)

- How to summarize all mentioned factors ?
  - IMRT, Dmax, V55Gy, V110, V107, breast size, prone/supine: **Dose Homogeneity**
  - Hypofx, boost no boost, Young Boost: **Dose (EQD2)**
  - Excisional volume, tumor size, re-excision, time between surgery and RT, oncoplastic surgery (?): **Boost volume**
  - Excisional volume, tumor size, location of tumor, post-operative complications: **baseline cosmesis** (oncoplastic surgery??)
- Other possible important factors:
  - **Adjuvant systemic treatment;** chemotherapy, (concurrent) endocrine treatment
  - **Case mix factors** like Diabetes, Hypertension, Smoking, Age (fibrosis vs cosmesis), breast size

Contents

- How to measure cosmetic results?
- Cosmetic results after BCT and influencing factors
- Tools to improve cosmetic outcome
- Take home messages

How to improve cosmetic outcome ?

RT factors:

1. Optimize dose – homogeneity

2. Dose as low as considered to be oncologically safe
   - Hypofx 15 x 2.67 Gy instead of 25 x 2 Gy
   - Minimize indications for a boost – only in case of heavy risk factors

3. If a boost is required: minimize the irradiated boost volume

→ several strategies to minimize boost volume !

How to reduce the boost volume ?

- Pathology; discuss with your pathologist:
  - Free margins in 6 directions → smaller delineated CTV

- Surgery; discuss with your surgeon:
  - Limit excision volumes; no tumor on ink is sufficient !
  - Limit size of seroma cavity
  - Place clips to reduce uncertainty→ to reduce volume
  - Avoid oncoplastic surgery in case of indication for boost ?

- Chemotherapy:
  - If required anyway: consider to give it upfront → Smaller tumor, smaller excision volumes.
  - Consider to give it prior to RT to increase time between OK and RT ?

Take Home Messages (1)

- Cosmetic outcome after BCT varies from 56 - 92%
- Interpretation of literature difficult due to differences in endpoints and duration of follow-up
- Most important factor seems to be: **cosmesis prior to RT**
- Other factors that worsen cosmetic outcome:
  - Inhomogeneous dose distribution, high EQD2, large boost volumes, young age, large breast size, smoking, chemotherapy
- Questionable influence:
  - Endocrine therapy, oncoplastic surgery

Take Home Messages (2)

- Approaches to improve cosmetic outcome:
  - Improve dose homogeneity
  - Reduce total dose
  - Reduce boost volume
    - Multidisciplinary approach required !!
      - Pathologist
      - Surgeon
      - Medical oncologist
      - Radiation oncologist

How to reduce boost volume ?

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 75, No. 3, pp. 757–763, 2009
Copyright © 2009 Elsevier Inc.
Printed in the USA. All rights reserved
0360-3016/09/$–see front matter

doi:10.1016/j.ijrobp.2008.11.048

CLINICAL INVESTIGATION **Breast**

CUSTOMIZED COMPUTED TOMOGRAPHY-BASED BOOST VOLUMES IN BREAST-CONSERVING THERAPY: USE OF THREE-DIMENSIONAL HISTOLOGIC INFORMATION FOR CLINICAL TARGET VOLUME MARGINS

BIANCA HANBEUKERS, M.A.,* JACQUES BORGER, M.D., PH.D.,*† PIET VAN DEN ENDE, M.D.,*† FRED VAN DER ENT, M.D., PH.D.,‡ RUUD HOUBEN, M.SC.,* JOS JAGER, M.D., PH.D.,*† KRISTIEN KEYMEULEN, M.D.,§ LARS MURRER, PH.D.,*† SUPRAPTO SASTROWIJOTO, M.D.,¶ KOEN VAN DE VIJVER, M.D., PH.D.,‖ AND LIESBETH BOERSMA, M.D., PH.D.†*

- Plannings study to compare V95 for boost volume for:
  - PTV_conventional simulator
  - PTV_CT planning – isotropic CTV margins
  - PTV_CT planning – anisotropic margins based on 3D pathology data

Hanbeukers et al 2009

How to reduce boost volume ?

- V95:
  - PTV_CT plan- isotrop margins = 1.6 times larger than PTV_conv sim
  - PTV_CT plan – anisotrop margins ~ PTV_con sim

- Most important factor for boost volume:

  - Size of excisional volume → related to time between surgery and RT

How to reduce boost volume ?

Does a pre-operative CT in treatment position help ?

- Boersma et al (2012):
  - Boost CTV 42 cc to 36 cc (translating in V95 from 117cc to 105cc)
- Verhoeven et al (2016)
  - No difference in size of CTV with or without pre-op CT..
- → No clinically significant reduction in V95

Summary (1)

- Wide variation in cosmetic results after BCT reported 56- 92% good-excellent outcomes.
- Variation probably due to a.o. methodological differences:
  - Difference types of scoring (Patient, Physician, Objective)
  - Difference in f-up time
    - Cosmetic worsening progresses over the years – fibrosis mainly first 4 years: Time to follow-up extremely important !

Which factors influence cosmetic result ?

- Several *radiotherapy-related* factors have been reported to be related to cosmetic outcome:
  - Total dose (EQD2) and/or fraction size ?
  - Boost volume
  - All kind of factors related to dose inhomogeneity, e.g.:
    - IMRT
    - Prone vs supine
    - Dmax
    - V107
    - V110
    - Breast size (or is this an independent variable ?)
    - …

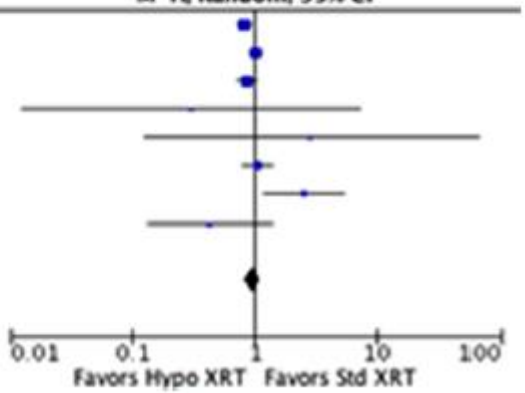
Hypofx does not adversely influence cosmetic outcome

(b)

Study or Subgroup	Hypofractionated XRT Events	Total	Standard Whole breast XRT Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Haviland 2013 START A (39 Gy)	251	737	307	749	27.0%	0.83 [0.73, 0.95]
Haviland 2013 START A (41.6 Gy)	314	750	307	749	27.9%	1.02 [0.91, 1.15]
Haviland 2013 START B	145	462	167	461	23.1%	0.87 [0.72, 1.04]
Li 2014	0	185	1	167	0.2%	0.30 [0.01, 7.34]
Saha 2009	1	24	0	23	0.2%	2.88 [0.12, 67.29]
Whelan 2010	71	235	62	216	15.9%	1.05 [0.79, 1.40]
Yarnold 2011 (28.5 Gy)	23	242	9	239	3.9%	2.52 [1.19, 5.34]
Yarnold 2011 (30 Gy)	4	248	9	239	1.7%	0.43 [0.13, 1.37]
Total (95% CI)		**2883**		**2843**	**100.0%**	**0.95 [0.81, 1.12]**
Total events	809		862			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 15.92$, $df = 7$ ($P = 0.03$); $I^2 = 56\%$

Test for overall effect: $Z = 0.59$ ($P = 0.55$)



Valle et al, review 2017

Clinical Studies on local treatment: maturing, accruing and nurturing

Youlia M. Kirova,

Department of Radiation Oncology

institutCurie

youlia.kirova@curie.fr

Clinical Studies on local treatment

- Maturing
- Accruing
- Nurturing

Clinical Studies in local treatment

- Maturing
  - DCIS
  - Invasive

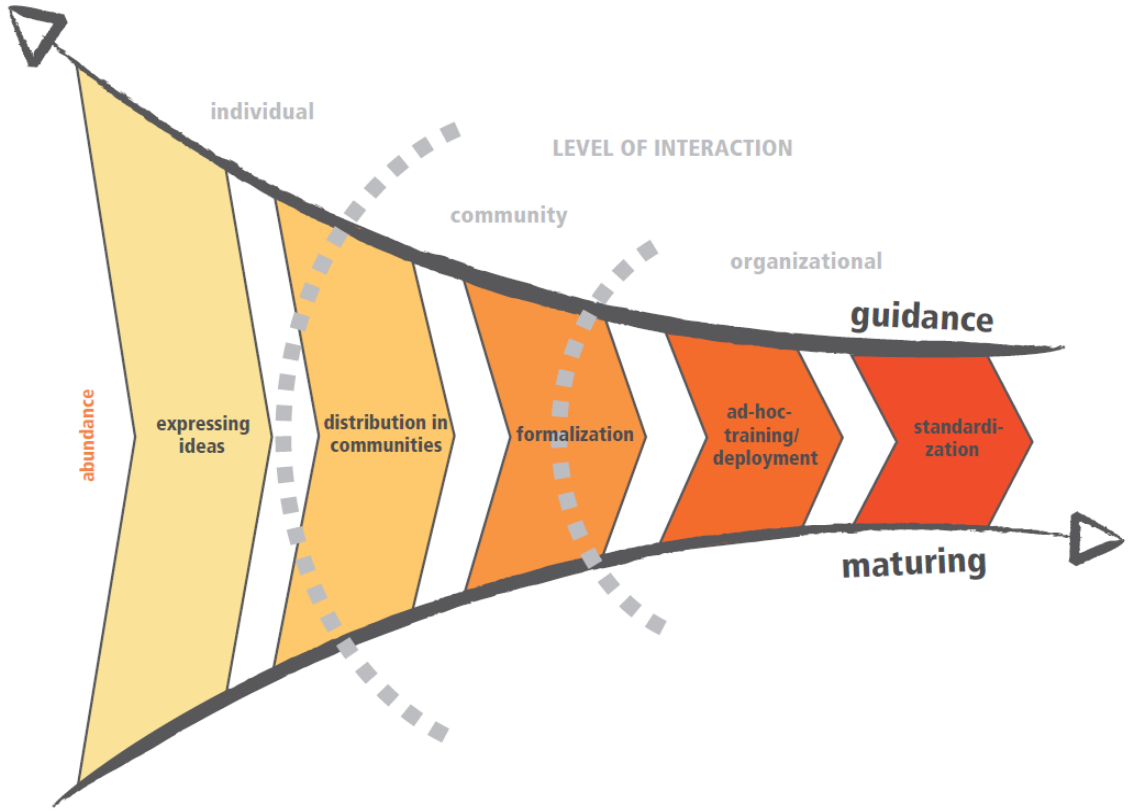


Fig. 1 Knowledge Maturing Process model

Schmidt, A. et al. (2009).

ROMANCE: Phase III Open Labeled Randomized Trial of Omission of Whole-Breast Radiation Therapy in patients with very low risk DCIS

MAIN OBJECTIVE : *TO DETERMINE WHETHER THE COMBINED USE OF CLINICAL, MORPHOLOGICAL, AND IMMUNOHISTOCHEMICAL MARKERS OF LOW RECURRENCE RISK IN DCIS, COULD BE USED TO IDENTIFY PATIENTS WHO COULD BE SAFELY OMITTED THE DELIVERY OF WHOLE-BREAST IRRADIATION FOLLOWING BREAST-CONSERVING EXCISION WITH TUMOUR-FREE MARGINS*

HYPOTHESES AT 5-YEAR:

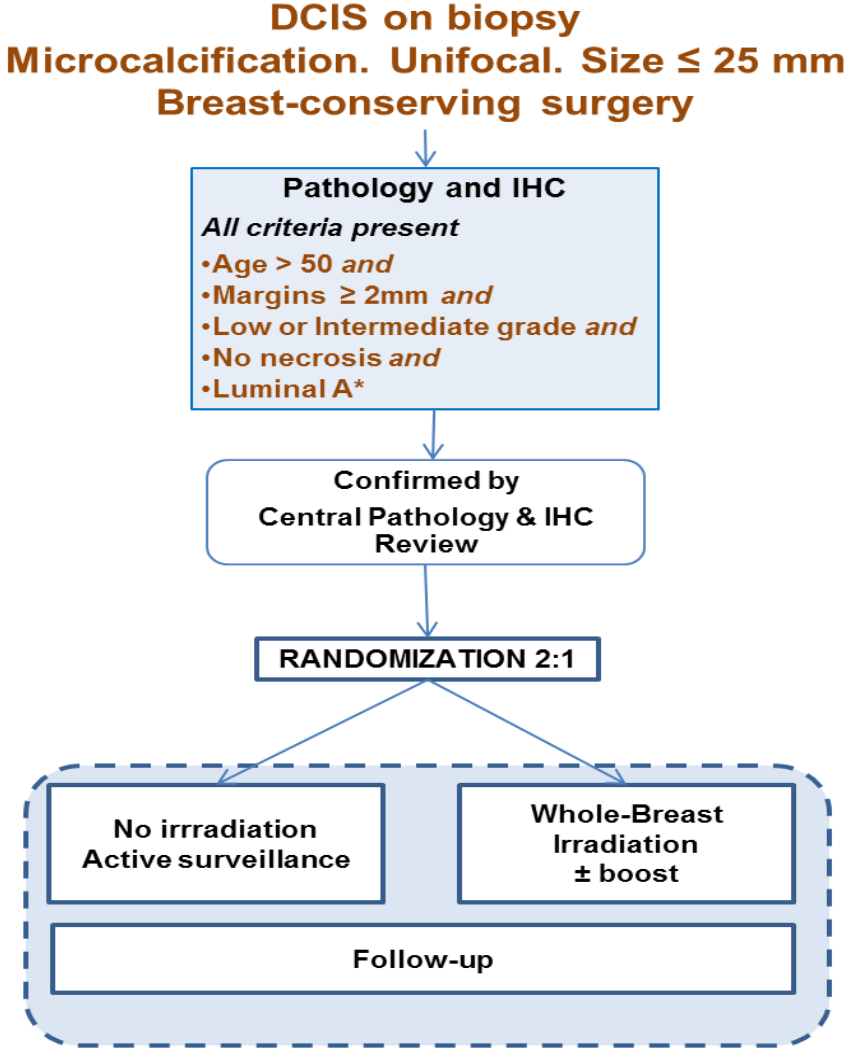
< 3,5 % IBR IN EXPERIMENTAL ARM (NO RT)

0,8 % IBR IN REFERENCE ARM (RT)

A (UNILATERAL) = 2% ; B = 97%

666 PATIENTS (444 : 222)

institutCurie



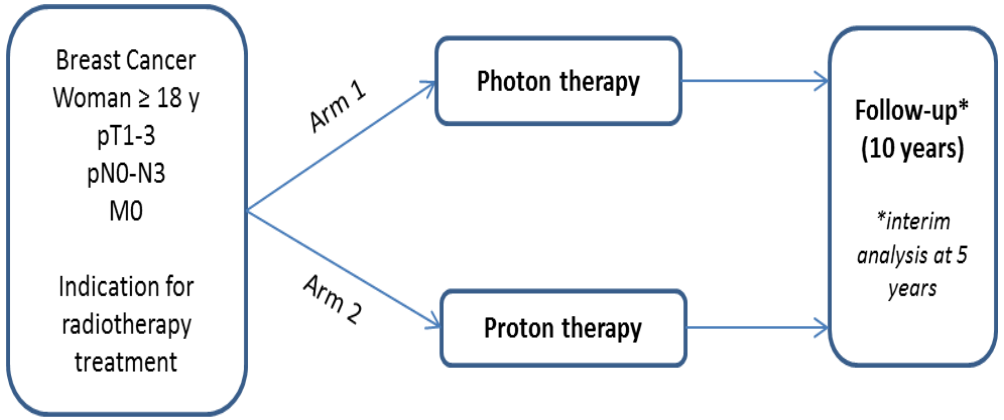
* Luminal A: ER ≥ 10 % *and* PR ≥ 20 % *and* HER2 0/1/2+ *and* Ki 67 < 15 %

BREAST P1: Multicenter randomized phase III trial comparing protons versus standard photon radiation therapy in breast cancer with an indication for regional lymph node irradiation in terms of cardiac toxicity occurrence

- **MAIN OBJECTIVE:** *TO ASSESS THE SUPERIORITY OF THE PROTON LOCOREGIONAL RADIOTHERAPY TO CURRENTLY USED PHOTON-ELECTRONS 3D-CONFORMAL OR INTENSITY MODULATED RADIATION THERAPY (IMRT) IN TERMS OF CARDIAC TOXICITY AT 10 YEARS.*

n=1310 patients, open for International participation

- **SECONDARY OBJECTIVE S:**
- *TO SHOW THAT PROTON LOCOREGIONAL RT IS NOT INFERIOR TO CURRENTLY USED PHOTON-ELECTRONS 3D CONFORMAL RT OR IMRT IN EARLY STAGE BREAST CANCER WITH AN INDICATION FOR REGIONAL LYMPH NODE IRRADIATION IN TERMS OF LOCAL-REGIONAL RECURRENCE*
- *TO ASSESS LOCO-REGIONAL ACUTE AND LATE TOXICITIES (RADIODERMATITIS, ARM MOTION AND FUNCTION, COSMETIC RESULT,*
- *LUNG AND CONTRALATERAL BREAST EVENTS*
- *CANCER RELATED-EVENTS: LOCOREGIONAL RELAPSE-FREE SURVIVAL, DISTANT DISEASE-FREE SURVIVAL, OVERALL SURVIVAL, CAUSES OF DEATH,*
- *TO ASSESS AND COMPARE HEALTH RELATED QUALITY OF LIFE BETWEEN ARMS*
- *TO CONDUCT A COST-UTILITY ANALYSIS*
- *TRANSLATIONAL RESEARCH*



Interim analysis at 5 years

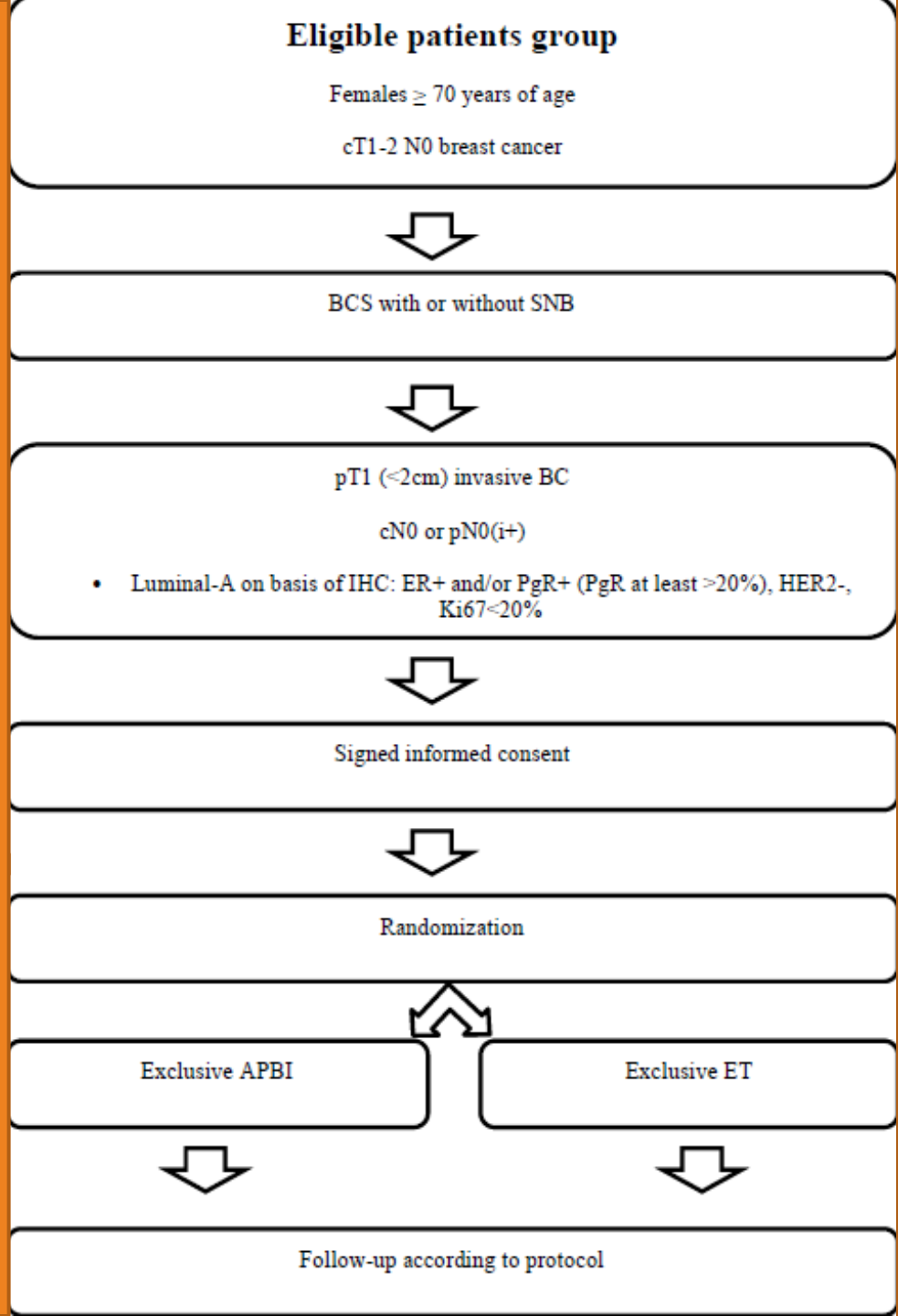
Stratification factors:
- *Surgical type: mastectomy versus lumpectomy*
- *Center*
- *Side: left vs right vs bilateral*
- *Age <65 vs ≥65*
- *Cardiovascular risk : 0-2 vs > 2 risk factors*

Partial Breast Irradiation versus Endocrine Therapy for women age ≥70 years with Luminal-A early stage breast cancer: a randomized phase III trial comparing Quality of Life by Patient Reported Outcome Measures

Main objective	To determine the patient reported outcome (PRO) HRQoL, as assessed by the QLQ-C30 and BR23 questionnaires, of exclusive APBI as compared to exclusive ET after BCS in very low-risk early BC patients aged ≥70, assuming an equivalent rate of LR.
Secondary objective(s)	• To compare the time to IBTR between the two therapeutic policies • To compare the time to locoregional recurrence between the two therapeutic policies • To compare clinical outcomes (as measured by RFI, IDFS, DFS and OS) between the ET and APBI arms • To compare the breast cancer specific survival (BCSS) between the two therapeutic policies • To assess the difference in cosmetic outcome between the two therapeutic policies • To describe the late and acute toxic effects for both therapeutic policies • To determine the adherence to treatment for both therapeutic policies • To collect biological material to perform translational research

Number of patients	600
Expected duration of recruitment	3 years
Expected duration of follow-up after end of accrual	24 months

icro.meattini@unifi.it



Clinical Studies in local treatment

- Accruing
  - DCIS
  - Invasive

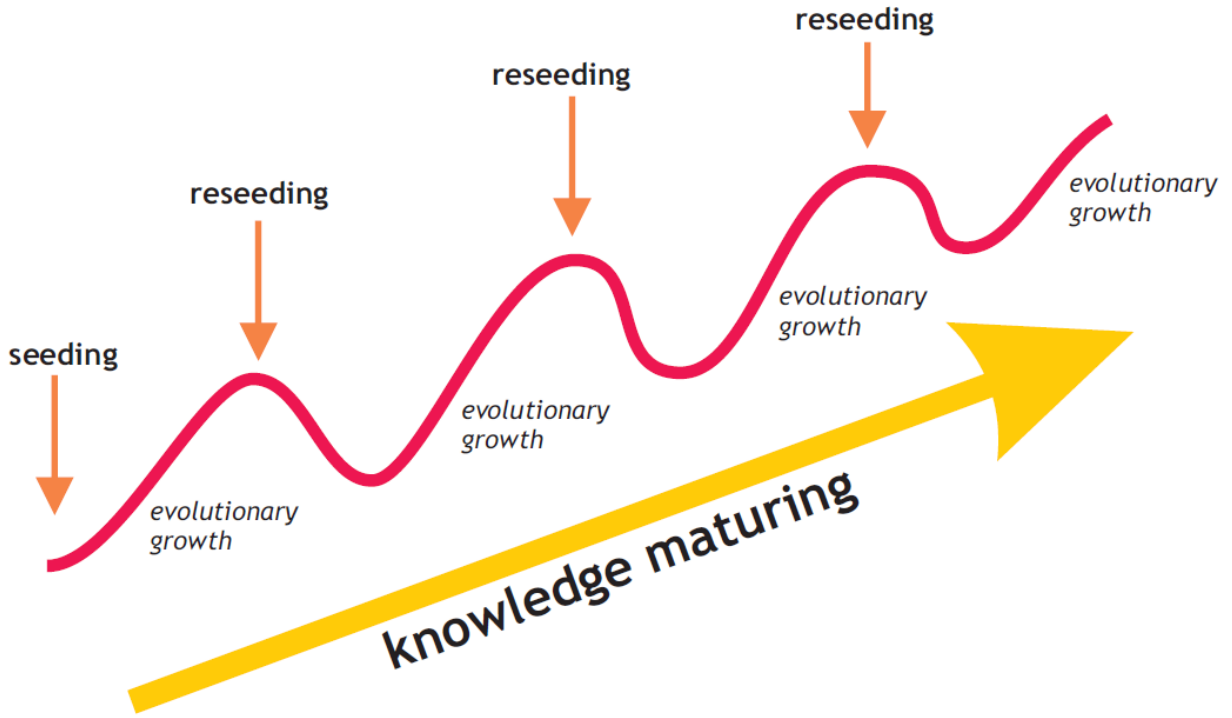


Fig. 3 The SER model and knowledge maturing

Schmidt, A. et al. (2009).

LORD: Phase III Open Labeled Randomized Non-Inferiority Randomized Clinical Trial

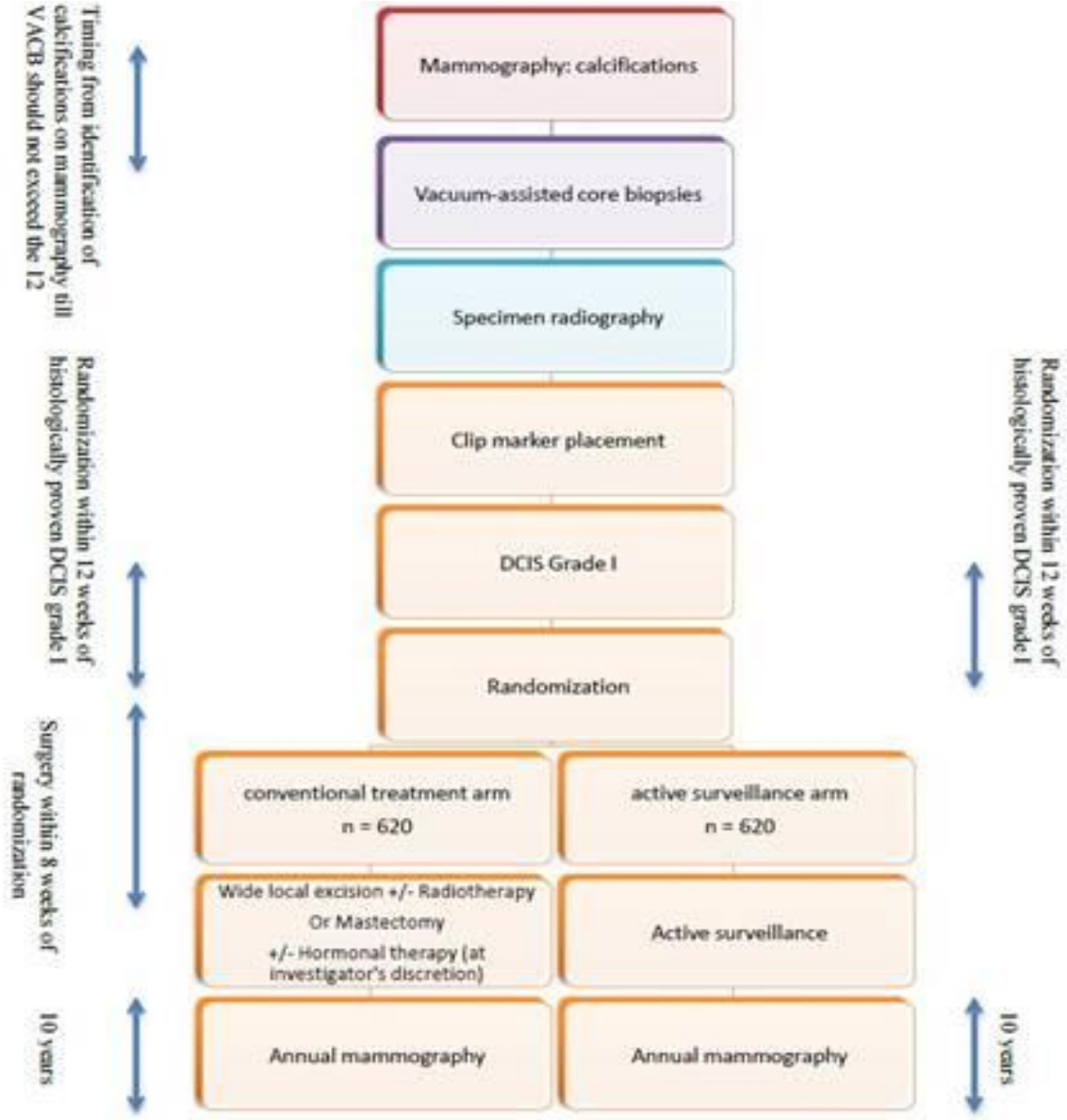
MAIN OBJECTIVE : *TO COMPARE THE ACTIVE SURVEILLANCE WITH STANDARD TREATMENT APPROACH (CONVENTIONAL ARM) IN PATIENTS WITH LOW- GRADE DCIS.*

PRIMARY END-POINT:
IPSILATERAL INVASIVE BREAST CANCER-FREE RATE AT 10 YEARS.

SECONDARY END-POINTS *(BOTH TREATMENT ARMS):*

- *TIME TO IPSILATERAL DCIS GRADE II- III*
- *TIME TO CONTRALATERAL DCIS GRADE I-II-III*
- *TIME TO CONTRALATERAL INVASIVE BREAST CANCER*
- *TYPE OF FIRST EVENT FOR PRIMARY ENDPOINT*
- *DISTANT METASTASES AND DEATH DUE TO BREAST CANCER*
- *OVERALL SURVIVAL*
- *TIME TO FAILURE*
- *QUALITY OF LIFE*
- *COST-EFFECTIVENESS*

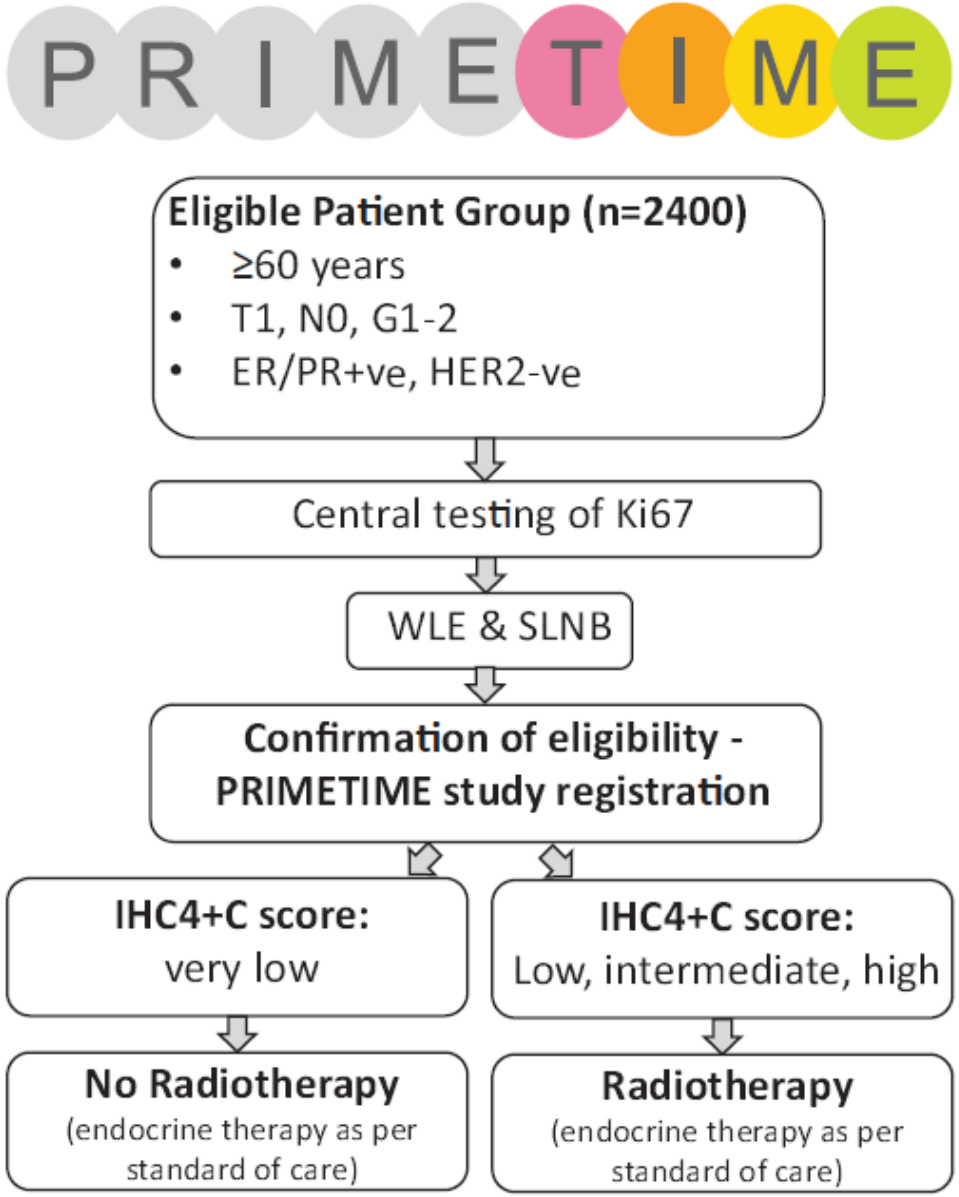
Target sample size	1240
Actual accrual	6

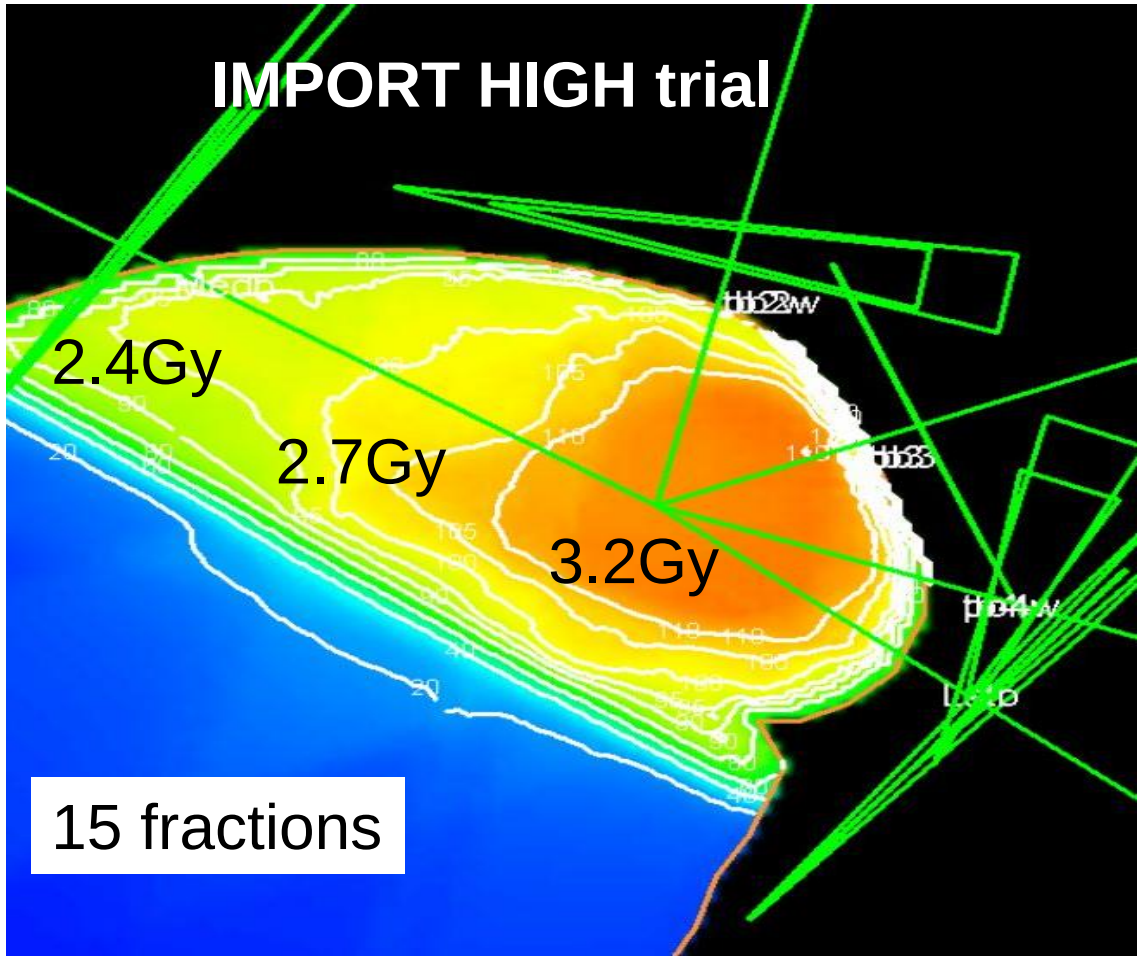


PRIMETIME: Postoperative Avoidance of Radiotherapy: Biomarker Selection of Women at Very Low Risk of Local Recurrence

The primary end point is ipsilateral breast disease rate at 5 years. PRIMETIME requires recruitment of 2400 patients at the preoperative stage, to allow 1550 patients to actively avoid radiotherapy, based on a local relapse rate, in the absence of radiotherapy, of ≤4% at 5 years. The two-stage study design necessitates engagement of the surgical community to facilitate recruitment at the preoperative stage. The study has been designed through collaboration between surgeons and clinical oncologists, with surgeons

colesc@doctors.org.uk

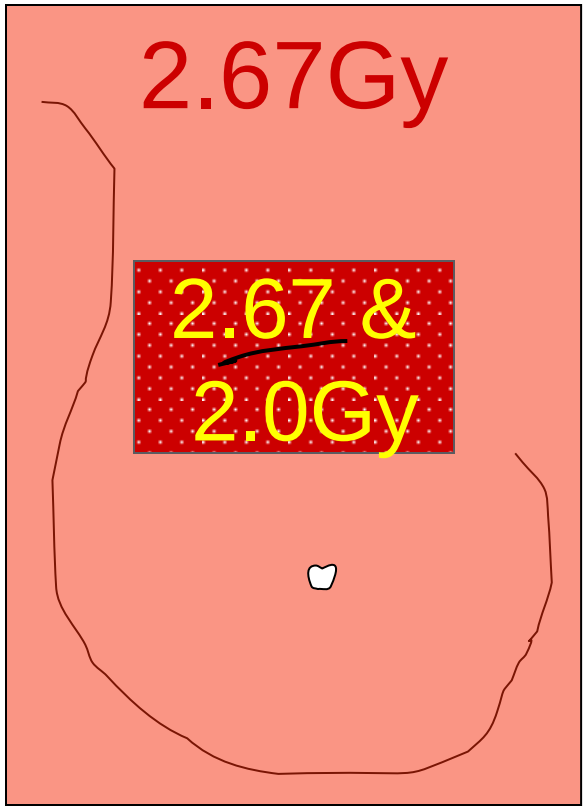




- 2,600 patients – in follow up
- Tailor dose across breast according to risk of relapse
- Uses complex IMRT & IGRT
- Secondary endpoints of normal tissue toxicity will report 2018

IMPORT HIGH Trial (N=2,600)

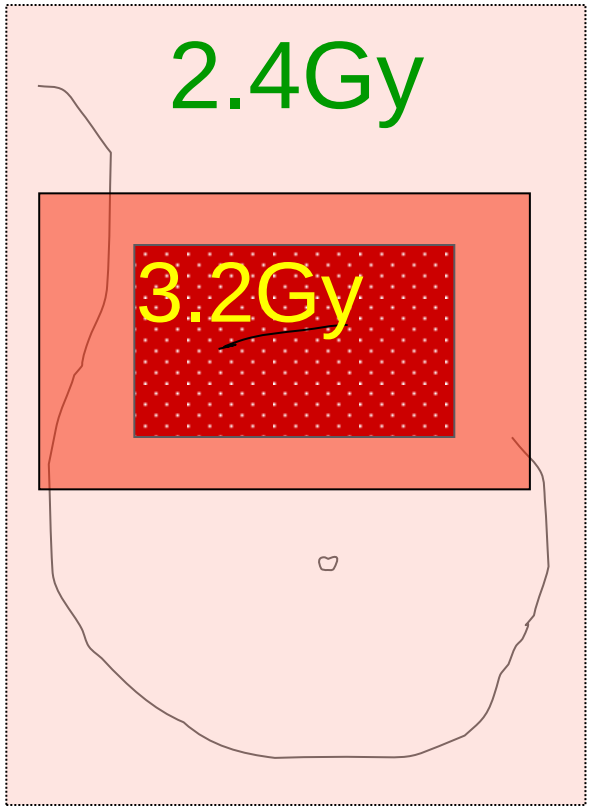
Sequential Boost



15+8 Fractions

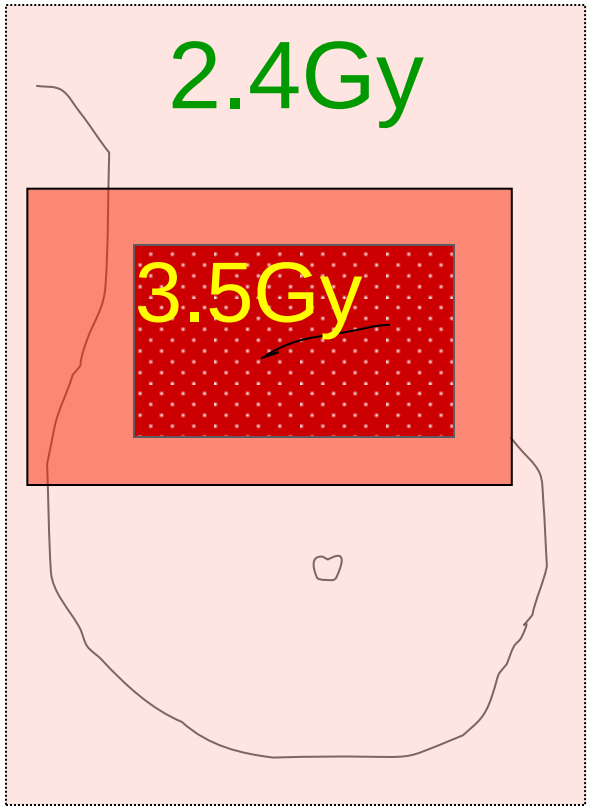
Concomitant Boost

Test 1



15 Fractions

Test 2



15 Fractions

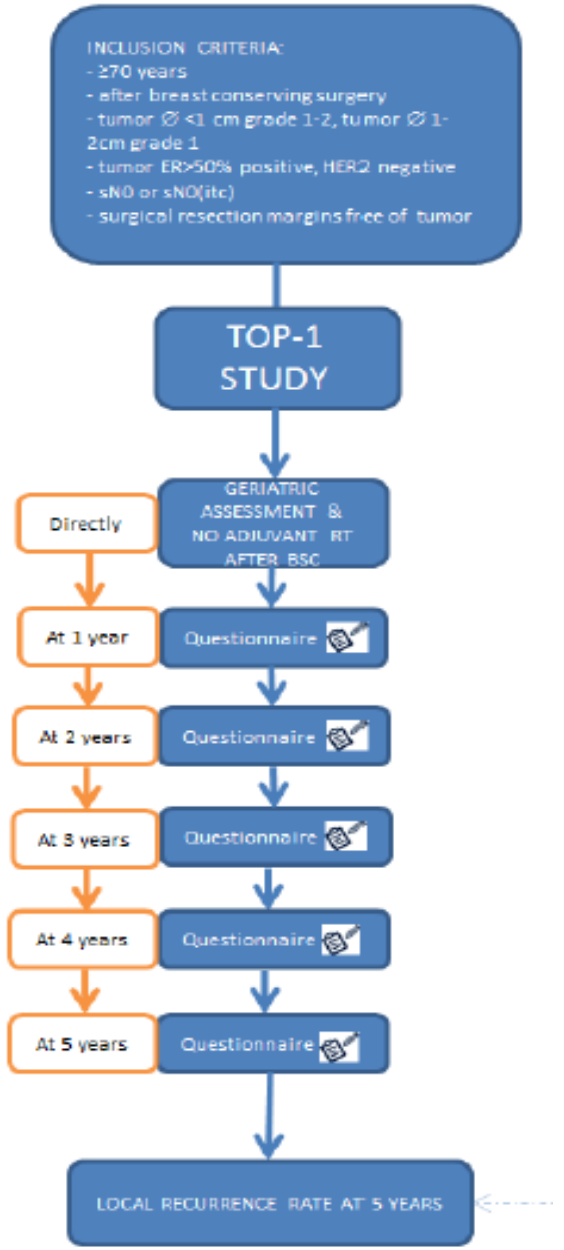
Tailored treatment in Older Patients

TOP-1: Omission of radiotherapy in elderly patients with low risk breast cancer

Primary Objective: To determine if radiotherapy (RT) can safely be omitted after breast conserving surgery (BCS) in elderly patients at low risk of developing a local recurrence (LR)

Secondary Objectives:

1. To determine the DMFS, BCSS, and OS rates in this study population.
2. To determine the QoL of patients after they received treatment regarded as new standard practice, directly after BCS and at 12, 24, 36, 48 and 60 months after BCS.
3. To determine the geriatric status of the study population.
4. To determine the cosmetic outcome of the study population.
5. To determine if omitting RT after BCS in elderly patients with a low local recurrence rate (LRR) is cost efficacious.
6. To determine if poor outcome of the study population can be predicted at diagnosis by clinicopathological factors including IHC, ER, PR, HER2 and Ki-67 and emerging omics technology.



19 PATIENTS INCLUDED

Leids Universitair Medisch Centrum

ANTONI VAN LEEUWENHOEK

umcg

UMC Utrecht Julius centrum

KWF KANKER BESTRIJDING

STUDY PROTOCOL

IRMA

BREAST CANCER WITH LOW RISK OF LOCAL RECURRENCE: PARTIAL AND ACCELERATED RADIATION WITH THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY (3DCRT) VS. STANDARD RADIOTHERAPY AFTER CONSERVING SURGERY (PHASE III STUDY)

Primary Objective

The main aim of the study is to evaluate whether partial hypofractionated and accelerated irradiation of the sole surgical cavity, in patients suffering from breast cancer with low risk of local recurrence and undergoing conservative surgery, is not inferior to postoperative irradiation with conventional fractionation of the entire breast as regards local control, measured in terms of incidence of ipsilateral recurrences as first event.

←**TREATMENT**

RADIOTHERAPY:

Trial arm 38.5 Gy total in 10 fractions (3.85 Gy per fraction), twice a day with an interval of at least 6 hours between the two fractions, for five consecutive working days.

Control arm 45 Gy/18 fractions, or 50 Gy/25 fractions, or 50,4 Gy/28 fractions, or isoeffective fraction schemes, once a day for 5 days a week. A 10 - 16 Gy boost is allowed in centers where it is part of the standard treatment.

Secondary Objectives

To compare the two methods of irradiation in terms of:

a)overall survival;

b)locoregional recurrence free survival (with exception of contralateral tumors and second tumors);

c)distant relapse-free survival (except for local or regional relapses or in the contralateral breast);

d)cosmetic results;

IRMA study:

Aimed to include 3302
Overall trial accrual July 2017: 2927 patients (1462 PBI - 1466 WBI)
Lymph nodes: 2697 N0 - 230 N1
Dim T: 978 =1cm
Chemotherapy: 352 yes - 2575 no
Open in Italy, Holland…

PAPBI-2 phase III trial

Preoperative Accelerated Partial Breast Irradiation: open in Holland

Preop PBI vs postop PBI (5 x 5.7 Gy)

Endpoint: cosmetic outcome

Side study: tumour response on RT

Hypothesis: fair/poor cosmesis 20% vs 10%

Aim: 500 patients

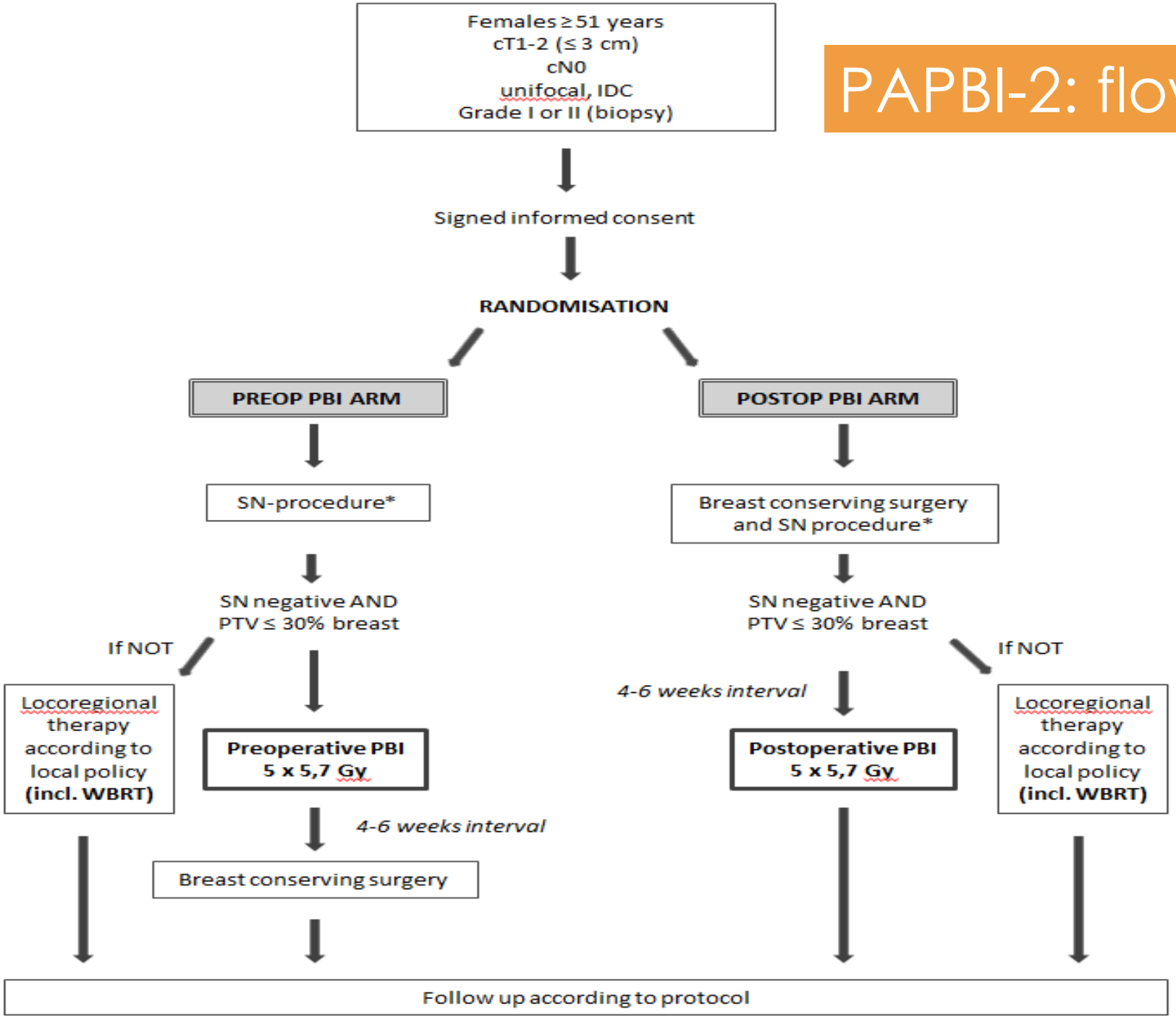
Inclusion criteria:

- Female patients ≥ 51 years
- cT1-2N0 (≤3 cm)
- Grade I or II (biopsy)
- Histologically proven ductal invasive carcinon
- Unifocal lesion on mammogram and MRI

Exclusion criteria:

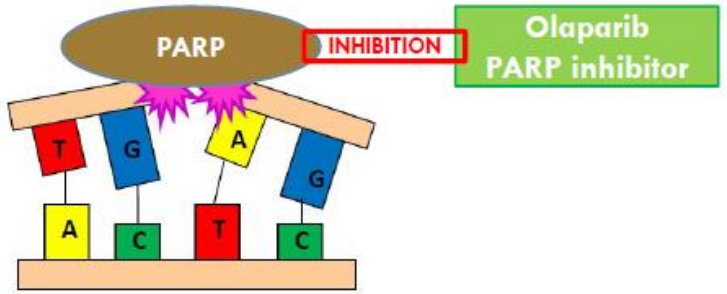
- Lobular invasive carcinoma
- Pure DCIS without invasive tumour
- Triple negative tumours
- Lymphvascular invasion in biopsy

PAPBI-2: flowchart



*SN- procedure according to local policy

Current projects in IC Department of Radiation Oncology



- **RADIOPARP**

  Phase I, open recently, translational work associated

  PI: Y. Kirova

BRCA-ness study: M-H Stern

→ A Phase I of Olaparib With Radiation Therapy in Patients With Inflammatory, Loco-regionally Advanced, or Metastatic TNBC (triple negative breast cancer) or Patient with Operated TNBC with Residual Disease.

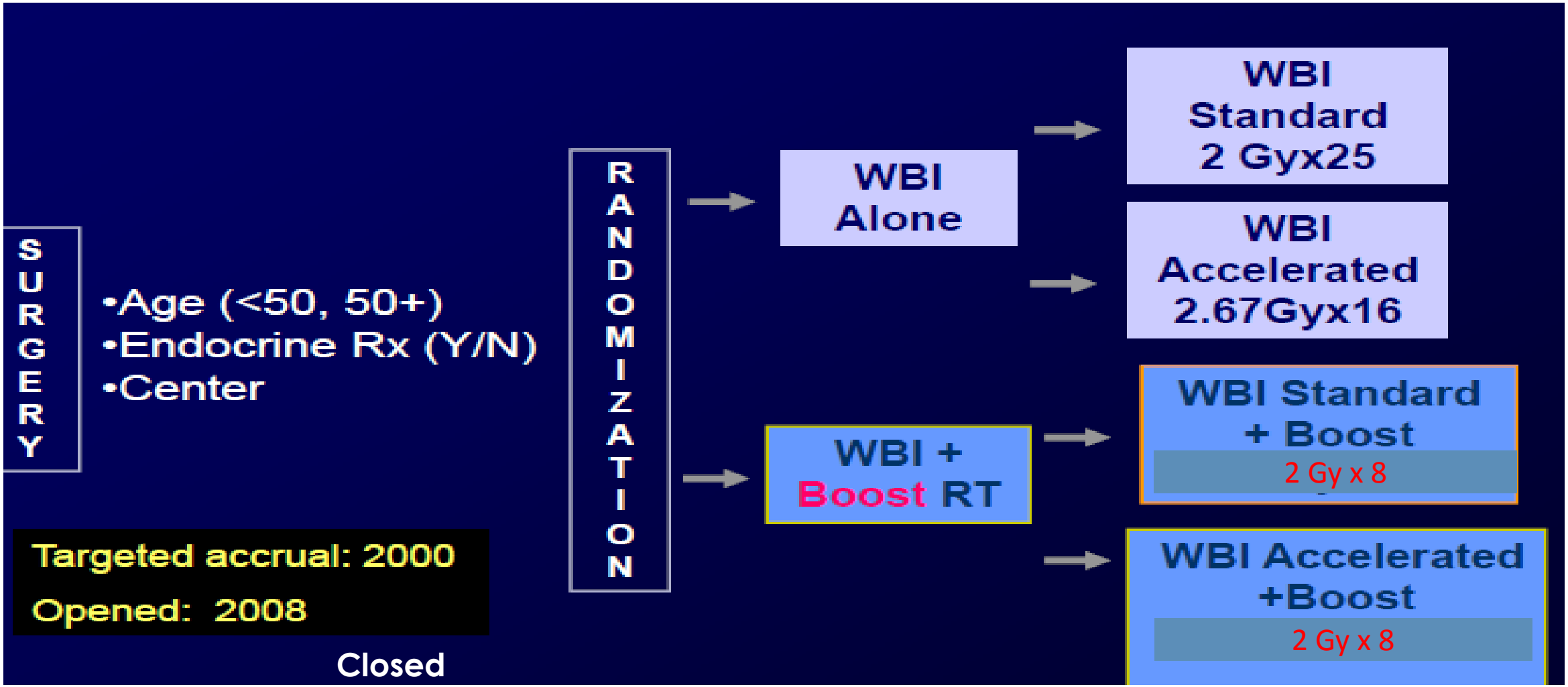
NKI-Curie collaboration at the end of these phase I studies

Differences, similarities	NKI/AVL	Inst Curie
Pat population	Metast breastca, also ER pos	Mets and loc adv breast ca, TN
Dose esc schedule	50, 100, 200, 300	50, 100, 150,200 bid
RT dose	46.69/23 fr, 14.49Gy SIB	50 Gy+/-16 Gy boost sequ
Additional treatment	no surgery	surgery
Translational res	HRD, par assay	HRD, ctDNA, parp1 IHS
Tite CRM	DLT period 12 weeks	DLT period 12 weeks
Late tox	See synopsis	See full protocol
Pat with bolus on skin/WEM	Separate groups in protocol	Not specified

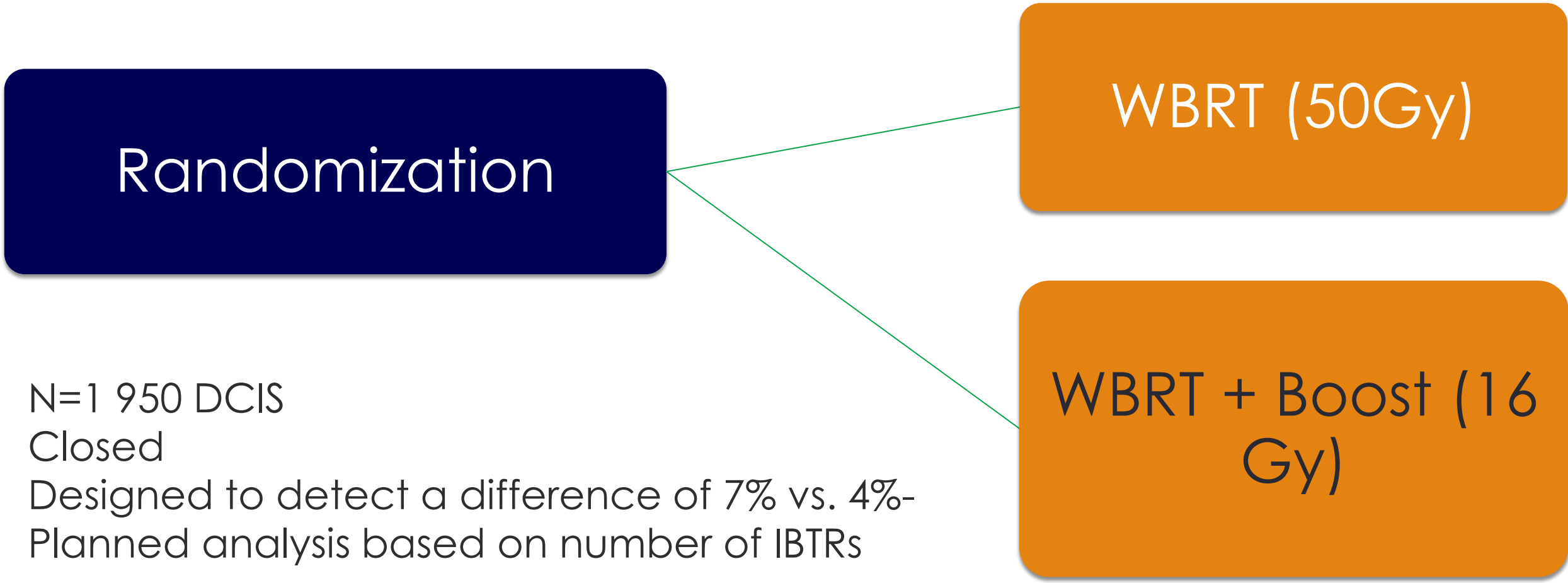
Clinical Studies in local treatment

- **Nurturing**
  - DCIS
  - Invasive

Phase III: Boost for DCIS: TROG 07.01/BIG 3-07



Phase III: Boost for DCIS: BONBIS Trial (France)



- N=1 950 DCIS
- Closed
- Designed to detect a difference of 7% vs. 4%-
- Planned analysis based on number of IBTRs

Young boost phase III trial: Radiation dose intensity study in breast cancer in young women: a randomized phase III trial of additional dose to the tumor bed: closed

Main objective: is to compare the effect of a high boost dose (26 Gy) with a low boost dose (16 Gy) in breast conserving therapy, on the local recurrence rate.

Secondary objective: to compare the effect of the high boost dose (26 Gy) with a low boost dose (16 Gy) in breast conserving therapy, on the cosmesis and possible sequelae.

Additional objectives:

A. To test the genotypic and phenotypic profiles of breast tumors in young patients with invasive breast cancer, and its relation to:

a. Local recurrence after BCT
b. Lymph node metastases
c. Distant metastases and survival
d. Radiosensitivity
e. Age

B. To determine whether improved genotypic and phenotypic profiles can be determined related to the endpoints mentioned previously.

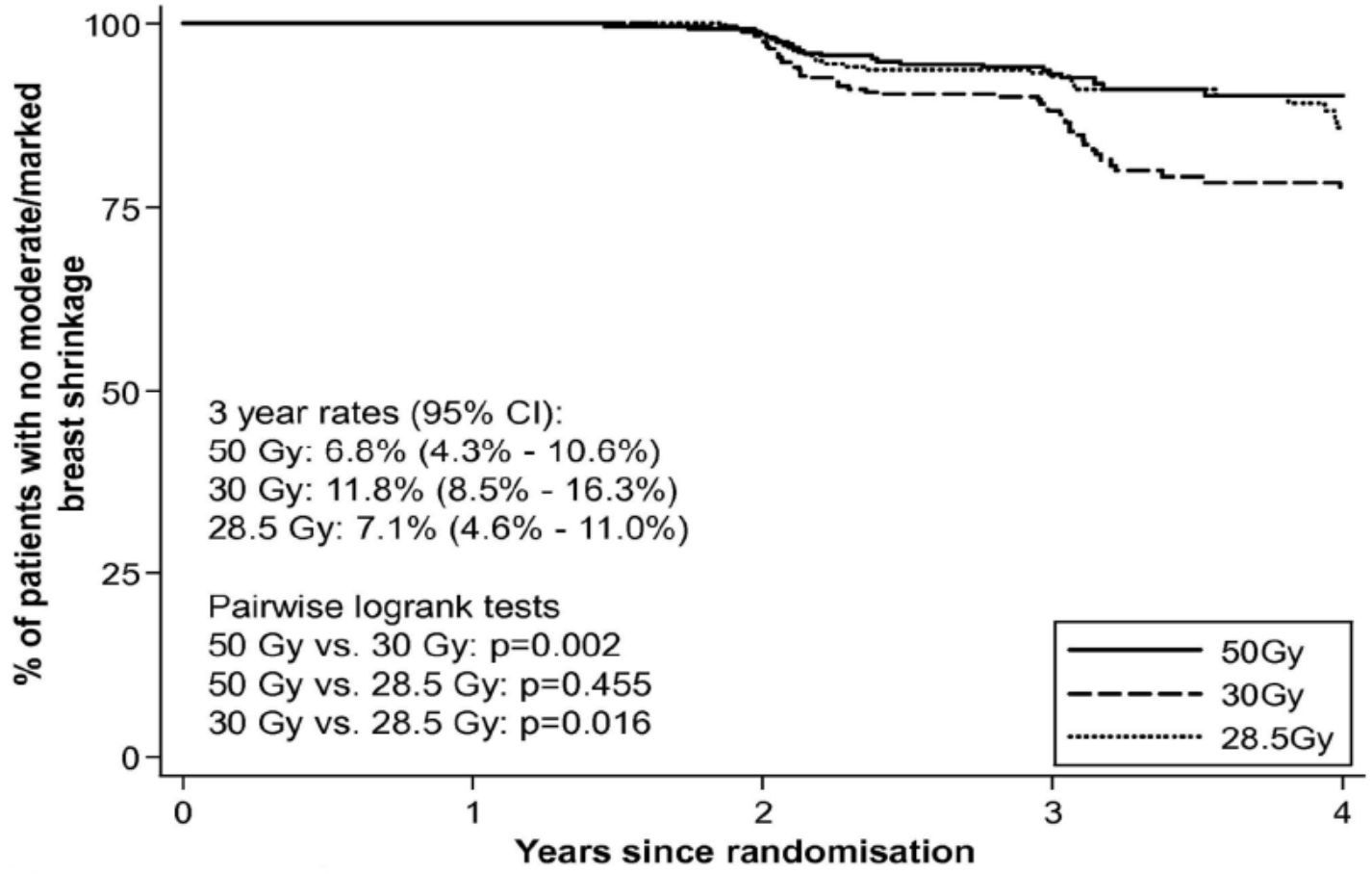
End-points

Primary endpoint: Local control at 10 year
Secondary endpoint: Cosmetic outcome

Expected Results in ….

UK FAST Trial

Physician-assessed moderate/marked breast shrinkage



Fast Trialists Group (2011) Radiother Oncol 100: 93-100

Reported at 3 years, long term results are expected

EBCC 10 European Breast Cancer Conference
Multidisciplinary Innovation in Breast Cancer Care
9 - 11 MARCH 2016
AMSTERDAM THE NETHERLANDS
Organised by ecco
EBCCouncil

ICR The Institute of Cancer Research

Cambridge University Hospitals NHS NHS Foundation Trust

CANCER RESEARCH UK

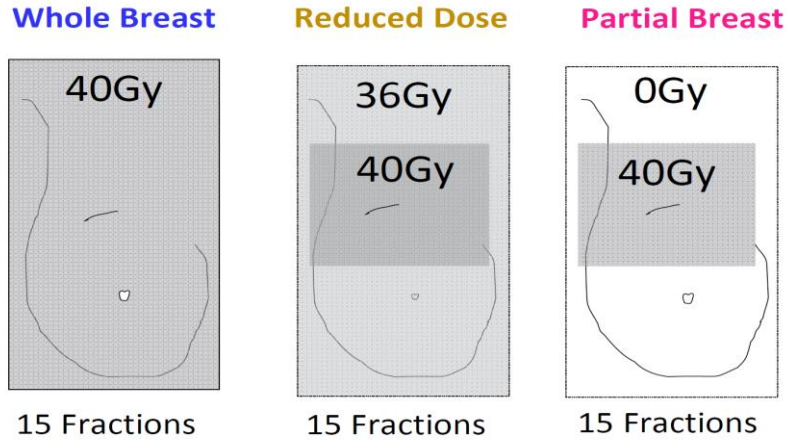
IMPORT

Intensity modulated partial breast radiotherapy (IMPORT) for women with early breast cancer: First analysis of local relapse (CRUK/06/003)

Dr Charlotte Coles

(R.Agrawal, M.L.Ah-See, H.Algurafi, A.Alhasso, A.M.Brunt, C.Chan, C.Griffin, A.Harnett, P.Hopwood, A.Kirby, E.Sawyer, I.Syndikus, J.Titley, Y.Tsang, D.Wheatley, M.Wilcox, J.Yarnold, J.M.Bliss on behalf of the IMPORT Trial Management Group)

Intensity Modulated Partial Organ RT



Primary endpoint: Local relapse

Local relapse (LR)	Whole N=674	Reduced N=674	Partial N=670
Number of LR events	9	3	4
KM 5 year cumulative LR incidence estimate (95% CI)	**1.1% (0.5-2.3)**	**0.2% (0.02-1.2)**	**0.5% (0.2-1.4)**
Hazard ratio (95% CI)		0.32 (0.09, 1.20)	0.44 (0.14, 1.42)
Pr(HR>2.03), test for NI		p=0.003	p=0.005
Log rank p-value		p=0.08	p=0.16
Absolute difference in LR rate at 5 years (95% CI)		**0.74% (0.99, -0.21)**	**0.61% (0.94, -0.46)**

Closed and reported at 5 years; long term results are expected

DBCG PBI trial

AIM

Investigate the risk of grade 2-3 breast induration after PBI compared with whole breast RT

Breast cancer, ≥60 yr, breast conservation,
margin ≥2mm,
non-lobular type,
pT1, pN0, ER pos,
HER2 neg, grade 1-2

R

Whole breast RT 40 Gy / 15 fr

Stratum: institution, endocrine treatment

Partial breast RT 40 Gy / 15 fr

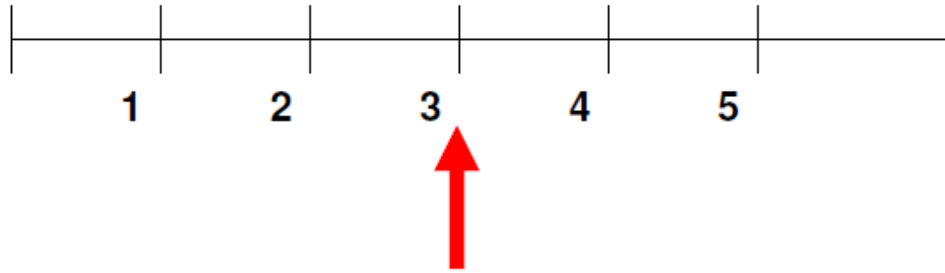
Endpoints

Primary

- grade ≥2 breast induration 3 years post RT

Secondary

- other RT-related morbidities
- body image scale
- patient satisfaction with therapy
- pattern of recurrences
- genetic risk profile for late RT-related morbidity



Conclusion DBCG PBI:

APBI based on 40 Gy/15 fr does not result in more grade 2-3 induration at 3 yrs
RT doses to heart and lung are lower with APBI

Offersen et al, EBCC 2016: Closed and reported at 3 years; long term results are expected

Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial

Ian H Kunkler, Linda J Williams, Wilma J L Jack, David A Cameron, J Michael Dixon, on behalf of the PRIME II investigators

1326 patients, treated 2003-2009 in 4 countries, 76 centres
Inclusion: ≥65 yr, ≤3 cm invasive carcinoma of the breast, pN0, ER+, ≥1mm margin, one of either grade III or LVI allowed
All had BCS and endocrine therapy 5 years

RESULTS
Median follow up: 5 yr (IQR 3.84-6.05)

IBTR

RT: **1.3%** (95% CI, 0.2-2.3)
No RT: **4.1%** (95%, 2.4-5.7)
No difference in:
-Distant metastasis
-Contralat BC
-Overall Survival

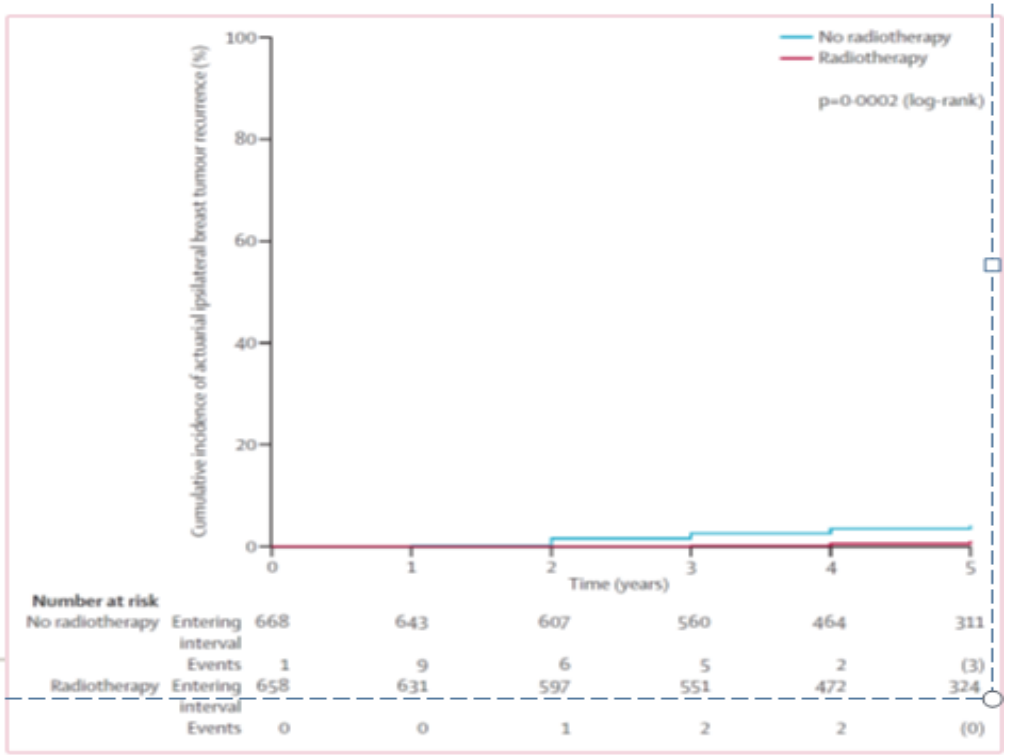


Figure 2: Time to actuarial ipsilateral breast tumour recurrence

Lancet Oncol 2015; 16: 266–73

Closed and reported at 5 years; long term results are expected

Thank you for your attention

Questions?

Breast Surgery Intraoperative Assessment

T.Kuehn

Klinikum Esslingen, Germany

Scenarios for Breast Surgery

- Non invasive disease (B3, DCIS)
- Invasive disease
  - Primary surgery
  - After primary systemic treatment

- Palpable
- Non palpable

Objective of Breast Surgery

- Avoid invasive disease (B3, DCIS)
- Ensure local control (invasive disease)
- Provide diagnostic information (T-Stage)

- Ensure aesthetic result
- Avoid Reexcisions

Challenge to the Surgeon

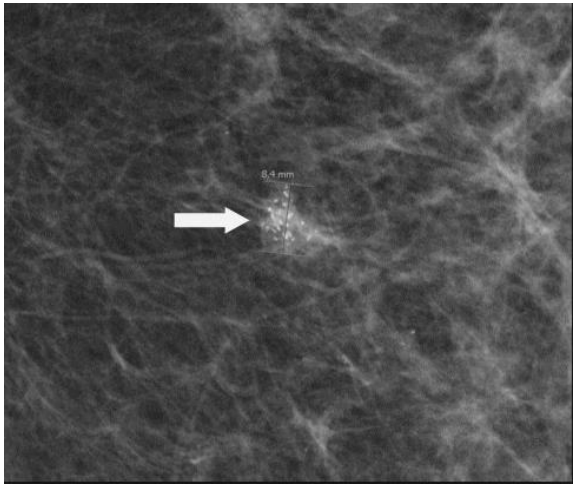
1. **Localisation of the lesion / target**
2. **Definition of the Target Volume**
3. **Intraoperative Verification of adequate resection volume**
4. **Handling of the specimen**
5. **Margin assessment**
6. **Closure of the defect**
7. **localisation of resection margins to improve postoperative radiation**

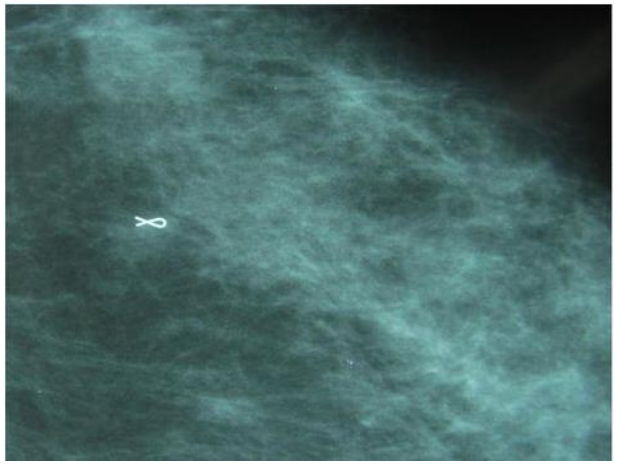
ESTRO School

Management of the non palpable lesion

Localisation techniques

Non palpable targets



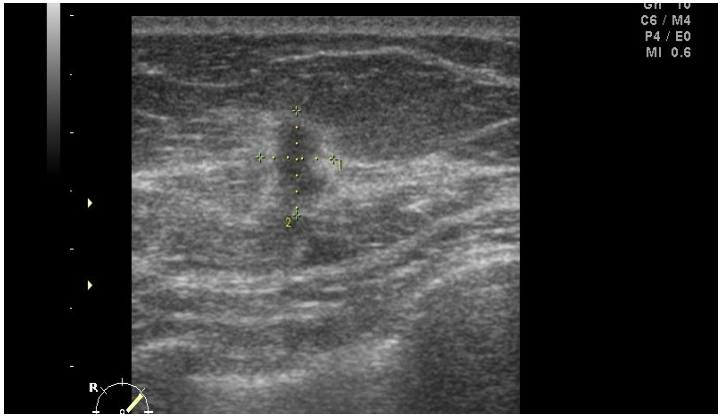


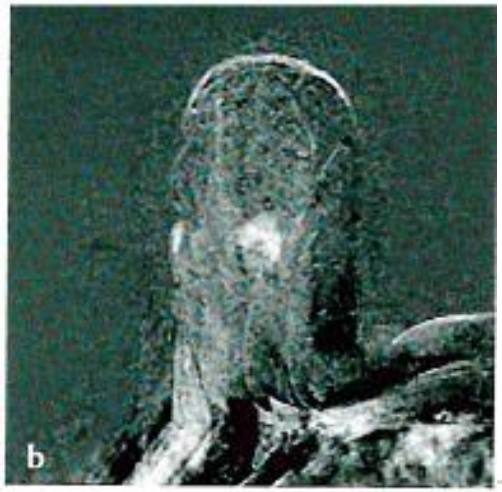
Localisation Techniques

Techniques

- Injection of Dye
- Injection of charcoal
- Image guided wire localisation
- Radio-guided occult lesion localisation (ROLL)

Lesions and Imaging Techniques





ESTRO School

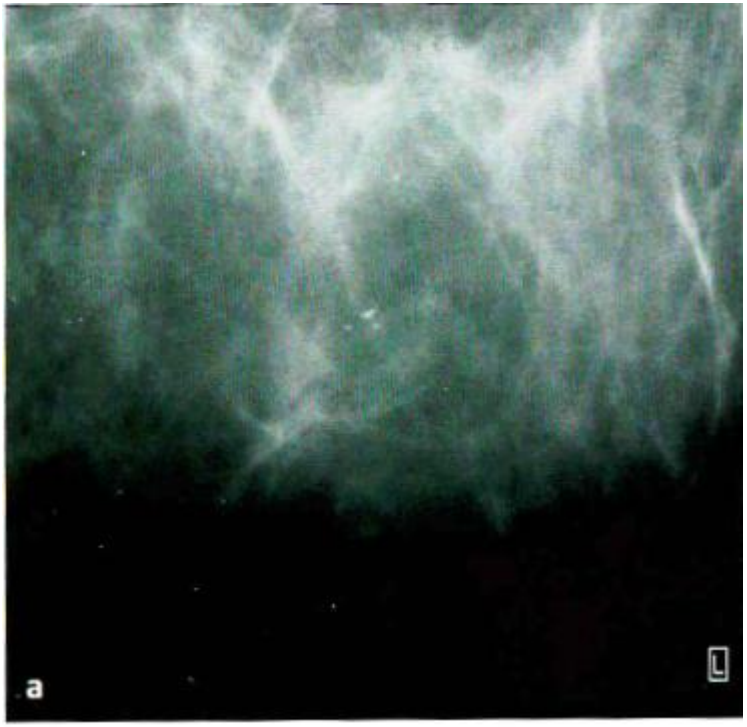
Basic Rule for Image Guided Localisation

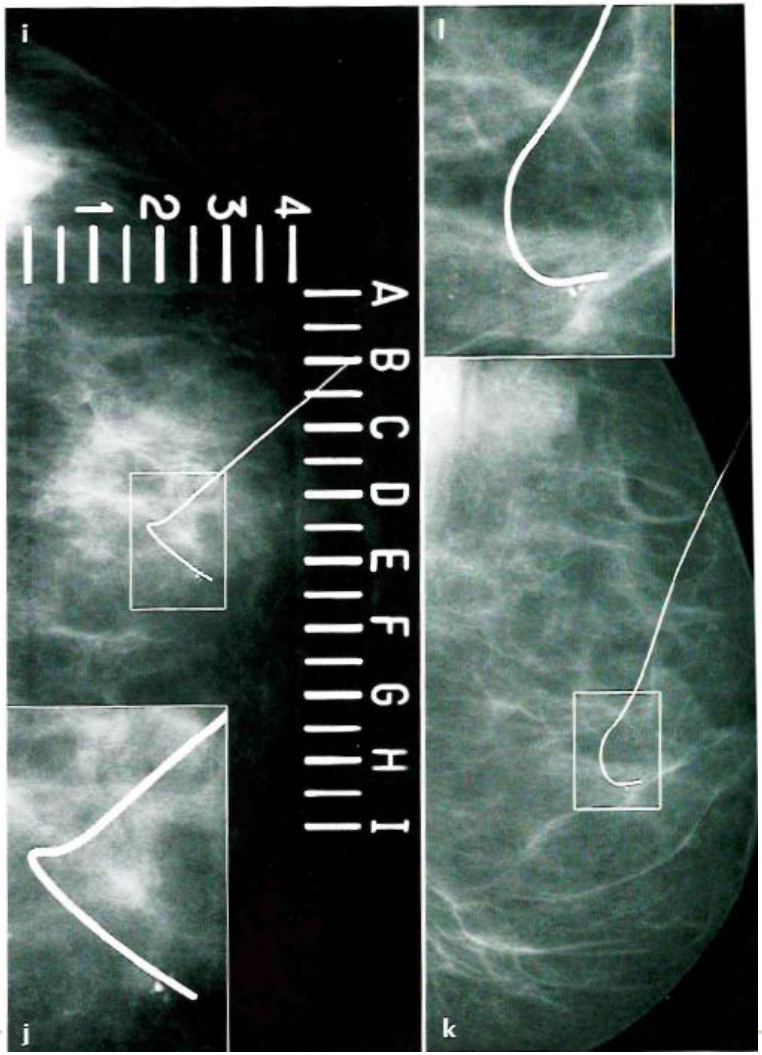
Chose the easiest access

- **Ultrasound**
- **Mammography**
- **MRI**

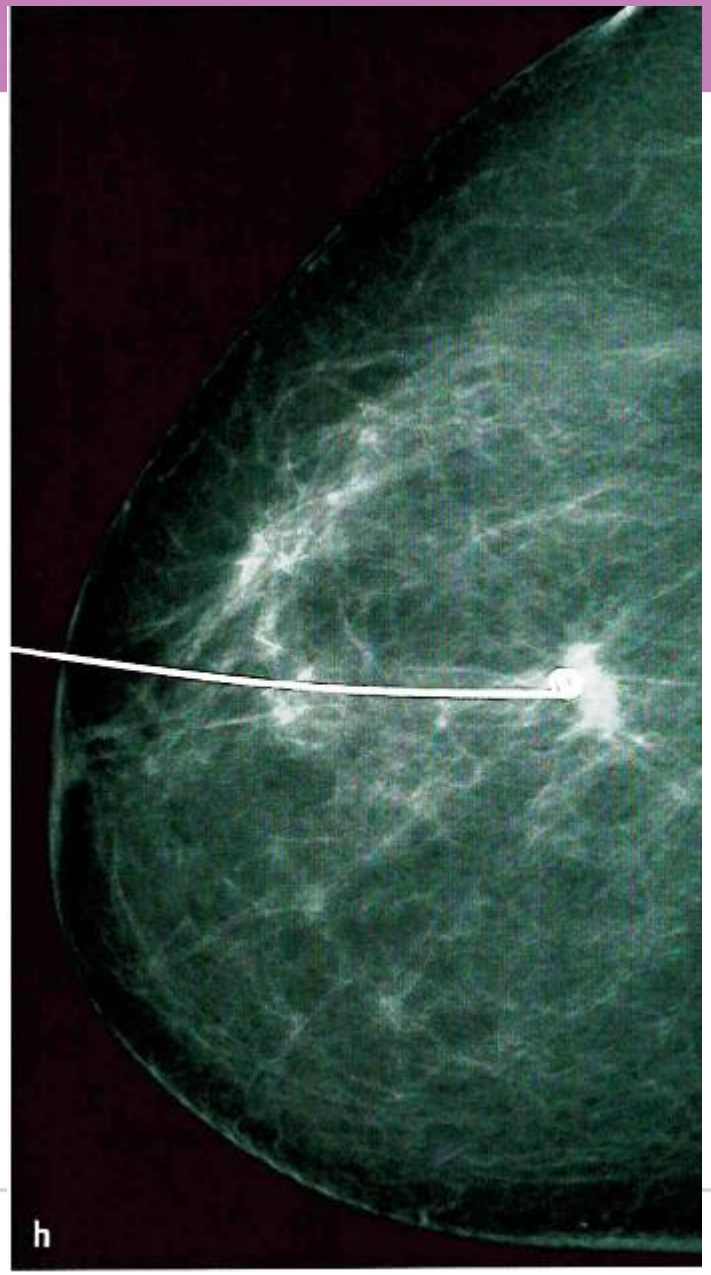
Specimen Imaging with the same technique

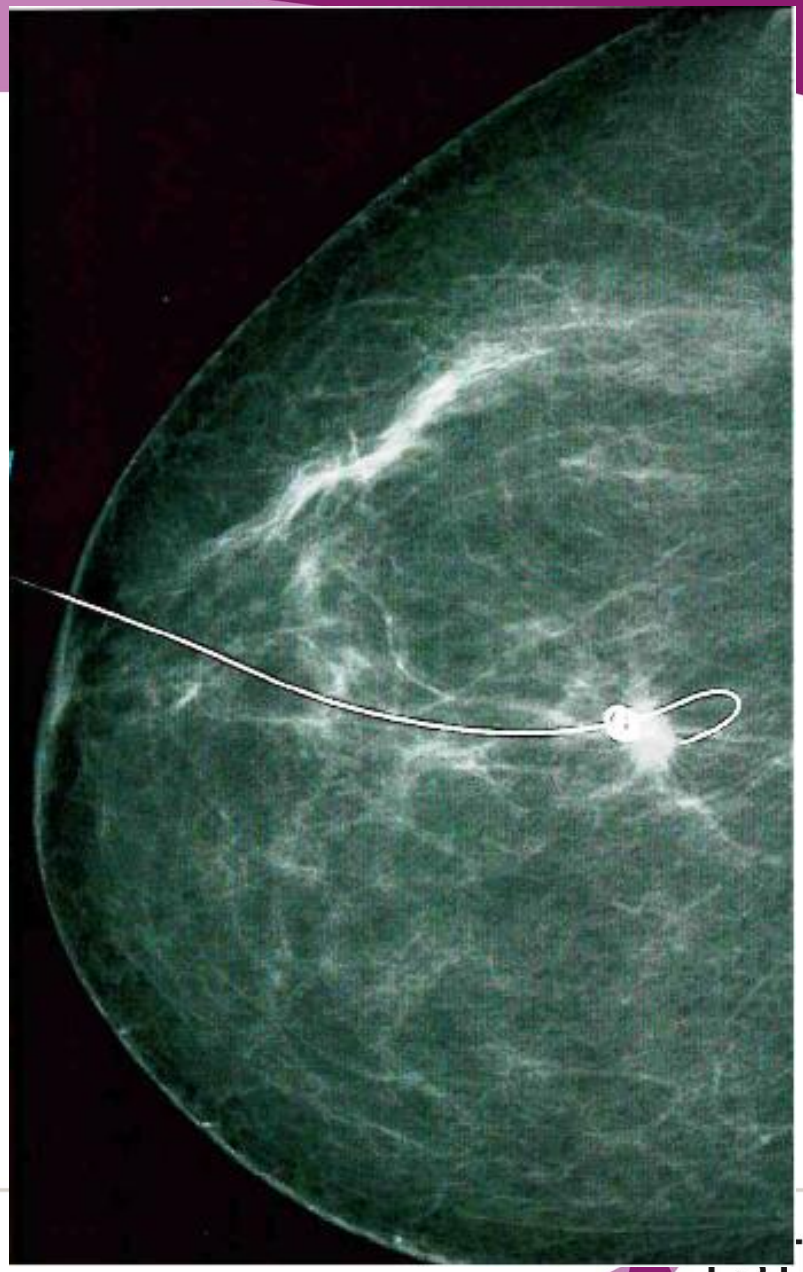
Stereotactic Wire Localisation



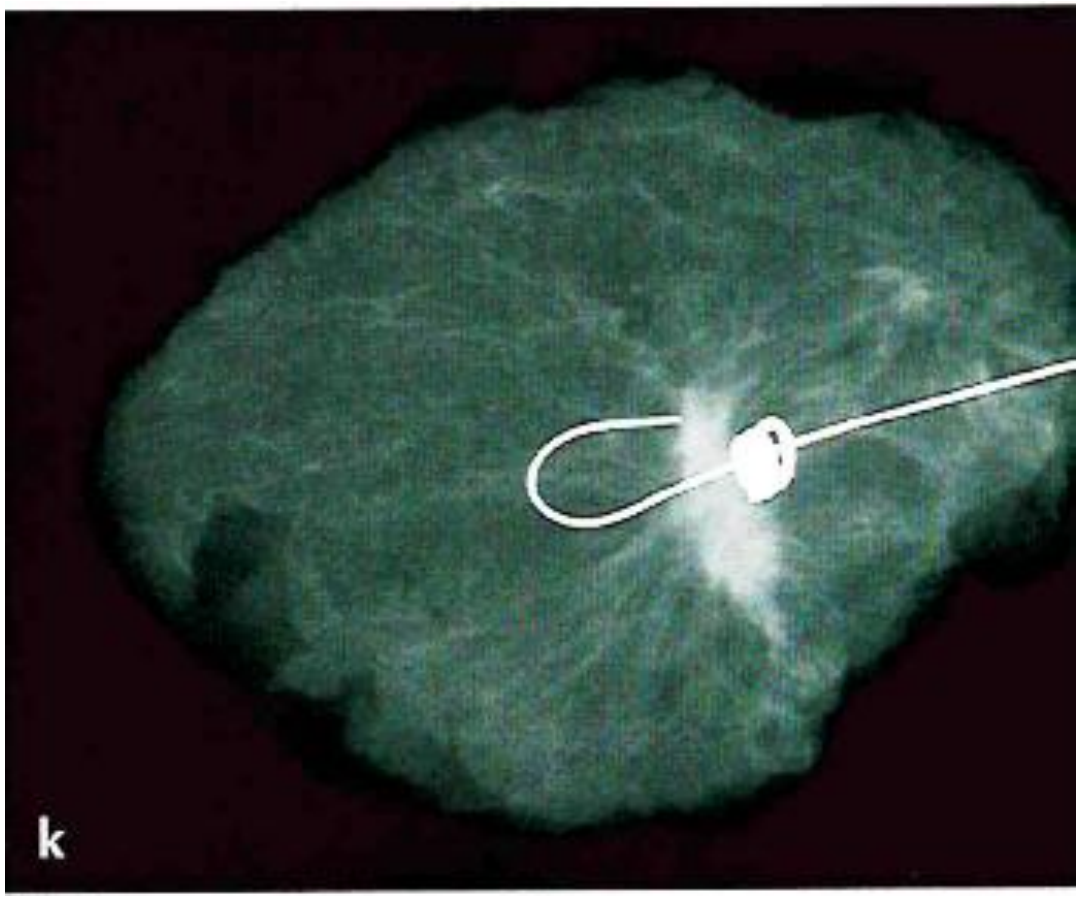


ESTRO School

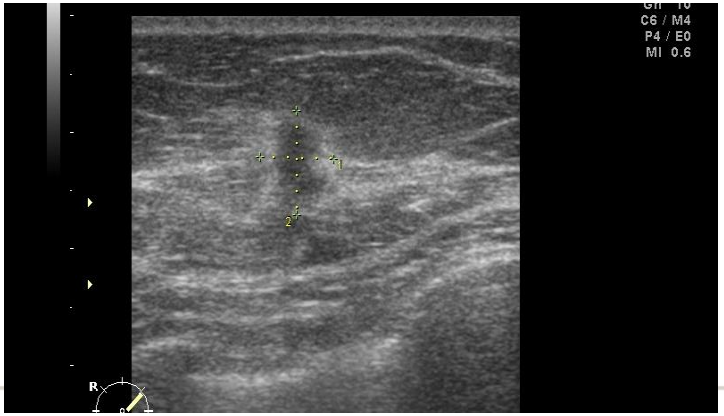

h



Specimen Radiography



Imaging of the specimen should be performed with same technique that was used for localisation



ESTRO School

Technical details

Radioguided Occult Lesion localisation (ROLL)

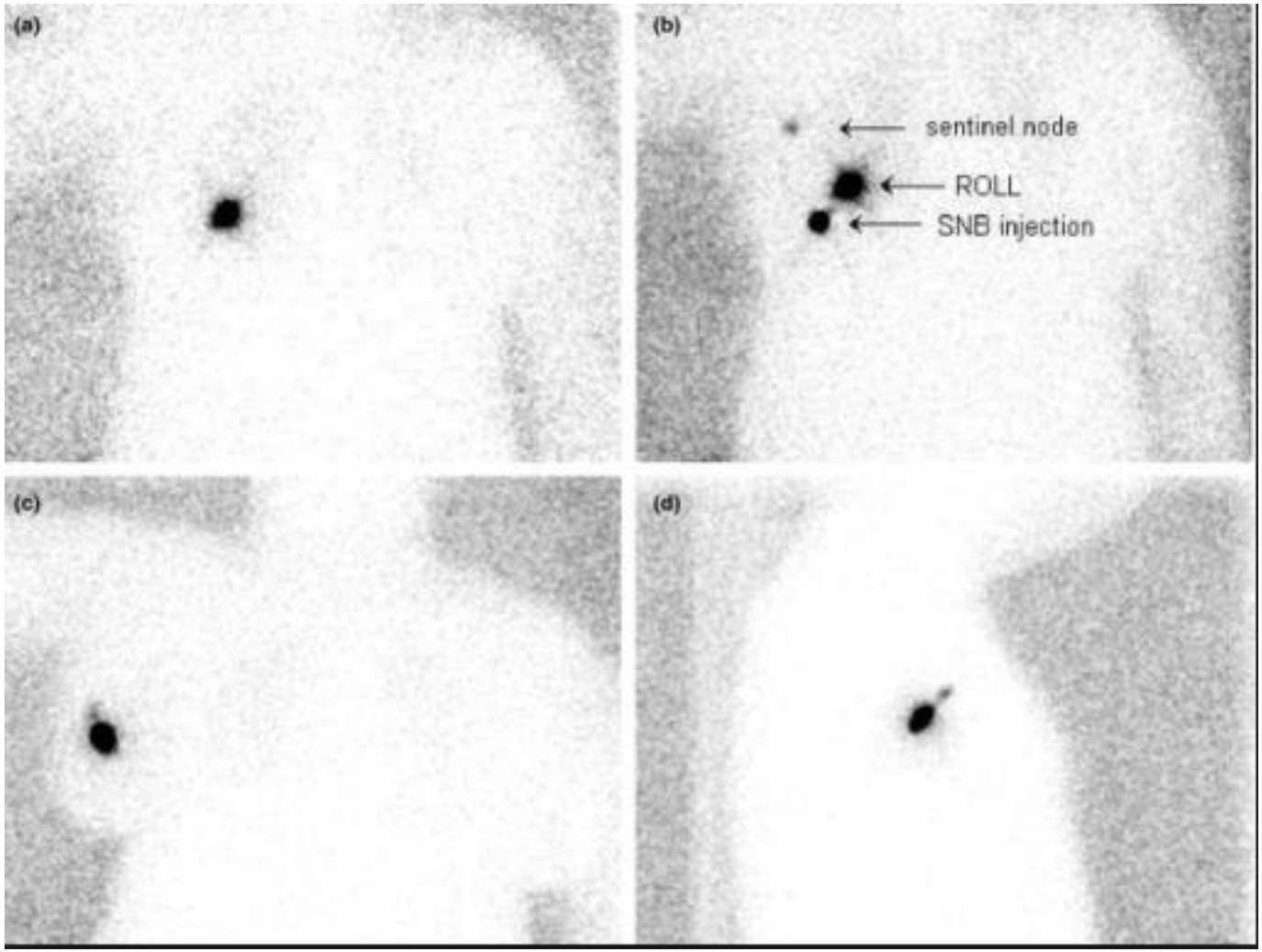
^{99m}Tc- labelled colloid particle (10-150 micrometer) injected into the lesion one day before surgery

- ^{99m}Tc activity of 74 MBq.
- Front and lateral planar scintigraphy images
- Excisional biopsy performed day after guided by γ-probe to localise the hot spot

Paganelli G. Nucl Med Comm 2002

Gennari R. J Am Coll Surg 2000

IEO
European Institute of Oncology


(a)
(b)
sentinel node
ROLL
SNB injection
(c)
(d)

Randomized controlled clinical trial comparing radioguided occult lesion localization with wire-guided lesion localization to evaluate their efficacy and accuracy in the localization of nonpalpable breast lesions

Carlos Duarte, MD,[a] Faustino Bastidas, MD,[a] Amelia de los Reyes, MD,[b] María Cristina Martínez, MD,[b] Gloria Hurtado, MD,[c] María Constanza Gómez, MD,[d] Ricardo Sánchez, MD, MS,[e,f] *and* Jorge Manrique, MD,[a] *Bogotá D.C., Colombia*

Variable	WGLL	ROLL
n	65	64
Localisation rate	65/65	62/64
centricity	14.4	11.7
volume	20.7 ml	18.3 ml
Weight	10.4 g	9.3 g
reexcision	16	12

Duarte et al Surg 2016

ESTRO School

©AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2017.1

Breast Conservation: Surgical Technical Aspects

	Oxford / AGO LoE	GR	
➢ **Non-palpable lesion**			
➢ Wire guided localisation	2b	B	++
➢ Radionuclide guided localisation	2b	B	+/-
➢ Specimen radiography or ultrasound	2b	B	++
➢ **Tumor-free margins required** (also in unfavorable biology „no cells on ink“ are enough)	2a	A	++
➢ **Immediate intraoperative re-excision for close margins (specimen radiography and/or intra-operative pathology)**	1c	B	++
➢ **Re-excision required for involved margins (paraffin section)**	3b	C	+
➢ **Therapeutic stereotactic excision alone**	4	D	- -
➢ **Ultrasound guided surgery to prevent re-excision**	1a	A	+/-
➢ **Intraop. margin evaluation with margin probe**	1b	A	+/-

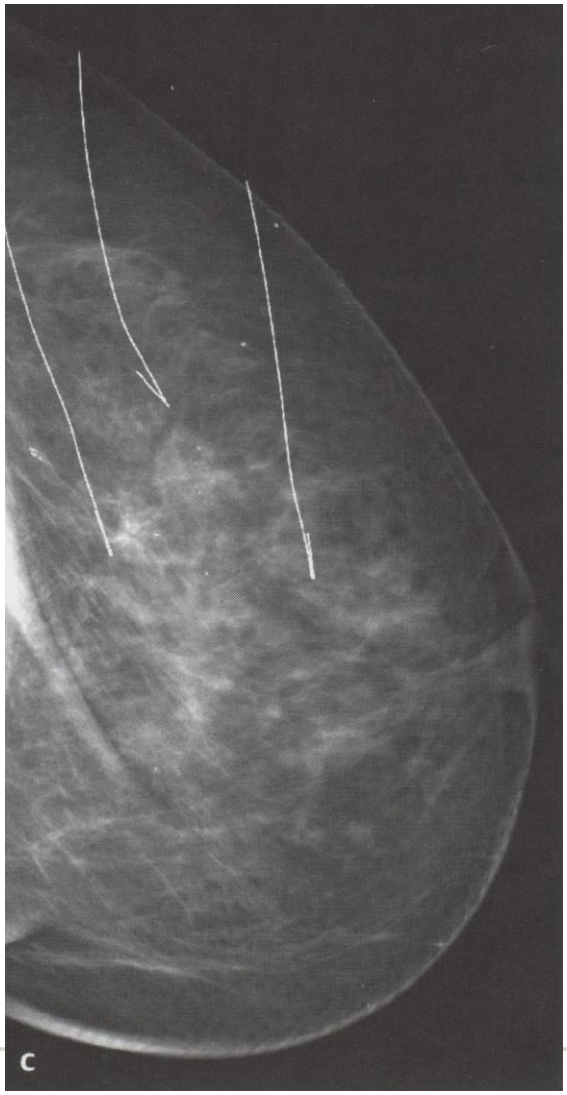
www.ago-online.de

Further Information

References

FORSCHEN
LEHREN
HEILEN

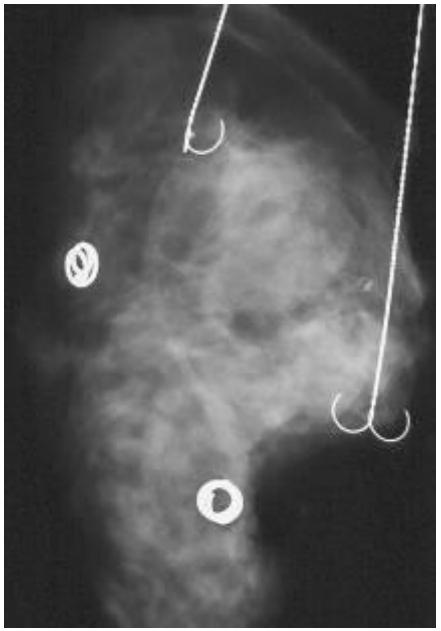
Localisation and Volume Definition



Wire localsation of non palpable lesion

Stereotactic localisation

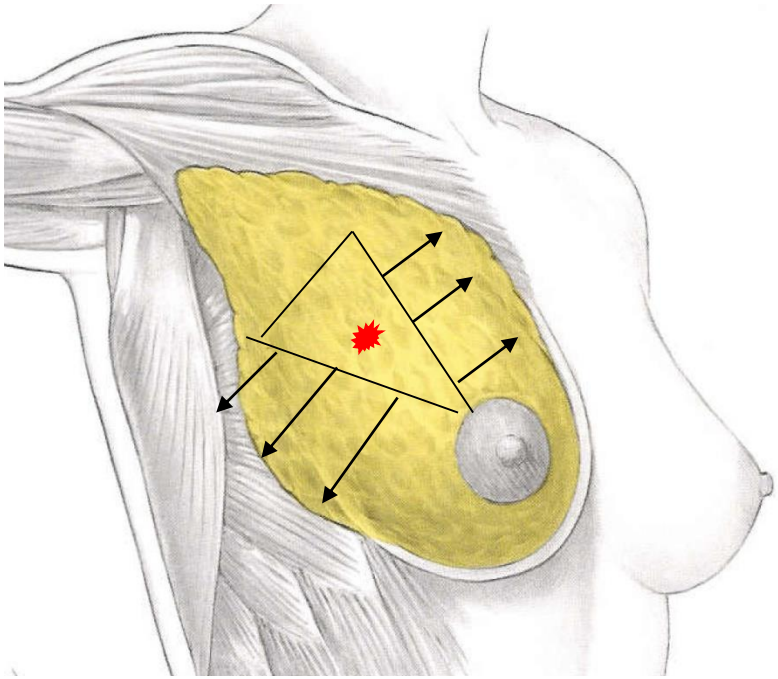
Definition of localisation and Volume

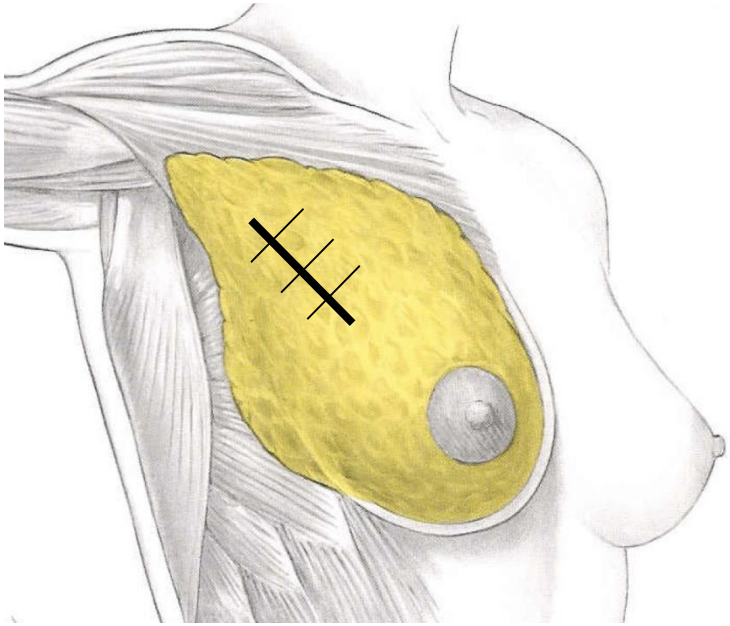


Have plan B in mind !!

ESTRO School

Surgical technique





Resection + Reconstruction

Strategy for defect closure

- Avoidance of seroma
- Close every (partial) mastectomy defect
- Chose the easiest technique
  - Local glandular flaps (tissue displacement)
  - Tumorspecific reduction mammoplasty
  - Distant flaps (Lat dorsi)

Intraoperative Margin Assessment

Palpation

Imaging

New Technologies

Extent of Resection / Margins

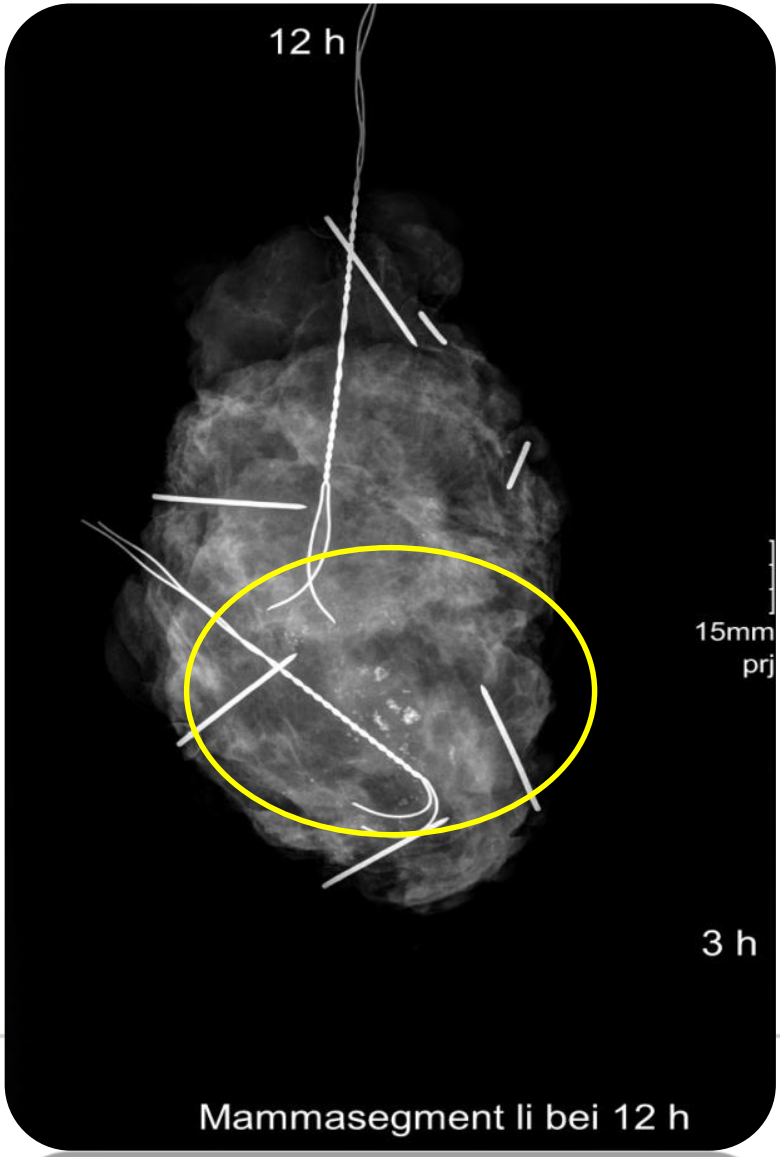
B3: no residual suspicious finding on imaging (no specific margin width based on histopathologic examination)

DCIS: 2mm (in case of BCT and Radiotherapy)

Invasive disease (primary surgery): no ink on tumor

Invasive disease (after PST): no ink on tumor

Radiography of the Specimen



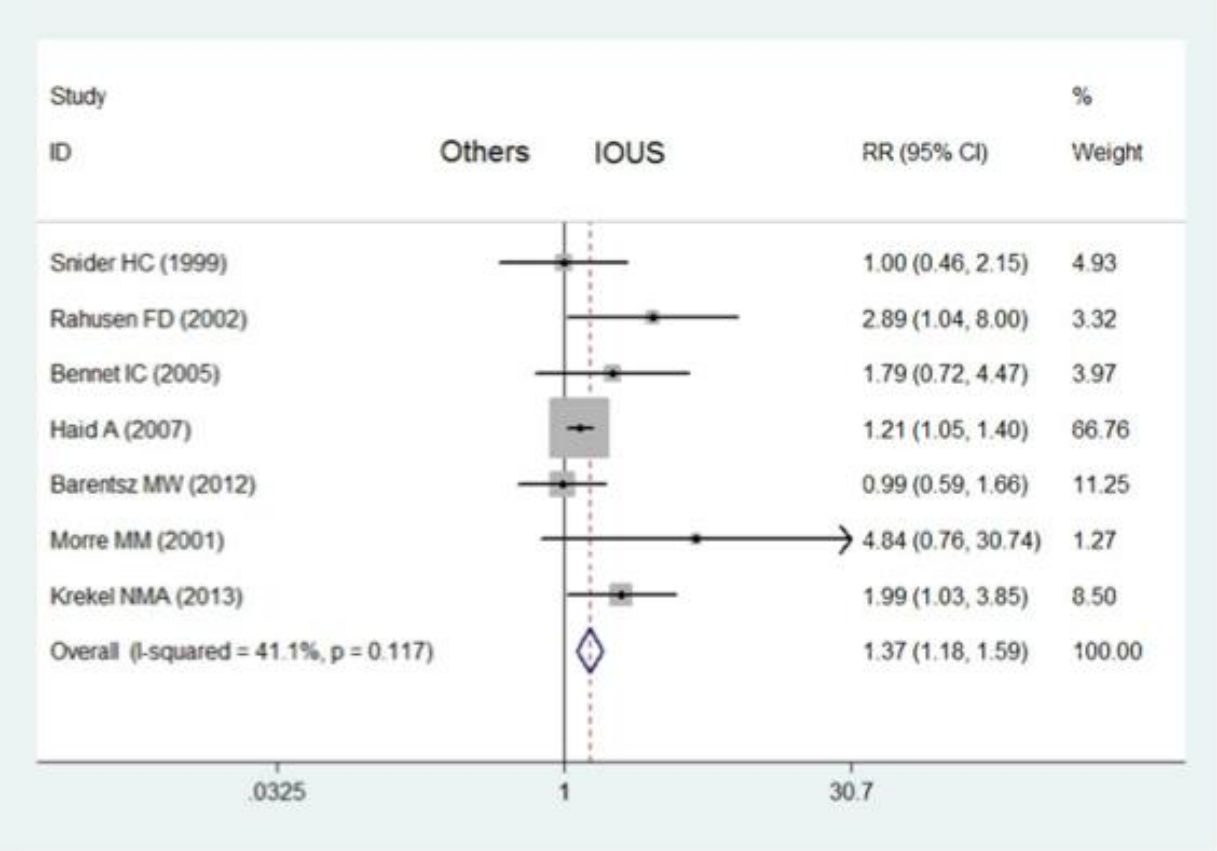
New Techniques: Ultrasound guided surgery

Courtesy M.Marx, Radebeul

Intraoperative Ultrasound Guidance Is Associated with Clear Lumpectomy Margins for Breast Cancer: A Systematic Review and Meta-Analysis

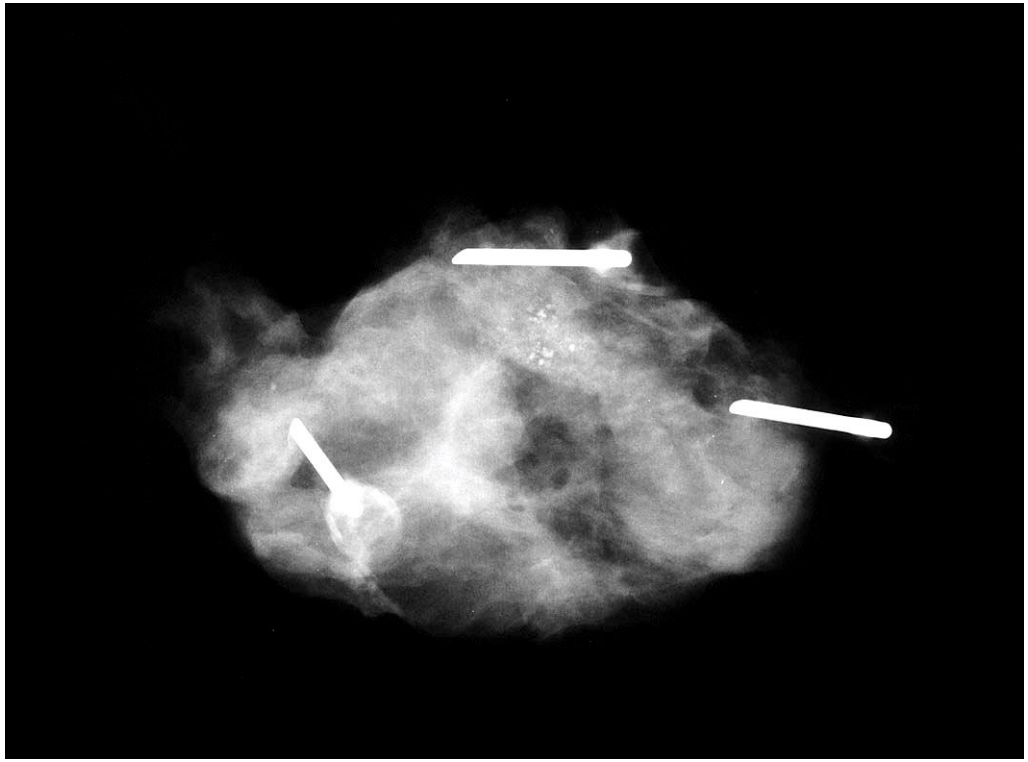
Hong Pan[1☯], Naping Wu[1☯], Hao Ding[2☯], Qiang Ding[1], Juncheng Dai[3], Lijun Ling[1], Lin Chen[1], Xiaoming Zha[1], Xiaoan Liu[1]*, Wenbin Zhou[1]*, Shui Wang[1]

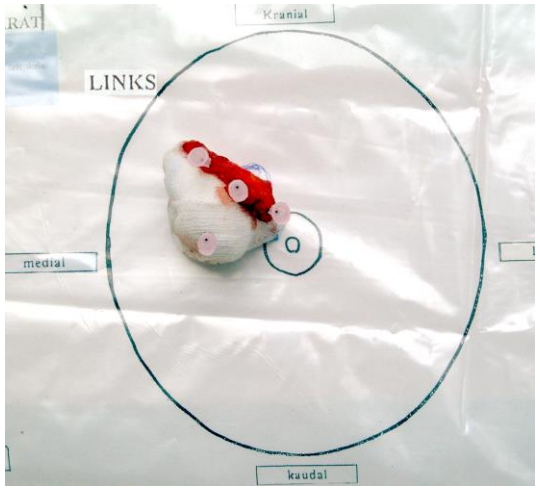
1 Department of Breast Surgery, The First Affiliated Hospital with Nanjing Medical University, Nanjing, Jiangsu, China, **2** Department of Surgery, Baoying County Hospital, Yangzhou, Jiangsu, China, **3** Department of Epidemiology and Biostatistics, Nanjing Medical University School of Public Health, Nanjing, Jiangsu, China



ESTRO School

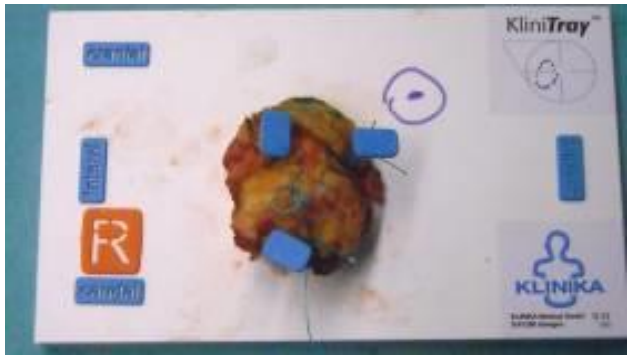
Handling of the Specimen / Template

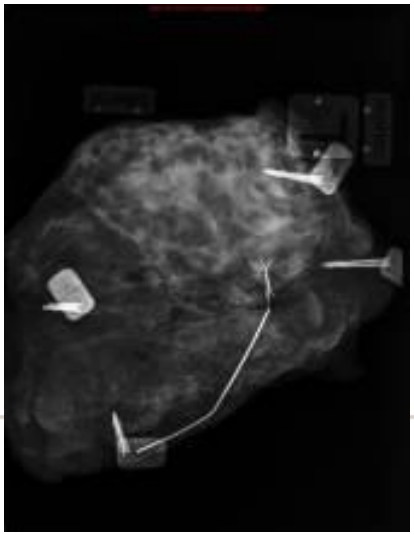


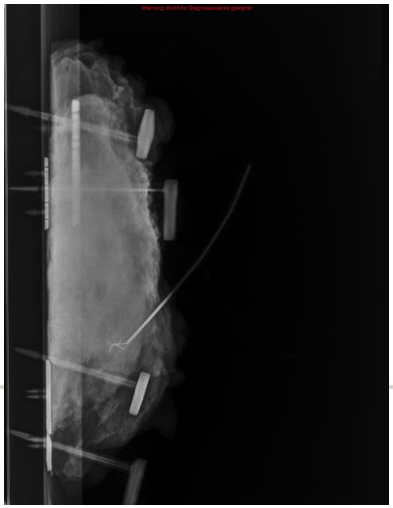


Handling of the specimen - radiography

Specimen radiography in two planes[28]



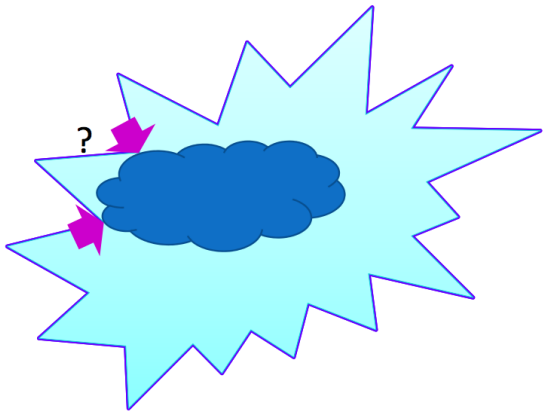


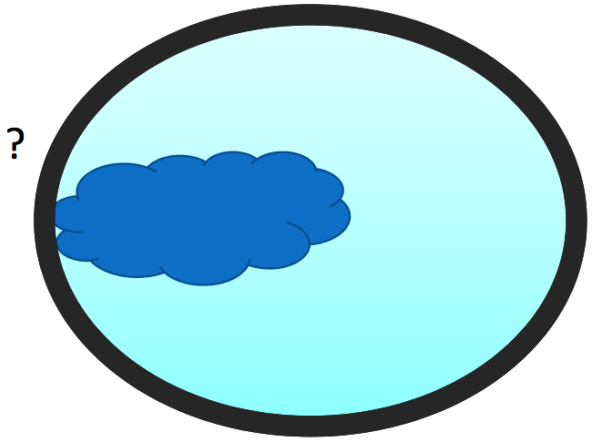


ESTRO School

Reliability of Margin Assessment

Features of the Specimen





Soft
Malleable
Tissue around the tumor shiftable

Surface incised

Surface coagulated

Courtesy A.Lebeau, Luebeck, Germany

ESTRO School

Excerpta Medica

The American Journal of Surgery

The American Journal of Surgery 184 (2002) 89–93

Scientific paper

The pancake phenomenon contributes to the inaccuracy of margin assessment in patients with breast cancer

Roger A. Graham, M.D.[a,e]*, Marc J. Homer, M.D.[b], Judith Katz, M.D.[b],
Jar A.[d]

[d]Bio USA

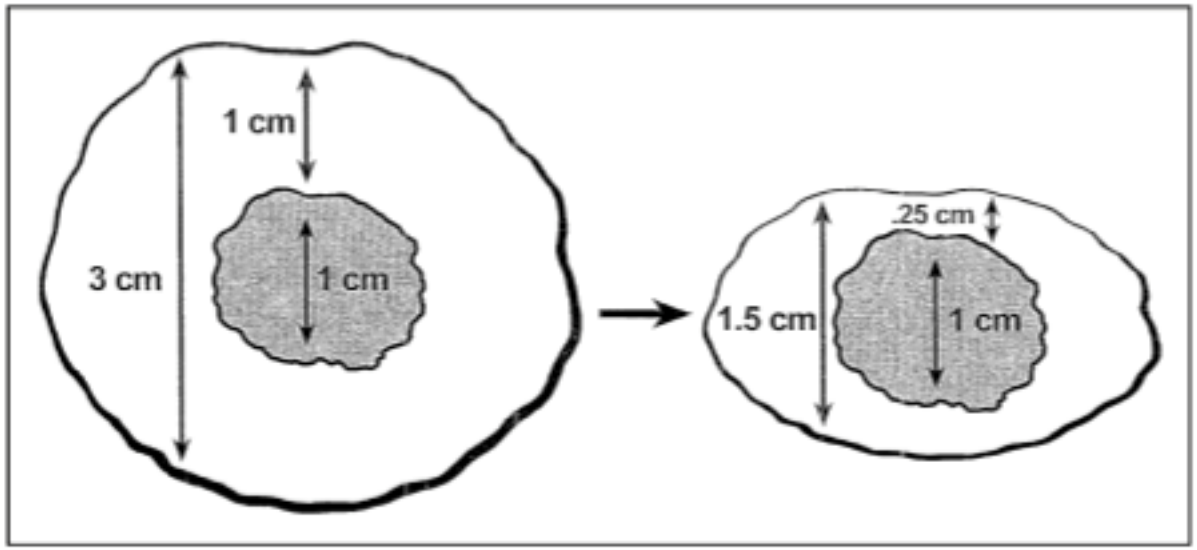


Fig. 3. Demonstration of typical specimen flattening and its impact on margin assessment.

Graham RA et al., Am J Surg 2002

ESTRO School

EXPERT REVIEWS

MarginProbe®: intraoperative margin assessment during breast conserving surgery by using radiofrequency spectroscopy

Expert Rev. Med. Devices 10(3), 301–315 (2013)

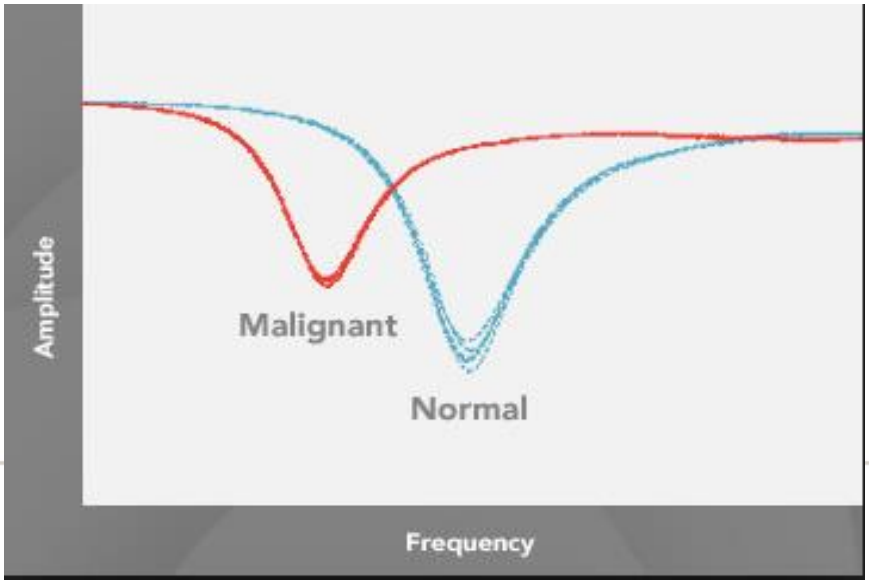
Marc Thill

Department of Gynecology and Obstetrics and Breast Cancer Center, Agaplesion Markus Hospital, Wilhelm-Epstein-Strasse 4, 60431 Frankfurt, Germany
Tel.: +49 699 533 2228
Fax: +49 699 533 2733
marc.thill@fdk.info

In breast conserving surgery, the tumor should be removed with a clean margin, a rim of healthy tissue surrounding. Failure to achieve clean margins in the initial surgery results in a re-excision procedure. Re-excision rates are reported as being 11–46% for invasive carcinoma and ductal carcinoma *in situ* (DCIS). Re-excisions can have negative consequences such as increased postoperative infections, negative impact on cosmesis, patient anxiety and increased medical costs. Therefore, the surgical margin of invasive and intraductal (DCIS) breast tissue is a subject of intense discussion. Different options for intraoperative assessment are available, but all in all, they are unsatisfying. Frozen section margin examination is possible but is time consuming and restricted to the assessment of invasive carcinoma. In the case of DCIS, there is no procedure for intraoperative margin assessment. Thus, a solution for efficient intraoperative surgical margin assessment is needed. For this purpose, an innovative, real-time, intraoperative margin-assessment device (MarginProbe®, Dune Medical Devices, Caesarea, Israel) was designed, and recent published clinical data reported a reduction of re-excisions by more than 50%.

Thill M, Expert Rev Med Dev 2013

New Technologies – Margin Probe



A Randomized Prospective Study of Lumpectomy Margin Assessment with Use of MarginProbe in Patients with Nonpalpable Breast Malignancies

Freya Schnabel, MD,[✉] Susan K. Boolbol, MD, Mark Gittleman, MD, Tami Karni, MD, Lorraine Tafra, MD, Sheldon Feldman, MD, Alice Police, MD, Neil B. Friedman, MD, Scott Karlan, MD, Dennis Holmes, MD, Shawna C. Willey, MD, Moshe Carmon, MD, Kristen Fernandez, MD, Stephanie Akbari, MD, Jay Harness, MD, Lisa Guerra, MD, Thomas Frazier, MD, Karen Lane, MD, Rache M. Simmons, MD, Alison Estabrook, MD, and Tanir Allweis, MD

Table 2

Positive margin status and reexcision lumpectomy procedures

Variable	Treatment group		Reduction	*p*
	Device (*n* = 298)	Control (*n* = 298)		
Positive margins after initial surgery				
All patients	92/298 (30.9 %)	124/298 (41.6 %)	26 %	0.008
At skin or fascia	15/298 (5.0 %)	18/298 (6.0 %)		0.72
Candidates for reexcision	77/298 (25.8 %)	106/298 (35.9 %)	27 %	0.013
Due to positive margin on main specimens	47/298 (15.8 %)	97/298 (32.9 %)	52 %	<0.001
Due to positive margin on shavings	30/298 (10.1 %)	9/298 (3.0 %)		<0.001
Reexcision lumpectomy procedures	59/298 (19.8 %)	77/298 (25.8 %)	23 %	0.097; 0.018[a]
Due to positive margin on main specimens	33/298 (10.0 %)	62/298 (20.8 %)	47 %	0.002
Due to positive margin on shavings	19/298 (7.4 %)	4/298 (1.3 %)		0.002
Due to close margins or other considerations	7/298 (2.3 %)	11/298 (3.7 %)		0.47

Has the Invasive Guideline Changed Anything? Re-Excision Rate

	Cedars-Sinai	MSKCC
	n = 846	n = 1205
Pre-guideline	19%	21%
Post-guideline	13%	15%
	p = .03	p = .006
	Chung A, Ann Surg Oncol 2015;22(Suppl 3):5422	Rosenberger L, Ann Surg Oncol 2016;23:3239

This presentation is the intellectual property of the author/presenter. Contact them at morrowm@mskcc.org for permission to reprint and/or distribute.

©AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2016.1

www.ago-online.de

Further Information

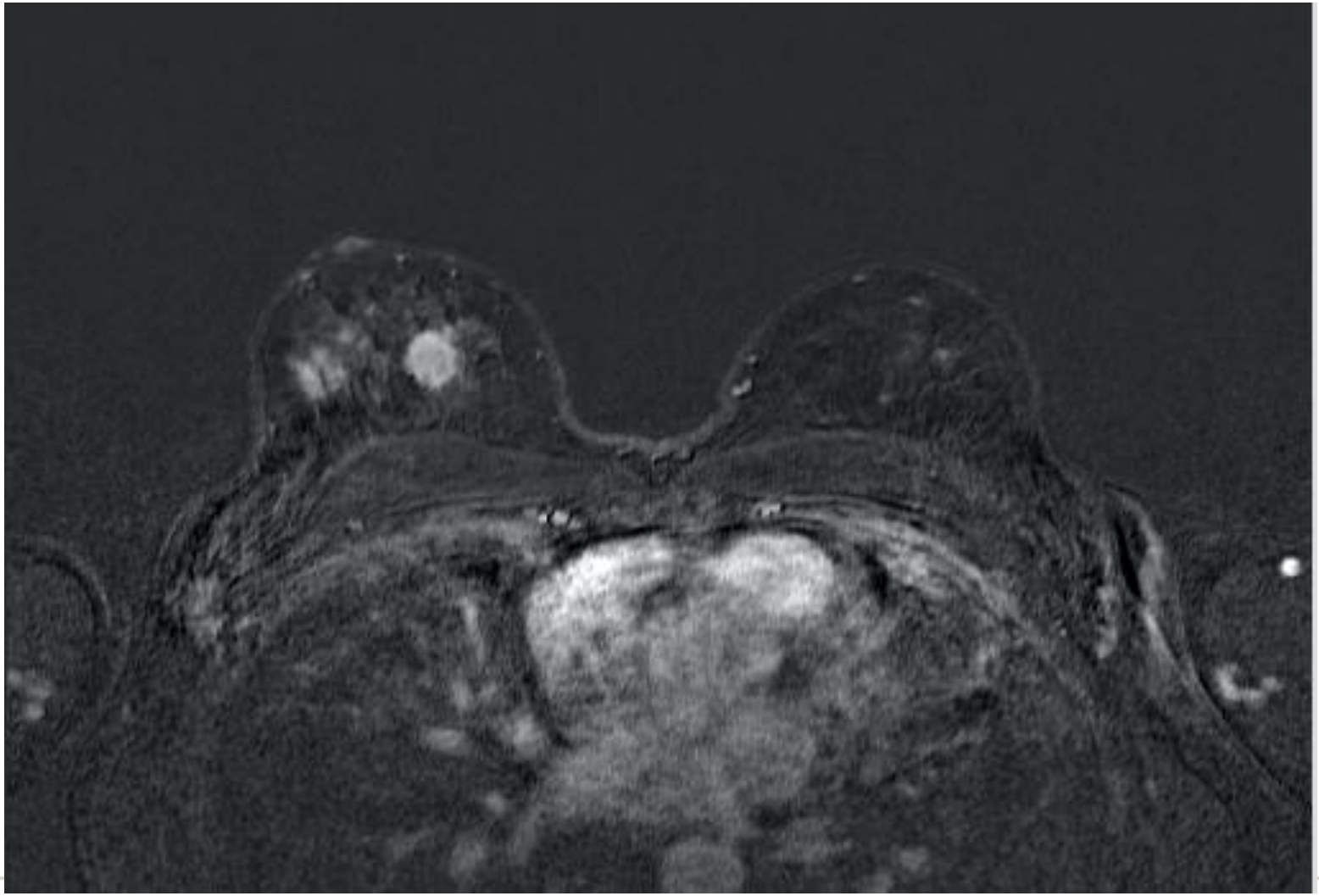
References

FORSCHEN
LEHREN
HEILEN

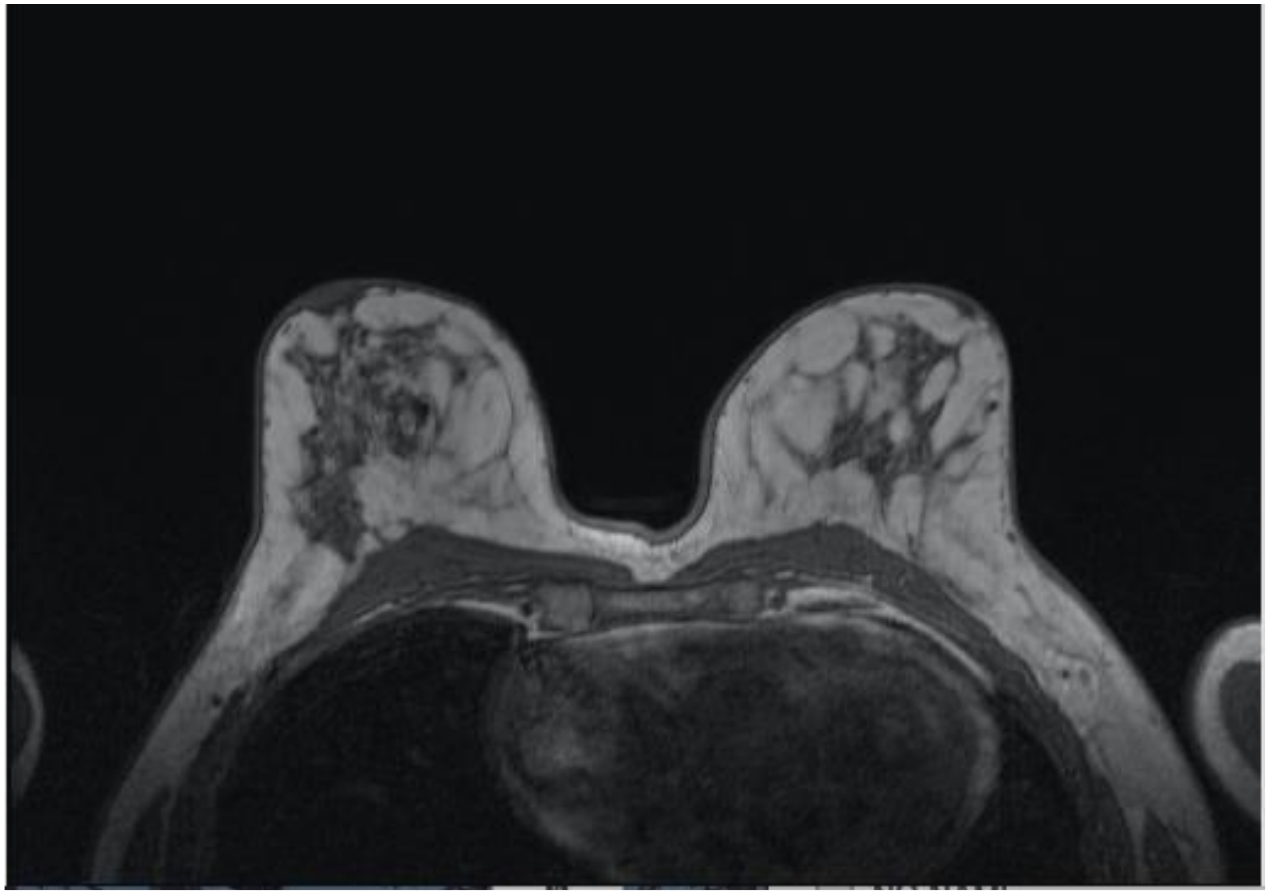
Breast Conservation: Surgical Technical Aspects

	Oxford / AGO LoE	GR	
➢ **Non-palpable lesion**			
➢ Wire guided localisation	2b	B	++
➢ Radionuclide guided localisation	2b	B	+/-
➢ Specimen radiography or ultrasound	2b	B	++
➢ **Tumor-free margins required** (also in unfavorable biology „no cells on ink" are enough)	2a	A	++
➢ **Immediate intraoperative re-excision for close margins (specimen radiography and/or intra-operative pathology)**	1c	B	++
➢ **Re-excision required for involved margins (paraffin section)**	3b	C	+
➢ **Therapeutic stereotactic excision alone**	4	D	- -
➢ **Ultrasound guided surgery to prevent re-excision**	1a	A	+/-
➢ **Intraop. margin evaluation with margin probe**	1b	A	+/-

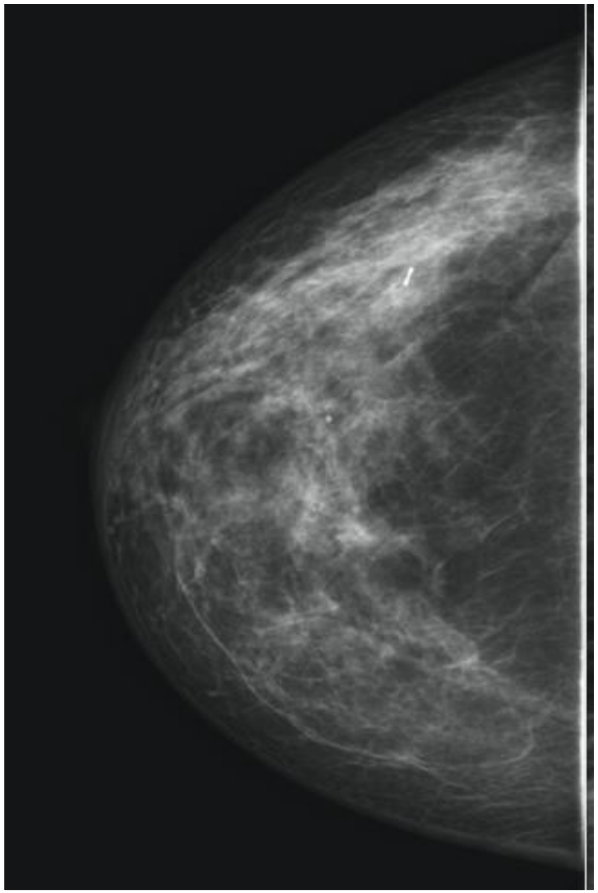
Surgery after Primary Systemic Treatment

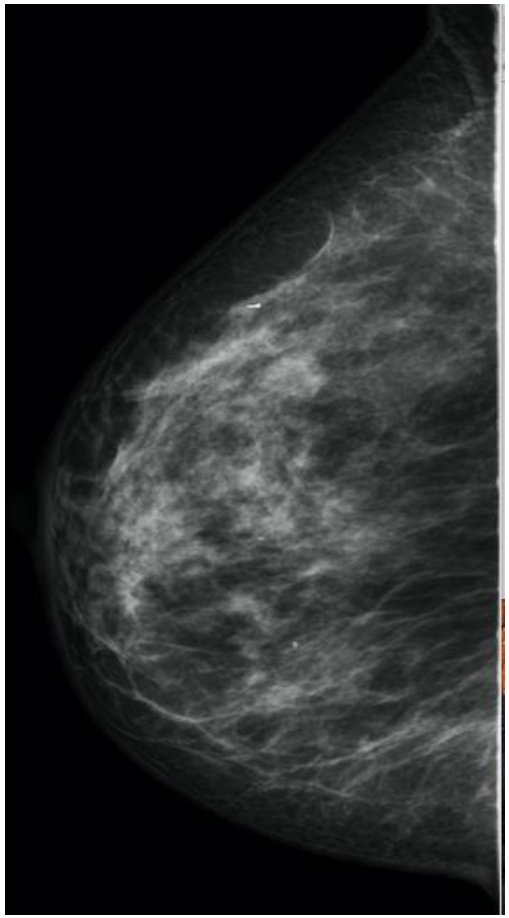


Surgery after Primary Systemic Treatment



Surgery after Primary Systemic Treatment





Extension of surgery to assess pCR

review

Annals of Oncology 00: 1–12, 2015
doi:10.1093/annonc/mdv161

Recommendations for standardized pathological characterization of residual disease for neoadjuvant clinical trials of breast cancer by the BIG-NABCG collaboration

V. Bossuyt[1*], E. Provenzano[2], W. F. Symmans[3], J. C. Boughey[4], C. Coles[5], G. Curigliano[6], J. M. Dixon[7], L. J. Esserman[8], G. Fastner[9], T. Kuehn[10], F. Peintinger[11,12], G. von Minckwitz[13], J. White[14], W. Yang[15], S. Badve[16], C. Denkert[17], G. MacGrogan[18], F. Penault-Llorca[19], G. Viale[20] & D. Cameron[21] of the Breast International Group-North American Breast Cancer Group (BIG-NABCG) collaboration

„Surgical resection volume is based on preoperative imaging. All detectable residual disease should be removed by the surgery with clear margins. In case of complete radiologic response the center of the tumor bed should be removed“

ESTRO School

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2016.1

Procedure after Neoadjuvant Therapy

	Oxford / AGO LoE / GR		
➢ Marking of tumor in a timely manner	5	D	++
➢ Surgery	2b	C	++
➢ Microscopically clear margins	5	D	++
➢ Tumor resection in the new margins	3b	C	+

For „Surgery after neoadjuvant chemotherapy“ see chapter „Neoadjuvant chemotherapy“

www.ago-online.de

Further Information

References

FORSCHEN
LEHREN
HEILEN

Breast Conservation: Surgical Technical Aspects

©AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2017.1

	Oxford / AGO LoE / GR		
➢ **Non-palpable lesion**			
➢ Wire guided localisation	2b	B	++
➢ Radionuclide guided localisation	2b	B	+/-
➢ Specimen radiography or ultrasound	2b	B	++
➢ **Tumor-free margins required** (also in unfavorable biology „no cells on ink“ are enough)	2a	A	++
➢ **Immediate intraoperative re-excision for close margins (specimen radiography and/or intra-operative pathology)**	1c	B	++
➢ **Re-excision required for involved margins (paraffin section)**	3b	C	+
➢ **Therapeutic stereotactic excision alone**	4	D	- -
➢ **Ultrasound guided surgery to prevent re-excision**	1a	A	+/-
➢ **Intraop. margin evaluation with margin probe**	1b	A	+/-

www.ago-online.de

Further Information

References

FORSCHEN
LEHREN
HEILEN

ESTRO School

ESTRO Teaching Course on the Multidisciplinary management of Breast Cancer.
Dublin, Republic of Ireland. September 2017

Oncoplastic Surgery

Lynda Wyld

Reader In Surgical Oncology

University of Sheffield

Consultant Oncoplastic Breast Surgeon

Doncaster and Bassetlaw Teaching Hospital

UK.

Disclosure:

- I have no conflict of interest to report

Lecture plan

- Indications and Oncology of oncoplastic surgery
- Classification and Techniques
- Surgical and patient outcomes

Indications and Oncology of Oncoplastic Surgery

Oncoplastic surgery is tumour specific immediate breast reconstruction.

The integration of plastic surgery techniques and breast cancer surgery to preserve aesthetic outcomes without compromising local disease control.

Breast Conservation versus Mastectomy

- **Shrinking indications for mastectomy:**
  - Inflammatory breast cancer
  - Failed conservation (primary or secondary)
  - Extensive DCIS
  - Risk reduction ??
  - Multicentric cancer??

Expanding Conservation Options:

- Tumour size relative to breast size: Used to be 25%, now OPS allows 50% volume resection
- Position of tumour in the breast: OPS options for all quadrants
- Multicentric and multifocal no longer taboo
- Neoadjuvant options improving

Impact of Oncoplastic Surgery on Survival and Local Recurrence. Case series

- Large series report 5 year rates of LRR 4%. Overall Survival rate 94.5% and DFS of 90.9% (Rezai et al, 2014).
- Lee et al, 2017, compared surgery types and 6 year LRR, OS and DFS and found no significant difference by surgery type.
- Mansell et al, 2017, compared LRR at 5 years between standard WLE, OPS and Mastectomy with LRRs of 3.4, 2 and 2.6% respectively (P = NS) despite WLE cases being smaller and less adverse histologically.
- DFS rates of OPS and Mastectomy were similar in keeping with their similar stage and grade profiles

A large meta analysis (De La Cruz et al, 2016) confirmed that there is no LRR, DFS or OS disadvantage compared to case matched standard BCS or mastectomy

How easy is local recurrence to detect after flap based oncoplastic surgery

- Level 1 and 2 procedures just move normal parenchyma around but may cause additional scarring. Recurrence is usually easy to see on mammograms. Little published about diagnostic delay but 1 personal experience of recurrence being called scarring on mammography for 6 months or so until symptomatic biopsy.

- For LD miniflaps a large series showed 21 local recurrences out of 261 cases with mean follow up of 10 years (Mele et al, 2017) and noted that lesions were found by palpation of easy to see on mammography.

- In lipomodelling cases, calcifications due to fat necrosis have a typical appearance and are not usually mistaken for recurrence.

Margin positivity and re excision rates

- Tumour resection volumes may be much higher with oncoplastic techniques than standard BCS
- Rezai, in a large series of 1035 oncoplastic cases, achieved primary clear margins in 88%, which compares favourably with the UK figure of 60-80%.
- Most studies report margin re excision rates similar to those of standard BCS
- Systematic review (Yiannakopoulou 2016) showed rates varying between 0 and 36% (this being a DCIS only series where margins are more challenging) and generally tending to be low.
- This may reflect the increased volume resection making it easier to excise widely for relatively large tumours

Marking of specimen site and specimen

- Standardisation: 6 quadrants (inferior, superior, anterior, posterior, medial and lateral clips to the cavity) to facilitate radiotherapy targeting.
- Communication and documentation
- Careful specimen orientation and labelling, including shaves. Detailed diagram in the operation note and on the pathology form
- Difficult to target radiotherapy boost without site marking. Equally difficult for the surgeon to go back for shaves

Importance of clips

- Scars may be widely distant from the tumour bed so skin scars do not permit localisation
- Seroma cavity is not reliable as internal breast scaring may be extensive and again, distant from the tumour site
- Cavity marker clips should be applied to the tumour bed

Lipomodelling Oncological Safety

- Lipomodelling has been around for 100 years but safety concerns (imaging calcification artefact) in the 1980s caused a loss of interest. Subsequently it was realised that it is easy to tell malignant change from lipofilling artefact.
- In the 1990s, Sydney Coleman reported on his technique and it saw a resurgence of popularity and an expansion of indications.
- Concerns regarding 'adipose stem cells' trigger cancer recurrence have never been proven.
- Numerous studies and meta analyses have confirmed oncological safety.
- UK Lipomodelling guidelines exist (Fatah et al, ABS and BAPRAS, 2012)

Indications for Primary Oncoplastic Surgery

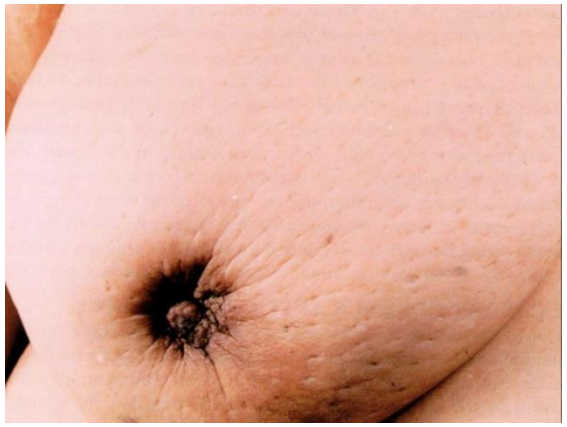
- Relatively large tumour compared to breast size and patient/disease not suitable for neoadjuvant therapy.
- Adverse location: medial, inferior or central
- Large breast size such that patient may benefit from reduction or uplift and risk of radiotherapy induced lymphoedema and severe radiotherapy side effects
- Likelihood of nipple malposition after surgery
- Likelihood of size or shape asymmetry

Indications for secondary oncoplastic surgery

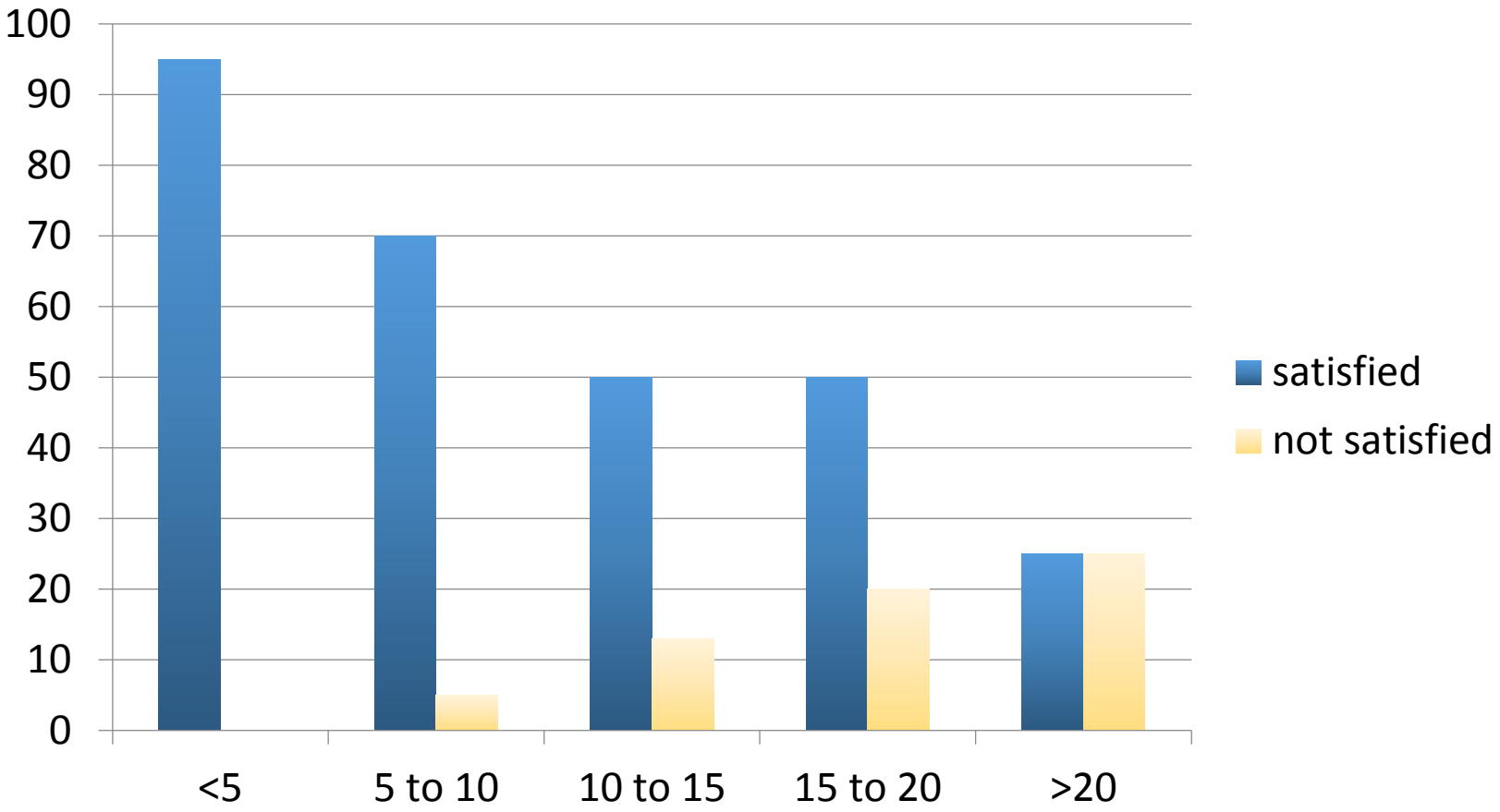
- Positive margins after first wide excision
- Late cosmetic issues requiring correction: nipple height asymmetry, size asymmetry, indentation, distortion.

Contra-indications

- Positive margins
- Inflammatory breast cancer
- Relative contraindications:
  - Prior radiotherapy
  - Smoking
  - Diabetes
  - Multicentric cancer?

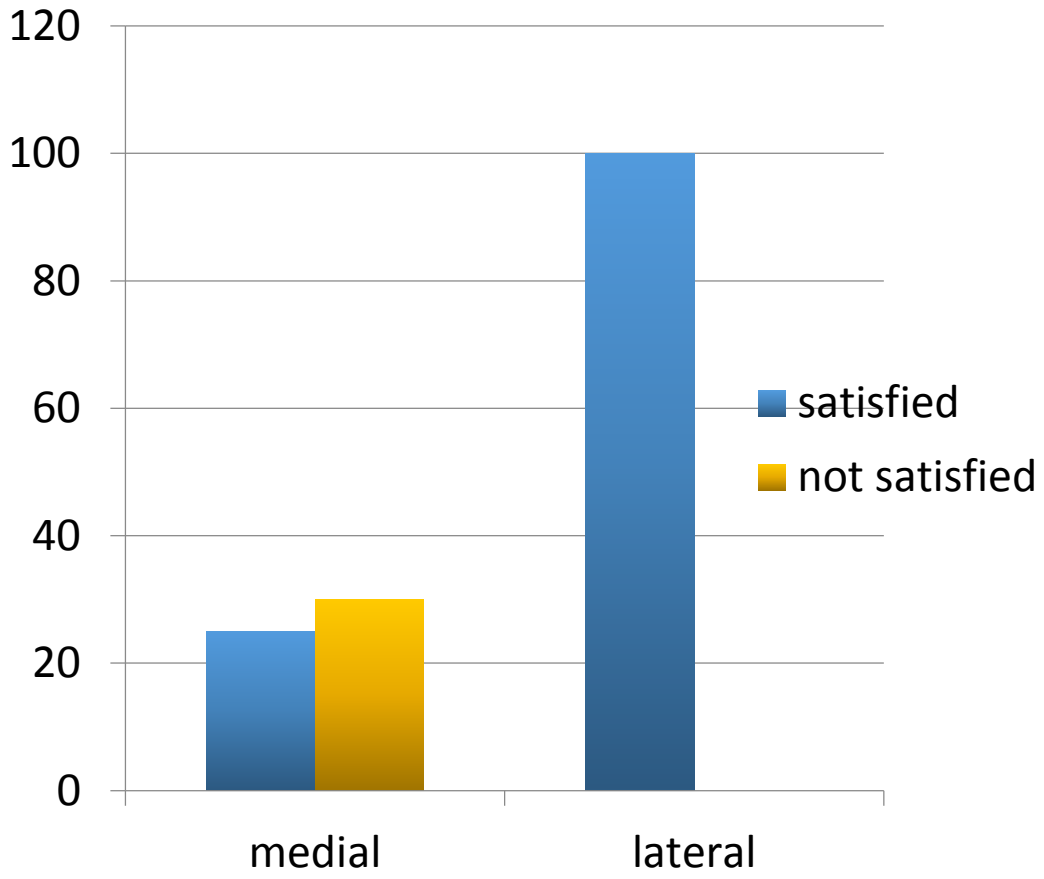


Breast Conservation Outcomes by % volume excised



Cochrane 2003, BJS

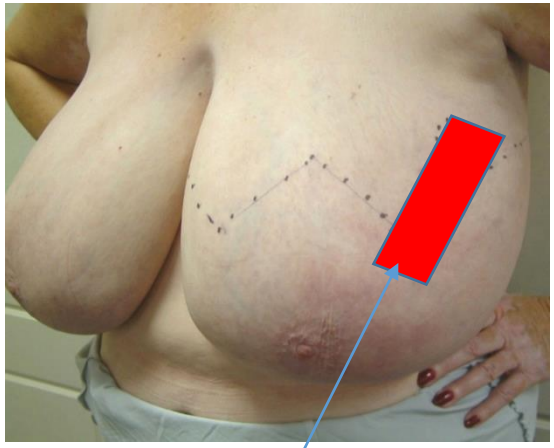
Media versus lateral location at 10-15% volume loss



Cochrane 2003, BJS

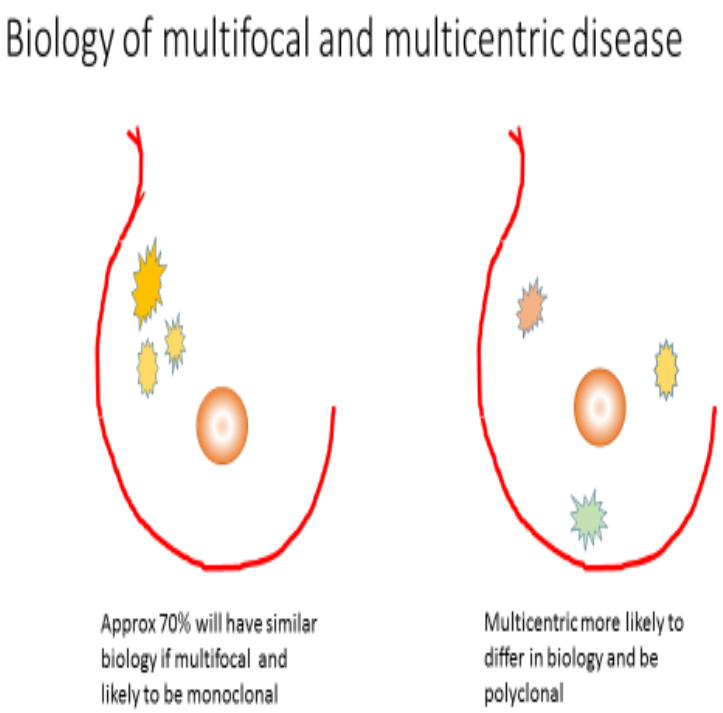
Extreme Oncoplasty

- Patients who would normally be offered mastectomy.
- Multifocal, multicentric or >5cm tumour
- Series by Silverstein et al, 2015, The Breast Journal.
- 83% (extreme) versus 96% (normal BCS) achieved clear margins (no tumour at ink) with 9% having re excision and 6% having a mastectomy.
- 1.5% local recurrence rate at 2 years versus 1.2% in the standard arm (P=not significant). Both slightly higher than the more usual 0.5% per year rate seen for standard BCS)



7 cm area of DCIS extending towards nipple.
Bracketted with 2 wires and inferior pedicle wise pattern reduction plus contralateral immediate symmetrization

Multicentric and multifocal disease



Plan pedicle position.

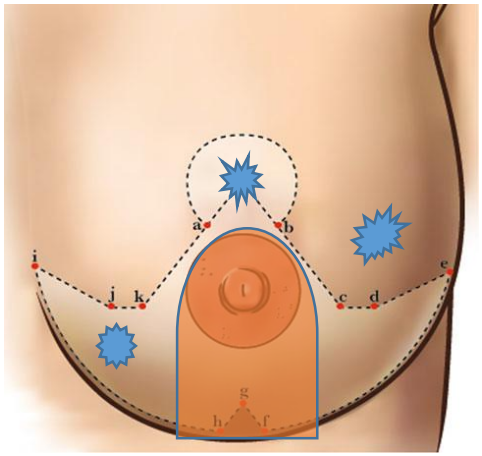
Intra-operative margin assessment (specimen X-ray, margin probes of various sorts) to avoid positive margins.

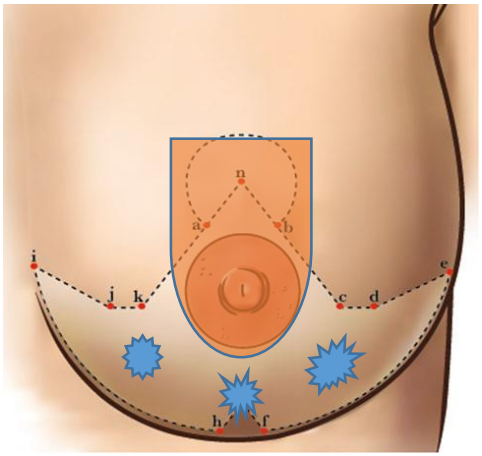
Careful recording of flaps and pedicles relative to tumour

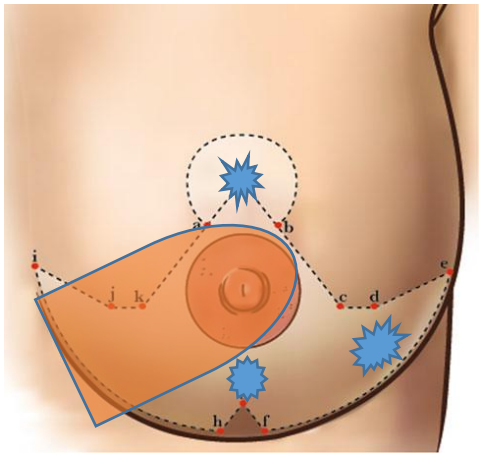
Mark with clips for both Xray an margin re excision if needed

Planning examples.

- More complex dermoglandular flaps/ therapeutic mammoplasty techniques.
- May achieve resection volumes of 20-50%
- Many techniques available depending on the site of the affected quadrant; Quadrant by quadrant atlas of procedures plus bespoke modifications. E.g. Batwing for superior periareolar, grisotti for central, superior pedicle for inferior tumours etc.
- If planning conservation for multicentric disease, MRI is necessary, patient must be warned about risk of subsequent mastectomy and lack of level 1 evidence of safety.
- May need multiple tumour wires



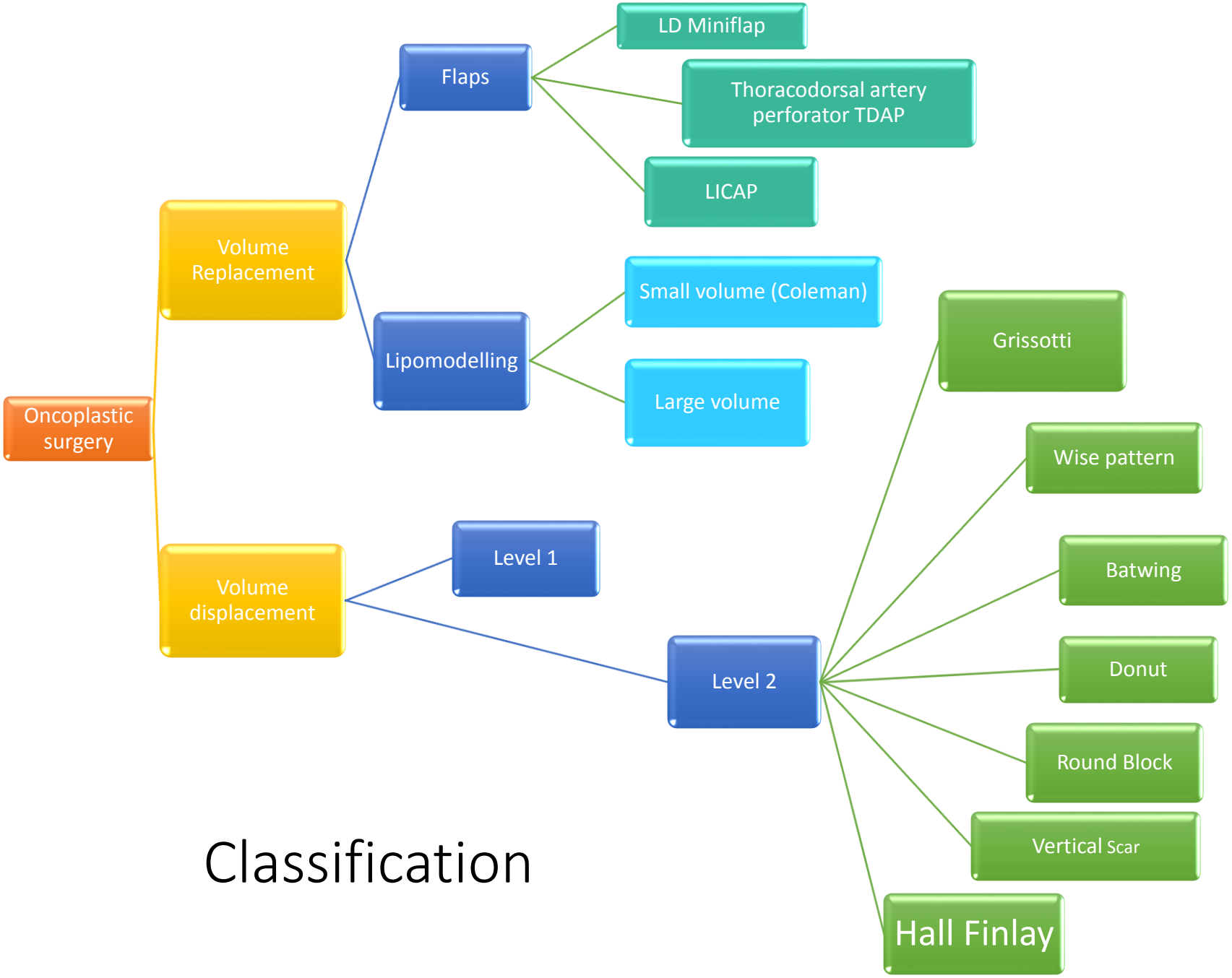

n
a
b
i
j
k
c
d
e
h
f


a
b
i
j
k
c
d
e
h
f

Key issues

- Oncoplastic options offered to all patients requiring mastectomy
- **MDT discussion of all cases**
- Training and CPD requirements
- Rates of implant loss less than 5%: Antibiotic use specified
- Regular audit
- Patient reported outcomes audited

Classification and Techniques



Classification

Volume Displacement Techniques

- Selection of technique depends on the breast size, degree of ptosis, breast density, tumour size.

- Level 1: parenchymal mobilisation to fill relatively small defects with or without nipple re positioning

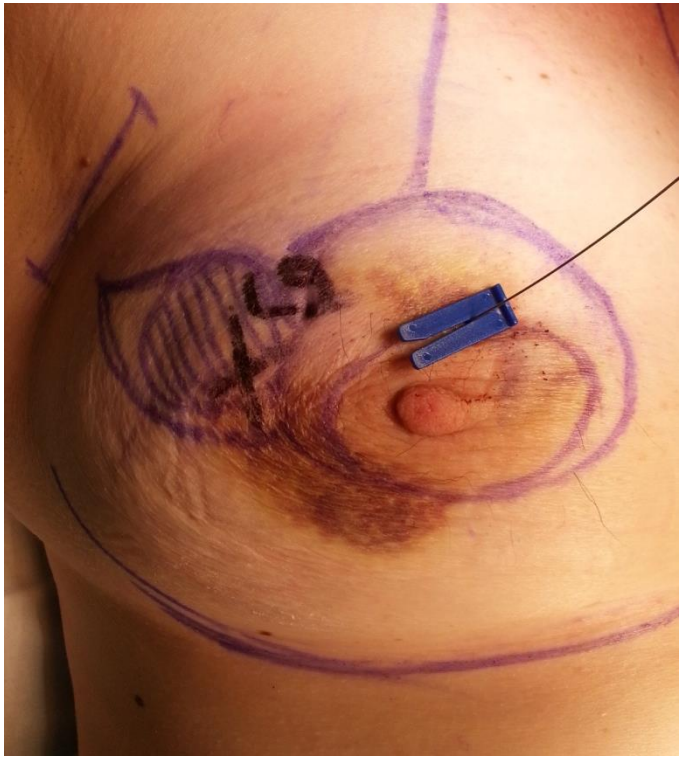
- Level 2: therapeutic mammoplasty

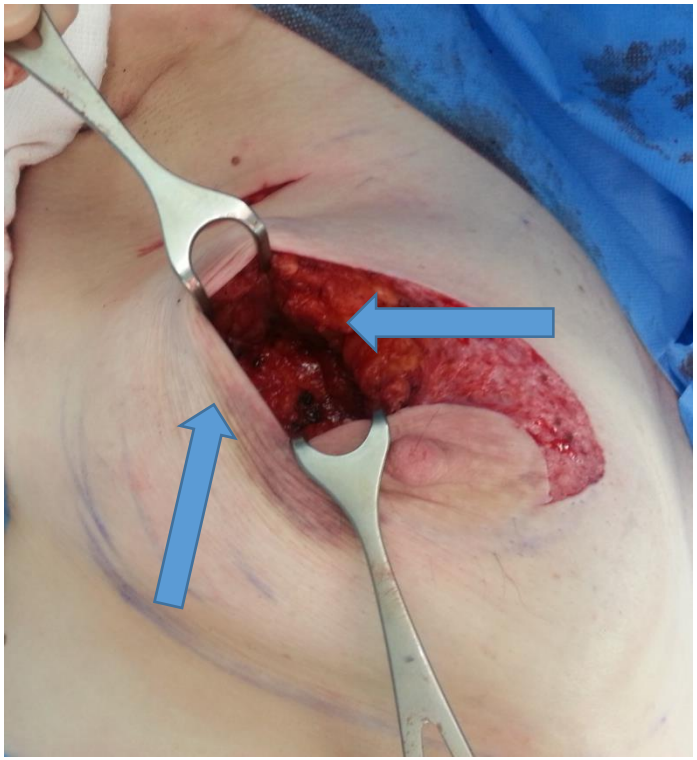
Level 1. Local parenchymal flaps

- For small defects, parenchymal flap mobilisation to reduce indentation.
- Caution in the fatty breast, diabetics, smokers, post-radiotherapy as increased risk of fat necrosis.
- Useful for small to moderate volume defects
- Nipple re positioning may not be necessary

Level 1 technique

Techniques involve wide skin flap elevation, tumour resection, parenchymal mobilisation from the pectoral attachment and advancement into the defect. Nipple repositioning with concentric de-epithelialisation may or may not be needed.





Level 2 Oncoplastic techniques: formal therapeutic mammoplasty with nipple re-positioning.

- More complex dermoglandular flaps and mammoplasty techniques
- Success depends on a good understanding of the vascular supply of the breast and in particular the nipple.
- Many techniques available depending on which quadrant contains tumour and the size and degree of breast ptosis.

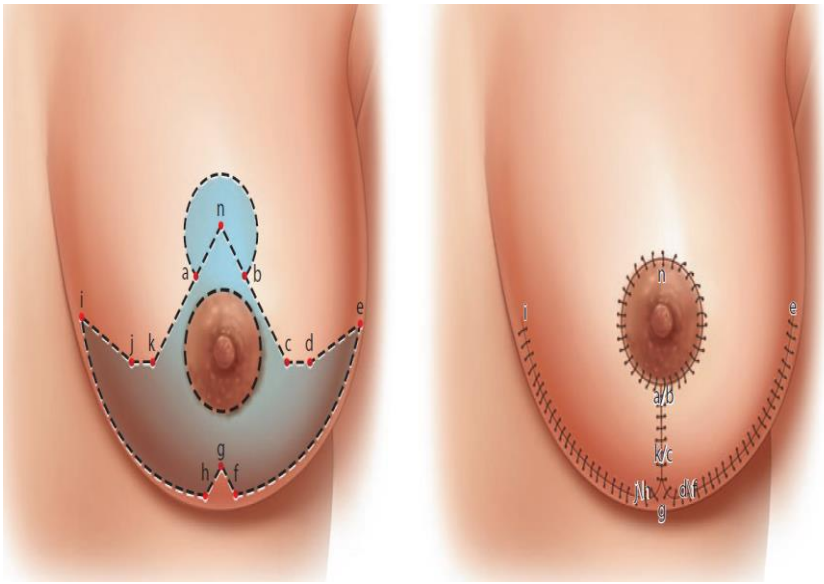
Not a ‘one size fits all’ option

- Need to modify and tailor the operative approach to the patient:
- Ptosis is used to permit higher volume resection with skin envelope tightening to achieve a perter breast.
- Nipple height adjustment and re-centralisation integral to techniques
- Contralateral symmetrisation may be required at the same time or later
- Tumour position relative to flap blood supply must be considered so may need to modify techniques. Some women may have anatomic variants with few feeding vessels to areolar plexus

Ptosis

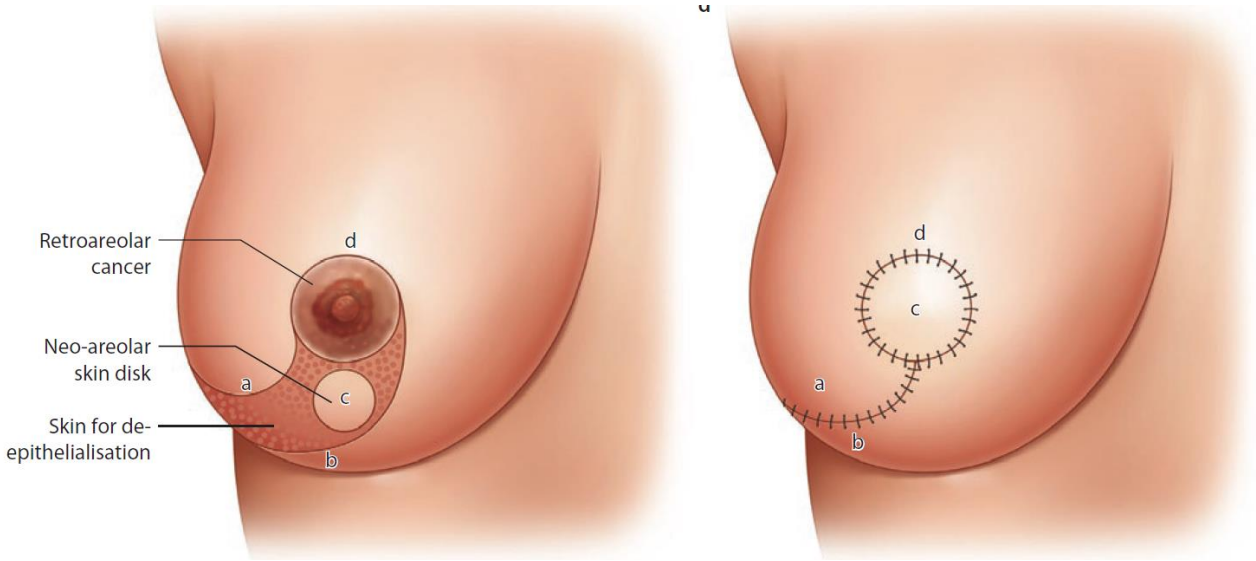
- Pedicle length may be a consideration in very large breasts.
- For a superior pedicle, elevating the nipple by 6 cm may be the upper limit. If more elevation is required a medial or inferiorly based flap is used.
- Very large ptotic breasts may be better with a broad inferior pedicle
- Pedicles may be ‘supercharged’, i.e base procedure around an inferior pedicle but leave another de-epithelialised pedicle attached.

The Wise Pattern Mammoplasty

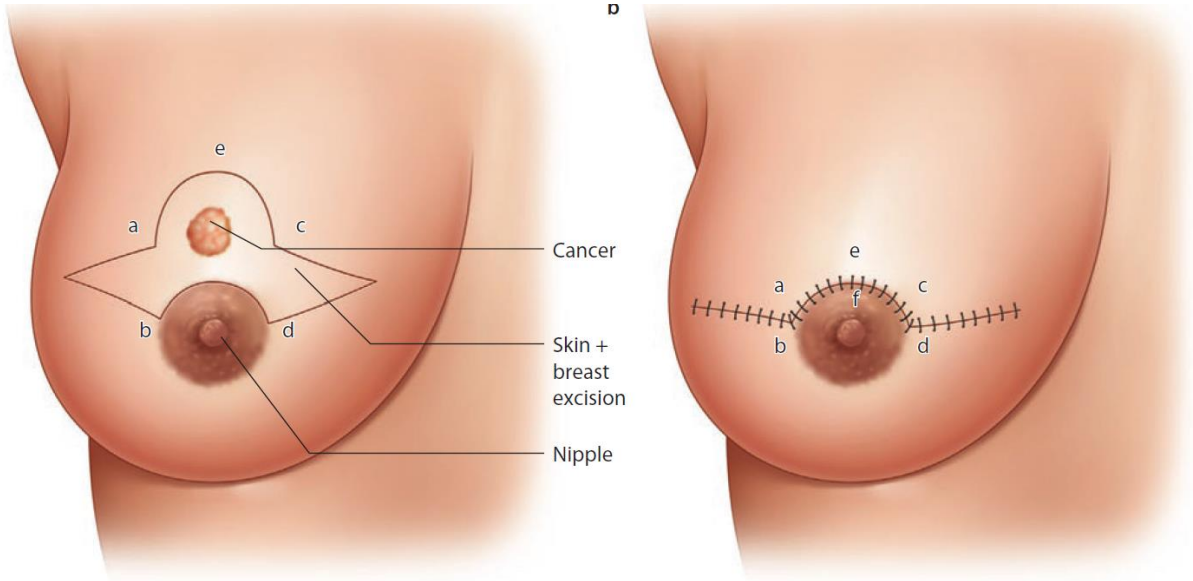


- Suitable for tumours in many locations in the breast, suitable for very large breasts with significant ptsosis
- Pedicle position can be varied from inferior, inferomedial or lateral to supero medial or lateral depending on pedicle length and tumour position.
- The angle and orientation of the W may vary from medial to central to lateral depending on tumour location
- Excellent cosmesis

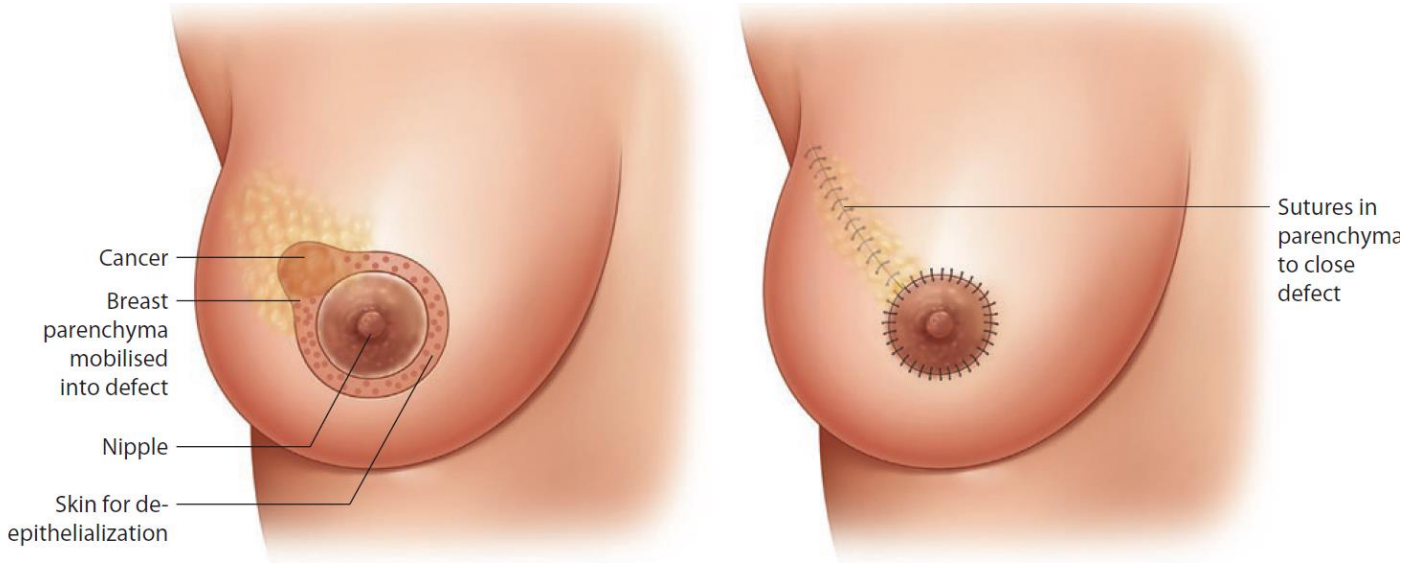
Grissoti type procedure for centrally located tumours



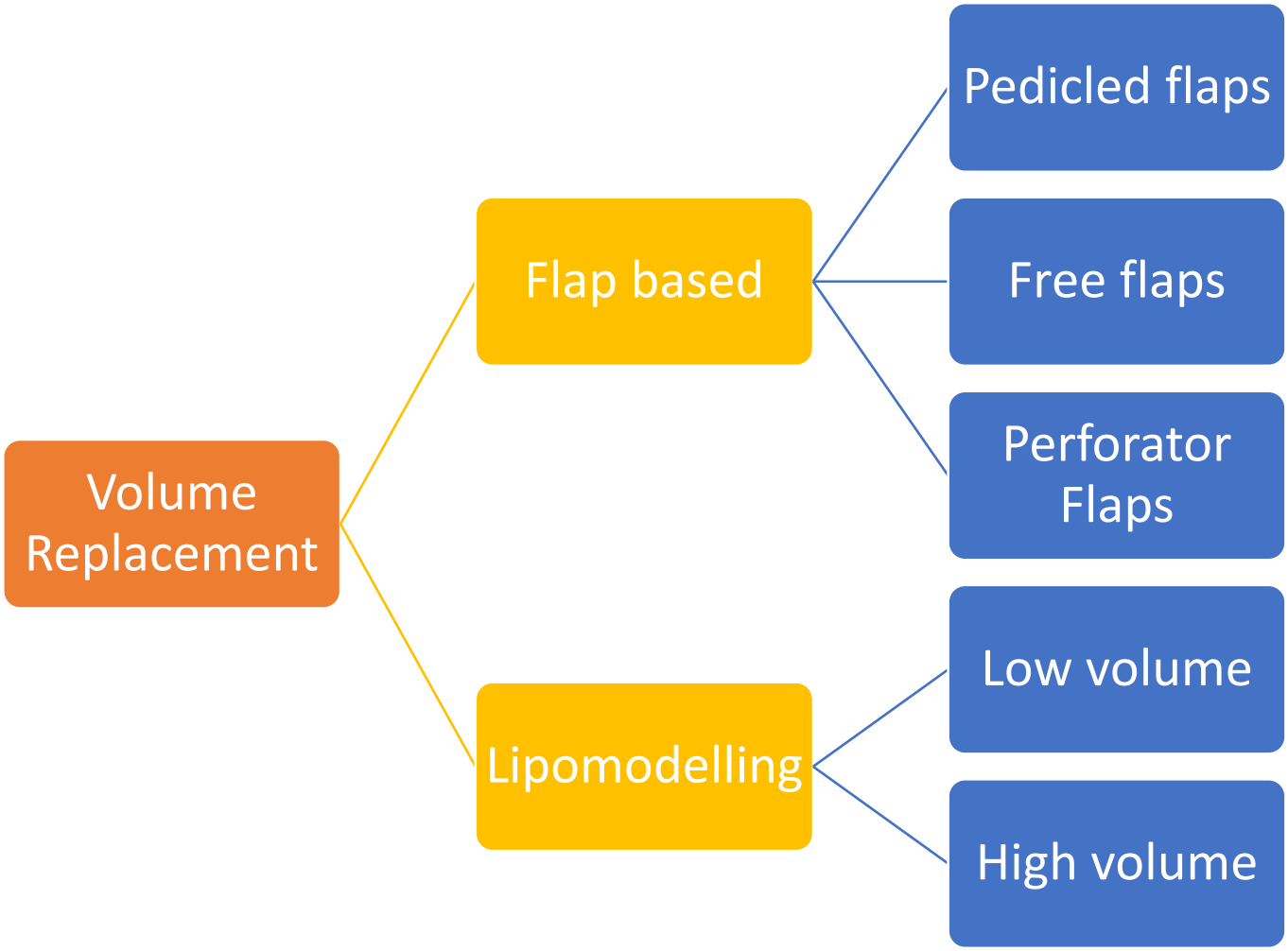
Central tumours: Batwing mammoplasty



Donut mastopexy



Volume Replacement Techniques



Pedicled Flap:
The Latissimus Dorsi Mini-Flap

Used for significant skin and or volume replacement in the upper outer, central or upper lower quadrants of up to 50% breast volume/skin loss

Robust flap.

Now largely superceded in the partial replacement setting by the less morbid TDAP/LICAP flaps.

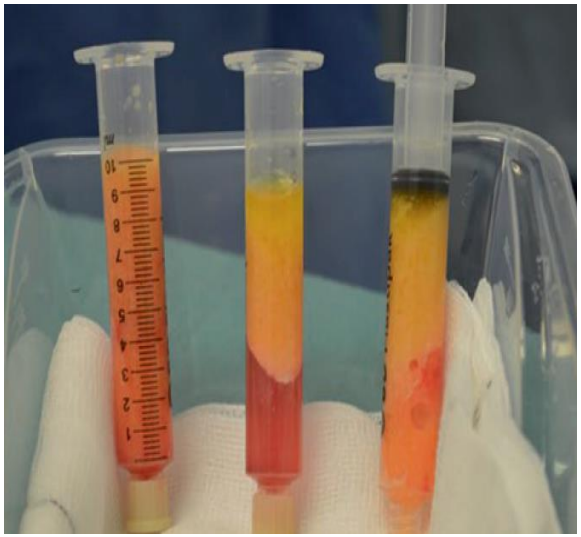
Free Flaps

- Rarely used in the partial breast volume replacement setting and usually reserved for post mastectomy reconstruction

- DIEPs, TRAM, TUG.

Lipomodelling

- Based on injection of tiny fragments of living adipose.
- Small fragments will revascularise and remain viable
- Fat harvested from fat deposits with liposuction or small bore canulae and reinjected diffusely so no large ‘puddles’ of fat
- Aspirate centrifuged in theatre to remove liquid fat layer
- Small volume (Coleman) or large volume techniques



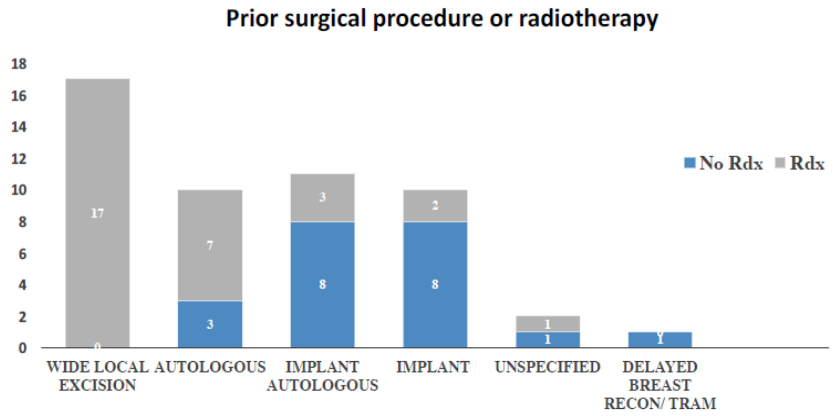
Riccardo Bonomi
2016

Lipomodelling Indications

- Correction of defects due to breast conservation scarring
- Softening and relaxing of tethered scars
- Volume adjustment to correct asymmetry
- Whole breast reconstruction

Results: Indications for surgery

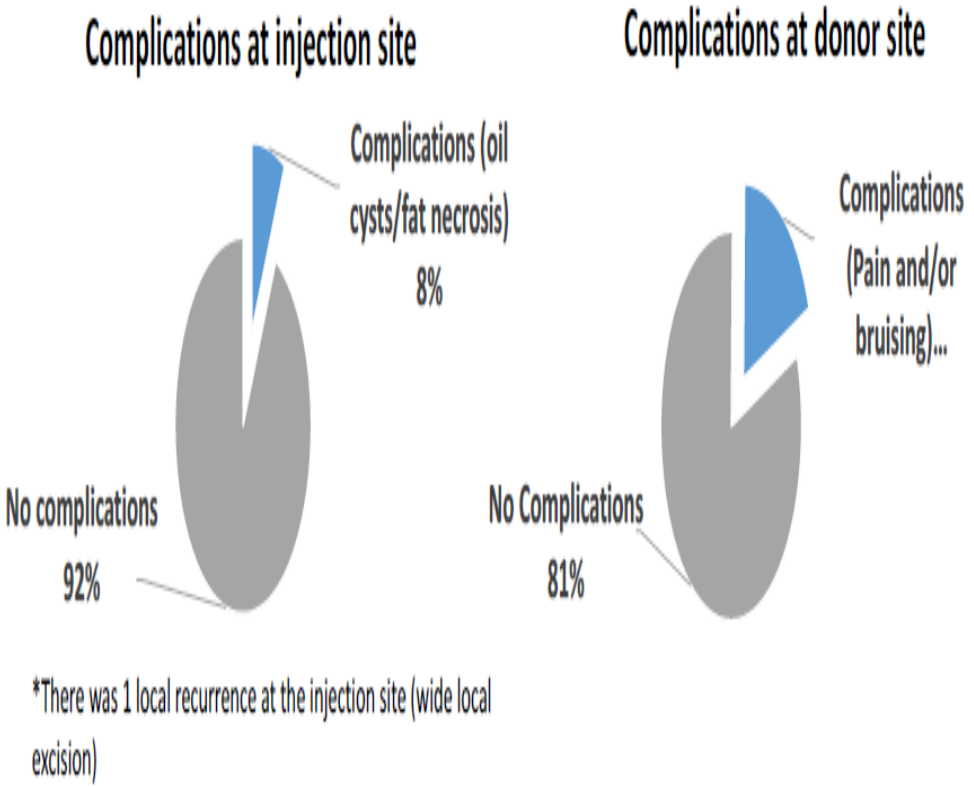
- 52 cases were performed with a median age of 53 (range 32-68).
- In 85% of cases the small volume technique (Coleman) was used and more recently, large volume lipofilling was used, in 15% of cases.
- 77% were day surgery.



Technique or indication	Percentage
Volume replacement for indentation	44%
Volume symmetrisation	23%
Shape symmetrization	27%
Prior Conservation surgery	34%
Prior mastectomy and reconstruction	64%
Coleman	85%
High volume	15%

Lipomodelling Outcomes

- 92% had no early injection site complications
- 8% had late fat necrosis or oil cysts.
- 73% had no donor site complications.
- 21% complained of donor site pain and 21% donor site bruising of bleeding.
- There was 1 local recurrence at the injection site.
- Patient satisfaction was good with only 12% expressing dissatisfaction.



Surgical and Patient Outcomes

Problems and Complications

- Fat necrosis may delay adjuvant therapy
- Breast nodularity may necessitate biopsy and cause patient concern
- Increased complications of surgery such as wound dehiscence, nipple necrosis, flap failure, lipomodelling donor site issues
- Difficulty when re excising if margins positive
- Need for symmetrisation in some cases which adds morbidity to the surgery

- Costs are higher

Quality of life

- Quality of life is not necessarily just influenced by cosmesis and patients perceptions of subjective cosmesis may vary from objective assessments.

- Results from studies are variable and quality of life does not necessarily correlate with cosmesis

Thank You

Any Questions

DCIS – CRITICAL ISSUES

Reasons to reduce Treatment Intensity

New Approaches and Ongoing Trials

Current Treatment Standard

- Surgical Excision (BCT vs Mastectomy)
- Radiotherapy
- Tamoxifen (in ER+)

Ann Surg Oncol (2015) 22:3273–3281
DOI 10.1245/s10434-015-4740-8

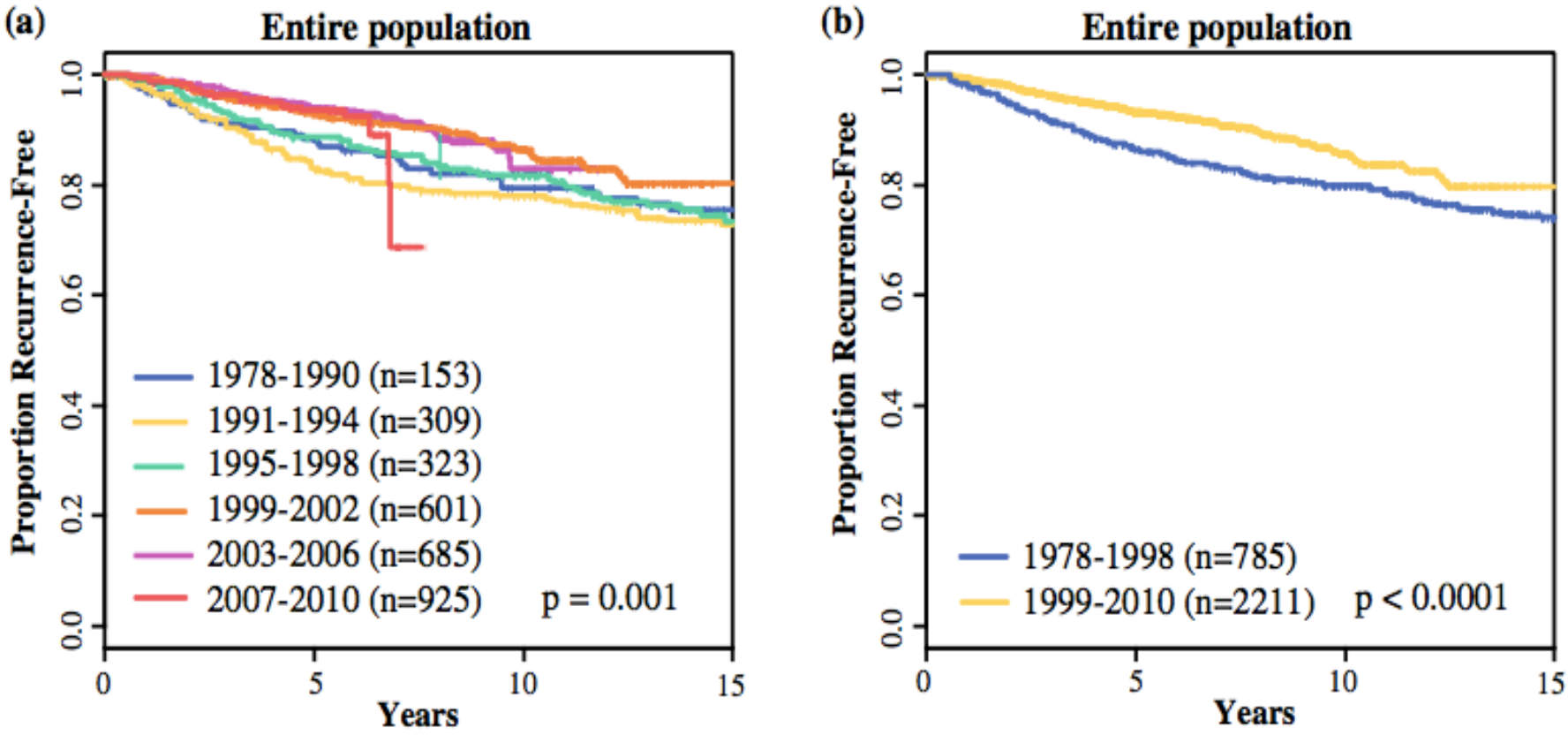
Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

CrossMark

ORIGINAL ARTICLE – BREAST ONCOLOGY

Decreasing Recurrence Rates for Ductal Carcinoma In Situ: Analysis of 2996 Women Treated with Breast-Conserving Surgery Over 30 Years

Preeti Subhedar, MD[1], Cristina Olcese, BS[1], Sujata Patil, PhD[2], Monica Morrow, MD, FACS[1], and Kimberly J. Van Zee, MS, MD, FACS[1]



Rate of irradiated patienst DCIS and BCT in Germany

Ductal carcinoma in situ

- DCIS per se does not increase breast cancer mortality
- Tumour cells are restricted to ductulo-lobular units not invading beyond the basement membrane
- Non-obligate precursor for invasive disease
- Risk for progression 14 – 53 %
- 50 % of recurrences are invasive
- Due to screening activities lesions are identified at an earlier stage
- Improved pathologic work up – improves risk assessment

VOLUME 27 · NUMBER 10 · APRIL 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

22 studies
4660 pts

Effect of Margin Status on Local Recurrence After Breast Conservation and Radiation Therapy for Ductal Carcinoma In Situ

Clive Dunne, John P. Burke, Monica Morrow, and Malcolm R. Kell

Table 2. Optimum Margin Threshold for DCIS Resection (n = 2,514)

Negative Margin Width	No. of Patients	% of Patients With IBTR	Relapse *v* > 5 mm		
			OR	95% CI	*P*
No cells on ink	914	9.4	2.56	1.1 to 7.3	< .05
1-mm margin	1,239	10.4	2.89	1.3 to 8.1	< .05
2-mm margin	207	5.8	1.51	0.51 to 5.0	> .05
≥ 5-mm margin	154	3.9	1		

Abbreviations: DCIS, ductal carcinoma in situ; IBTR, ipsilateral breast tumor recurrence; OR, odds ratio.

J Clin Oncol 2009

Network Meta-analysis of Margin Threshold for Women With Ductal Carcinoma In Situ

Shi-Yi Wang, Haitao Chu, Tatyana Shamliyan, Hawre Jalal, Karen M. Kuntz, Robert L. Kane, Beth A. Virnig

Manuscript received April 13, 2011; revised July 17, 2011; accepted January 28, 2012.

Correspondence to: Shi-Yi Wang, MD, MS, Division of Health Policy and Management, University of Minnesota School of Public Health, 420 Delaware St S.E., MMC 729, Minneapolis, MN 55455 (e-mail: wang1018@umn.edu).

21 studies 7654 patients

Table 2. Multiple treatment comparisons among groups with different margin threshold in breast-conserving surgery (BCS) with or without radiotherapy*

	With RT adjustment only			With covariate adjustment†		
	Frequentist	Bayesian		Frequentist	Bayesian	
Margin threshold and treatment	Mean OR (95% CI)	Mean OR (95% CrI)	Probability of best option	Mean OR (95% CI)	Mean OR (95% CrI)	Probability of best option
T = 0 mm‡	0.45(0.38 to 0.53)§	0.46(0.38 to 0.54)	0	0.46(0.38 to 0.53)§	0.45(0.38 to 0.53)	0
T = 2 mm‡	0.37(0.26 to 0.49)§	0.38(0.27 to 0.51)	8.7×10^{-5}	0.38(0.27 to 0.49)§	0.38(0.28 to 0.51)	4.0×10^{-5}
T = 5 mm‡	0.46(0 to 0.94)‖	0.49(0.13 to 1.17)	.064	0.55(0 to 1.11)‖	0.55(0.15 to 1.30)	.043
T = 10 mm‡	0.17(0.11 to 0.24)§	0.18(0.12 to 0.25)	.936	0.18(0.11 to 0.24)§	0.17(0.12 to 0.24)	.957
T = 10 vs 2 mm	0.47(0.27 to 0.67)§	0.47(0.30 to 0.71)		0.46(0.27 to 0.66)§	0.46(0.29 to 0.69)	
BCS plus radiotherapy vs BCS alone	0.48(0.33 to 0.63)§	0.49(0.34 to 0.69)		0.43(0.32 to 0.54)§	0.45(0.32 to 0.62)	

J Natl Cancer Inst 2012

Breast Conserving Surgery of the Primary (DCIS)

1. In women undergoing breast conserving surgery for DCIS and planned whole breast radiation treatment which minimum margin width is sufficient to avoid re-excision?

St. Gallen Result of Voting

No ink on DCIS?	**34,6%**
2 mm clearance?	**61,5%**
5 mm clearance?	**0%**
Margin is irrelevant?	**0%**
Abstain	**3,8%**

Stellungnahme der dt. Expertengruppe**:**
Zustimmung; AGO empfiehlt bei Rändern <2mm über Nachresektion nachzudenken

Long-term outcomes of ductal carcinoma in situ of the breast: a systematic review, meta-analysis and meta-regression analysis

Kirsty E. Stuart[1,2,3*], Nehmat Houssami[4], Richard Taylor[1,5], Andrew Hayen[5] and John Boyages[1,6]

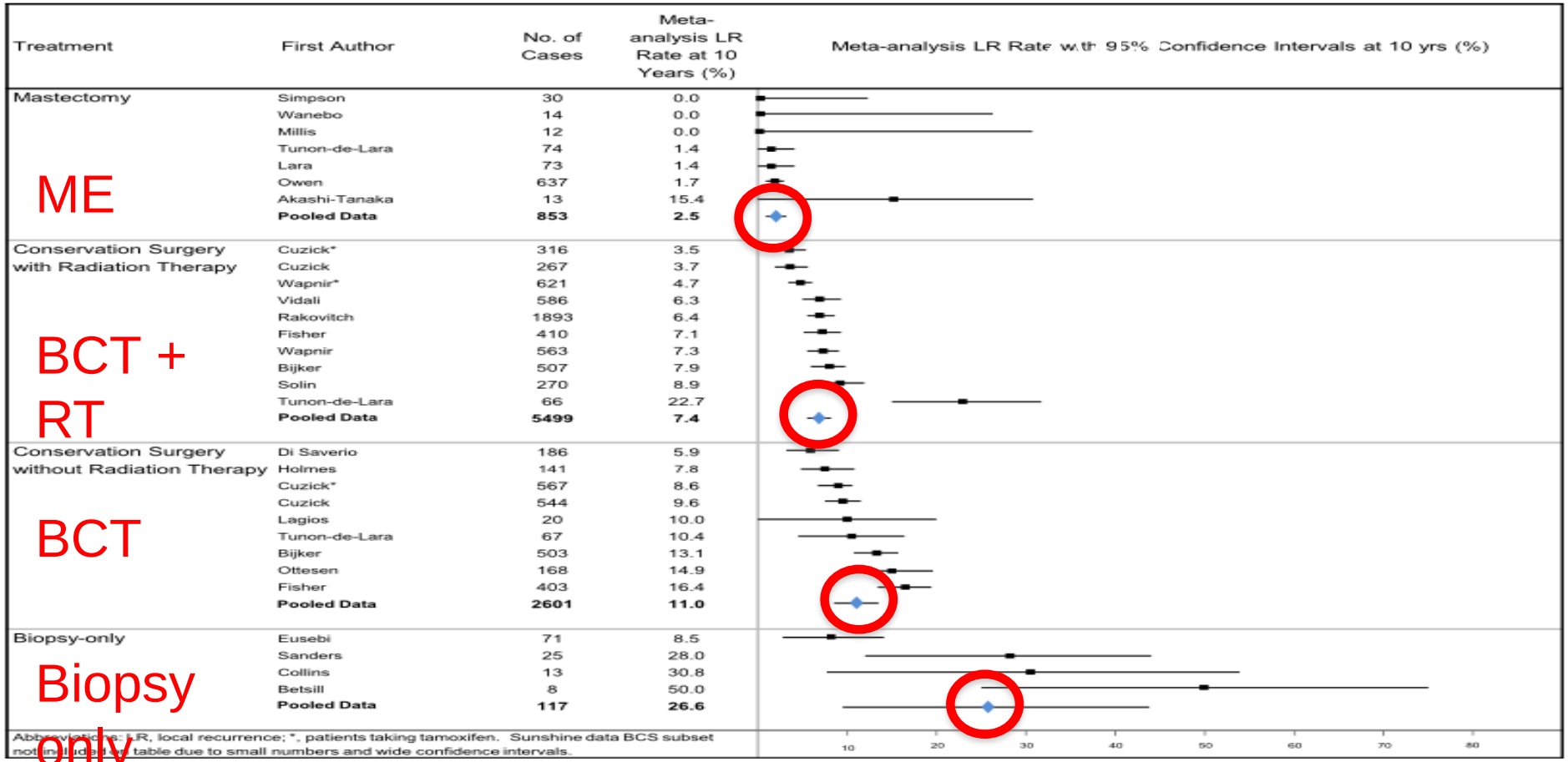


Fig. 2 Meta-analysis results: invasive ipsilateral local recurrence rates at 10 years in cases of ductal carcinoma in situ

Treatment Objective

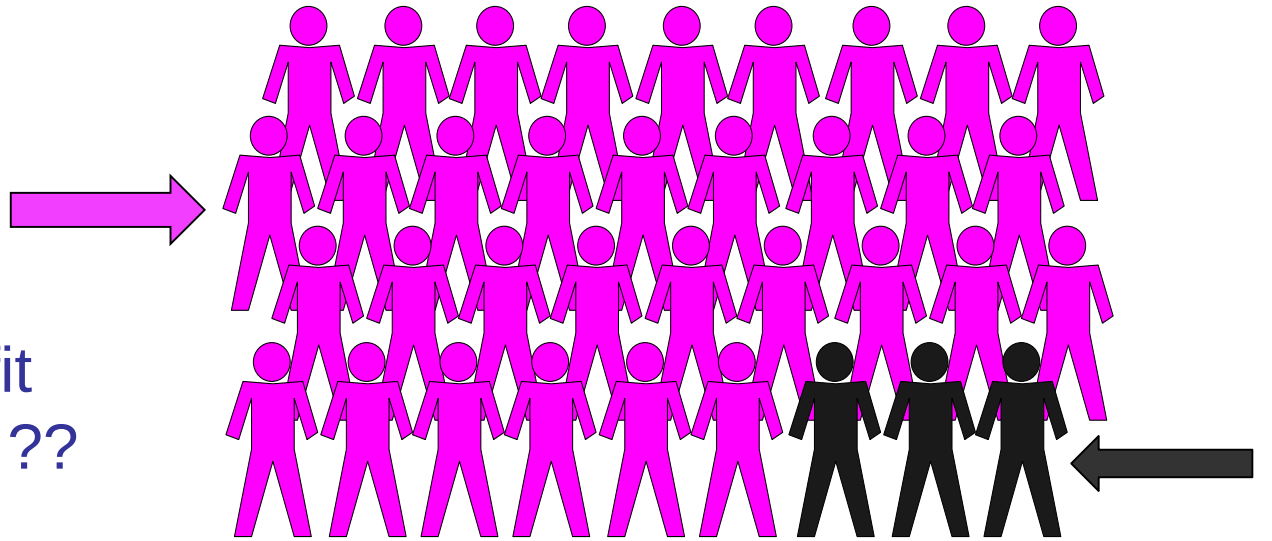
Overall Survival ?

Invasive Recurrence ?

Any Recurrence ?

Time Interval to Recurrence ?

How can I select Patients ?



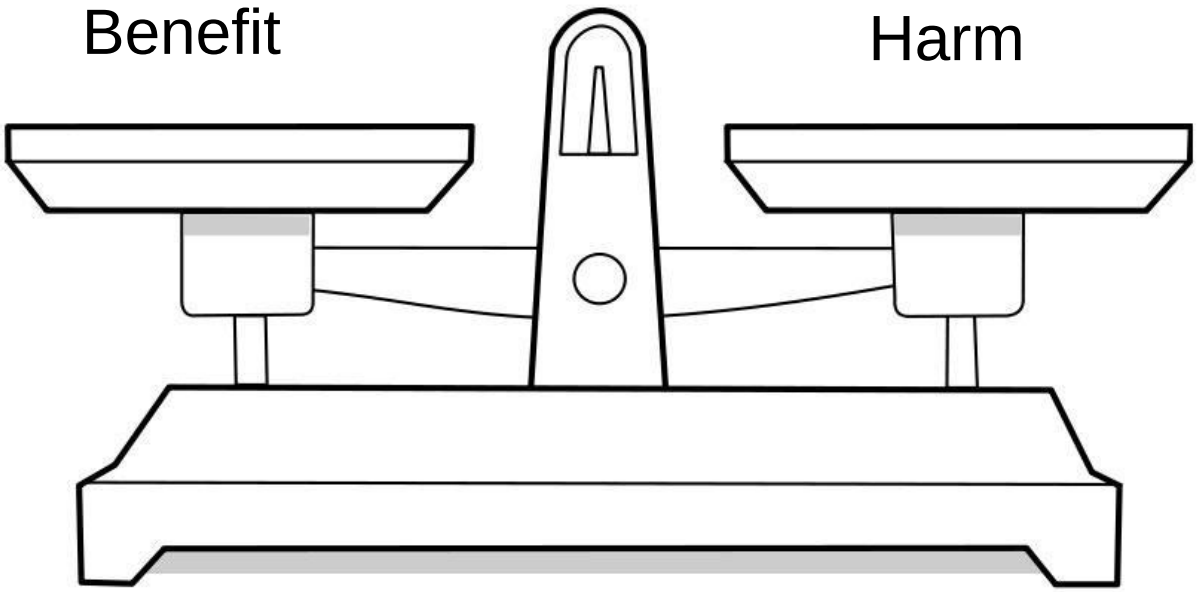
No
Benefit
Harm ??

Benefit

Can we identify these patients ?

Individual Decision Making in DCIS – Patient Counseling

Age
Individual Risk
Patients preference



Risk Factors for Recurrence in DCIS

	Oxford / AGO		
	LoE / GR		
Resection margins	1a	A	++
Age	1a	A	++
Size	1a	A	++
Grading	1a	A	++
Comedo necrosis	1a	A	++
Method of diagnosis	1a	A	++
Focality	1a	A	++

Relative and Absolute Risk Reduction

Relative Risk Reduction by Therapy: 50 %

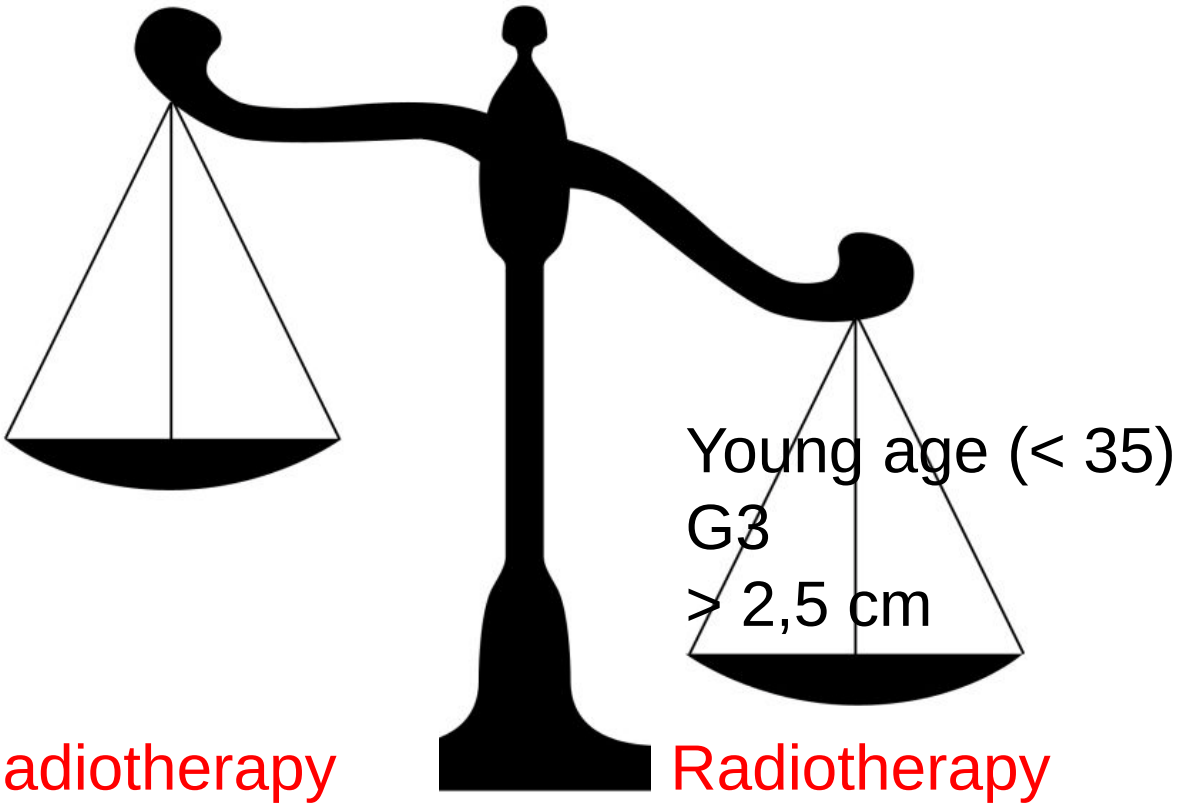
Absolute Risk	50 %	Individual Benefit	25 %
Absolute Risk	10 %	Individual Benefit	5 %

Absolute Benefit:
Number Needed To Treat

Results Low risk RCT

	Remarks	F-up (yr)	BCS	BCS + RT	
EORTC 10853		15	31%	18%	NNT:7.7%
NSABP 17		17	35%	20%	NNT:6.6%
SweDCIS		20	32%	20%	NNT:8.3%
UK/NAZ	+/ - Tamoxifen	12	17%	2.6%	NNT:6.9%
RTOG9804	Low risk: Grade 1-2, tumorsize < 2.5 cm, margin > 3 mm	7	6.7%	0.9% NNT: 17.2 %	

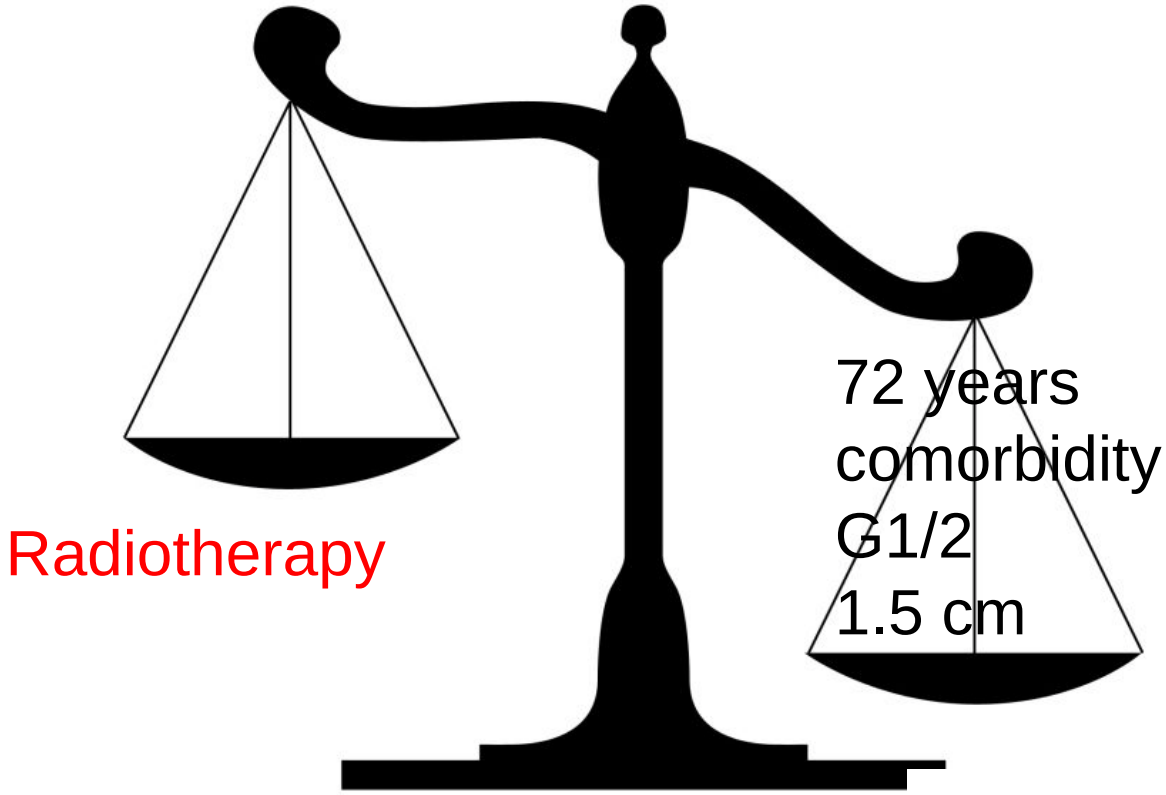
Individual Decision Making in DCIS – Patient Counseling



No Radiotherapy

Radiotherapy

Individual Decision Making in DCIS – Patient Counseling



Prognostic score used by Sagara et al JCO 2016

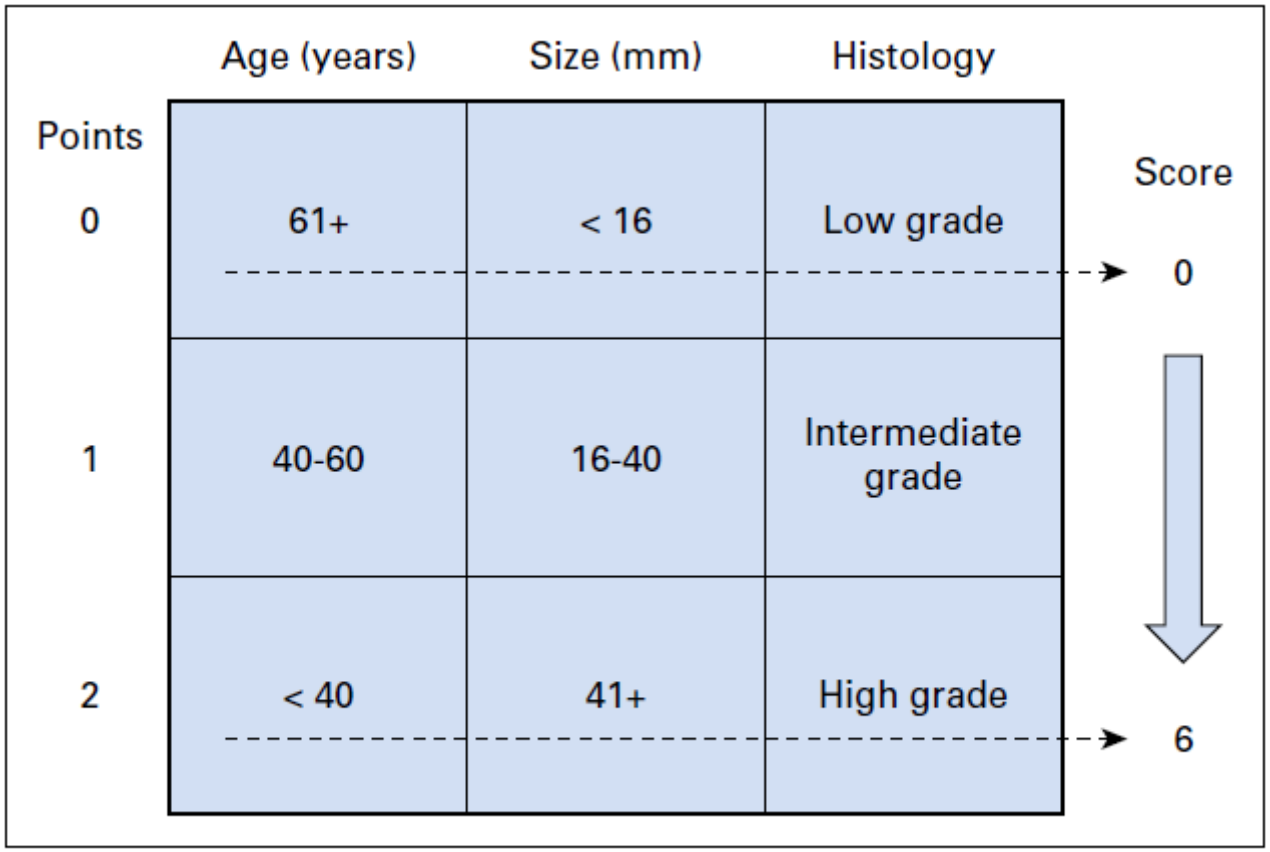
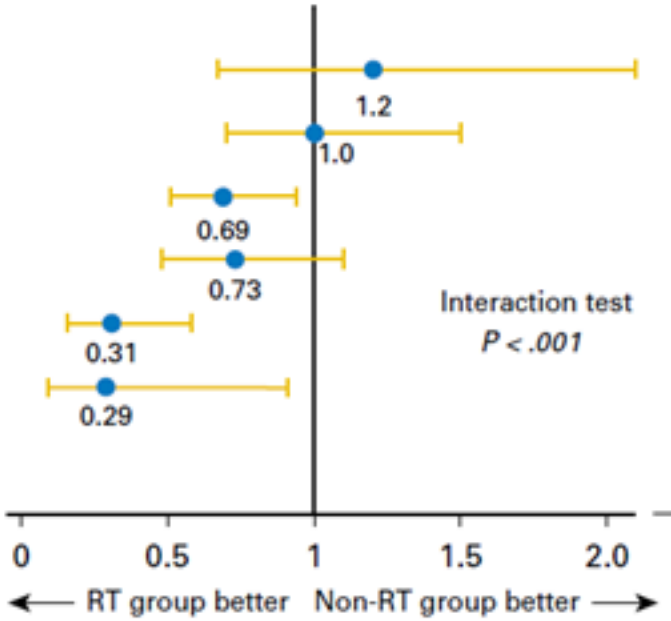


Fig 1. Patient prognostic score: risk stratification. Modified from Smith et al.[20]

Smith et al (2006): Likelihood of IBTR increases by 22% with every 1-point increase in the prognostic score.

Sagara et al JCO 2016

Prognostic Score	No. of Patients Non-RT Group	No. of Patients RT Group	10-Year BCM* (%) Non-RT Group	10-Year BCM* (%) RT Group	Hazard Ratio*† of BCM	P†
0	782	1,388	3.0	3.4	1.2	.58
1	2,677	4,480	2.0	2.5	1.0	.95
2	4,105	7,080	2.0	1.5	0.69	.02
3	3,048	5,417	1.5	1.3	0.73	.13
4	965	1,701	3.2	1.3	0.31	< .001
5	223	248	6.3	2.3	0.29	.03
6	15	15		NA		NA



Still: some caution warranted, i.e. retrospective validation…..

VOLUME 28 · NUMBER 23 · AUGUST 10 2010
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Nomogram for Predicting the Risk of Local Recurrence After Breast-Conserving Surgery for Ductal Carcinoma In Situ

Udo Rudloff, Lindsay M. Jacks, Jessica I. Goldberg, Christine A. Wynveen, Edi Brogi, Sujata Patil, and Kimberly J. Van Zee

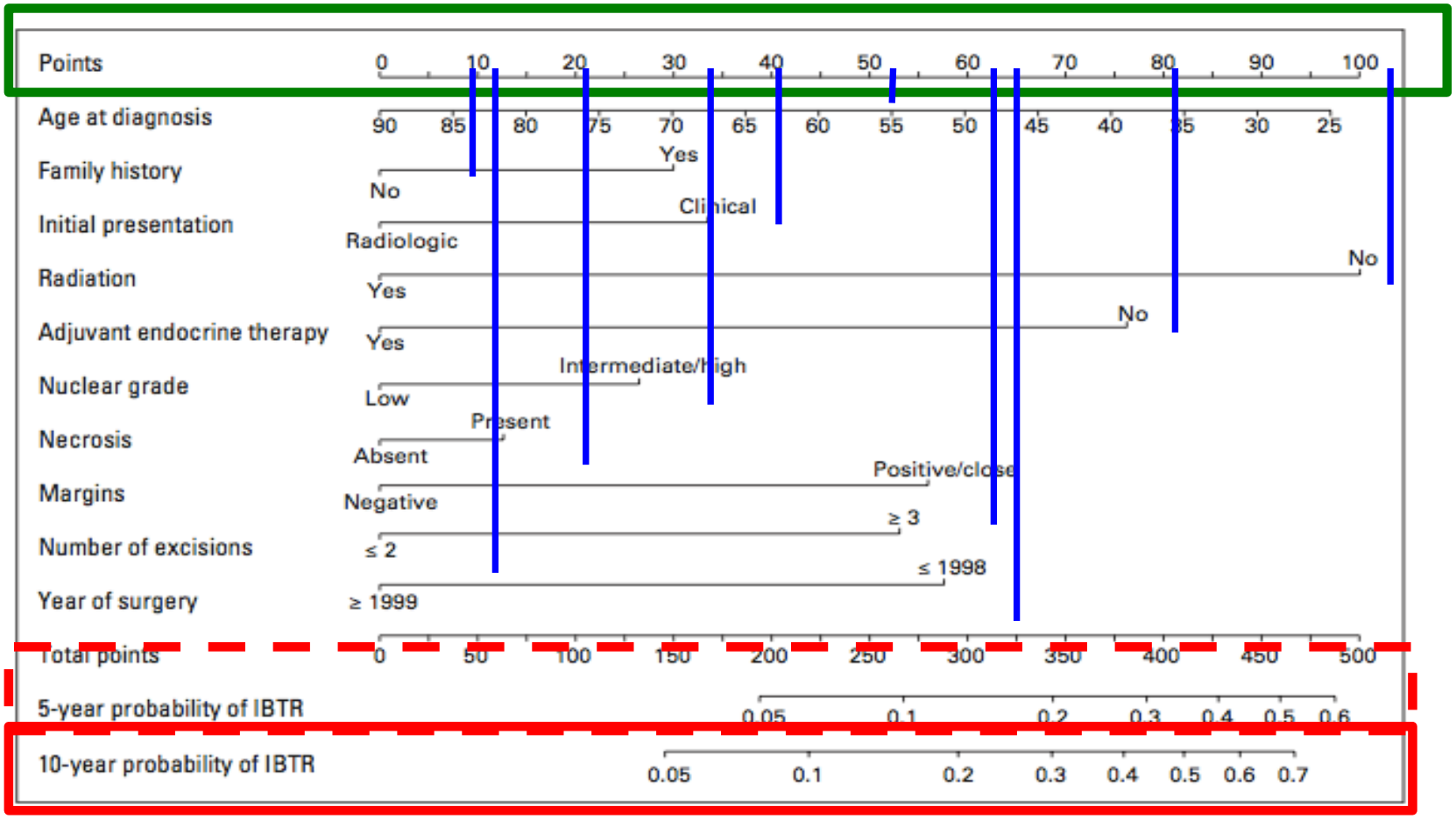
Nomogram: A statistically based tool, that provides overall specific outcome for an individual patient. Instead of considering 1 single risk factor, or several factors seperately the nomogramm intergrates a number risk factors according to their weight

1868 patients from 1991 to 2006

10 clinical, pathologic and treatment variables identified

Cox proportional hazard model was constructed

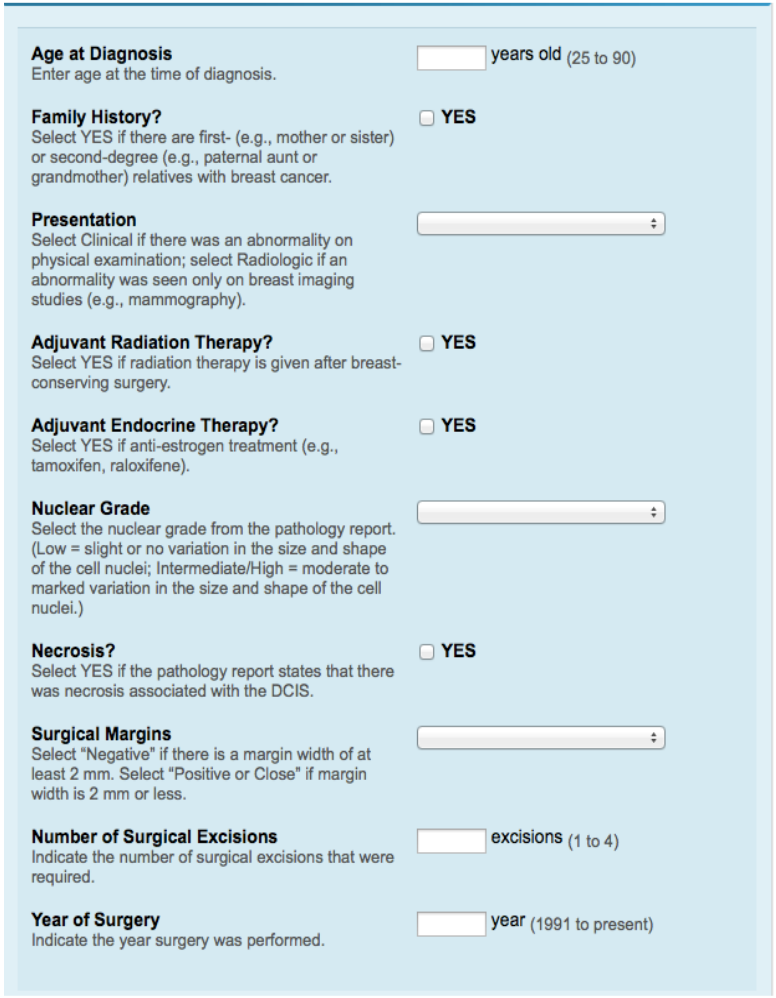
Nomogram to predict DCIS recurrence



MAASTRO CLINIC

ESTRO School

Nomogram for DCIS recurrence



Age at Diagnosis
Enter age at the time of diagnosis.
_____ years old (25 to 90)

Family History?
Select YES if there are first- (e.g., mother or sister) or second-degree (e.g., paternal aunt or grandmother) relatives with breast cancer.
☐ YES

Presentation
Select Clinical if there was an abnormality on physical examination; select Radiologic if an abnormality was seen only on breast imaging studies (e.g., mammography).
[ ]

Adjuvant Radiation Therapy?
Select YES if radiation therapy is given after breast-conserving surgery.
☐ YES

Adjuvant Endocrine Therapy?
Select YES if anti-estrogen treatment (e.g., tamoxifen, raloxifene).
☐ YES

Nuclear Grade
Select the nuclear grade from the pathology report. (Low = slight or no variation in the size and shape of the cell nuclei; Intermediate/High = moderate to marked variation in the size and shape of the cell nuclei.)
[ ]

Necrosis?
Select YES if the pathology report states that there was necrosis associated with the DCIS.
☐ YES

Surgical Margins
Select "Negative" if there is a margin width of at least 2 mm. Select "Positive or Close" if margin width is 2 mm or less.
[ ]

Number of Surgical Excisions
Indicate the number of surgical excisions that were required.
_____ excisions (1 to 4)

Year of Surgery
Indicate the year surgery was performed.
_____ year (1991 to present)

http://nomograms.mskcc.org/Breast/DuctalCarcinomaInSituRecurrencePage.aspx

MAASTRO CLINIC

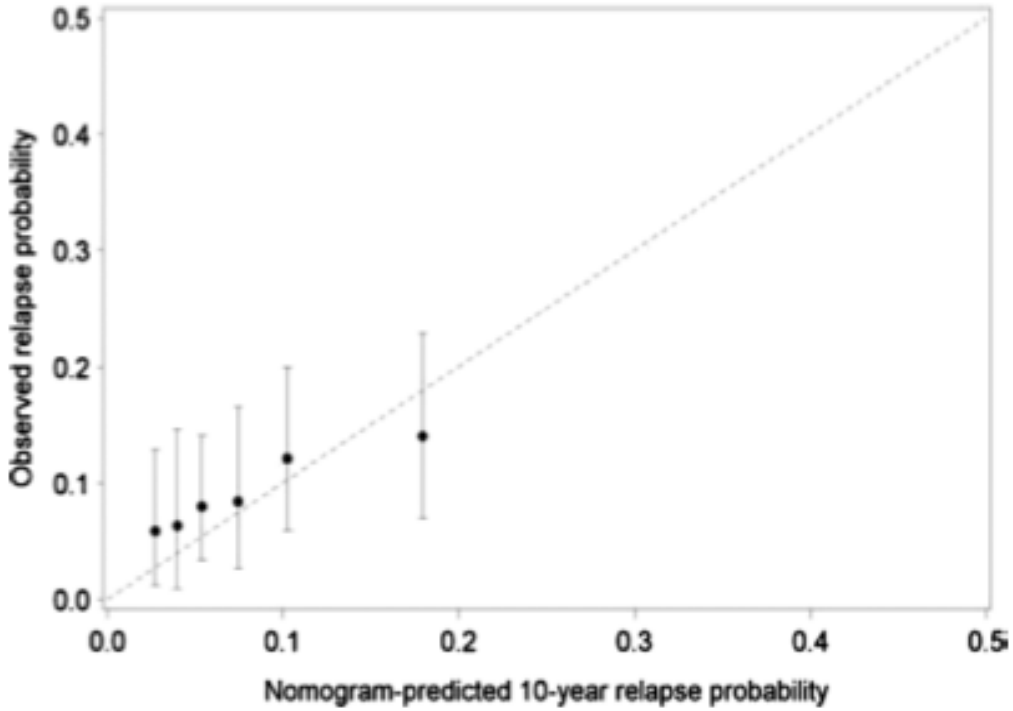
ESTRO School

Local Relapse After Breast-Conserving Therapy for Ductal Carcinoma In Situ

A European Single-Center Experience and External Validation of the Memorial Sloan-Kettering Cancer Center DCIS Nomogram

Caroline Sweldens, MD, Stephanie Peeters, MD, PhD,† Erik van Limbergen, MD, PhD,†*
Hilde Janssen, MD, PhD,† Annouschka Laenen, PhD,‡ Sujata Patil, PhD,§
Kimberly J. Van Zee, MD,|| and Caroline Weltens, MD, PhD†

467 pts



The Cancer Journal 2014

New approaches

Biological approach

Can we identify patients with DCIS that will not become clinically apparent (and need no treatment at all ?)

Prognostic / Predictive approach

Can we identify patients with a very low recurrence risk ?

Can we identify factors, that indicate a benefit from RT ?

A Multigene Expression Assay to Predict Local Recurrence Risk for Ductal Carcinoma In Situ of the Breast

Lawrence J. Solin, Robert Gray, Frederick L. Baehner, Steven M. Butler, Lorie L. Hughes, Carl Yoshizawa, Diana B. Cherbavaz, Steven Shak, David L. Page, George W. Sledge Jr, Nancy E. Davidson, James N. Ingle, Edith A. Perez, William C. Wood, Joseph A. Sparano, Sunil Badve

Manuscript received August 22, 2012; revised February 7, 2013; accepted February 20, 2013.

Correspondence to: Lawrence J. Solin, MD, FACR, FASTRO, Department of Radiation Oncology, Albert Einstein Medical Center, 5501 Old York Rd, Philadelphia, PA 19141 (e-mail: solin@einstein.edu).

JNCI 2013

DCIS Score® Wert: Genpanell

Proliferation	Hormone receptor group	Reference genes
Ki-67 STK15 Survivin Cyclin B1 MYBL2	PR GSTM1	Beta-actin GAPDH RPLPO GUS TFRC

DCIS Score™ value:

- Continuous variable
- Values from 0 – 100

DCIS Score™ value risk groups

- low < 39
- intermediate 39 – 54
- high ≥ 55

MAASTRO CLINIC

ESTRO School

ECOG E5194 (PARENT STUDY)

Prospective multicenter study 1997-2000 (n = 670)

- **cohort 1: low/intermediate grading, extent ≤ 2.5 cm**
- **cohort 2: high grading, extent ≤ 1 cm**

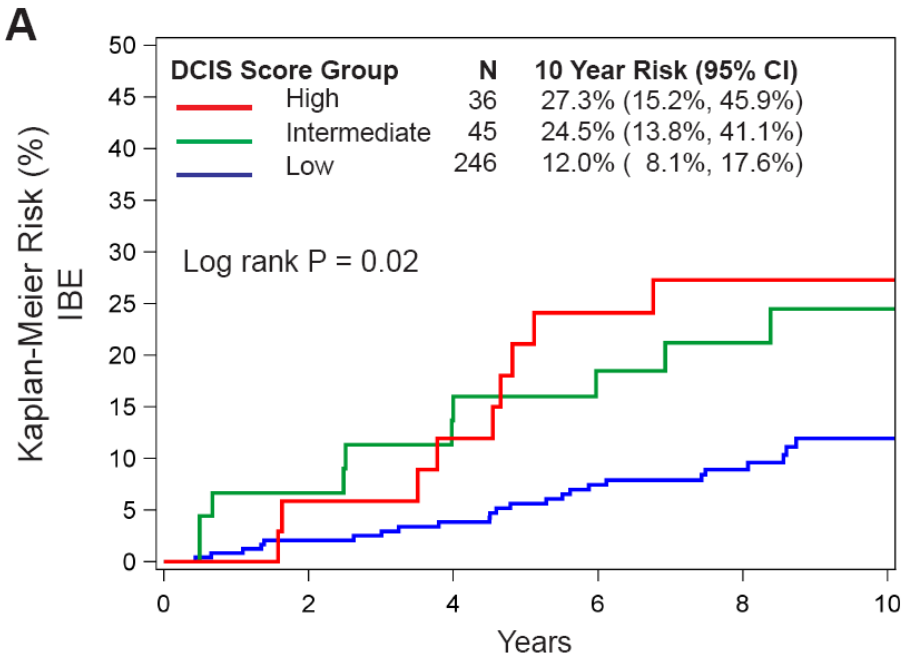
Treatment

- **Surgical excision**
- **free margins at least 3 mm**
- **no RT**
- **Tamoxifen optional**

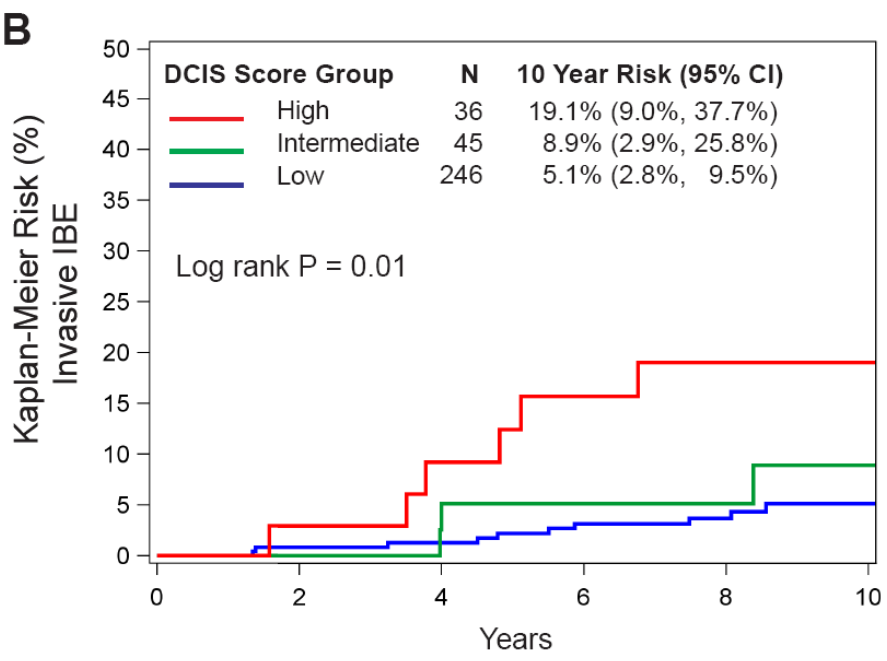
Solin et al. JNCI 2013

Annual risk of recurrence according to risk score

ALL IBE



Invasive IBE



Solin et al. JNCI 2013

Ongoing Trials for ductal carcinoma in situ

Study name	Study design	Main patient inclusion criteria	Aimed number of patients	Recruit-ment
LORIS (UK)	Randomizes between active surveillance versus surgery ± RT ± Tamoxifen Yearly mammography	Female, > 46 years; screen detected or incidental microcalcification (unilateral or bilateral); Nonhigh-grade DCIS confirmed by local pathologist on either small volume core biopsy or VACB	932	Since June 2014
LORD (EORTC)	Randomizes between active surveillance versus surgery ± RT ± Tamoxifen Yearly mammography	Woman of age ≥45 years, Calcifications only lesions, detected by population-based or opportunistic screening mammography; Representative vacuum-assisted core biopsy with pure low-grade DCIS	1240	Since December 2015
CALGB 40903	Neoadjuvant treatment with letrozol for 6 month with MRT controls at 3 and 6 month Resection in case of progression	DCIS without invasive cancer or with microinvasion on diagnostic core biopsy; Estrogen and/or progesterone receptor positive; postmenopausal patient	115	Since February 2012

Ongoing Trials – Critical Issues

- Reliability of Imaging (Extent of the lesion)
- Reproducibility of Grading
- Sampling Error
- Definition of an acceptable endpoint
- Proportion of patients that can be included

To treat or not to treat DCIS ?
Take Home Messages

- Standard treatment for DCIS is still local excision followed by whole breast RT, however:

- Subgroups may be identified in whom RT can safely be omitted, based Nomogram and DCIS Score – but these need to be validated !!

- Currently 2 studies aimed at investigating whether *any treatment* can be omitted in screen-detected/ asymptomatic – extremely low risk DCIS

  LORIS study: recruiting

  LORD study: starts this Autumn

DCIS: New Insights

Liesbeth Boersma, radiation oncologist
MAASTRO Clinic/ University Hospital Maastricht, The Netherlands
Thorsten Kuehn, surgical oncologist
Klinikum Esslingen, Germany

ESTRO Teaching Course on Breast Cancer, Dublin, September 2017

DCIS: New Insights

- State of the art treatment of DCIS – current evidence
  L. Boersma

- Critical issues – Reasons to reduce treatment intensity
  T. Kuehn

- New approaches and ongoing trials
  T. Kuehn

Current evidence

- Effect of radiotherapy after lumpectomy on **local recurrence**
- Systematic review on effect of use of endocrine treatment
- Effect of RT on **BCSS/OS**
- RT – specific aspects
  - Boost required?
  - Hypofractionation?
  - Partial breast RT

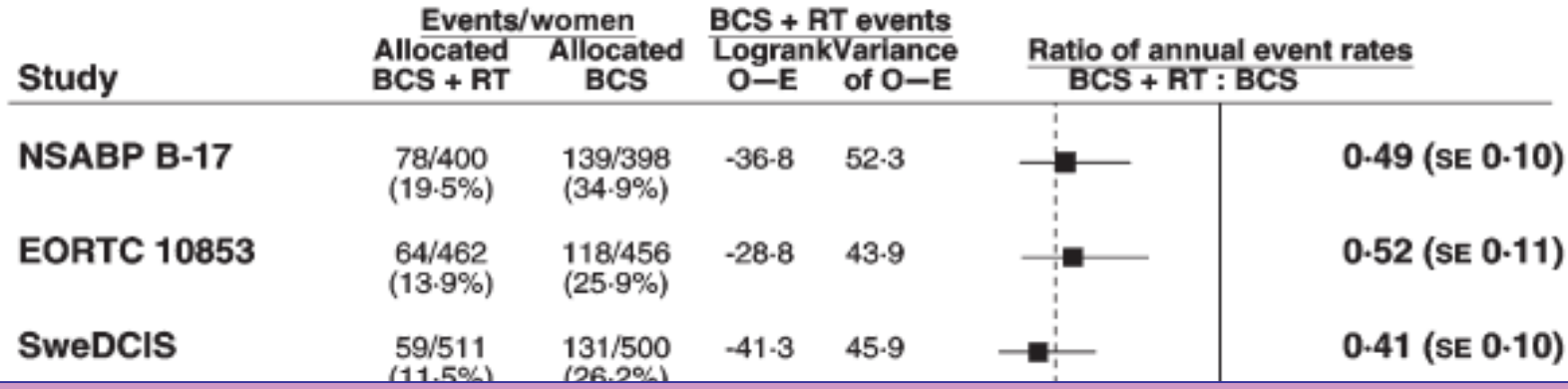
- Who to treat ? → Risk factors → Thorsten Kuehn

Overview of studies on effect of RT on breast recurrences in DCIS

- 3 large meta-analyses

  - Meta-analysis EBCTCG (2010), N = 3729: Lumpectomy +/- RT:
    - *Individual patient data of 4 RCTs*
  - Meta-analysis Stuart et al (2015), N = 9404: Lumpectomy +/- RT:
    - *Analysis of published data: 3 RCTs, 2 prospective and 21 retrospective series*
  - Meta-analysis Garg et al (2017), N = 3680, Lumpectomy +/- RT:
    - *Meta-analysis of 4 published RCTs with longterm follow-up*

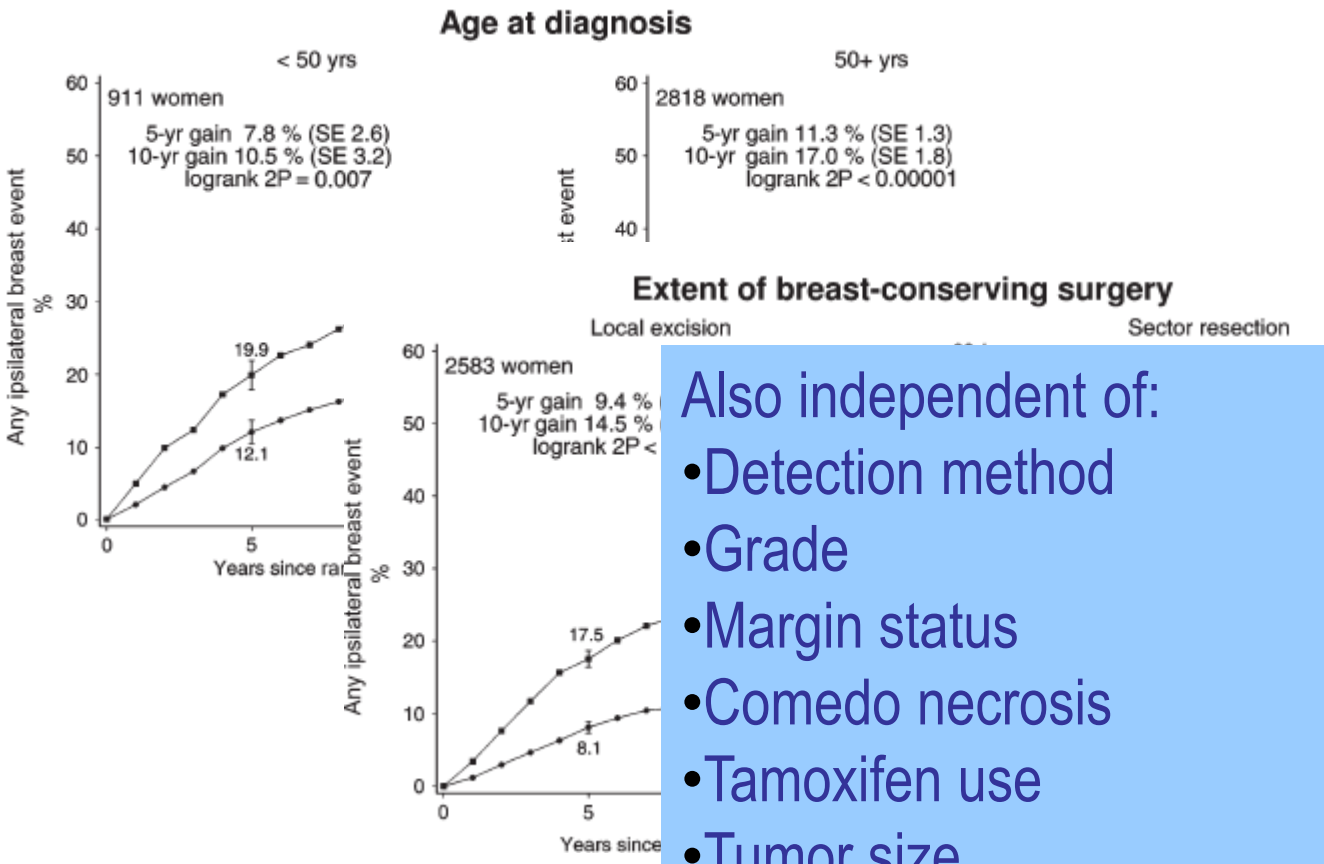
Results of the EBCTCG meta-analysis: lumpectomy +/- RT: Ipsilateral breast events*



Conclusion of all analyses:

- *RT reduces LR with factor 2;*
- *about 50% of recurrences concerns an invasive recurrence (~ 40% probability to become invasive if untreated at all)*

Relative effect of RT independent of other factors



Also independent of:

- Detection method
- Grade
- Margin status
- Comedo necrosis
- Tamoxifen use
- Tumor size
- Etc…

Absolute incidence of ipsilat breast recurrences*

	Remarks	F-up (yr)	BCS	BCS + RT
EORTC 10853[1]		15	31%	18%
NSABP-17[2]		17	35%	20%
SweDCIS[3]		20	32%	20%
UK/ANZ[4]	+/ - Tamoxifen	12	17%	2.6%

[1]Donker et al JCO 2013
[2]Wapnir et al JNCI 2011
[3]Warnberg et al JCO 2014
[4]Cuzick et al Lancet Oncol 2012

*: in all trials, about 50% of recurrences concerns an invasive recurrence

Meta-analysis Stuart et al: 10 yr Ipsilateral Breast Recurrence

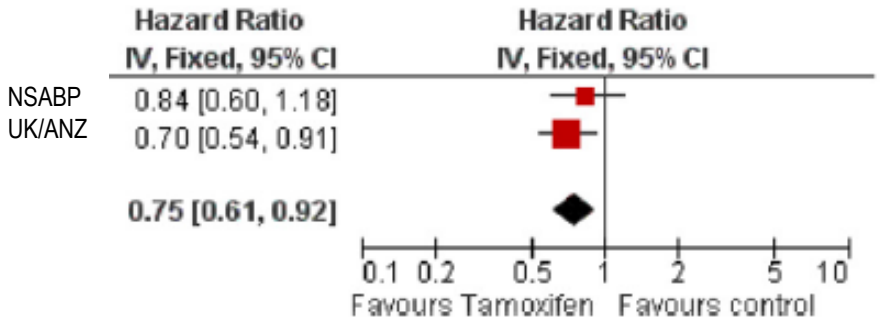
	All	Subset NOT receiving Tam	Subset also receiving Tamoxifen
Mastectomy	2.6%		
Lumpectomy + RT	13.6%	14.1% (7.2% invasive)	9.7%
Lumpectomy - RT	25.5%	25.1% (11.3% invasive)	24%
Biopsy only	27.8%		

2 adjuvant Rx significantly less invasive LR than one or none adjuvant Rx

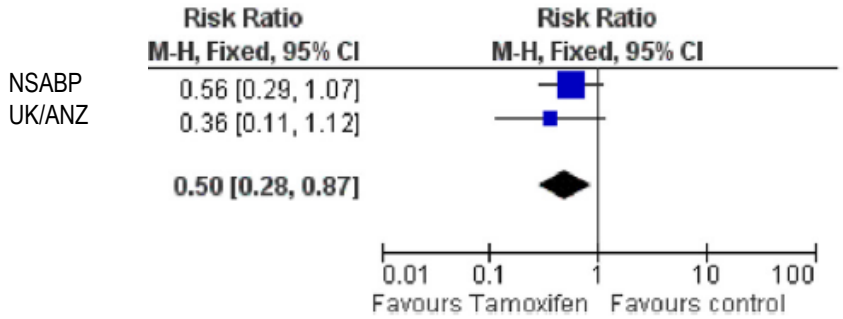
Effect of Tamoxifen in DCIS ?

NSABP-24 trial, 2011: N =1799 Tam vs placebo (all RT)

UK/ANZ trial, 2011: N = 1576 Tam vs placebo (half +/- RT)



Preventive effect on Ipsilateral DCIS



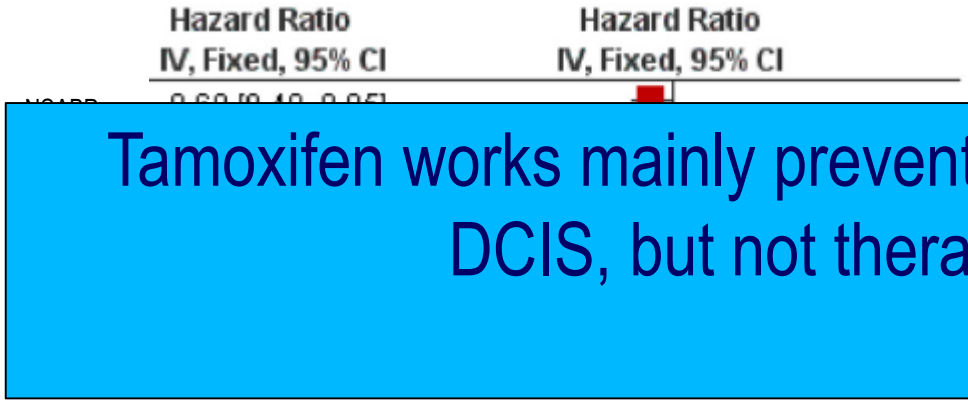
Preventive effect on contralateral DCIS

Staley et al, The Breast 2014

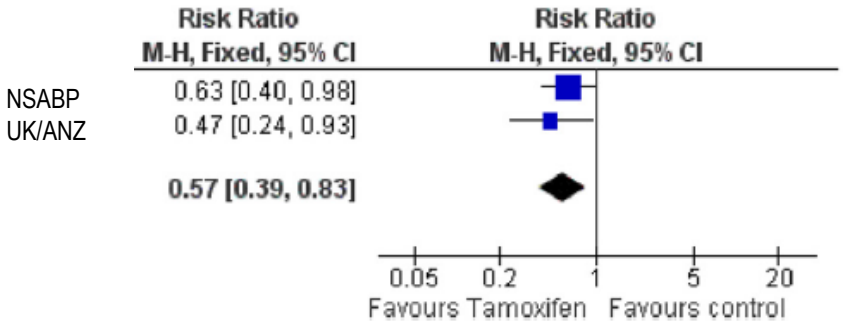
Effect of Tamoxifen in DCIS?

NSABP-24 trial, 2011: N =1799 Tam vs placebo (all RT)

UK/ANZ trial, 2011: N = 1576 Tam vs placebo (half +/- RT)



Tamoxifen works mainly preventive in patients with DCIS, but not therapeutic



Preventive effect on Contralateral invasive ca

Staley et al, The Breast 2014

Does RT influence BCSS/ OS ?

- All meta-analyses (EBCTCG, Stuart et al, Garg et al):

No influence of RT on Breast Cancer Specific Survival (i.e. 97-98%) , nor on overall survival

- However, several studies show:

IF invasive recurrence occurs: BCSS is worse !

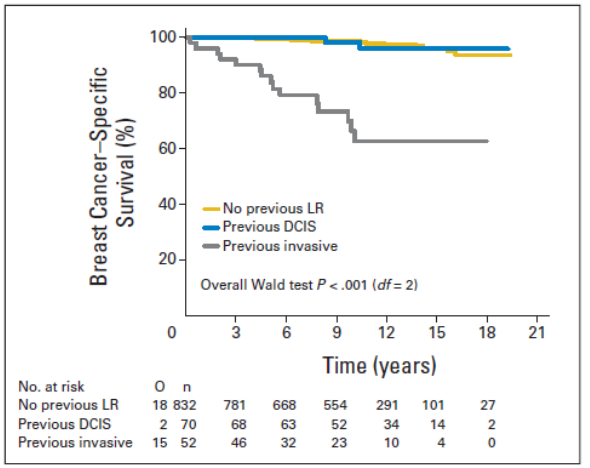


Fig 4. Breast cancer–specific survival after a local recurrence (LR) 5 years after random assignment. DCIS, ductal carcinoma in situ; n, number of patients; O, observed.

15 yr BCSS for invasive LR after biopsy only: 44.8% ! *Donker et al, JCO 2013*

SEER- analyses – main focus at survival

	Period	Number of patients	Main focus
Narod et al, JAMA 2015	1988-2011	108.196	10-20 yr BCSS
Qian et al, OncoTargets &Therapy 2015	1998-2007	56.968	7 yr BCSS & OS (No mastectomies)
Sagara et al, JCO 2016	1988-2007	32.144	Prognostic score for survival (No mastectomies)

Effect of RT on 20 yr Breast Cancer Mortality

Table 3. Breast Cancer–Specific Mortality and Hazard Ratios (HRs) for Breast Cancer Mortality After Ductal Carcinoma In Situ, by Type of Treatment, 1998 to 2011

Treatment	Cases, No.	10-Year Mortality (95% CI), %	Univariate HR (95% CI)	*P* Value	Multivariate[a] HR (95% CI)	*P* Value
Lumpectomy						
Without radiotherapy	19 762	0.9 (0.7-1.1)	1 [Reference]		1 [Reference]	
With radiotherapy	42 250	0.8 (0.7-1.0)	0.86 (0.67-1.10)	.22	0.81 (0.63-1.04)	.10
All	63 319	0.8 (0.7-1.0)	1 [Reference]		1 [Reference]	
Unilateral mastectomy	19 515	1.3 (1.1-1.5)	1.45 (1.18-1.79)	<.001	1.20 (0.96-1.50)	.11

[a] Adjusted for year of diagnosis, age at diagnosis, ethnicity, income, estrogen receptor status, tumor size, and grade.

Significant risk factors: Age; Race; ER status; Grade; Size

The risk of dying of breast cancer increased *after experience of an ipsilateral invasive breast cancer* (HR, 18.1 [95%CI, 14.0-23.6]; $p < .001$), but RT does not improve BCSS

Narod et al, 2015

Effect of RT on 7 yr OS and Breast Cancer Mortality

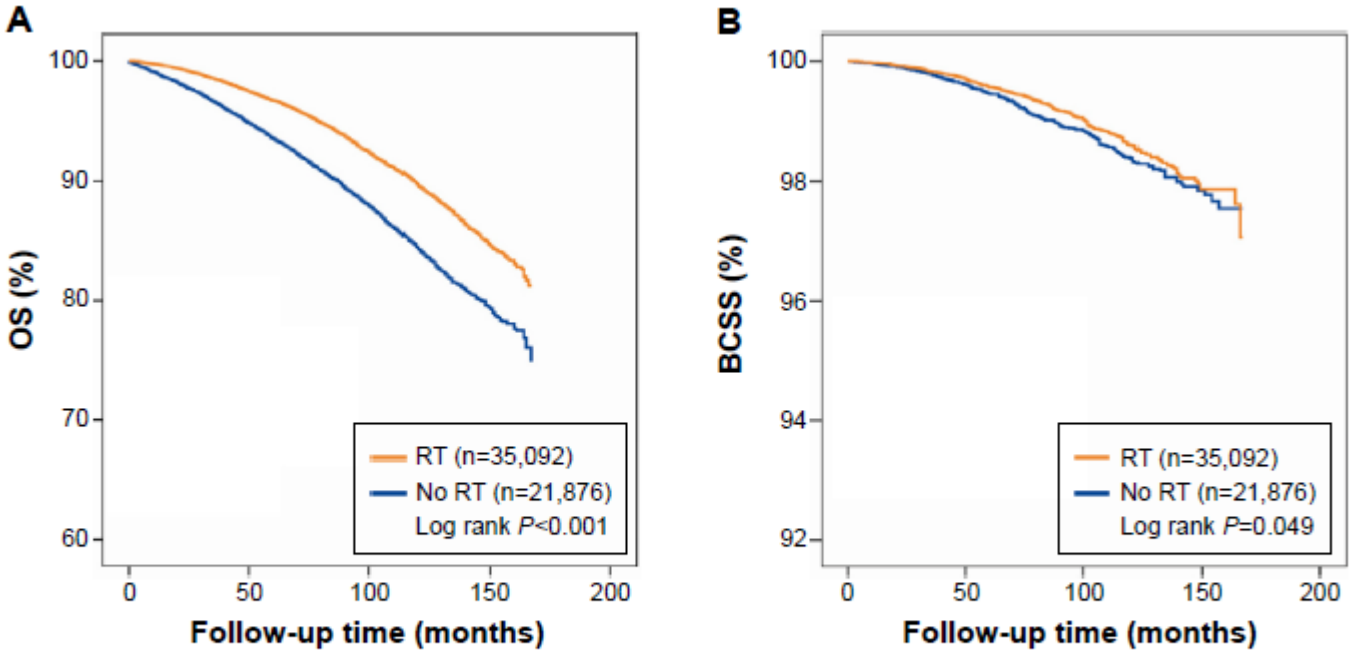


Figure 2 Kaplan–Meier survival analysis within locally excised ductal carcinoma in situ according to the delivery of RT.
Notes: (**A**) OS. (**B**) BCSS.
Abbreviations: RT, radiotherapy; OS, overall survival; BCSS, breast cancer-specific survival.

Better OS after RT

Better BCSS after RT, especially in young and ER negative patients

Qian et al, 2015

Prognostic score used by Sagara et al JCO 2016

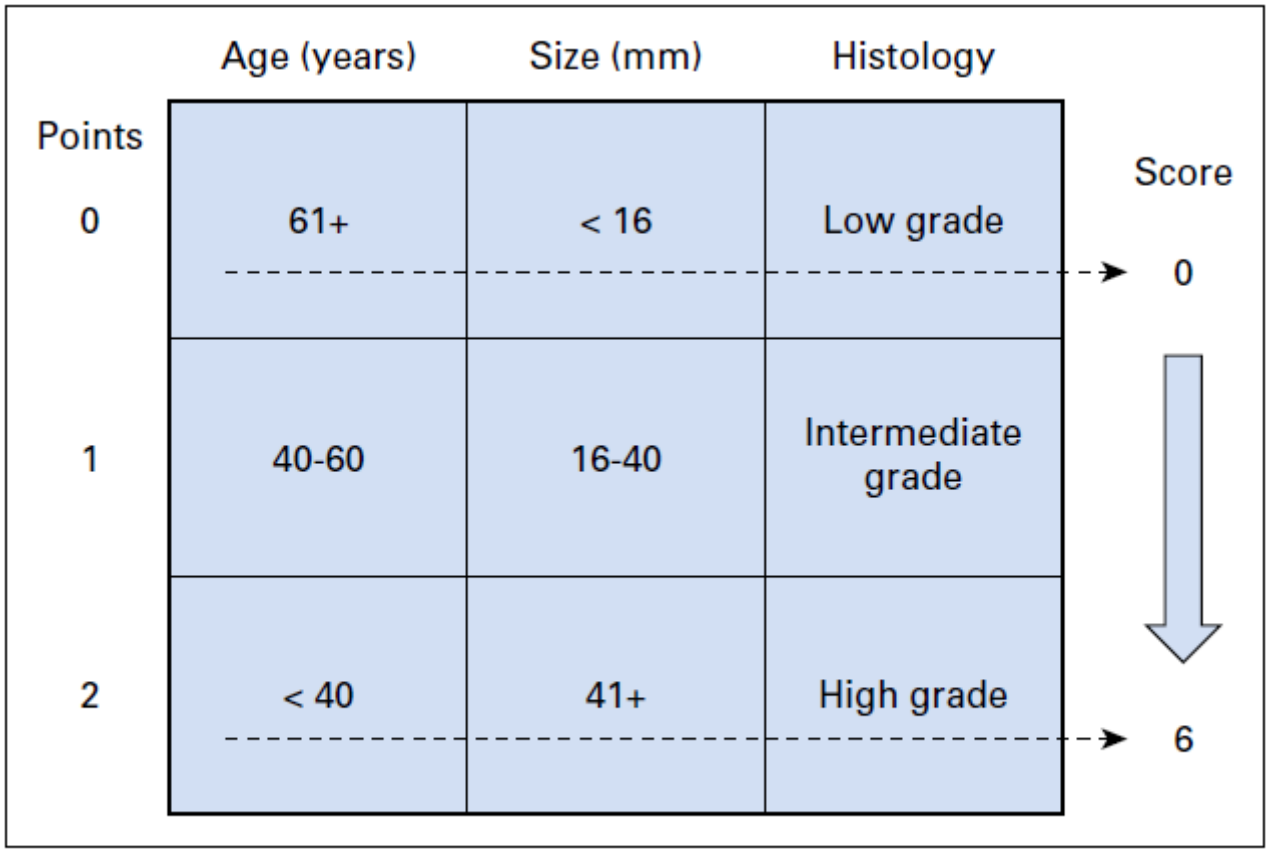
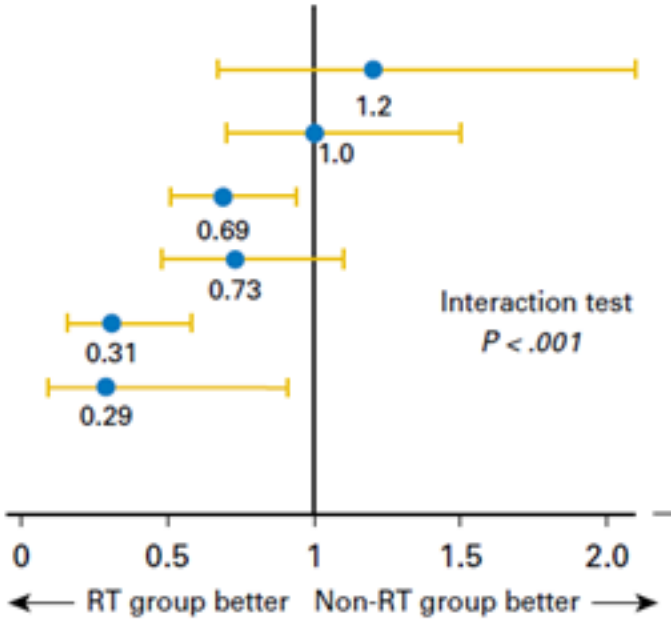


Fig 1. Patient prognostic score: risk stratification. Modified from Smith et al.[20]

Smith et al (2006): Likelihood of IBTR increases by 22% with every 1-point increase in the prognostic score.

Sagara et al JCO 2016

Prognostic Score	No. of Patients Non-RT Group	No. of Patients RT Group	10-Year BCM* (%) Non-RT Group	10-Year BCM* (%) RT Group	Hazard Ratio*† of BCM	P†
0	782	1,388	3.0	3.4	1.2	.58
1	2,677	4,480	2.0	2.5	1.0	.95
2	4,105	7,080	2.0	1.5	0.69	.02
3	3,048	5,417	1.5	1.3	0.73	.13
4	965	1,701	3.2	1.3	0.31	< .001
5	223	248	6.3	2.3	0.29	.03
6	15	15		NA		NA



Still: some caution warranted, i.e. retrospective validation…..

Summary: risk on LR and on dying from DCIS

All studies show that:

- RT after lumpectomy reduces local recurrences
- About 50% of LR are invasive
- Risk of dying of breast cancer after DCIS is very low (2-3%)
- IF an invasive recurrence develops: risk of dying from breast cancer increases enormously (18 fold acc. to SEER data Narrod et al)
- But: preventing invasive LR by RT does not influence breast cancer specific survival…?! →

- Suggestion that RT indeed does improve survival in subgroups
- → We need more knowledge on biology, apart from Grade

RT specific aspects: Boost required ?

JAMA Oncology | Original Investigation

Association of Radiotherapy Boost for Ductal Carcinoma In Situ With Local Control After Whole-Breast Radiotherapy

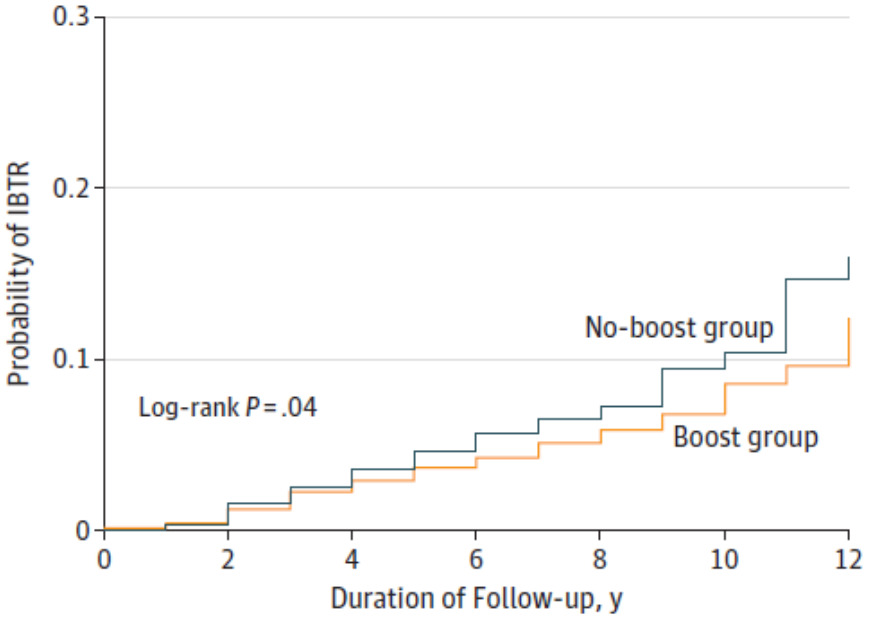
Meena S. Moran, MD; Yinjun Zhao, MS; Shuangge Ma, PhD; Youlia Kirova, MD; Alain Fourquet, MD; Peter Chen, MD; Karen Hoffman, MD, MHSc, MPH; Kelly Hunt, MD; Julia Wong, MD; Lia M. Halasz, MD; Gary Freedman, MD; Robert Prosnitz Jr, MD; Michael Yassa, MD; David H. A. Nguyen, MD; Tarek Hijal, MD; Bruce G. Haffty, MD; Elaine S. Wai, MD; Pauline T. Truong, MDCM

- Retrospective series of 4243 DCIS patients from 4 countries, 10 academic institutions, treated 1980-2010, with BC + WBRT +/- boost.

Moran et al, 2017

RT specific aspects: Boost required ?

Figure 1. Comparison of Ipsilateral Breast Tumor Recurrence (IBTR) by Treatment Group



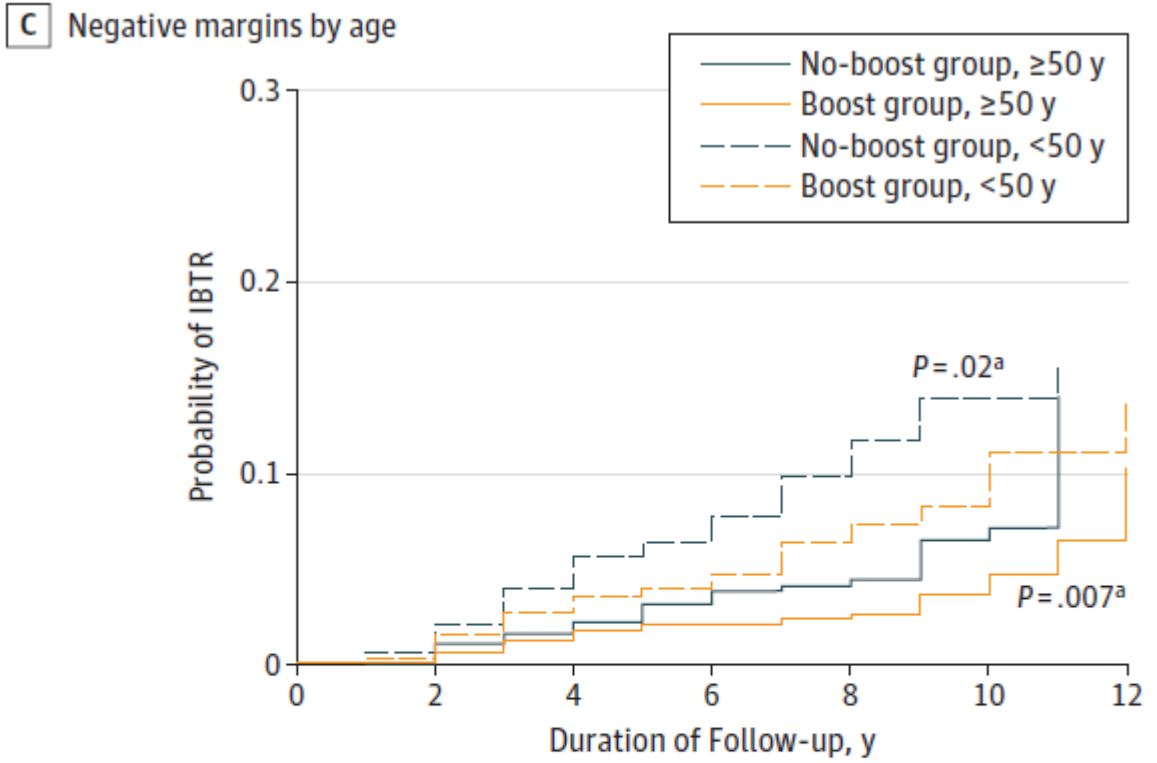
No. at risk

No-boost group	1210	1136	1023	821	507	277	74
Boost group	2123	2052	1878	1600	1034	535	166

Patients were stratified by those who received a radiotherapy boost (boost group) vs those who did not (no-boost group).

Moran et al, JAMA Oncol 2017

RT specific aspects: Boost required ?



No. at risk

No-boost group, ≥50 y	794	744	672	526	308	155	41
No-boost group, <50 y	292	274	247	212	140	81	18
Boost group, ≥50 y	1331	1294	1195	1030	647	338	103
Boost group, <50 y	579	558	511	428	276	130	37

Moran et al, JAMA Oncol 2017

RT specific aspects: Boost required ?

Table 3. Studies Reporting Outcomes of DCIS by Receipt of Boost vs No Boost

Source	Total No. of Patients (Patients Receiving Boost, %)	Median Follow-up, y	Effect of Boost on IBTR
Omlin et al,[21] 2006 [a]	316 (52.0)	6.0	Yes

Waiting for results of TROG 0701 DCIS study (NCT00470236)
RCT with 4 arms:

Boost- no boost AND
Hypof vs conventional fx

N = 1608
Inclusion 2007 – 2014

Moran et al, JAMA Oncol 2017

RT specific aspects: hypofractionation ?

Original Study

Hypofractionation Is an Acceptable Alternative to Conventional Fractionation in the Treatment of Postlumpectomy Ductal Carcinoma In Situ With Radiotherapy

Naghmeh Isfahanian,[1] Thuraya Al-Hajri,[1] Horia Marginean,[2] Lynn Chang,[1] Jean-Michel Caudrelier[1]

Journal of Medical Imaging and Radiation Oncology **60** (2016) 407–413 2016

RADIATION ONCOLOGY—ORIGINAL ARTICLE 2016

Hypofractionated versus conventionally fractionated radiotherapy for ductal carcinoma in situ (DCIS) of the breast

Andrew J Oar,[1,2,3] Miriam M Boxer,[1,4] George Papadatos,[1,2,3] Geoff P Delaney,[1,3,4,5] Penny Phan,[1,2] Joseph Descallar,[4,5] Kirsten Duggan,[5,6] Kelvin Tran[3] and Mei Ling Yap[1,2,3,4,5]

1 Liverpool Cancer Therapy Centre, Liverpool Hospital, Liverpool, NSW, Australia
2 Macarthur Cancer Therapy Centre, Campbelltown Hospital, Campbelltown, NSW, Australia
3 Western Sydney University, Campbelltown, NSW, Australia
4 University of NSW, Kensington, NSW, Australia
5 Ingham Institute for Applied Medical Research, Liverpool, NSW, Australia
6 South Western Sydney and Sydney Local Health Districts Clinical Cancer Registry, Liverpool, NSW, Australia

ESTRO School

Hypofx in DCIS

Original Study

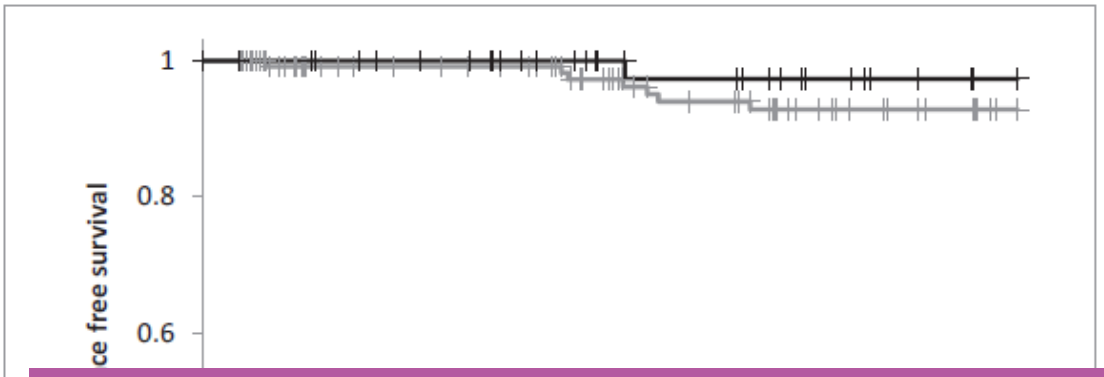
Hypofractionation Is an Acceptable Alternative to Conventional Fractionation in the Treatment of Postlumpectomy Ductal Carcinoma In Situ With Radiotherapy

Naghmeh Isfahanian,[1] Thuraya Al-Hajri,[1] Horia Marginean,[2] Lynn Chang,[1] Jean-Michel Caudrelier[1]

- 2003-2008
- N = 348: 202 patients 2 Gy per fraction; 146 patients 2.67 Gy per fraction
- 5 yr: LR 91% vs 94%
- Groups seem to be comparable regarding most risk factors, but retrospective and very small study..

Isfahanian, Clin Breast Cancer 2016

RT specific aspects: hypofractionation ?



- 197 patients 2 centers in Australia:

Waiting for results of TROG 0701 DCIS study (NCT00470236)
RCT with 4 arms:

Boost- no boost AND
Hypof vs conventional fx

N = 1608
Inclusion 2007 – 2014

Fig. 1. Kaplan–Meier curve showing ipsilateral recurrence free survival for hypofractionated radiotherapy (RT) (Hypo) versus conventionally fractionated RT (Conv). —, Conv; —, Hypo.

Oar et al, 2016

ESTRO School

Partial breast irradiation in DCIS

Practical Radiation Oncology (2017) 7, 73-79

practical radiation oncology
pro
www.practicalradonc.org

Special Article

Accelerated Partial Breast Irradiation: Executive summary for the update of an ASTRO Evidence-Based Consensus Statement

Candace Correa MD [a], Eleanor E. Harris MD [b], Maria Cristina Leonardi MD [c], Benjamin D. Smith MD [d], Alphonse G. Taghian MD, PhD [e], Alastair M. Thompson MD [f], Julia White MD [g], Jay R. Harris MD [h,*]

[a]*Department of Radiation Oncology, Faxton St. Luke's Healthcare, Utica, New York*
[b]*Department of Radiation Oncology, East Carolina University, Greenville, North Carolina*
[c]*Department of Radiation Oncology, European Institute of Oncology, Milan, Italy*
[d]*Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[e]*Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts*
[f]*Department of Breast Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[g]*Department of Radiation Oncology, Ohio State University Cancer Center, Columbus, Ohio*
[h]*Department of Radiation Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, Massachusetts*

Received 18 August 2016; accepted 12 September 2016

Partial breast irradiation in DCIS

- DCIS is considered suitable for PBI, if acc. to RTOG 9804 low risk:
  - Screen-detected, Grade 1-2, ≤ 2.5 cm, free margins ≥ 3 mm
    - IBTR risk w/o RT: 6.7% at 7.2 yr (RTOG 9804)
    - IBTR risk w/o RT: 14.2% at 12 yr (ECOG E 5194)

- Applying these criteria to APBI with mammosite:
  - 40 patients: 5 yr risk IBTR 0%

- Pooled analysis DCIS treated with mammosite:
  - 300 patients, 5 yr IBTR 2.5%

"These patients could also be offered endocrine Rx or observation alone"

- RCTs PBI vs WBRT for DCIS are underway..!

Summary

- RT reduces LR rate after BCS with a factor 2, but effect on OS doubtful/ limited to subgroups.

- Probably we can discriminate 3 risk groups:
  - *High risk:* RT is indicated, yields survival benefit – and boost may give additional benefit
  - *Intermediate risk:* RT is to be discussed with patients, and burden can be reduced by hypofractionation and/or partial breast RT
  - *Low risk:* RT can be withheld at all !

- → How to discriminate these subgroups ?

ESTRO School

ESTRO Teaching Course on the Multidisciplinary management of Breast Cancer.
Dublin, Republic of Ireland. September 2017

Are Resection Margins Still Relevant In The Management Of Invasive Breast Cancer

Lynda Wyld

Reader In Surgical Oncology

University of Sheffield

Consultant Oncoplastic Breast Surgeon

Doncaster and Bassetlaw Teaching Hospital

UK.

Disclosure:

- I have no conflict of interest to report

Voting 1

- Please indicate the minimal acceptable margin in your unit?.

1. < 5 mm
2. < 2 mm
3. <1mm
4. No tumour at ink
5. Involved over less than 4 mm (focally involved)
6. Involved over > 4 mm

Voting 2

- What factor would make you opt for a bigger margin than your unit minimum standard

1. Age under 40
2. DCIS only
3. Triple Negative cancer
4. Her-2 positive cancer
5. None of the above
6. All of the above

Voting 3.

- A 36 year old female with a 2 cm cancer (luminal B, grade 3) undergoes breast conservation resulting in the following margins:
  - Deep: <1mm, not at ink
  - Anterior: 2mm
  - Lateral: pleomorphic LCIS at ink over 3mm, invasive clear
  - Medial: classical LCIS at ink, invasive clear
  - Superior: 4mm clear
  - Inferior: 10mm clear

- Which margins would you excise?

1. Deep, anterior, lateral
2. Lateral only
3. Lateral and medial
4. All margins except inferior
5. Would suggest mastectomy because of LCIS
6. No margins need re excising

The damage done in pursuit of the clear margin….

- 20-40% rate of margin re excision, including some mastectomies
- Increase costs for re excision
- Use of costly margin assessment devices
- Pain and stress of re excisional surgery for the patient

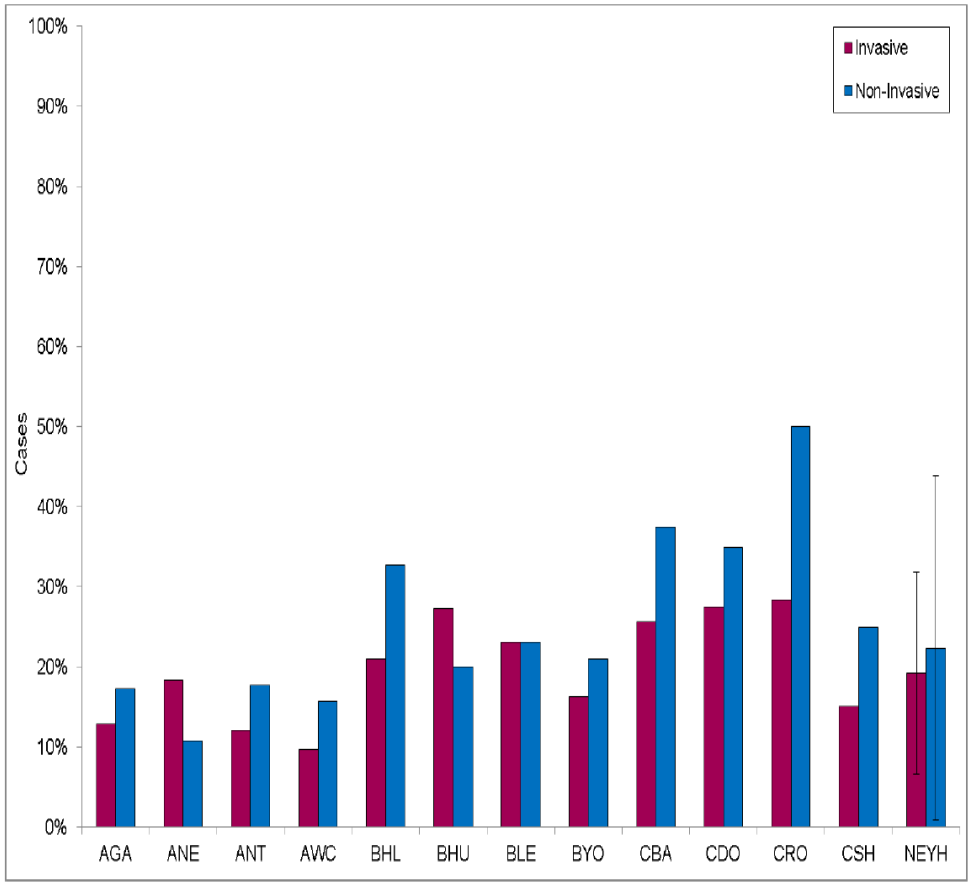
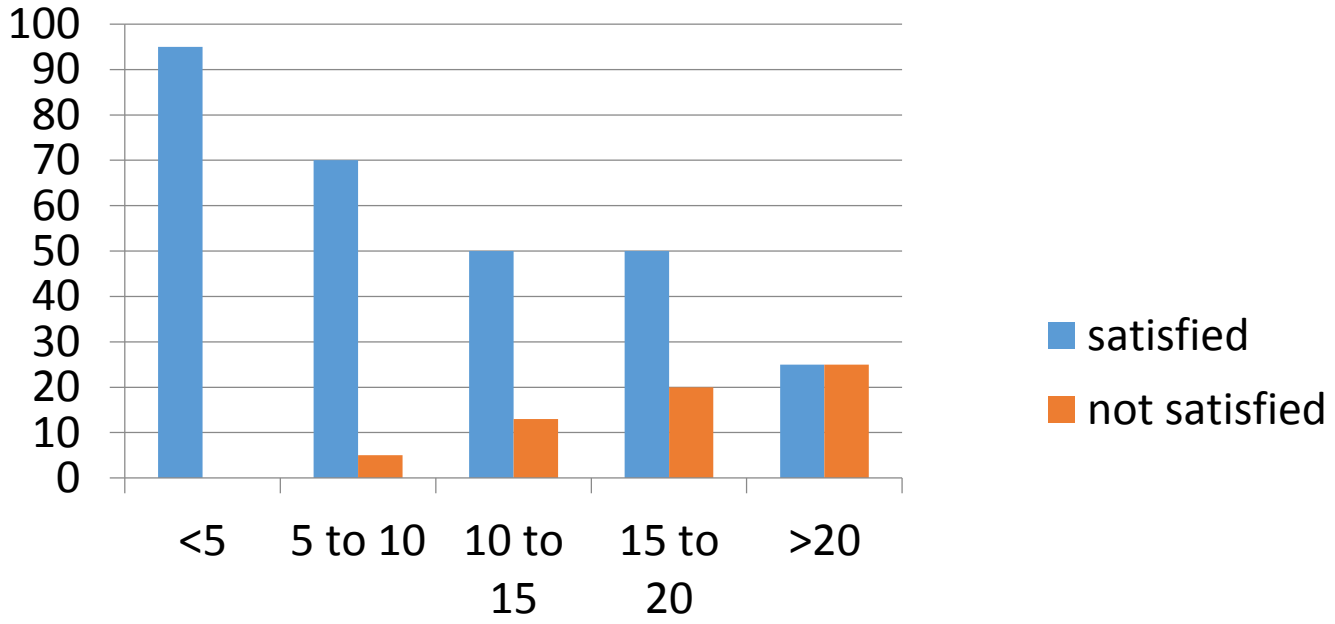


Figure 24: Cases with two or more therapeutic operations (ABS)

Poor Cosmesis

- Breast Conservation Outcomes by % volume excised

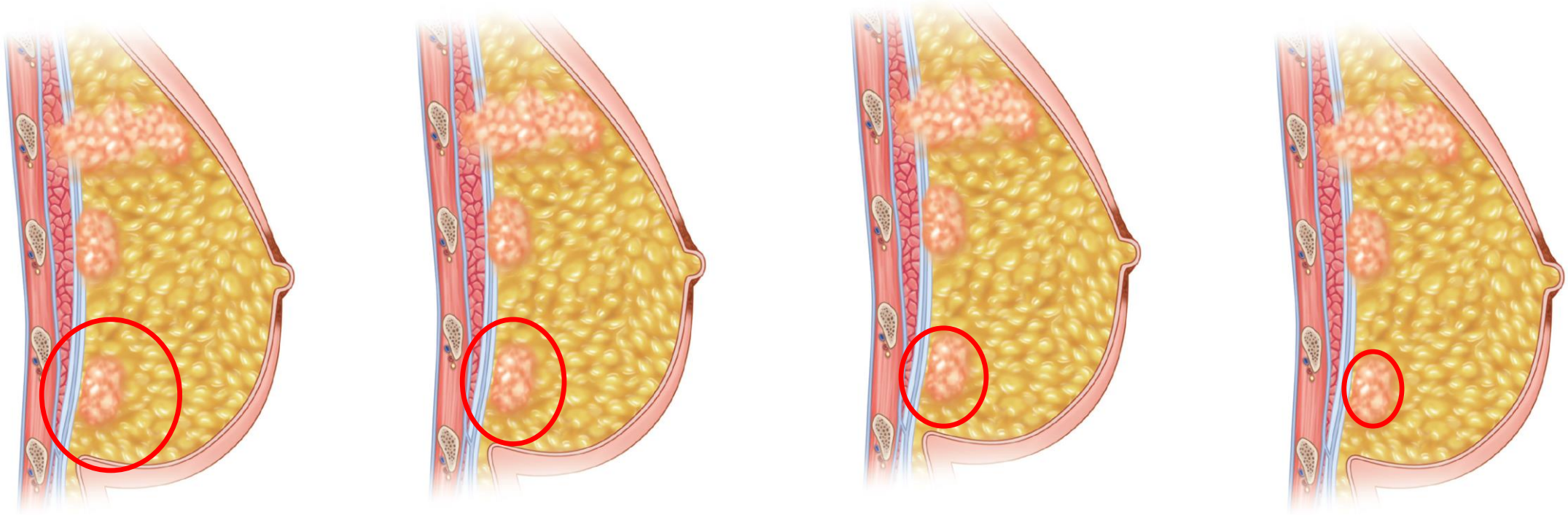


Cochrane and Macmillan 2003, BJS

What constitutes a clear margin?

- General direction of travel is downwards….removal of the adjacent organ, removal of the whole breast, removal of the segment……

…….and then 5mm, 2mm, 1mm, no tumour at ink and ?focal +ve

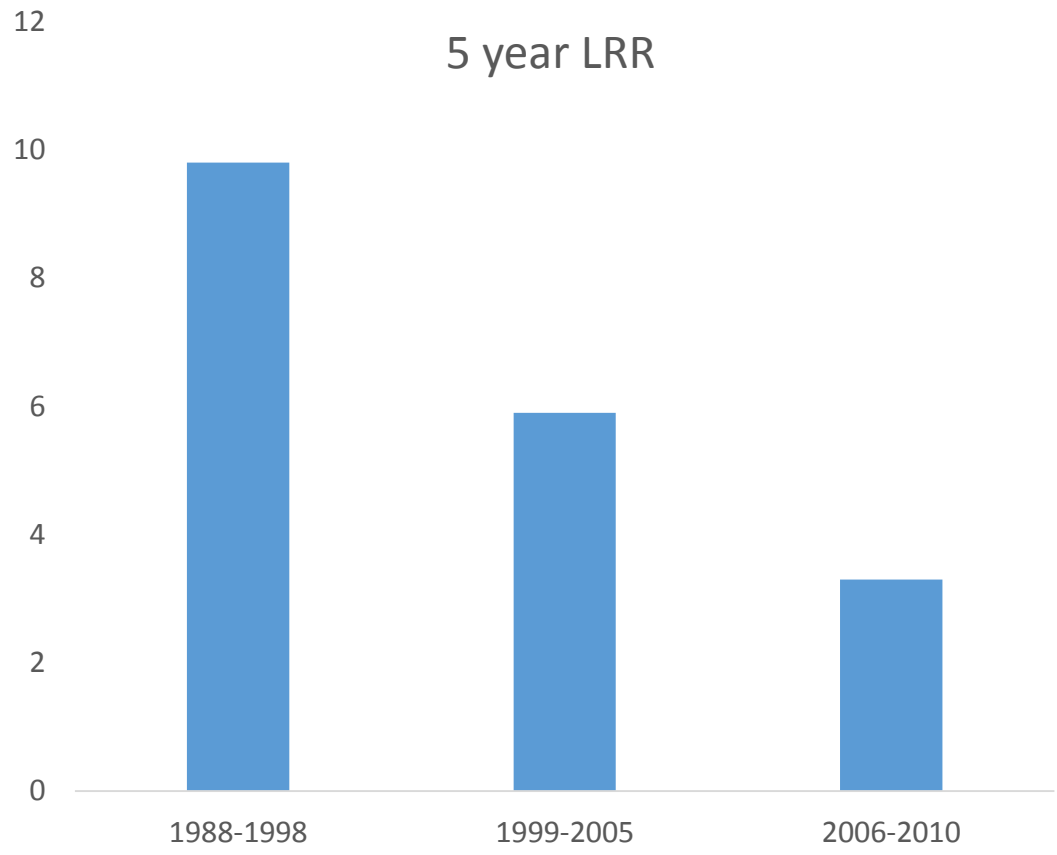


Holland *et al* 1985, Vaidya *et al*, 1996

Excision margin around primary tumour (cm)	Patients in whom foci would be left after BCS (%)
2	47
3	33
4	20
5	10

Local Recurrence Rates Falling

- Downwards trend towards 0.5% per year
  - Better pathology assessment
  - Better surgery/Intraoperative margin assessment
  - Better RT plus boost
  - Adjuvant systemic therapy



Local Recurrence rates in women under age 40 (van Laar 2013)

The Question:

- Are resection margins still relevant in the era of modern pathology, targeted RT and systemic therapy to tidy up inevitable small volume foci remote from the primary?

Factors affecting local recurrence risk

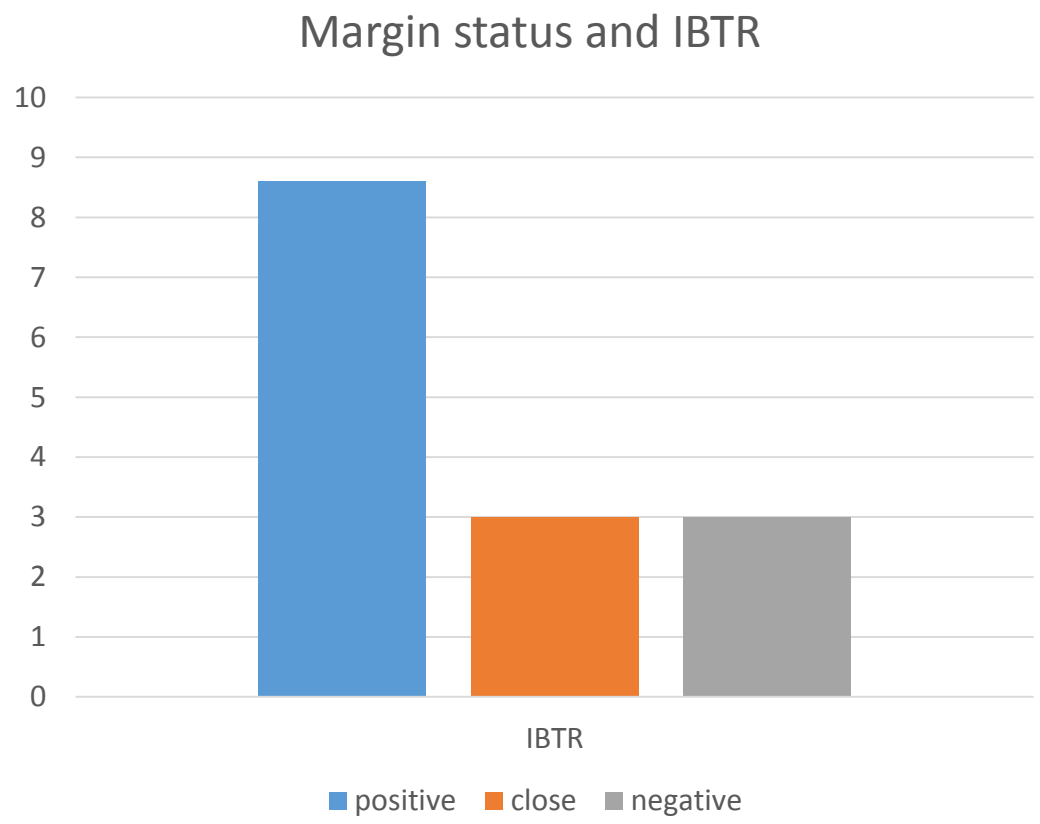
- Tumour and patient factors:
  - Tumour size and stage
  - Vascular Invasion
  - **Surgical positive margin**
  - Young age
  - Tumour biological subtype
- Treatment:
  - Radiotherapy
  - Adjuvant systemic therapy

Positive versus negative margins:

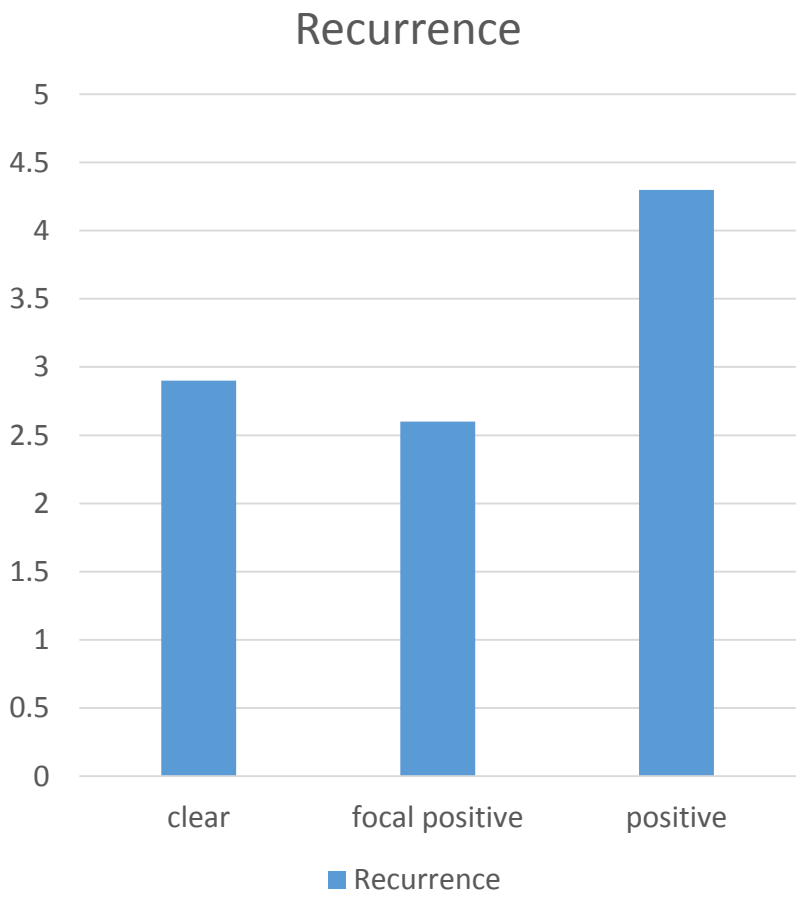
- *Housami et al. Ann Surg Onc, 2014*
- Large Meta-analysis of 28000 women undergoing BCS for invasive cancer, 1506 local recurrences across 33 studies
- Overall mean LR rate was 5.3% at 79 months
- Relative risk of recurrence 2.44 for positive versus negative margin. Margin width made no difference

Large Danish Cohort (Bodilsen et al, 2016)

- 11 900 women treated with BCS
- Median FU 4.9 years
- Hazard ratio for a positive margin 2.51 but final positive margins very rare (<1% of population.
- Chemotherapy reduced risk by about half but small numbers preclude assessment according to margin status



Dutch guideline early data



Proffered Paper Session
Breast Cancer - Early Disease
Omitting a re-excision for a focally positive surgical margin after primary breast conserving surgery is safe

E. Vos[1], S. Siesling[2], A. Voogd[2], L. Koppert[1]
[1]Erasmus MC Cancer Institute, Surgery, Rotterdam, Netherlands
[2]Netherlands Comprehensive Cancer Center, Research, Utrecht, Netherlands

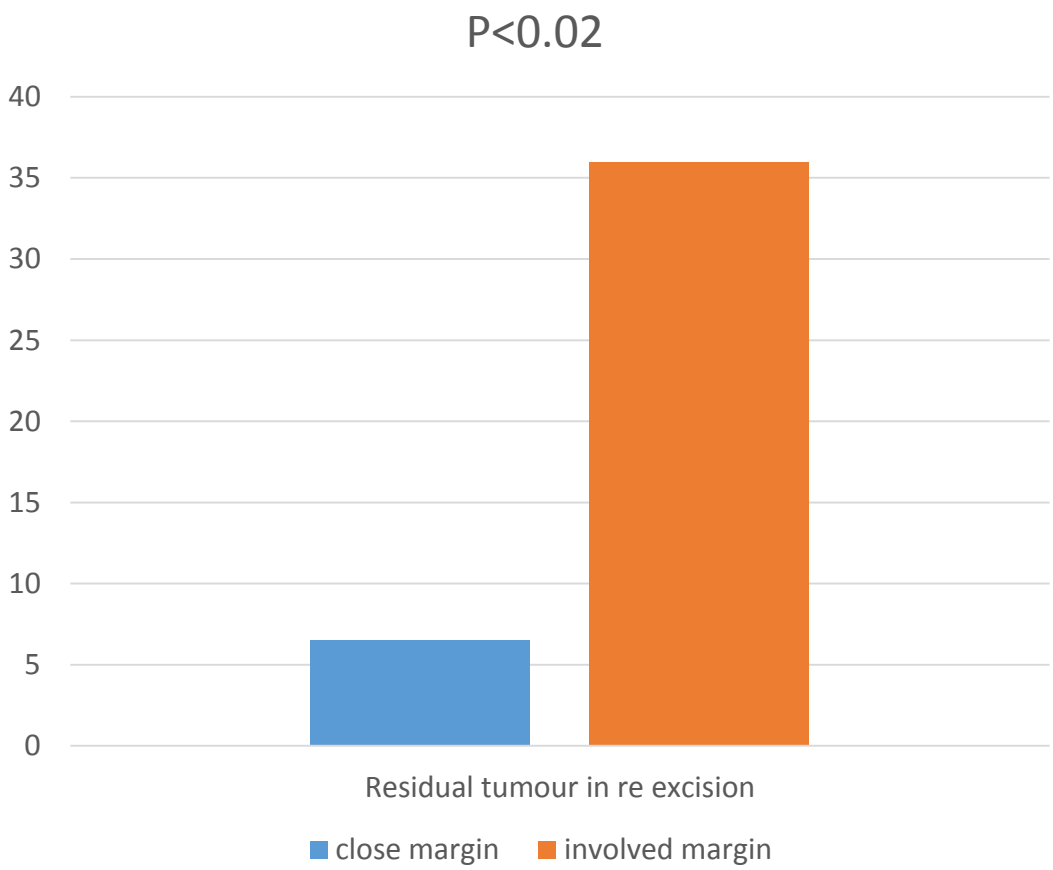
Note of caution: LRR was higher on subgroup analysis of younger women (<50 years) so probably NOT appropriate in this higher risk group.

Longer term follow up and more data are probably needed before adoption and pathology review of each case

Can we accept a positive margin?

- Rivere et al, 2016. 247 patients
- Margin re excision performed in 23%
  - 46 patients with a close margin,
  - 11 had a positive margin

- The following variables were not predictive of residual disease:
  - tumor stage,
  - ER/PgR status,
  - HER2/neu receptor status,
  - nodal status.

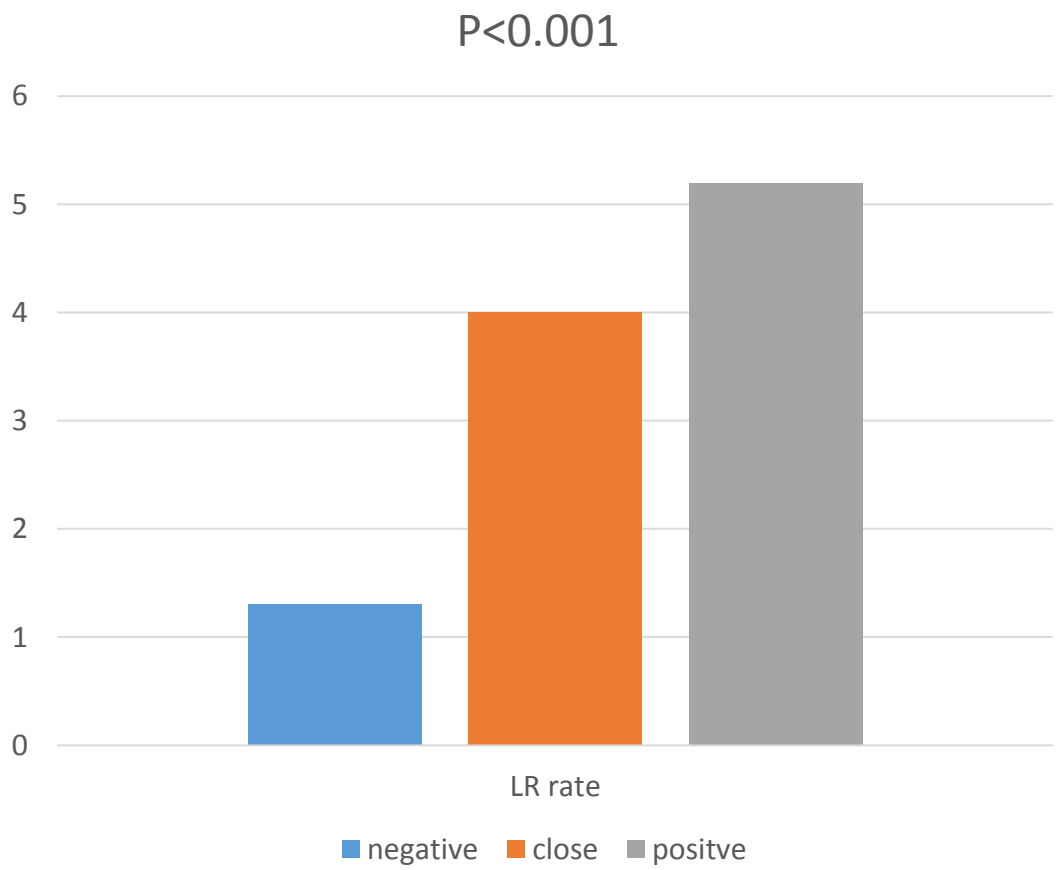


Better imaging to define disease extent

- Digital tomosynthesis, contrast enhanced mammography and MRI all give better definition of disease extent and multifocality
- May detect cases where bulky residual disease may be present.
- *Pathological correlates with pre operative imaging may be challenging however*

Can Boost remove the need for clear margins?

- Lupe et al, 2011. 2264 women treated with BCS and WBRT and boost. 1980 had clear margins, 222 close and 62 positive margins. 5.2 year follow up. 92% of close or positive cases had boost.
- When close/positive margin cases were matched to negative margin controls for other risk factors such as age, grade, subtype, the difference in 5-year LR remained significant (4.25% vs. 0.7%, $p < 0.001$).
- Housami meta-analysis found that correction for boost rates did not reduce the impact of a positive versus a negative margin



Can systemic endocrine therapy remove the need for clear margins?

- The NSABP B14 Trial of Tamoxifen versus placebo demonstrated a 14 versus 4% LRR
- Houssami meta-analysis showed +ve margin had significant negative effect even when adjusted for anti-oestrogen use and ER status.

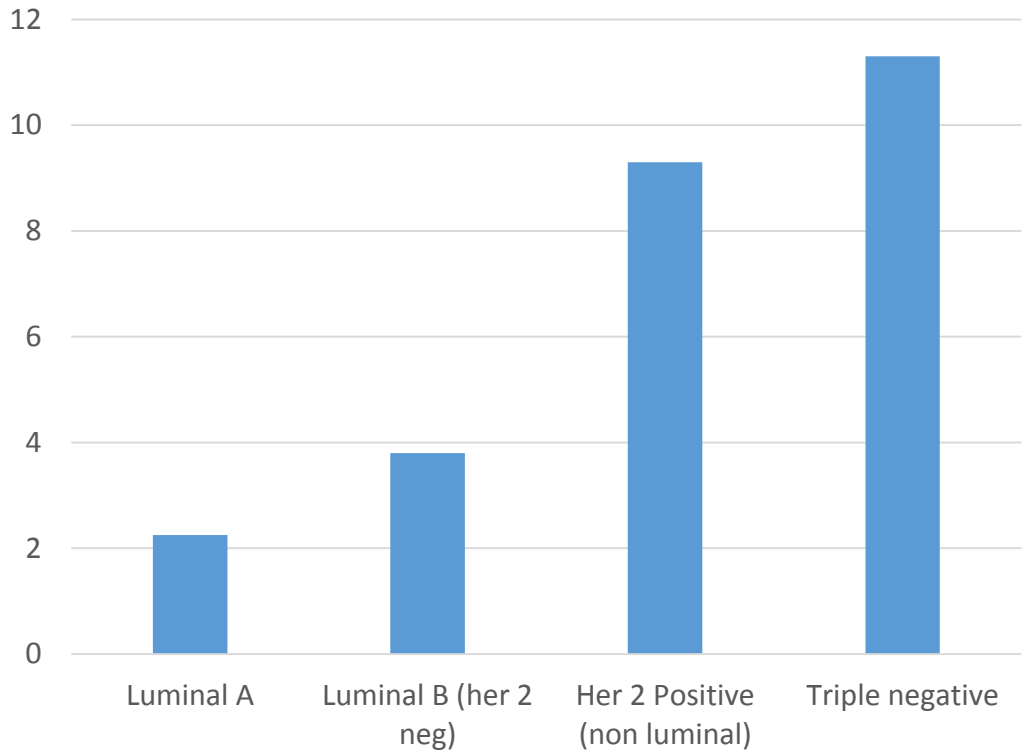
Impact of chemotherapy on local recurrence

- NSABP B13, methotrexate plus 5FU versus no chemotherapy, LRR dropped from 13% to 2.6%.

- Housami meta-analysis was not able to look at positive margins corrected for chemotherapy or trastuzumab. Most studies with adequate follow up predated use of trastuzumab.

- Most chemotherapy RCTs specify adequate surgery with clear margins

Impact of subtype: Perhaps need to take into account when assessing whether to go back



ELSEVIER
The Breast
journal homepage: www.elsevier.com/brst

Original article

Breast conservative surgery and local recurrence

Mahdi Rezai [a,*], Stefan Kraemer [b], Rainer Kimmig [c], Peter Kern [c]

[a] European Breast Center – Dr. Rezai, Hans-Günther-Sohl-Str.6-10, D-40235 Düsseldorf, Germany
[b] University Medical Center Cologne, Kerpener Str. 34, D-50931 Cologne, Germany
[c] University Hospital of Essen, Women's Department, Hufelandstr.55, D-45147 Essen, Germany

2015

Tailoring risk factors

- Subtype, margin involvement extent (focal or gross), planned adjuvant therapy.
- Are we at the stage where we can tailor our decisions?

- ***Probably not yet***
- ***Most studies have excluded grossly positive margins and recruitment to trials would be challenging***

Summary 1

- Consistent evidence that positive margins result in higher LRR, regardless of
  - Tumour biotype
  - Age
  - Systemic Treatment
  - Boost

- Uncertainty regarding whether residual disease is present or not or whether it is small volume (and likely to respond to RT/CT) or large volume.

- Data shows that local recurrence at 5 years translates into increased mortality rates at 15 years (EBCTCG)

Summary 2

- Despite the costs:
  - Increased mastectomy rates
  - Increased costs
  - Inferior cosmesis
  - Additional technical costs (margin probes)
  - Patient distress

- **Margin negativity remains the gold standard.**

Voting 1

- Please indicate the minimal acceptable margin in your unit?.

1. < 5 mm
2. < 2 mm
3. <1mm
4. No tumour at ink
5. Involved over less than 4 mm (focally involved)
6. Involved over > 4 mm

Thank You.

Are resection margins still relevant? Role of radiotherapy…

Liesbeth Boersma, radiation oncologist

Maastro Clinic/ University Hospital Maastricht, The Netherlands

ESTRO Teaching Course on Breast Cancer, Dublin, Sept. 10-13th 2017

5. Radiation therapy delivery

The choice of WBRT delivery technique, fractionation, and boost dose should not be dependent on margin width.

Moran et al, IJRBOP 2014

i.e. in case of a free margin width > 0 mm…

Why is there no relation between LR and margin width > 0 cm ?

Actual key-questions:

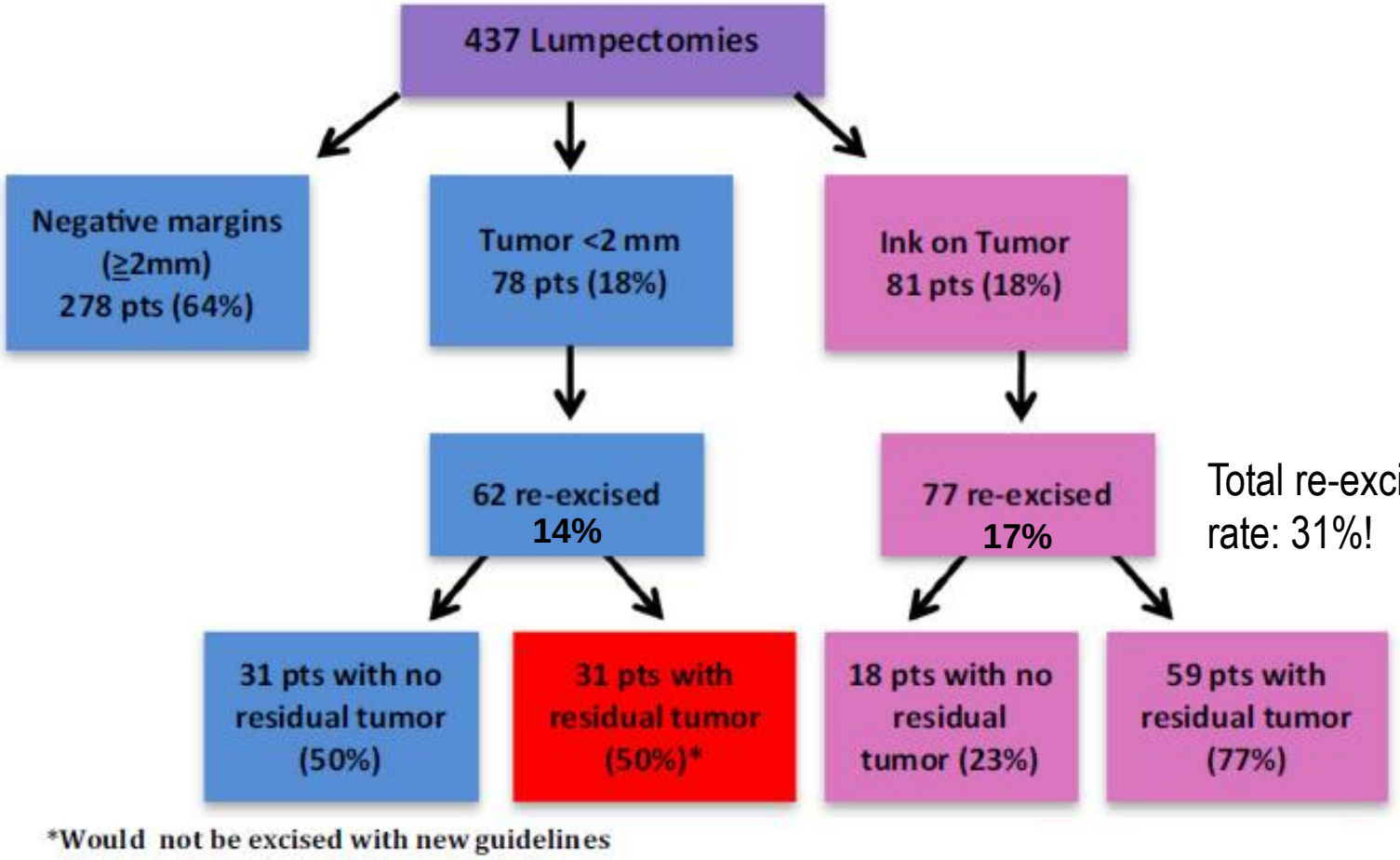
→ What is the probability that residual tumorcells are present ?

- Is this dependent on margin width ?

→ What is the estimated amount of residual tumorcells ?

- Is this dependent on margin width ?

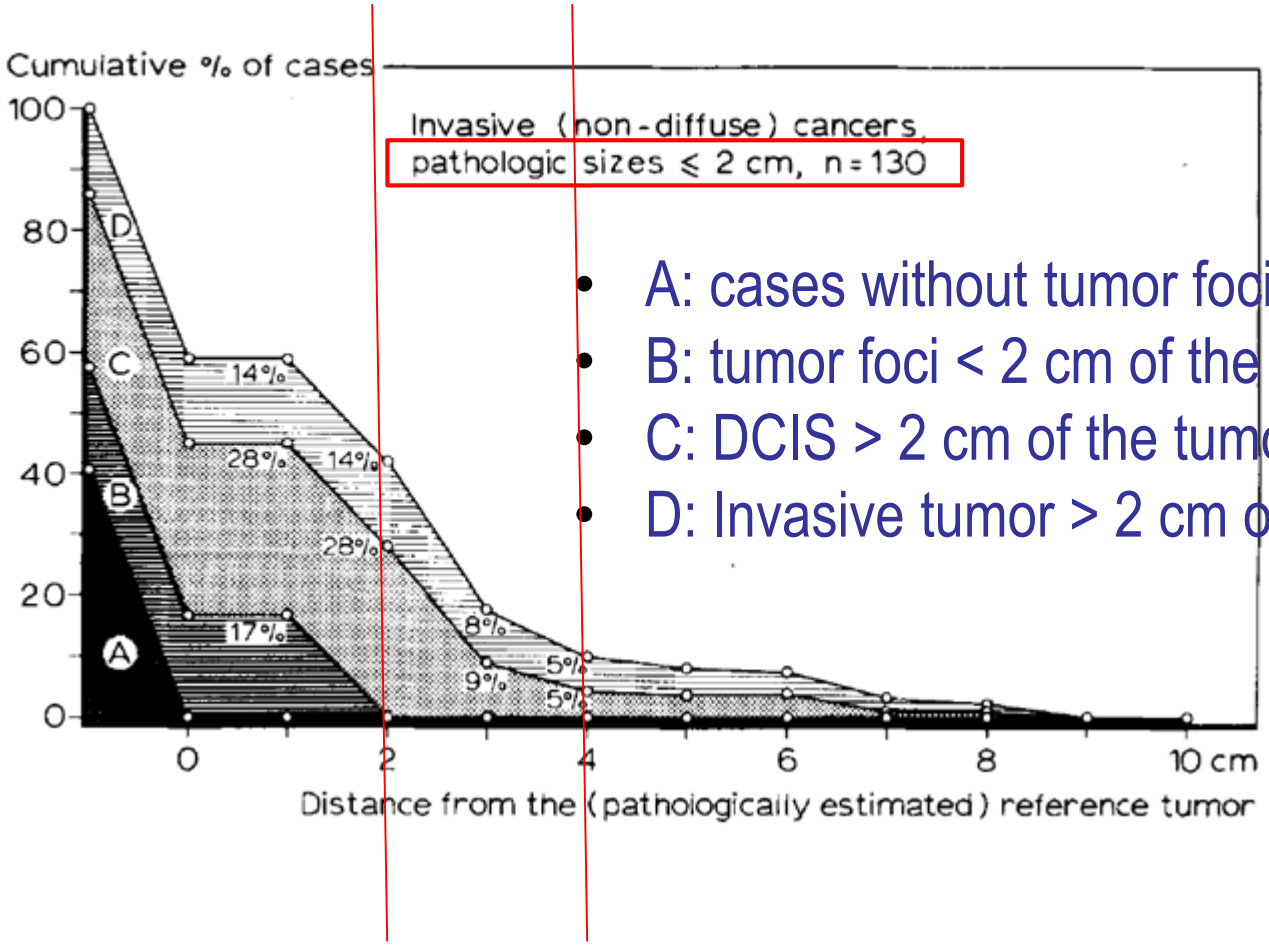
What if we apply SSO guidelines to a retrospective cohort ?



Total re-excision rate: 31%!

Merill et al, 2016

Probability of residual disease as a function of distance from primary tumor



- A: cases without tumor foci outside the tumor
- B: tumor foci < 2 cm of the tumor
- C: DCIS > 2 cm of the tumor
- D: Invasive tumor > 2 cm of the tumor

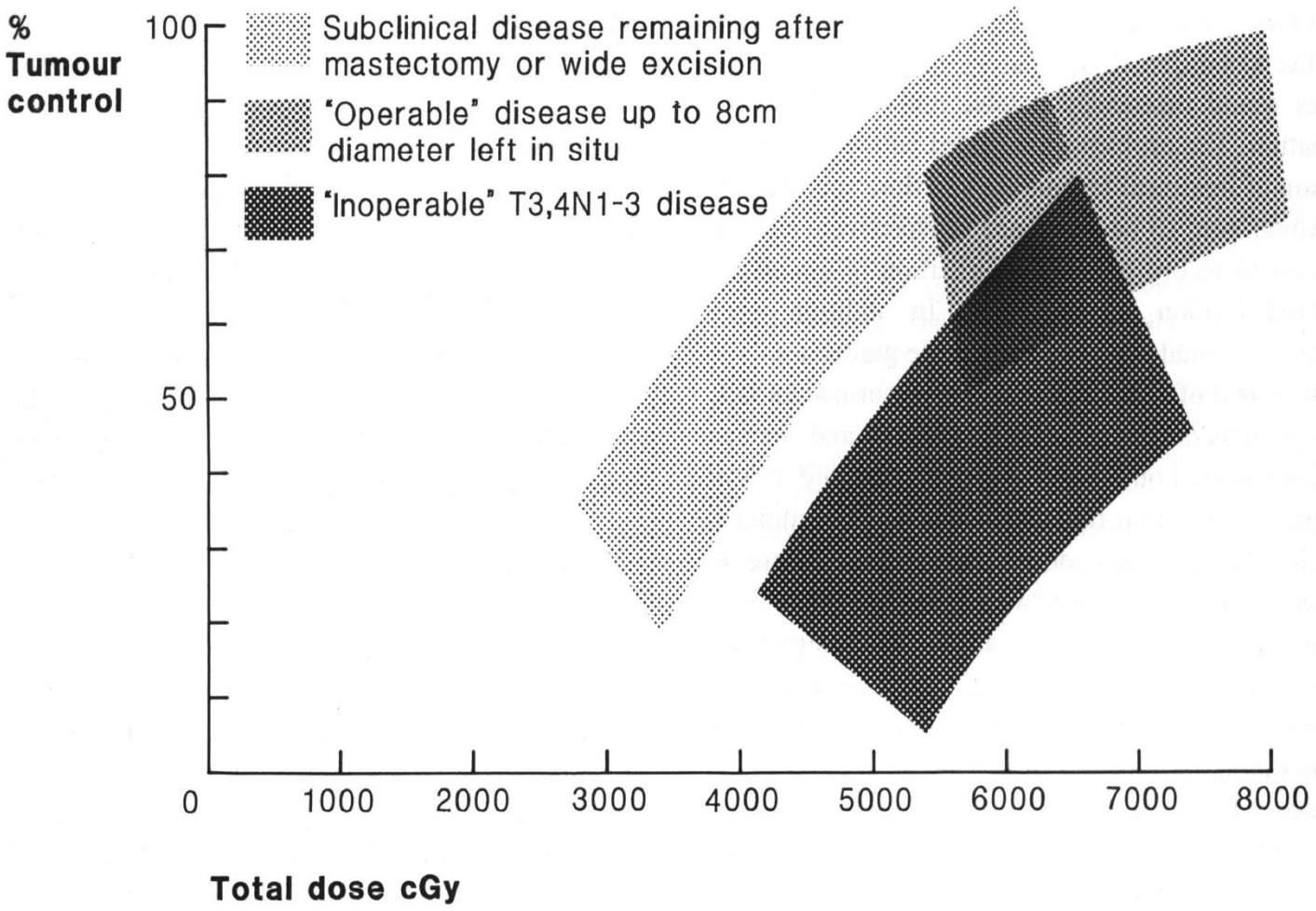
Holland et al, 1985

Why is there no relation between LR and margin width > 0 cm ?

Actual key-questions:

- → What is the probability that tumorcells are left in situ?
  - Is this dependent on margin width ? YES !
- → What is the estimated amount of tumorcells left in situ ?
  - Is this dependent on margin width ?

Dose-effect relations are dependent on tumorload…



JW Denham, Radiother Oncol 1986

Elegant simulation study from NKI, The Netherlands

Radiotherapy and Oncology 104 (2012) 148–154

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Breast conserving therapy

Impact of negative margin width on local recurrence in breast conserving therapy

Wei Chen [a,b], Joep Stroom [a,d], Jan-Jakob Sonke [a], Harry Bartelink [a], Annemarie C. Schmitz [b,c], Kenneth G. Gilhuijs [b,c,*]

[a] *Department of Radiotherapy;* [b] *Department of Radiology, The Netherlands Cancer Institute-Antonie van Leeuwenhoek Hospital, Amsterdam, The Netherlands;*
[c] *Department of Radiology, The University Medical Centre Utrecht, Utrecht, The Netherlands;* [d] *Department of Radiotherapy, Fundação Champalimaud, Lisbon, Portugal*

MAASTRO CLINIC

ESTRO School

Methods

- Use of 2 important datasets

1. EORTC boost no boost trial:

   N = 1282, all margins with < 10 mm, no EDCIS, including LR rates & margin widths

2. MARGINS database:

   Database of 60 patients, with pre-operative MRI matched with pathology of wide local excision specimens

   Described the relation between residual volume of disease and margin width.

Methods

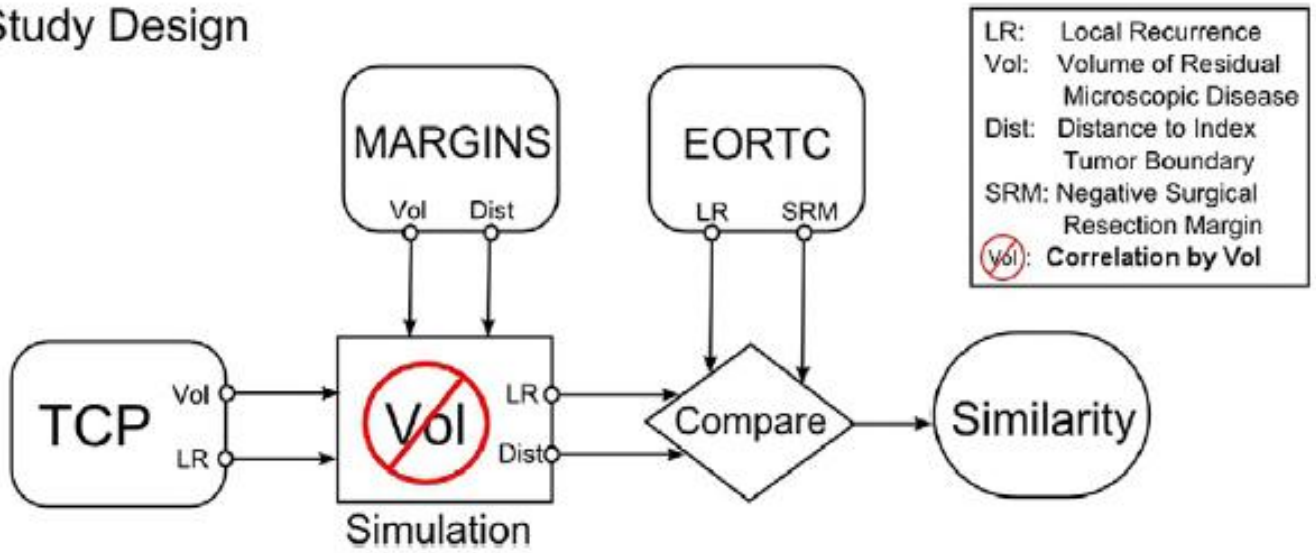
1. Determine residual tumor volume in wide local excision specimens in MARGINs database in relation to distance of invasive primary tumor, i.e. margin width

2. Calculate the TCP (LR) for different residual volumes using Webb-Nahum model

3. Combine 1 and 2 to calculate the LR as a function of margin width

4. Compare the estimated LR with the observed LR rate in the EORTC dataset, as a function of margin width

Study Design



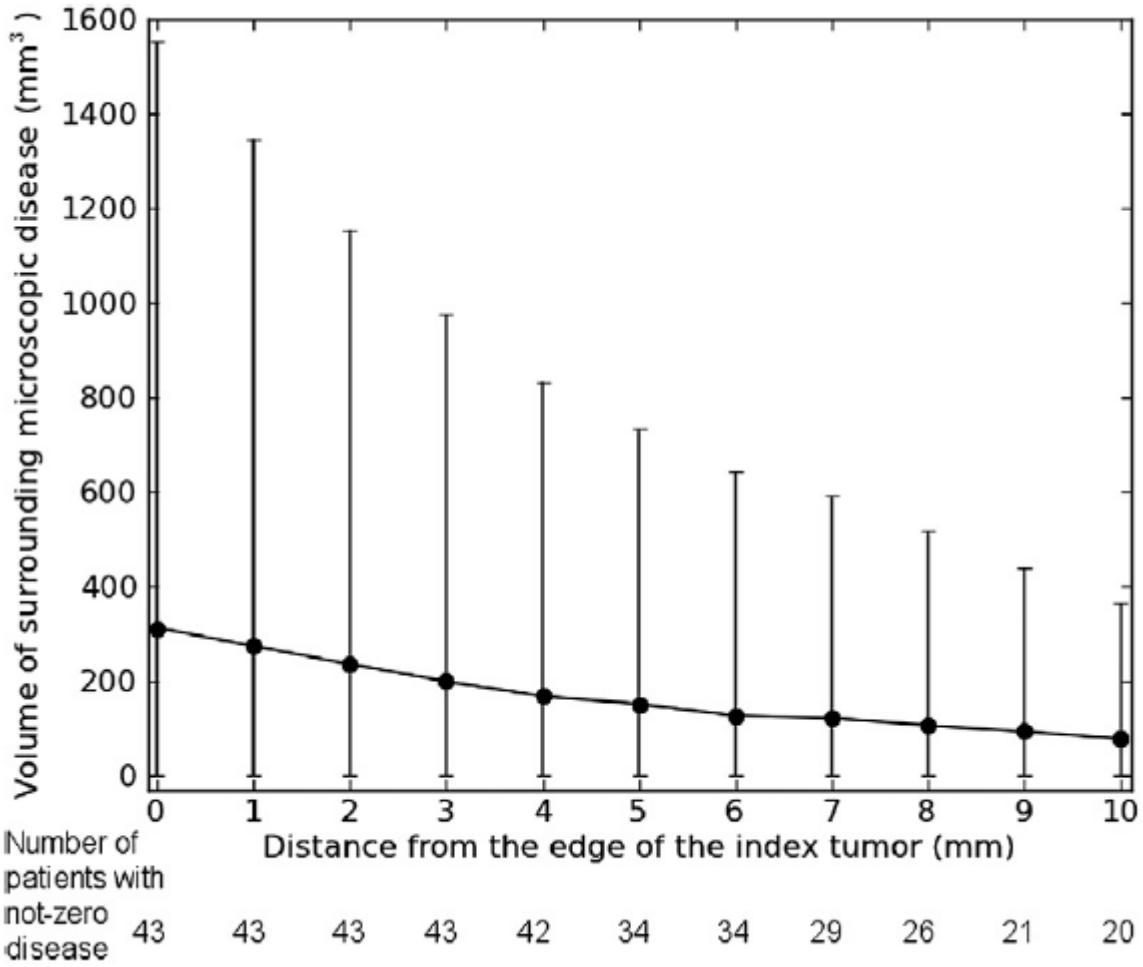
Matched for age and grade

Table 1
Patient and tumor characteristics in the original EORTC dataset and the MARGINS dataset.

	EORTC 50 Gy ($n = 627$)		EORCT 66 Gy ($n = 654$)		MARGINS ($n = 60$)	
	Number	%	Number	%	Number	%
Age (year)						
Mean	54.0		53.7		58.4	
Range	29–75		27–76		36–80	
Younger (⩽50)	238	38.0	255	39.0	12	20
Older (>50)	389	62.0	399	61.0	48	80
Tumor grade						
Grade 1	300	47.8	352	53.8	27	45
Grade 2	173	27.6	148	22.7	22	36.7
Grade 3	141	22.5	142	21.7	11	18.3
Missing	13	2.1	12	1.8	0	0

485 in boost and 499 in no boost arm randomly selected, to match for age and grade

Results of margins database



Large variation in volume of disease around the primary tumor!

TCP model Webb-Nahum

Webb's TCP model describes the probability of tumor control (TCP) as a function of the radiosensitivity (α), the volume of tissue containing tumor cells (Vol), the density of tumor cells (ρ) and the total radiation dose (D) considering a homogeneous dose distribution, as follows:

$$\mathrm{TCP} = \int f(\alpha)\exp[-\rho\ \mathrm{Vol}\ \exp(-\alpha D)]\ d\alpha, \qquad (1)$$

TCP calculation as a function of residual microscopic disease for 50 Gy or 66 Gy

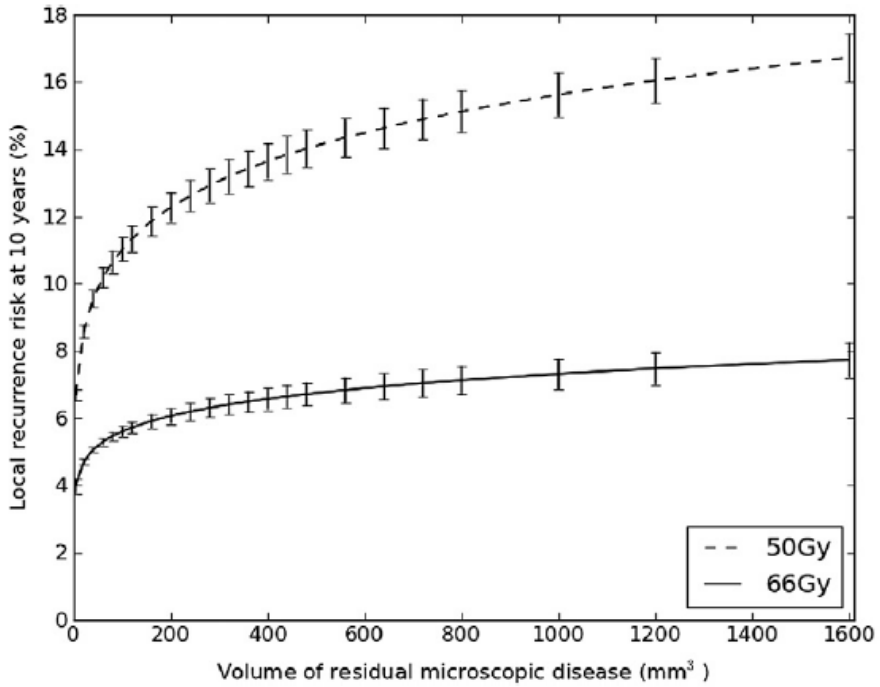
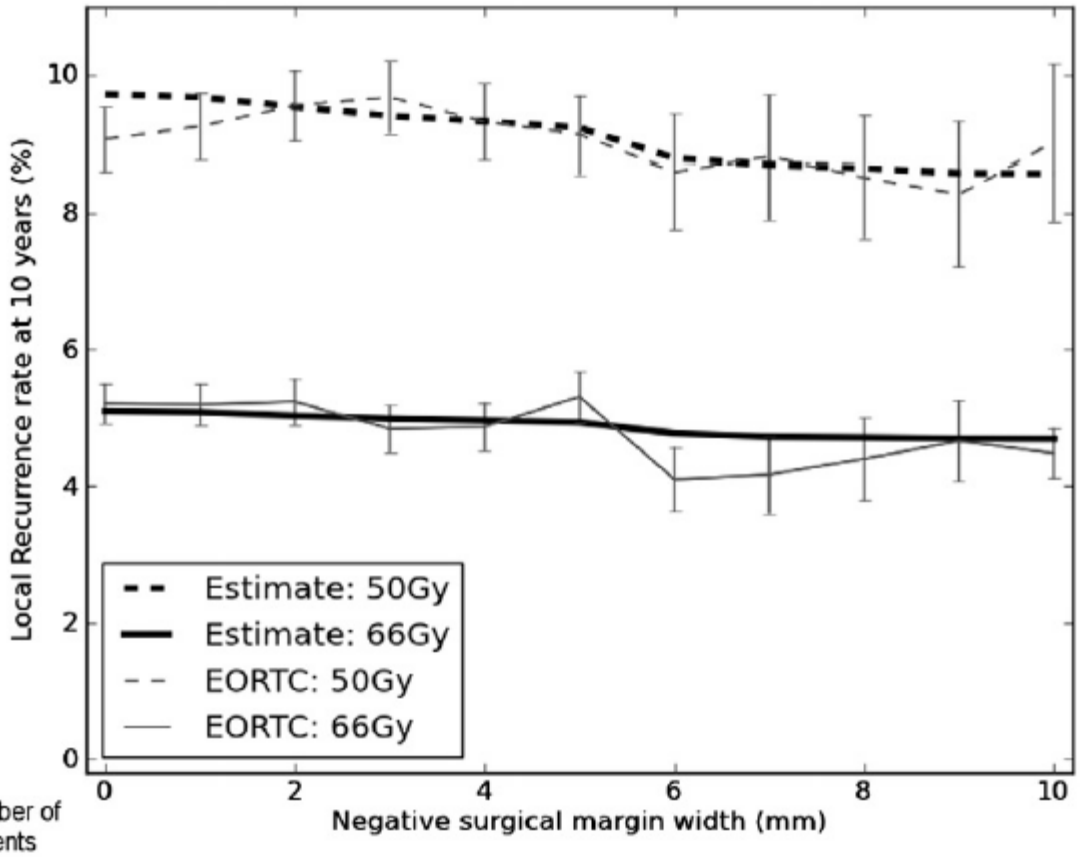


Fig. 3. Webb's TCP model of two radiation-dose arms illustrating the relationship between volume of residual microscopic disease and the risk of LR at 10 years. The error bar illustrates the 95% confidence interval of the estimated LR values.

- LR increases if residual volume of microscopic disease increases
- Higher dose for same amount of residual volume yields lower LR, especially for the larger volumes

Predicted TCP vs observed TCP as function of margin width



Number of Patients											
50 Gy	LR	48	47	44	39	36	32	15	13	11	9	9
	Total	495	480	427	370	344	305	149	129	117	97	90
66 Gy	LR	28	27	25	21	20	20	8	7	7	6	5
	Total	499	481	430	390	362	330	164	133	127	113	106

Only very weak association between LR rate and margin width !

Probably due to fact that patients with close or negative margins have large variation in residual volume

MAASTRO CLINIC

ESTRO School

Why is there no relation between LR and margin width > 0 cm ?

Actual key-questions:

→ What is the probability that tumorcells are left in situ?

- Is this dependent on margin width ? YES !

→ What is the estimated amount of tumorcells left in situ ?

- Is this dependent on margin width ? NO ! Other factors more important, like age, grade and subtype:

  - Chen et al 2014: simulation study &
  - Mihalcik et al 2017, analysis of LR, re-excision and residual disease, N = 1073

What to do in case of involved margins ?

What in case of *more than focally* involved margins ?

→ Re-excision:

- > 50% of patients: tumor is found in the re-excision specimen

  [Schnitt et al, 1987; Gwin et al, 1993; Kearny et al 1995; Schmidt-Ullrich et al 1995, Merill et al, 2016].

- Risk on finding a lot of residual disease especially high in case of EDCIS (67%), multinodular disease, or diffuse invasive lobular ca (50%) [Schnitt et al, 1987]

What to do in case of involved margins ?

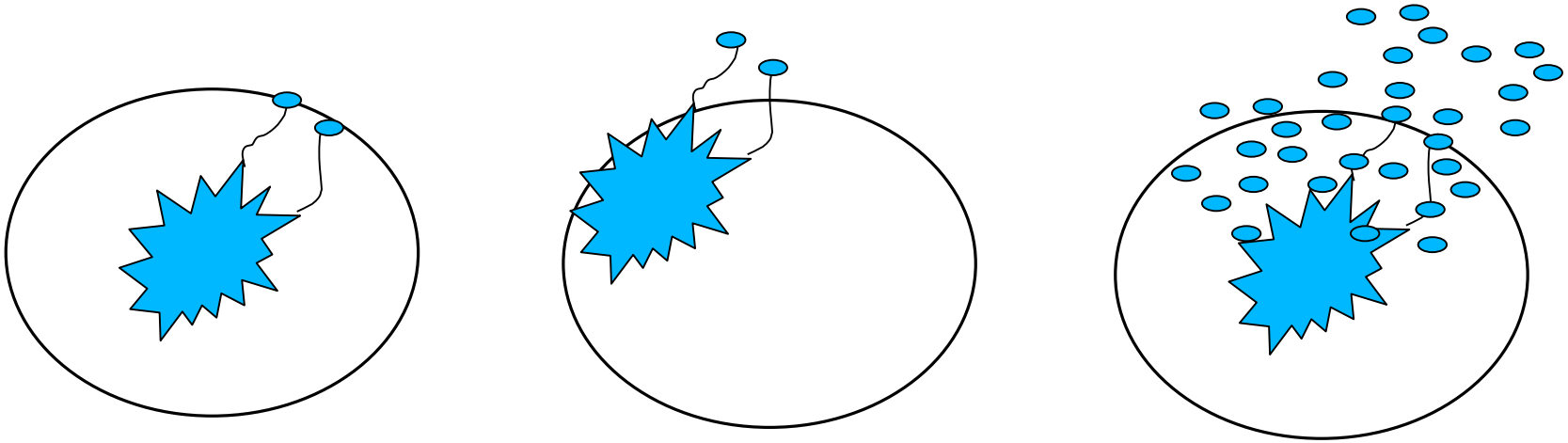
What in case of *focally* involved margins ?

- Focally involved: < 4 mm (acc to Dutch Guideline)
  - Very doubtful whether re-excision is useful
  - LR is increased: higher boost dose ?
  - Discuss with your pathologist !!!!

What to do in case of involved margins ?

What in case of *focally* involved margins ?

- Focally involved: < 4 mm (acc to Dutch Guideline)
  - Very doubtful whether re-excision is useful
  - LR is increased: higher boost dose ?
  - Discuss with your pathologist !!!!



What to do in case of involved margins ?

Recent study on value of MRI to detect residual disease:

Eur Radiol
DOI 10.1007/s00330-017-4823-y

BREAST

Breast MR imaging for the assessment of residual disease following initial surgery for breast cancer with positive margins

Julia Krammer[1,2] · Elissa R. Price[3] · Maxine S. Jochelson[2] · Elizabeth Watson[2] · Melissa P. Murray[4] · Stefan O. Schoenberg[1] · Elizabeth A. Morris[2]

- 175 pts with re-excision for involved margins: 80% with residual disease
- **Conclusion:** MRI can accurately predict residual disease > 5 mm.

What happens if you accept focally involved margins ?

Results in the Netherlands:

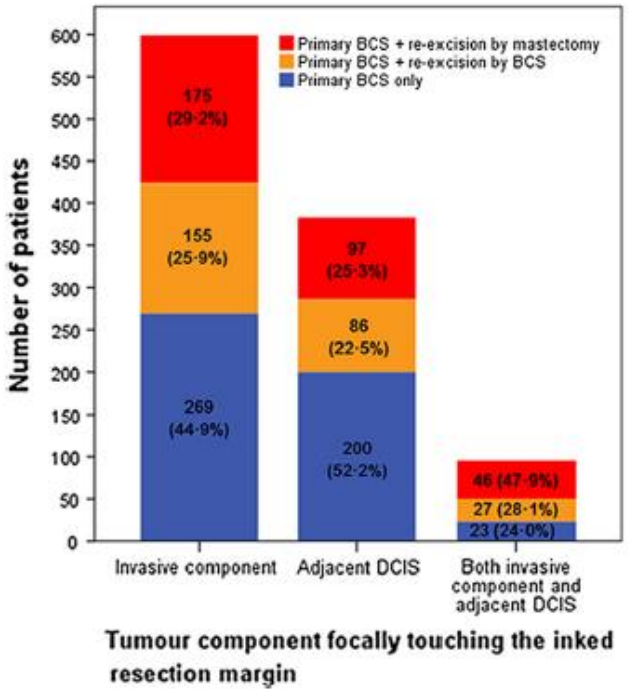


Fig. 2 Re-excisions according to the tumor component focally touching the inked margin. Figure only shows the patients with focally positive margins after primary BCS from the subcohort ($n = 1078$). Re-excision was omitted in 492 (45.6%) patients (total of *blue bars*) and was performed in 586 (54.4%) patients (total of *orange* and *red bars*). The frequency and type of re-excision is shown according to which component of the tumor was focally touching the inked margin

Vos et al, 2017

What happens if you accept focally involved margins ?

Results in the Netherlands:

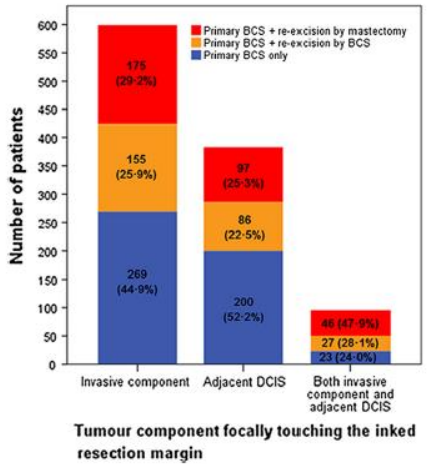


Fig. 2 Re-excisions according to the tumor component focally touching the inked margin. Figure only shows the patients with focally positive margins after primary BCS from the subcohort ($n = 1078$). Re-excision was omitted in 492 (45.6%) patients (total of *blue bars*) and was performed in 586 (54.4%) patients (total of *orange* and *red bars*). The frequency and type of re-excision is shown according to which component of the tumor was focally touching the inked margin

N = 1078 with focally involved margins

(out of 10.433 patients treated 2003-2008, and of whom resection margins were known (total treated 32.119 patients))

5 yr LR no re-excision + boost: 2.9%
5 yr LR with re-excision +/- boost : 1.1%

→ This difference is statistically significant, but clinical relevance doubtful, since:

→ No effect on 5 yr DFS and 5 and 10 yr OS

Vos et al, 2017

Conclusions (1)

Literature shows that:

- Margin width is related to *probability* that residual tumor is left in situ, but NOT to the *amount* of tumor left in situ !
- Higher boost dose results in lower LR, especially in case of LARGE VOLUME
- BCT with boost for focally involved margins yields acceptable LR of about 3% at 5 yrs

Conclusions (2)

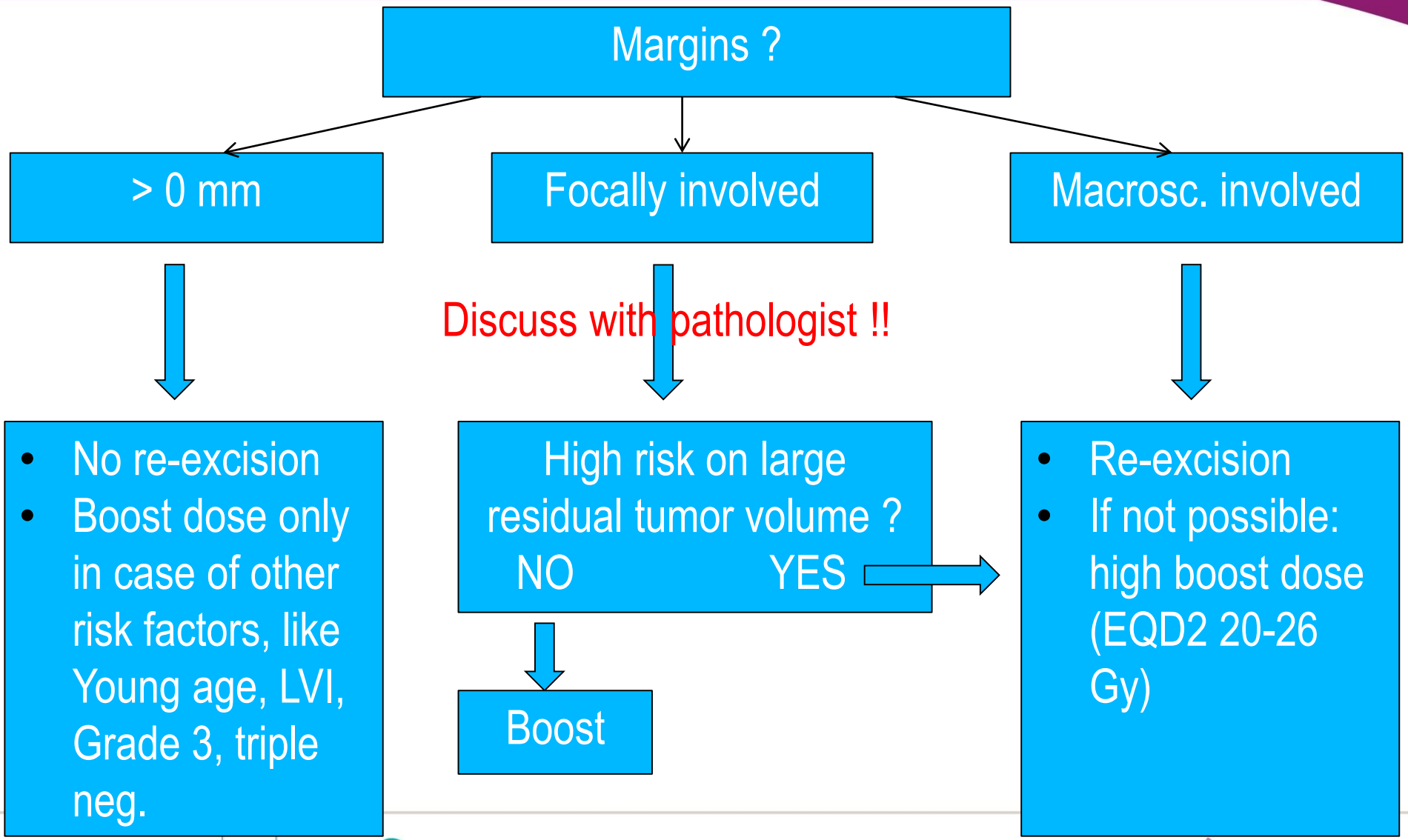
Thus:

- Since estimated risk on large volume residual disease is a more important risk factor for LR than probability on residual disease:

- High boost dose and / or re-excision: only if high risk on LARGE VOLUME residual disease

- Risk factors like Young Age, LVI, Grade, TN, seem to be associated with larger residual VOLUMES, and require a boost.

Conclusions (2)



Questions ?

What if we apply SSO guidelines to a retrospective cohort ?

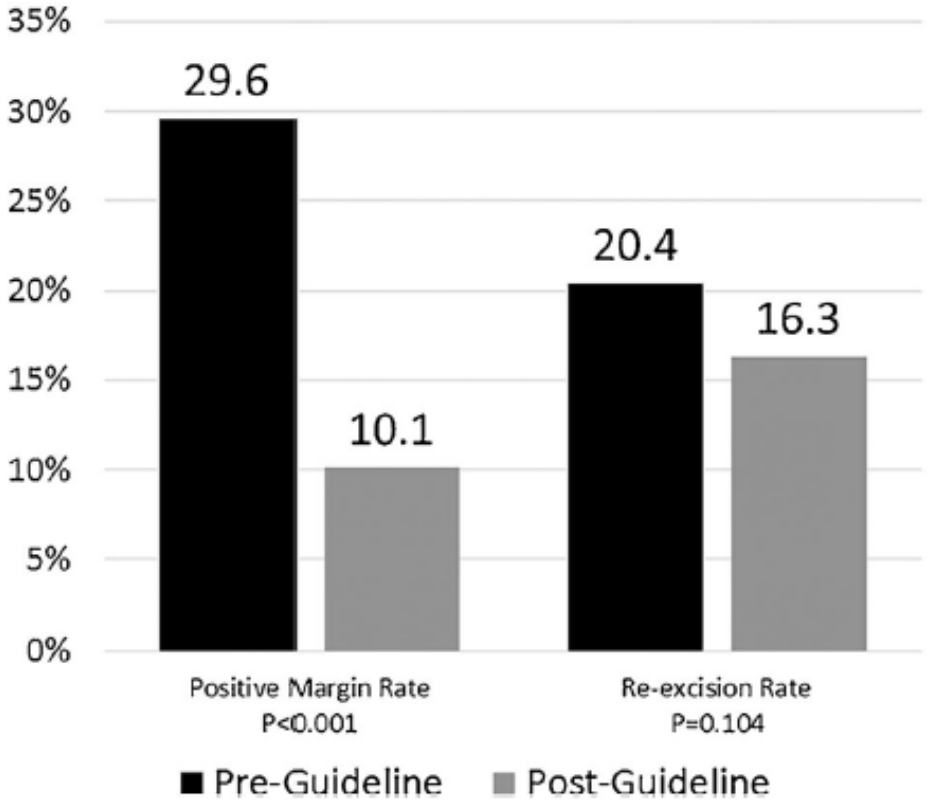


FIGURE 1 Positive margin and re-excision rates

Less “positive margins”, and less re-excisions, with same LR 1.2 vs 1.5%, short follow-up !!

Patten et al 2017

What happens if you accept focally involved margins ?

Results in The Netherlands:

Margin involvement in 2009:

Table 2 Surgical margin status after initial BCS for 7,345 breast cancer patients

	DCIS		Invasive (±DCIS)		Total	
	n	%	*n*	%	*n*	%
Clear margins	641	67.8	5,075	79.3	5,716	77.8
Focally positive margins	108	11.4	591	9.2	699	9.5
More than focally positive margins	147	15.6	584	9.1	731	10.0
Unknown or inconclusive	49	5.2	150	2.4	199	2.7

Van der Heiden et al, Br C Res Tr 2012

5 yr IBTR in NL (2003-2006) : only 2.38% (2.18-2.60%) !!

N = 22.450

Van der Heiden et al, Ann Oncol 2015

What happens if you accept focally involved margins ?

Results in the Netherlands:

- Dutch Cancer Registry, 2003-2006: N = 22.450
- Boost only given if Risk Factors like G3, LVI, Age < 50 yr, or *Focally involved margins*
- 5 yr IBTR : 2.38% (2.18-2.60%)

Van der Heiden et al, Ann Oncol 2015

- NKI/AVL, 1980-2008 : N = 8485
- 5 yr IBTR: 2% (if < 40 yr: 4%)
- 10 yr IBTR: 5% (if < 40 yr: 9%)

Bosma et al, Br C Res Tr 2016

Boost and APBI - delineation

Liesbeth Boersma, radiation oncologist

MAASTRO Clinic/ University Hospital Maastricht, The Netherlands

ESTRO Teaching Course on Breast Cancer, Dublin, September 2017

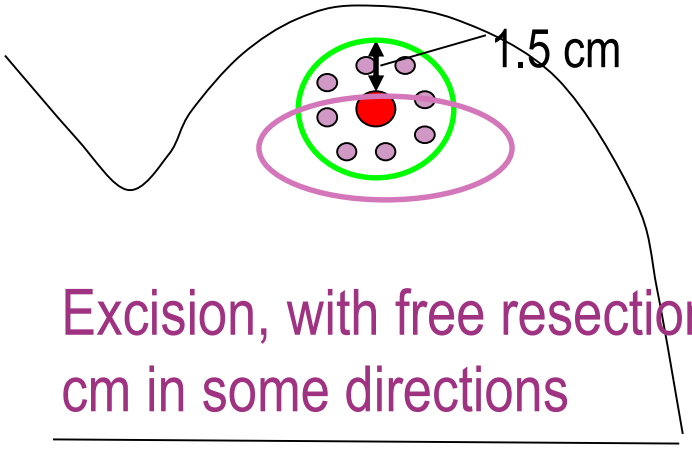
Theoretical concept of the Clinical Target Volume for the boost

- CTV for the boost:
  - The rim of breast tissue – that has been localized < 1.5 - 2 cm around the primary tumor.
  - Margin of 1.5 - 2 cm is debatable – e.g.< 3.0 cm in case of PBI (Kirby et al, R&O 2010).

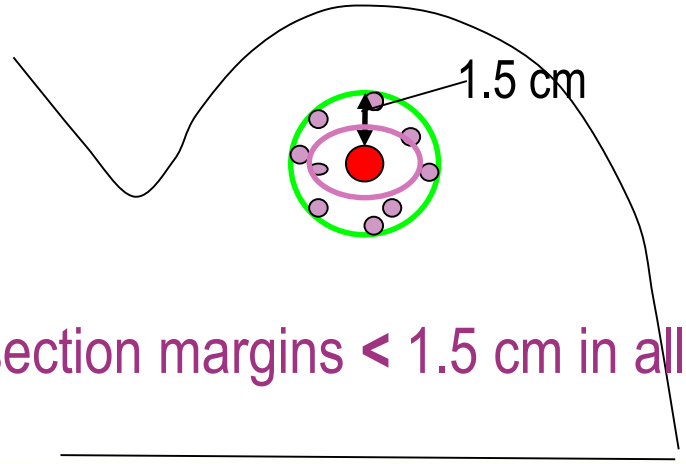
- Delineation is dependent on the post-op situation; 3 post-operative situations can be recognized:
  - Clear seroma cavity present
  - No seroma cavity present
  - Partial seroma cavity present

Pre-operative situation

- Tumor
- Micr. extension
- Region with microscopic extension, within 1.5 cm of primary tumor
- Rim of excision



Excision, with free resections margins **>** 1.5 cm in some directions

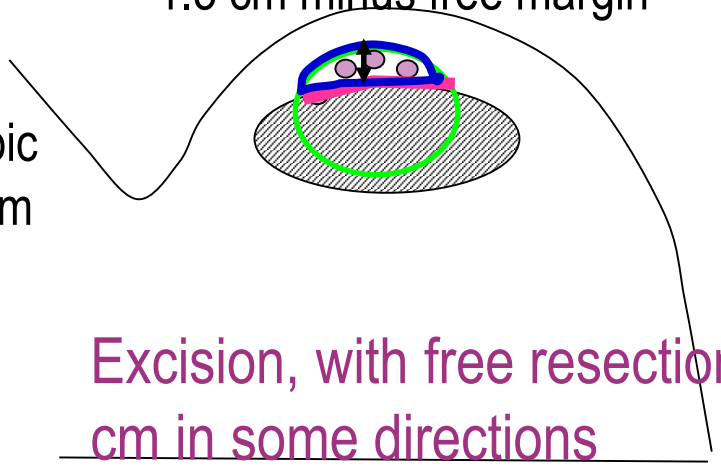


Excision, with free resection margins **<** 1.5 cm in all directions

1. Post-op situation: complete seroma cavity present

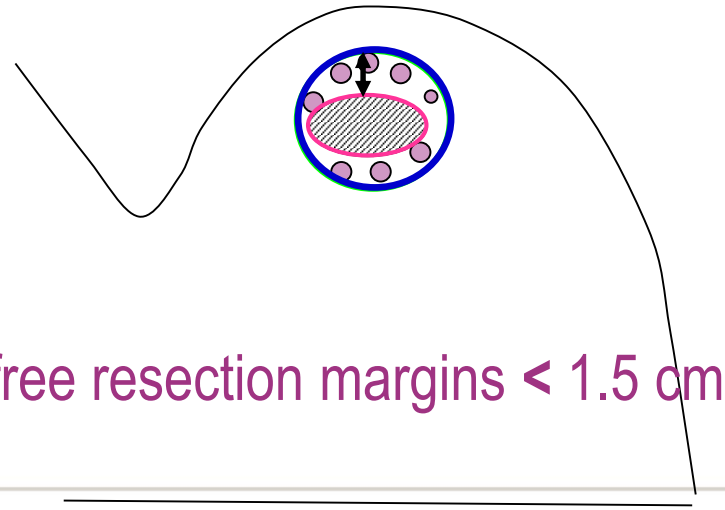
- Tumor
- Micr. extension
- Region with microscopic extension, within 1.5 cm of primary tumor
- Rim of excision
- Seroma cavity
- $Tumorbed_{cav}$: That part of the rim of the seroma cavity where the resection margin is < 1.5 cm
- CTV

1.5 cm minus free margin



Excision, with free resections margins **>** 1.5 cm in some directions

1.5 cm minus free margin



Excision, with free resection margins **<** 1.5 cm in all directions

Boersma et al, 2012

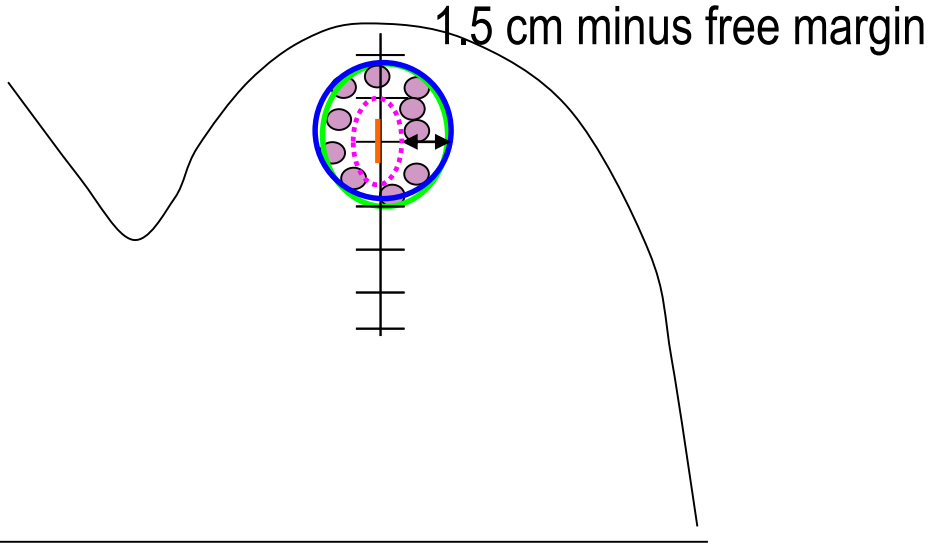
2. Post-op situation: no seroma cavity present

- Micr. extension

Region with microscopic extension, within 1.5 cm of primary tumor

Internal surgical scar

Tumorbed after closure of lump cavity

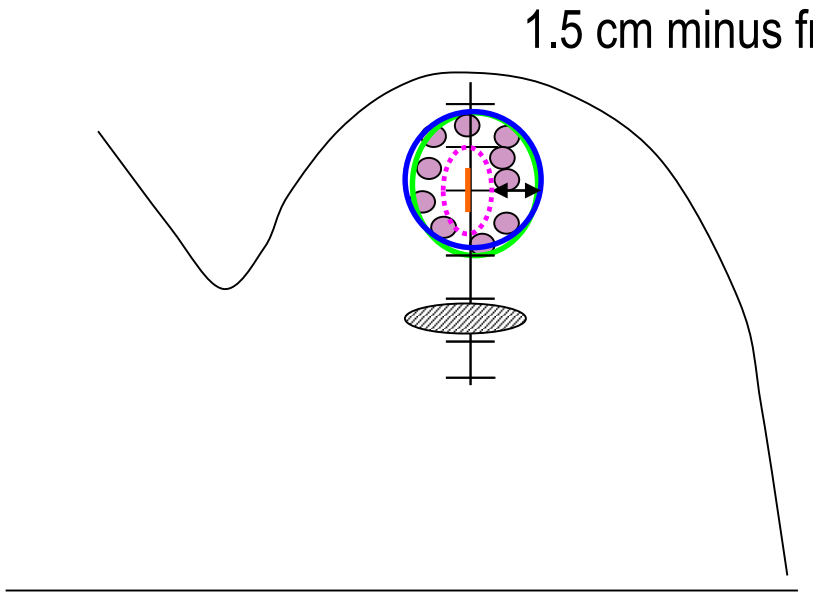


Region estimated to encompass the tumorbed

CTV

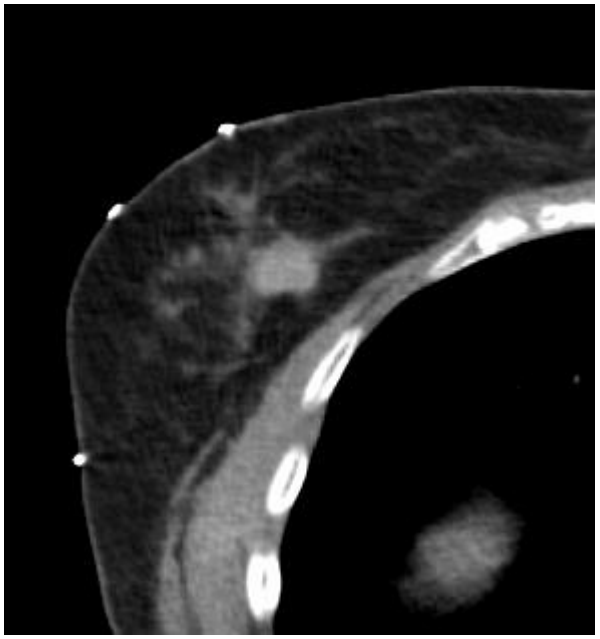
3. Post-op situation: partial seroma cavity present

- Micr. extension
- Region with microscopic extension, within 1.5 cm of primary tumor
- Internal surgical scar
- Partial seroma cavity
- Tumorbed after closure of lump cavity
- Region expected to encompass the tumorbed
- CTV



Example ....

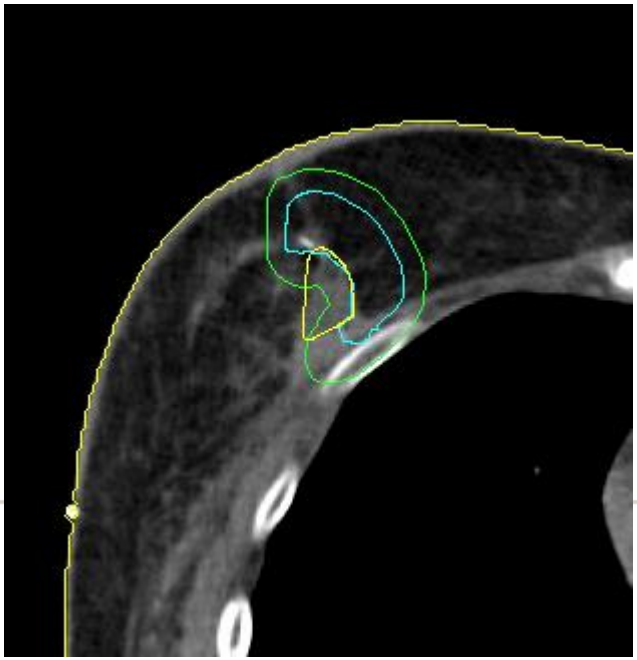
Pre-operative imaging



Tumorbed

CTV

PTV



•Minimal free margin = 2 mm;

•CTV margin 1.3 cm

•Free margins > 1.5 cm in all directions, except in medial direction, free margin 2 mm.

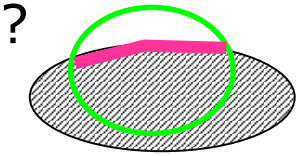
•CTV margin 1.3 cm medial

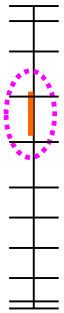
MAASTRO CLINIC

ESTRO School

Key-question:

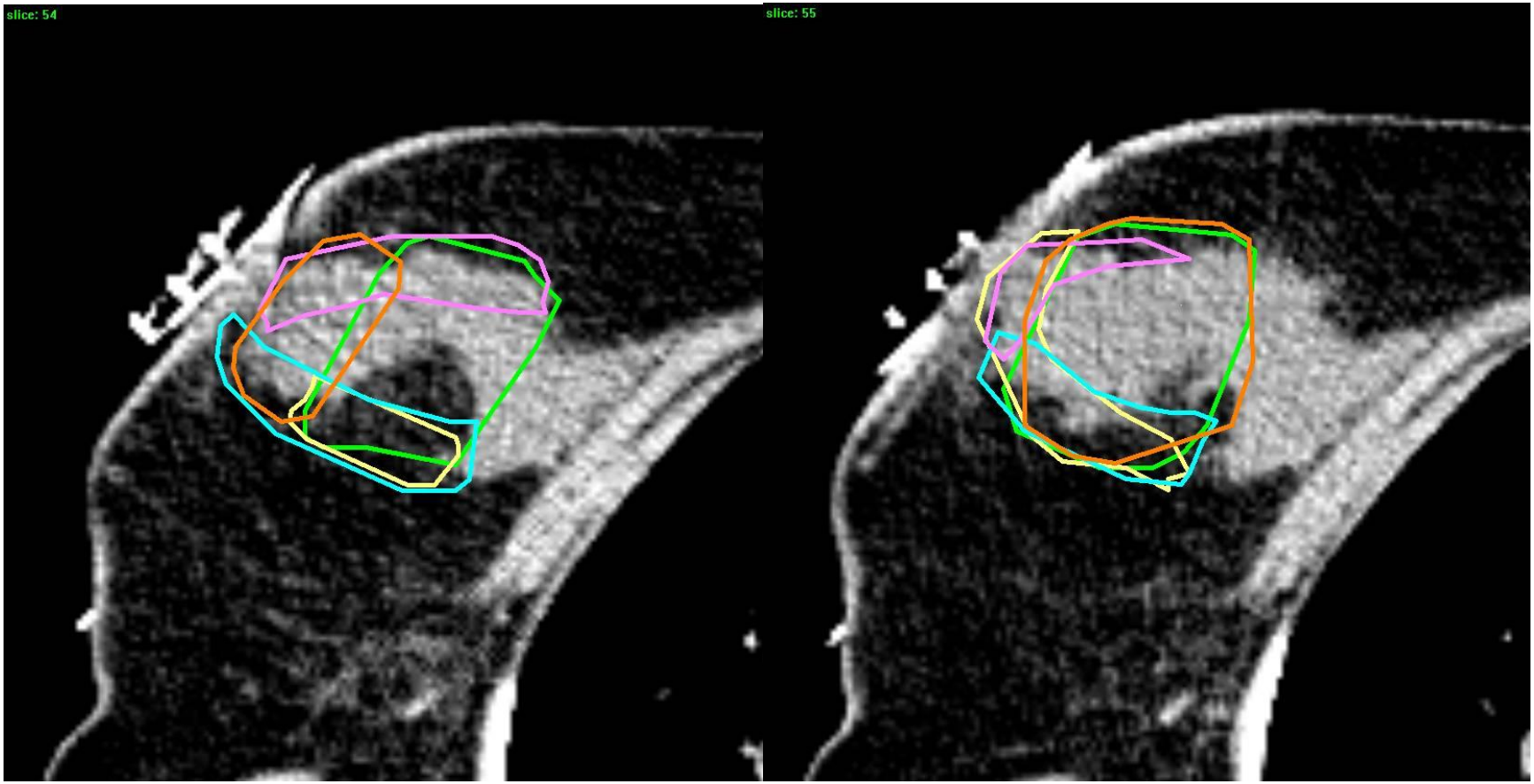
How to find this tumorbed or "the rim of the excision cavity with a resection margin < 1.5 cm" on a plannings CT?





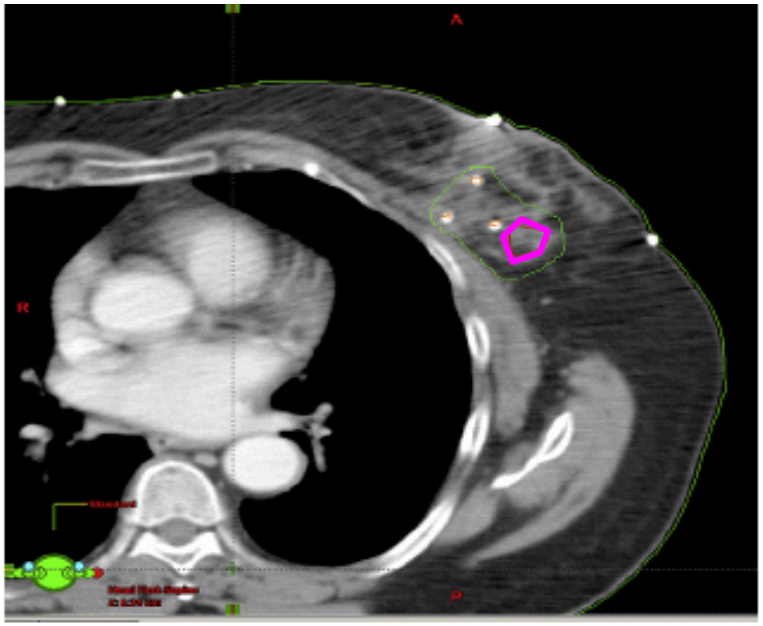
- Use of pre-operative information:
  - Physical examination, Mammography, MRI
  - MRI/CT/ultrasound in treatment position ?
- Use of post-operative information:
  - Imaging: Clips, density data on CT, MRI, ultrasound
  - Surgical report
  - Knowledge on the 3D distribution of free margins

Difficult interpretation of resection margins in 3 D, especially in case of seroma AND ≥ 1 margin > 15



Boersma et al, Radiother Oncol 2012

Use of a pre-operative (contrast-enhanced ?) CT in RT position

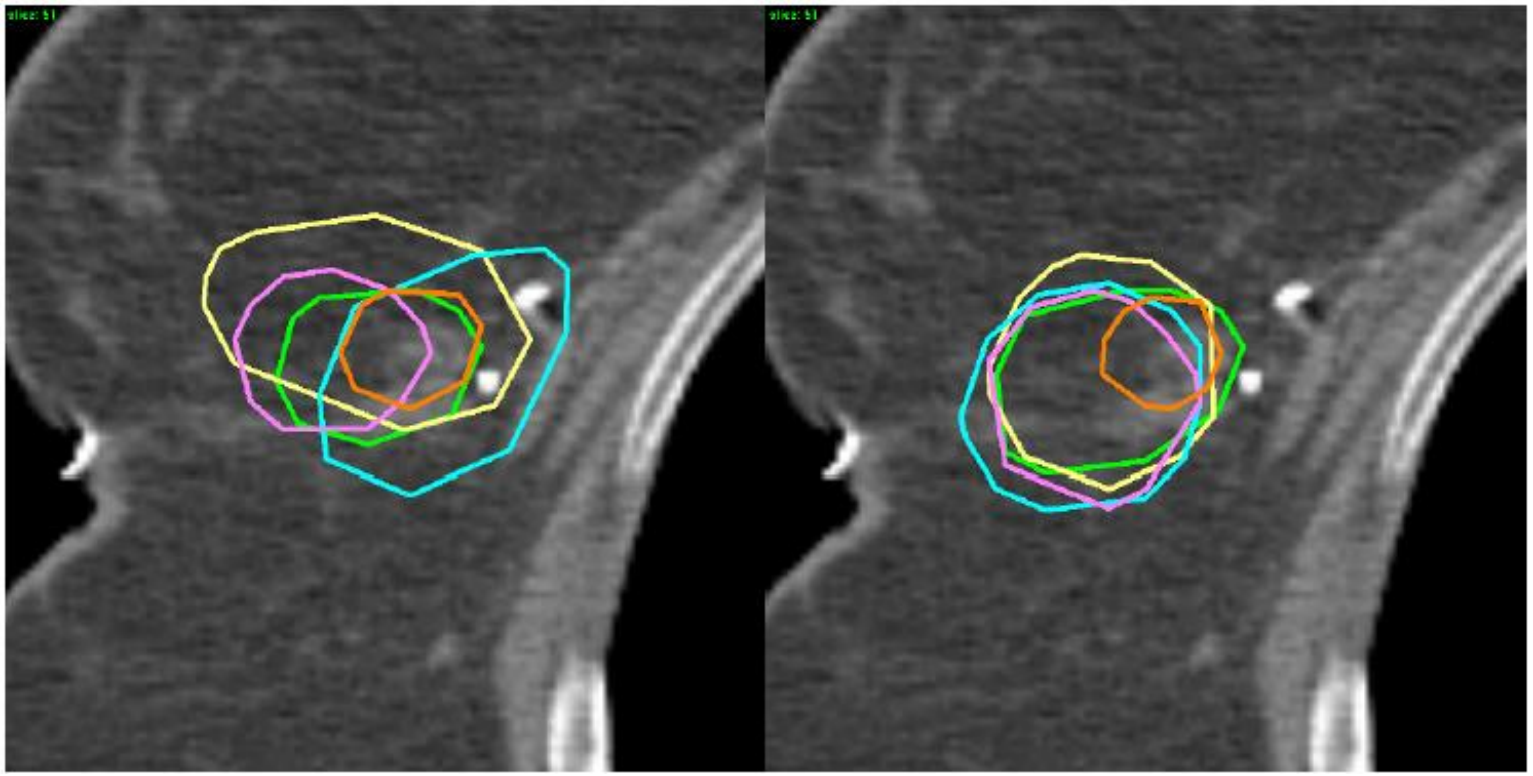


Kirova et al, IJRBOP 2008

— Gross Tumor Volume prior to surgery

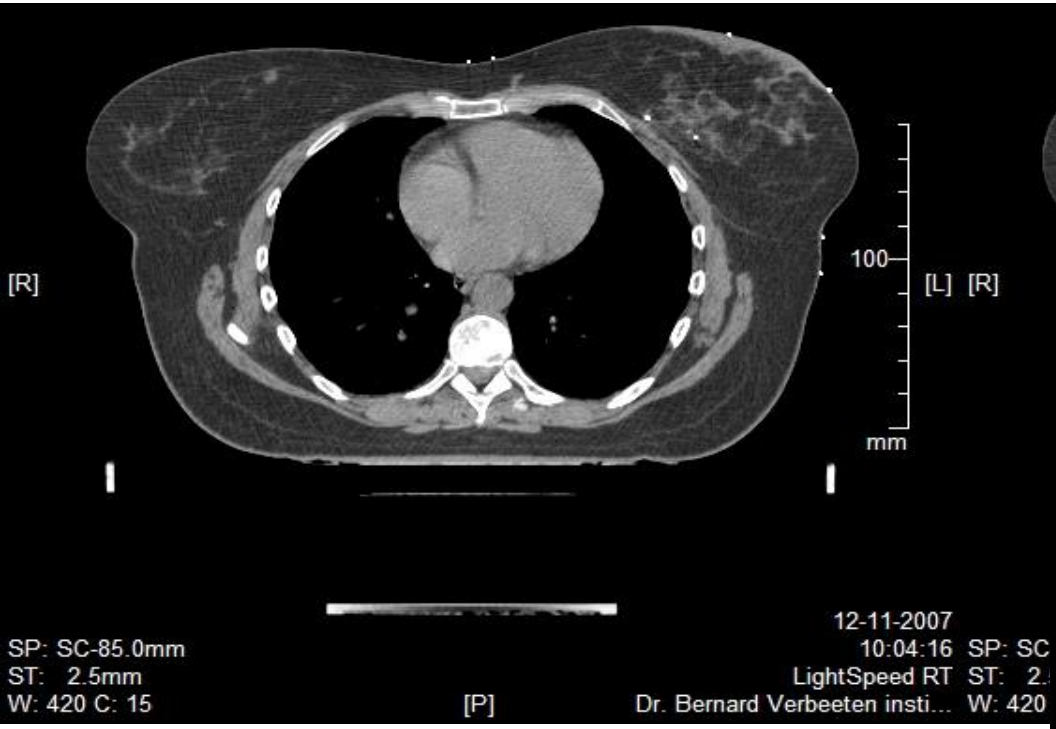
Preliminary results delineation study+/- pre-op CT
N = 26, 5 observers

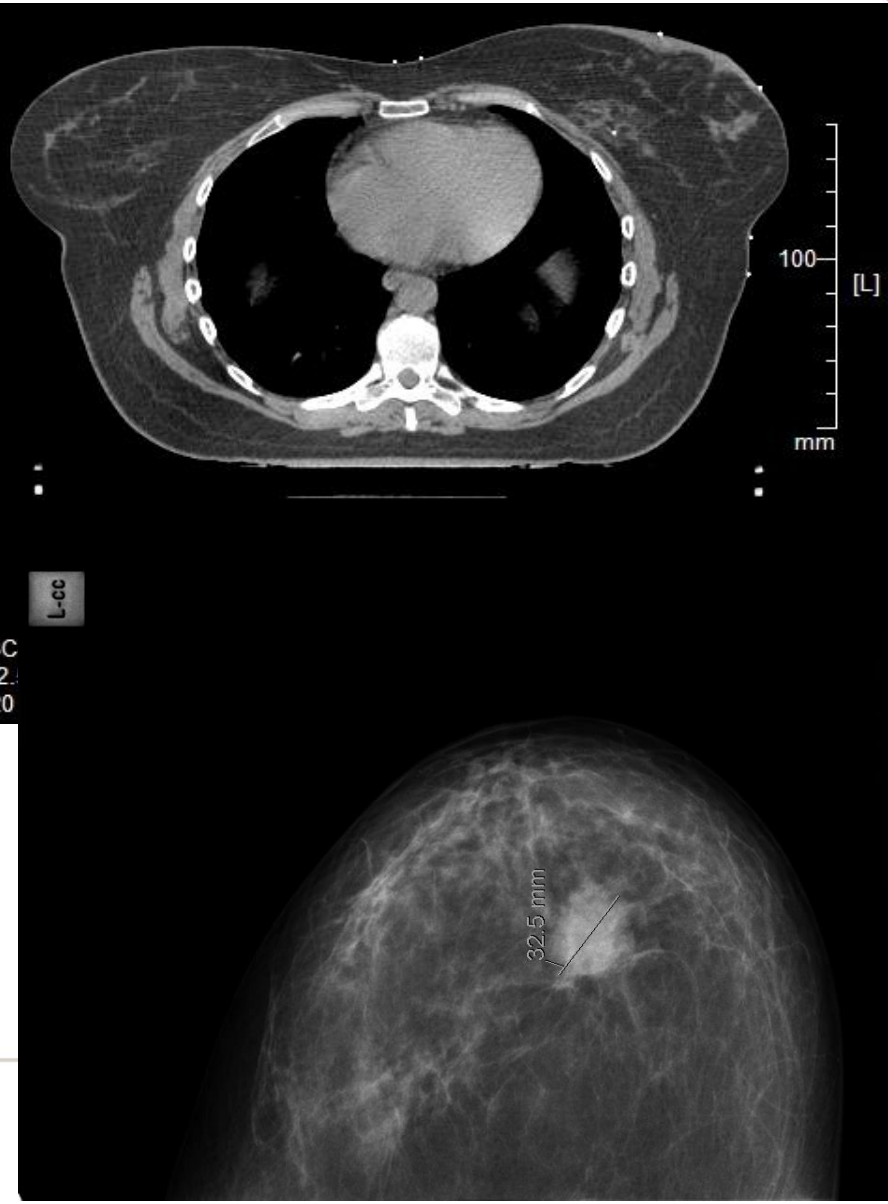
Use of a pre-op CT in RT position for delineation of the boost CTV, yields significant smaller interobserver variation, and smaller boost volume. However, the effects are rather modest.



Boersma et al, Radiother Oncol 2012

Localization of the boost: are clips reliable ?





Slide courtesy Ph. Poortmans

MAASTRO CLINIC

Placement of clips using a strict protocol

UK-protocol:

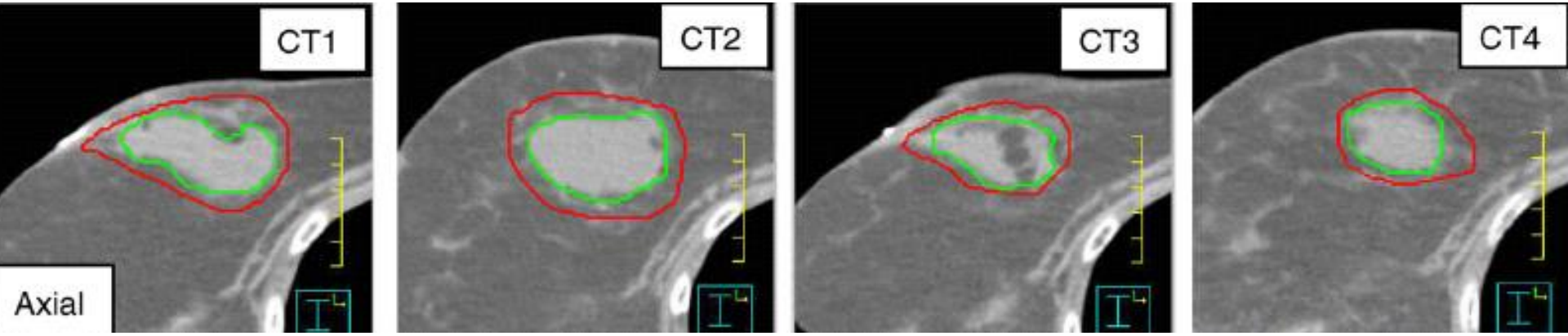
6 x 2 clips

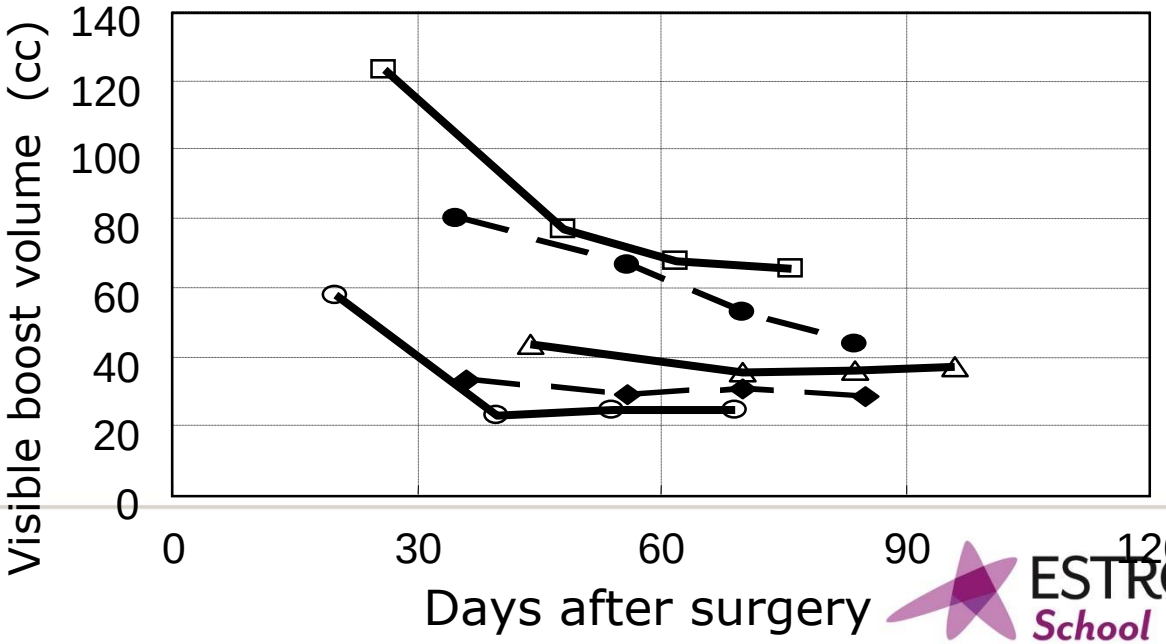
At 4 points: medial, lateral, superior & inferior, at the level of the tumor.

In the center of the deep margin, usually at the fascia, and superficially, beneath the skin.

Coles et al, EJSO 2008

Shape and size of the cavity change with time after surgery





Hurkmans et al, R&0 2008

How to deal with a changing excision cavity ?

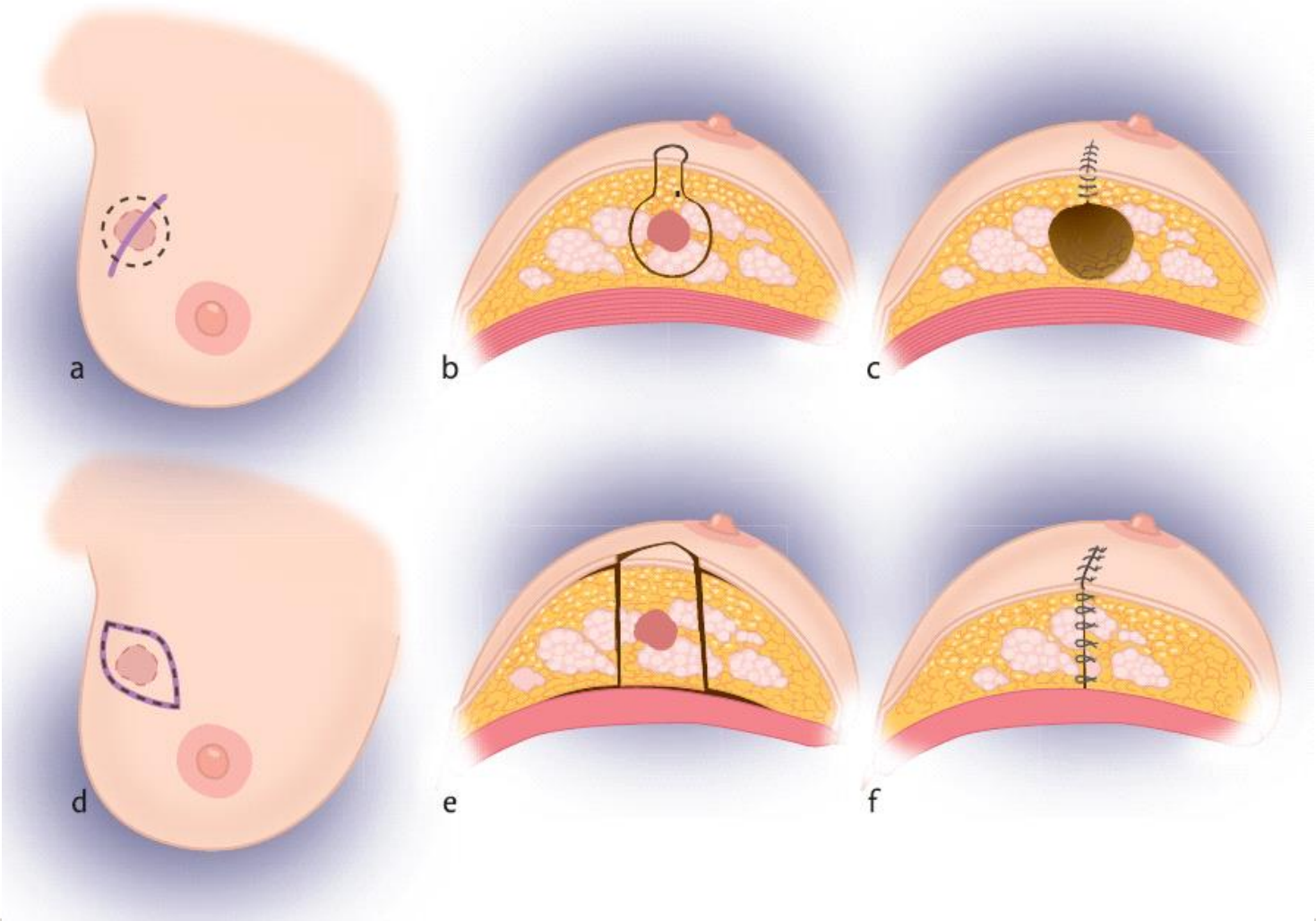
- Make planning CT > or < 8 weeks ?

- MRI data suggest that seromas do no shrink entirely; Instead, new tissue may be laid down in concentric rings.

From Whipp & Halliwell, IJROBP 2008

- Ask surgeon to adapt surgical technique, to avoid presence of excision cavity ?

Oncoplastic surgery



Menke et al, NTVG 2007

GEC-ESTRO guidelines for PBI/ boost in case of multicatether brachytherapy: five steps

1. Detailed knowledge on:
   - Preoperative imaging (mammography and/or MRI and/or ultrasound);
   - Surgical procedure: number of clips/ how placed ?
   - Free margins in 6 directions
2. Tumor localization before BCS, translation into CT planning scan
3. Calculation safety margins for the CTV in all 6 directions.
4. Definition of the CTV and PTV
5. Delineation of the CTV and PTV

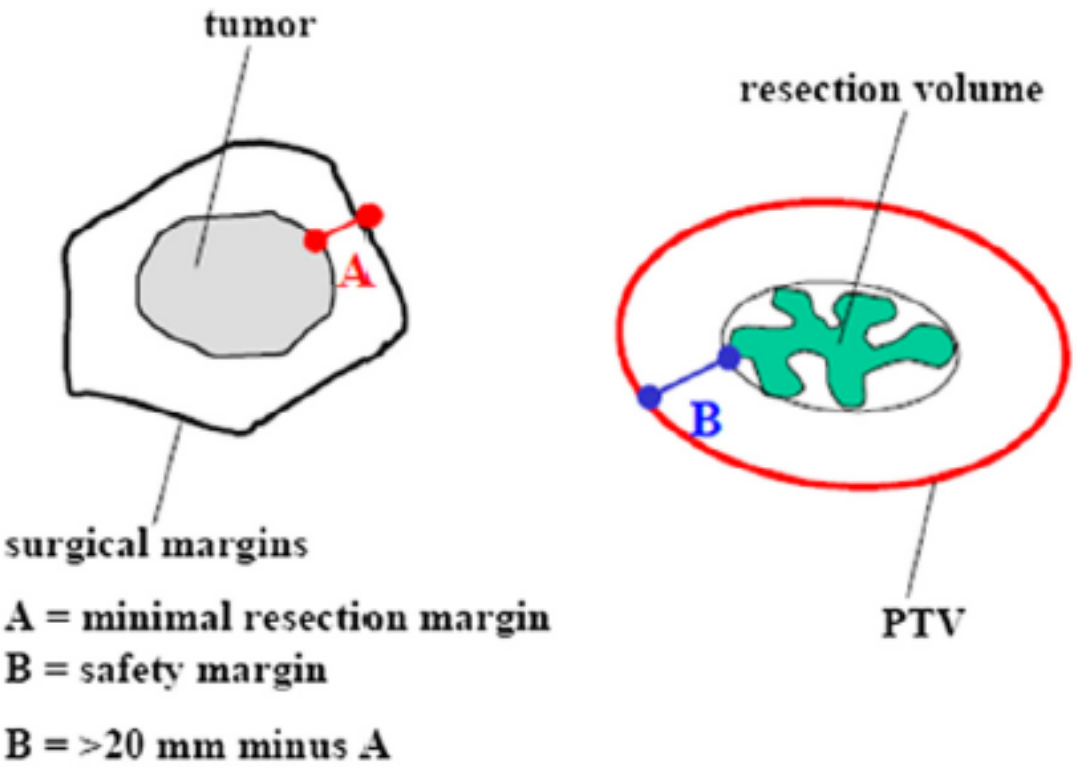


Fig. 2. Schedule of estimation of safety margins.

Aim for size of CTV between 50-250 cc:

CTV < 50 cc: large risk on geograohical miss

CTV > 200- 250 cc: large risk on complications

Strnad et al, 2015

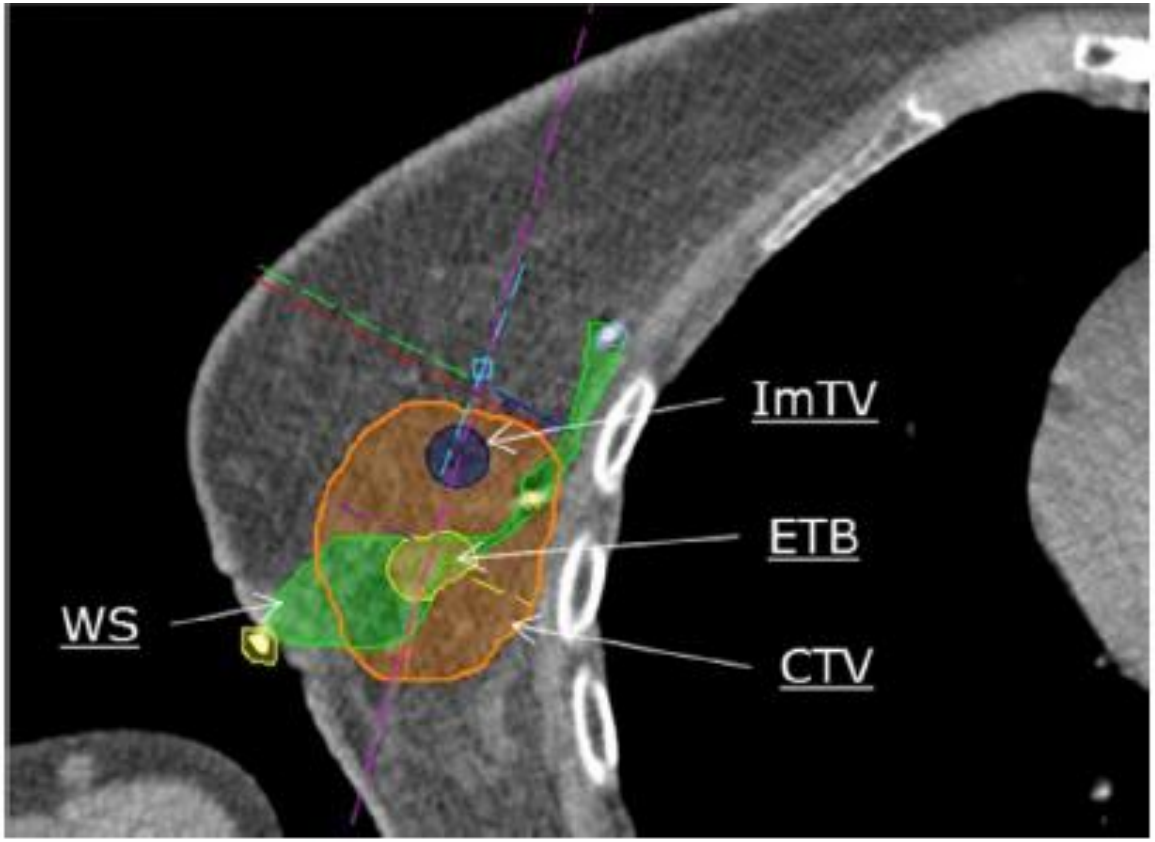


Fig. 4. Clinical Target Volume (CTV).

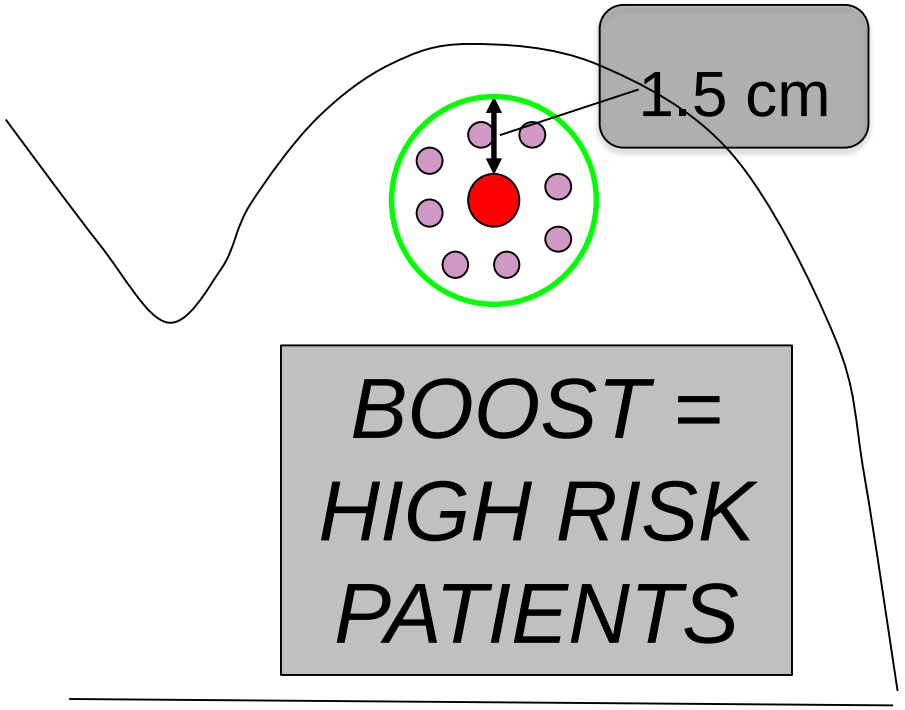
WS: Whole Scar

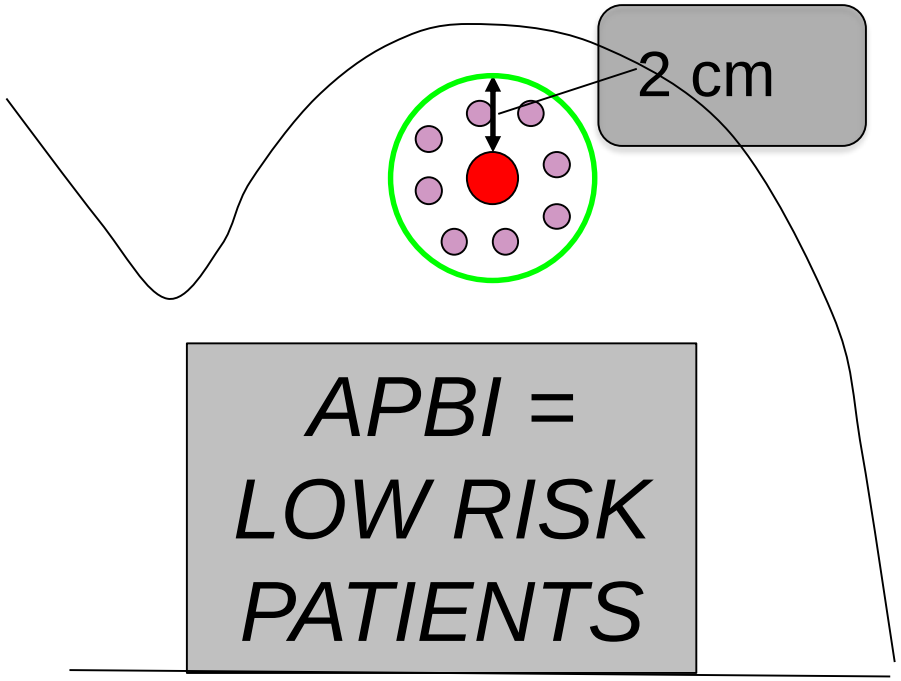
ImTV: Imaging related target volume

ETB: Estimated Tumorbed

CTV = ETB + 20 mm minus resection margin, but al teast 10 mm

Summary CTV boost and CTV PBI





Questions ?

The homework case: case 1 - APBI

- 52 years; 62 kg/168 cm, with a screen detected lesion, upper-inner quadrant of right breast
- Pathology: IDC

- Surgical report of lump with SN:

- Tumour marked with iodine seed, incision just outside areola from 10h30 – 01h30;
- Mobilising of skin in all directions;
- Marking of lumpectomy cavity with clips;
- Mobilising glandular tissue above pectoral fascia; closure of cavity and skin

The homework case: case 1 - APBI

Pathology report:

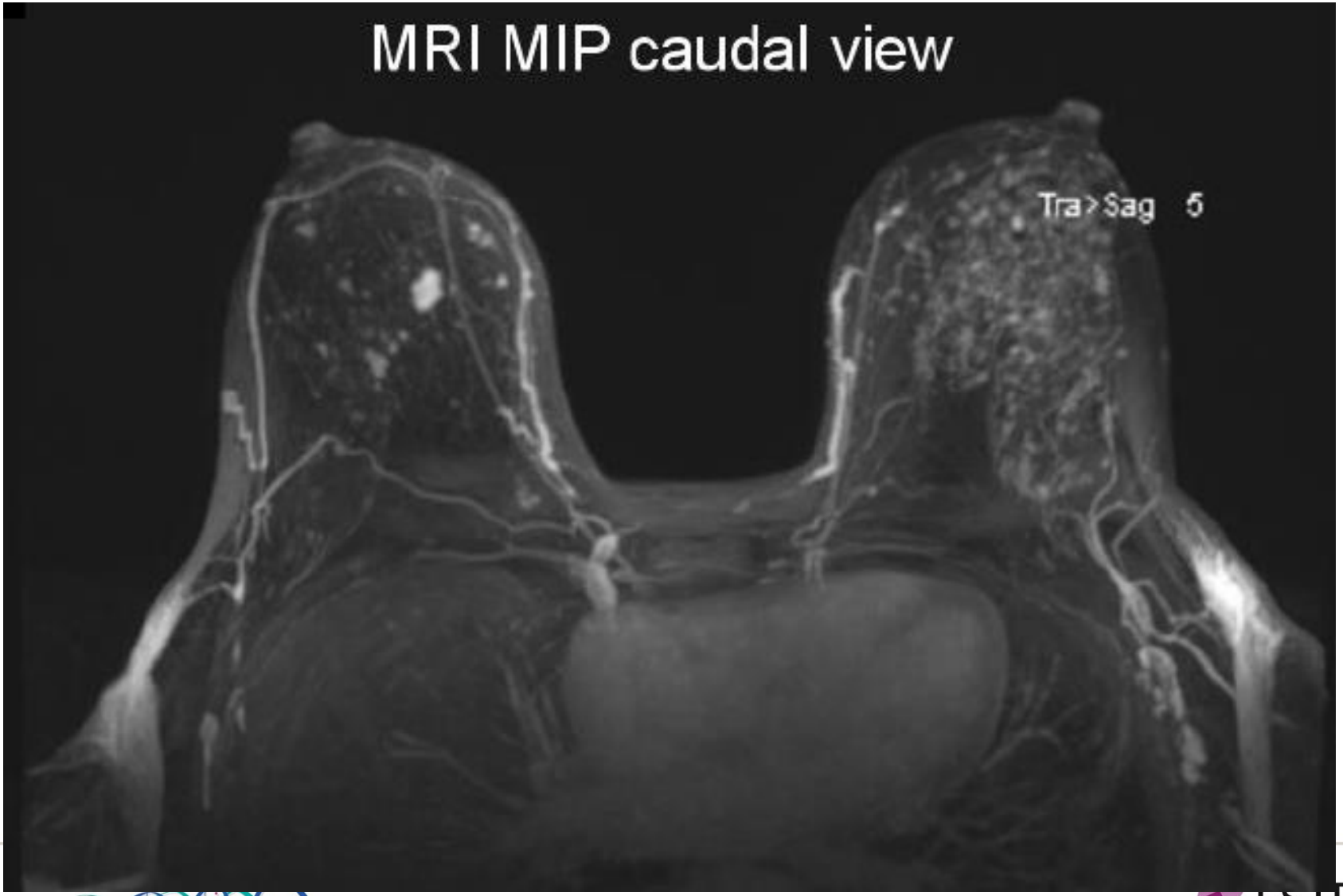
- pT1bG1N0(SN 0/1)M0; ER ++; PR ++; Her-2-Neu -

- Tumour-free margins:
- cranial = 0.6 cm
- caudal = 1.5 cm
- medial = 1.2 cm
- lateral = 0.8 cm
- anterior/ventral/skin = 0.4 cm
- posterior/dorsal/pectoral = 0.4 cm

Treatment:

- No adjuvant systemic treatment.
- Participates in IRMA trial (® WBI vs EB-APBI): randomised for APBI.

The homework case: case 1 - APBI



Smaller volumes: boost and APBI

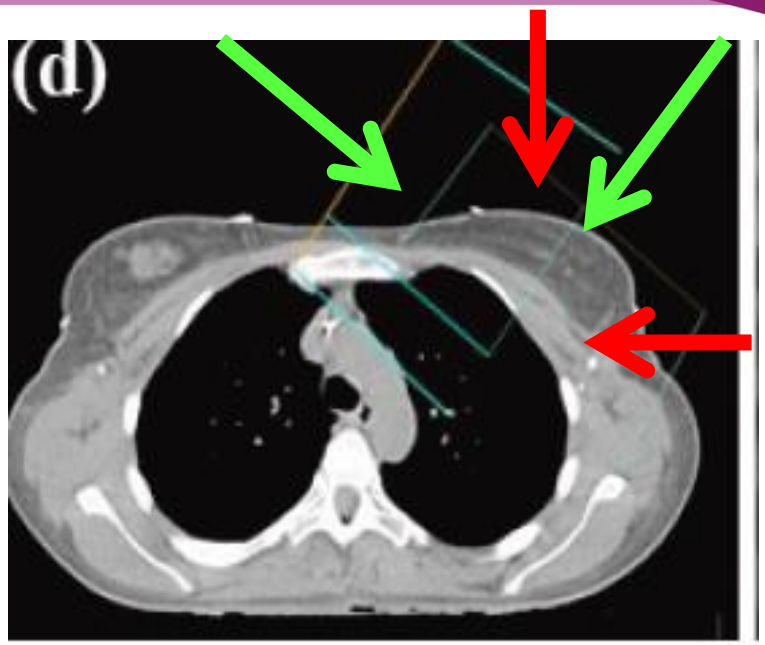
Marianne Aznar

The Christie/University of Manchester

University of Oxford

Rigshospitalet, Denmark

ESTRO School



And how can we do this ???? With image guidance !

IMAGE GUIDANCE:

WHICH MODALITY?
HOW OFTEN
WHICH STRUCTURE?

Availability of IGRT to day

ESTRO-HERO survey

Radiotherapy equipment and departments in the European countries: Final results from the ESTRO-HERO survey

Cai Grau [a,*], Noémie Defourny [b], Julian Malicki [c], Peter Dunscombe [d], Josep M. Borras [e], Mary Coffey [f], Ben Slotman [g], Marta Bogusz [h], Chiara Gasparotto [b], Yolande Lievens [i], on behalf of the HERO consortium [1]

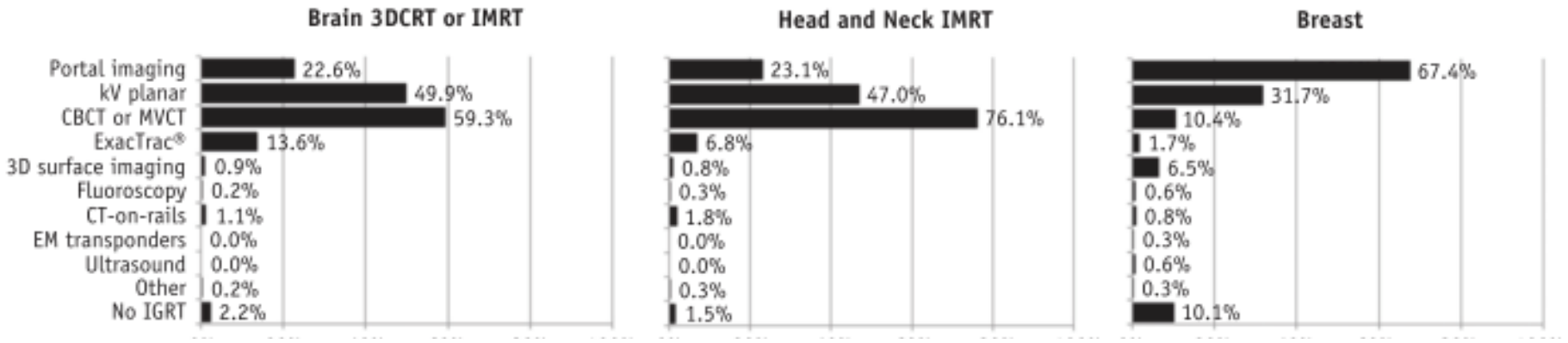
[a] *Aarhus University Hospital, Denmark;* [b] *European Society for Radiotherapy and Oncology, Brussels, Belgium;* [c] *University of Medical Sciences, Greater Poland Cancer Center, Poznan, Poland;* [d] *University of Calgary, Canada;* [e] *University of Barcelona, Spain;* [f] *Trinity College Dublin, Ireland;* [g] *VU Medical Center, Amsterdam, The Netherlands;* [h] *Cancer Diagnosis and Treatment Center, Katowice, Poland;* [i] *Ghent University Hospital, Belgium*

69% of MV machines equipped for IMRT
49% equipped for IGRT

R&O 2014

ESTRO School

IGRT: patterns of practice in the US

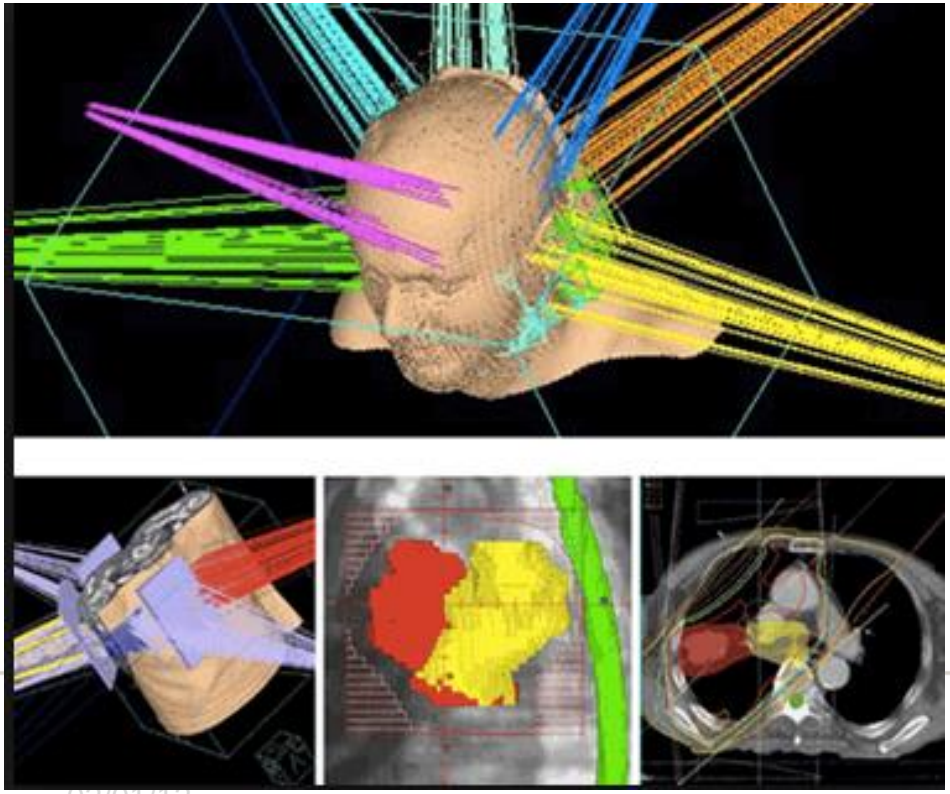


Lung, oesophagus, anus, prostate: same patterns

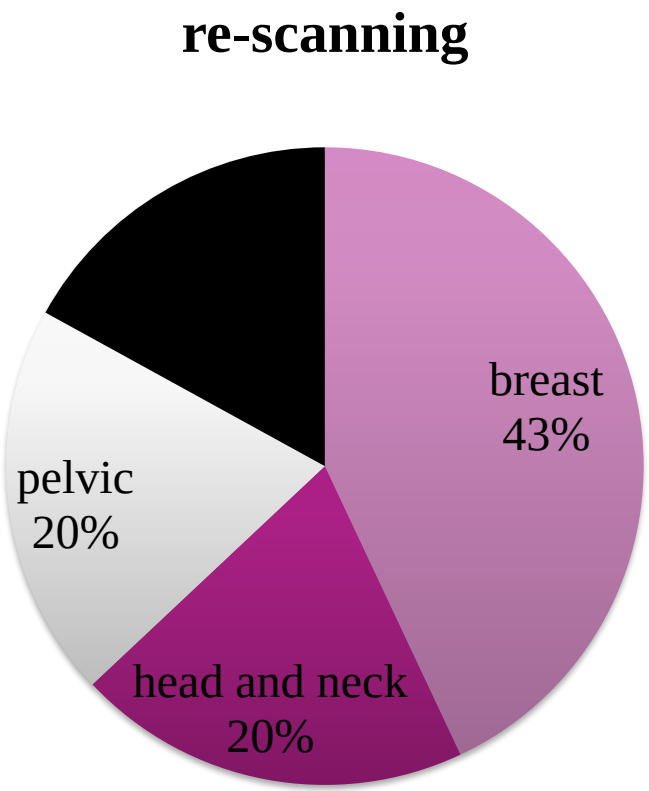
Nabavizadeh et al IJROBP 2016

ESTRO School

Technology party !!!



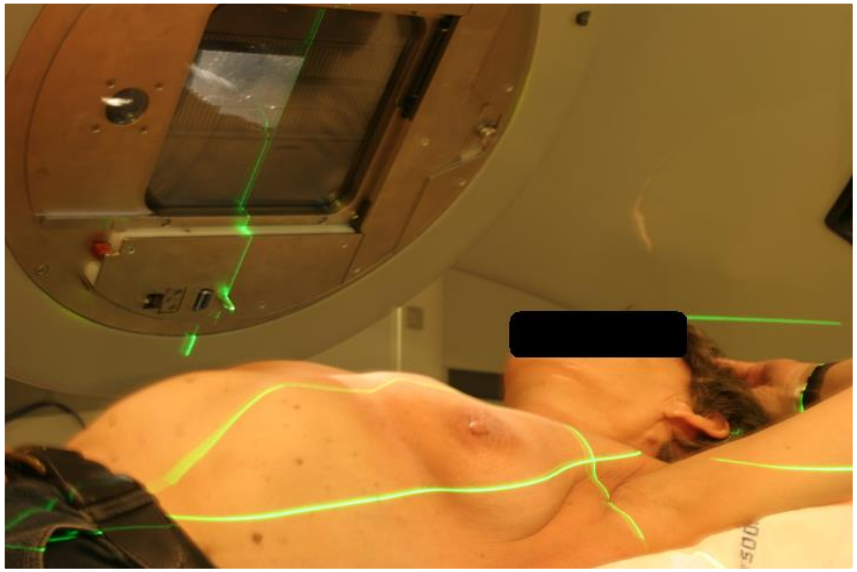
How important is it ?

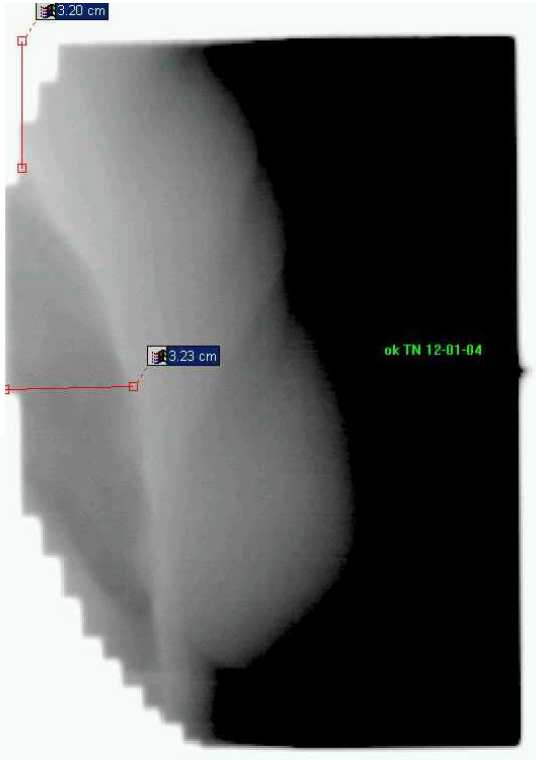


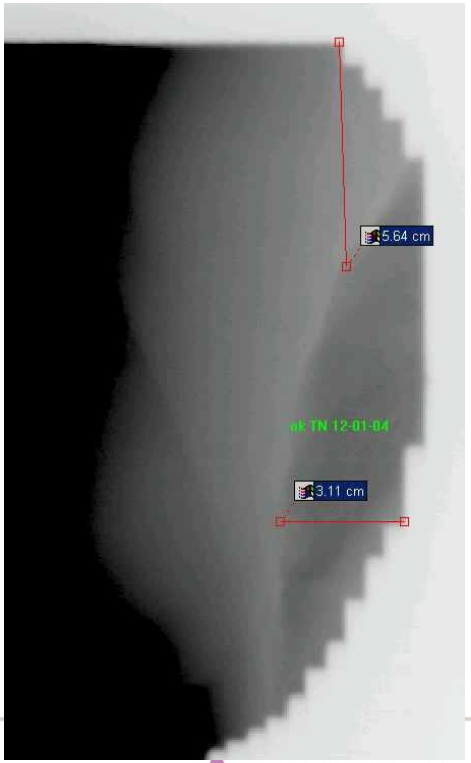
Data courtesy of Rob Chuter, the Christie

WHOLE BREAST/ CHEST WALL

Field light / Beam's-eye-view (portal) images, MV



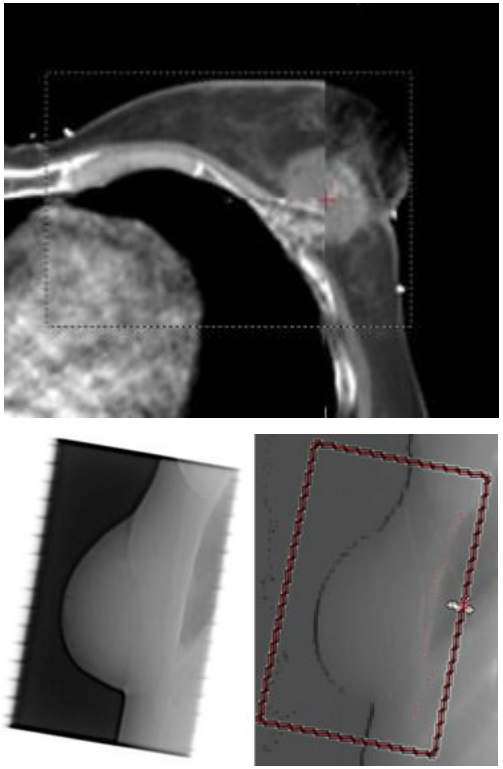




- Check the CLD
- long or vert ?
- Only one "direction"

ESTRO School

Image-guidance for whole breast (+/- nodes)

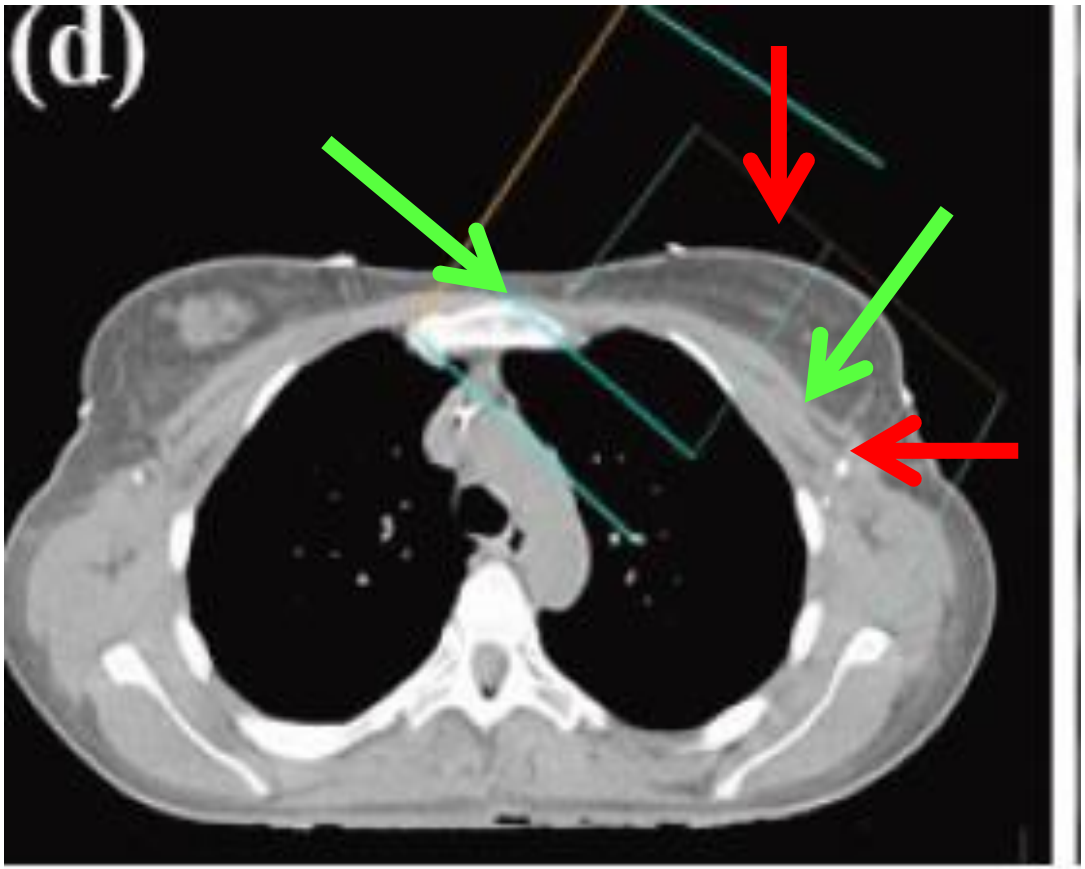


Topolnjak IJROBP 2010

- EPID field images (i.e. not orthogonal) underestimate bony set-up errors by 20% to 50%
- Difference probably insignificant for tangential whole breast irradiation
- Loco-regional treatment or more advanced techniques (SIB? IMRT?) could benefit from a more accurate set up.

ESTRO School

Image-guidance for chest wall or whole breast



Solution: use orthogonal images

- AP-lat
- tangential +orthogonal
- kV-MV
- kV-kV

Petillion et al JACMP 2015 :
Tangential kV-kV (green) superior to AP-lat kV-MV (red)

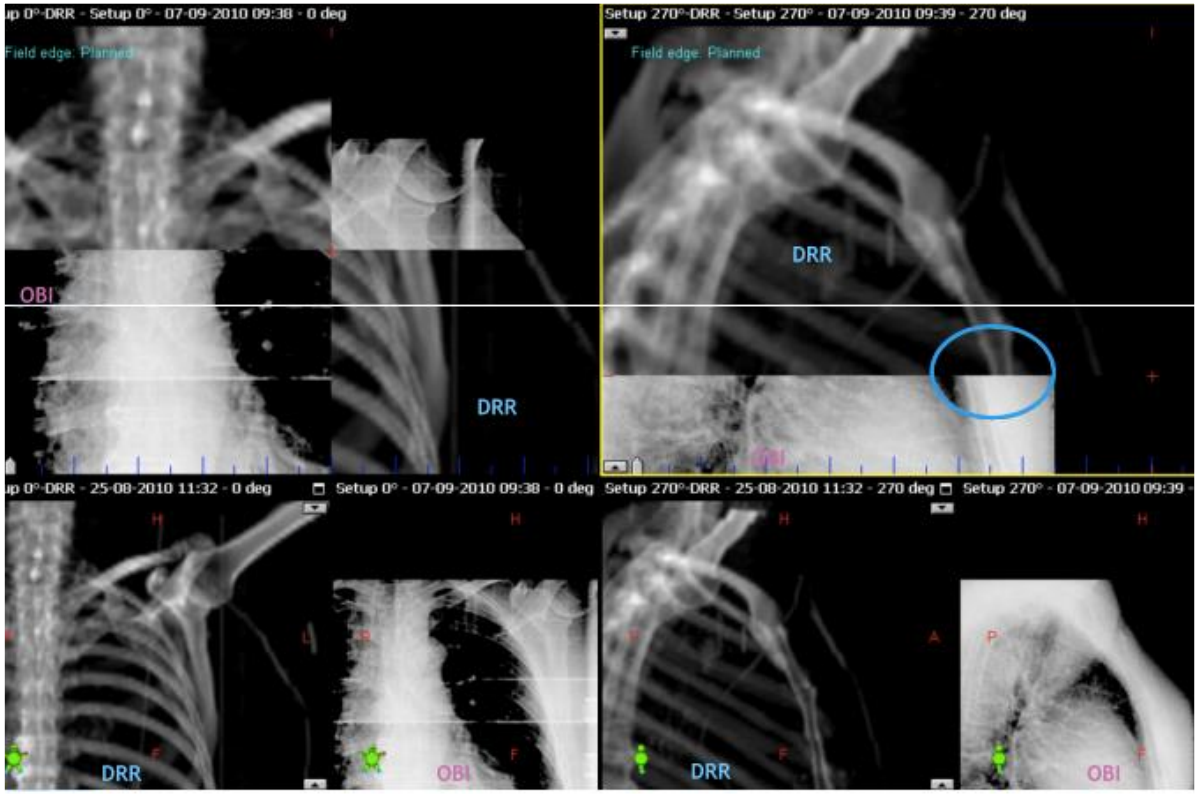
ESTRO School

kV versus MV

EPID (MV) images: low constrat

- Planar kV images: better image quality

Orthogonal images: registration

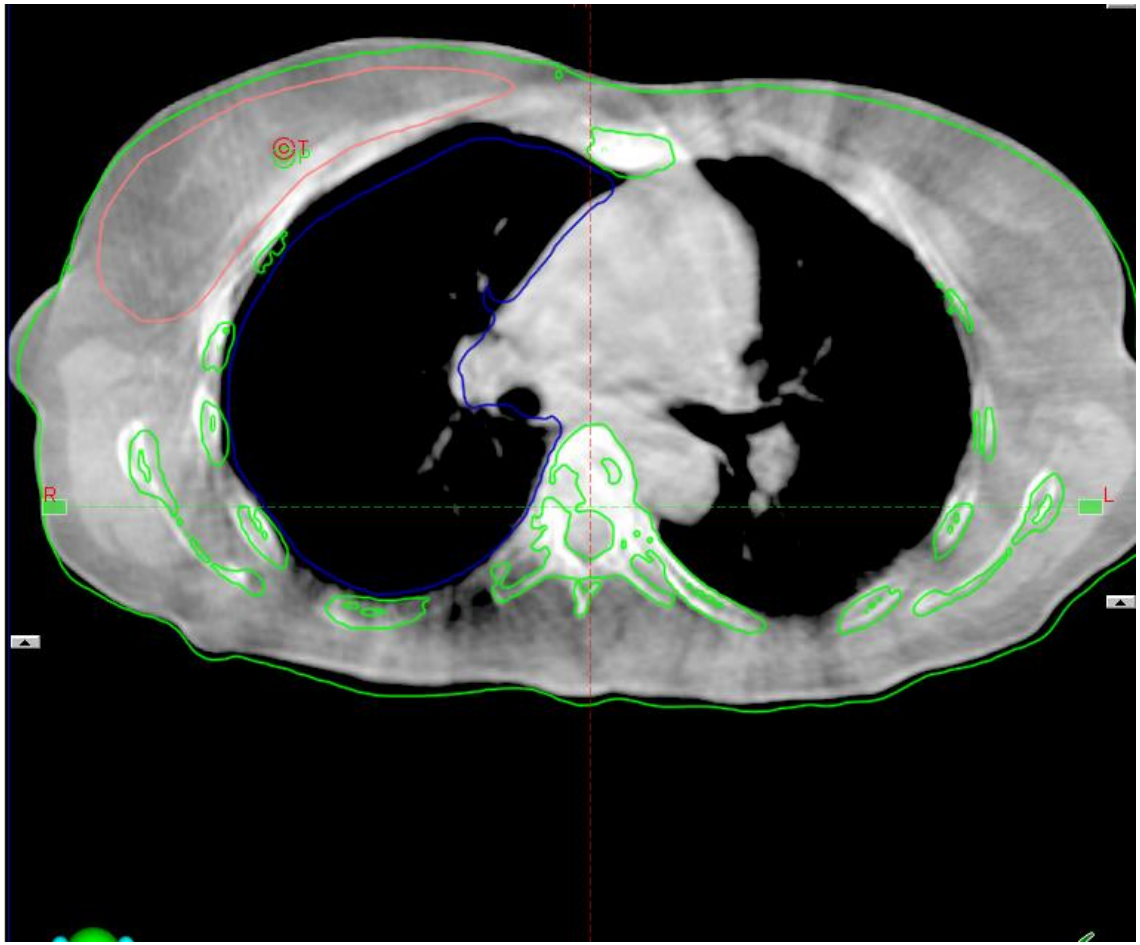


Verify:

- sternum/ribs
- spinal cord
- clips (if visible)

- Skin contour (for swelling, not positioning)

Other possible improvements

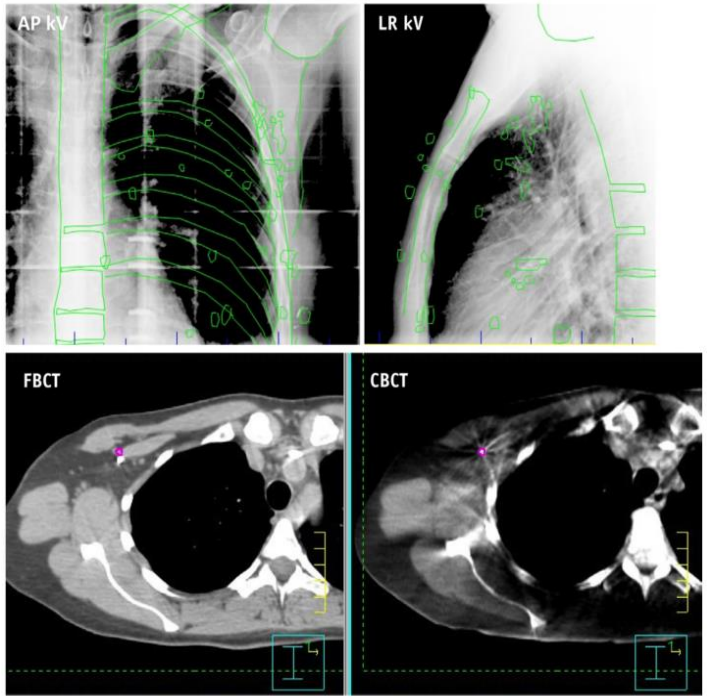


CBCT images (3D information)

ESTRO School

Image-guidance for whole breast/CW (+/- nodes)

Highly conformal /complex techniques

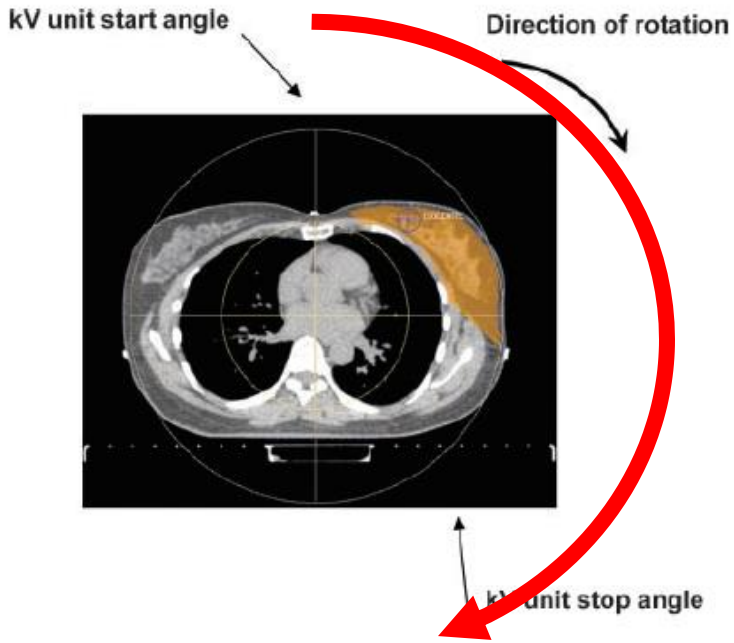


Even with daily kV, the remaining set up error justifies a considerable margin (8mm SI)

(compared to CBCT, registered on clips)

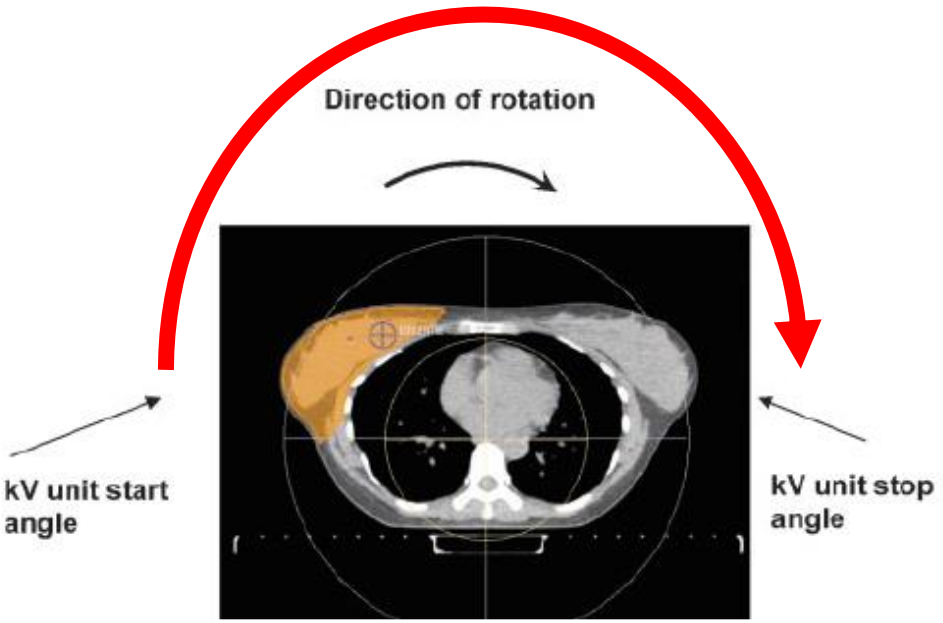
ESTRO School

CBCT acquisition

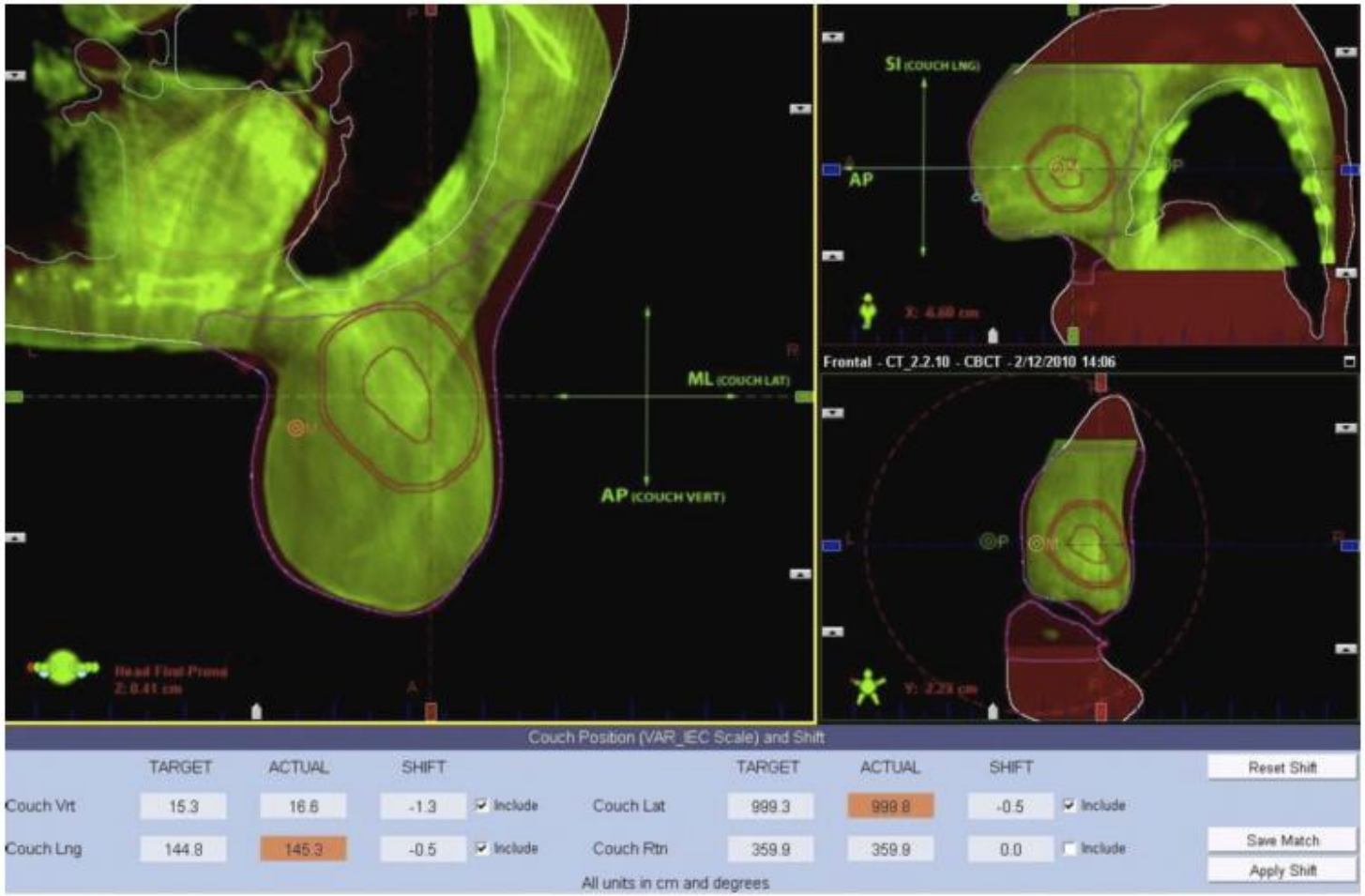


Donovan et al BJR 2012

Note difference in avoidance of contralateral breast



CBCT: also possible (and maybe more necessary) for non-supine positioning



Jozsef et al, IJROBP 2011

Take home message: bony registration

Tangential MV will underestimate positioning uncertainties
orthogonal images (MV or kV)

CBCT will offer more information about the position of the OAR
exact benefit unclear
data vs qualitative experience (see more? Faster?)

IMAGE GUIDANCE: HOW OFTEN?
IMAGING DOSE?

Dose burden from different image modalities

PVI set of orthogonal images (about 1 MU / image)

~ 4 mSv

CBCT

~ **1.5 mSv (maximum value)**

kV set of orthogonal images

< 1 mSv

IR

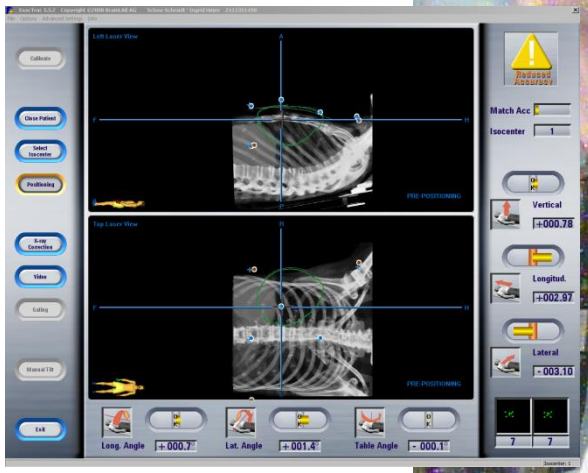
No dose

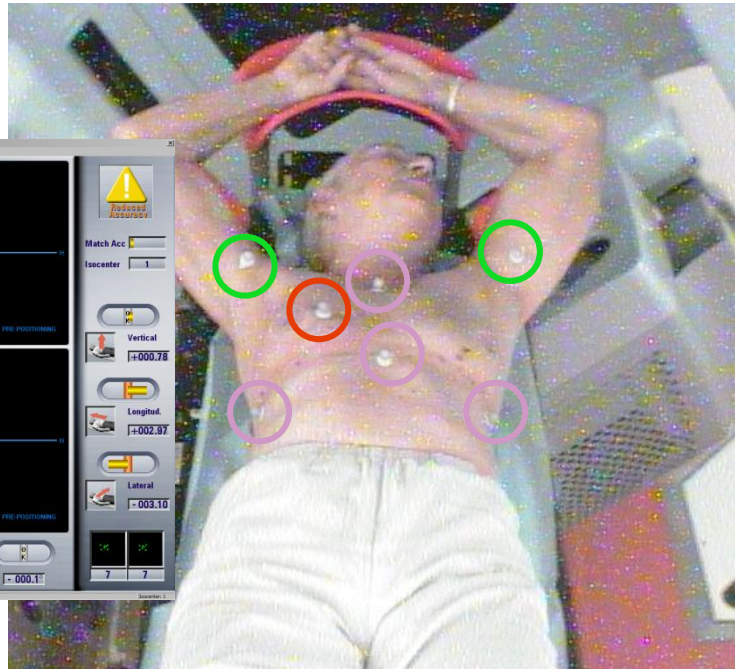
NB: approximate numbers !!

Other possible improvements

IR

Exac Track Infrared





Courtesy of BH Kristensen, DK

Surface scanning

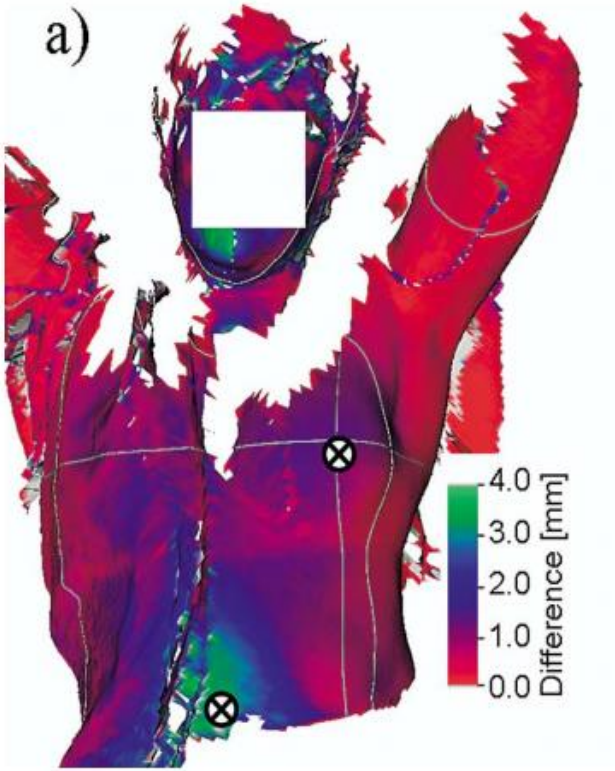
Image-guidance for whole breast (+/- nodes)

Target with “high deformability”

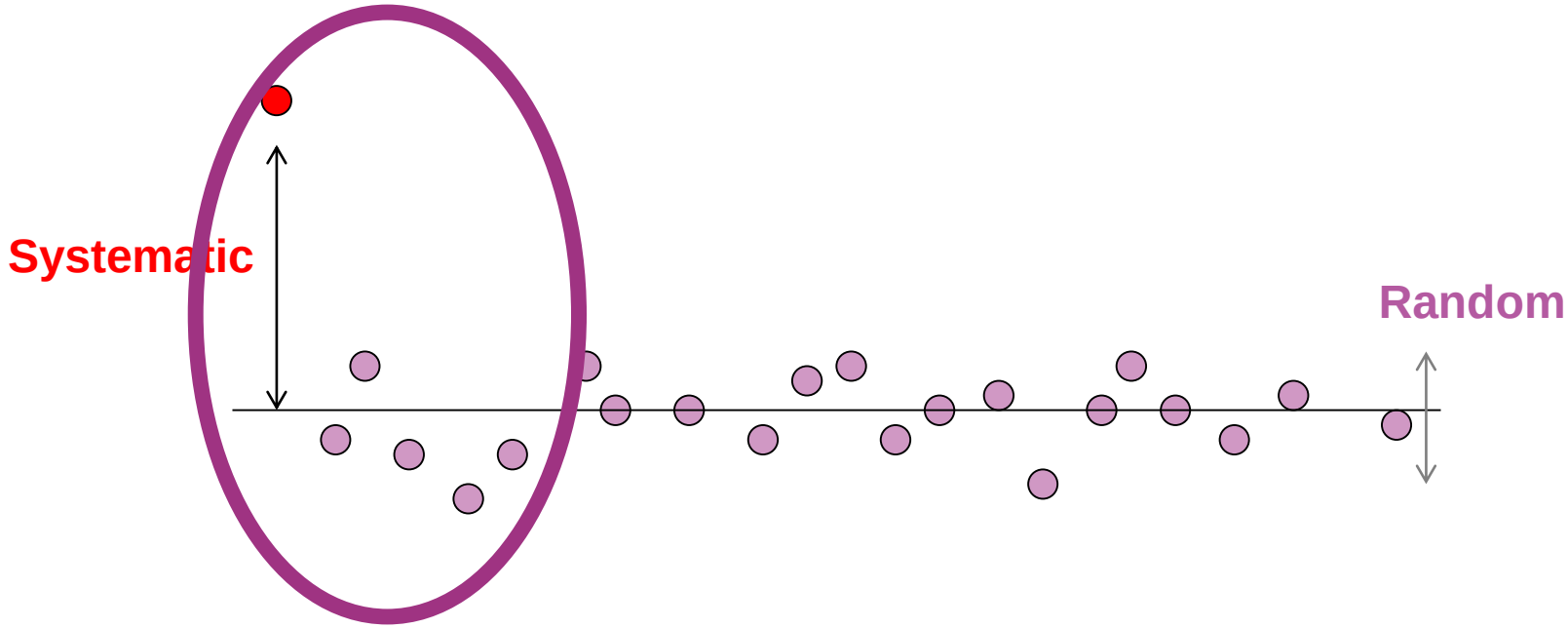
Number of cameras ???

Difficult to distinguish between set-up error and anatomical changes (or breathing)

Combination with x-ray IGRT still recommended (Betgen RO 2013)



Imaging every day versus few days



OFFLINE protocol: NAL or ”no action level“
Imaging first3-5 days…. + once in the middle

De Boer at al IJROBP 2005

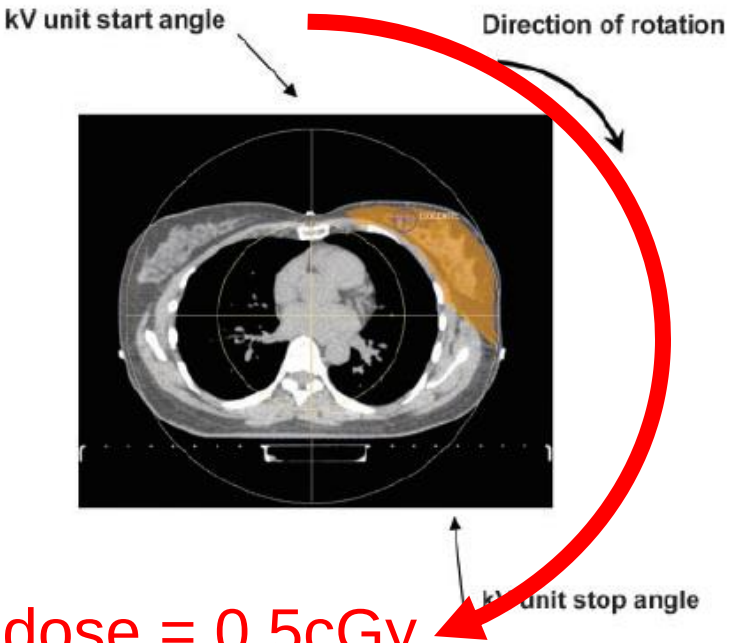
How much accuracy do we actually gain ??

Comparing no images at all to one image on first day: reduction of the systematic uncertainty

1SD	systematic [mm]		
	lat	lng	vrt
no imaging	3.7	3.3	3.5
no tolerance			
1st fraction	3.7	3.3	3.4
tolerance of 5 mm			
with NAL	1.5	1.6	1.6

Courtesy of Mirjana Josipovic, Rigshospitalet

Still concerned about the dose?

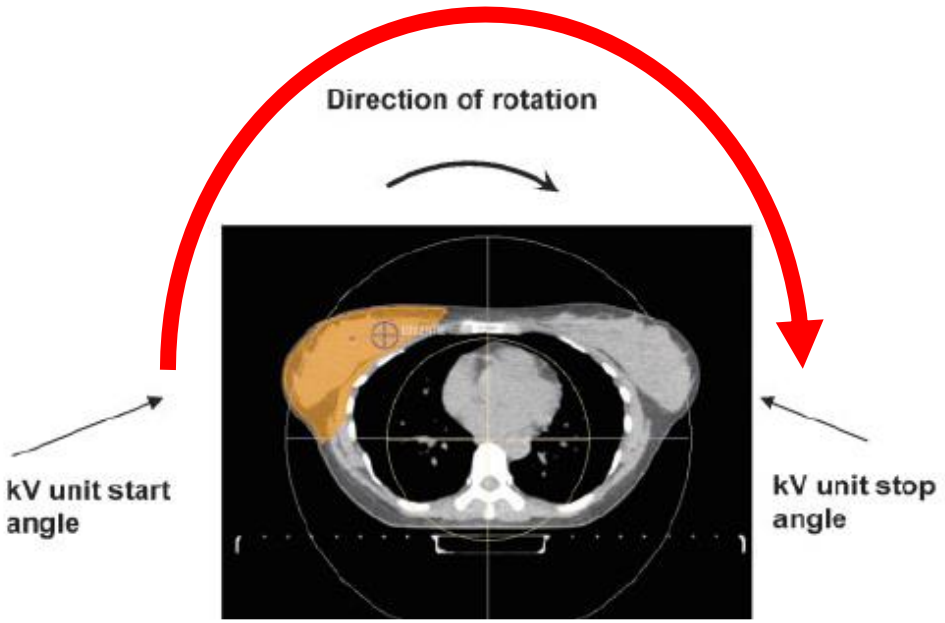


CB dose = 0.5cGy

Donovan et al BJR 2012

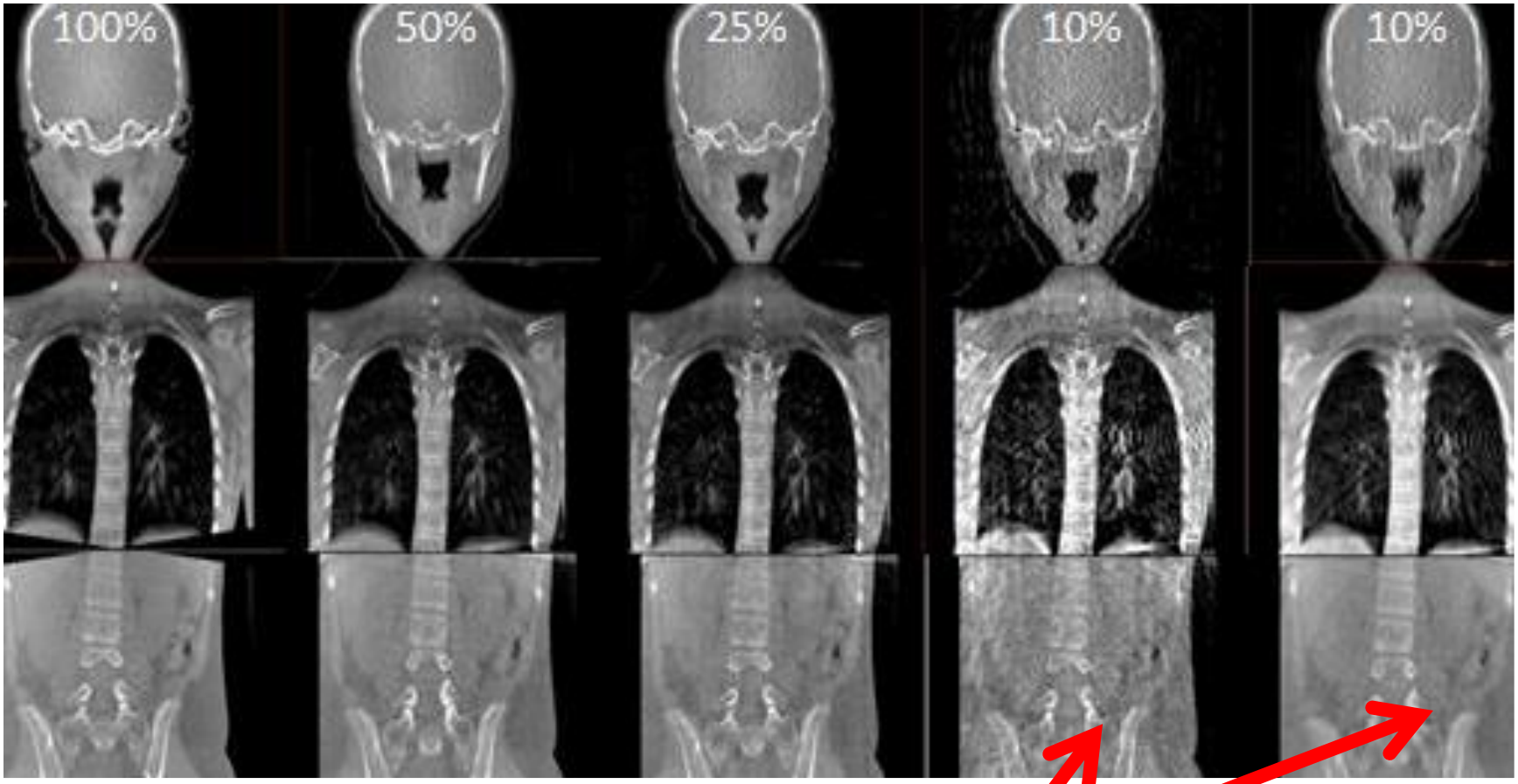
CB dose = 1.2cGy

Note difference in avoidance of contralateral breast



Still concerned about the dose?

CBCT dose and image quality



Courtesy of A. Bryce-Atkinson
, U of Manchester

< 0.2 cGy per image

ESTRO School

Take home message for IGRT modality/frequency:

- IGRT still under-used in breast (compared to other sites)

- Weekly images are **not** an efficient way to reduce uncertainties
  - Consider an offline (NAL / eNAL) protocol
  - Optimise image quality vs dose

- Daily imaging is the only way to address both systematic and random uncertainties

APBI/BOOST

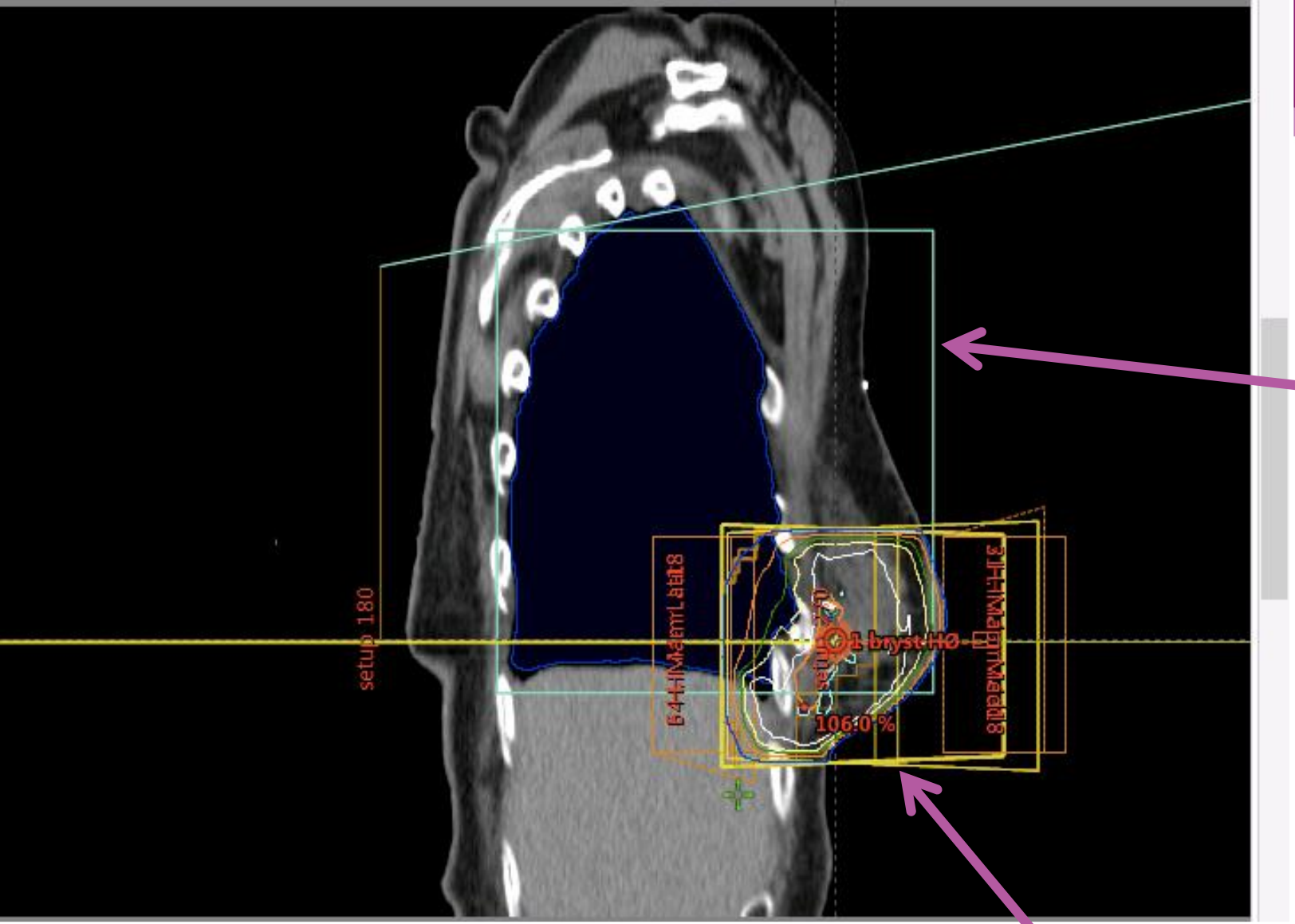
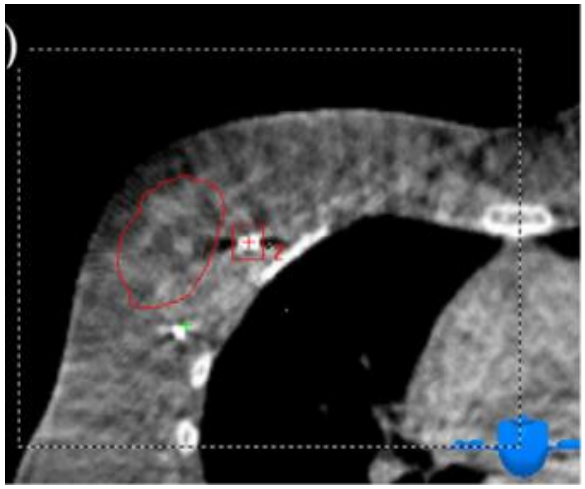
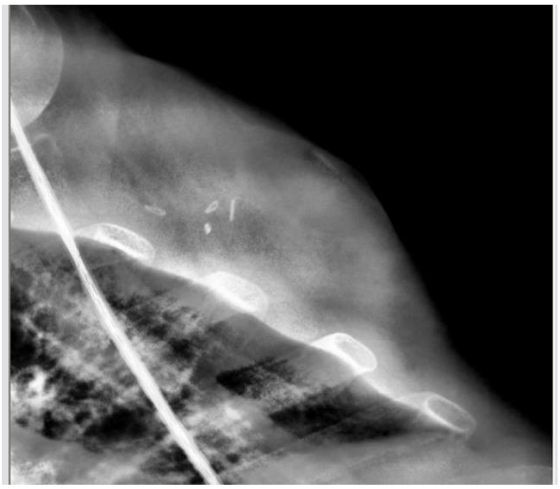

setup 180
106.0 %

Image-guidance in partial breast implanted markers

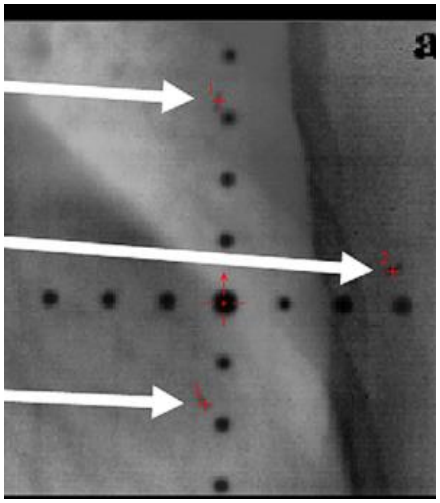


CBCT: match on soft tissue/clips

Topolnjak 2011



2D kV images: match on clips

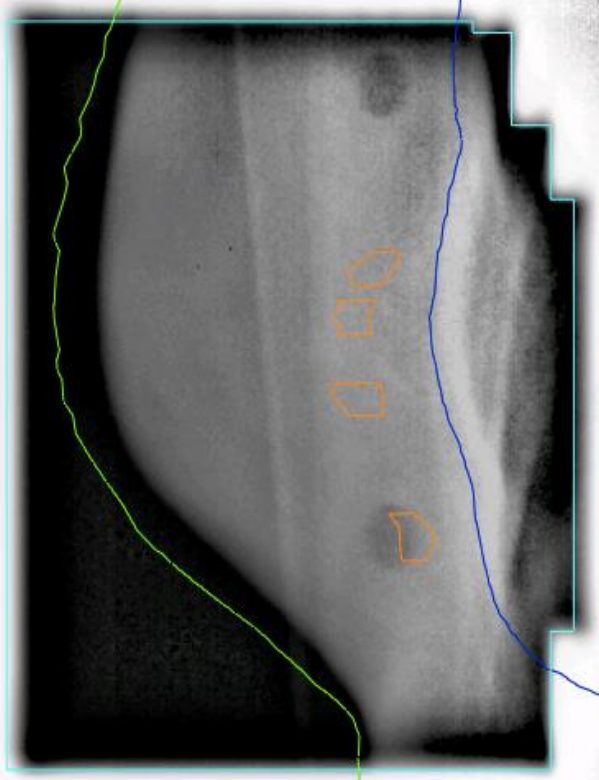


MV images: match on clips

Leonard 2010

Visibility in MV imaging ?

Titanium vs gold



ESTRO School

Example: 2D imaging for APBI

3 **gold** markers (1.2 x 3mm)

AP kV, lateral MV daily + MV acquisition (open fields)

1cm PTV

No evidence of migration

Average shifts:

- 3mm AP
- 2mm LR
- 2mm sup inf

But displacements of up to 10 mm observed

Leonard et al IJROBP 2010

Example: CBCT for sequential and integrated boost

Import HIGH

IMRT (tangential and “real”)

sequential vs integrated boost

1 cm whole breast PTV, 5mm boost PTV

38 patients with boost CBCT (offline or daily)

Systematic and random errors of

approx 3mm (before correction)

1.5 mm after correction

Donovan BJR 2012

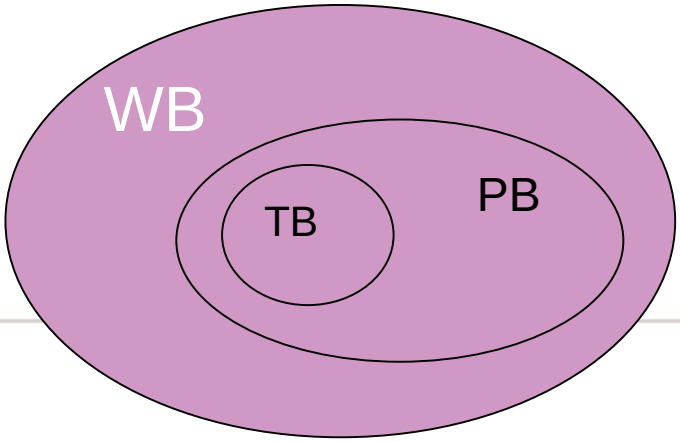
Partial breast /integrated boost the example of ”IMPORT HIGH”

A multicentre observational study evaluating image-guided radiotherapy for more accurate partial-breast intensity-modulated radiotherapy: comparison with standard imaging technique

2014

Emma J Harris,[1†] Mukesh Mukesh,[2†] Rajesh Jena,[2] Angela Baker,[3] Harry Bartelink,[4] Corrinne Brooks,[1] June Dean,[2] Ellen M Donovan,[1] Sandra Collette,[5] Sally Eagle,[6] John D Fenwick,[7] Peter H Graham,[8] Jo S Haviland,[9] Anna M Kirby,[10] Helen Mayles,[3] Robert A Mitchell,[1] Rosalind Perry,[11] Philip Poortmans,[12] Andrew Poynter,[13] Glyn Shentall,[14] Jenny Titley,[9] Alistair Thompson,[15] John R Yarnold,[10] Charlotte E Coles[2‡] and Philip M Evans[1,16*‡] on behalf of the IMPORT Trials Management Group

[1]Joint Department of Physics at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, UK
[2]Oncology Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[3]Department of Radiotherapy and Physics, The Clatterbridge Cancer Centre NHS Foundation Trust, Wirral, UK
[4]Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, the Netherlands
[5]Statistics Department, EORTC Headquarters, Brussels, Belgium
[6]Department of Radiotherapy, Royal Marsden Hospital NHS Foundation Trust, London, UK
[7]Department of Oncology, University of Oxford, Oxford, UK
[8]Cancer Care Centre, St George Hospital, Kogarah, Sydney, NSW, Australia
[9]ICR-CTSU, Institute of Cancer Research, London, UK
[10]Breast Unit, Royal Marsden NHS Foundation Trust, London, UK
[11]Radiotherapy Department, Ipswich Hospitals NHS Trust, Ipswich, UK
[12]Department of Radiation Oncology, Dr Bernard Verbeeten Instituut, Tilburg, the Netherlands
[13]Radiotherapy Department, Peterborough City Hospital, Peterborough, UK
[14]Rosemere Cancer Centre, Lancashire Teaching Hospitals NHS Trust, Preston, UK
[15]School of Medicine, University of Dundee, Dundee, UK
[16]Centre for Vision, Speech and Signal Processing, Faculty of Engineering and Physical Sciences, University of Surrey, Guildford, UK



Comparing bone registration to clips-based reg

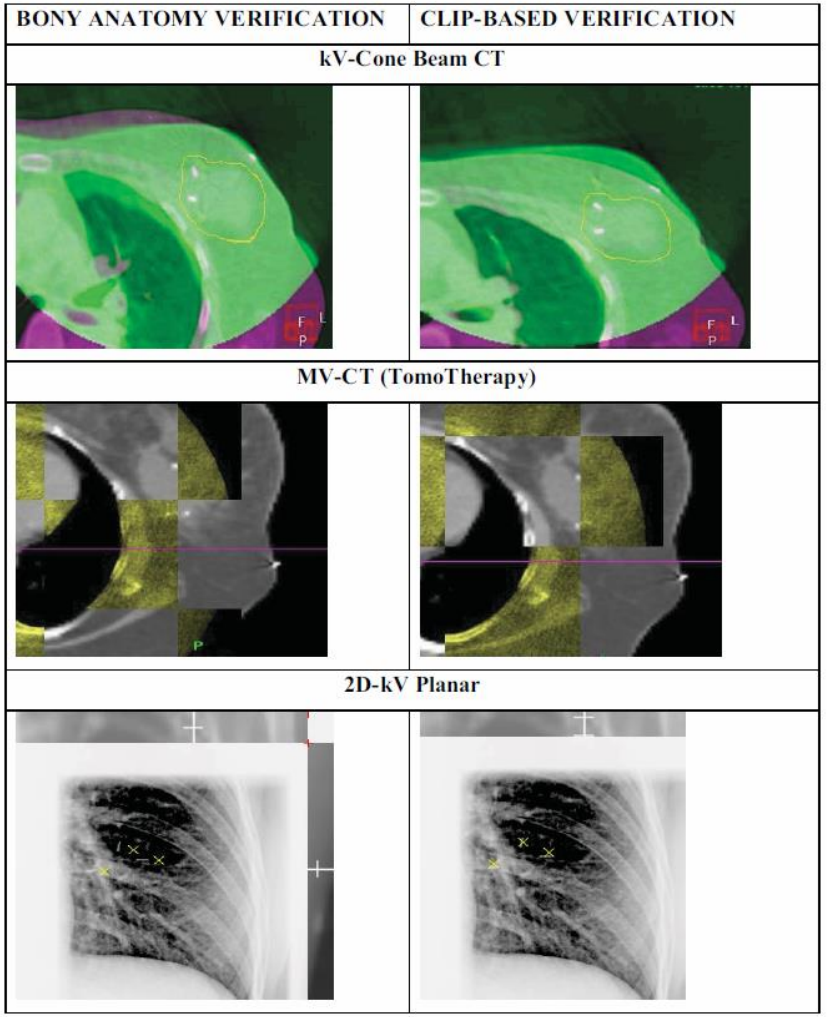


TABLE 8 Delta errors (difference between bony anatomy and clips, S_{DIFF}) in the LR, SI and AP directions and the magnitude of their 3D vector. Time required for image matching with both techniques has also been summarised

	Delta error (S_{DIFF}), mean absolute delta [cm (range)]				Time, median [seconds (range)]	
Centre	LR	SI	AP	3D vector	T_{BA}	T_{clips}
All	0.20 (0–1.7)	0.26 (0–3.2)	0.21 (0–2.0)	0.32 (0–10.2)	73 (8–240)	66 (8–178)
A (kV-CBCT)	0.19 (0–0.7)	0.24 (0–3.2)	0.22 (0–1.7)	0.28 (0–10.2)	26 (8–51)	92 (11–177)
B (MV-CT)	0.14 (0–0.7)	0.12 (0–1.2)	0.18 (0–1.3)	0.17 (0–2.0)	102 (70–230)	110 (25–178)
C (2D-kVPI)	0.23 (0–1.7)	0.29 (0–2.4)	0.20 (0–2.0)	0.38 (0–6.29)	22 (20–76)	16 (8–52)
D (2D-kVPI)	0.21 (0–1.3)	0.32 (0–1.3)	0.21 (0–1.0)	0.35 (0–2.2)	79 (60–154)	28 (20–85)
E (2D-kVPI)	0.20 (0–1.5)	0.31 (0–1.4)	0.23 (0–1.0)	0.36 (0–3.3)	110 (28–240)	34 (16–120)

Clips can be used as a surrogate of the PTV (tumour bed)

Reduction in PTV (tumourbed) from 8 to 5 mm with clips-based IGRT, daily or with eNAL

Modest dosimetric impact

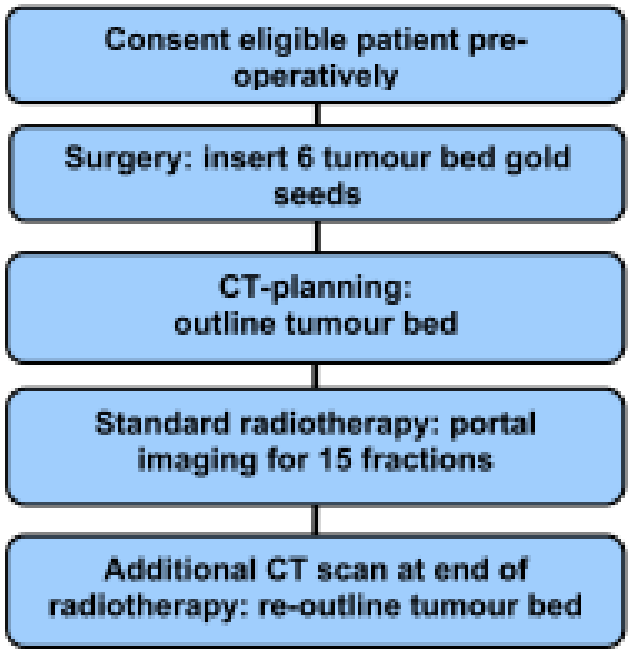
TABLE 8 Delta errors (difference between bony anatomy and clips, S_{DIFF}) in the LR, SI and AP directions and the magnitude of their 3D vector. Time required for image matching with both techniques has also been summarised

	Delta error (S_{DIFF}), mean absolute delta [cm (range)]				Time, median [seconds (range)]	
Centre	LR	SI	AP	3D vector	T_{BA}	T_{clips}
All	0.20 (0–1.7)	0.26 (0–3.2)	0.21 (0–2.0)	0.32 (0–10.2)	73 (8–240)	66 (8–178)
A (kV-CBCT)	0.19 (0–0.7)	0.24 (0–3.2)	0.22 (0–1.7)	0.28 (0–10.2)	26 (8–51)	92 (11–177)
B (MV-CT)	0.14 (0–0.7)	0.12 (0–1.2)	0.18 (0–1.3)	0.17 (0–2.0)	102 (70–230)	110 (25–178)
C (2D-kVPI)	0.23 (0–1.7)	0.29 (0–2.4)	0.20 (0–2.0)	0.38 (0–6.29)	22 (20–76)	16 (8–52)
D (2D-kVPI)	0.21 (0–1.3)	0.32 (0–1.3)	0.21 (0–1.0)	0.35 (0–2.2)	79 (60–154)	28 (20–85)
E (2D-kVPI)	0.20 (0–1.5)	0.31 (0–1.4)	0.23 (0–1.0)	0.36 (0–3.3)	110 (28–240)	34 (16–120)

Time varies per institution, even when using the same techniqu
2D kV scores both as fastest and slowest !
Inter and intra- observer error < 1.4mm for all modalities

IMPORT (low: APBI, high: SIB)

A



- Gold seeds visible both in planning CT and in verification imaging
- Stable (no migration)
- Artefacts in 1/50 patients

Coles CE. R&O 2011

Take home message for APBI/Boost:

Clips <u>can</u> be representative for

- the location of the tumor bed
- the location of the whole breast

Penninkhof Radiother Oncol 2009

Registering on clips is time-efficient and can allow for margin reduction of the tumour bed PTV

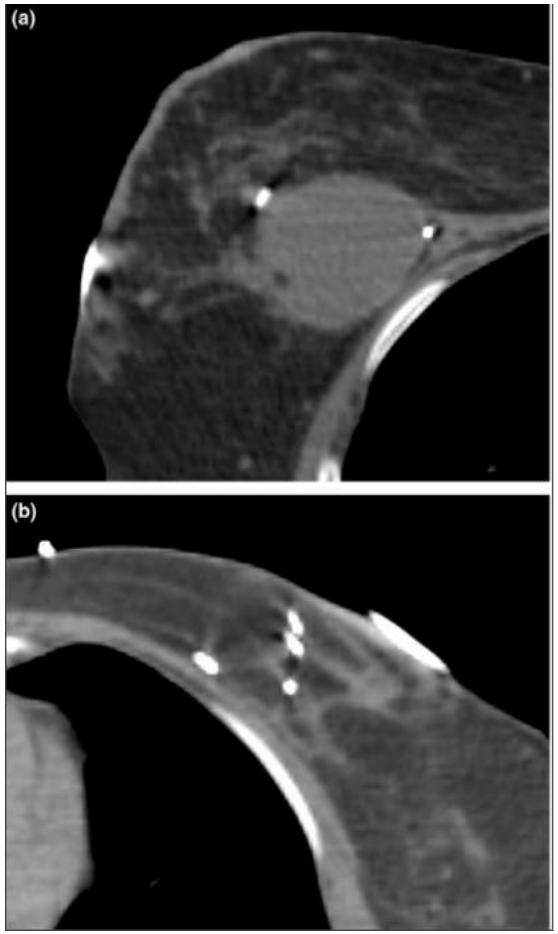
kV-CBCT, MV-CBCT, 2D kV are equivalent in terms of accuracy if registering on clips

➢ 2D MV as well, if clips are visible

ESTRO School

Note of caution using clips for registration

seroma



Lewis et al J Med Rad Sci 2015

ESTRO School

What margin for YOUR institution?

It depends on many parameters:

Immobilization/interfraction motion

Breathing/intrafraction motion

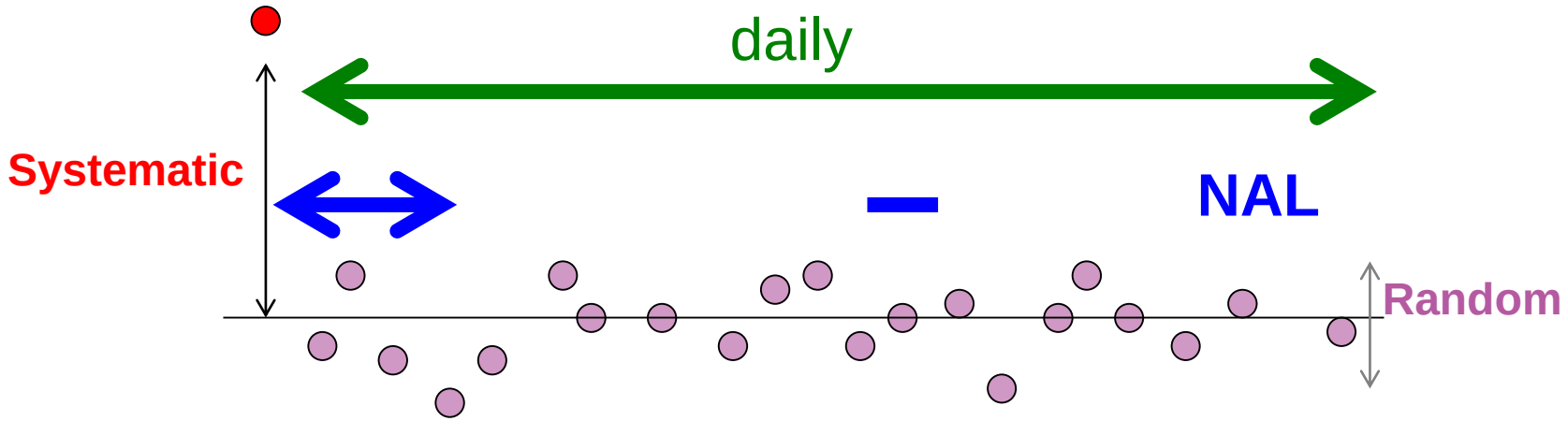
Observer uncertainty (delineation + matching)

Set-up verification (IGRT): type and frequency

Random vs systematic uncertainties

$$M = 2.5\,\Sigma_{tot} + 1.64\,(\sigma_{tot}-\sigma_p)$$

$$\text{Where } \Sigma_{tot}=\sqrt{(\Sigma_1^2+\Sigma_2^2+\Sigma^2_3\ldots)}$$



Take home message for IGRT in general:

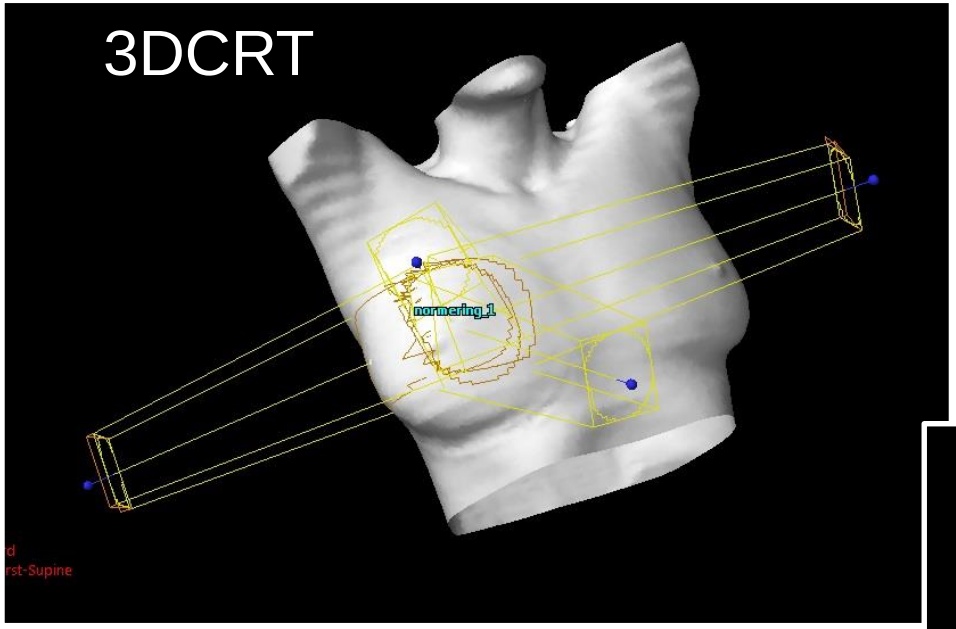
- IGRT may be the most efficient way to reduce uncertainties in breast cancer RT
- Even more crucial with hypofractionation (see Wednesday)
- There are ways to reduce the dose from images/ the resources involved

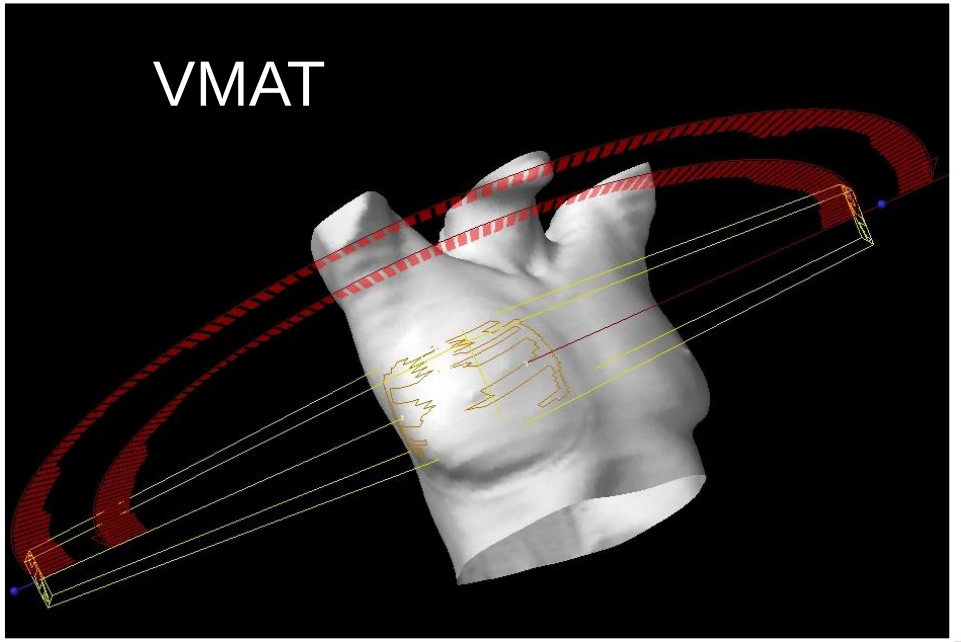
ESTRO School

APBI and SIB

Different techniques

APBI: 3DCRT non coplanar vs VMAT

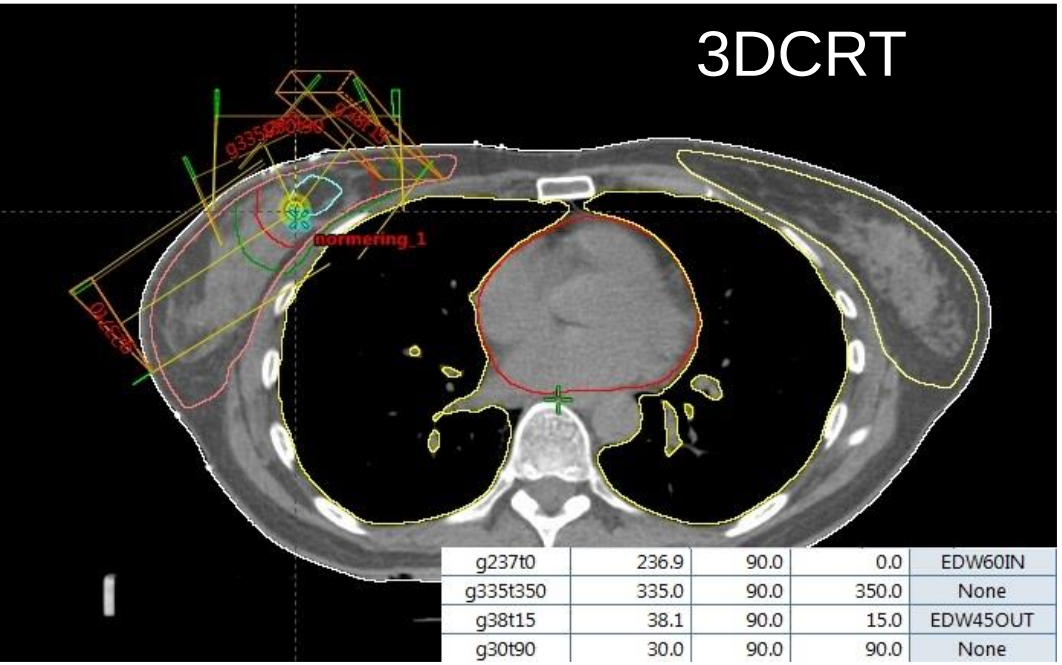




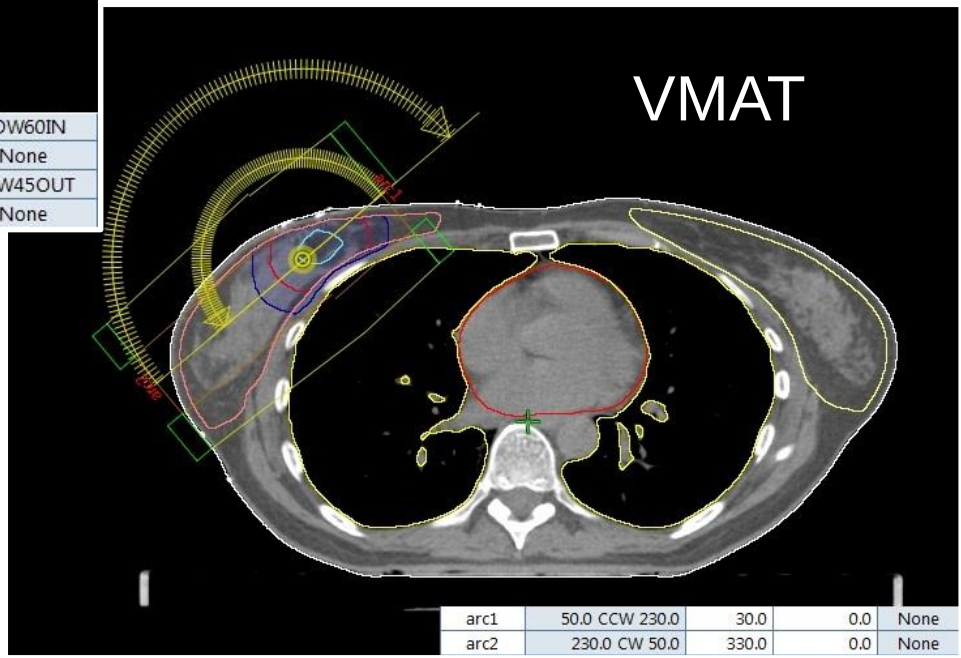
APBI Right

- 10 x 3,85 Gy twice per day

Beams



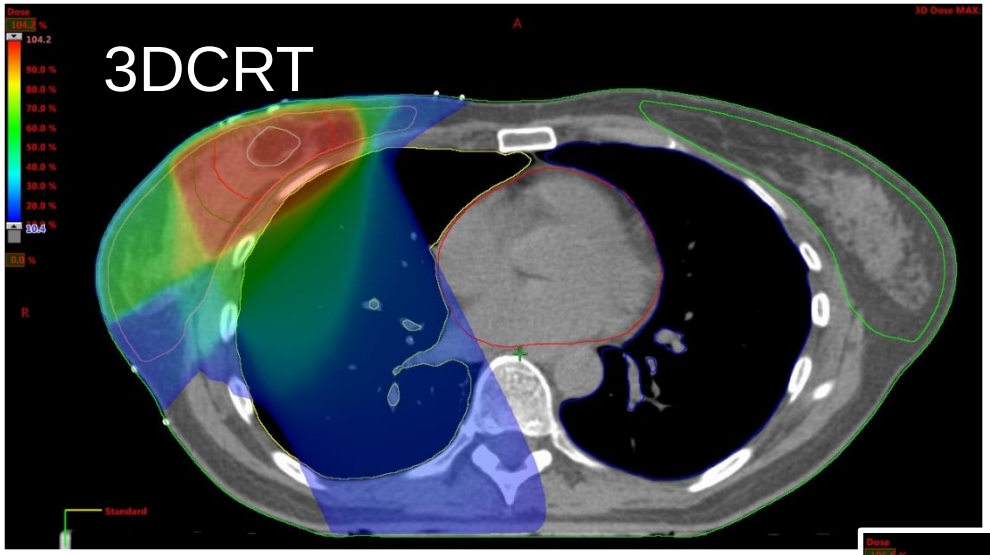
g237t0	236.9	90.0	0.0	EDW60IN
g335t350	335.0	90.0	350.0	None
g38t15	38.1	90.0	15.0	EDW45OUT
g30t90	30.0	90.0	90.0	None

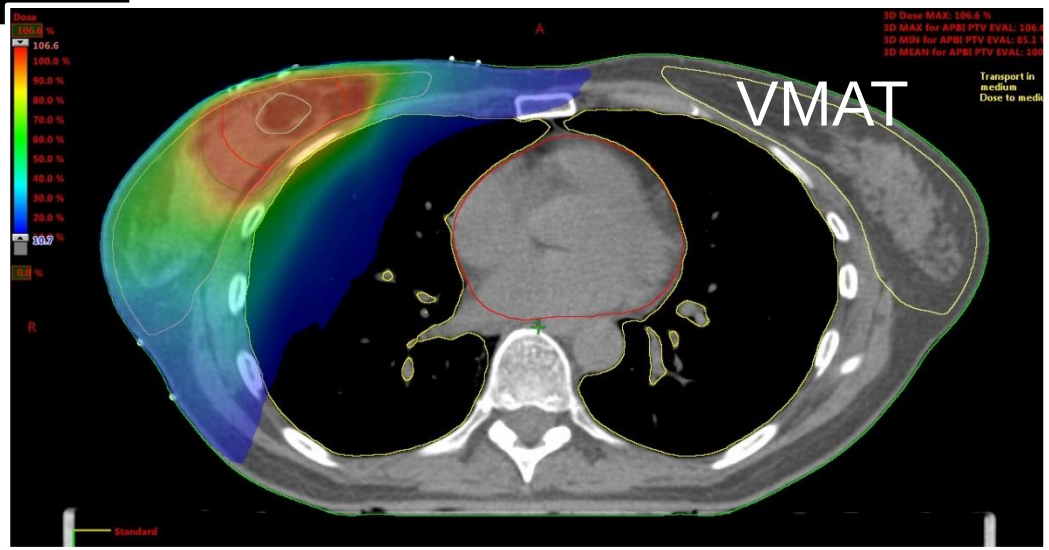


arc1	50.0 CCW 230.0	30.0	0.0	None
arc2	230.0 CW 50.0	330.0	0.0	None

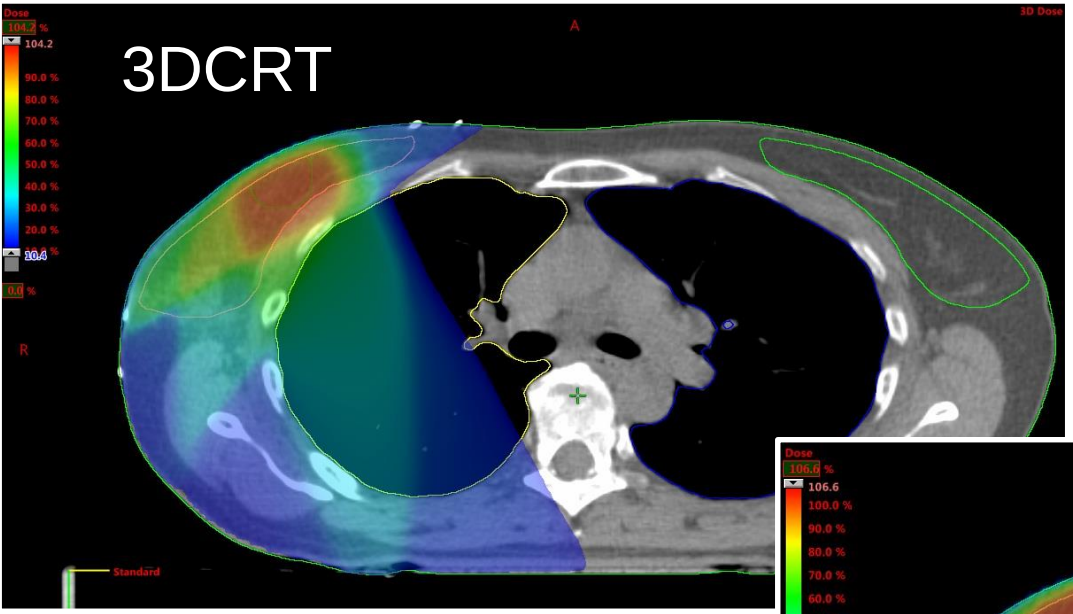
ESTRO School

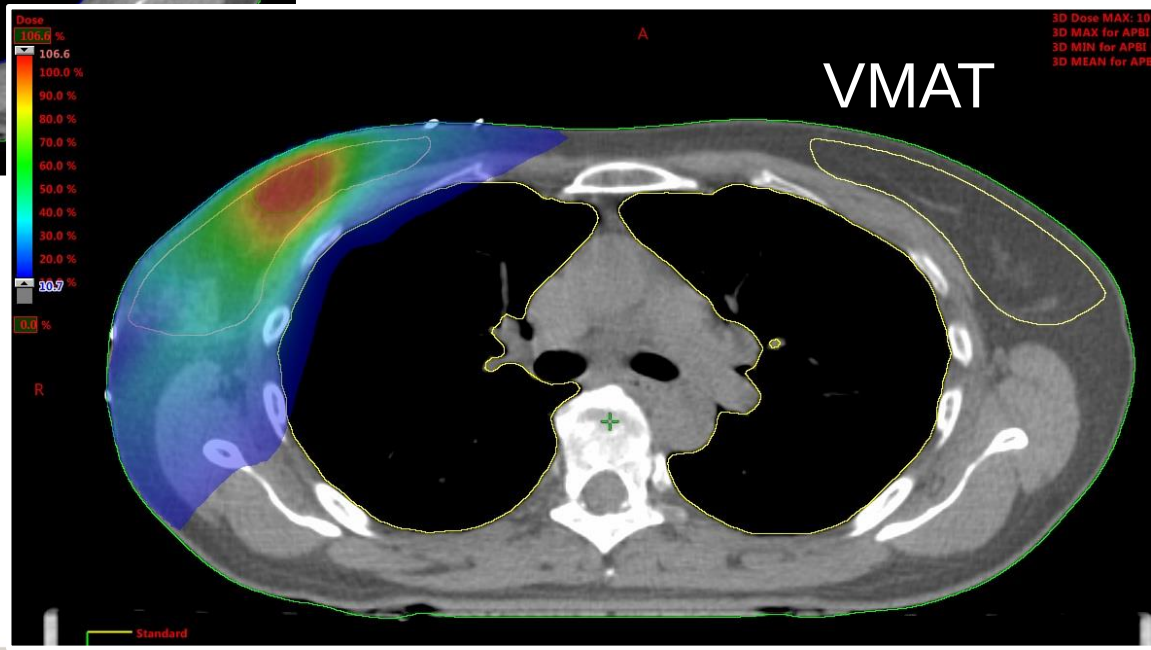
Isodoses



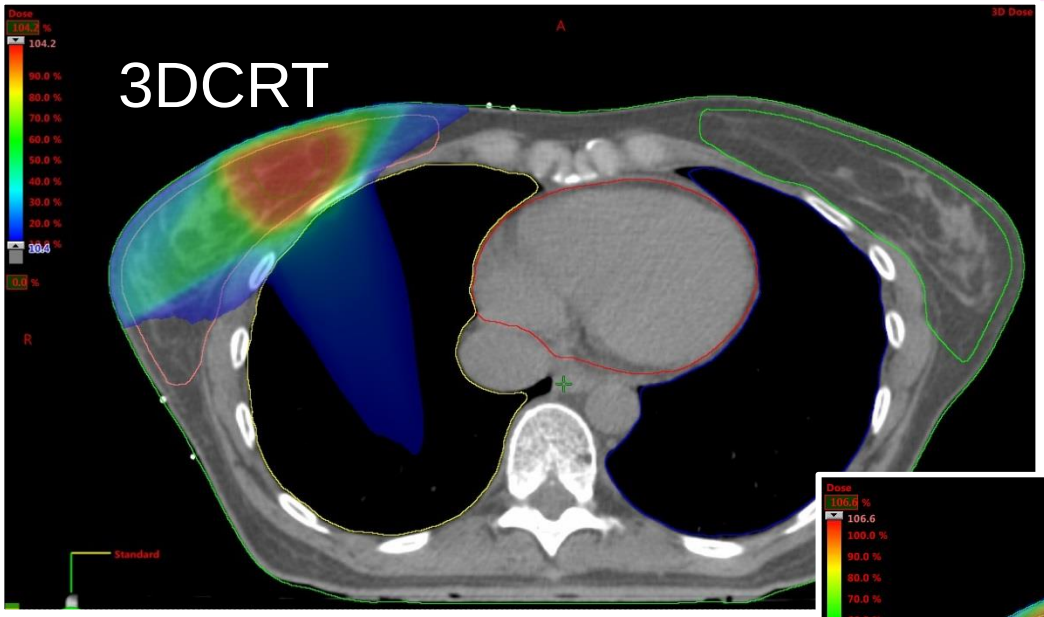


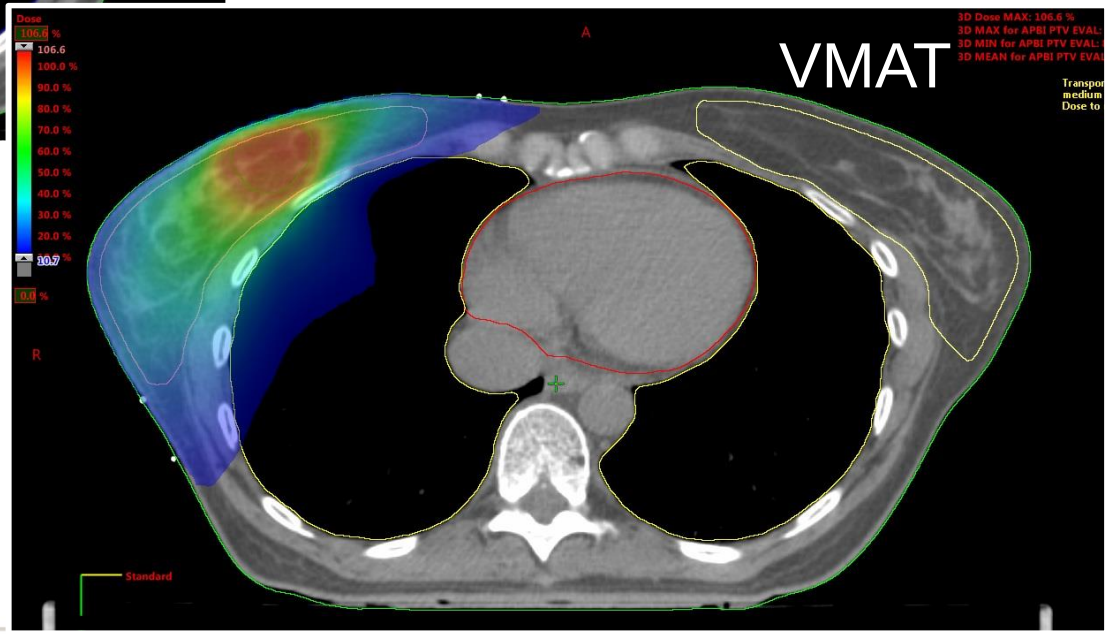
Isodoses


3DCRT
Dose
104.2 %
104.2
90.0 %
80.0 %
70.0 %
60.0 %
50.0 %
40.0 %
30.0 %
20.0 %
10.4
0.0 %
A
3D Dose
R
Standard


VMAT
Dose
106.6 %
106.6
100.0 %
90.0 %
80.0 %
70.0 %
60.0 %
50.0 %
40.0 %
30.0 %
20.0 %
10.7
0.0 %
A
R
Standard

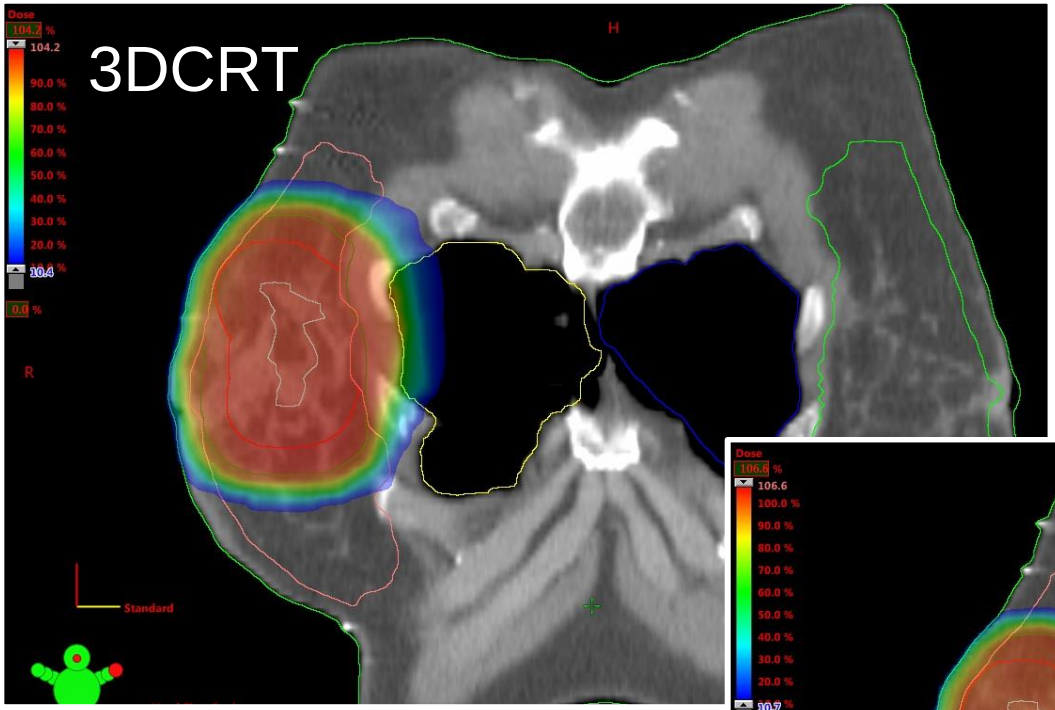
Isodoses

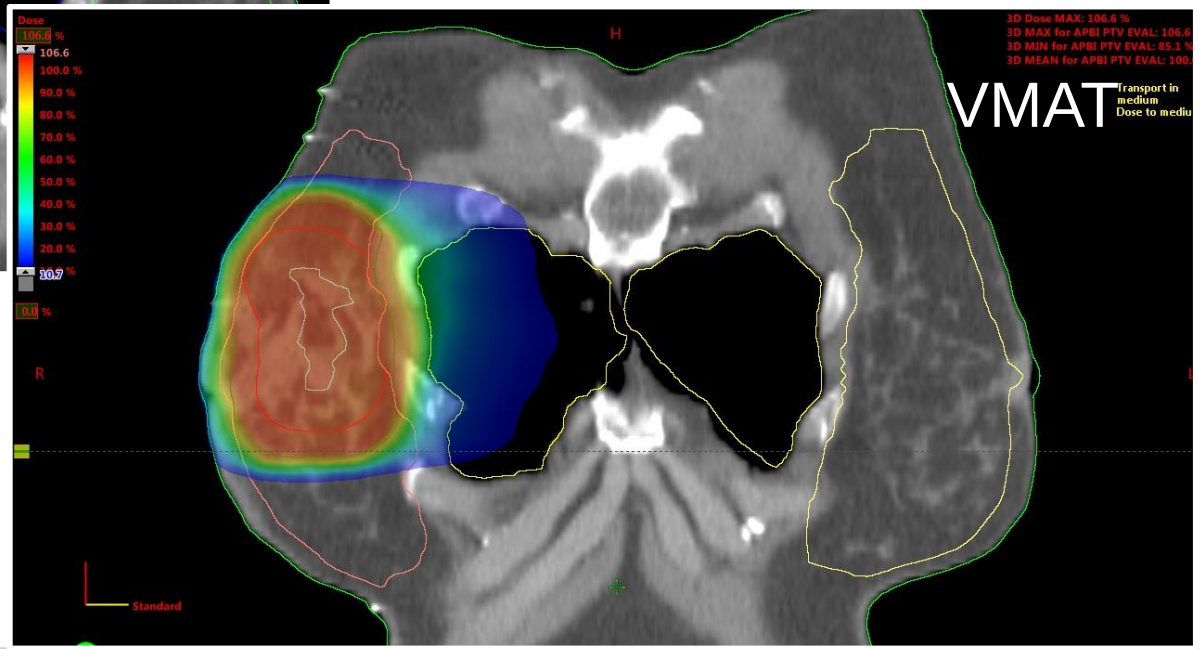




ESTRO School

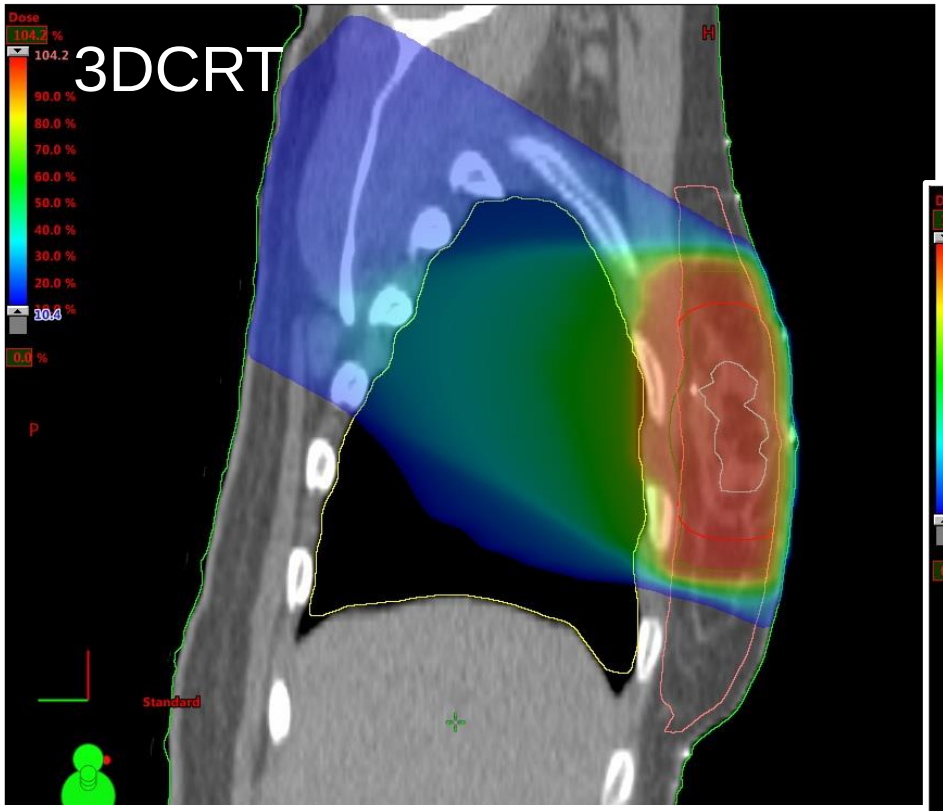
Isodoses

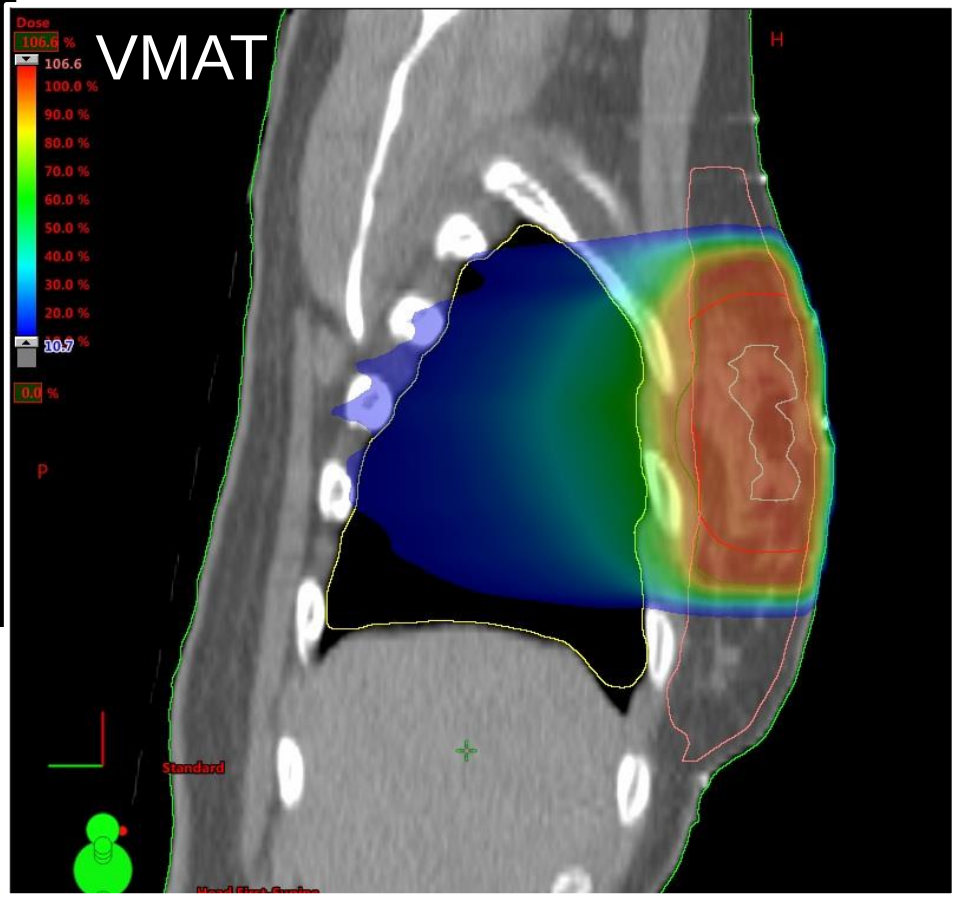




ESTRO School

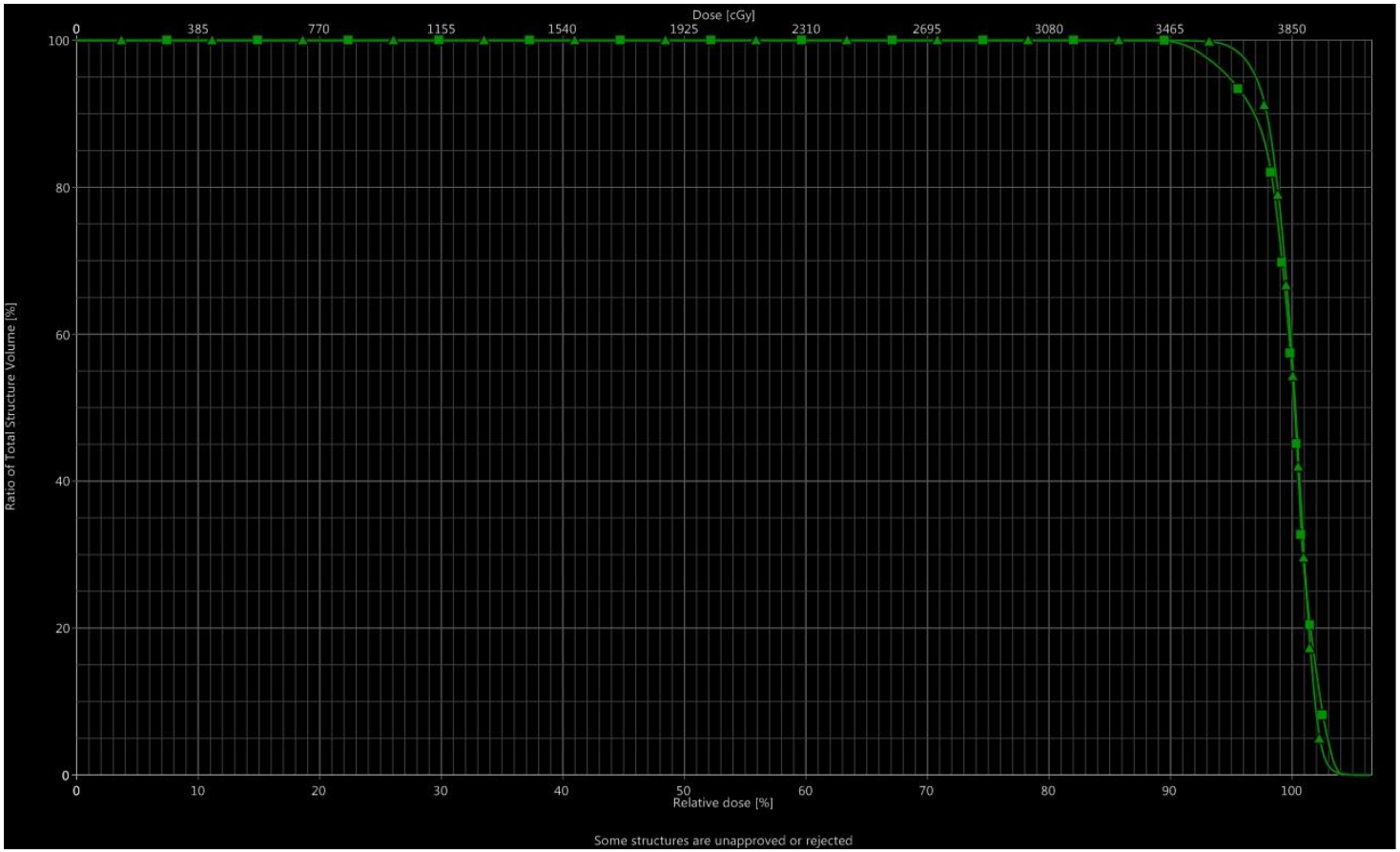
Isodoses





ESTRO School

PTV

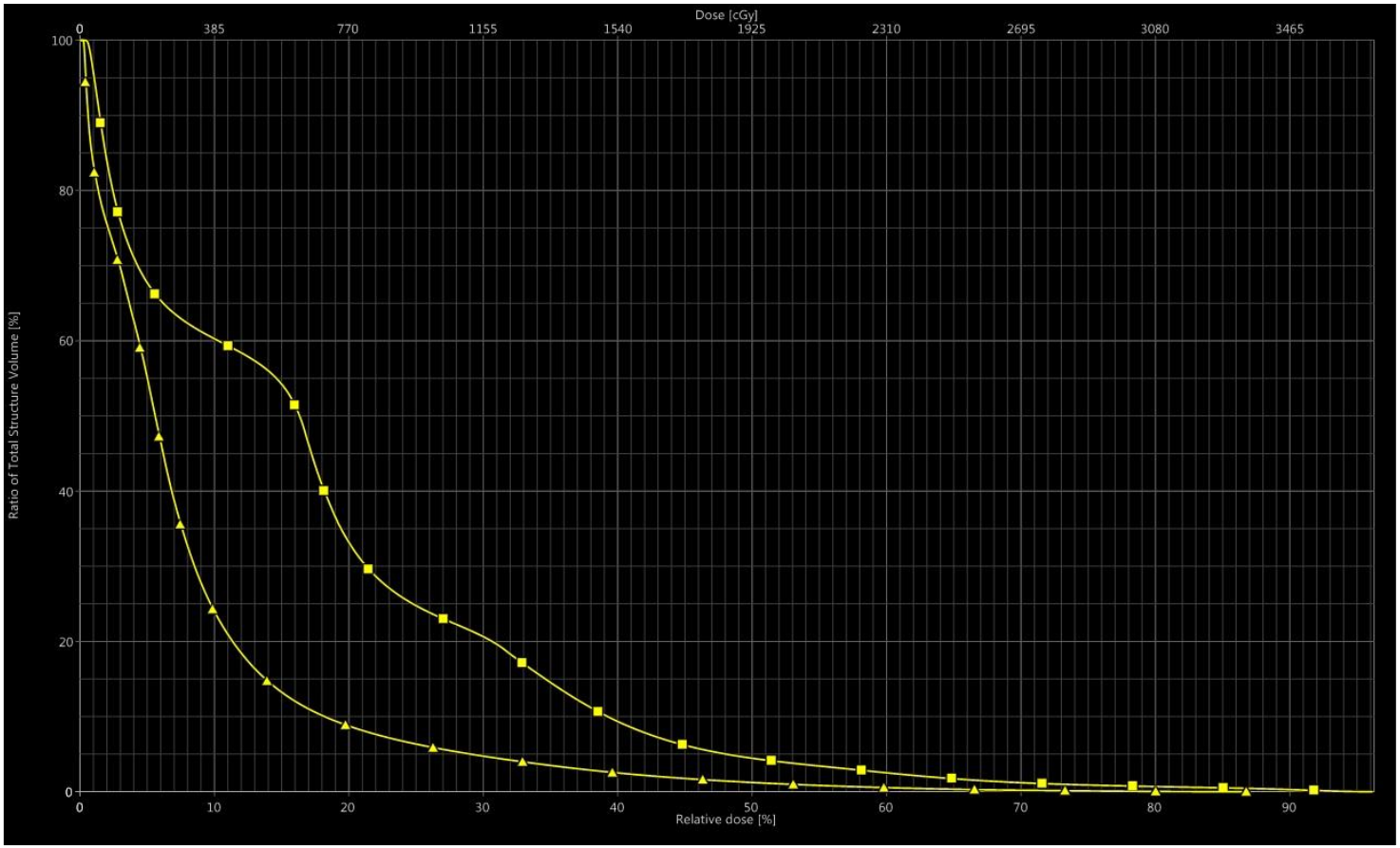


■ 3DCRT

▲ VMAT

ESTRO School

Lung Right

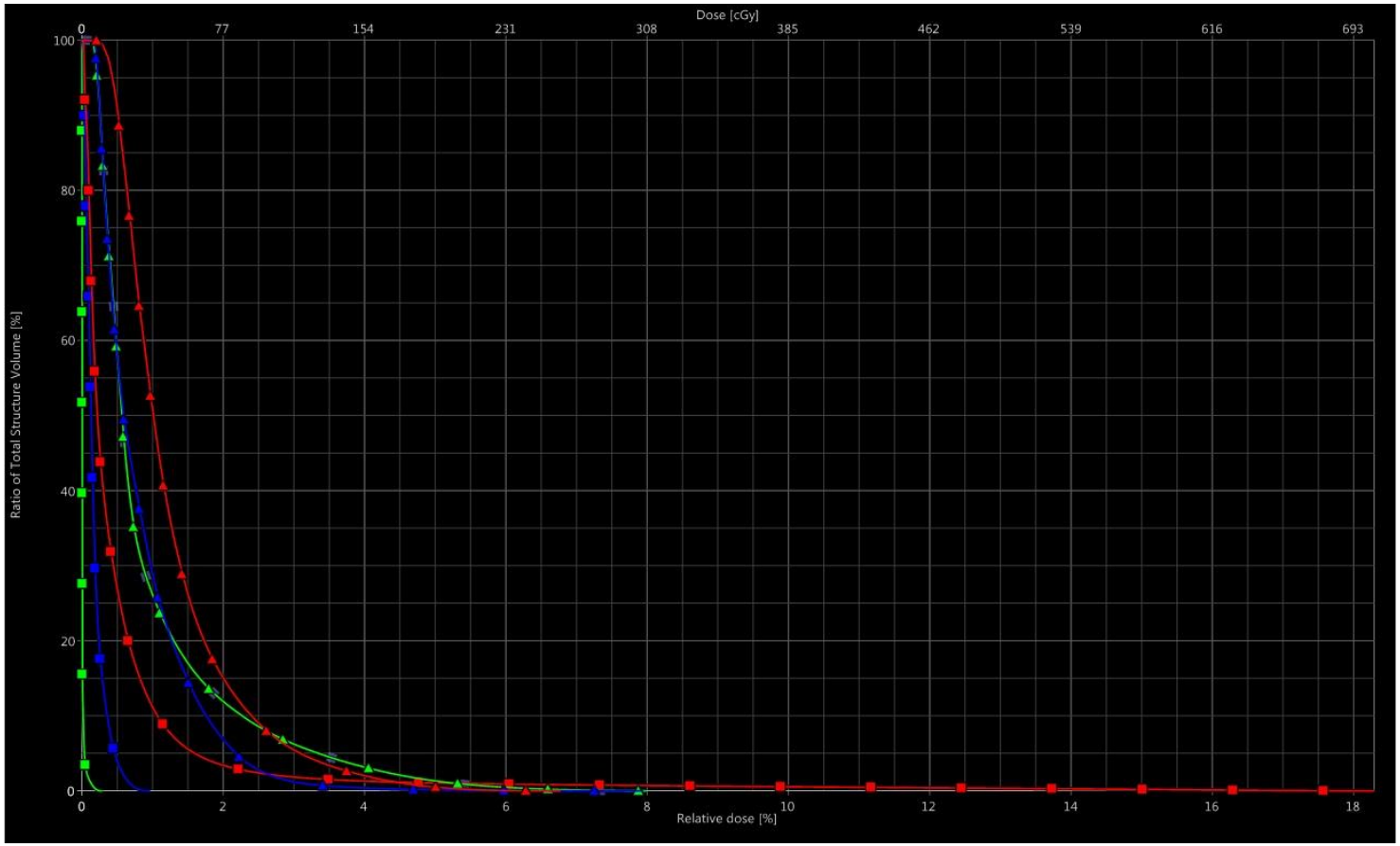


■ 3DCRT

▲ VMAT

ESTRO School

Contralateral

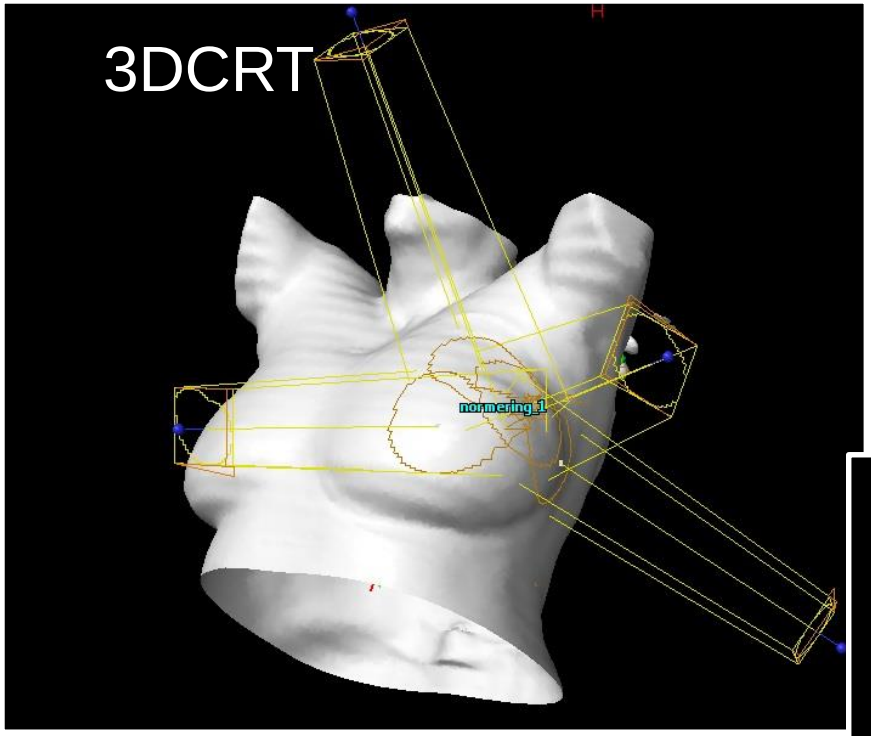


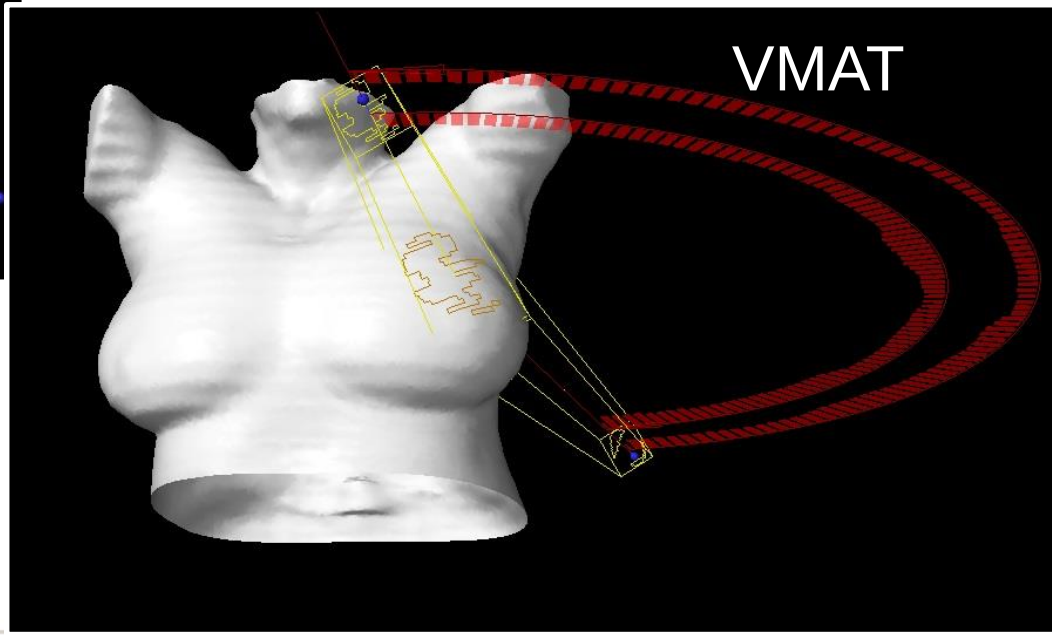
■ 3DCRT
▲ VMAT

Heart
Breast Left
Lung Left

ESTRO School

3DCRT non coplanar vs VMAT





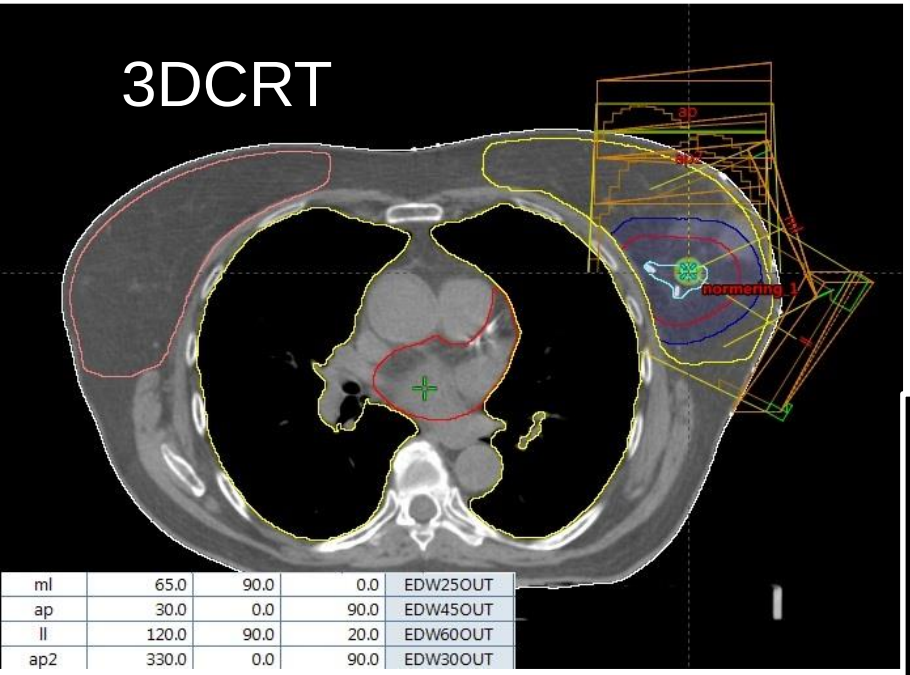
ESTRO School

APBI Left

- 10 x 3,85 Gy twice per day

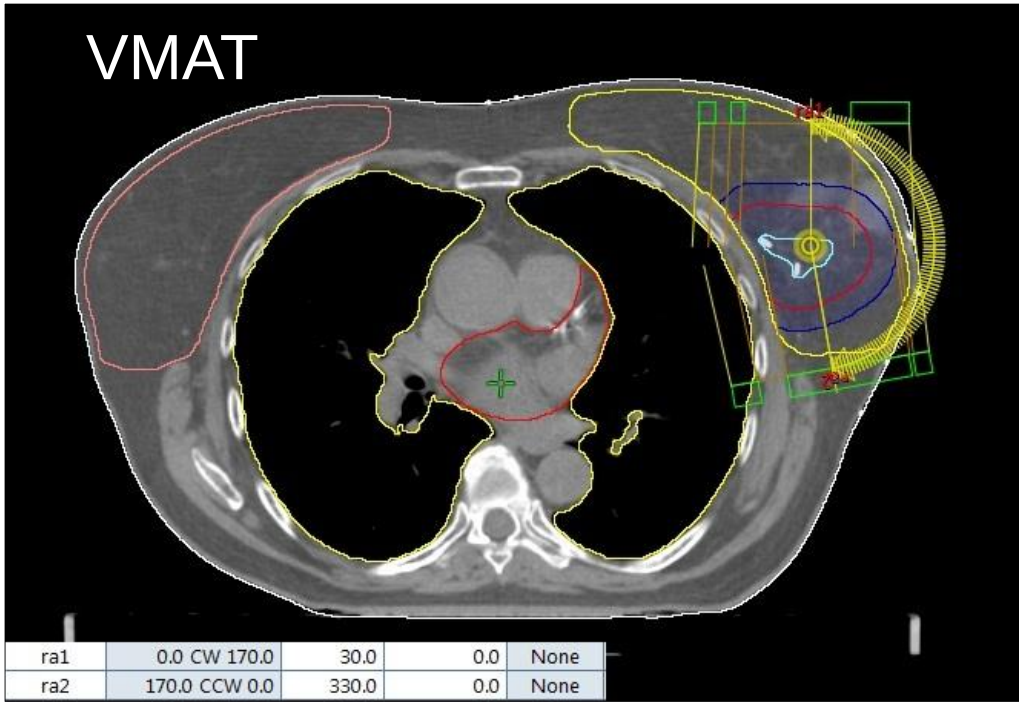
Beams

3DCRT



ml	65.0	90.0	0.0	EDW25OUT
ap	30.0	0.0	90.0	EDW45OUT
ll	120.0	90.0	20.0	EDW60OUT
ap2	330.0	0.0	90.0	EDW30OUT

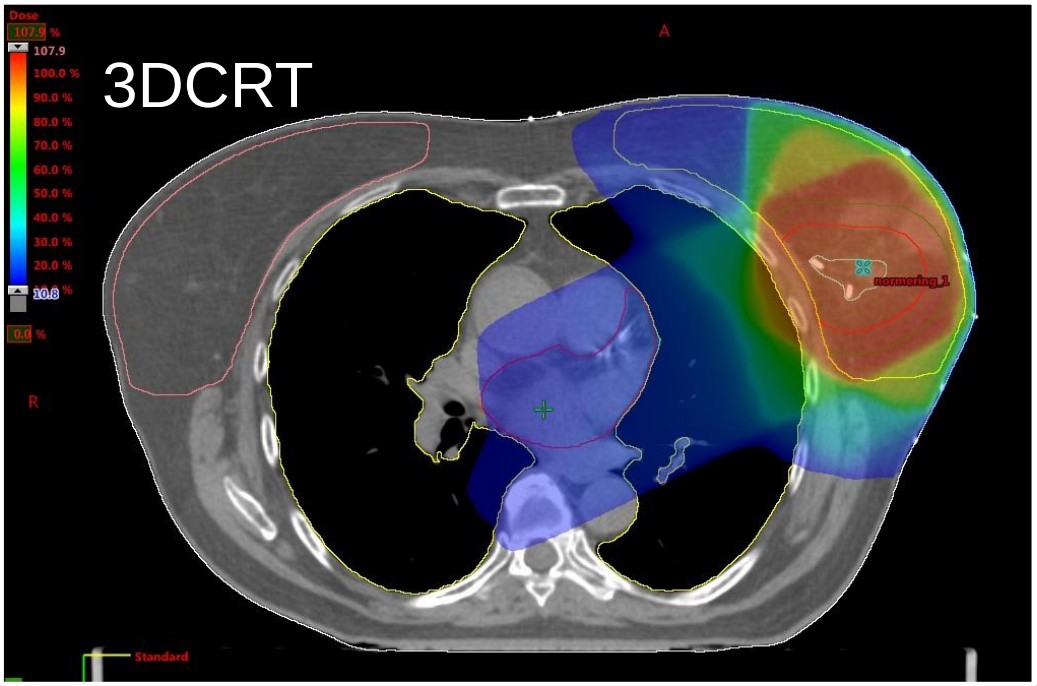
VMAT

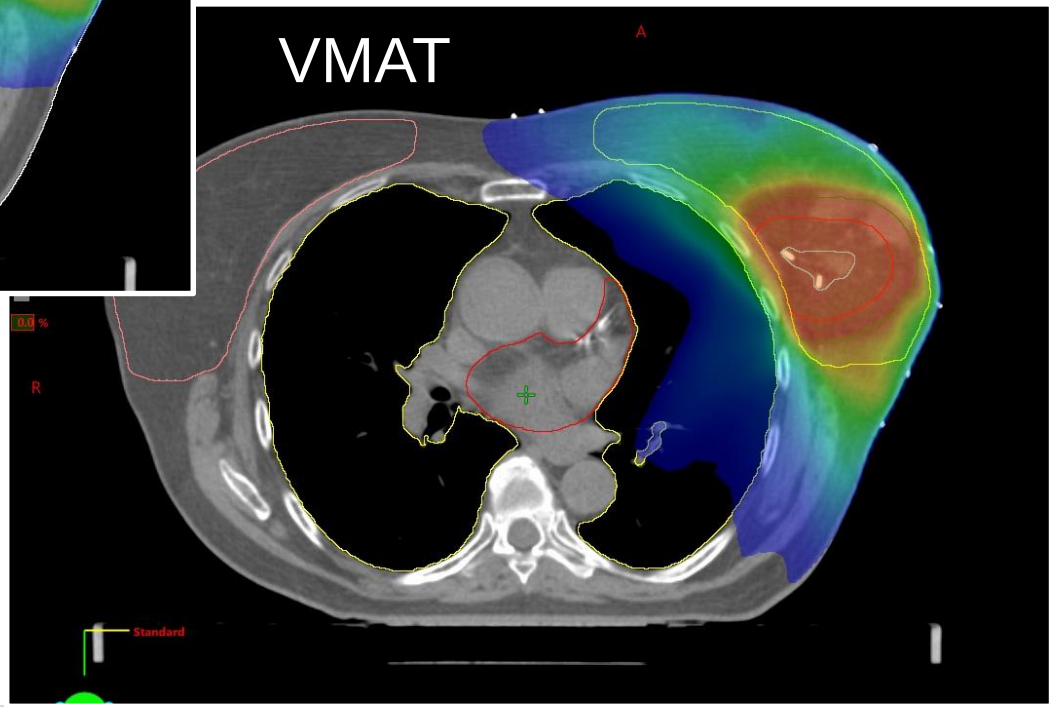


ra1	0.0 CW 170.0	30.0	0.0	None
ra2	170.0 CCW 0.0	330.0	0.0	None

ESTRO School

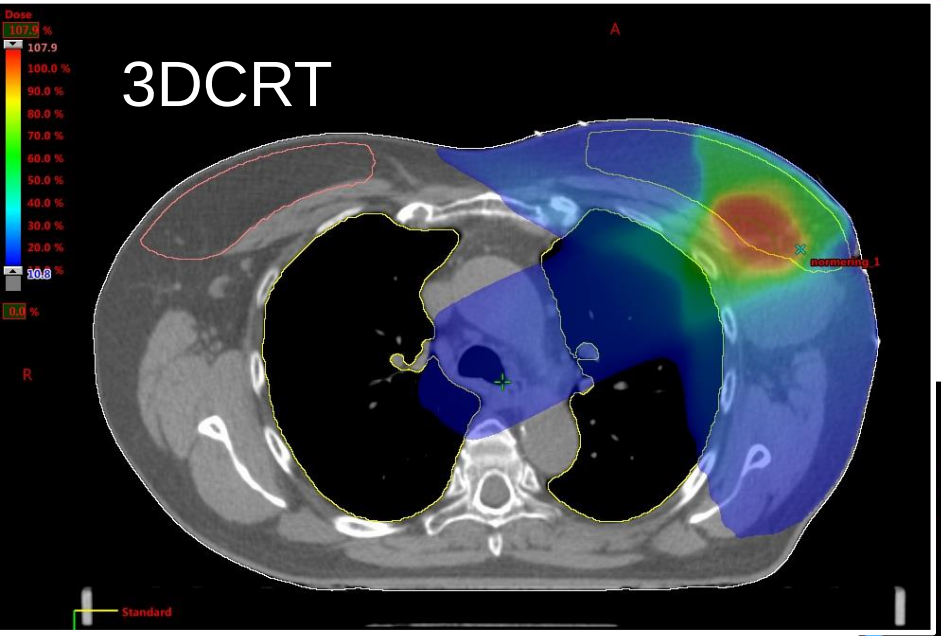
Isodoses

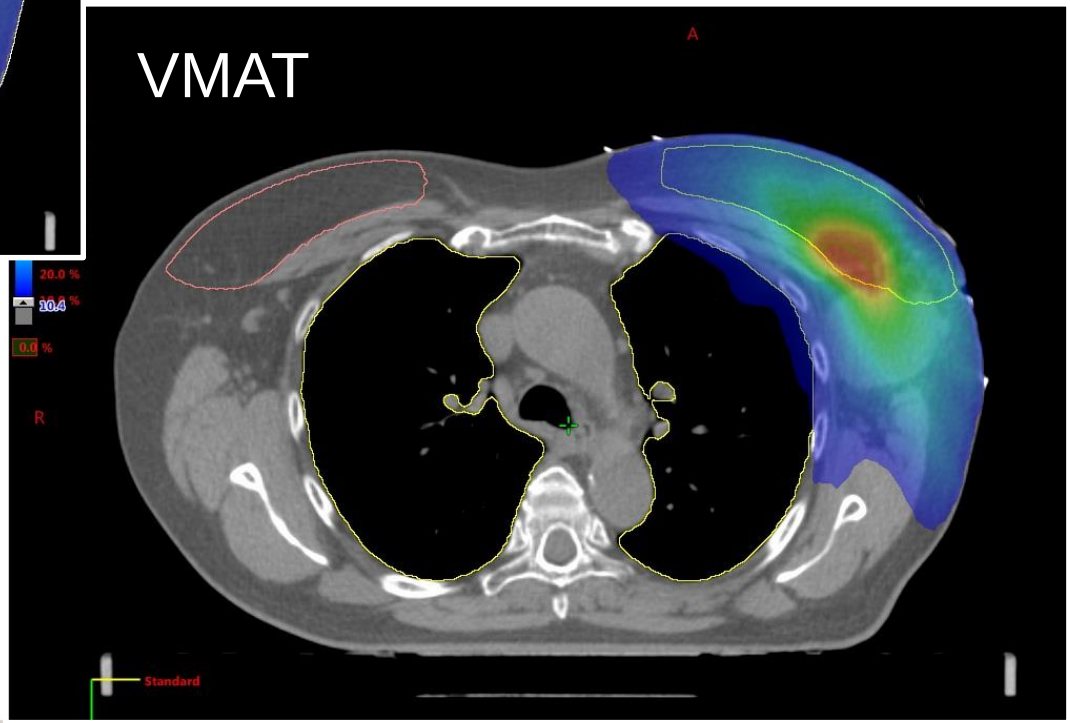




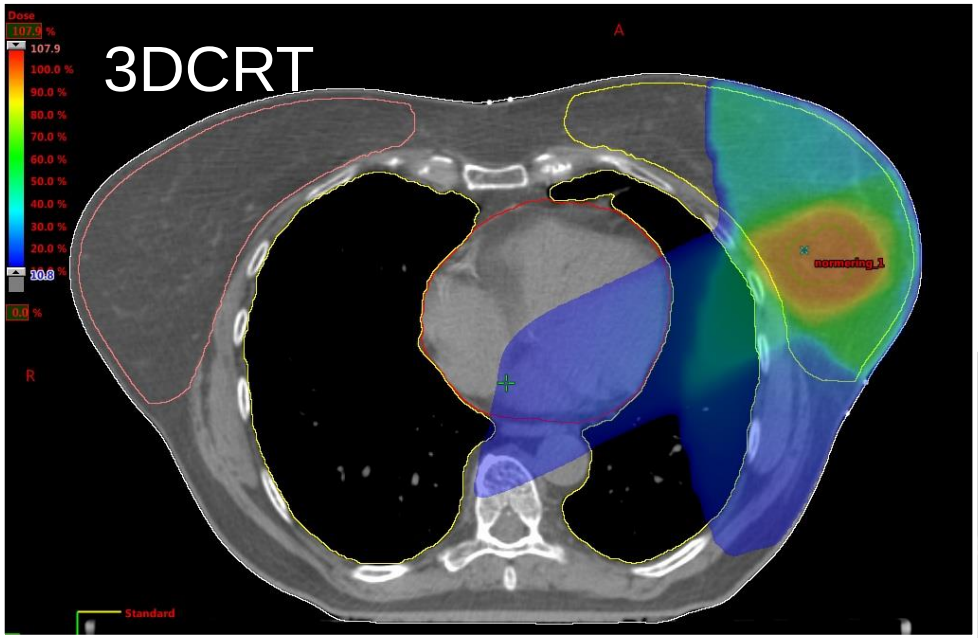
ESTRO School

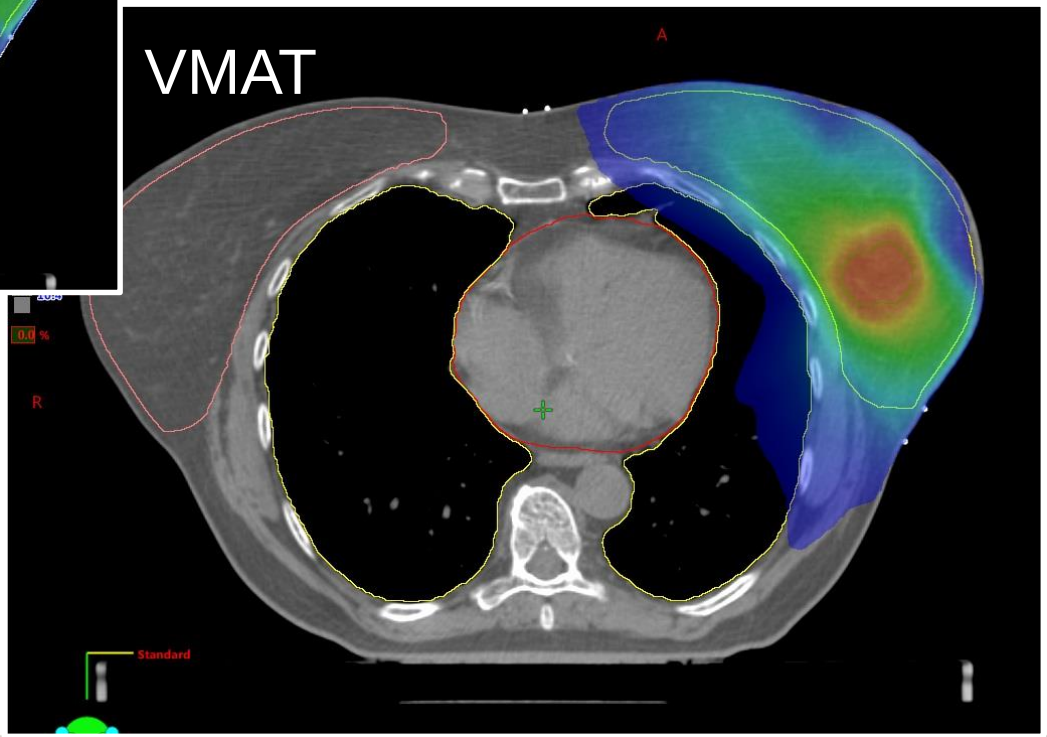
Isodoses


3DCRT
Dose
107.9 %
107.9
100.0 %
90.0 %
80.0 %
70.0 %
60.0 %
50.0 %
40.0 %
30.0 %
20.0 %
10.8 %
0.0 %
A
R
Standard


VMAT
20.0 %
10.4 %
0.0 %
A
R
Standard

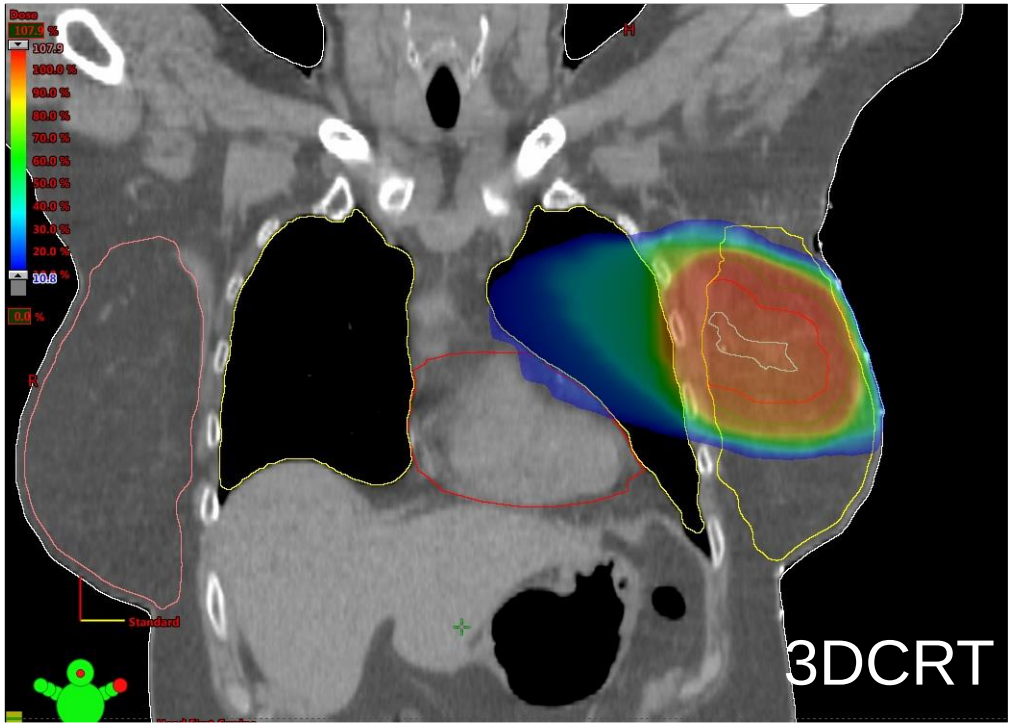
Isodoses

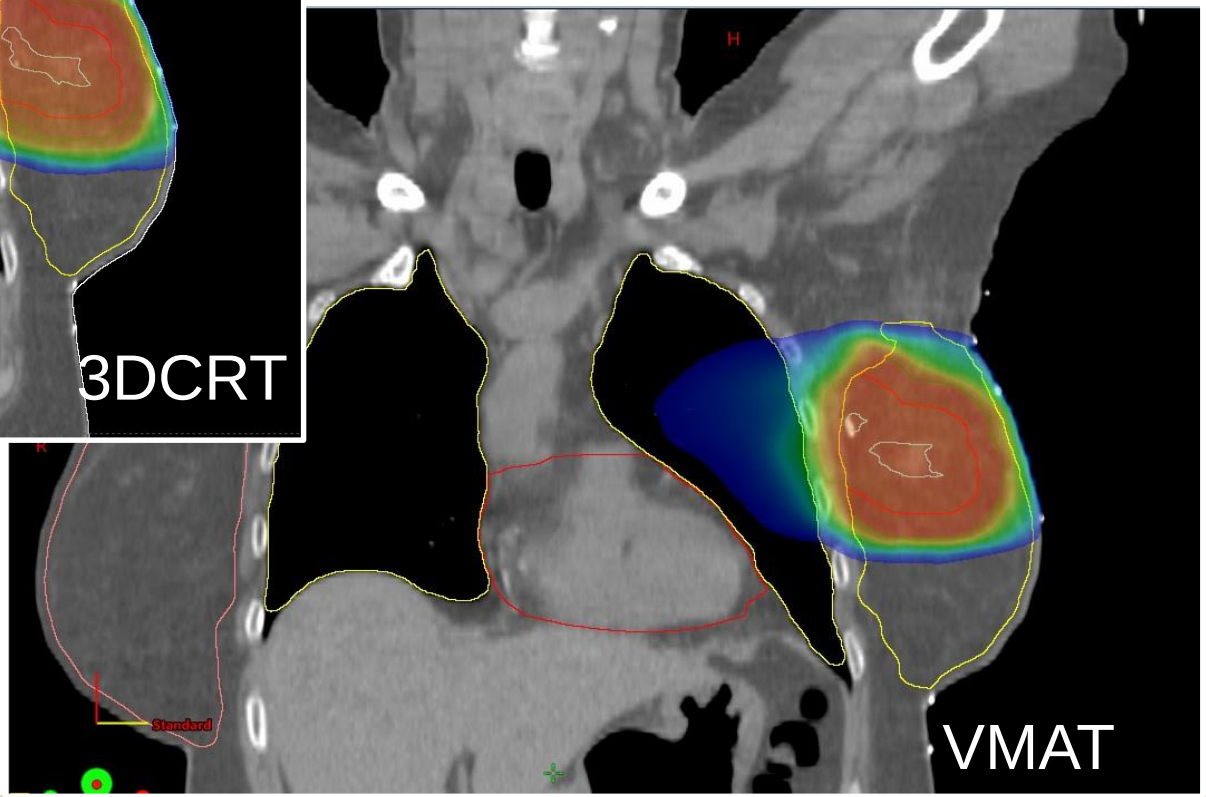




ESTRO School

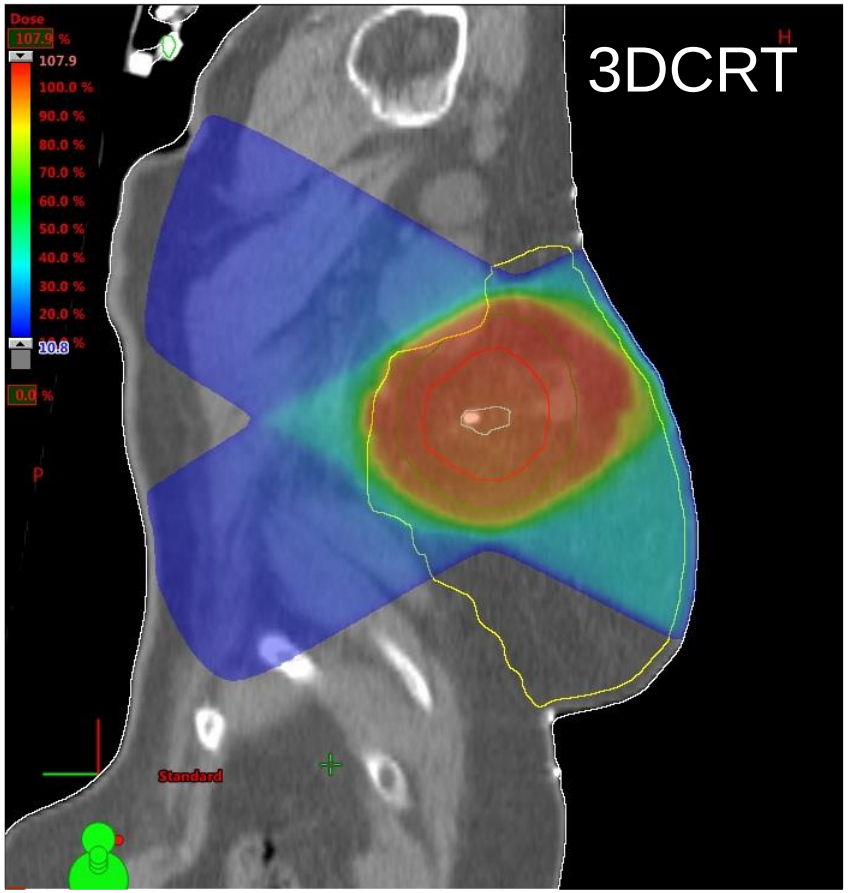
Isodoses

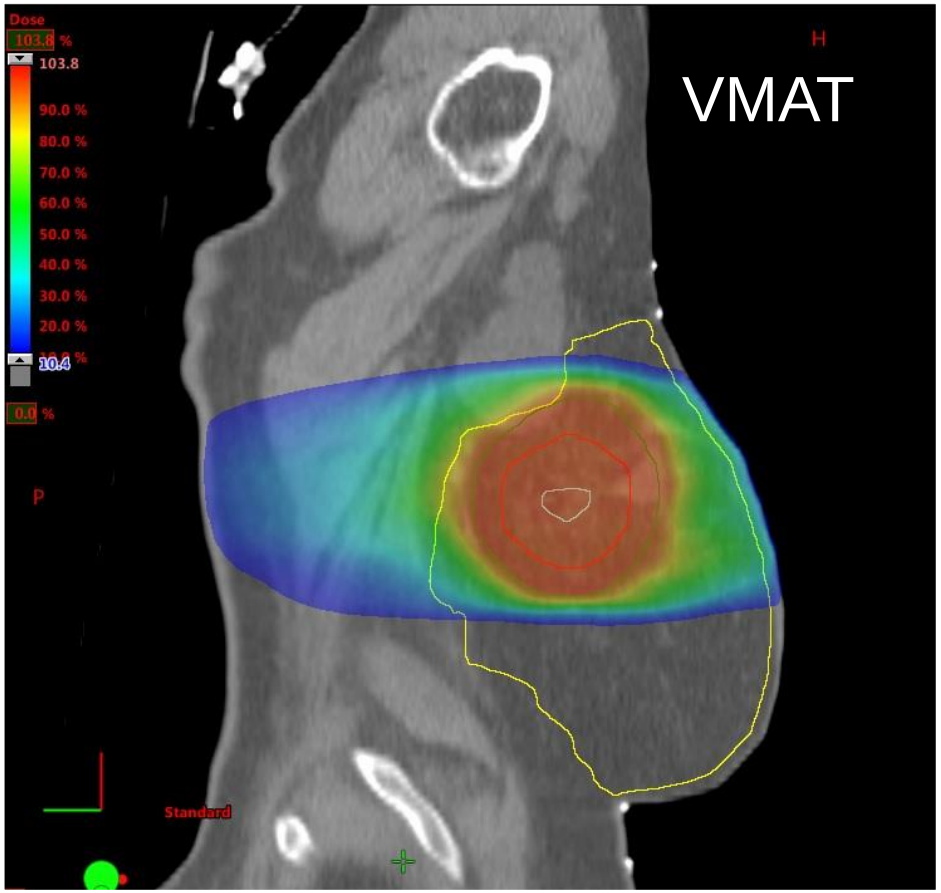




ESTRO School

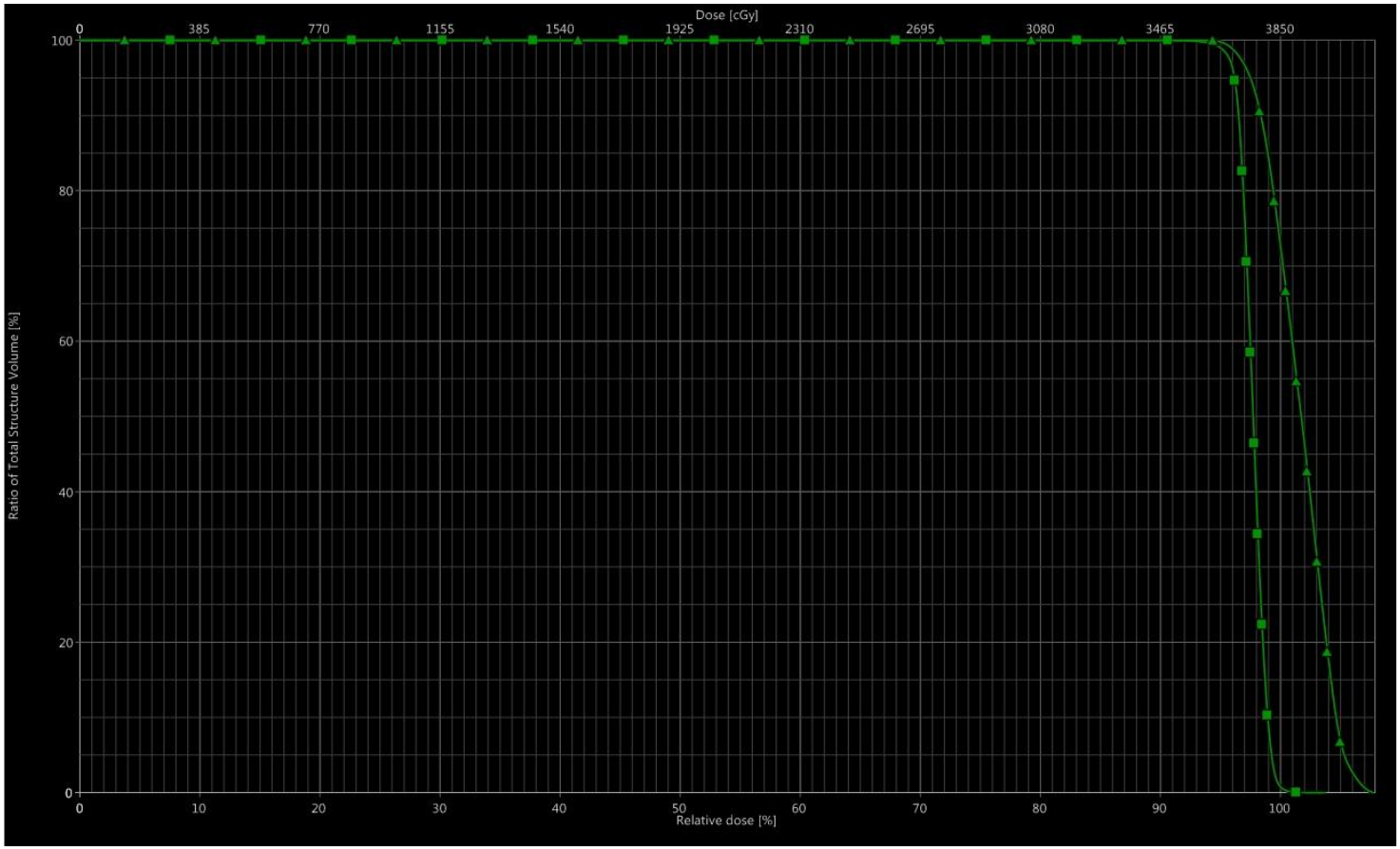
Isodoses





ESTRO School

PTV

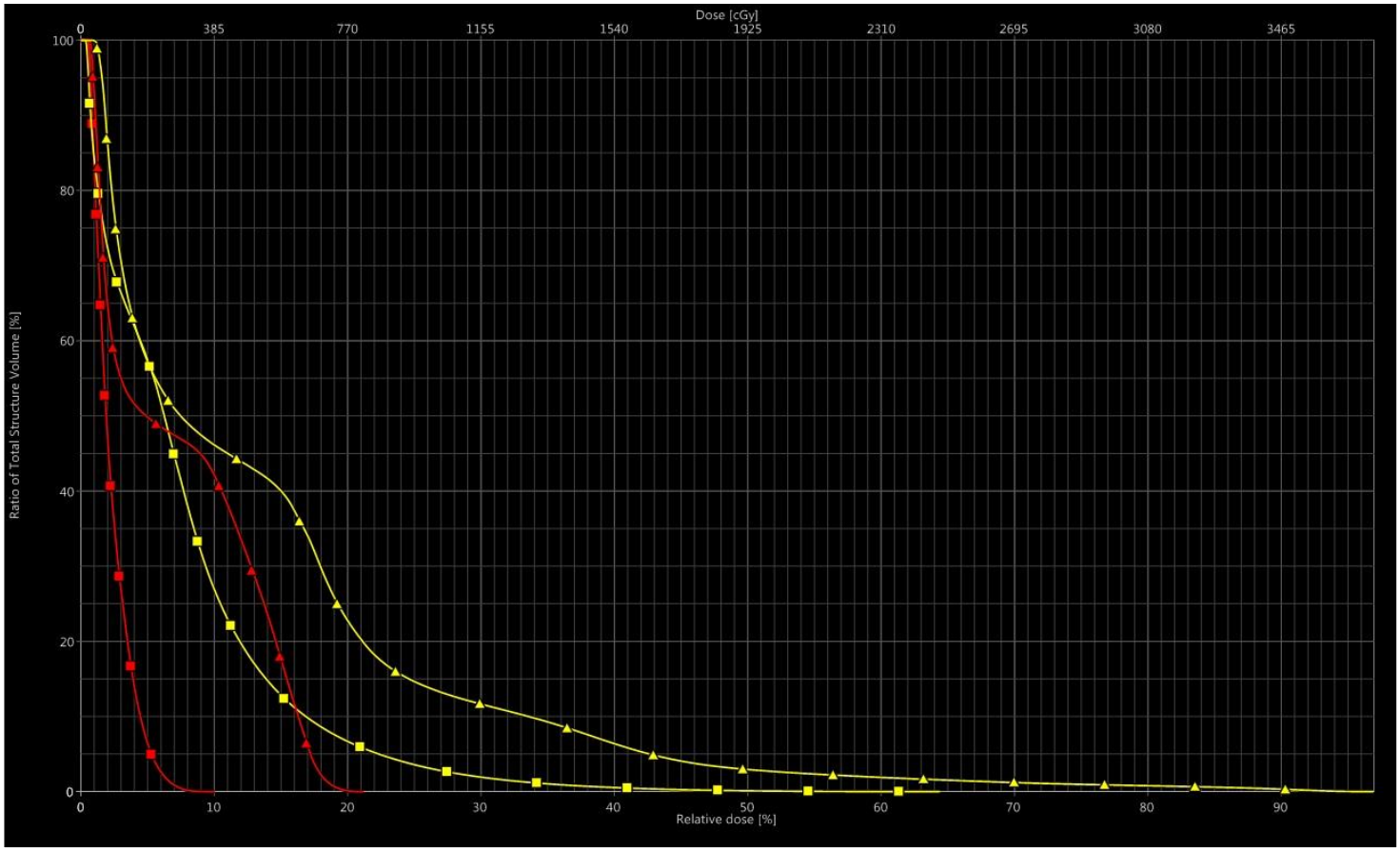


■ VMAT

▲ 3DCRT

ESTRO School

Heart and Lung Left

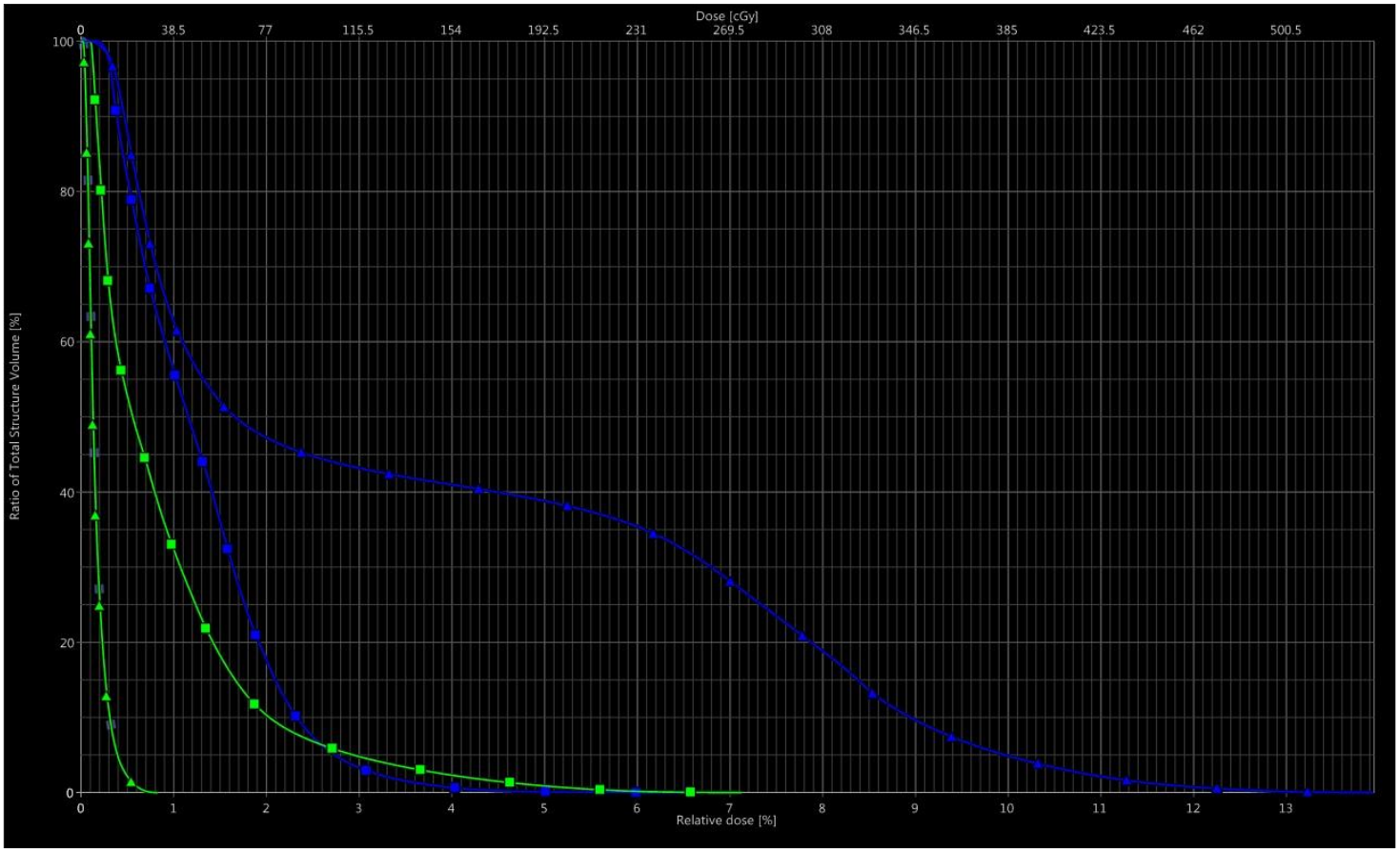


■ VMAT
▲ 3DCRT

Heart
Lung Left

ESTRO School

Contralateral



■ VMAT

▲ 3DCRT

Breast Right

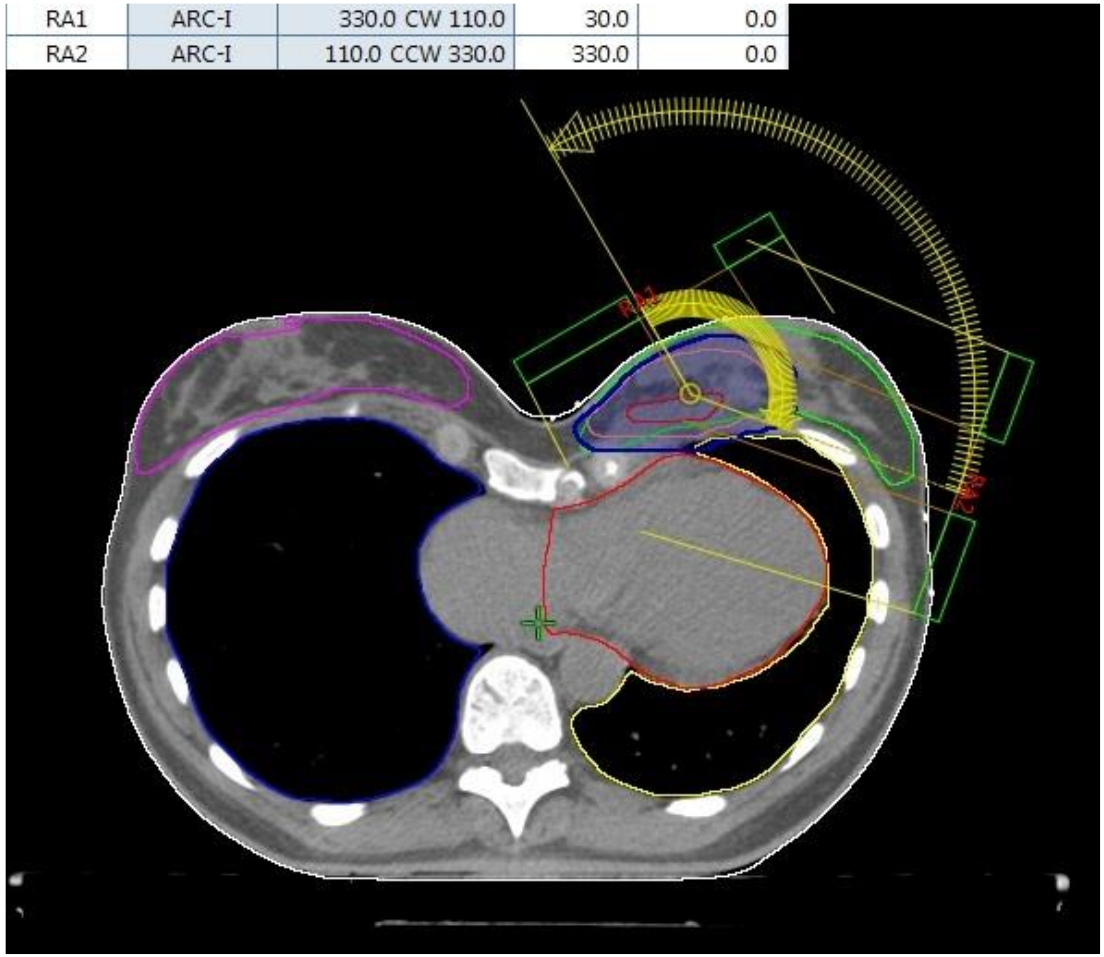
Lung Right

ESTRO School

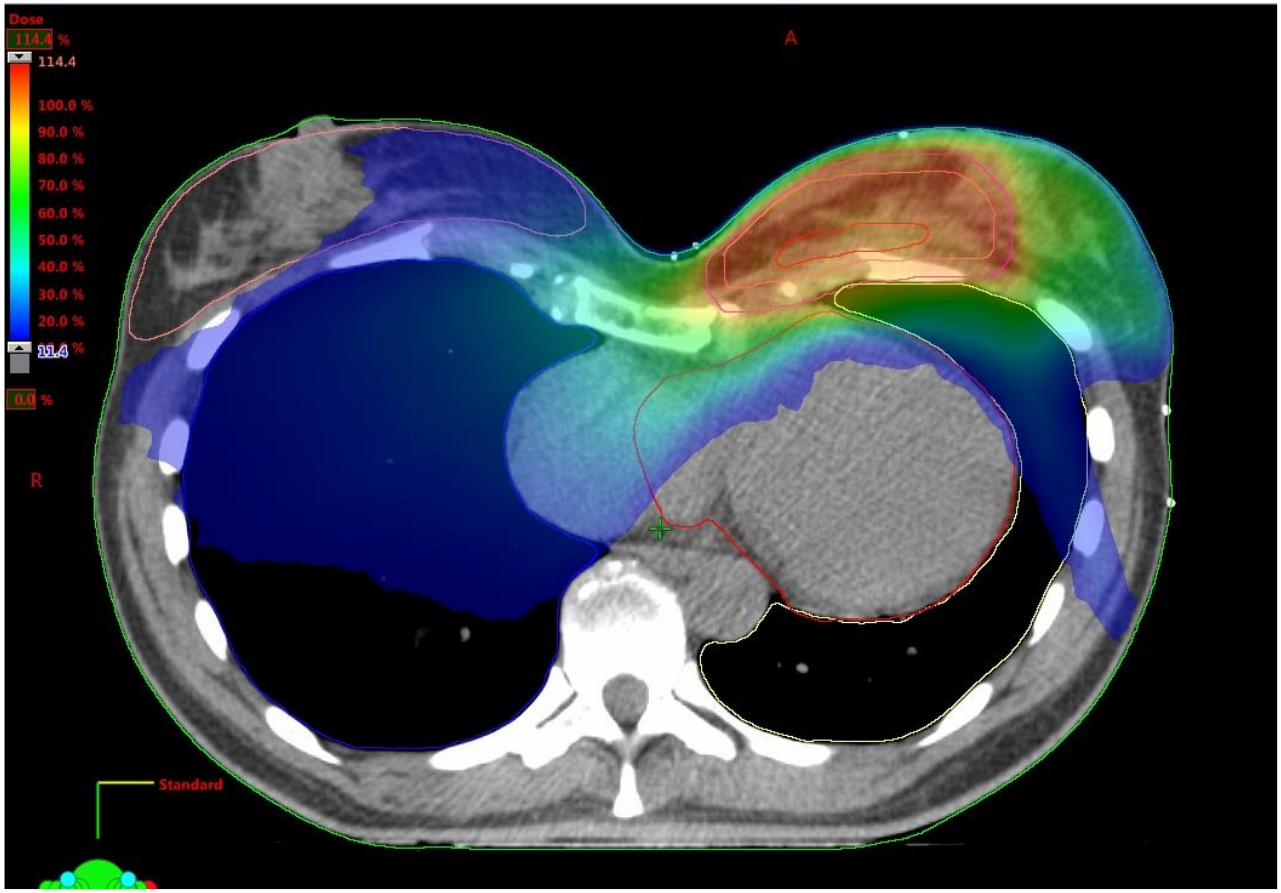
APBI Left

- 10 x 3,85 Gy twice per day

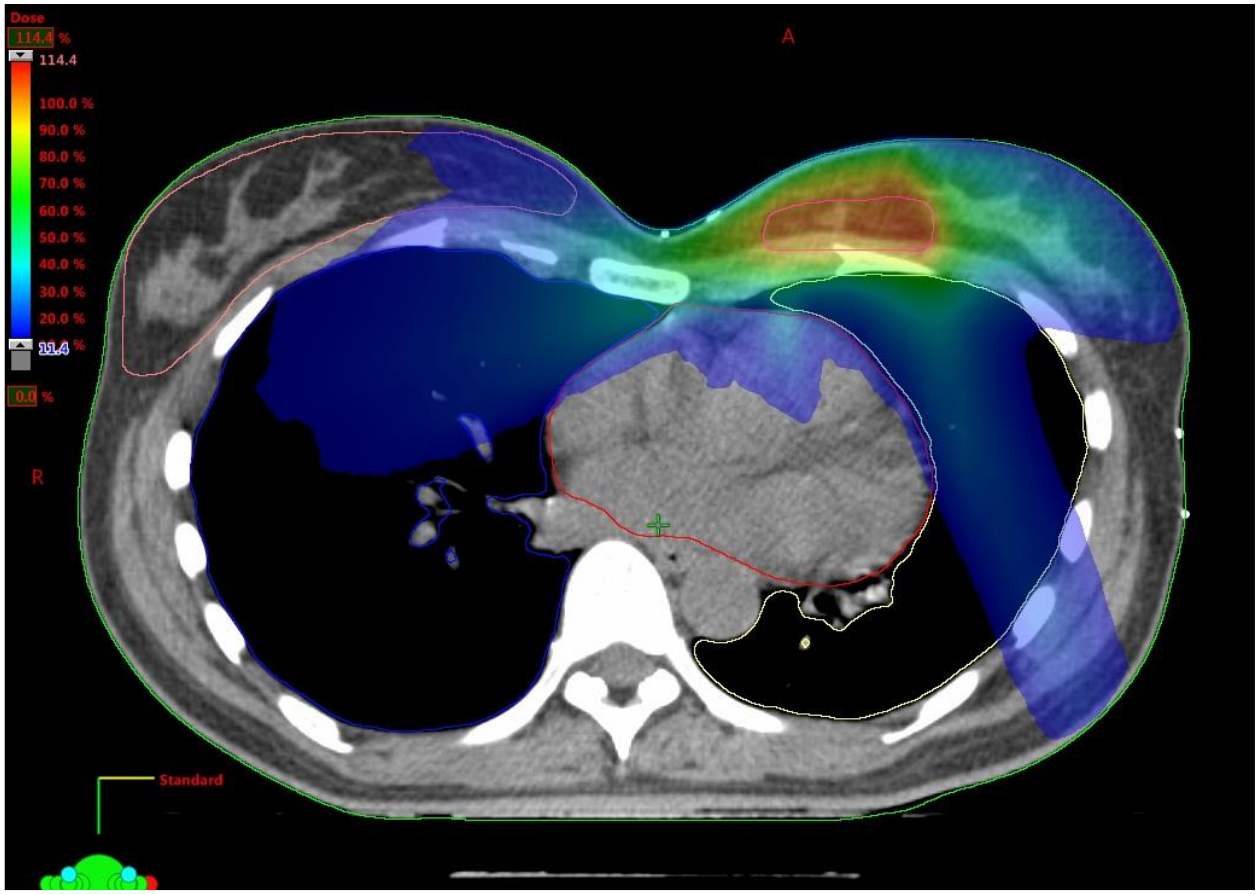
VMAT patient



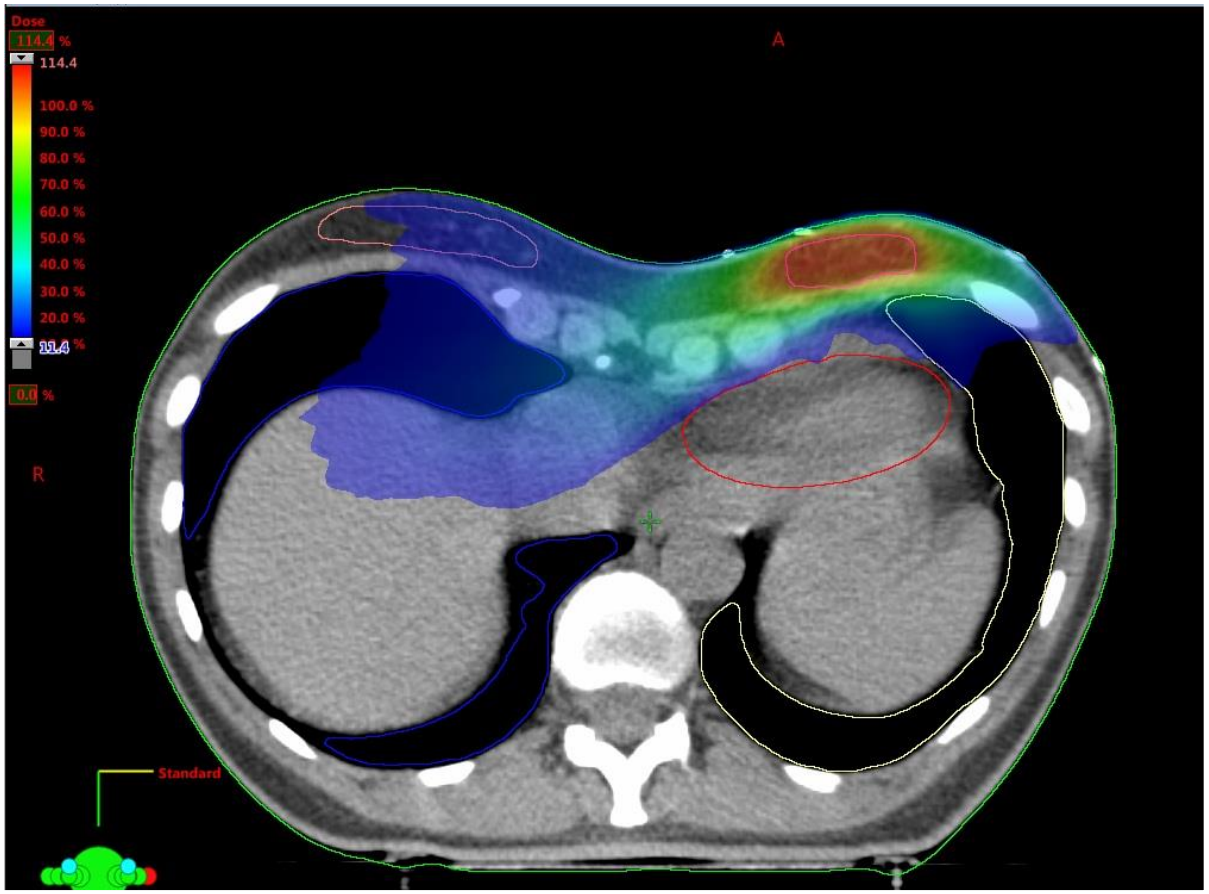
Isodoses


Dose
114.4 %
114.4
100.0 %
90.0 %
80.0 %
70.0 %
60.0 %
50.0 %
40.0 %
30.0 %
20.0 %
11.4 %
0.0 %
A
R
Standard

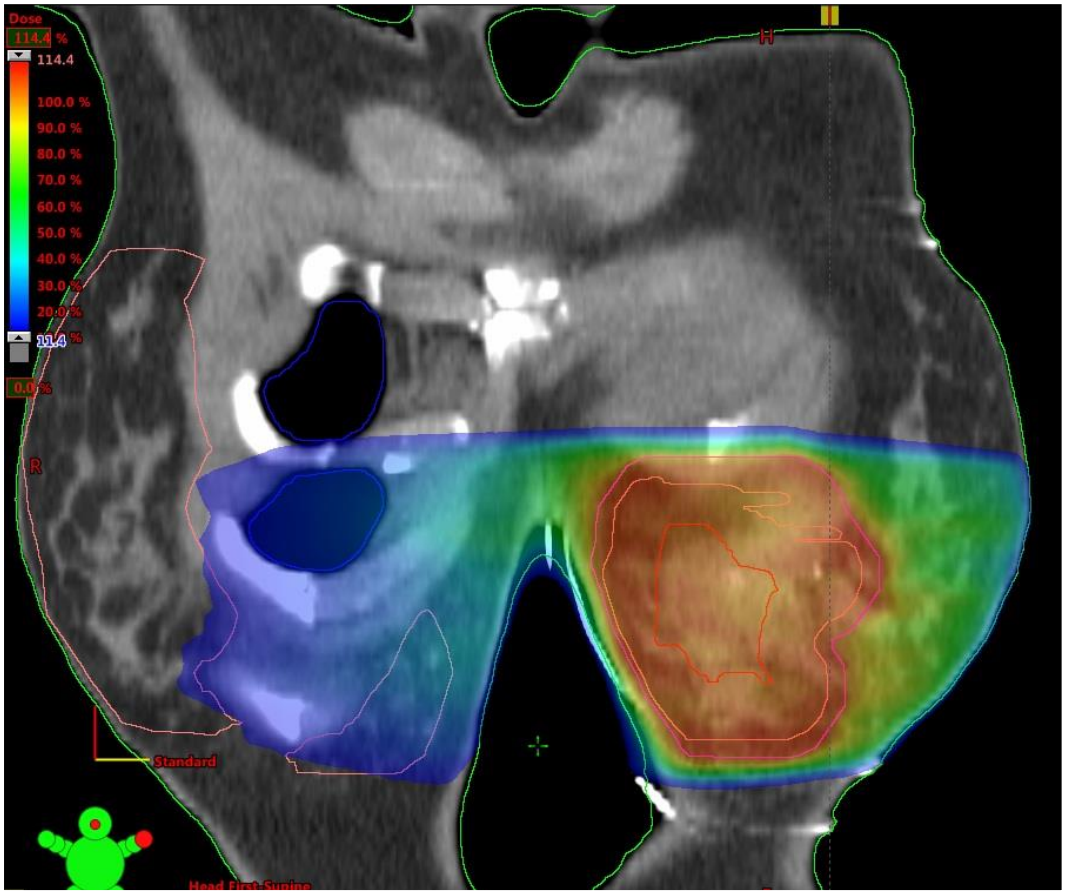
Isodoses


Dose
114.4 %
114.4
100.0 %
90.0 %
80.0 %
70.0 %
60.0 %
50.0 %
40.0 %
30.0 %
20.0 %
11.4 %
0.0 %
A
R
Standard

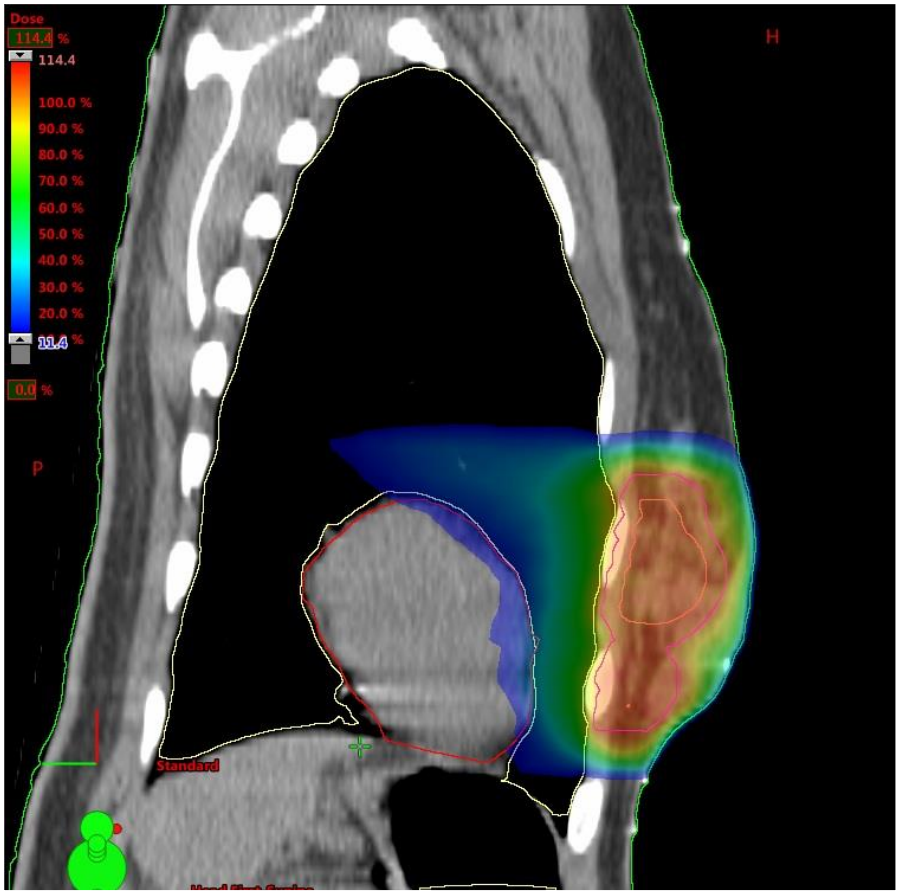
Isodoses


Dose
114.4 %
114.4
100.0 %
90.0 %
80.0 %
70.0 %
60.0 %
50.0 %
40.0 %
30.0 %
20.0 %
11.4 %
0.0 %
A
R
Standard

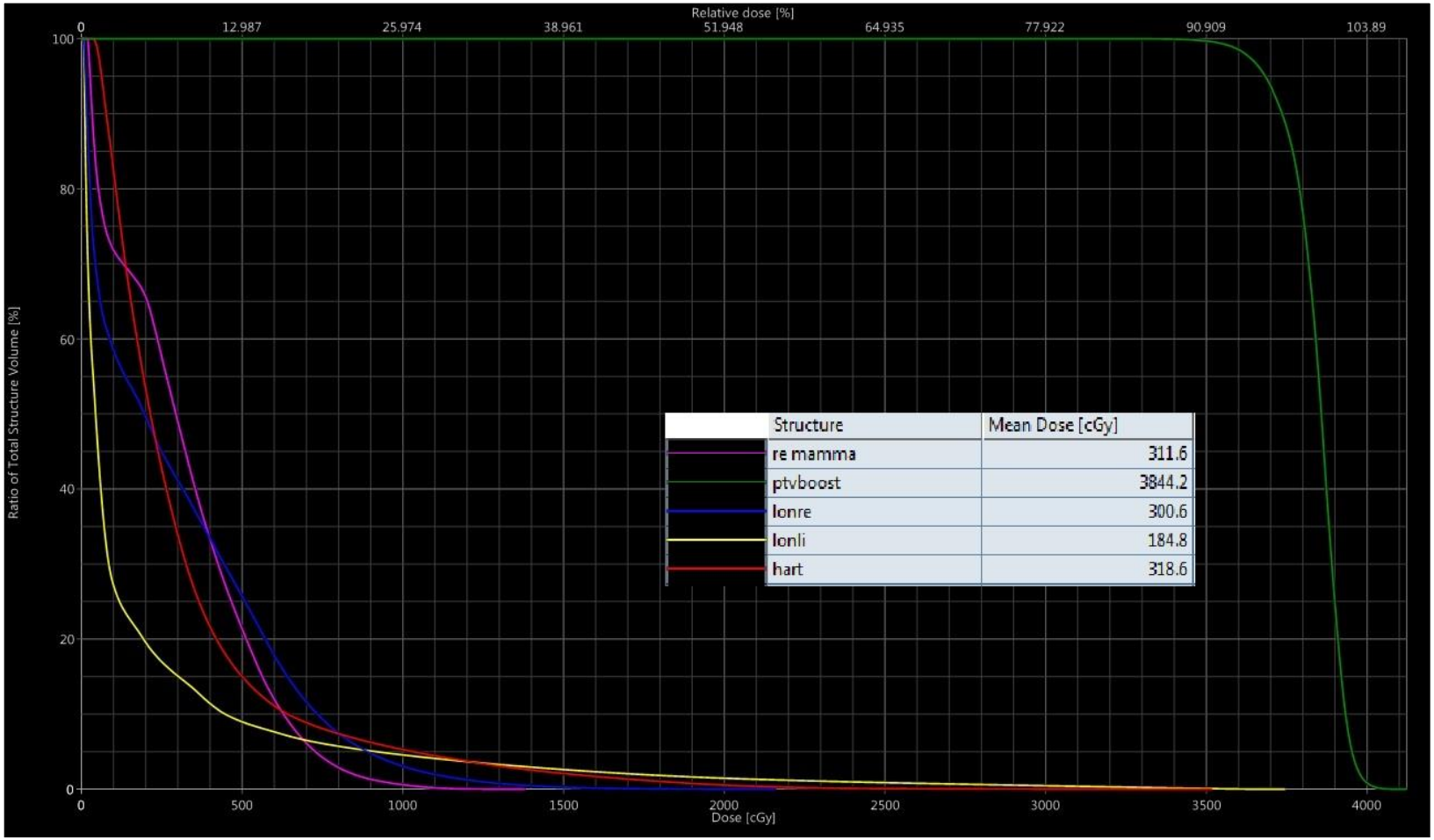
Isodoses


Dose
114.4 %
114.4
100.0 %
90.0 %
80.0 %
70.0 %
60.0 %
50.0 %
40.0 %
30.0 %
20.0 %
11.4
0.0 %
H
R
Standard
Head First-Supine

Isodoses


Dose
114.4 %
114.4
100.0 %
90.0 %
80.0 %
70.0 %
60.0 %
50.0 %
40.0 %
30.0 %
20.0 %
11.4 %
0.0 %
H
P
Standard

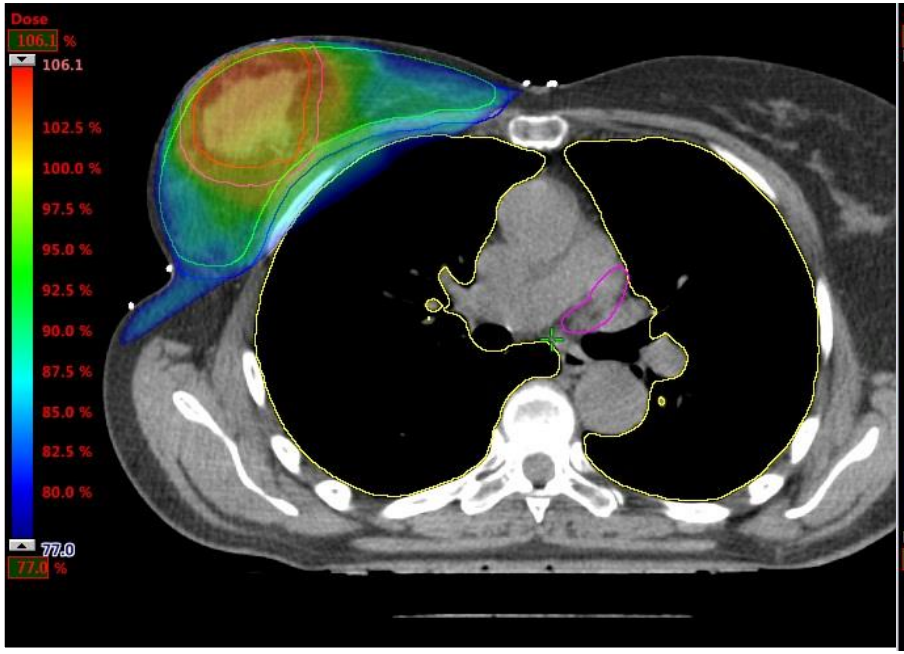
DVH


Relative dose [%]
0
12.987
25.974
38.961
51.948
64.935
77.922
90.909
103.89
100
80
60
40
20
0
Ratio of Total Structure Volume [%]
0
500
1000
1500
2000
2500
3000
3500
4000
Dose [cGy]
Structure
Mean Dose [cGy]
re mamma
311.6
ptvboost
3844.2
lonre
300.6
lonli
184.8
hart
318.6

SIB right

- 21 x 2,17 on whole breast
- 21 x 2,66 on primary tumorbed

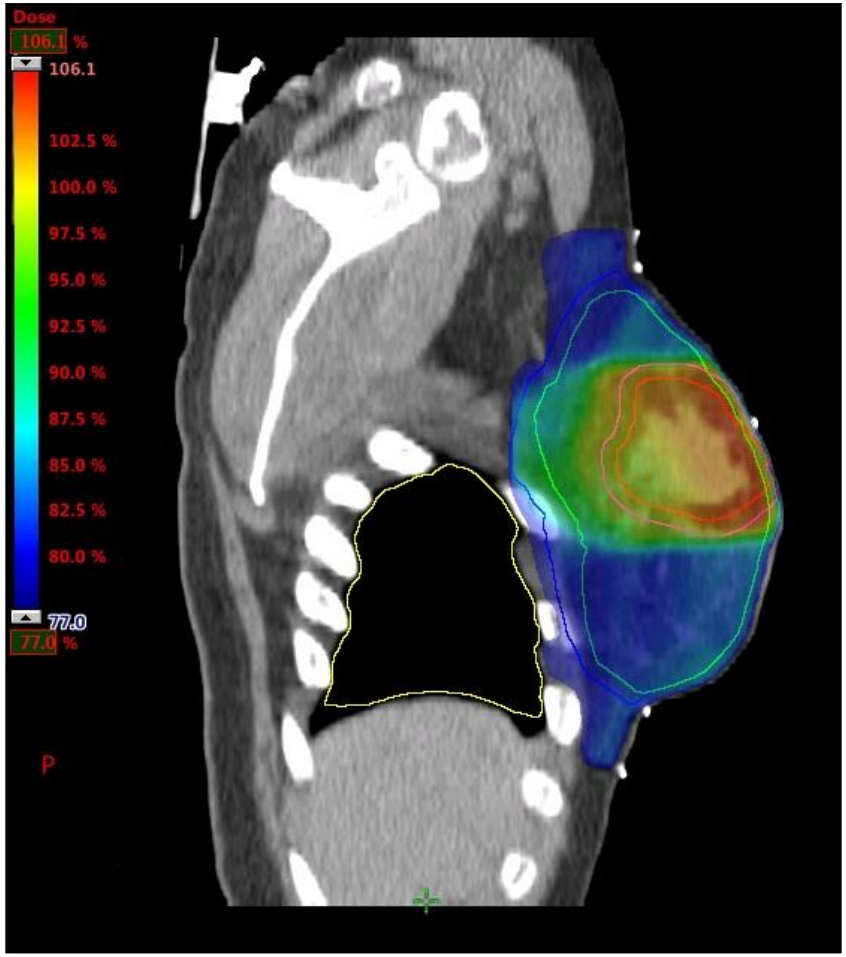
SIB



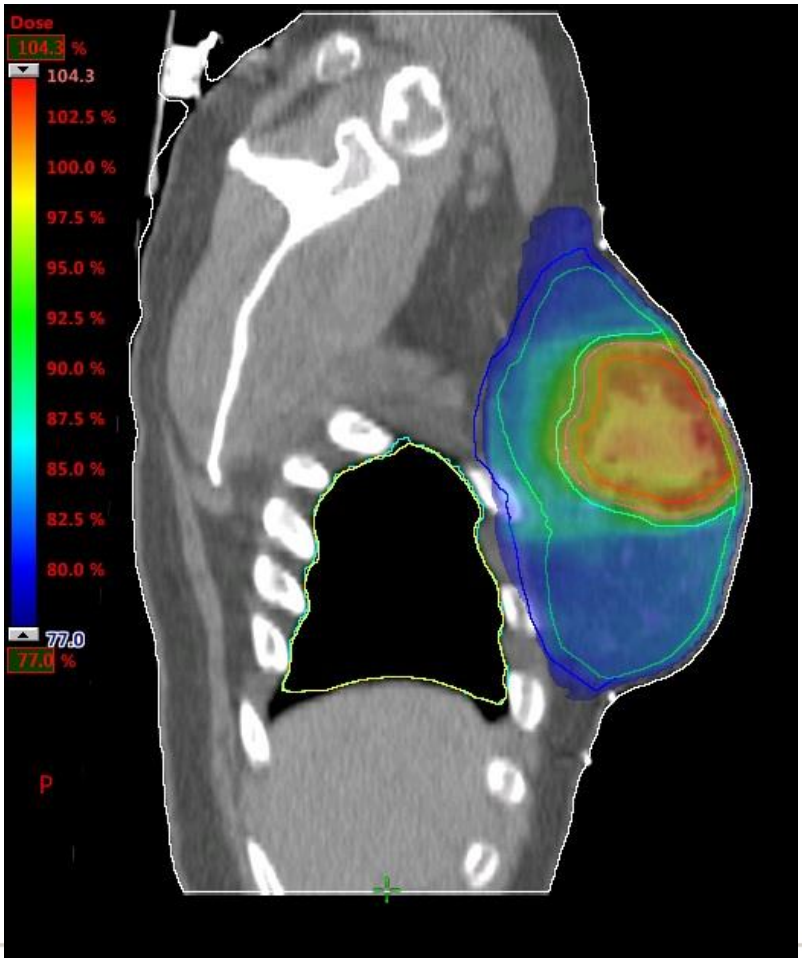
3DCRT

IMRT

ESTRO School



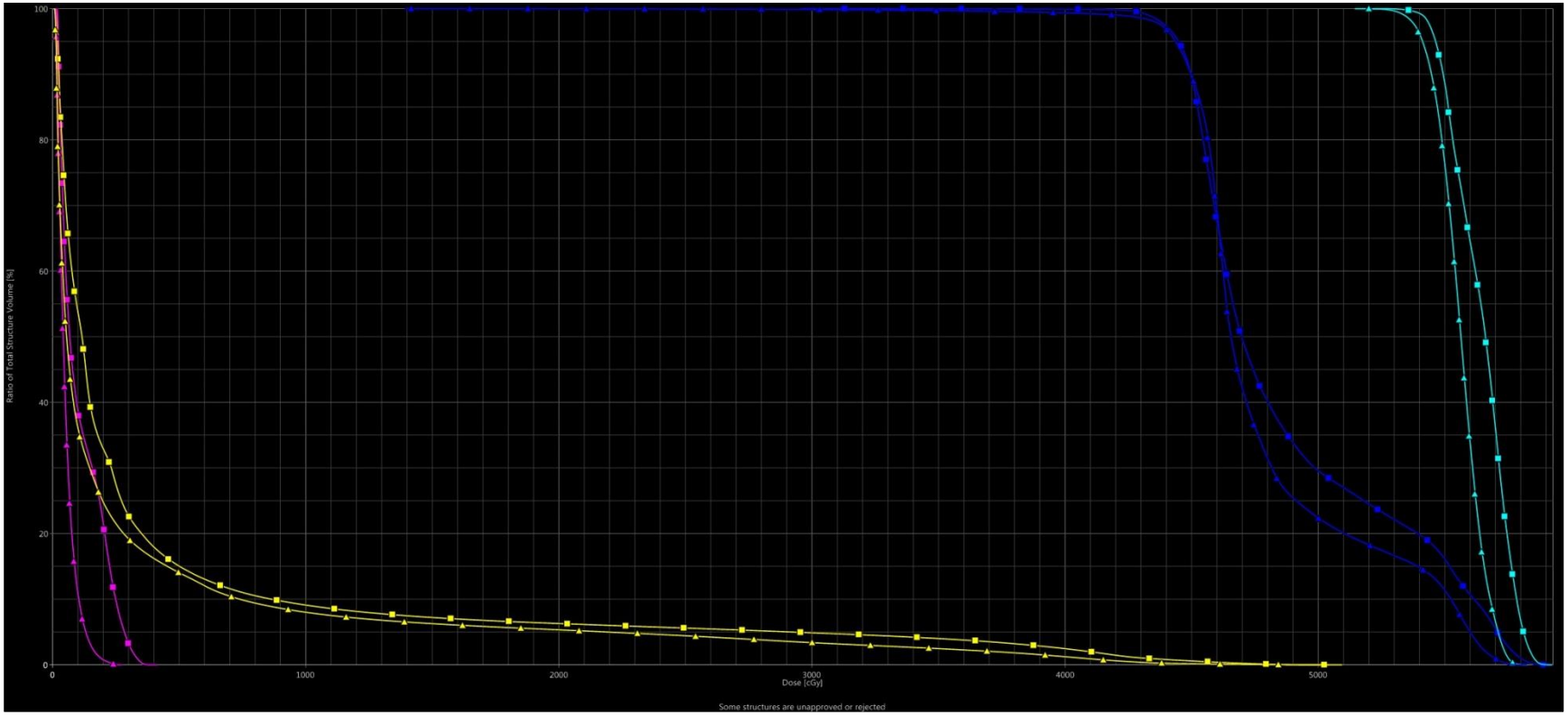
3DCRT



IMRT

ESTRO School

DVH



■ FiF

▲ IMRT

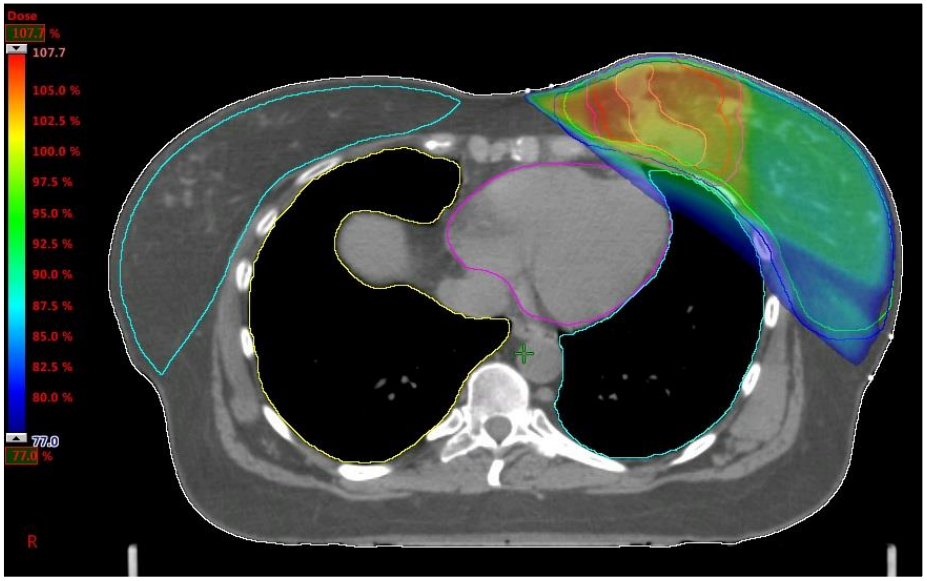
ESTRO School

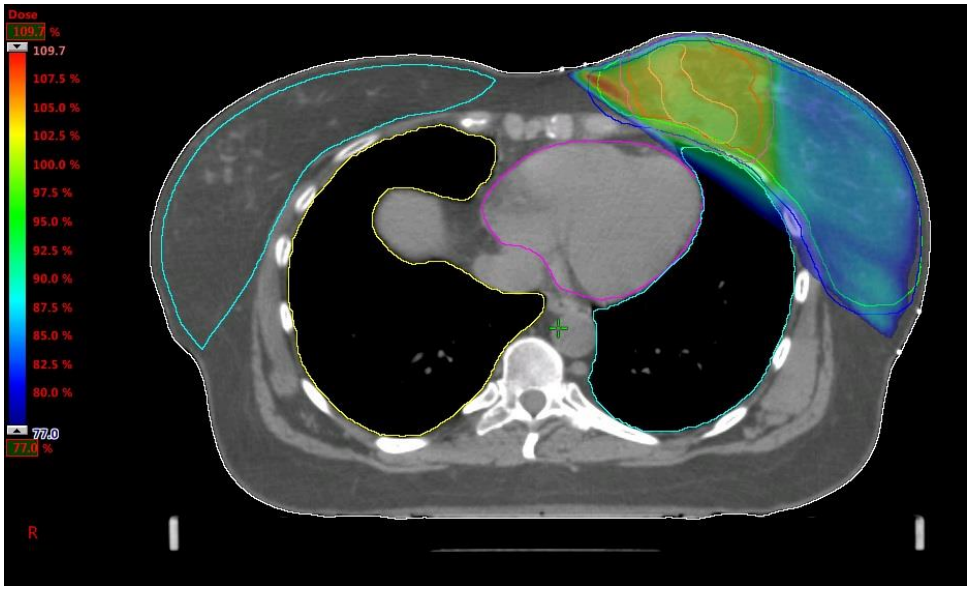
DVH values

	Lungs		Heart			
	V20	MLD	V20	V10	V5	MHD
FiF	6,3	414	0	0	0	110
IMRT	5,3	331	0	0	0	53

SIB Left

- 21 x 2,17 on whole breast
- 21 x 2,66 on primary tumorbed

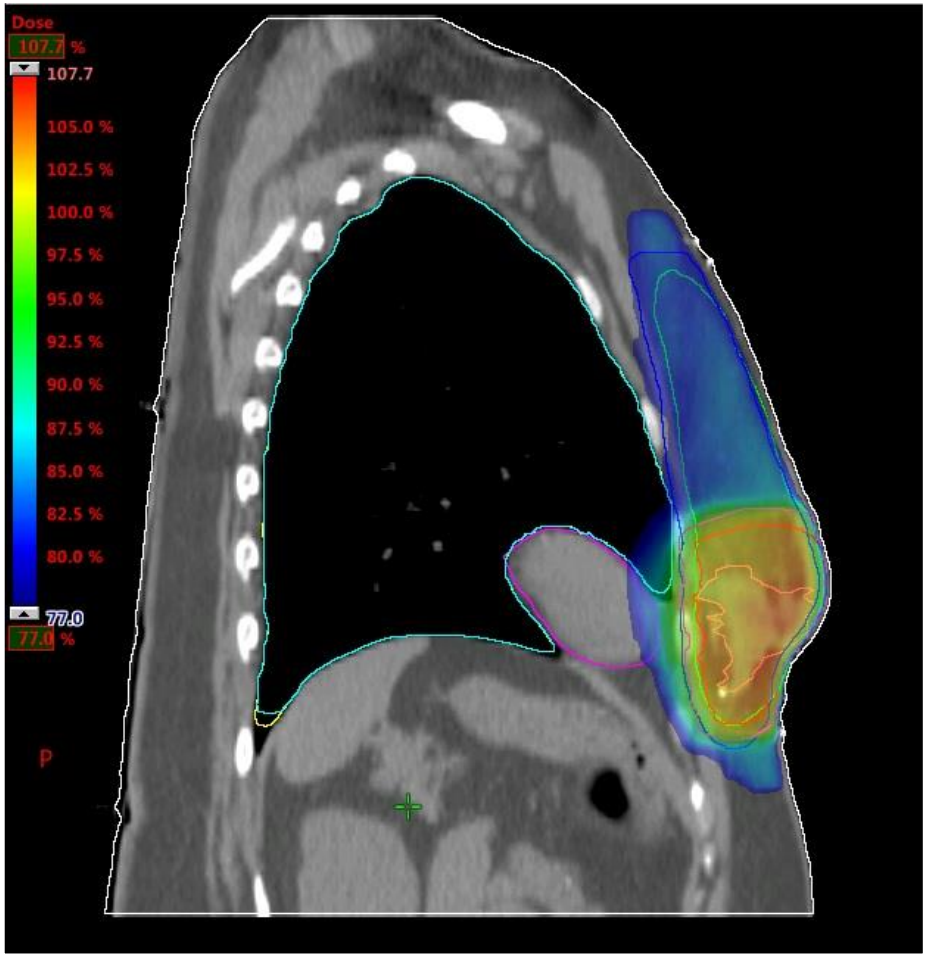




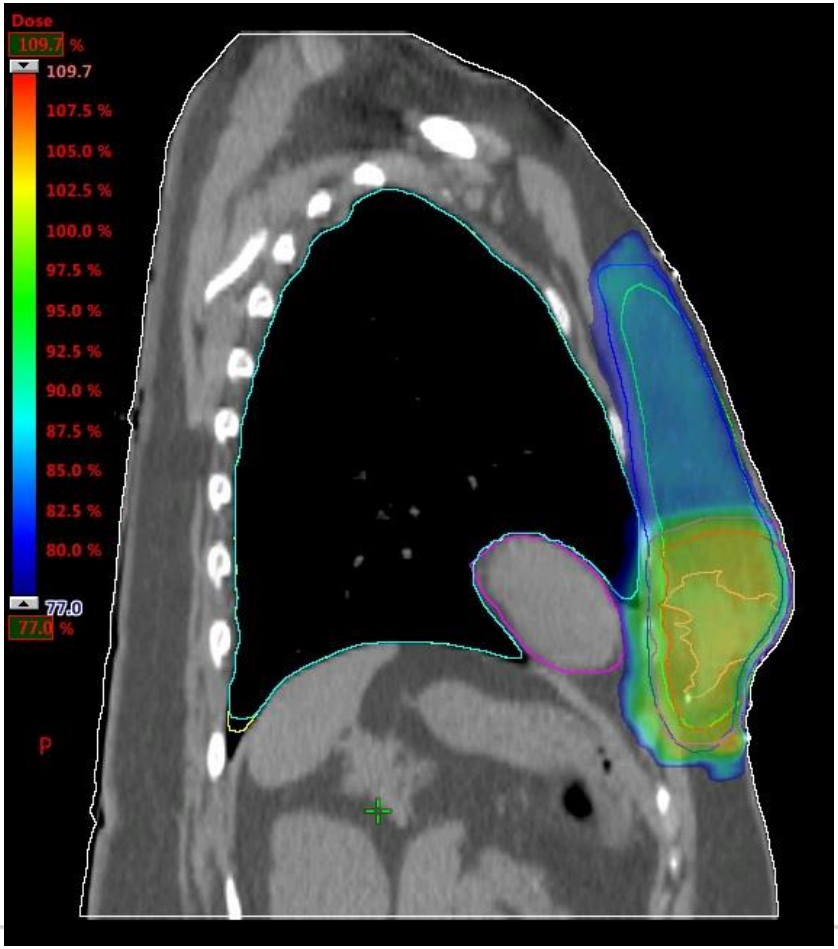
3DCRT

IMRT

ESTRO School



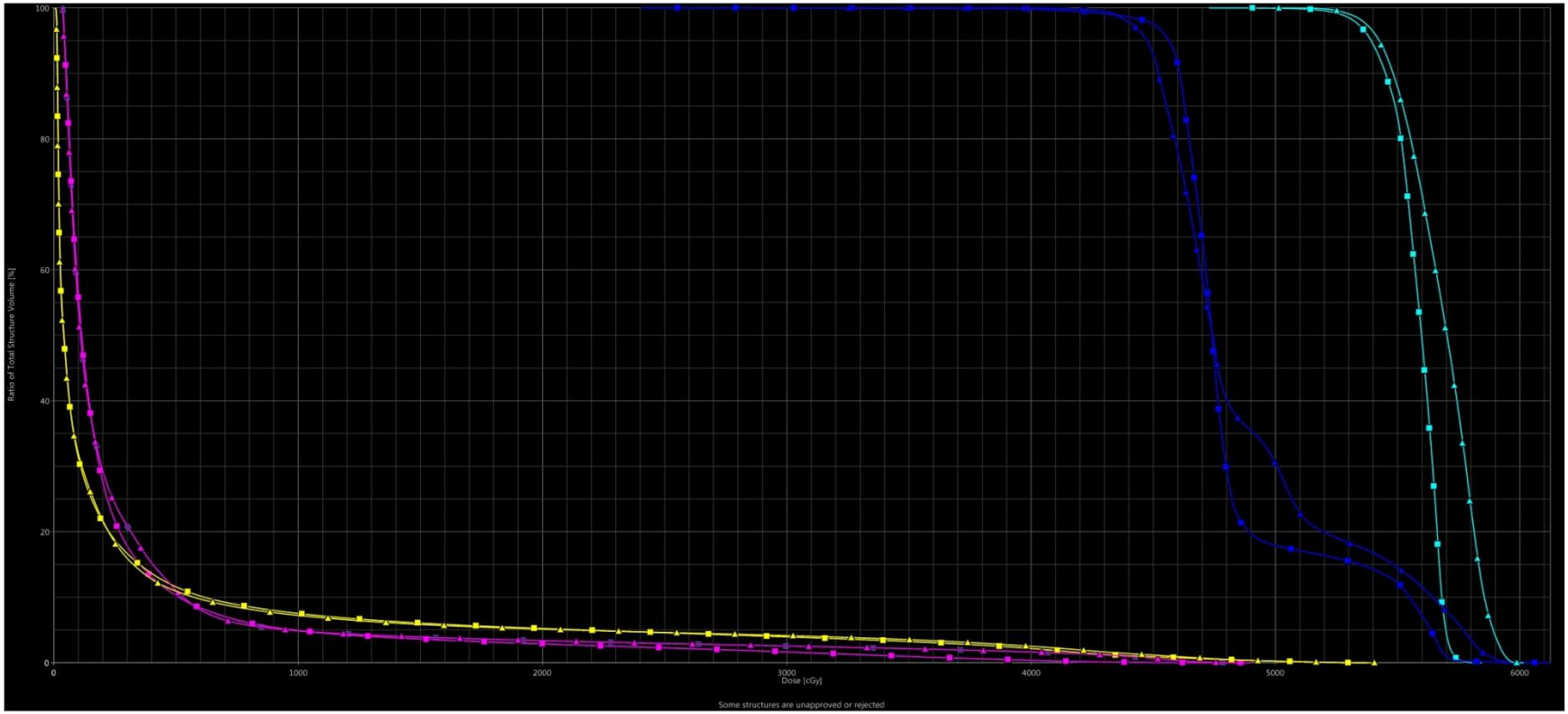
3DCRT



IMRT

ESTRO School

DVH



■ IMRT

▲ FiF

ESTRO School

DVH values

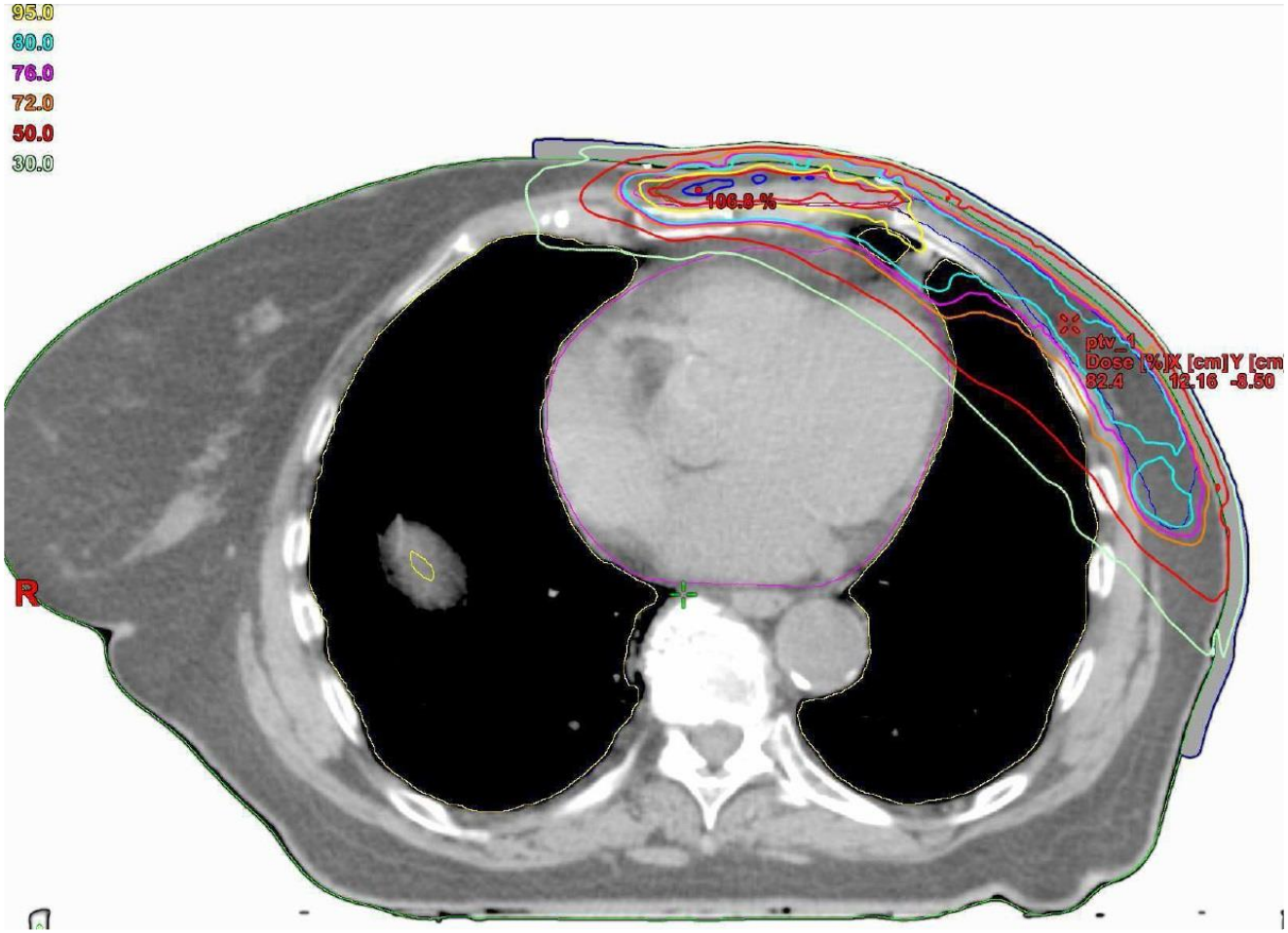
	Lungs		Heart			
	V20	MLD	V20	V10	V5	MHD
FiF	5,2	321	3,4	4,9	11,1	310
IMRT	5,2	321	2,9	4,9	10,3	278

Breast Left SIB RA

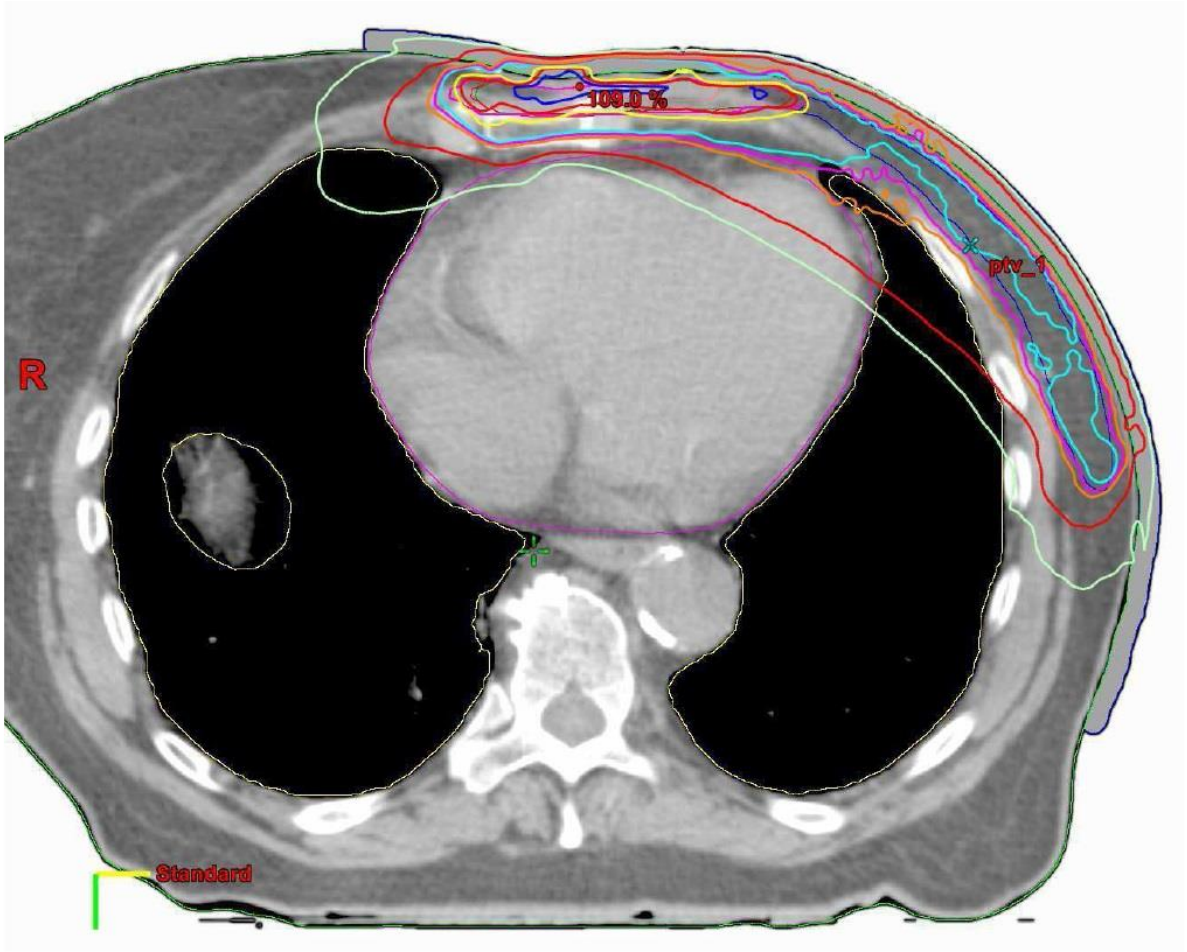
23 x 2,03 Gy on thoracic wall

23 x 2,66 Gy on primary tumorbed

Isodoses

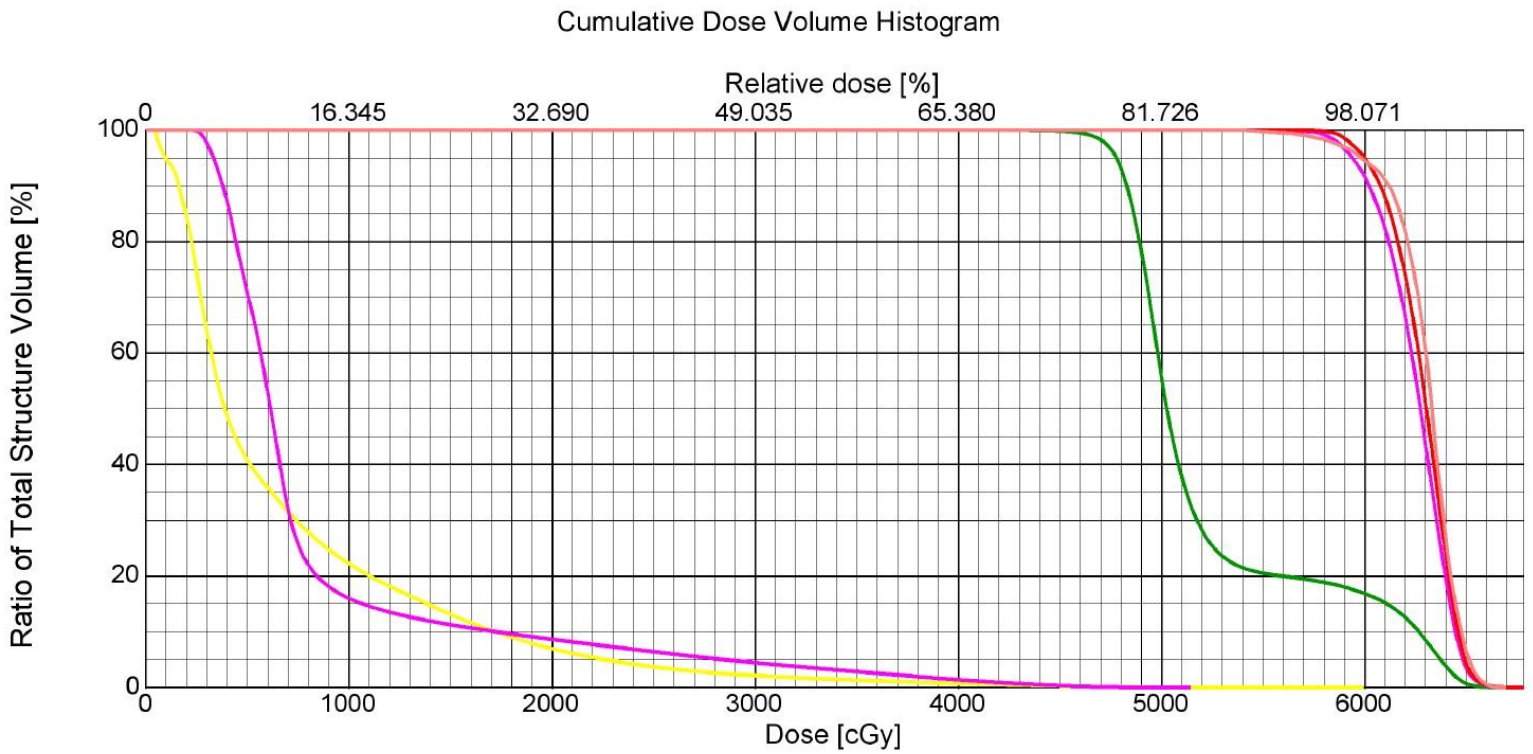


Isodoses



ESTRO School

DVH



Structure	Structure Status	Coverage [%/%]	Volume	Min Dose	Max Dose	Mean Dose	Modal Dose	Median Dose	Std Dev
ptvboost	Approved	100.0 / 100.0	59.7 cm³	5152.4 cGy	6784.7 cGy	6252.5 cGy	6324.2 cGy	6273.9 cGy	166.1 cGy
ctvthoraxwand	Approved	100.0 / 100.0	287.4 cm³	3959.9 cGy	6784.7 cGy	5240.1 cGy	4972.5 cGy	5025.7 cGy	519.4 cGy
hart	Approved	100.0 / 100.0	866.2 cm³	186.2 cGy	5143.7 cGy	852.4 cGy	650.0 cGy	613.5 cGy	783.1 cGy
longen	Approved	100.0 / 100.0	2878.9 cm³	35.3 cGy	5996.5 cGy	707.1 cGy	246.0 cGy	388.3 cGy	750.8 cGy
ctvboost	Approved	100.0 / 100.3	44.3 cm³	5678.2 cGy	6784.7 cGy	6284.5 cGy	6324.0 cGy	6303.5 cGy	150.3 cGy
lumpholte	Approved	100.0 / 100.3	5.3 cm³	5379.9 cGy	6697.1 cGy	6304.8 cGy	6339.7 cGy	6330.6 cGy	163.5 cGy

ESTRO School

Multidisciplinary Course on Breast Cancer

Dublin 10.-13.9.2017

Current Application of SLNB and ALND: Indications, Techniques and Timing

T. Kuehn

Klinikum Esslingen , Germany

Todays issues in lymph node surgery

1. Evolution of lymph node surgery and oncologic significance

2. Standard techniques and new developments

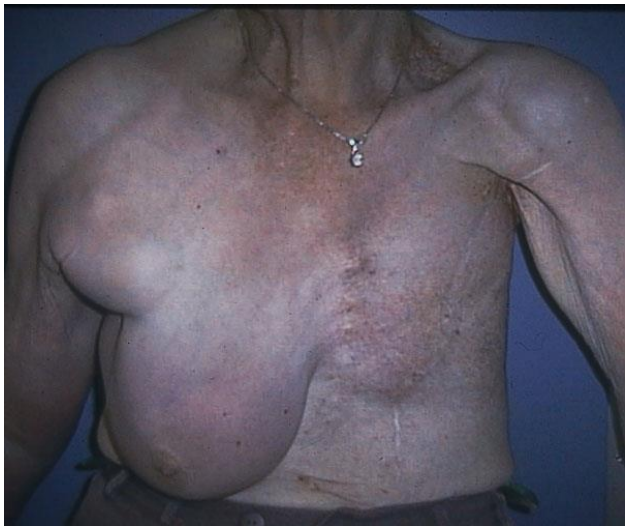
3. Reliability and utility of SLNB in primary surgery and after PST

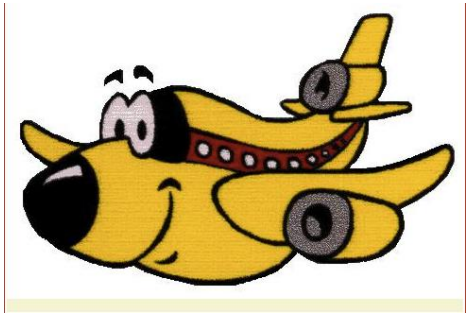
Time Journey of axillary management

The management of lymph nodes reflects treatment strategies

ESTRO School

Until 1980:





Exclusive
local strategy

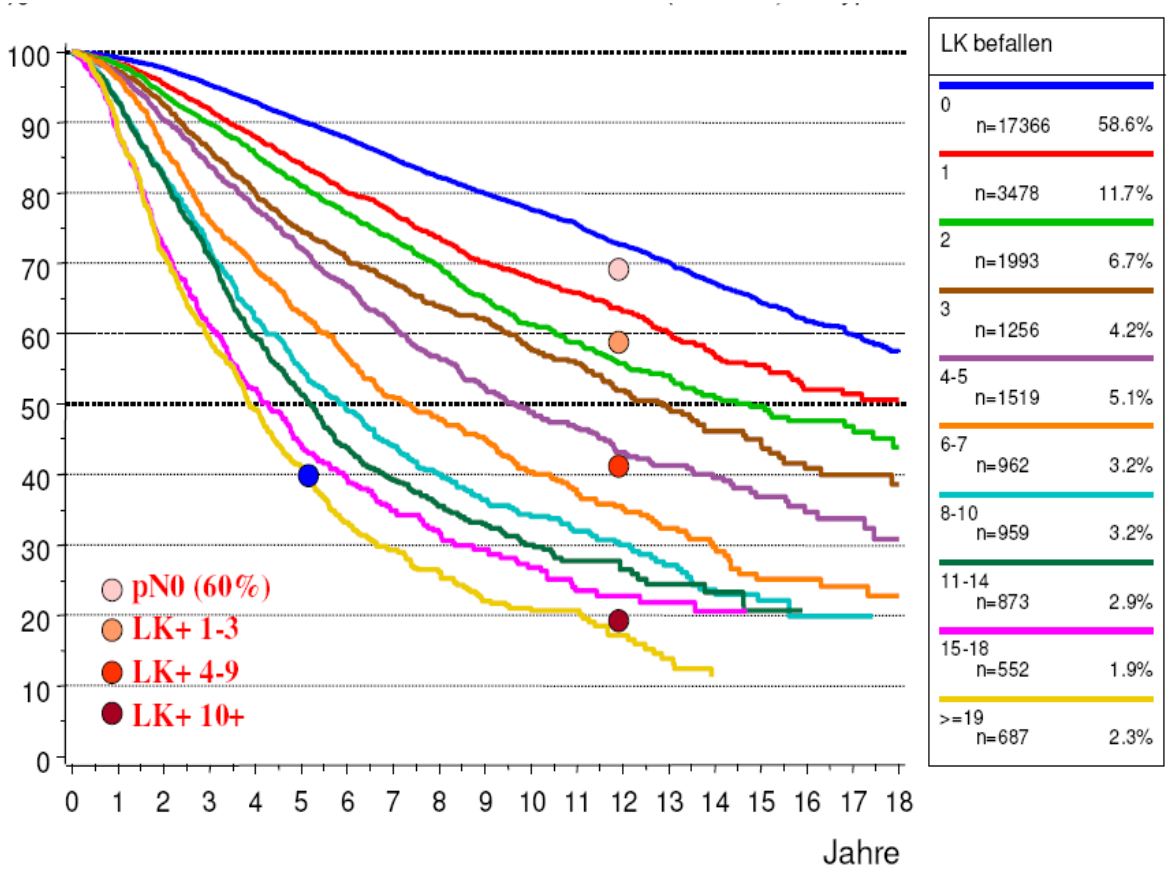
Objective of lymph node surgery:
Mechanical removal of tumor cells

NSABP 04

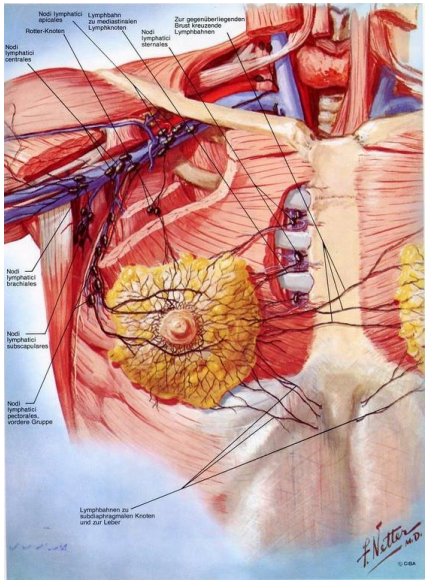
Fisher et al. NEJM 2002

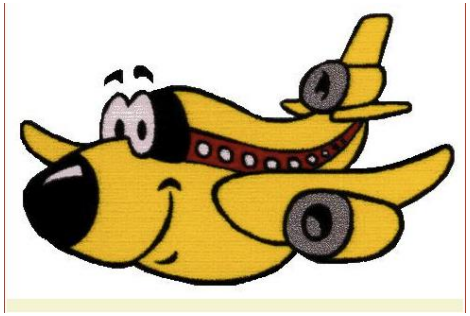
Lymph Node Involvement and Prognosis

Tumor Registry Munich: Breast Cancer
Overall survival according to LN involvement
(n=29645 pts)



AXILLARY DISSECTION (ALD)





Prognosis based strategy

Lymph Node Surgery became a diagnostic procedure in cN0 patients

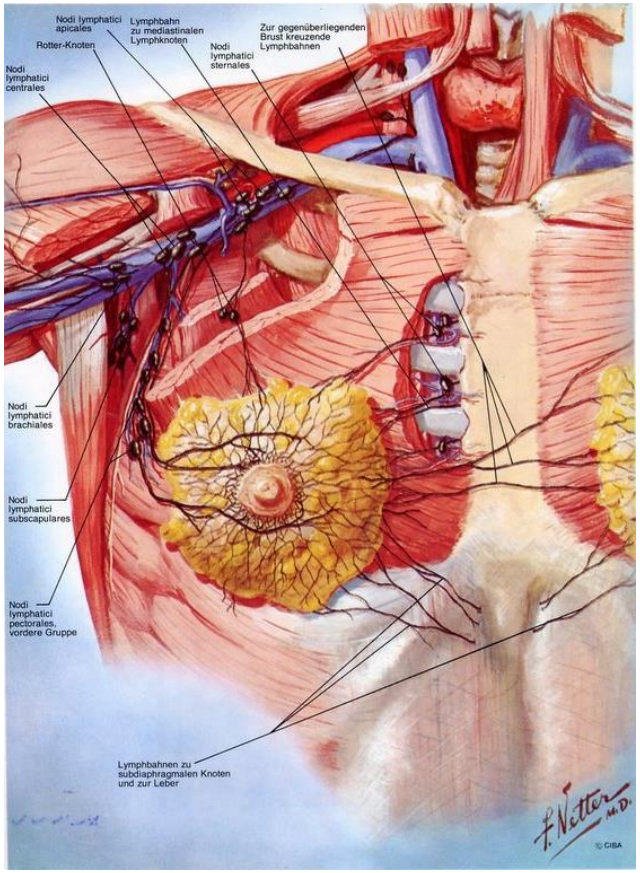
cN0 – good prognosis – no CHT

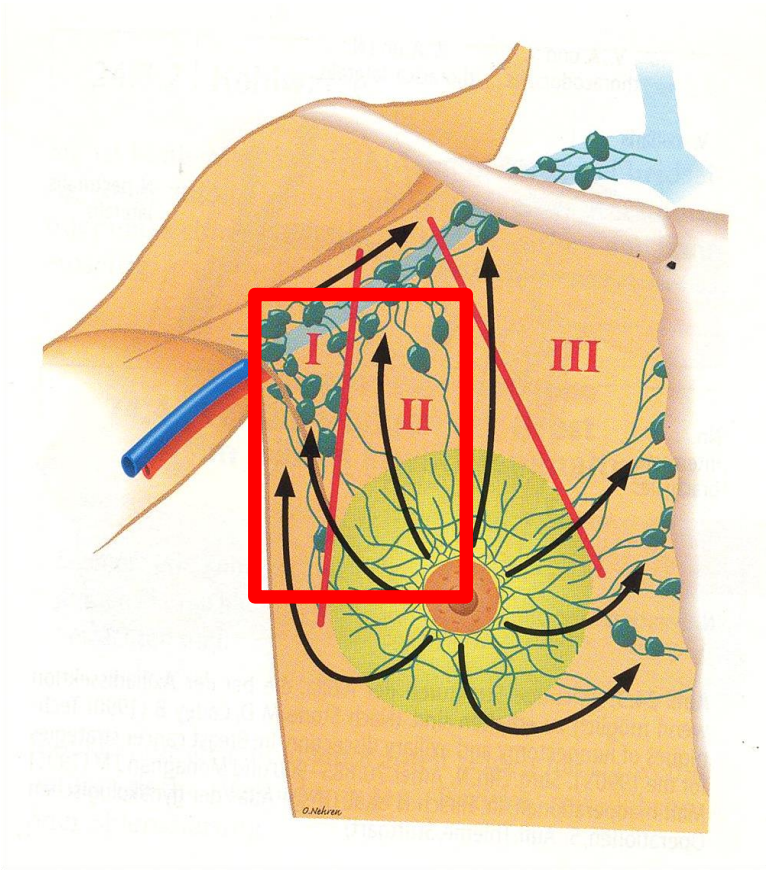
cN1 – bad prognosis - CHT

ESTRO School

Axillary Dissection

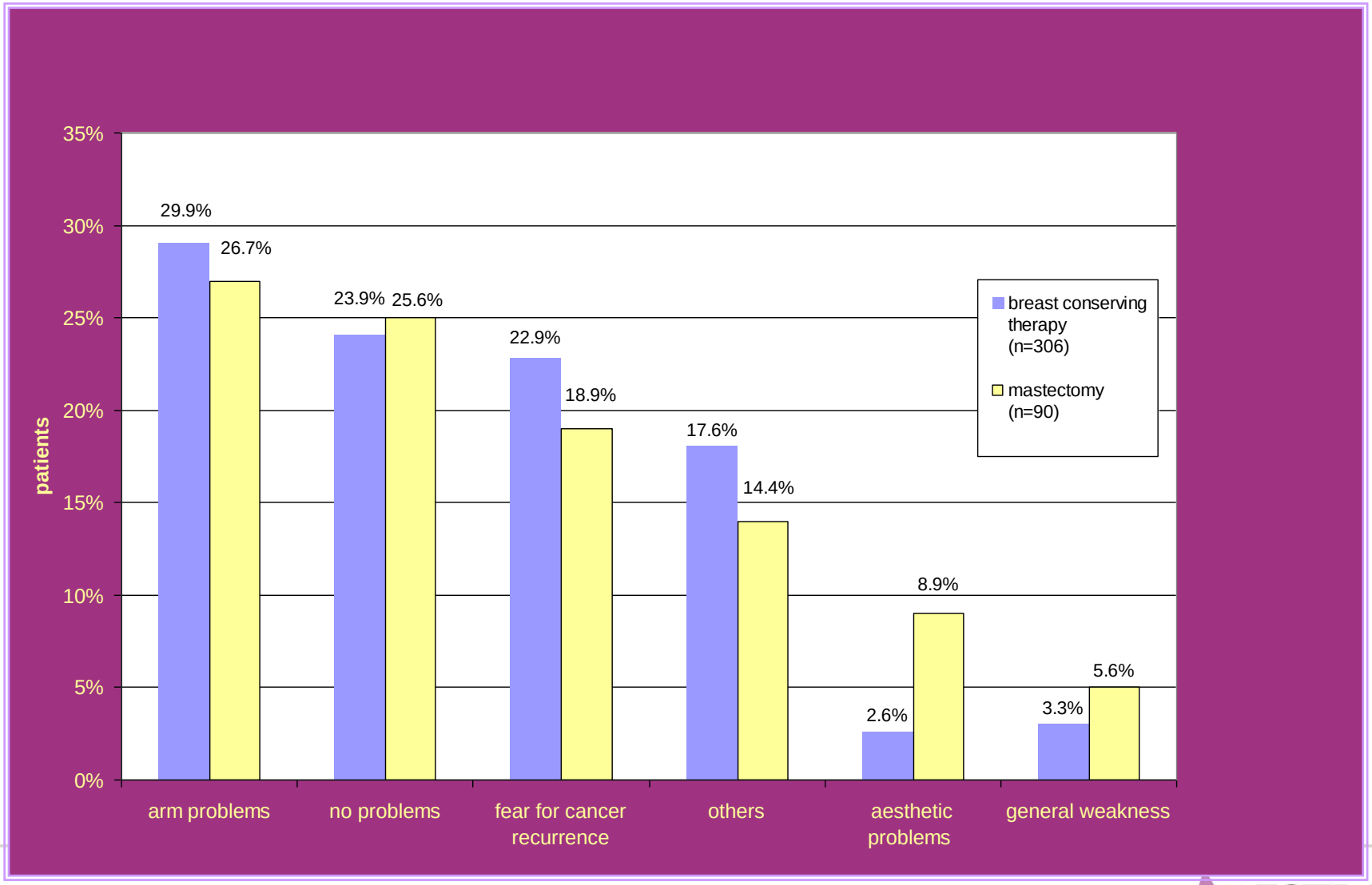
10 - 25 LNs





ESTRO School

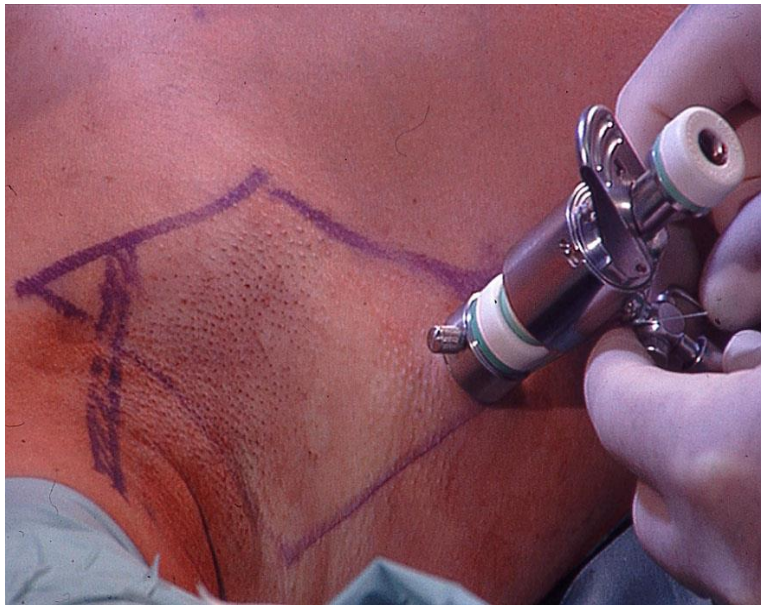
Long Term Morbidity after ALND

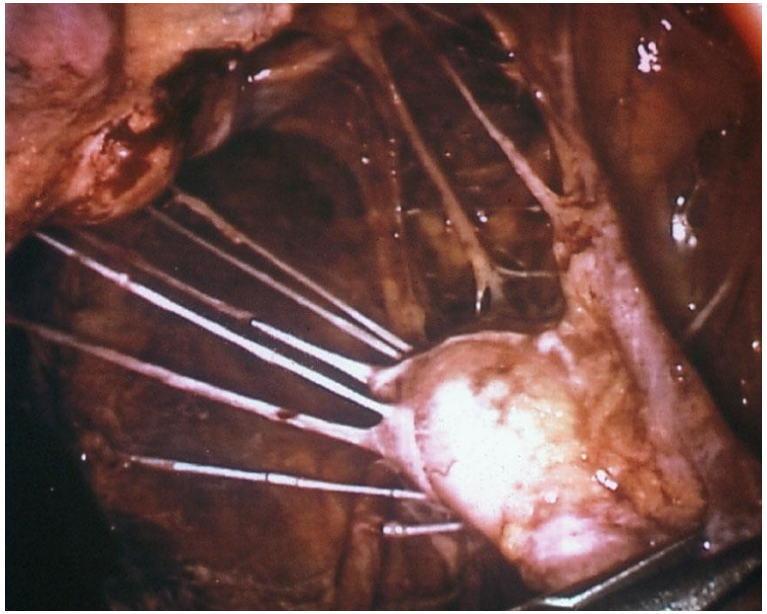


T.Kuehn et al. Breast Cancer Res Treat 2000

ESTRO School

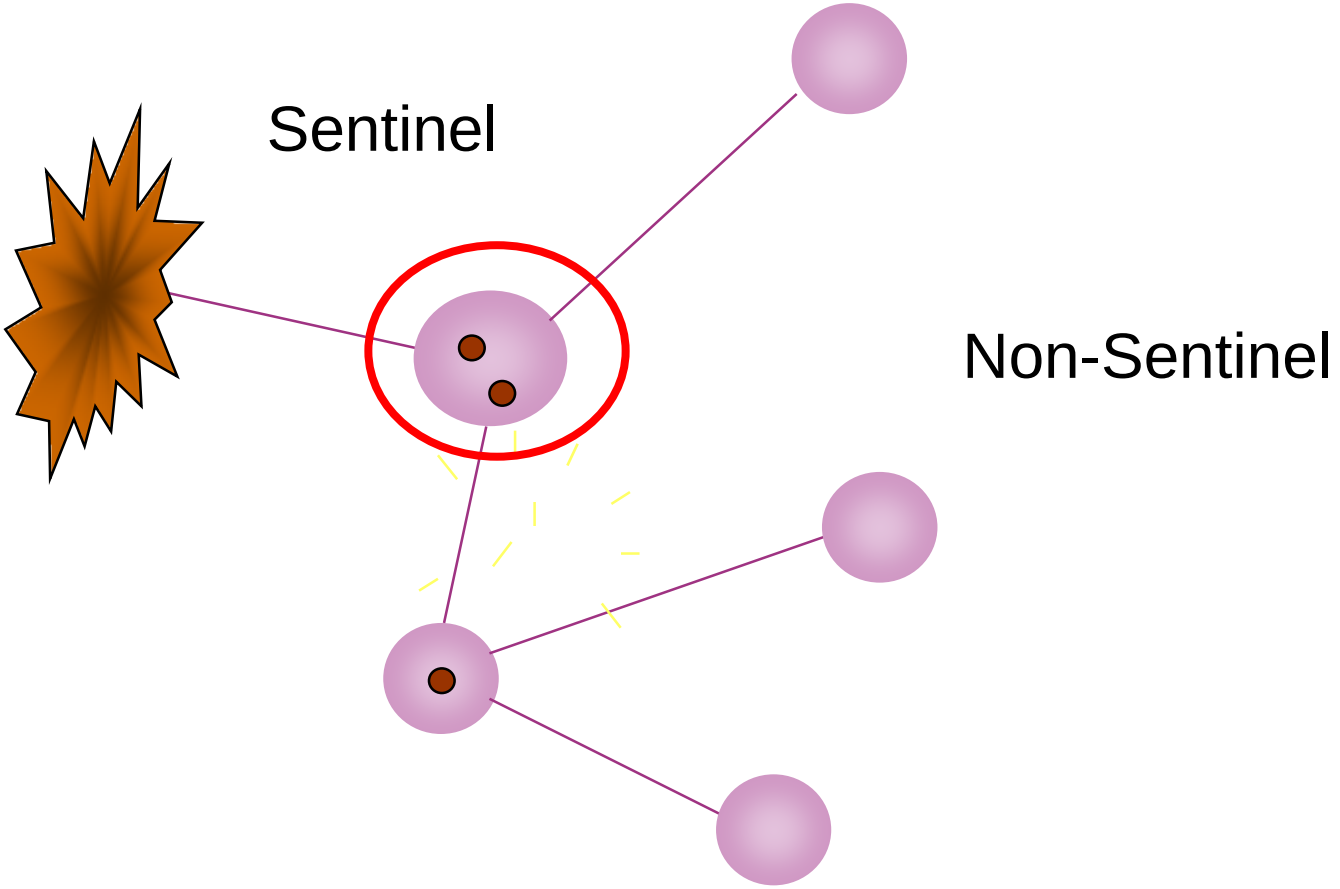
Endoscopic Axillary Dissection

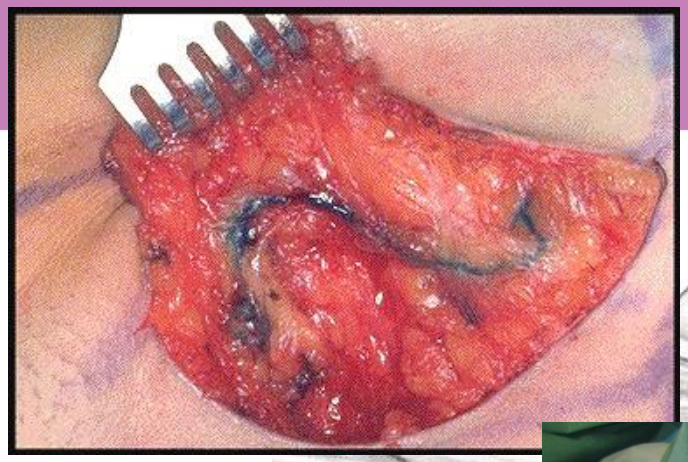


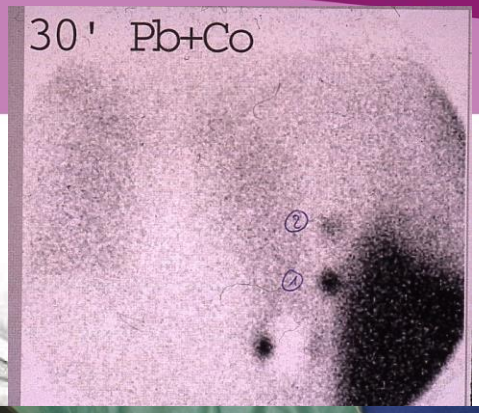


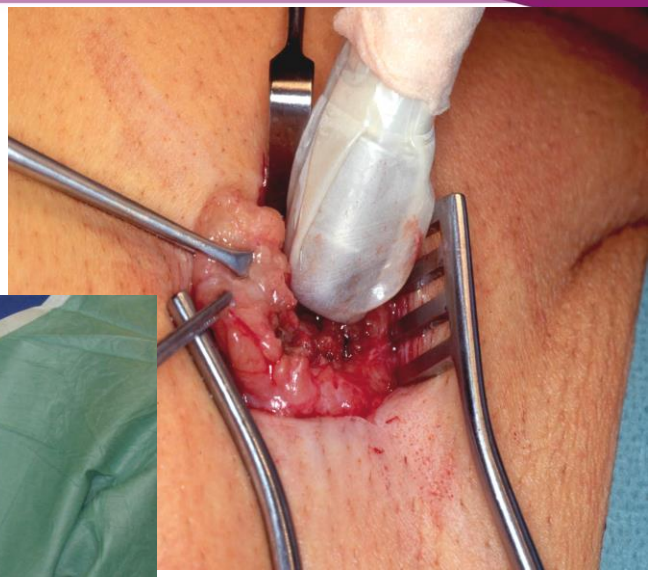
Kuehn et al. Br. J Surg 2001

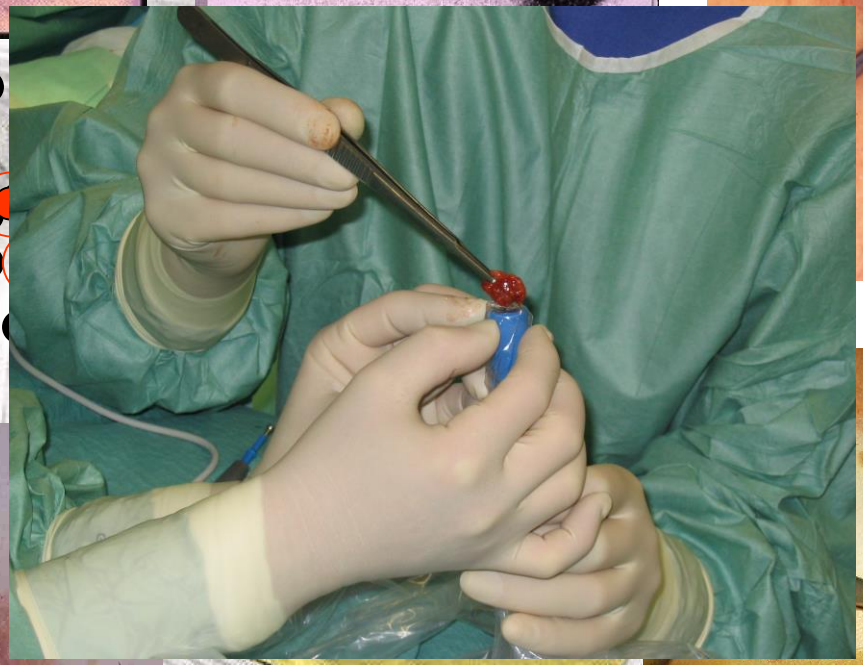
Sentinel Lymph Node Biopsy

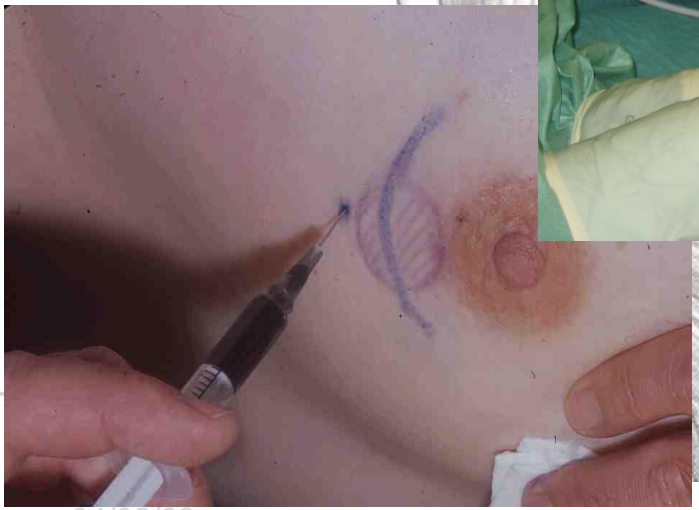


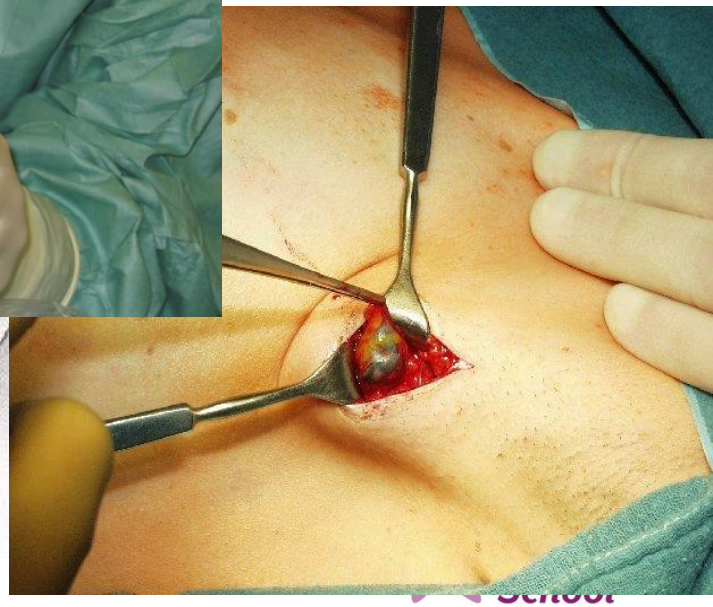



30' Pb+Co









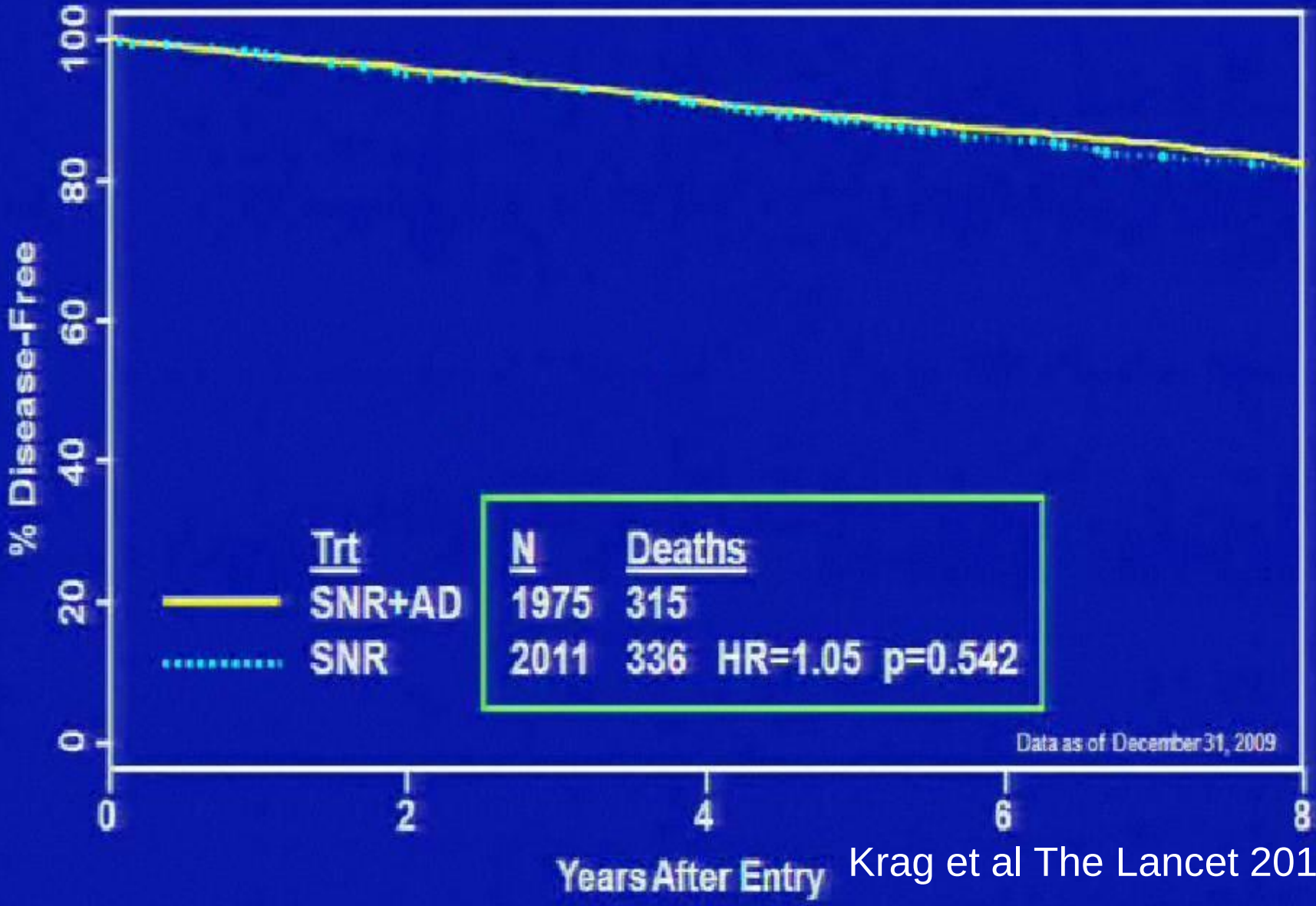
Feasibility and Accuracy of SLNB in primary Surgery

	No Patients	Feasibility Detection Rate	Accuracy	RR
Metaanalysis Kim 2006	8059	89.0 % CI 95% (80.0-92.0%)	7,14 % CI 95% (6.04-10.45%)	
NSABP B-32 Krag 2010	5611	97.2 %	9.8 % CI 95% (7.8-12.2%)	0.7 %

B-32 DFS

NSABP Protocol B-32

Disease-Free Survival for Sentinel Node Negative Patients



Krag et al The Lancet 2010

Current Status of axillary lymph node determination

SLNB is the standard procedure to determine the pN-status in all patients who undergo primary surgery

irrespective of

- size
- location
- focalty/centricity

Axillary dissection is no diagnostic procedure to determine the pN - status

ESTRO School

Injection Technique

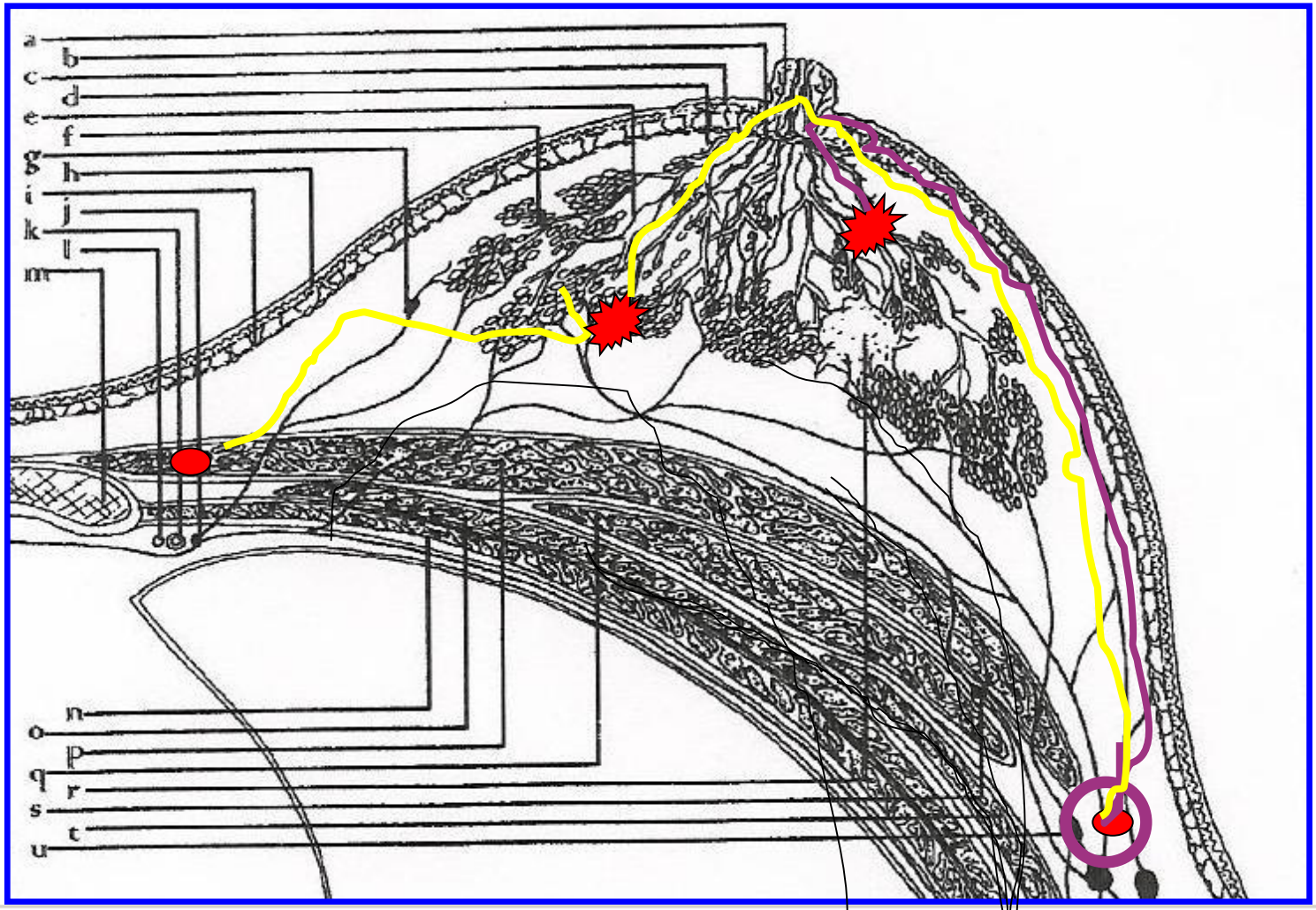
Tracer

- Radioactive colloid
- Blue dye (Patent blue, Isosulfane)
- Combined technique

Injection Technique

- peritumoral, intradermal, periareolar

lymphatic drainage form the breast
- functional anatomy -



ESTRO School

FNR and number of removed SLNs in

	All	1 SLN	2 SLN	3 SLN	> 3 SLN
NSABP B 32	9,8%	Primary Surgery 17,7 %	10,0 %	6,9 %	6,5 %
SENTINA	14,2 %	After PST 24,3 %	18,5 %	4,9 %	
ACOSOG 1071	14,7 %	31,5 %	21,1 %	9,0 %	9,09 %

A Concept for the Clinical Implementation of Sentinel Lymph Node Biopsy in Patients with Breast Carcinoma with Special Regard to Quality Assurance

Thorsten Kuehn, M.D.[1]
Andreas Bembenek, M.D.[2]
Thomas Decker, M.D.[3]
Dieter Ludwig Munz, M.D.[4]
Marie-Luise Sautter-Bihl, M.D.[5]
Michael Untch, M.D.[6]
Diethelm Wallwiener, M.D.[7]
For the Consensus Committee of the German Society of Senology

[1] Department of Gynecology and Obstetrics, Interdisciplinary Breast Center, Gifhorn, Germany.

[2] Department of Surgery and Surgical Oncology, Charite, Robert-Roessle-Klinik im HELIOS-Klinikum, Berlin, Germany.

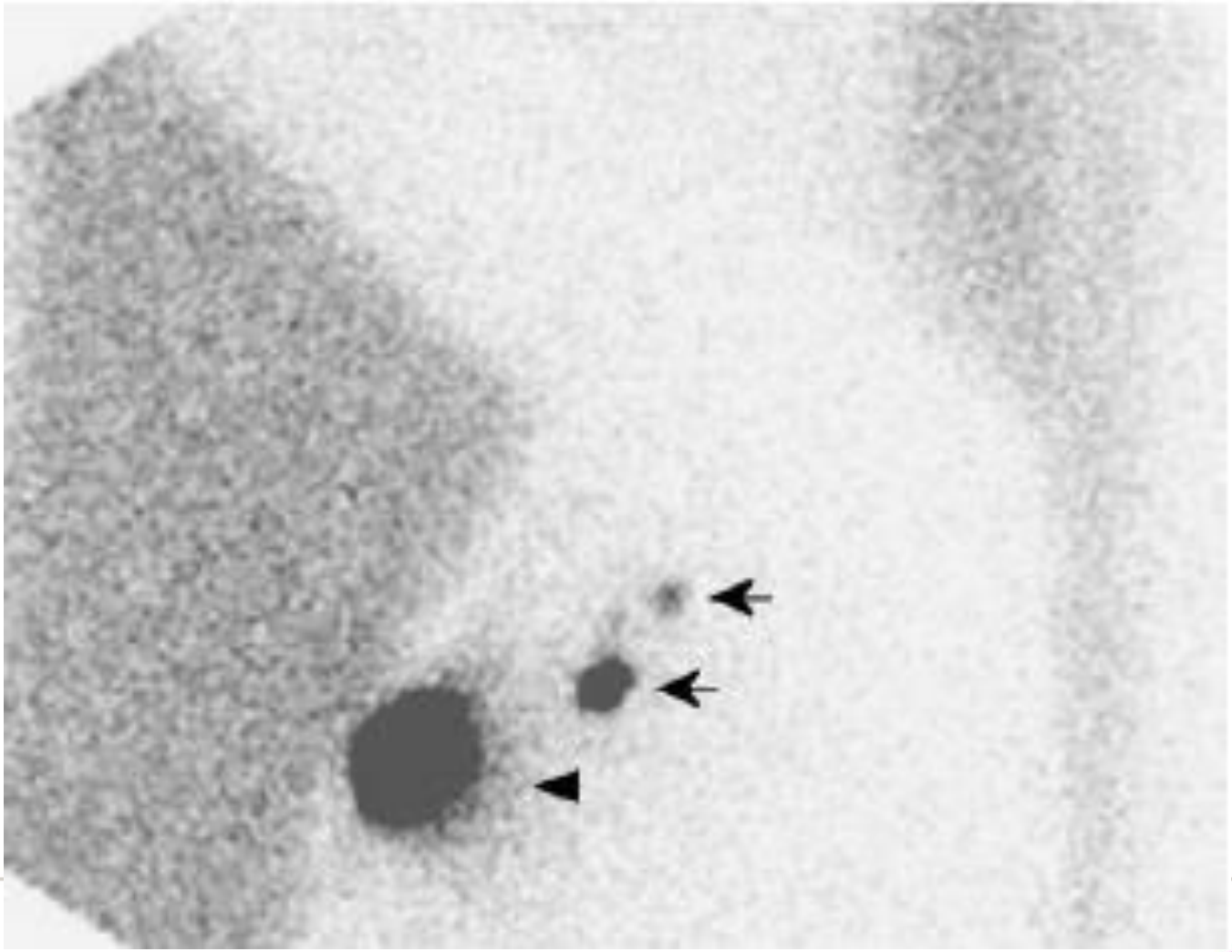
[3] Department of Pathology, Breast Unit, HELIOS-Klinikum Berlin, Berlin, Germany.

[4] Clinic for Nuclear Medicine, Charite-Berlin University Medicine, Charite Campus Mitte, Berlin, Germany.

The development of standardized and reproducible clinical pathways is an important precondition for quality assurance in medicine, especially if a new method has not yet been ultimately validated. Sentinel lymph node biopsy (SLNB) is a widely accepted new surgical procedure in the treatment of early breast carcinoma. However, numerous steps of the method and details of the technique are not standardized and, thus, hamper quality assurance for SLNB. The German Society of Senology appointed an interdisciplinary consensus committee to work out guidelines for the standardized performance and quality-assured implementation of SLNB on a nationwide, homogeneous standard. The committee consisted of surgeons, gynecologists, radiooncologists, nuclear physicians, oncologists, and pathologists. Relevant questions related to patient selection, lymphatic mapping, surgery, histopathologic work-up, further local and systemic treatment decisions, patient information, training, and follow-up were evaluated with respect to clinical evidence, objectivity, and reproducibility. Clinical pathways were developed on the basis of this analysis. Requirements to the performing institutions and surgeons were defined. ***Cancer* 2005;103:451–61.** *© 2004 American Cancer Society.*

KEYWORDS: breast carcinoma, sentinel lymph node biopsy, quality assurance, consensus panel.

Lymphoscintigraphy



Scenzi Study

Arm A

Surgeons aware of LS result

Injection of radiocolloid and lymphoscintigraphy

1:1

SLNB

Surgeon not aware of LS result

Arm B

Kuemmel, Kuehn et al. ASCO 2017

Primary Endpoint….

Number of SLN detected histologically

parameter	value	LSG known N=585	LSG unknown N=578	Overall N=1163	Difference in means	one-sided CI
Number of SLN detected histologically	Mean	2.207	2.258	2.232	0.051	(-0.18,inf)
	StD	1.470	1.497	1.483		
	Median	2.000	2.000	2.000		
	Min, Max	0.000, 13.000	0.000, 11.000	0.000, 13.000		

Secondary Endpoint….

Positive nodal status detected with SLNB

Parameter	LSG known (N=566) N(%)	LSG unknown (N=561) N(%)	Overall (N=1127) N(%)
All SLN negative	444 **(78.4)**	437 **(77.9)**	881 (78.2)
At least one SLN involved	122 **(21.6)**	124 **(22.1)**	246 (21.8)
95% CI for pN+	(18.2%, 25.2%)	(18.7%, 25.8%)	(19.4%,24.4%)

Conclusion

Lymphoscintigraphy does not improve the performance of radioguided SLNB

Kuemmel et al. ASCO 2017

Drawback of the radioguided SLNB

- ^{99}Tc is produced only in a few reactors worldwide which compromises its supply
- Dependency on a nuclear medicine unit
- Cannot be injected by the surgeon
- Radiation exposure of patients and health care personel
- Logistical challenges (handling and disposal of isotopes, training of staff, legislative requirements)

Availability of SLNB (estimated 500.000 patients / year)

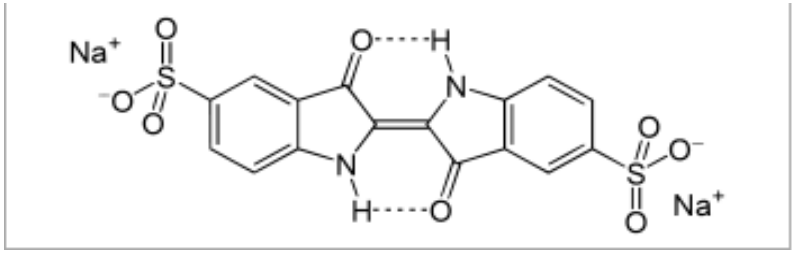
- 60 % in developed countries
- 5 % in China
- Even less in other parts of the world

Rescigno et al. Ann Surg Oncol 2009
Leong et al. Worl J Surg 2010

Alternative Detection Techniques - under investigation -

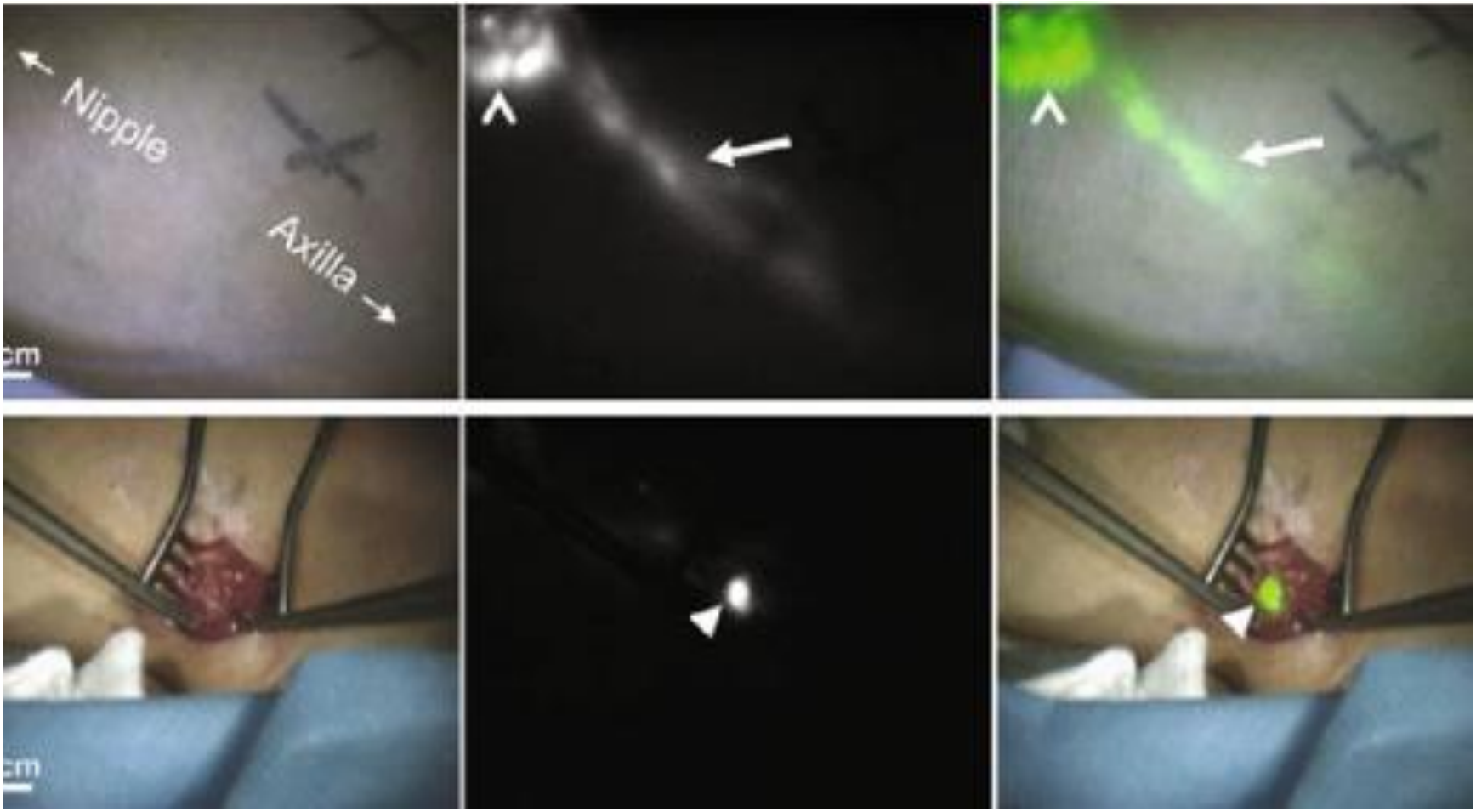
- ICG (Indocyanin Green Fluorescence)
- SPIO (Superparamagnetic Iron Oxide)
- CEUS (Contrast-enhanced ultrasound using microbubbles)

Indocyanin Green Fluorescence (ICG)



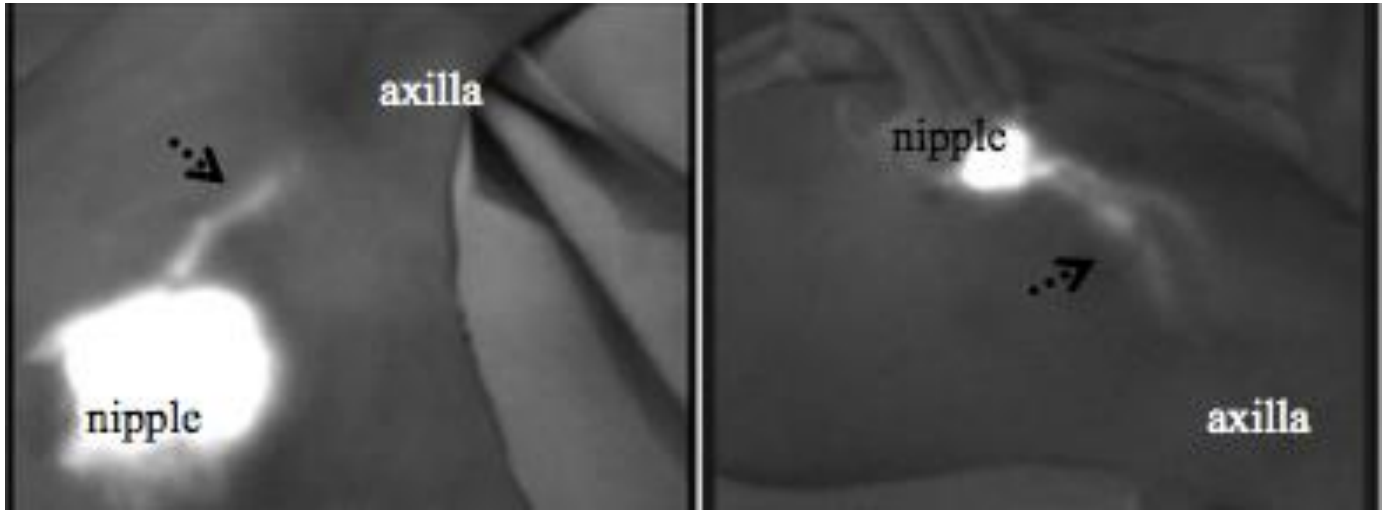
- Binds to plasma proteins
- Associated with a high affinity to the vascular compartment
- Illuminates tissues of interest (when excitation light of 760 nm is irradiated)
- Light emission at the wave lengh of 750 -800 nm
- Visualisation by an imaging system

Indocyanin Green



Van der Vorst Ann Surg Oncol 2012

Indocyanin Green



Patients: 312
Detection rate: 100 %
Mean number of SLN : 3.41
Non – SLN: 1.66
Total LN: 5,04

Aoyama et al W J Surg Oncol 2011

Superparamagnetic Iron Oxide (SPIO)

Novel techniques for sentinel lymph node biopsy in breast cancer: a systematic review

Muneer Ahmed, Arnie D Purushotham, Michael Douek

The existing standard for axillary lymph node staging in breast cancer patients with a clinically and radiologically normal axilla is sentinel lymph node biopsy with a radioisotope and blue dye (dual technique). The dependence on radioisotopes means that uptake of the procedure is limited to only about 60% of eligible patients in developed countries and is negligible elsewhere. We did a systematic review to assess three techniques for sentinel lymph node biopsy that are not radioisotope dependent or that refine the existing method: indocyanine green fluorescence, contrast-enhanced ultrasound using microbubbles, and superparamagnetic iron oxide nanoparticles. Our systematic review suggested that these new methods for sentinel lymph node biopsy have clinical potential but give high levels of false-negative results. We could not identify any technique that challenged the existing standard procedure. Further assessment of these techniques against the standard dual technique in randomised trials is needed.

Lancet Oncol 2014; 15: e351–62

Department of Research Oncology, King's College London, London, UK (M Ahmed MRCS, Prof A D Purushotham FRCS, M Douek FRCS); **and Oncology and Haematology, Guy's and St Thomas' NHS Foundation Trust, London, UK** (M Ahmed, Prof A D Purushotham, M Douek)

We could not identify any technique that challenged the existing standard procedure

ESTRO School

Implications of axillary staging

Systemic Treatment

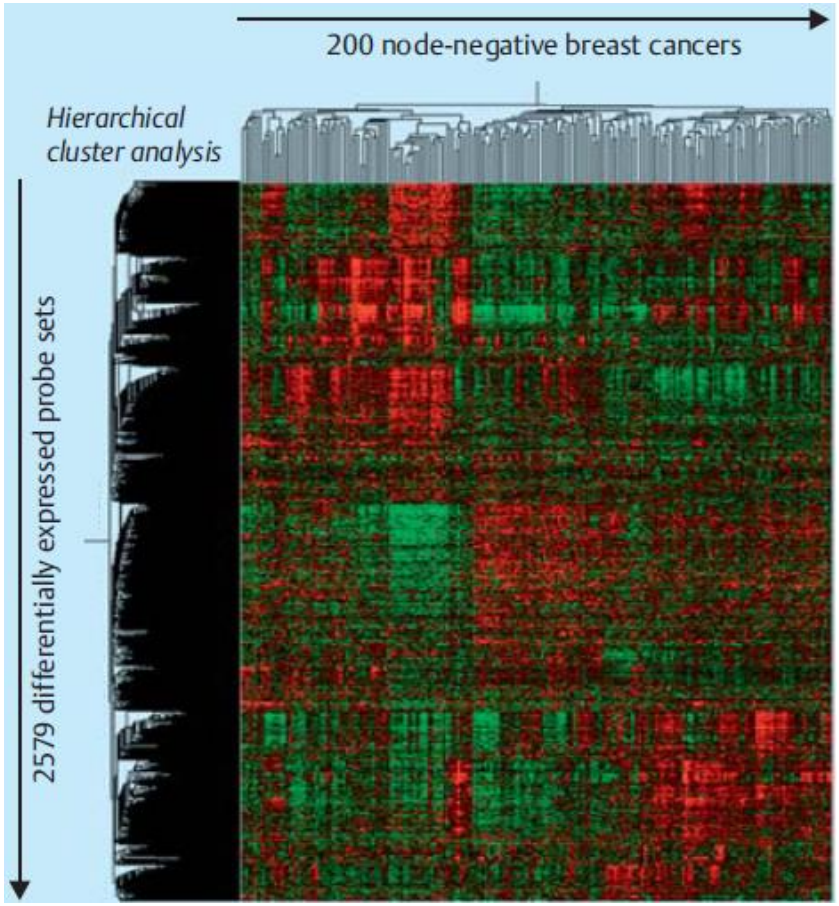
Local Treatment

- ALD

- Radiotherapy

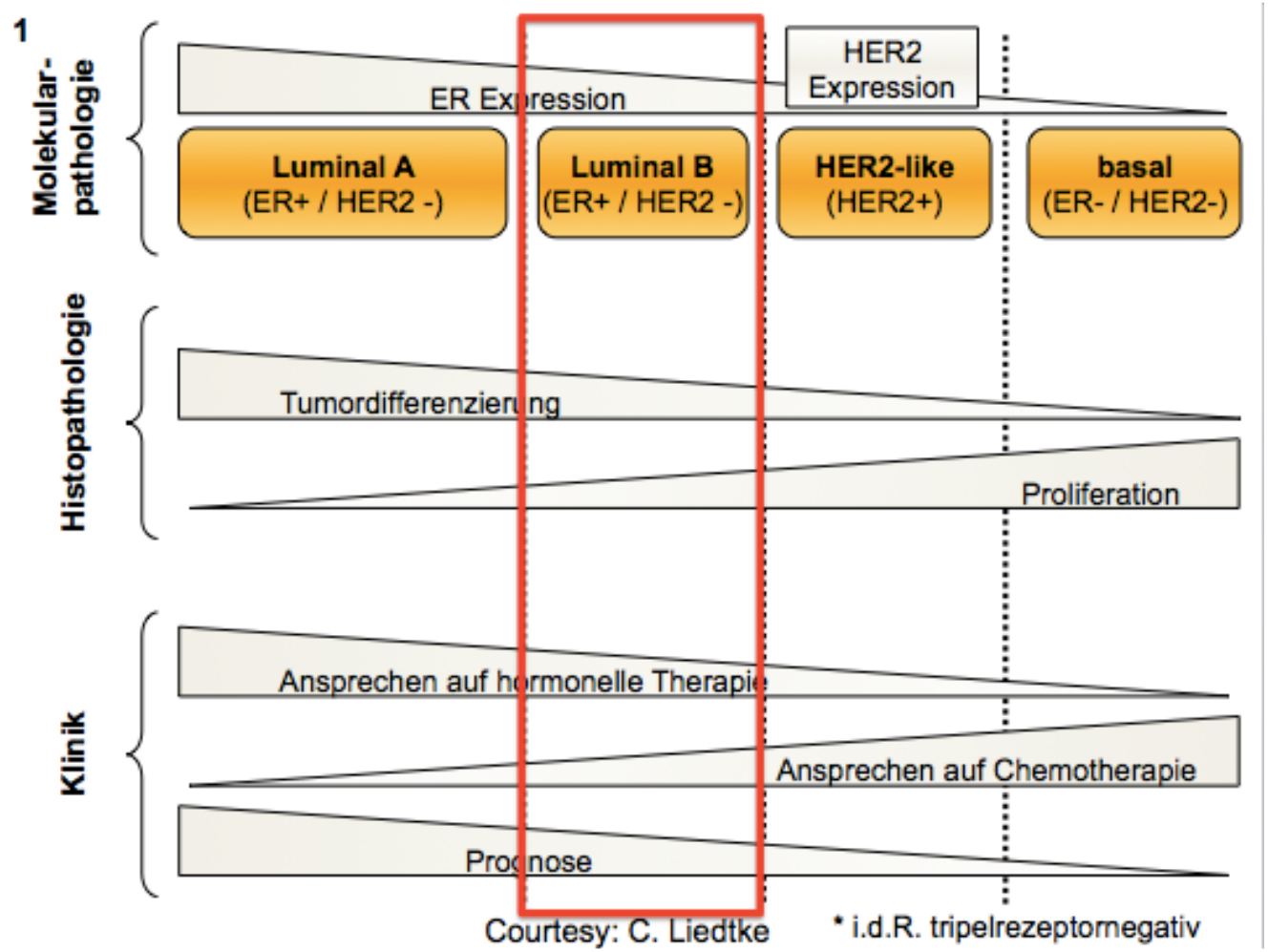
ESTRO School

Introduction of intrinsic subtypes



biology and prediction based strategy

Introduction of intrinsic subtypes



ESTRO School

Do we need the information of the axillary status ?

Luminal A	no CHT
Luminal B	→ Gene Expression
HER 2 pos	always CHT (except for very low tumor burden)
Triple Negativ	always CHT (except for very low tumor burden)

Therapeutic Implication of Axillary Status

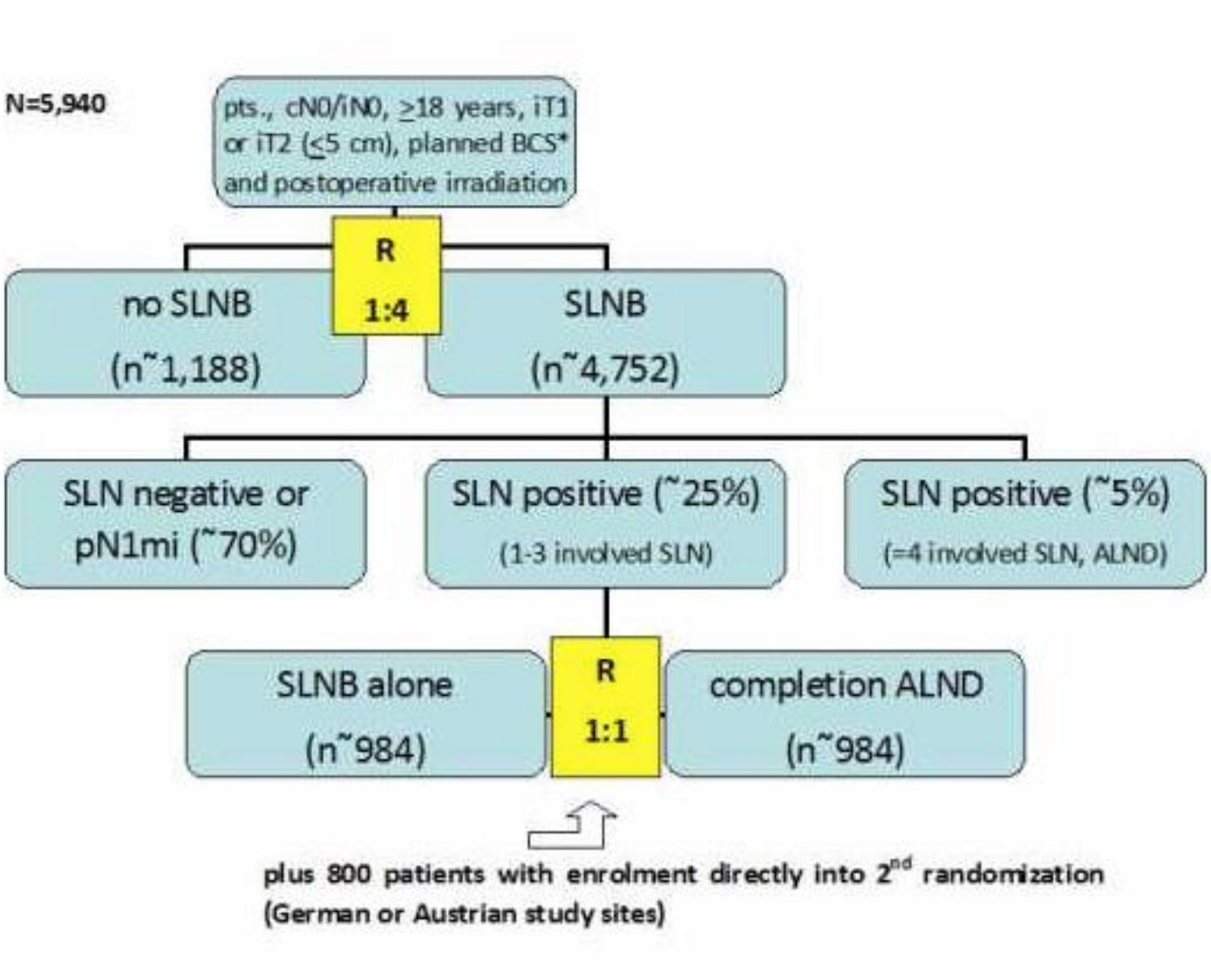
- Systemic Treatment

- Surgery

- Radiotherapy
  (EBCTCG, MA 20, EORTC)

Do we need axillary Staging at all ?

INSEMA – Study

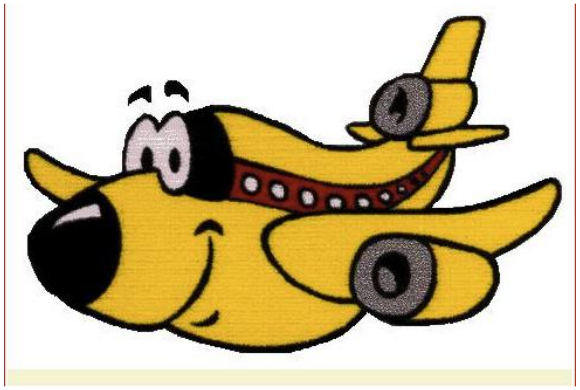


B.Gerber, T.Reimer

ESTRO School

Conclusion SLNB in Primary Surgery

- Is the current standard of care for every patient with invasive disease
- Easy to perform, high reproducibility
- High Accuracy
- Oncologic Safe (Negligible Recurrence Rate)



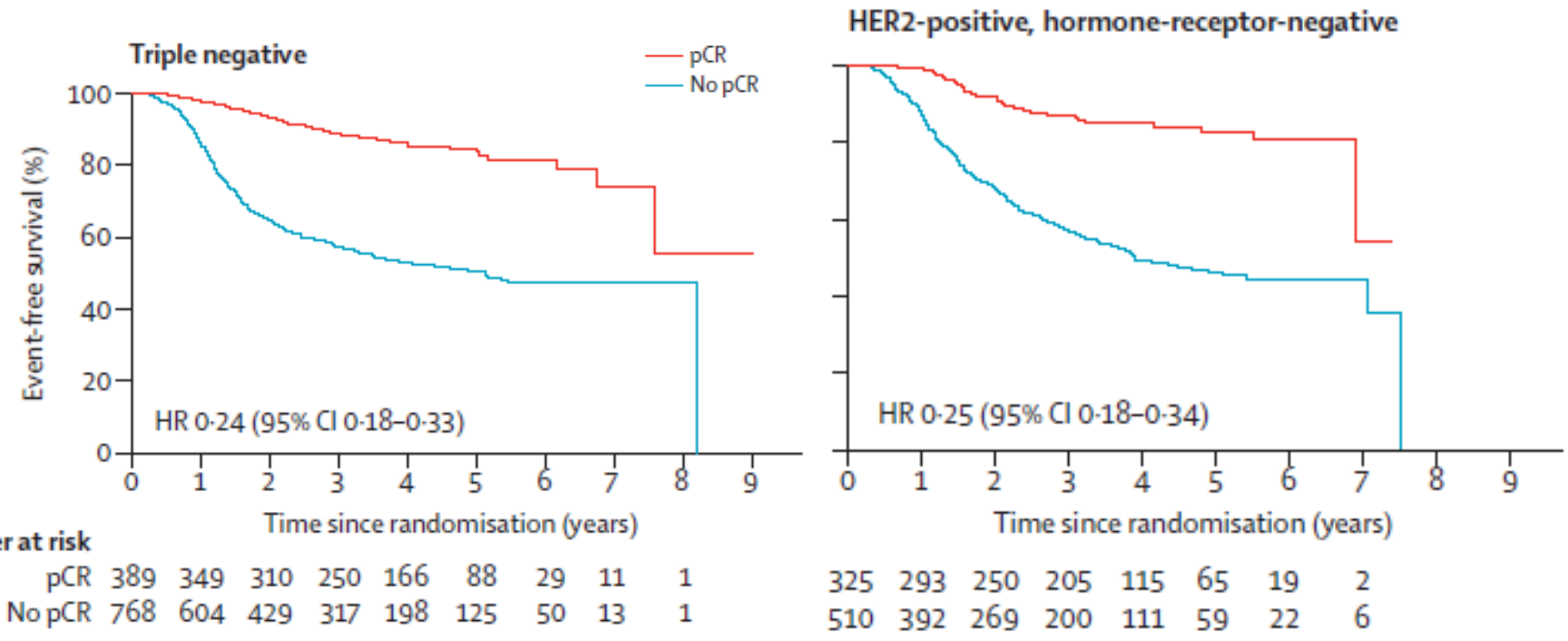
In 20 years ?

Neoadjuvant Chemotherapy

- Allows less extensive Surgery
- Increases the Rate of BCT
- Provides information on Response to Chemotherapy

Pathologic Complete Response and Long-Term Clinical Benefit in Breast Cancer: The CTNeoBC Pooled Analysis

Patricia Cortazar, Lijun Zhang, Michael Untch, Keyur Mehta, Joseph P Costantino, Norman Wolmark, Hervé Bonnefoi, David Cameron, Luca Gianni, Pinuccia Valagussa, Sandra M Swain, Tatiana Prowell, Sibylle Loibl, D Lawrence Wickerham, Jan Bogaerts, Jose Baselga, Charles Perou, Gideon Blumenthal, Jens Blohmer, Eleftherios P Mamounas, Jonas Bergh, Vladimir Semiglazov, Robert Justice, Holger Eidtmann, Soonmyung Paik, Martine Piccart, Rajeshwari Sridhara, Peter A Fasching, Leen Slaets, Shenghui Tang, Bernd Gerber, Charles E Geyer Jr, Richard Pazdur, Nina Ditsch, Priya Rastogi, Wolfgang Eiermann, Gunter von Minckwitz



Cortazar P, et al. *Lancet.* 2014;384(9938):164-172.

Guidance for Industry

Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval

The NEW ENGLAND JOURNAL of MEDICINE

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes

Comments and suggestions regarding this draft document should be submitted w
publication in the *Federal Register* of the notice announcing the availability of t
guidance. Submit electronic comments to http://www.regulations.gov. Submit
comments to the Division of Dockets Management (HFA-305), Food and Drug
5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be i
the docket number listed in the notice of availability that publishes in the *Federa*

For questions regarding this draft document contact Tatiana Prowell, M.D. at 30

Perspective

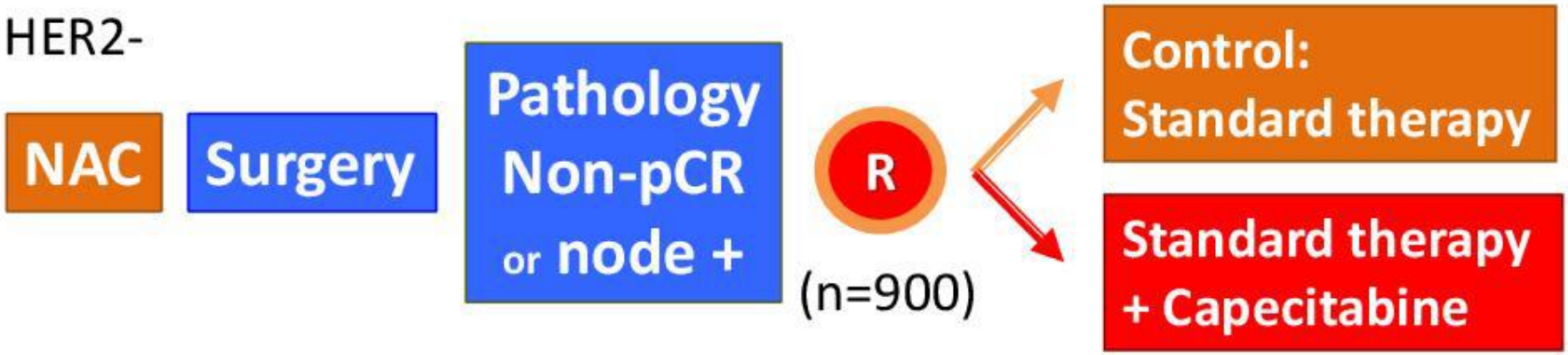
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2012
Clinical/Medical

Pathological Complete Response and Accelerated Drug Approval in Early Breast Cancer

Tatiana M. Prowell, M.D., and Richard Pazdur, M.D.

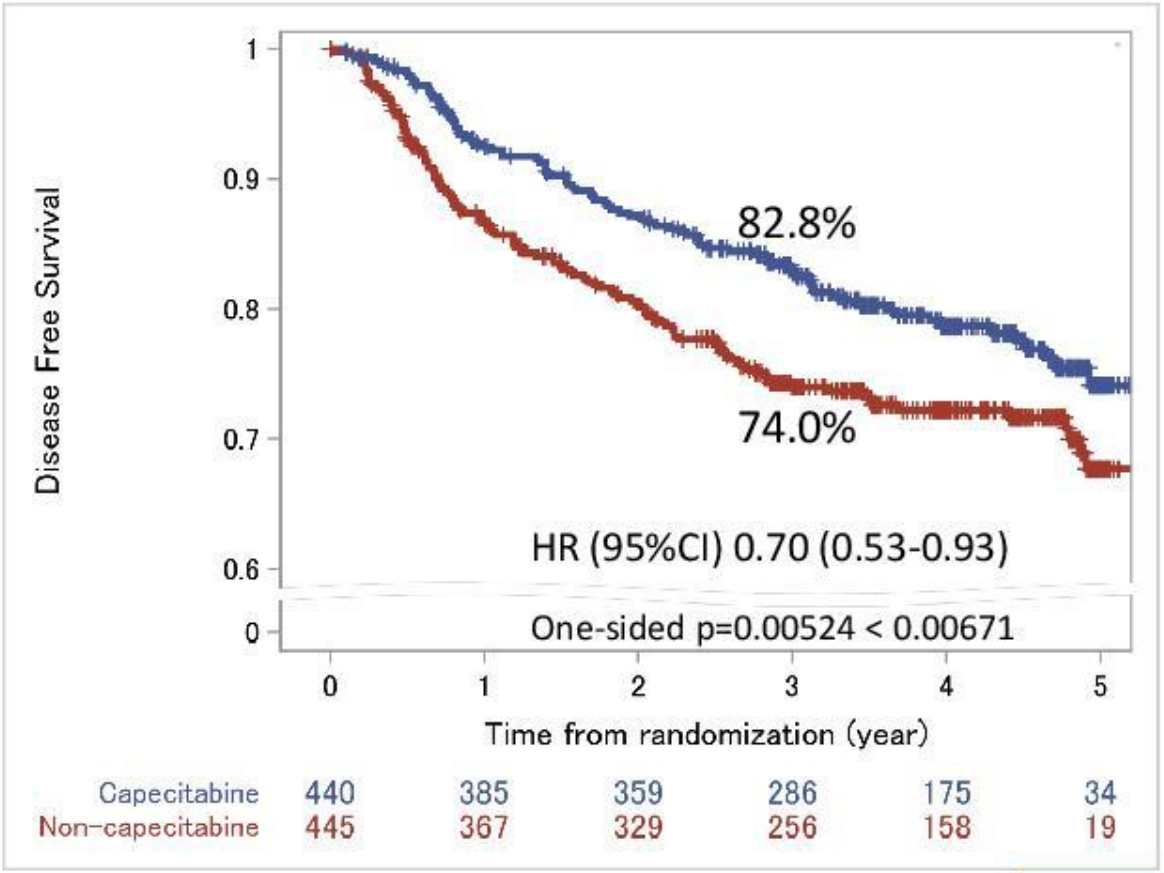
CREATE-X: Trial Design



Stratification factors:
ER, Age, NAC, ypN,
5FU and institution

Standard therapy:
HR+: Hormone therapy
HR-: No further systemic treatment

Disease Free Survival



5yr DFS

74.1% Capecitabine

67.7% Control

Definition: pathologic complete response (pCR) (FDA)

„Pathologic complete response (pCR) is defined as the absence of any residual invasive cancer on evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of neoadjuvant systemic treatment“

SLNB before or after PST
- clinical utility -

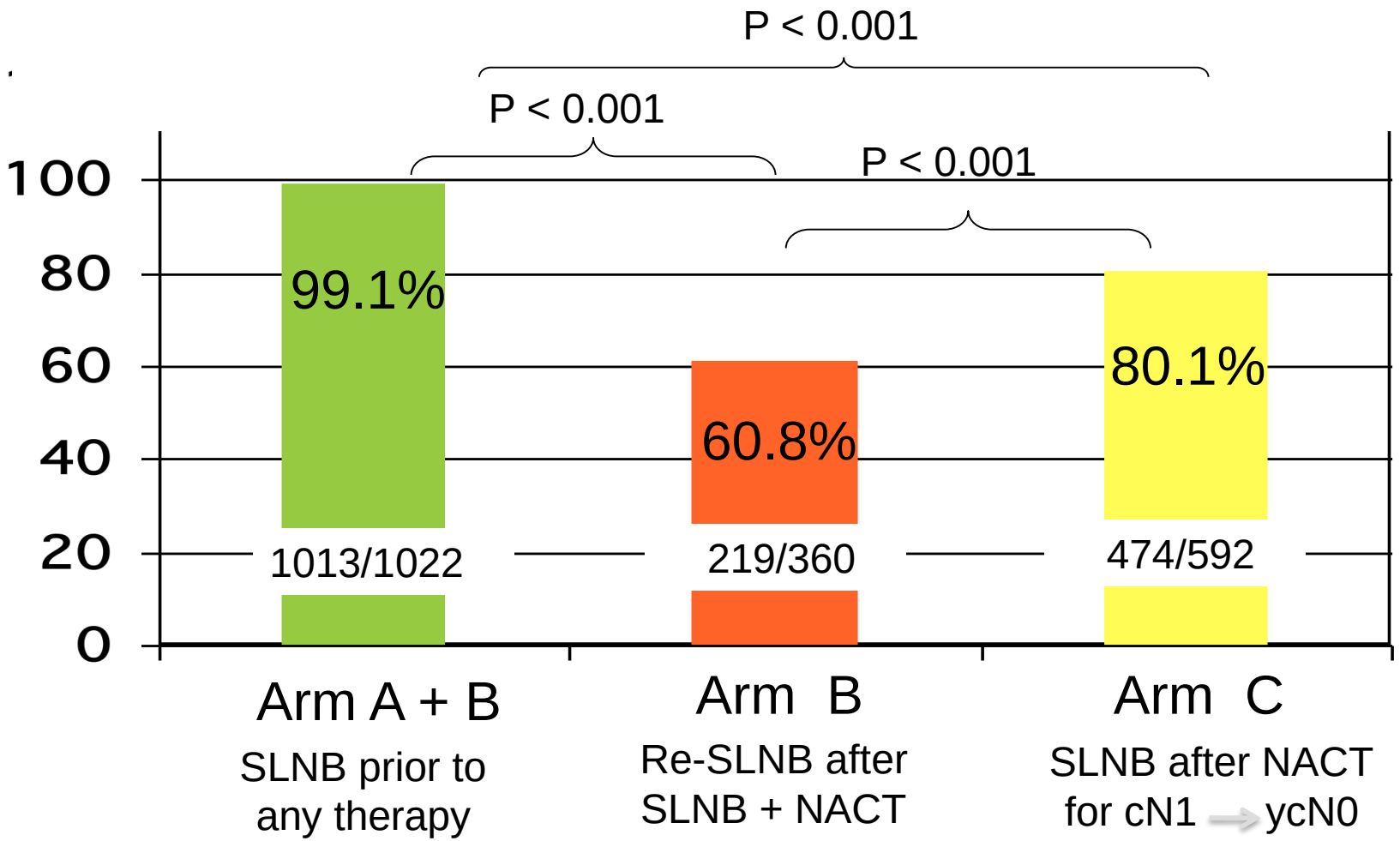
- **SLNB before NACT**
  - Provides information on original prognosis
  - Improves locoregional treatment decisions (radiotherapy)

- **SLNB after NACT**
  - Avoids 1 operation
  - Reduces the rate of axillary dissections
  - Provides information on pCR

SLNB after PST ?

- Feasible ?
- Reliable ?
- Safety ?

SLNs detected and removed



Kuehn et al. Lancet Oncol 2013;14:609-18

GANEA:
French Prospective Multicenter Trial

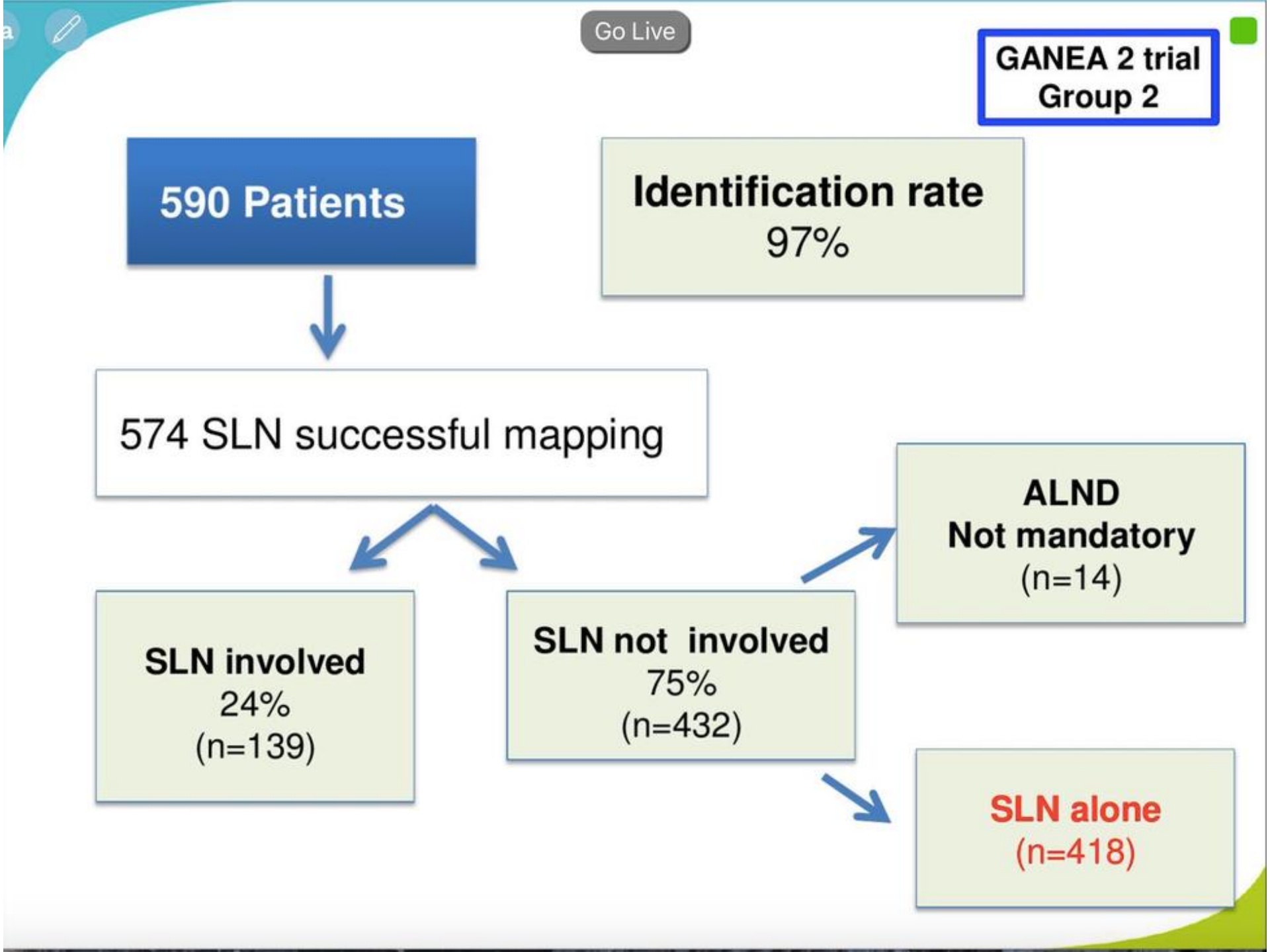
Detektionsrate

	%	No. of Patients	Total Patients	χ^2 P
All	90.1	176	195	
N0	94.6	123	130	0.008
N1	81.5	53	65	

Falsch-Negativ-Rate

	%	No. of Patients	Total Patients	χ^2 P
All	11.5	6	52	
N0	9.4	3	32	0.66
N1	15.0	3	20	

Classe et al. JCO 2008


Go Live
GANEA 2 trial
Group 2
590 Patients
Identification rate
97%
574 SLN successful mapping
SLN involved
24%
(n=139)
SLN not involved
75%
(n=432)
ALND
Not mandatory
(n=14)
SLN alone
(n=418)

Go Live

GANEA 2 trial
Group 2

Events

418 Patients SLN alone without ALND

Median Follow-up =36 months

Relapse	N=10
Metastasis	3
Breast relapse	3 homo L 3 contra L
Axillary relapse	1 (0.2%)

Annals of Oncology 00: 1–12, 2015
doi:10.1093/annonc/mdv161

Recommendations for standardized pathological characterization of residual disease for neoadjuvant clinical trials of breast cancer by the BIG-NABCG collaboration

V. Bossuyt[1*], E. Provenzano[2], W. F. Symmans[3], J. C. Boughey[4], C. Coles[5], G. Curigliano[6], J. M. Dixon[7], L. J. Esserman[8], G. Fastner[9], T. Kuehn[10], F. Peintinger[11,12], G. von Minckwitz[13], J. White[14], W. Yang[15], S. Badve[16], C. Denkert[17], G. MacGrogan[18], F. Penault-Llorca[19], G. Viale[20] & D. Cameron[21] of the Breast International Group-North American Breast Cancer Group (BIG-NABCG) collaboration

evaluation of the axilla pre-NAST

Systemic or local treatment decisions may be based on axillary status at presentation (pre-NAST). Pre-NAST sentinel lymph node biopsy (SLNB) is not recommended because assessment of nodal response in the axilla, a very important determinant of survival post-NAST, is unreliable after excision of a positive node.

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2016.1

Axillary Intervention Before or After NACT

	Oxford / AGO LoE	/ GR	
SLNB before or after NACT in cN0			
SLNB before NACT	**2b**	**B**	**+**
SLNB after NACT	**2b**	**B**	**+**

Further surgical procedures depending on SLNB status

cN-Status (before NST)	pN-Status (before NST)	cN-Status (after NST)		Surgical Procedure (after NST)			
cN0	**pN0(sn)**	**-**		**nihil**	**1a**	**A**	**+**
cN0	**pN+(sn)** (analog ACOSOG Z0011)	**ycN0**		**nihil** **Re-SLNB alone** **ALND**	**3** **2b** **3**	**B** **B** **B**	**+/-** **-** **+/-**
cN0	**pN+(sn)** (not analog ACOSOG Z0011)	**ycN0**		**Re-SLNB alone** **ALND** **Axilla XRT**	**2b** **2b** **2b**	**B** **B** **B**	**-** **+** **+**
cN0	**not done**	**ycN0**	**ypN0 (sn)**	**SLNB alone** **ALND**	**2b** **2b**	**B** **B**	**+/-** **+/-**
			ypN+ (sn)	**ALND**	**2b**	**B**	**+**
cN+	**cN+** **(CNB/FNA + clip placement)**	**ycN0** **ycN+**		**SLNB alone*** **ALND** **ALND**	**2b** **2b** **2b**	**B** **B** **B**	**+/-** **+** **++**

*** Analogue ACOSOGZ1071**

www.ago-online.de

Further Information

References

FORSCHEN
LEHREN
HEILEN

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2016.1

Axillary Intervention Before or After NACT

	Oxford / AGO LoE	GR	
SLNB before or after NACT in cN0			
SLNB before NACT	2b	B	+/-
SLNB after NACT	2b	B	+

Further surgical procedures depending on SLNB status

cN-Status (before NST)	pN-Status (before NST)	cN-Status (after NST)		Surgical Procedure (after NST)			
cN0	pN0(sn)	-		nihil	1a	A	+
cN0	pN+(sn) (analog ACOSOG Z0011)	ycN0		nihil Re-SLNB alone ALND	5 2b 3	D B B	+/- - +/-
cN0	pN+(sn) (not analog ACOSOG Z0011)	ycN0		Re-SLNB alone ALND Axilla XRT	2b 2b 2b	B B B	- + +
cN0	not done	ycN0	ypN0 (sn)	SLNB alone ALND	2b 2b	B B	+/- +/-
			ypN+ (sn)	ALND	2b	B	+
cN+	cN+ (CNB/FNA)	ycN0 ycN+		SLNB alone* ALND ALND	2b 2b 2b	B B B	+/- + ++

www.ago-online.de

Further Information

References

FORSCHEN
LEHREN
HEILEN

Surgery of the Axilla following Neo-Adjuvant Chemotherapy

19. In a patient who is clinically (at palpation and US) node negative at diagnosis:

When is the best time point for SN biopsy?

St. Gallen Abstimmungsergebnis:

Before the start of neoadjuvant chemo	**20%**
After neo-adjuvant chemo	**60%**
Either before or after chemo are valid options	**16,7%**
Abstain	**3,3%**

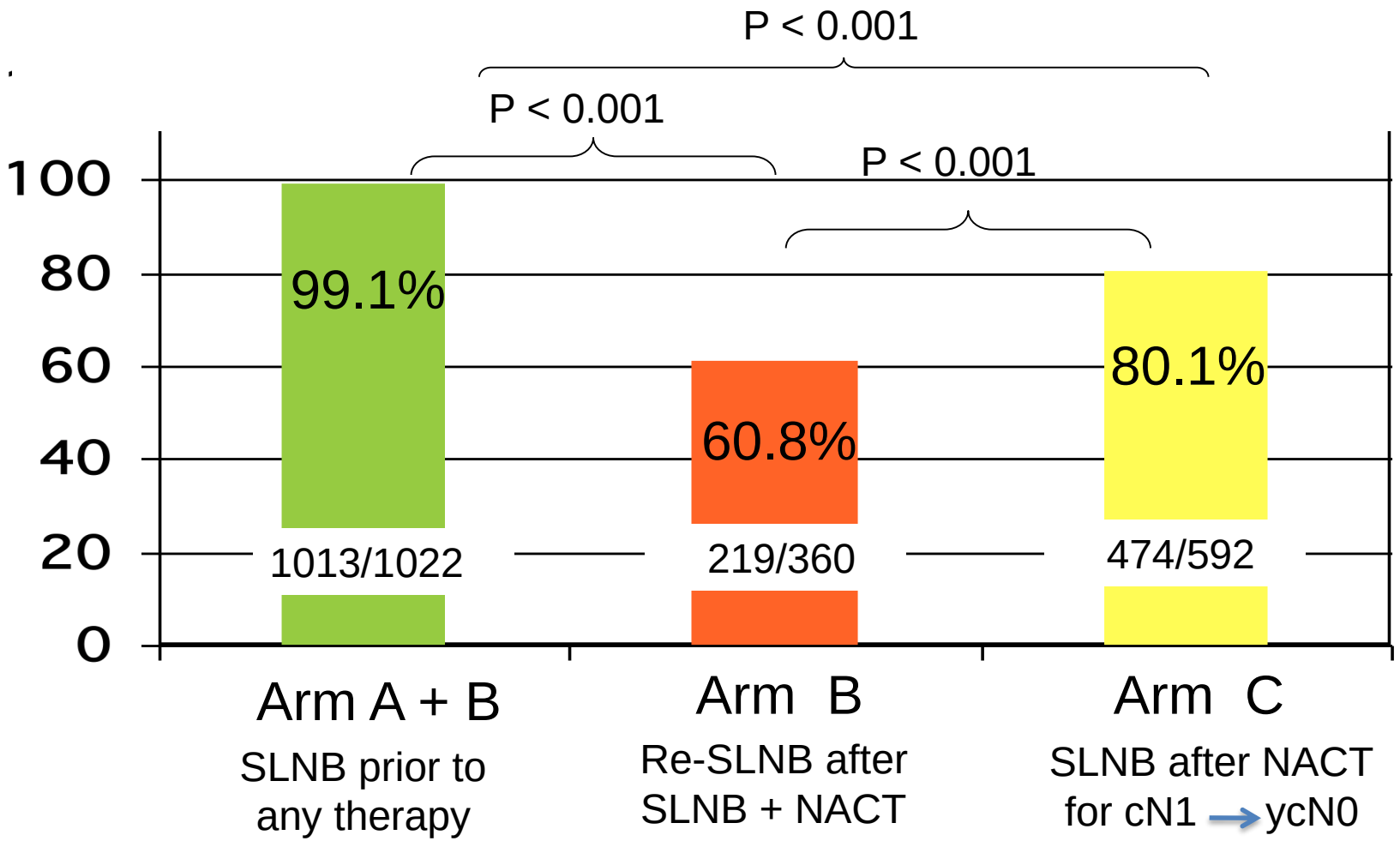
Stellungnahme der dt. Expertengruppe:
Zustimmung

SLNB after NACT in cN1 Patients

- **Clinical Utility**
- **Feasible ?**
- **Reliable ?**
- **Safe ?**

Do we have clinical need ?

SLNs detected and removed



Kuehn et al. Lancet Oncol 2013;14:609-18

FNR and number of removed SLNs in

	All	1 SLN	2 SLN	3 SLN	> 3 SLN
NSABP B 32	9,8%	Primary Surgery 17,7 %	10,0 %	6,9 %	6,5 %
SENTINA	14,2 %	After PST 24,3 %	18,5 %	4,9 %	
ACOSOG 1071	14,7 %	31,5 %	21,1 %	9,0 %	9,09 %

IJC
International Journal of Cancer

Sentinel node biopsy performance after neoadjuvant chemotherapy in locally advanced breast cancer: A systematic review and meta-analysis

Simone Mocellin, Elena Goldin, Alberto Marchet and Donato Nitti

Surgery Branch, Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy

N	7451
Detektion	89, 6 %
FN-Rate	14,2 %

„**Based on the largest series of studies ever meta**-analyzed, our findings highlight the limits of SNB performance in this population, where the **impact of SNB on patient survival is still to be defined**“.

Int J Cancer 2016

SLNB after NACT in cN1

- **Clinical utility:** ⇑
- **Feasibility:** →
- **Reliability:** →
- **Safety:** **??**

Can Success Rates be Improved ?

- Combined Tracer
- Resection of > 2 SLNs
- Ultrasound of the Axilla
- Search for Micromets and ITC
- Targeted Axillary Dissection

Original Investigation

Sentinel Lymph Node Surgery After Neoadjuvant Chemotherapy in Patients With Node-Positive Breast Cancer

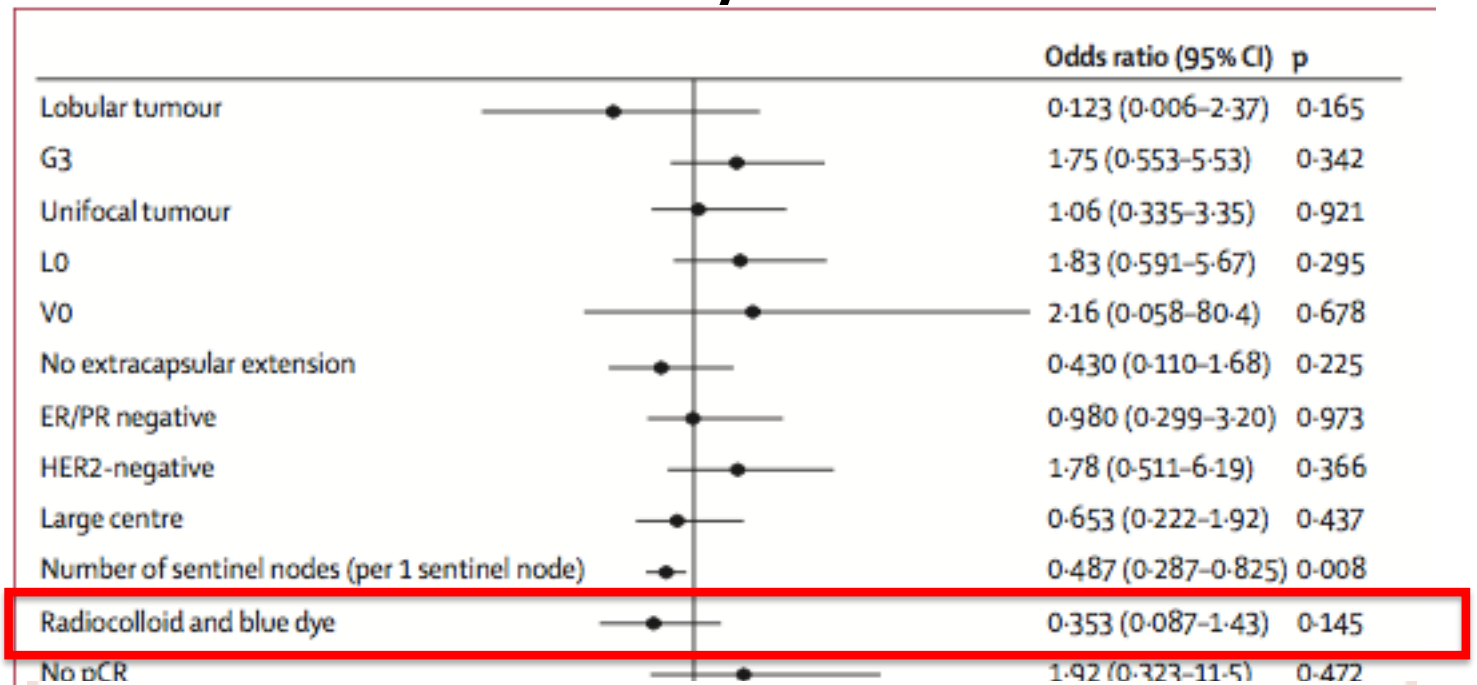
The ACOSOG Z1071 (Alliance) Clinical Trial

Boughey et al JAMA 2013

Table 3. Factors Affecting the Likelihood of a False-Negative Sentinel Lymph Node Finding in the 310 Women With cN1 Disease at Presentation, 2 or More SLNs Examined, and Residual Nodal Disease After Neoadjuvant Chemotherapy

Mapping agents used			
Single	12 (59)	20.3 (11.0-32.8)	.05
Dual	27 (251)	10.8 (7.2-15.3)	
Multiple injection sites[b]			
Yes	5 (70)	7.1 (2.4-15.9)	.21
No	30 (225)	13.3 (9.2-18.5)	
No. of SLNs examined			
2	19 (90)	21.1 (13.2-31.0)	.007
≥3	20 (220)	9.1 (5.6-13.7)	

Combined tracer ?
Mulivariate analysis SENTINA on FNR



	Odds ratio (95% CI)	p
Lobular tumour	0·123 (0·006–2·37)	0·165
G3	1·75 (0·553–5·53)	0·342
Unifocal tumour	1·06 (0·335–3·35)	0·921
L0	1·83 (0·591–5·67)	0·295
V0	2·16 (0·058–80·4)	0·678
No extracapsular extension	0·430 (0·110–1·68)	0·225
ER/PR negative	0·980 (0·299–3·20)	0·973
HER2-negative	1·78 (0·511–6·19)	0·366
Large centre	0·653 (0·222–1·92)	0·437
Number of sentinel nodes (per 1 sentinel node)	0·487 (0·287–0·825)	0·008
Radiocolloid and blue dye	0·353 (0·087–1·43)	0·145
No pCR	1·92 (0·323–11·5)	0·472

At least one sentinel node removed				
All patients	Mean 2·7, median 2·0	Mean 2·4, median 2·0	Mean 2·7, median 2·0	<0·0001
Radiocolloid alone	Mean 2·6, median 2·0	Mean 2·3, median 2·0	Mean 2·6, median 2·0	0·012
Radiocolloid and blue dye	Mean 2·8, median 2·0	Mean 2·6, median 2·0	Mean 2·9, median 3·0	0·059

Data are n/N (%), unless otherwise stated.

Table 3: **Detection of sentinel lymph nodes, according to selected factors**

Kuehn et al. Lancet Oncol 2013

Remove > 2 SLN ?

	Arms A and B	Arm B	Arm C	p
Hot spot on lymphoscintigraphy	1014/1022 (99%)	236/360 (66%)	476/592 (80%)	<0·0001
Overall surgical detection rate (n/N; 95% CI)	99·1% (1013/1022; 98·3–99·6)	60·8% (219/360; 55·6–65·9)	80·1% (474/592; 76·6–83·2)	<0·0001
Overall surgical detection rate with radiocolloid alone	98·8% (573/580; 97·5–99·5)	52·9% (126/238; 46·4–59·4)	77·4% (301/389; 72·9–81·4)	..
Overall surgical detection rate with radiocolloid and blue dye	99·5% (399/401; 98·2–99·9)	76·2% (80/105; 66·9–84·0)	87·8% (144/164; 81·8–92·4)	..
Sentinel lymph nodes removed				
0	9/1022 (1%)	141/360 (39%)	118/592 (20%)	..
1	284/1022 (28%)	96/360 (27%)	142/592 (24%)	..
2	294/1022 (29%)	56/360 (16%)	131/592 (22%)	..
3	186/1022 (18%)	22/360 (6%)	81/592 (14%)	..
4	114/1022 (11%)	20/360 (6%)	59/592 (10%)	..
>4	135/1022 (13%)	25/360 (7%)	61/592 (10%)	..

34 %

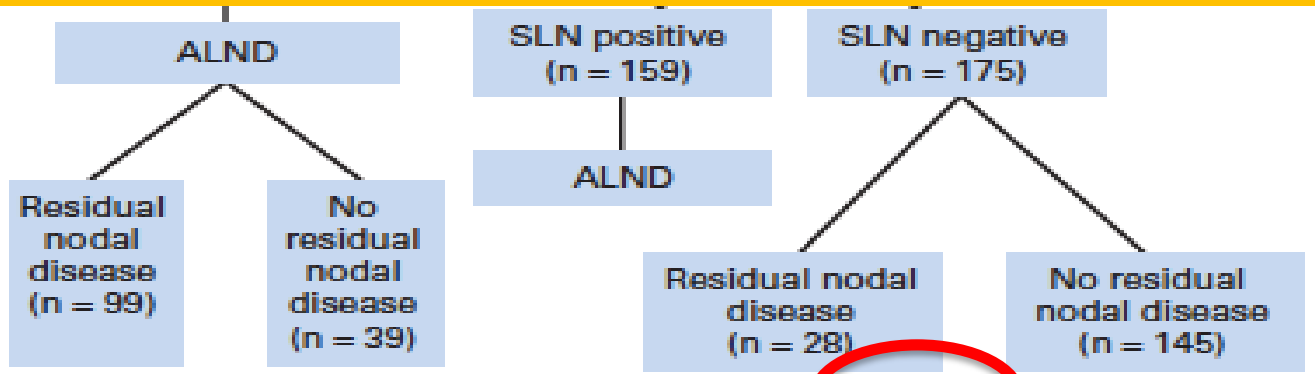
VOLUME 33 · NUMBER 30 · OCTOBER 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Axillary Ultrasound After Neoadjuvant Chemotherapy and Its Impact on Sentinel Lymph Node Surgery: Results From the American College of Surgeons Oncology Group Z1071 Trial (Alliance)

Not confirmed in the SENTINA TRIAL



FNR = 28 / (99 + 159 + 28) = 9.8%

VOLUME 33 · NUMBER 3 · JANUARY 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Sentinel Node Biopsy After Neoadjuvant Chemotherapy in Biopsy-Proven Node-Positive Breast Cancer: The SN FNAC Study

Jean-Francois Boileau, Brigitte Poirier, Mark Basik, Claire M.B. Holloway, Louis Gaboury, Lucas Sideris, Sarkis Meterissian, Angel Arnaout, Muriel Brackstone, David R. McCready, Stephen E. Karp, Isabelle Trop, Andre Lisbona, Frances C. Wright, Rami J. Younan, Louise Provencher, Erica Patocskai, Atilla Omeroglu, and Andre Robidoux

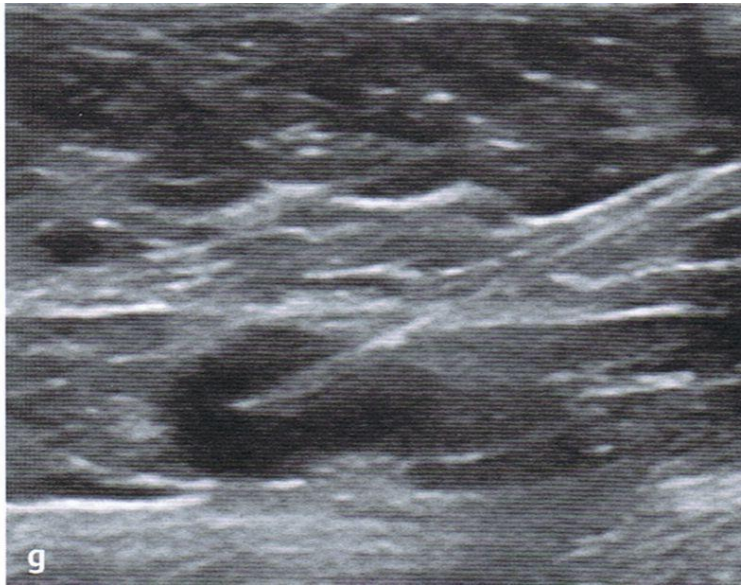
Jean-Francois Boileau, Mark Basik, and Andre Lisbona, Montreal Jewish General Segal Cancer Centre, McGill

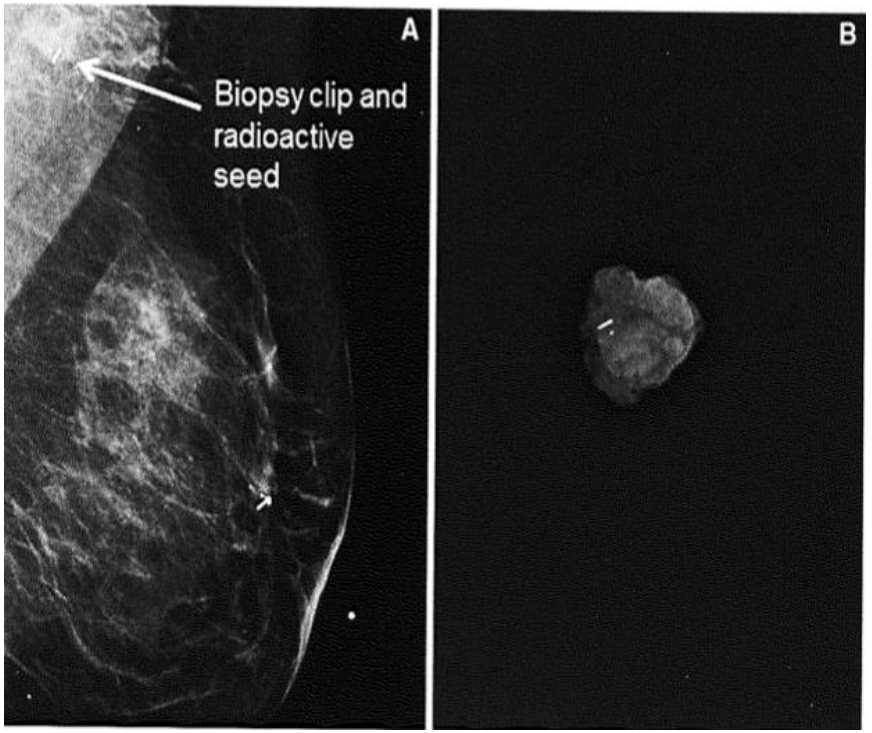
See accompanying editorial on page 232

Definition of positive SN		
Any size (ypN0[i+] + ypN1mi + ypN1)	7 of 83	8.4
> 0.2 mm (ypN1mi + ypN1)	11 of 83	13.3
> 2 mm (ypN1)	14 of 83	16.9

Targeted Axillary Dissection (TAD)

Clip localisation of a positive lymph node at the time of biopsy and targeted resection of this lymph node after PST



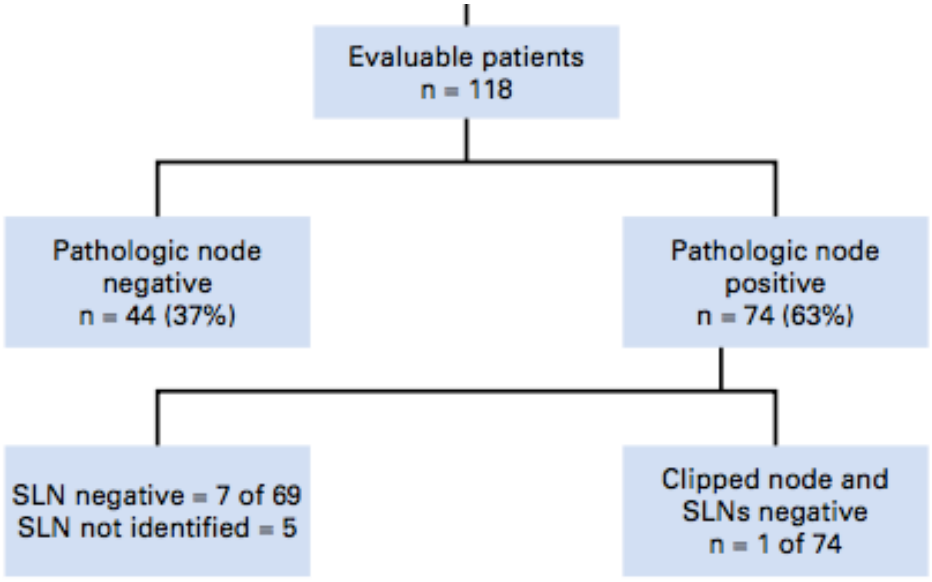


JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Unicenter retrospective

Improved Axillary Evaluation Following Neoadjuvant Therapy for Patients With Node-Positive Breast Cancer Using Selective Evaluation of Clipped Nodes: Implementation of Targeted Axillary Dissection

Abigail S. Caudle, Wei T. Yang, Savitri Krishnamurthy, Elizabeth A. Mittendorf, Dalliah M. Black, Michael Z. Gilcrease, Isabelle Bedrosian, Brian P. Hobbs, Sarah M. DeSnyder, Rosa F. Hwang, Beatriz E. Adrada, Simona F. Shaitelman, Mariana Chavez-MacGregor, Benjamin D. Smith, Rosalind P. Candelaria, Gildy V. Babiera, Basak E. Dogan, Lumarie Santiago, Kelly K. Hunt, and Henry M. Kuerer



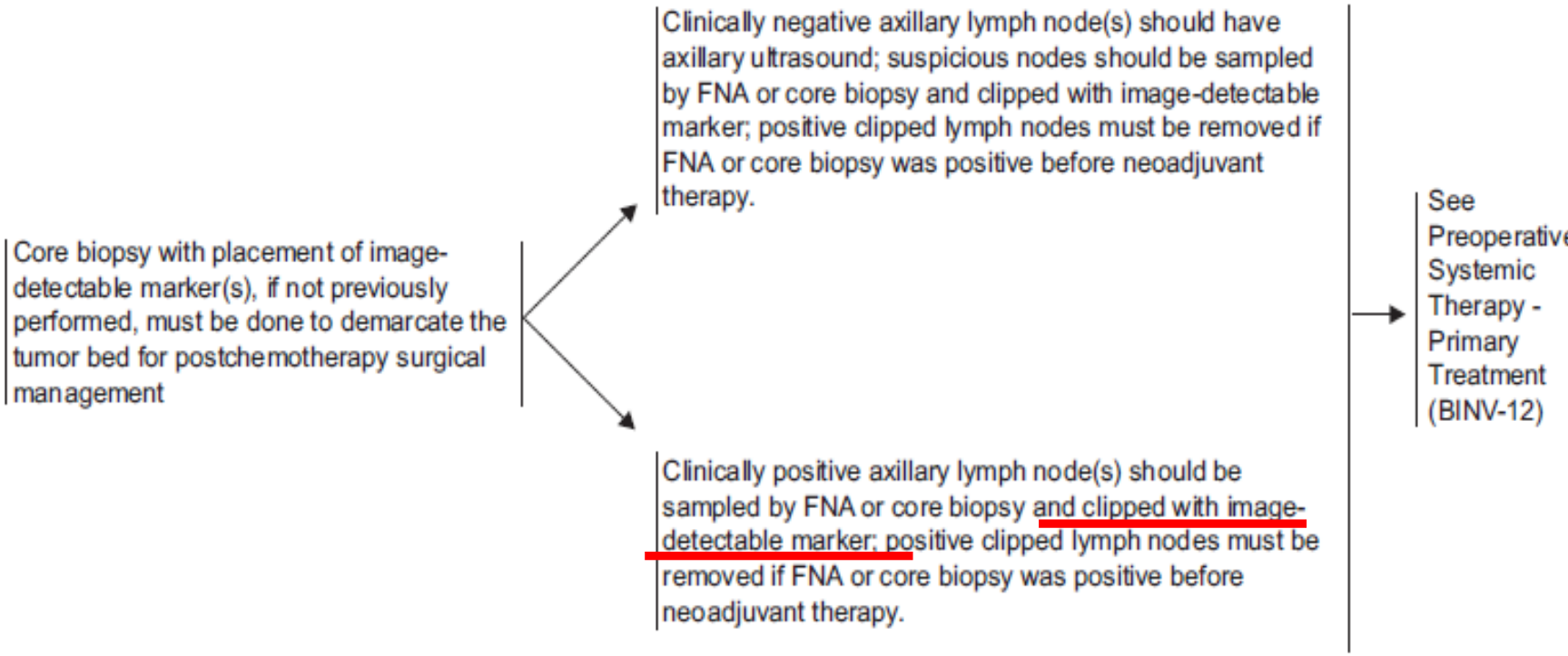
False-negative rate
SLN alone = 10.1% (95% CI 4.2 to 19.8)
SLN + evaluation of the clipped node = 1.4% (95% CI, 0.03 to 7.3)
P = .03

SLNB alone:
10.1 %

SLNB + TAD:
1.4 %

Caudle A et al. J Clin Oncol 2016

PREOPERATIVE SYSTEMIC THERAPY BREAST AND AXILLARY EVALUATION



Sentinel Lymph Node Biopsy (SLNB): Indications I

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2016.1

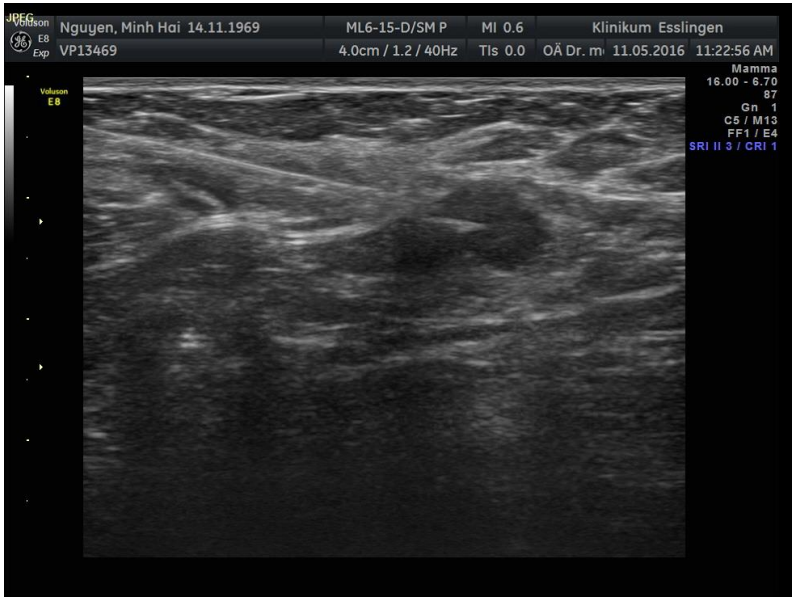
www.ago-online.de

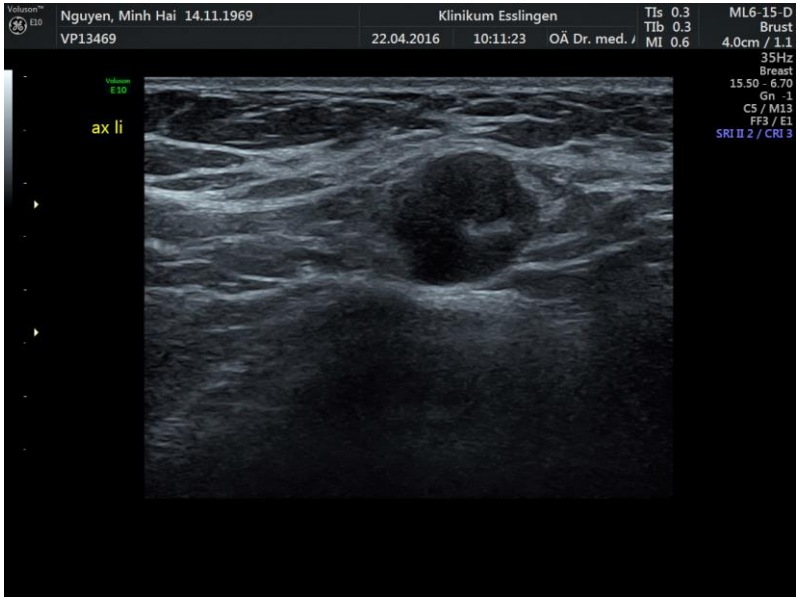
Further Information

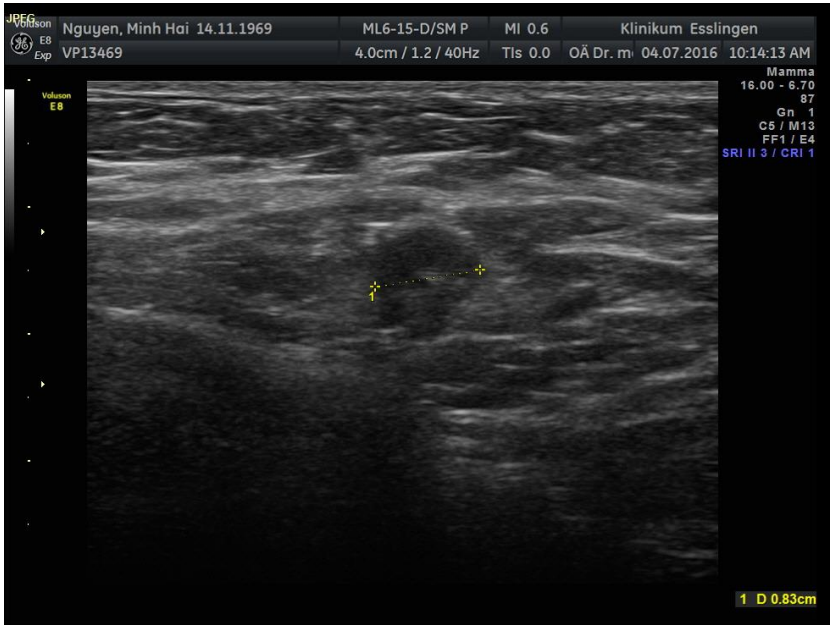
References

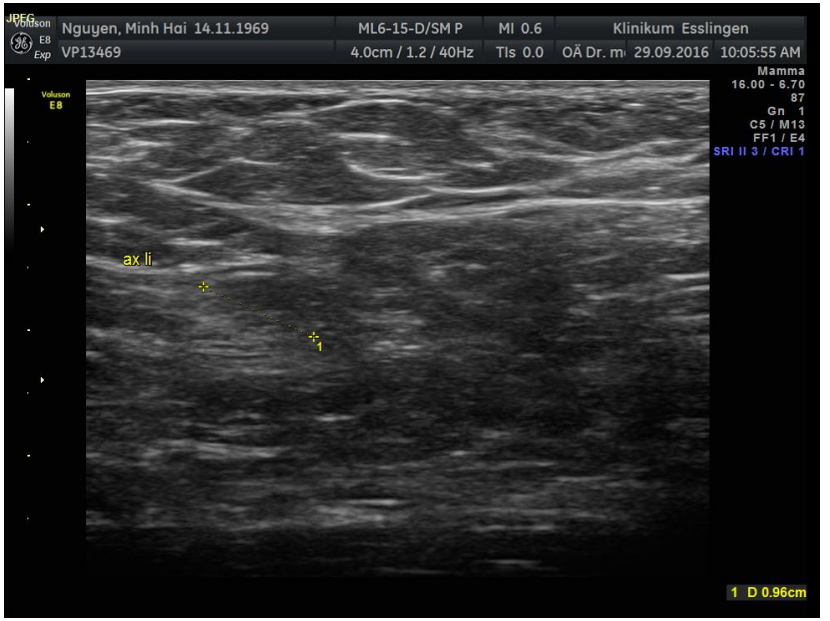
FORSCHEN
LEHREN
HEILEN

	Oxford / AGO LoE / GR		
➢ Clinically (cN0) / sonographically neg. axilla	1b	A	++
➢ Add. FNA/CNB of LN (clinical/sonogr. suspicious ~~+ Clip localization if NACT~~) in order to enable SLNB	2a	B	+
➢ T 1-2	2b	A	++
➢ T 3, 4a-c	3b	B	+
➢ Multifocal / multicentric lesions	2b	B	+
➢ DCIS	3b	B	+
➢ Mastectomy	3b	B	+
➢ DCIS in male	5	D	+
➢ BCT	3b	B	-
➢ Male breast cancer	2b	B	+
➢ In the elderly	3b	B	+


JPEG
Voluson E8 Exp
Nguyen, Minh Hai 14.11.1969
VP13469
ML6-15-D/SM P
4.0cm / 1.2 / 40Hz
MI 0.6
TIs 0.0
Klinikum Esslingen
OÄ Dr. m
11.05.2016 11:22:56 AM
Voluson E8
Mamma
16.00 - 6.70
87
Gn 1
C5 / M13
FF1 / E4
SRI II 3 / CRI 1


Voluson E10
Nguyen, Minh Hai 14.11.1969
VP13469
Klinikum Esslingen
22.04.2016 10:11:23
OÄ Dr. med.
TIs 0.3
TIb 0.3
MI 0.6
ML6-15-D
Brust
4.0cm / 1.1
35Hz
Breast
15.50 - 6.70
Gn -1
C5 / M13
FF3 / E1
SRI II 2 / CRI 3
ax li


JPEG
Voluson E8 Exp
Nguyen, Minh Hai 14.11.1969
VP13469
ML6-15-D/SM P
4.0cm / 1.2 / 40Hz
MI 0.6
TIs 0.0
Klinikum Esslingen
OÄ Dr. m
04.07.2016 10:14:13 AM
Voluson E8
Mamma
16.00 - 6.70
87
Gn 1
C5 / M13
FF1 / E4
SRI II 3 / CRI 1
1
1 D 0.83cm


JPEG
Voluson E8 Exp
Nguyen, Minh Hai 14.11.1969
VP13469
ML6-15-D/SM P
4.0cm / 1.2 / 40Hz
MI 0.6
TIs 0.0
Klinikum Esslingen
OÄ Dr. m
29.09.2016 10:05:55 AM
Voluson E8
Mamma
16.00 - 6.70
87
Gn 1
C5 / M13
FF1 / E4
SRI II 3 / CRI 1
ax li
1
1 D 0.96cm

TAD
- open issues -

- Exclusively Retrospective Data
- Technical Issues Unclear
  - Clip vs Seed vs coal
  - Legal limitations for the use of radioactive seeds
  - Localisation technique (wire, gamma probe)
  - No data available on surgical extent (number of removed Lns)

SenTa

Primäres Studienziel

Bestimmung der operativen Detektionsrate des Clip-markierten Target-Lymphknotens TLN

(Clip bei der Target-Lymphknoten-Biopsie TLNB
im resezierten Lymphknoten nachweisbar)

SenTa

Sekundäre (Haupt) -Studienziele

- Rate an abschließend unmöglicher Stanzbiopsie und Clipmarkierung – sonographisch suspekter Lymphknoten ist nicht biopsierbar (Lage, Schmerz, Antikoagulation, etc.)
- Rate an repräsentativen Stanzbiopsien (LK getroffen)

- DR für TAD (SLN und TLN detektiert)
- DR für TLNB
- DR für SLNB
- Übereinstimmung TLN mit SLN
- Anzahl entfernter LK bei TAD (SLNB+TLNB)
- Anzahl entfernter LK bei SLNB
- Anzahl entfernter LK wenn TLN nicht SLN
- FNR für TLNB
- FNR für SLNB

Surgery of the Axilla following Neo-Adjuvant Chemotherapy

23. In a patient who is clinically node-positive at diagnosis and who downstages after chemotherapy:

Is SN biopsy appropriate only in selected cases such as:
Clipping/seeding of involved nodes at diagnosis and targeted removal?

St. GallenVoting:

Yes	No	Abstain
50%	**28,6%**	**21,4%**

Stellungnahme der dt. Expertengruppe:
Dies ist eine Option, um die Falschnegativrate zu senken (AGO slide 200);
Verweis auf die SENTA-Studie

Axillary Intervention Before or After NACT

				Oxford / AGO LoE / GR		
SLNB before or after NACT in cN0						
SLNB before NACT **SLNB after NACT**				**2b** **2b**	**B** **B**	**+/-** **+**
Further surgical procedures depending on SLNB status						
cN-Status (before NST)	**pN-Status (before NST)**	**cN-Status (after NST)**		**Surgical Procedure (after NST)**		
cN0	**pN0(sn)**	**-**		**nihil**	**1a**	**A**	**+**
cN0	**pN+(sn)** (analog ACOSOG Z0011)	**ycN0**		**nihil** **Re-SLNB alone** **ALND**	**5** **2b** **3**	**D** **B** **B**	**+/-** **-** **+/-**
cN0	**pN+(sn)** (not analog ACOSOG Z0011)	**ycN0**		**Re-SLNB alone** **ALND** **Axilla XRT**	**2b** **2b** **2b**	**B** **B** **B**	**-** **+** **+**
cN0	**not done**	**ycN0**	**ypN0 (sn)**	**SLNB alone** **ALND**	**2b** **2b**	**B** **B**	**+/-** **+/-**
			ypN+ (sn)	**ALND**	**2b**	**B**	**+**
cN+	**cN+ (CNB/FNA)**	**ycN0** **ycN+**		**SLNB alone*** **ALND** **ALND**	**2b** **2b** **2b**	**B** **B** **B**	**+/-** **+** **++**

ESTRO

Multidisciplinary Course on Breast Cancer

Tokio 20.-22.5.2016

Current opinion regarding SLNB and ALND: Indications, techniques and timing

T. Kuehn

Klinikum Esslingen , Germany

Thank you very much

ESTRO School

ESTRO Teaching Course on the Multidisciplinary management of Breast Cancer.
Dublin, Republic of Ireland. September 2017

Current Application of SLNB and ALND:

What re we doing after Z11 and AMAROS?

Lynda Wyld
Reader In Surgical Oncology
University of Sheffield
Consultant Oncoplastic Breast Surgeon
Doncaster and Bassetlaw Teaching Hospital
UK.

Disclosure:

- I have no conflict of interest to report

Lecture plan

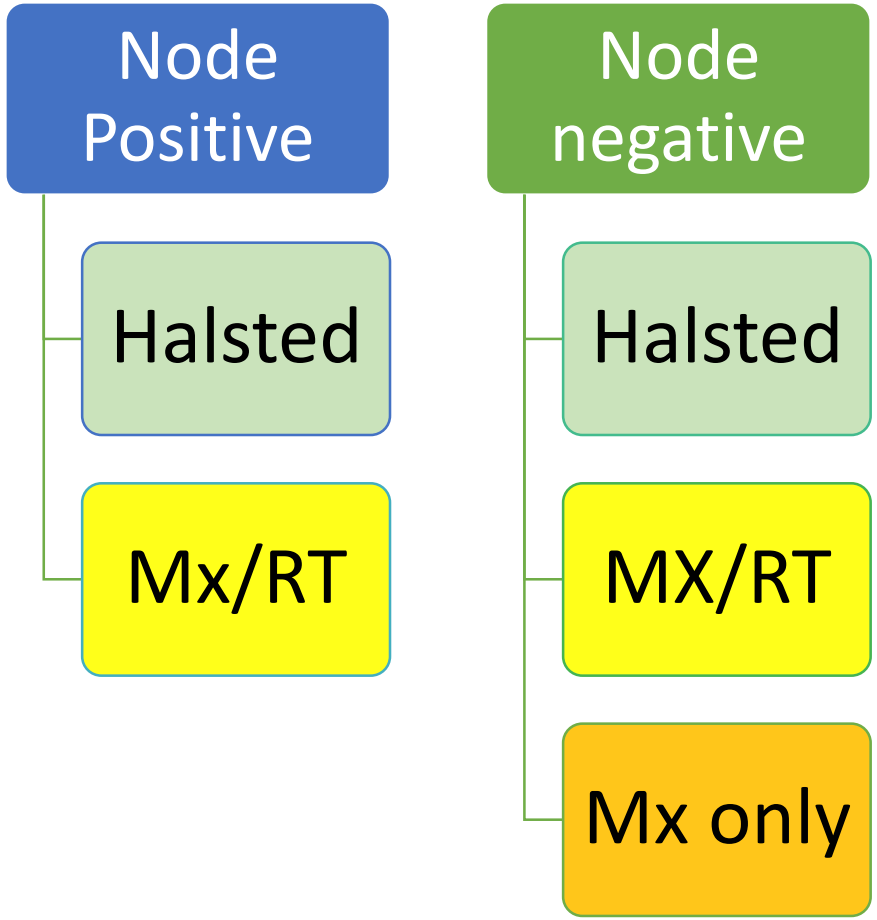
- Historical perspective
- Z11
- AMAROS and others
- A new management algorithm
- What is current practice?

Axillary Clearance

- Gold standard until 1990s: thought to be necessary for local control and staging.
- All women had clearance.
- No preoperative imaging or node biopsy.
- 60% of women had an unnecessary clearance, with negative nodes and a subsequent 15-35% risk of lymphoedema

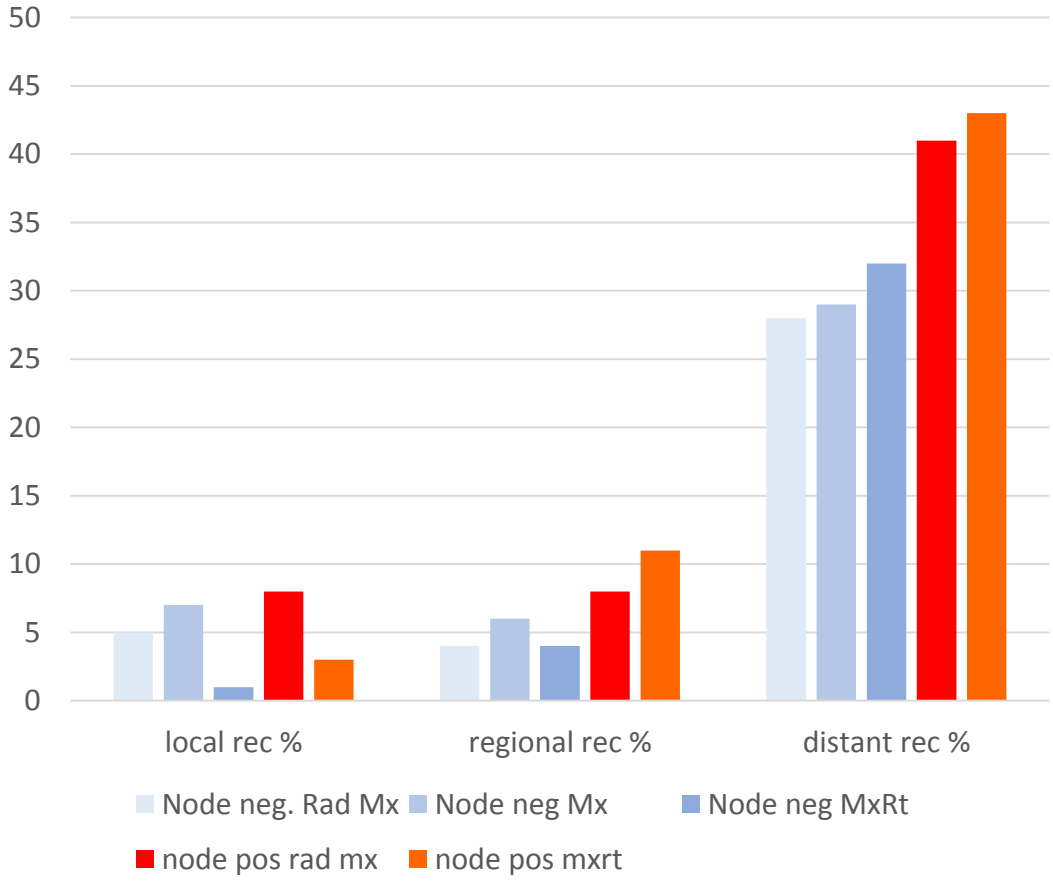
Is this necessary?

- NSABP B-04, (started in 1971), study of Fisher and colleagues, (2002)
- Women randomised according to whether clinically node positive or negative.
- No patients had adjuvant systemic therapy and tumours were large by modern standards
- 40% of the ‘clinically node negative’ cases had +ve nodes in the clearance group



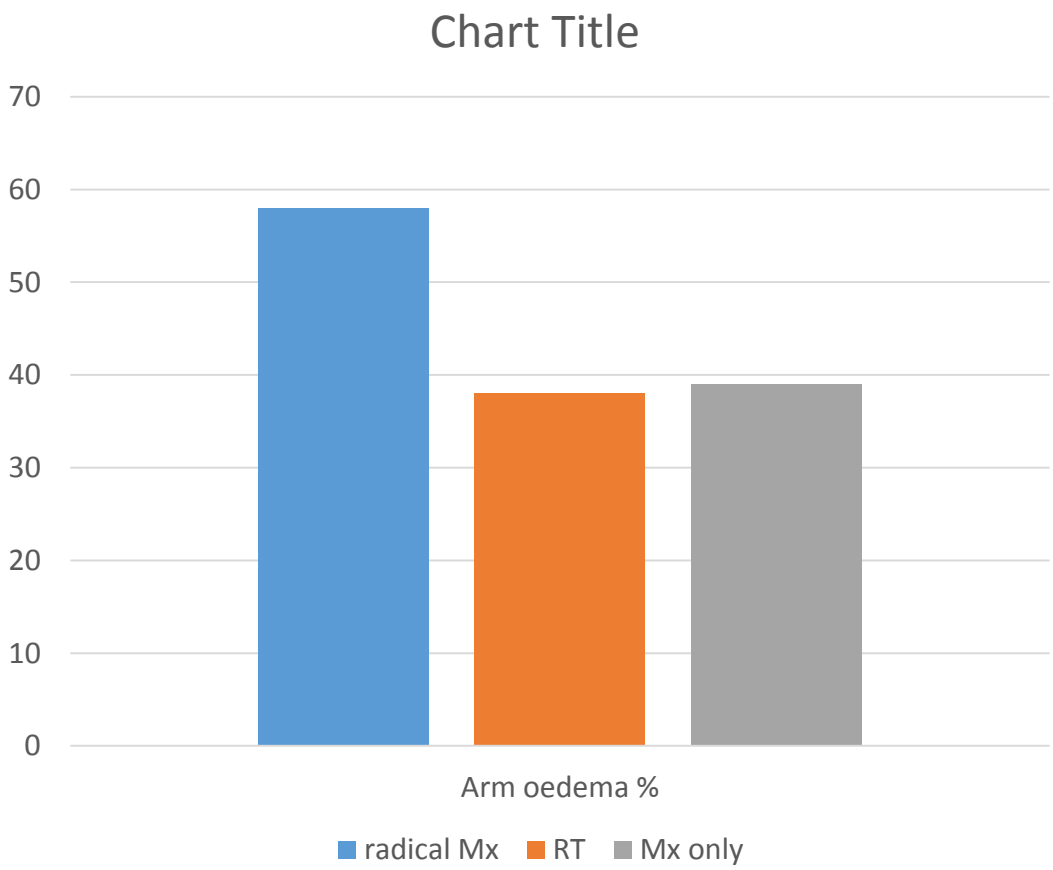
Long term disease control in NSABP B 04

- At 25 years of follow up no significant differences were found in any parameter
- Overall mortality rates were not significantly different regardless of axillary treatment type



Lymphoedema

- 46% of women experienced arm oedema during follow-up.
- Radical mastectomy was associated with the highest rate ($p<.001$) with no difference between Mx alone and RT.



Sentinel Node Biopsy

- David Krag and Armando Giuliano introduced SLNB for breast cancer in 1996

- The principle that the first draining lymph node in the lymphatic chain will be representative of the status of the lymphatic basin

- Large validation studies confirmed SLNB reliable and safe with a low morbidity and high sensitivity and specificity for staging the axilla

NSABP (National Surgical Adjuvant Breast and Bowel Project) B-32

- Women with invasive breast cancer were randomly assigned to either SLN resection plus ANC (group 1) or to SLN resection alone with ANC only if the SLNs were positive (group 2)
- No significant difference in OS, DFS at 8 years
- Overall survival (OS) , disease-free survival (DFS) , and regional control were statistically equivalent between groups.

A Paradigm Shift…..

And so we moved into the era of SLNB for patients with clinically negative axillas.

Axillary staging being a prime motivation for axillary surgery, used to guide adjuvant therapy choices, rather than solely for disease control

Even so, recent St Gallen guidelines (2013) suggest that the total number of nodes involved is less important than nodal status plus tumour biology, so further weakening the drive towards completion clearance

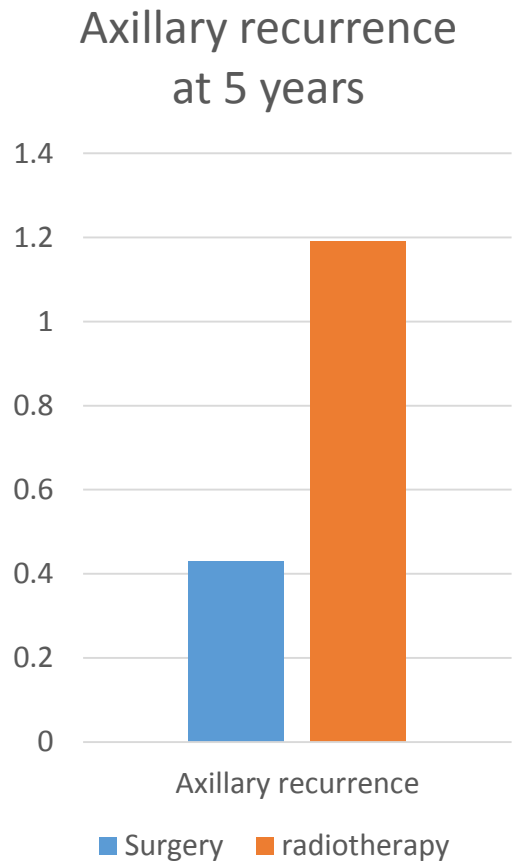
How to manage women with a positive SLNB?

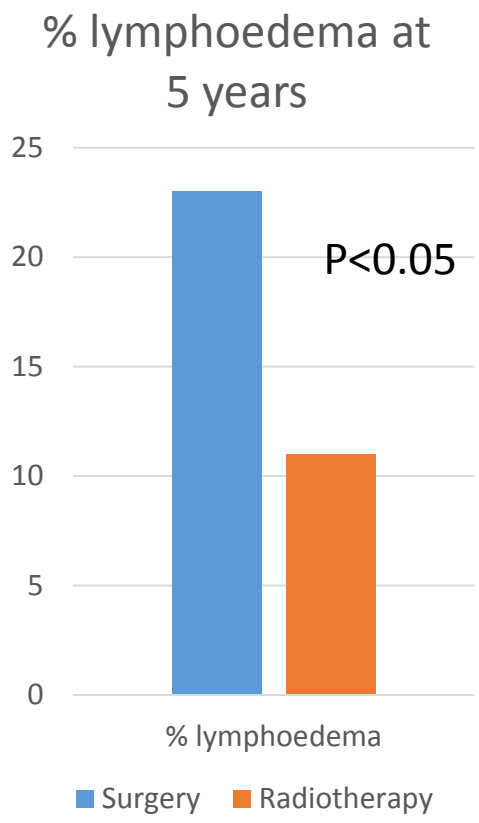
- Completion clearance or radiotherapy
- Regional recurrence rates are very low, (2%) and depend on tumour biology, patient age and tumour size

- Seminal trial: ACOSOG Z0011 trial.
- 800+ women with +ve SLN randomised to completion clearance or lower axillary RT as part of standard breast RT fields.
- At 6 years median FU, regional rates of recurrence were 0.5% versus 0.9% and not significantly different

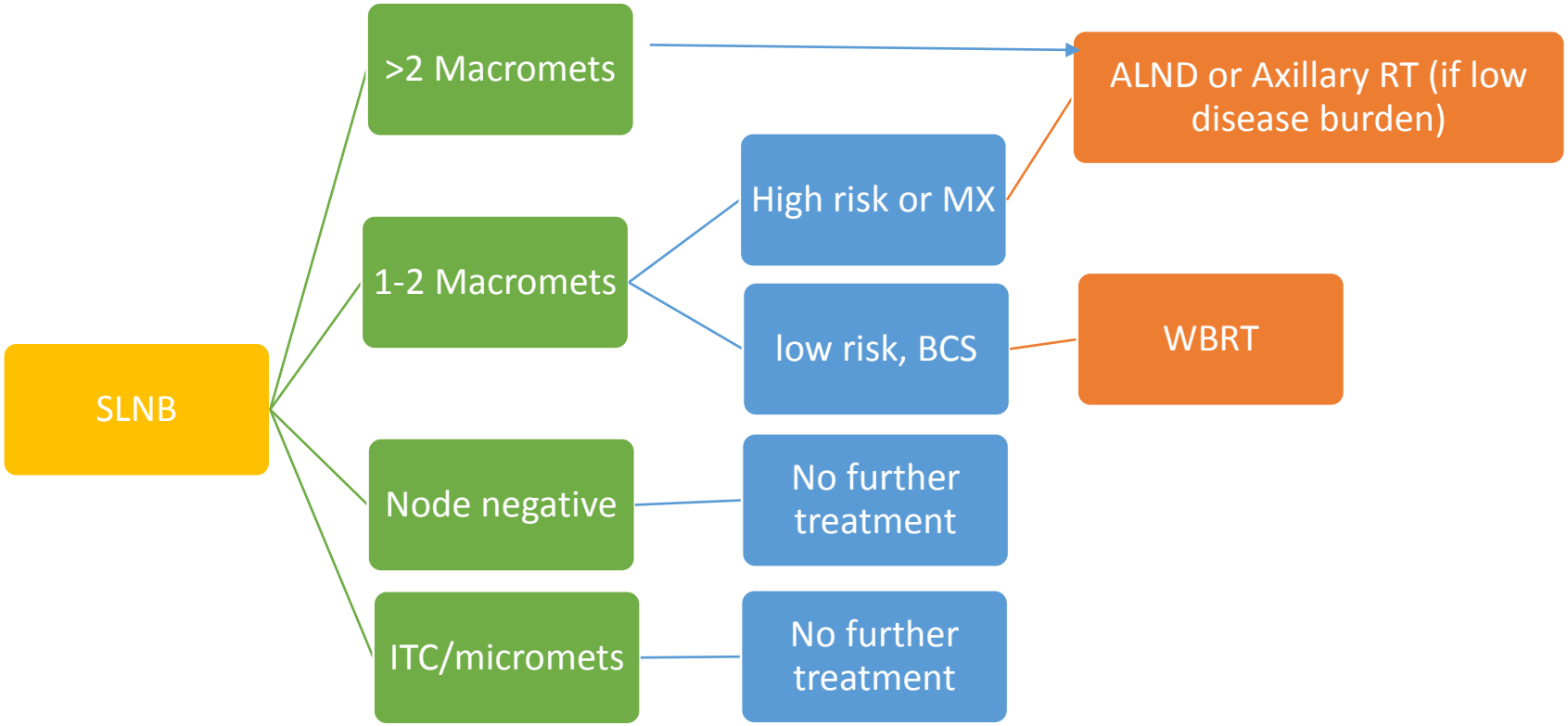
AMAROS

- Randomised trial of women with 3-5cm sized breast cancers and a positive sentinel node.
- 744 patients radnomised to axillary clearance versus 681 to axillary radiotherapy.
- 5 years follow-up
- Primary outcome: axillary recurrence (No significant difference).
- DFS, OS no significant difference





UK ABS Guidelines for the clinically negative axilla



Practice Elsewhere

Single US Institution

- Of 849 cases before Z11, 144 had +SLNB and 113 underwent ALND (79%)
- Of 932 patients after Z11: 139 had +SLNB and 73 underwent ALND (53%)
- If only those meeting the Z11 criteria were assessed, these percentages changed to 75 and 2.2% showing that Z11 has significantly changed practice in the USA.
- The completion AD rate in the BEFORE group was 78.5%, compared to 52.5% in the AFTER group
- (Le, 2016, the Breast)

Ireland

- Compared completion clearance rates pre and post Z011 publication.
- Rate of completion fell from 94% to 71% (92 versus 65 if only the last year of the study period was reviewed, suggesting an downwards trend).
- (Joyce, 2016, Irish J Med. Sci)

Question for Voting: What best describes your Unit's axillary management protocol?

1. All women with sentinel node macrometastases have ALND, regardless of surgery type or risk factors

2. Women with Z11 compliant disease are offered WBRT and full axillary RT (if not Z11 compliant) as an alternative to ALND

3. Women with Z11 compliant disease are offered WBRT but otherwise are only offered ALND

4. Women are **not** offered WBRT as an alternative to ALND but may be offered full axillary RT or ALND

Thank You.

Any Questions?

Randomized Trials of Post-mastectomy Radiotherapy following Axillary Dissection

Sarah Darby
Nuffield Department of Population Health
University of Oxford
United Kingdom

CANCER RESEARCH UK

UNIVERSITY OF OXFORD

Plan of talk

- Meta-analysis of radiotherapy after mastectomy and axillary dissection

- Analyses of any, local and distant recurrence

“Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials”

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)

Lancet 2014; 383:2127-35

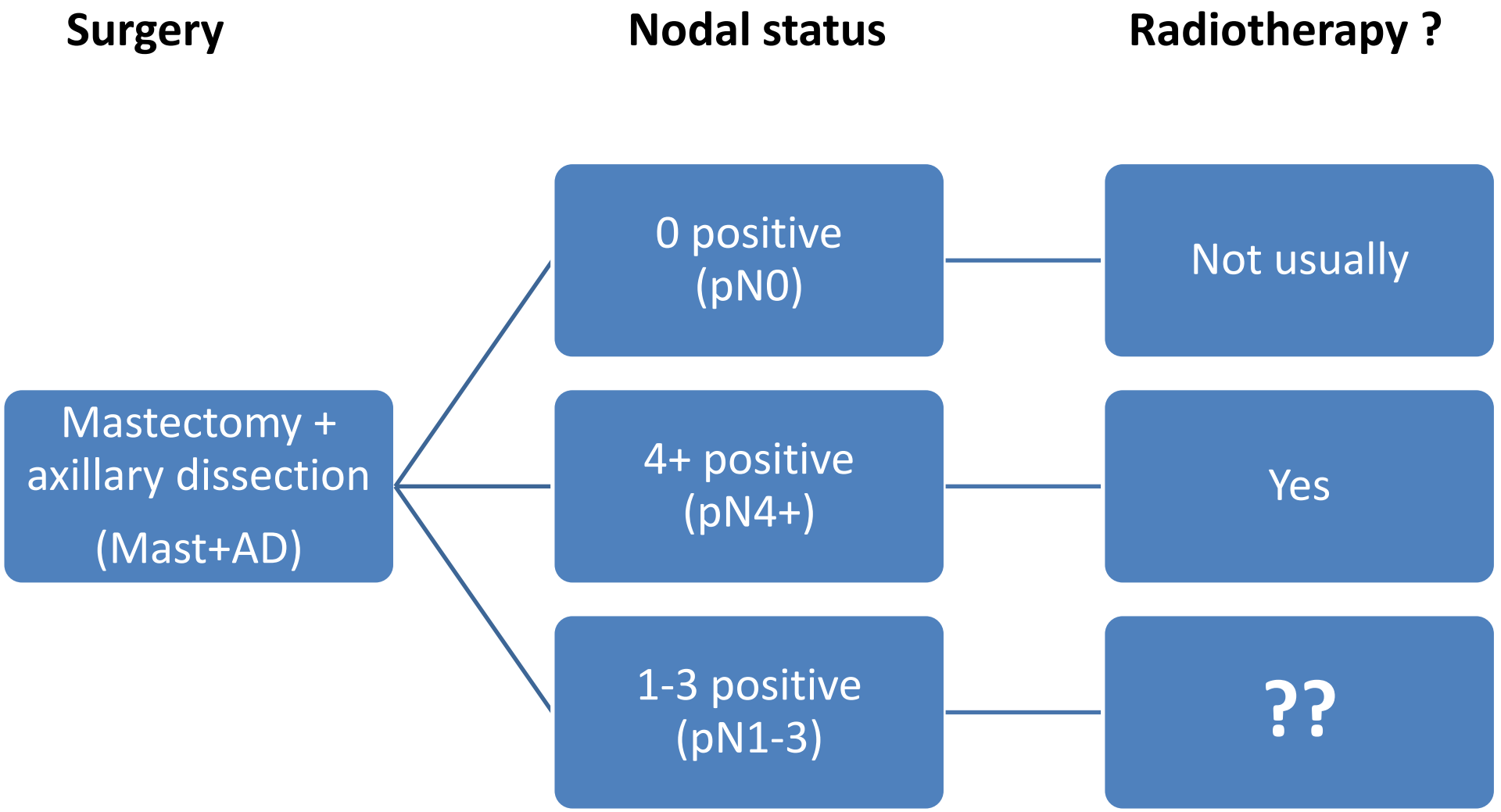
EBCTCG, Lancet 2014

Individual patient data to be presented

- **Criteria:**
  - Randomised trials of post-mastectomy radiotherapy (RT) versus same surgery but no RT
  - Started before 2000
  - Mastectomy and axillary dissection to at least level II
  - RT to include chest wall
  - Known pathological nodal status

- **Found:**
  - 3786 women in 14 trials (started 1964 to 1982)
  - 43 000 years of follow-up to 2009 (median 9.0 years)
  - RT to axillary, internal mammary and supraclavicular nodes

Current Guidelines

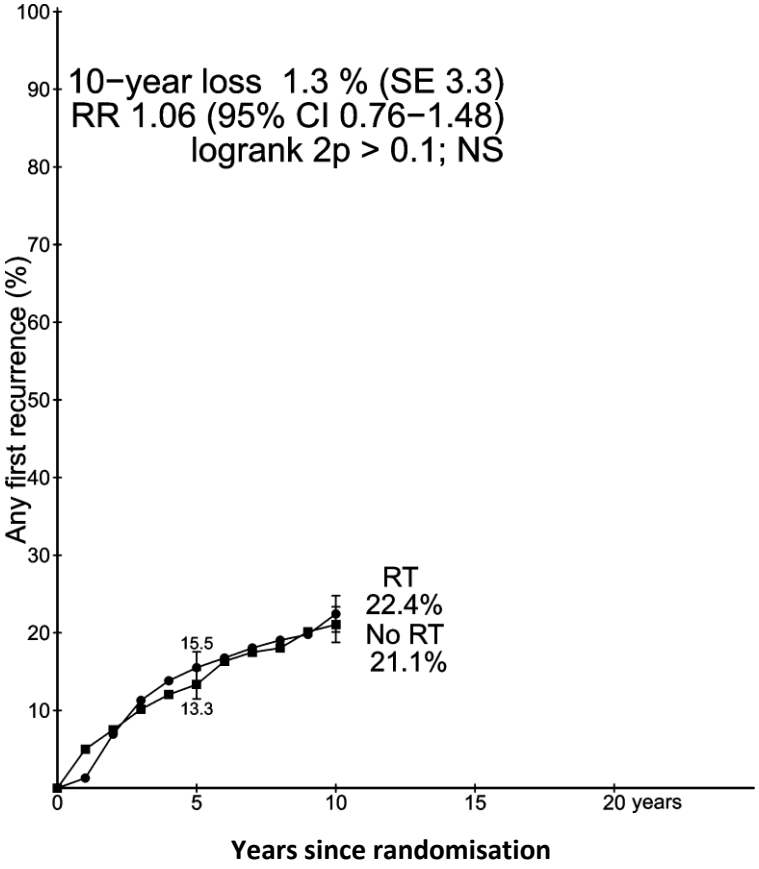


Trials of radiotherapy after mastectomy and axillary dissection

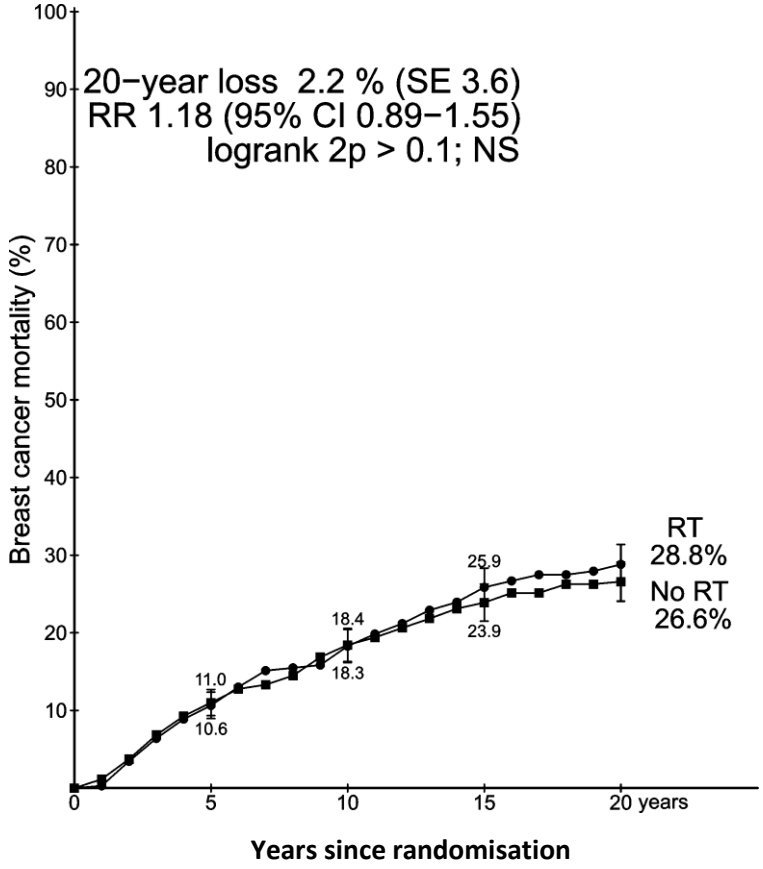
700 pN0 women

RT: No significant benefit

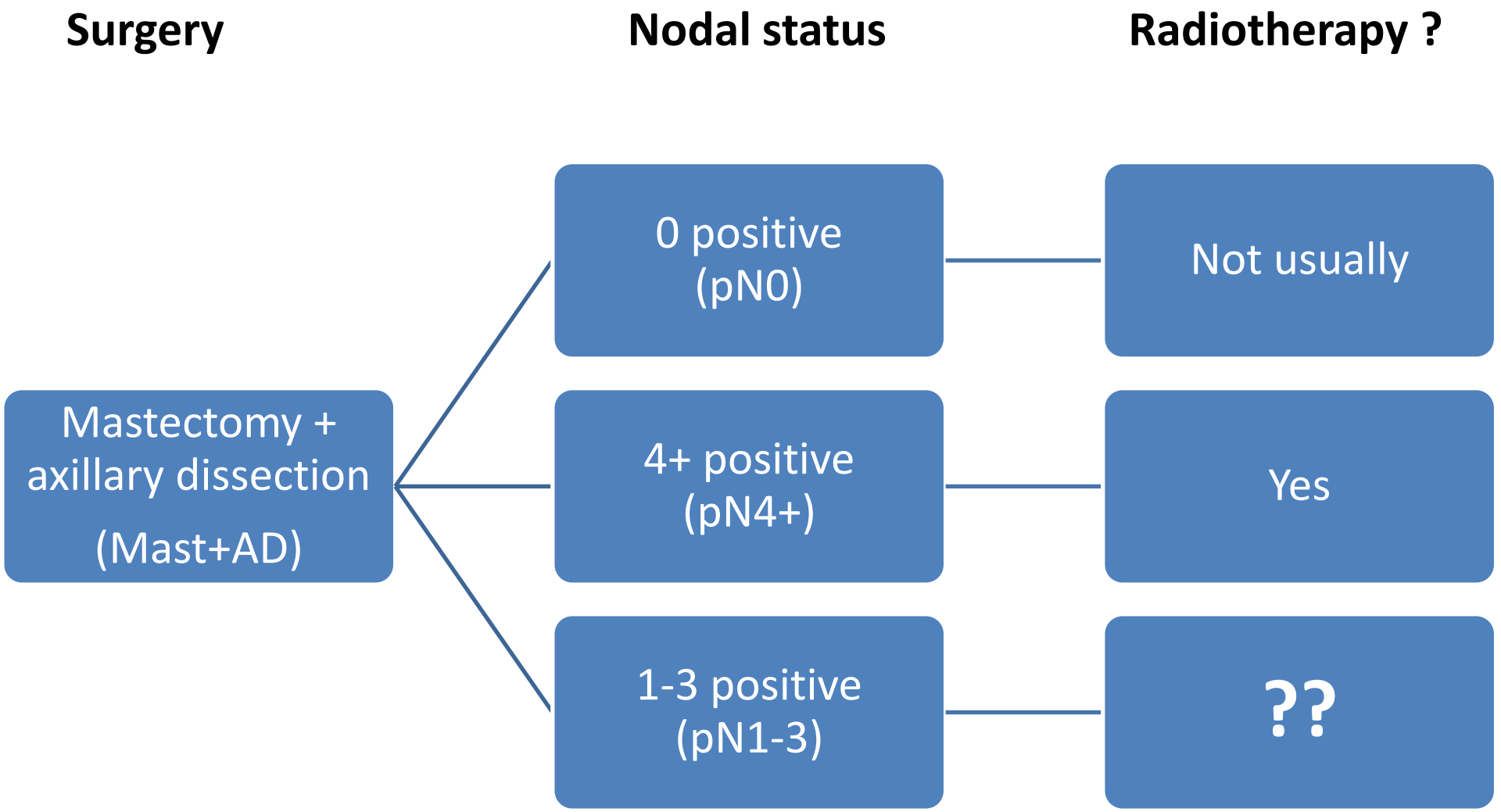
Any first recurrence



Breast cancer mortality



Current Guidelines

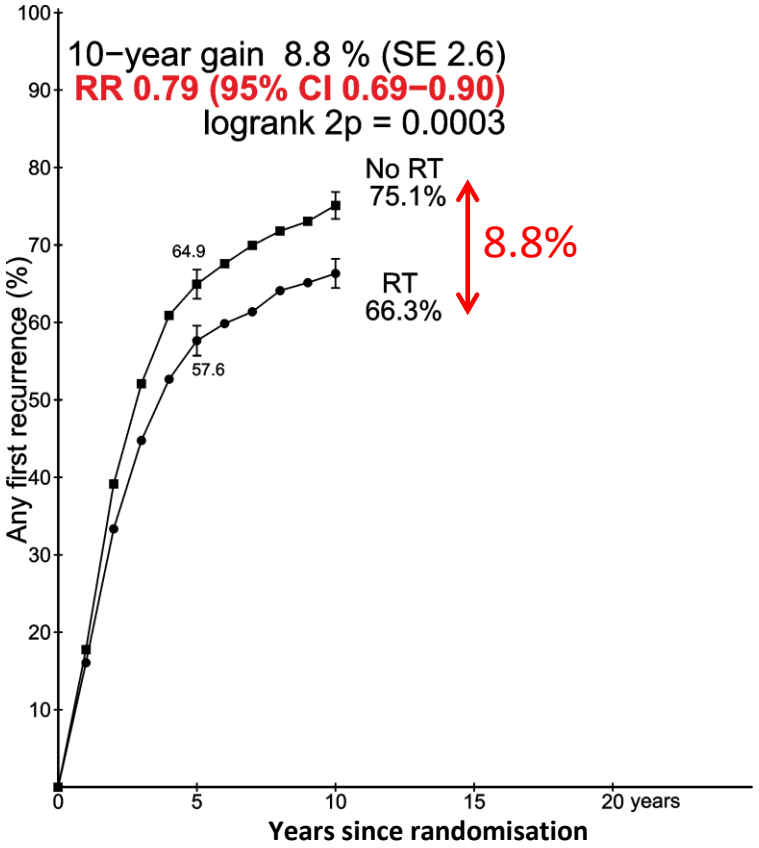


Trials of radiotherapy after mastectomy and axillary dissection

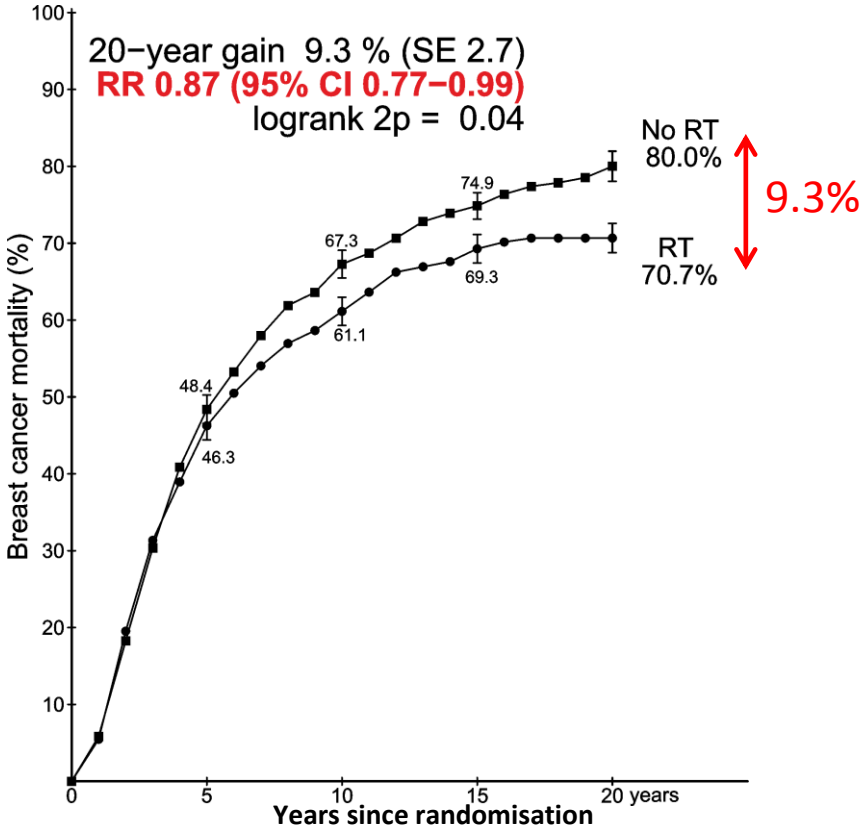
1772 pN4+ women

RT: Significant benefit

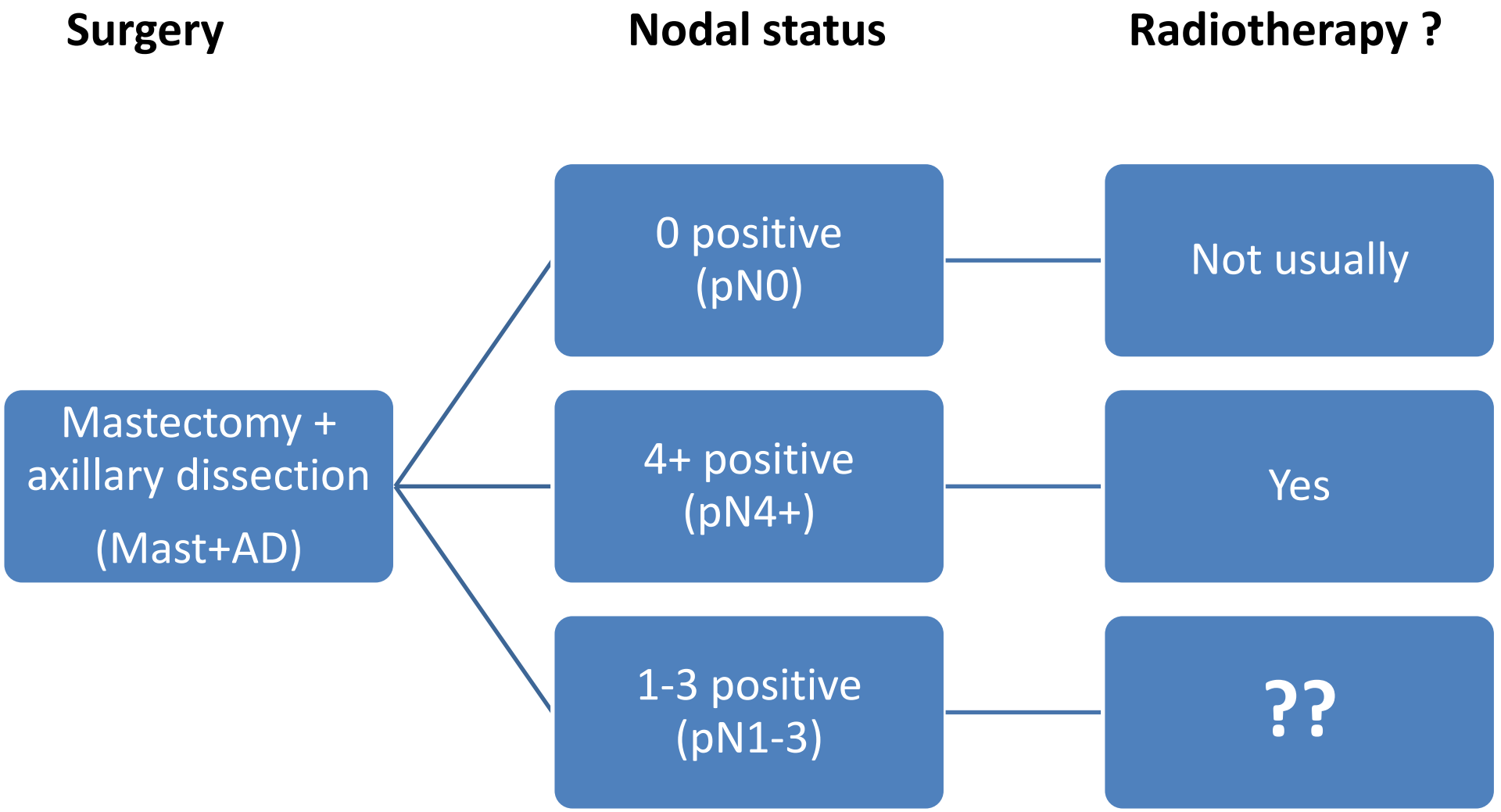
Any first recurrence



Breast cancer mortality



Current Guidelines

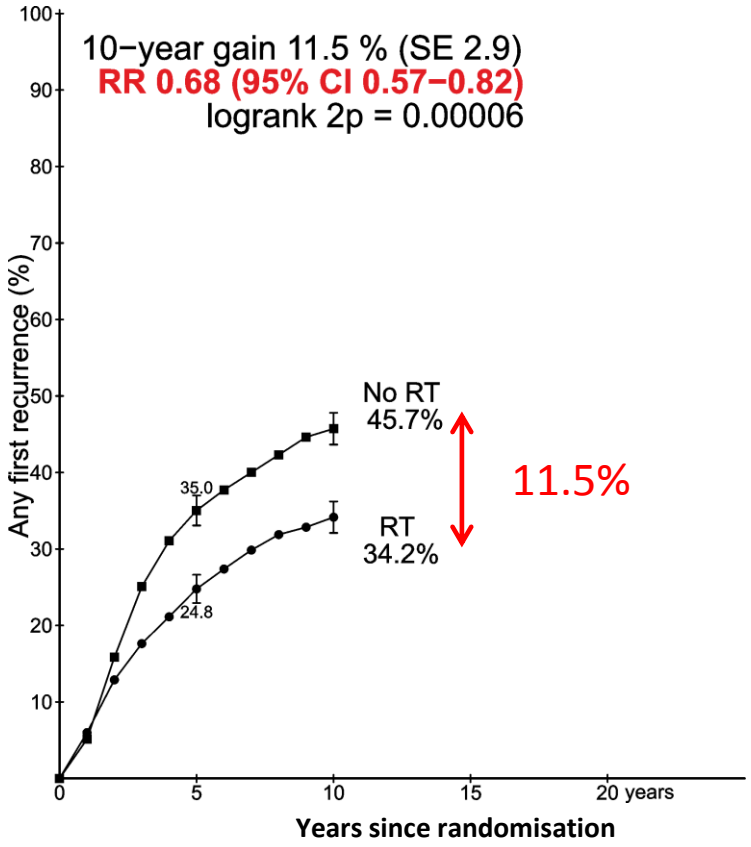


Trials of radiotherapy after mastectomy and axillary dissection

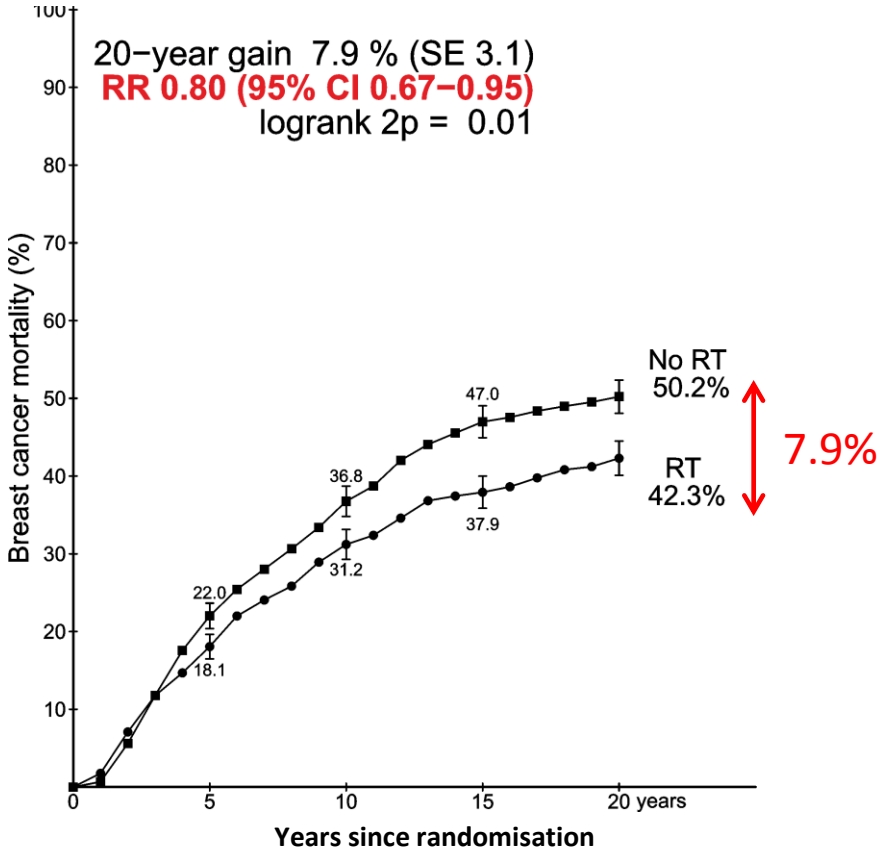
1314 pN1-3 women

RT: Significant benefit

Any first recurrence



Breast cancer mortality

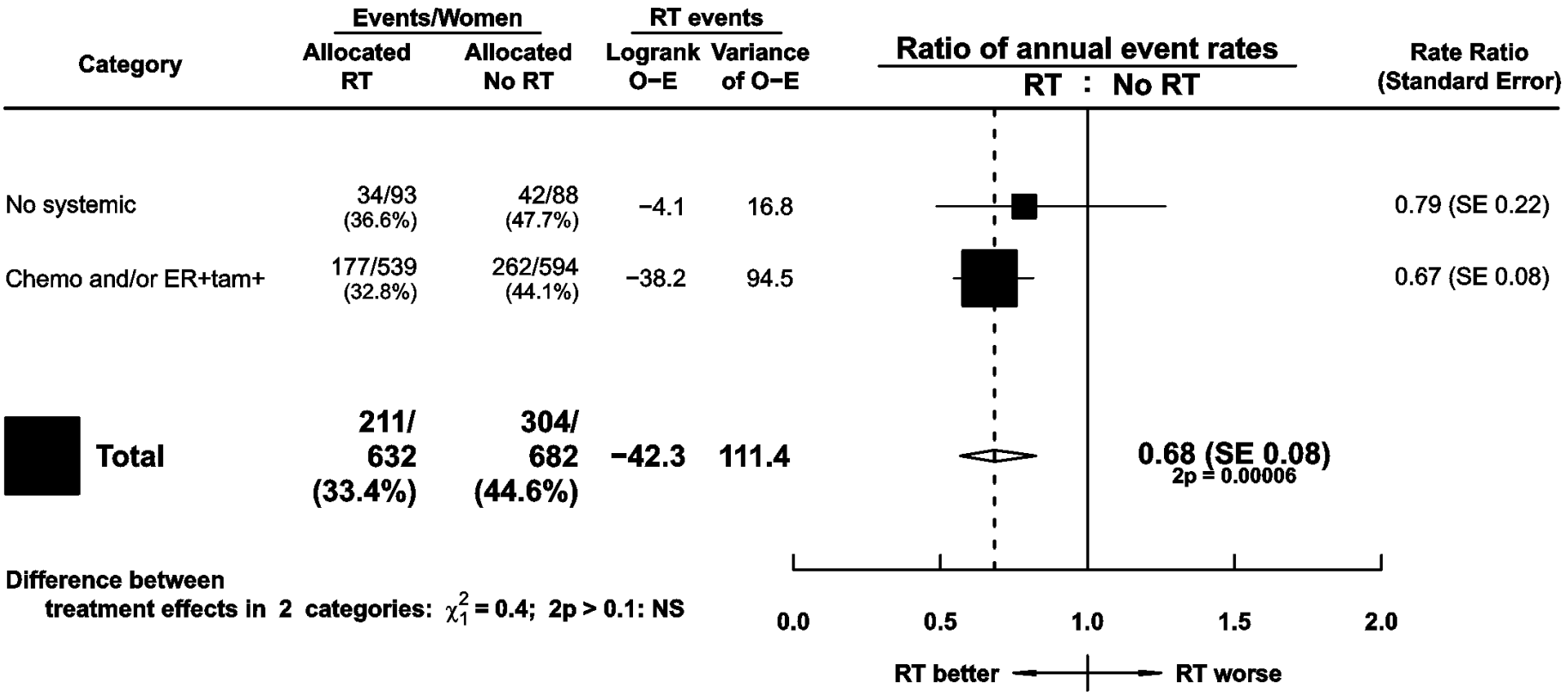


Trials of radiotherapy after mastectomy and axillary dissection

1314 pN1-3 women

RT: Significant benefit

Any first recurrence by use of systemic therapy

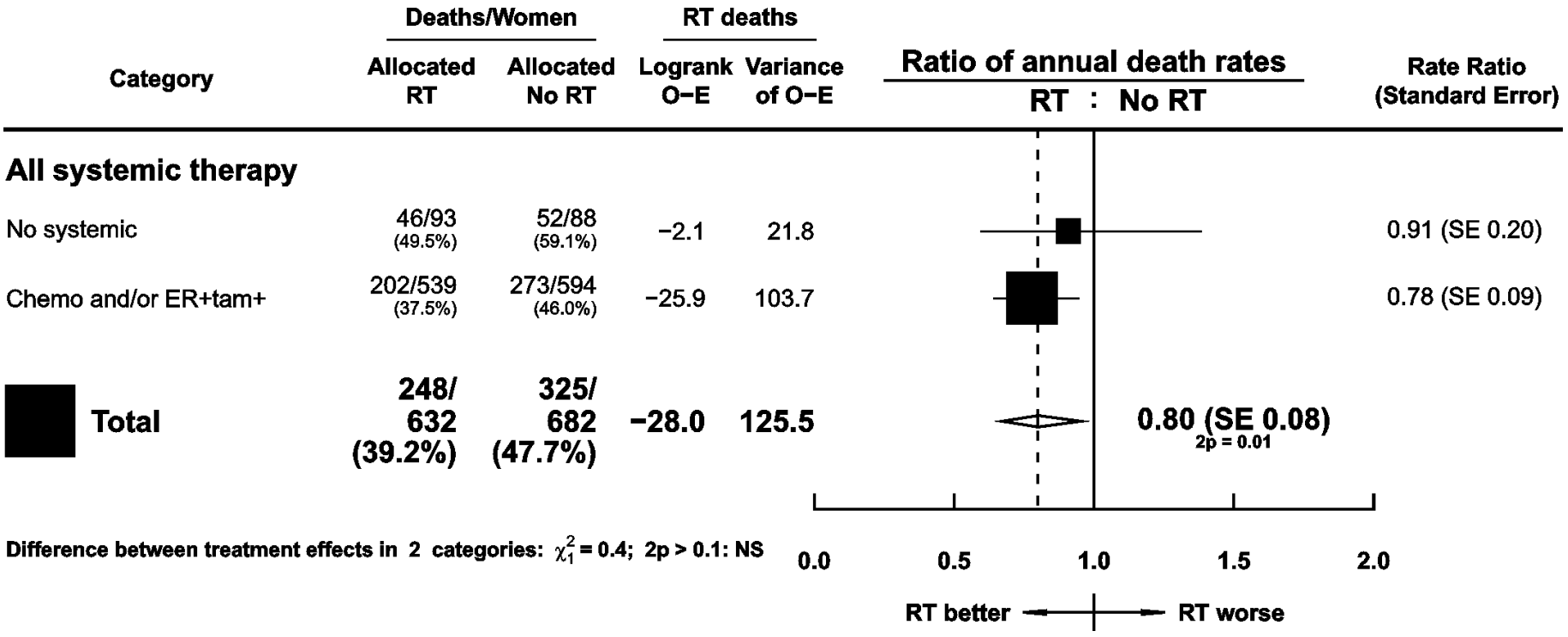


Trials of radiotherapy after mastectomy and axillary dissection

1314 pN1-3 women

RT: Significant benefit

Breast cancer mortality by use of systemic therapy

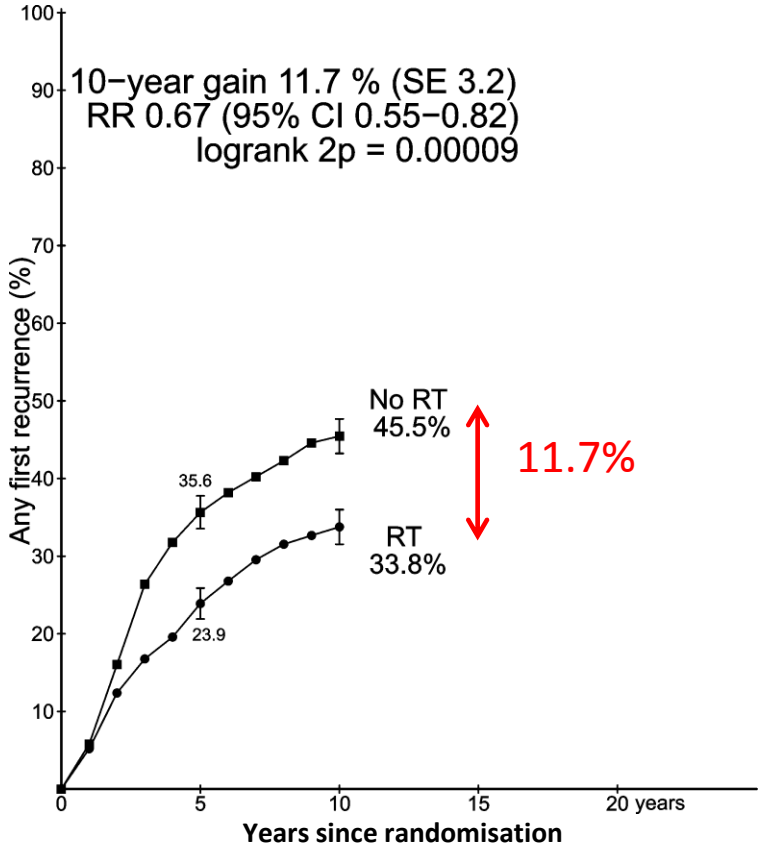


Trials of radiotherapy after mastectomy and axillary dissection

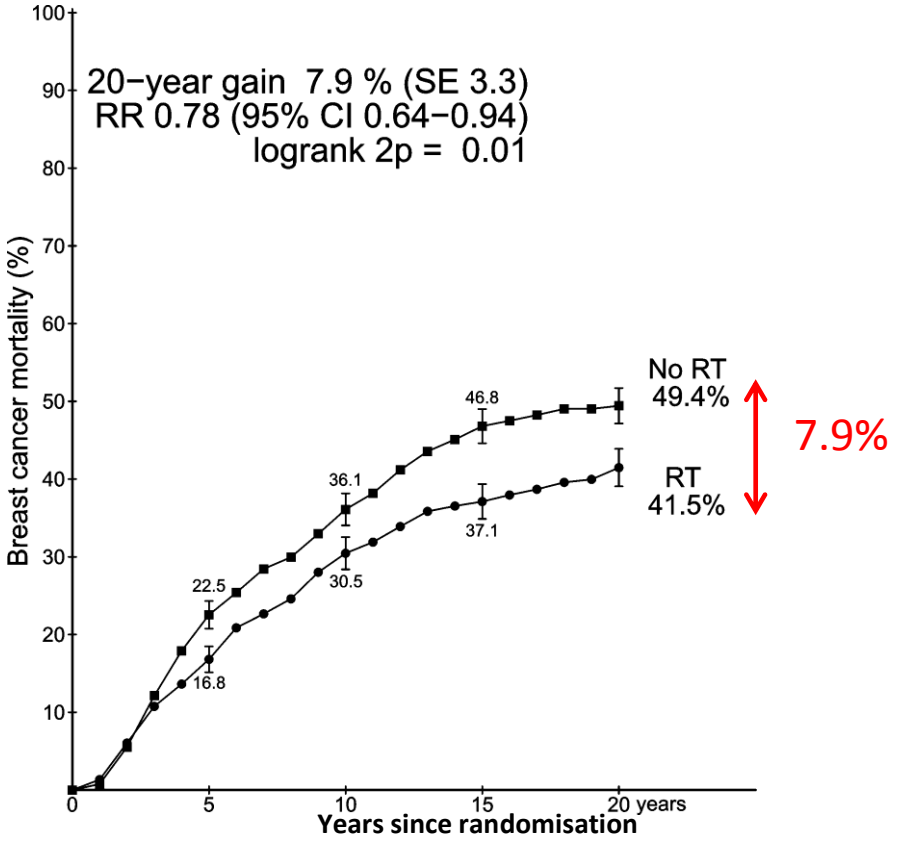
1133 pN1-3 women in trials with systemic therapy

RT: Significant benefit

Any first recurrence



Breast cancer mortality



Trials of radiotherapy after mastectomy and axillary dissection

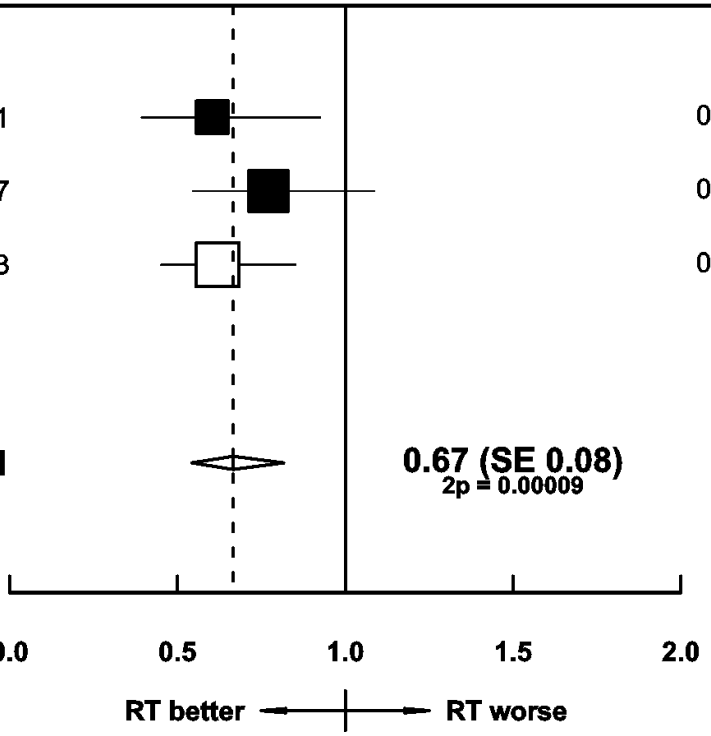
1133 pN1-3 women in trials with systemic therapy

RT: Significant benefit

Any first recurrence by number of nodes positive

Category	Events/Women: Allocated RT	Events/Women: Allocated No RT	RT events: Logrank O−E	RT events: Variance of O−E	Rate Ratio (Standard Error)
1 positive node	35/145 (24.1%)	63/173 (36.4%)	−10.6	21.1	0.60 (SE 0.17)
2−3 positive nodes	69/178 (38.8%)	92/187 (49.2%)	−8.5	32.7	0.77 (SE 0.15)
Unknown but pN1−3	73/216 (33.8%)	107/234 (45.7%)	−18.3	38.3	0.62 (SE 0.13)
Total	**177/539 (32.8%)**	**262/594 (44.1%)**	**−37.5**	**92.1**	**0.67 (SE 0.08)** 2p = 0.00009

Ratio of annual event rates
RT : No RT



Difference between treatment effects in 2 categories: $\chi^2_1 = 0.8$; 2p > 0.1: NS

Trials of radiotherapy after mastectomy and axillary dissection

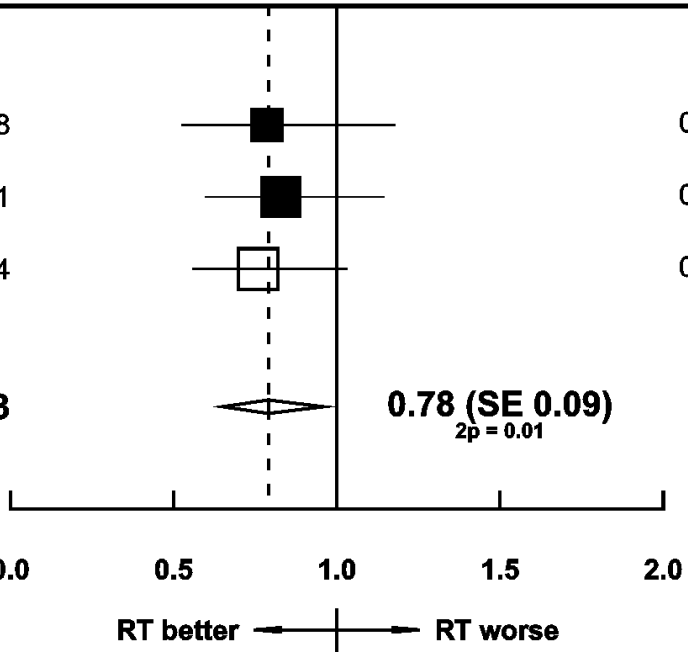
1133 pN1-3 women in trials with systemic therapy

RT: Significant benefit

Breast cancer mortality by number of nodes positive

Category	Deaths/Women: Allocated RT	Deaths/Women: Allocated No RT	RT deaths: Logrank O−E	RT deaths: Variance of O−E	Rate Ratio (Standard Error)
Number positive nodes					
1 positive node	46/145 (31.7%)	66/173 (38.2%)	−5.7	23.8	0.79 (SE 0.18)
2−3 positive nodes	76/178 (42.7%)	96/187 (51.3%)	−7.0	37.1	0.83 (SE 0.15)
Unknown but pN1−3	80/216 (37.0%)	111/234 (47.4%)	−11.4	41.4	0.76 (SE 0.14)
Total	**202/539 (37.5%)**	**273/594 (46.0%)**	**−24.1**	**102.3**	**0.78 (SE 0.09)** 2p = 0.01

Ratio of annual death rates
RT : No RT

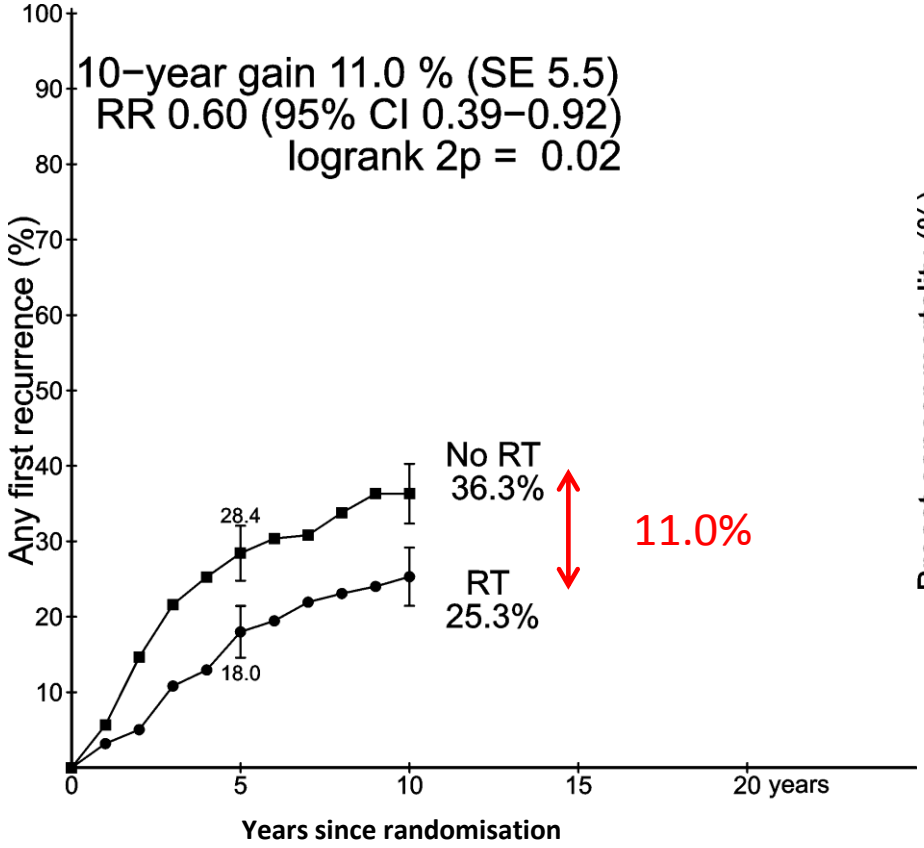


Difference between treatment effects in 2 categories: $\chi^2_1 = 0.0$; 2p > 0.1: NS

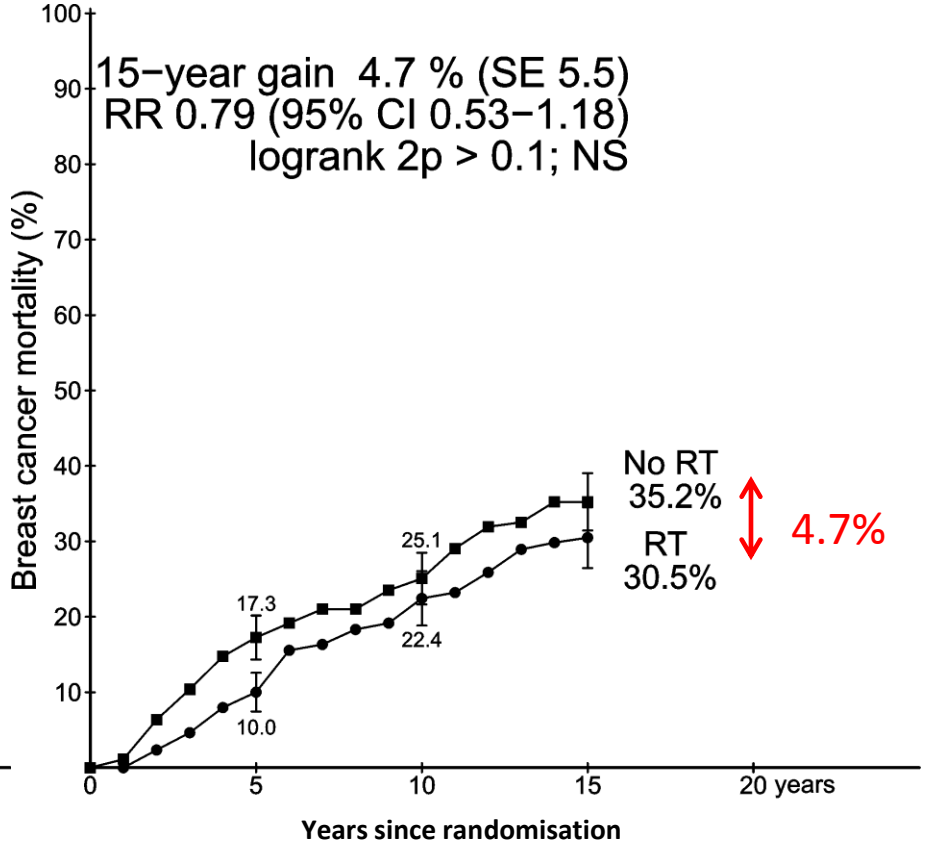
Trials of radiotherapy after mastectomy and axillary dissection

318 women with Mast+AD, systemic therapy and 1 positive node

Any first recurrence



Breast cancer mortality



Radiotherapy after Mastectomy and Axillary Dissection Conclusions 1

In these trials:

- **for pN0 women, RT gave no significant benefit**

- **for pN4+women, RT gave significant benefit**
  - Absolute reductions
    - 10-year recurrence: 8.8% (75.1% vs. 66.3%)
    - 20-year breast cancer mortality: 9.3% (80.0% vs. 70.7%)
  - Proportional reductions
    - Recurrence: 21% (SE 6)
    - Breast cancer mortality: 13% (SE 8)

Radiotherapy after Mastectomy and Axillary Dissection Conclusions 2

- **In these trials, for pN1-3 women, RT gave significant benefit**
  - Absolute reductions
    - 10-year recurrence: 11.5 % (34.2% vs. 45.7 %)
    - 20-year breast cancer mortality: 7.9% (42.3 % vs. 50.2 %)
  - Proportional reductions
    - Recurrence: 32 % (SE 8)
    - Breast cancer mortality: 20 % (SE 8)

- **For women today**
  - Absolute reductions with RT likely to be smaller
  - Proportional benefits of RT at least as big

Plan of talk

- Meta-analysis of radiotherapy after mastectomy and axillary dissection

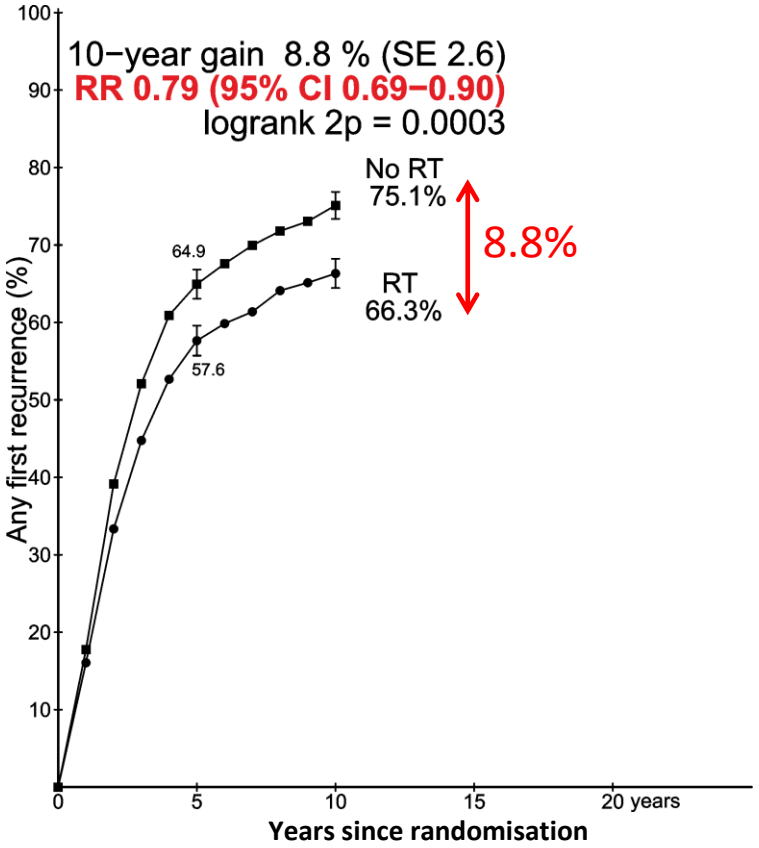
- Analyses of any, local and distant recurrence

Trials of radiotherapy after mastectomy and axillary dissection

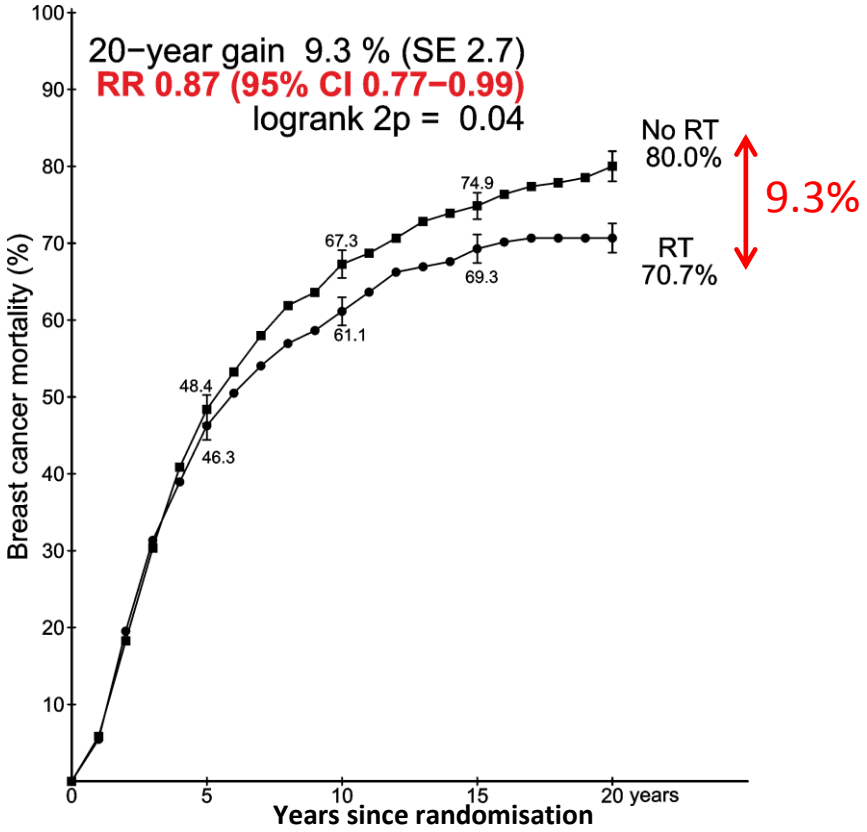
1772 pN4+ women

RT: Significant benefit

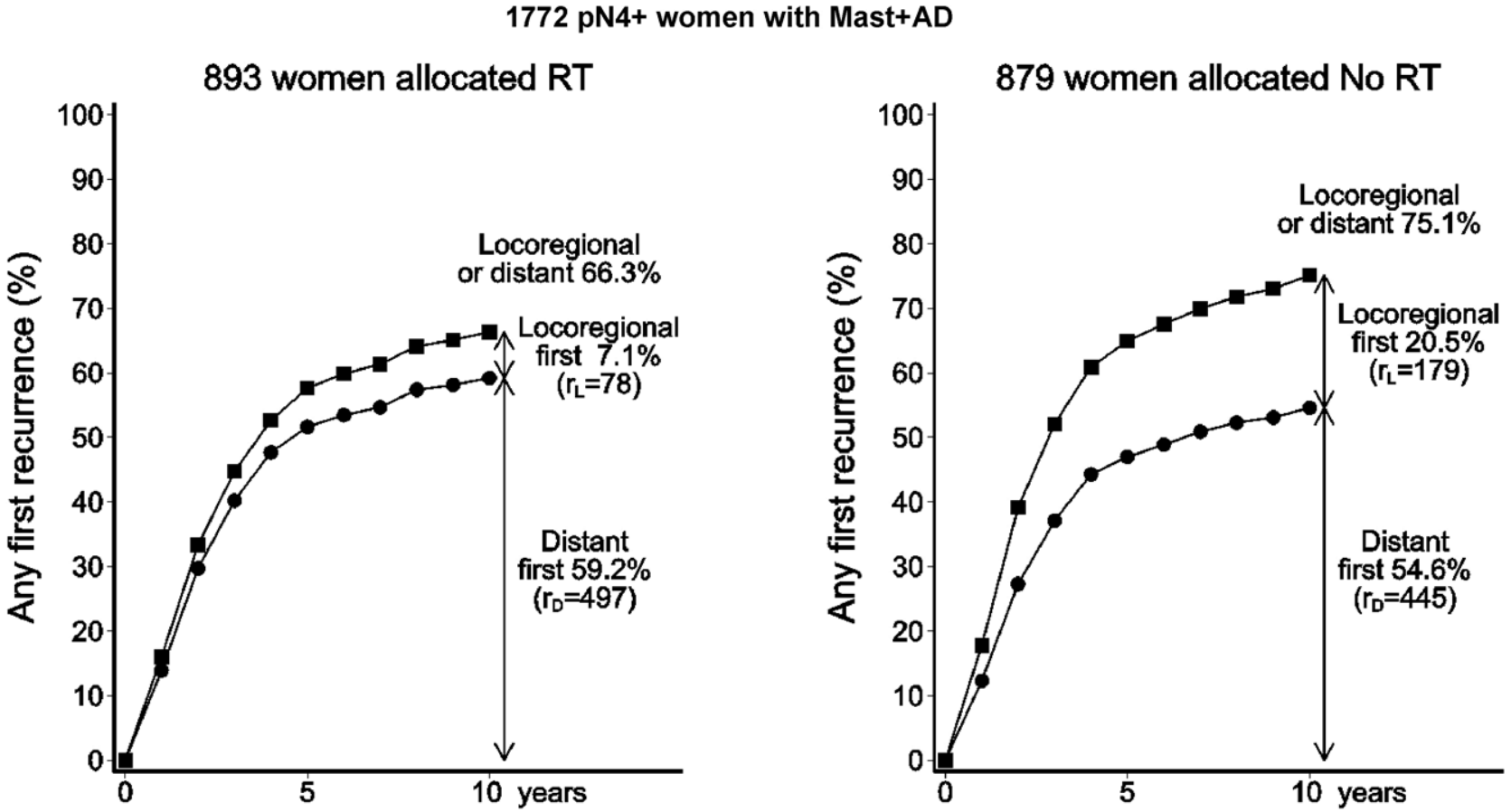
Any first recurrence



Breast cancer mortality



Webfigure 17. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1772 women with 4+ pathologically positive nodes (pN4+). (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)



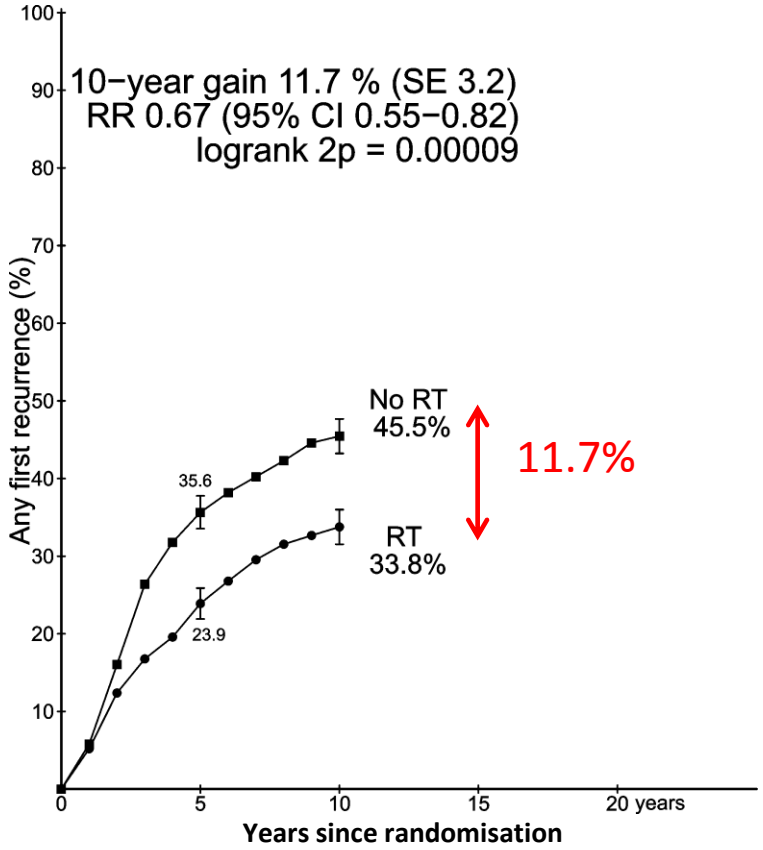
Lancet 2014; 383: 2127–35

Trials of radiotherapy after mastectomy and axillary dissection

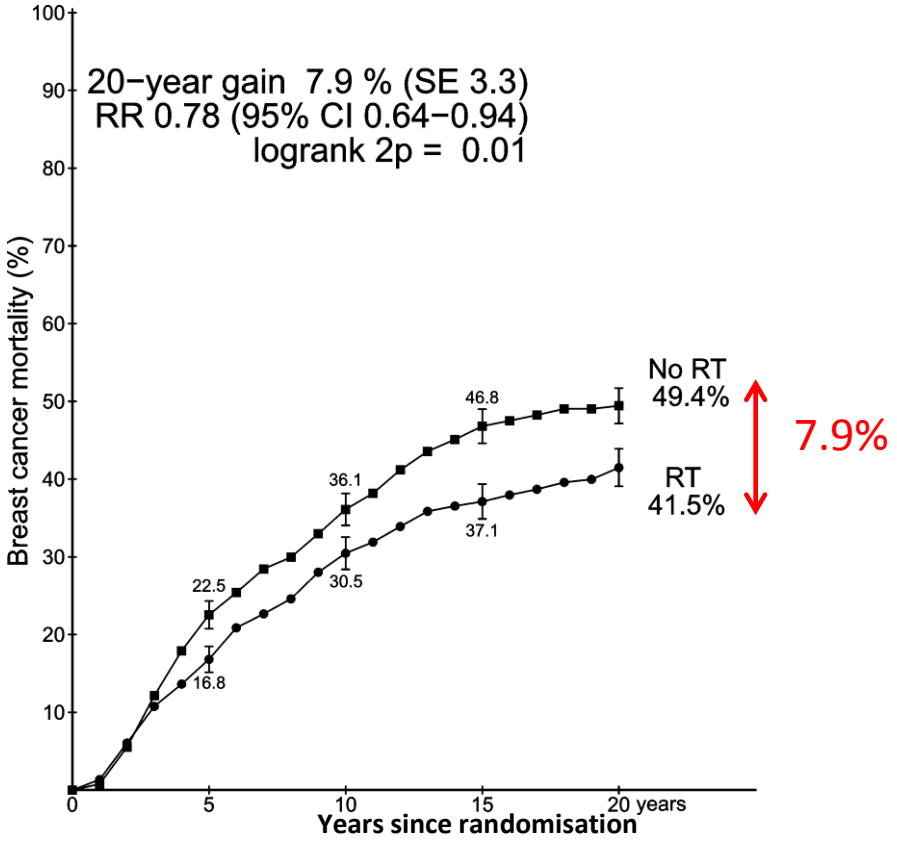
1133 pN1-3 women in trials with systemic therapy

RT: Significant benefit

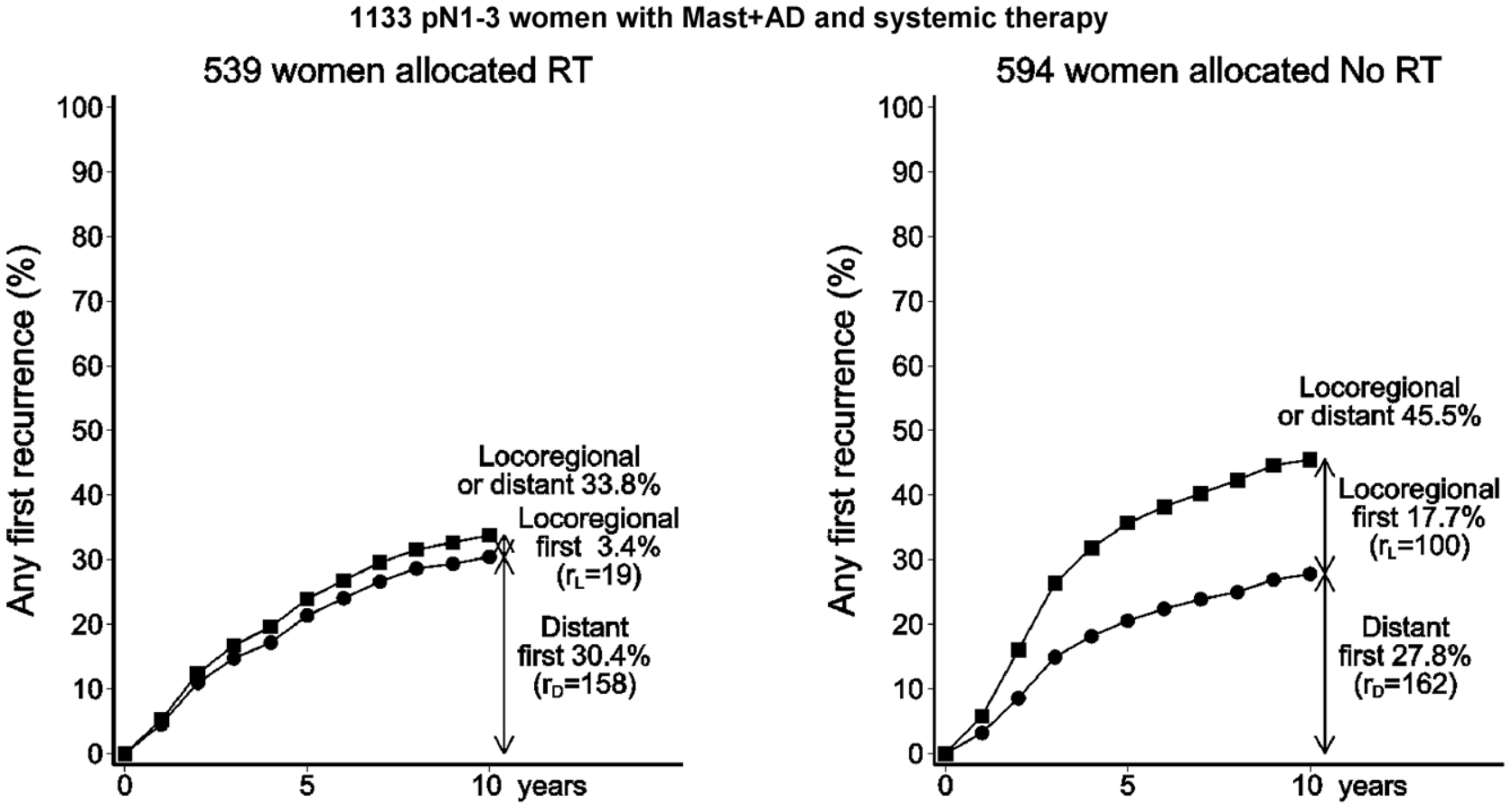
Any first recurrence



Breast cancer mortality



Webfigure 11. Effect of radiotherapy (RT) to the chest wall and regional lymph nodes versus not after mastectomy and axillary dissection (Mast+AD): 10-year risk of recurrence and type of first recurrence, by allocated treatment, in 1133 women with 1-3 pathologically positive nodes (pN1-3) in trials where systemic therapy was given to both randomised treatment groups. (r_L = number of women for whom first recurrence was locoregional, r_D = number women for whom distant recurrence was first.)



Valid Estimates of the Effect of Treatment on Recurrence Rates

- **Valid estimates of the causal effect of radiotherapy on recurrence rates can only be made in terms of any recurrence.**

- **Valid estimates of the effect of radiotherapy on local recurrence rates *cannot be made*** – *although many papers claiming to do so have been published*

- **Valid estimates of the effect of radiotherapy on distant recurrence rates can be made** – *but only if information on distant recurrences occurring after any earlier local recurrence are available, and these will be affected by the treatment given for the local recurrence as well as the initial radiotherapy*

The end

Post-mastectomy and elective regional irradiation: for all node-positive patients

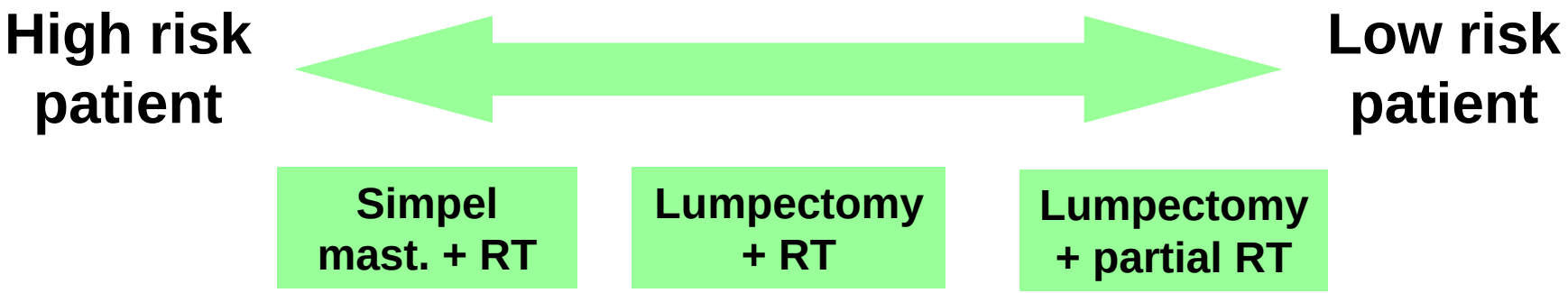
Birgitte V. Offersen,

Clinical oncologist

Aarhus University Hospital, Denmark

ESTRO School

Surgery and Radiotherapy complement each other, and is balanced with the risk of the patient



Most studies have tried to balance the effect of combined loco-regional therapy to yield same outcome, but more recently there has been a tendency to reduce the overall burden of local treatment

Loco-regional treatment in early breast cancer

Tendency of development

It must cover the essential parts – but as little as possible

ESTRO School

If you treat node-positive patients with less intensity in the axilla outside trial you must be sure you know what is going to happen…..

Can you predict what is going to happen in this situation?

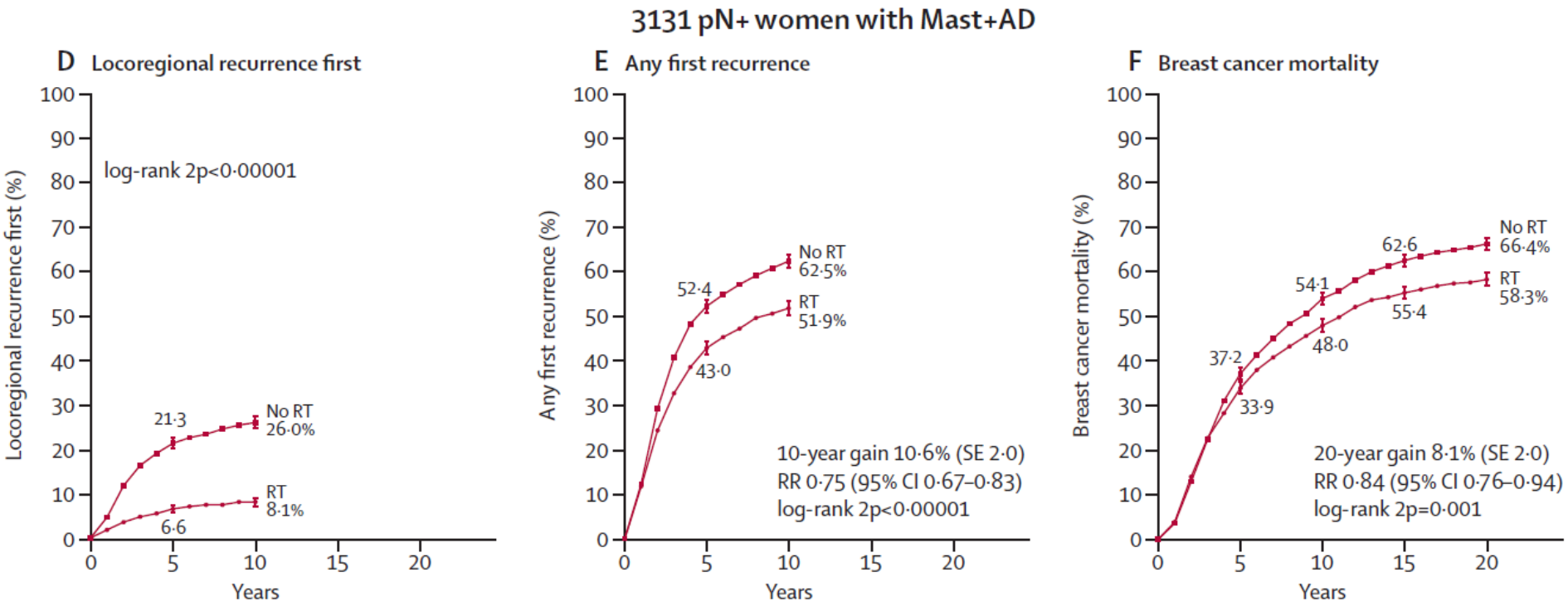
Do we have level 1 evidence from randomised trials?

RT after mastectomy and axillary surgery

RT after breast conserving surgery and axillary surgery

Postmastectomy radiotherapy, PMRT, 20 year update

Level 1a evidence

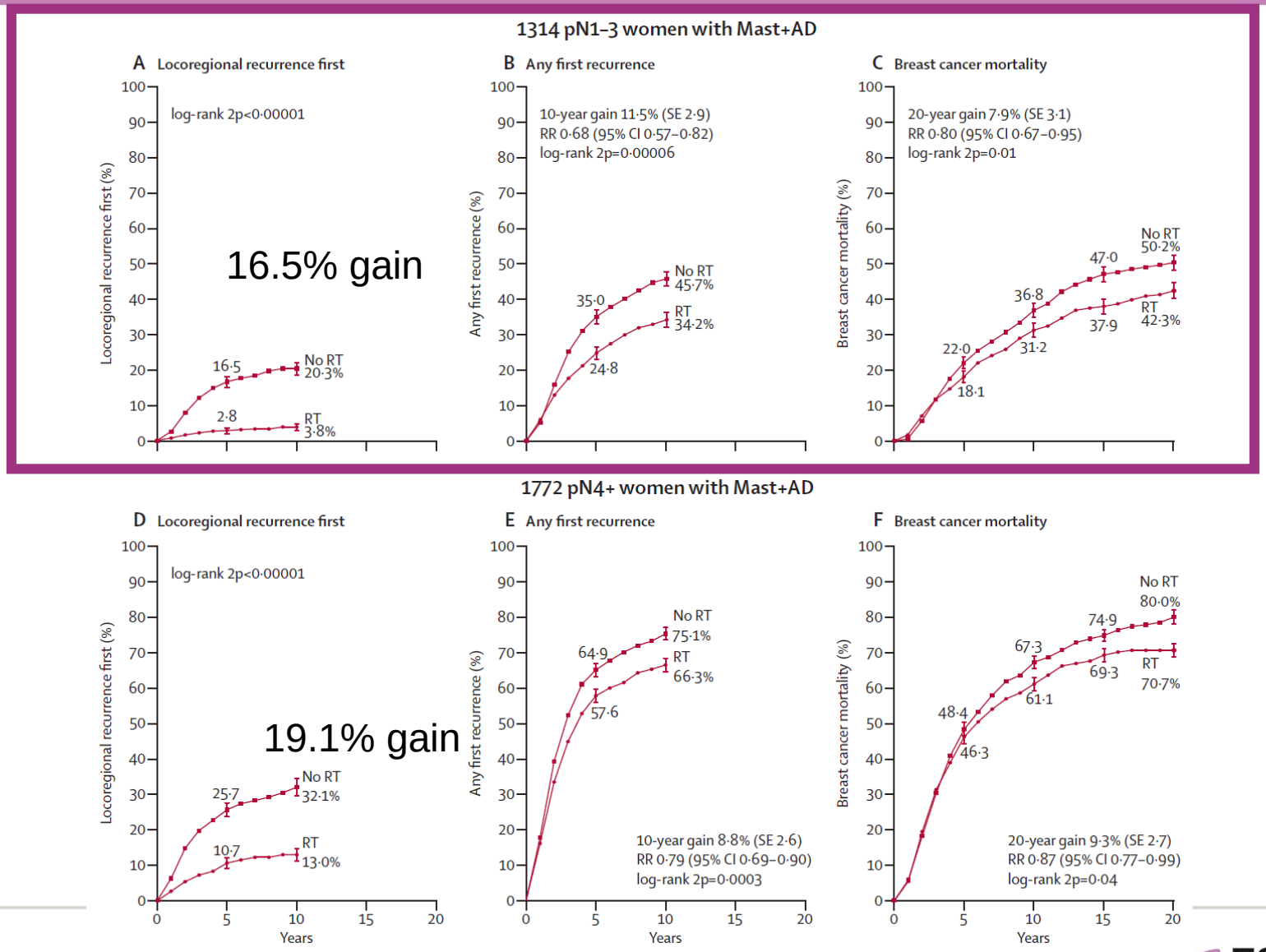


AD, axillary dissection = 10 or more nodes removed
Patients randomised during 1964-86 in 22 trials
PMRT given to chest wall, supraclavicular or axillary fossa (or both) and internal mammary chain

*EBCTCG (Early Breast Cancer Trialists' Collaborative Group)** **Lancet 2014; 383: 2127–35**

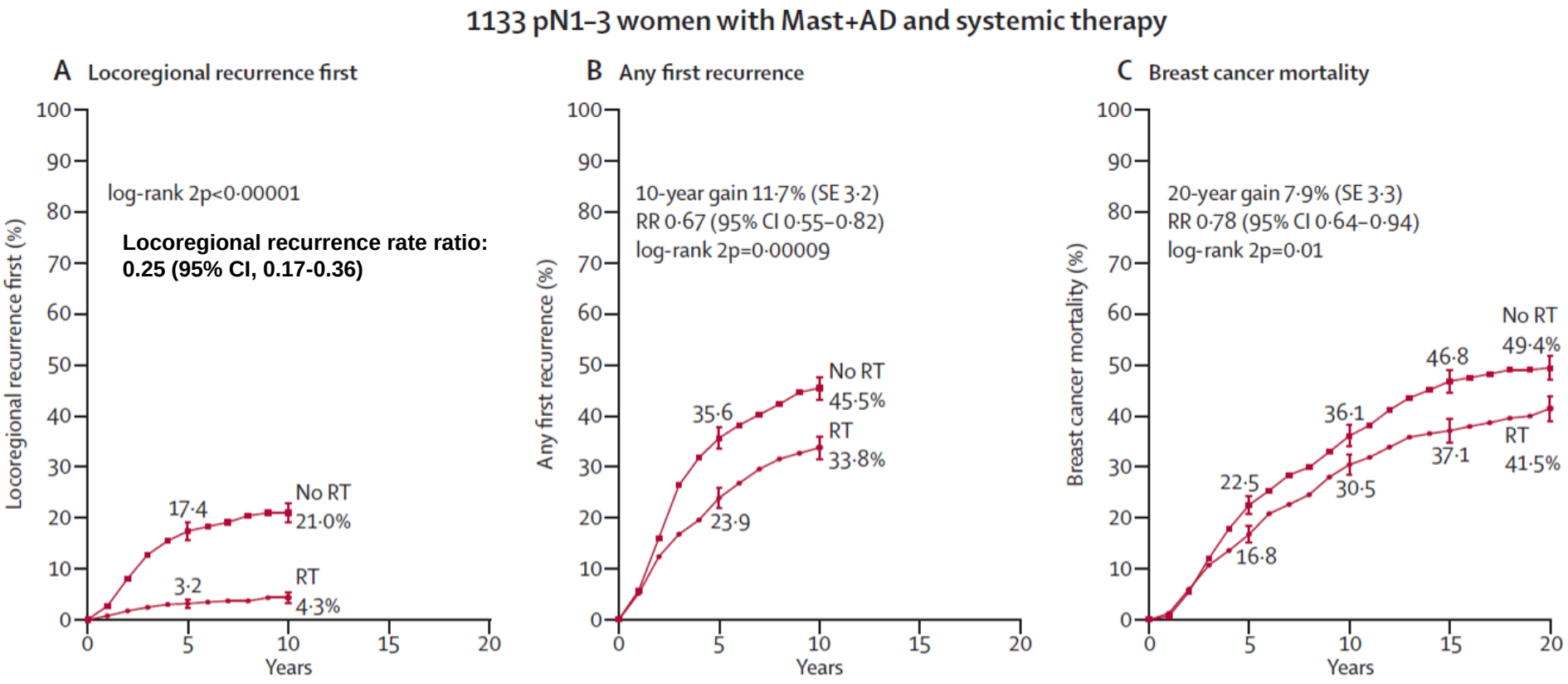
ESTRO School

Effect of PMRT in pN1-3 and pN4+



ESTRO School

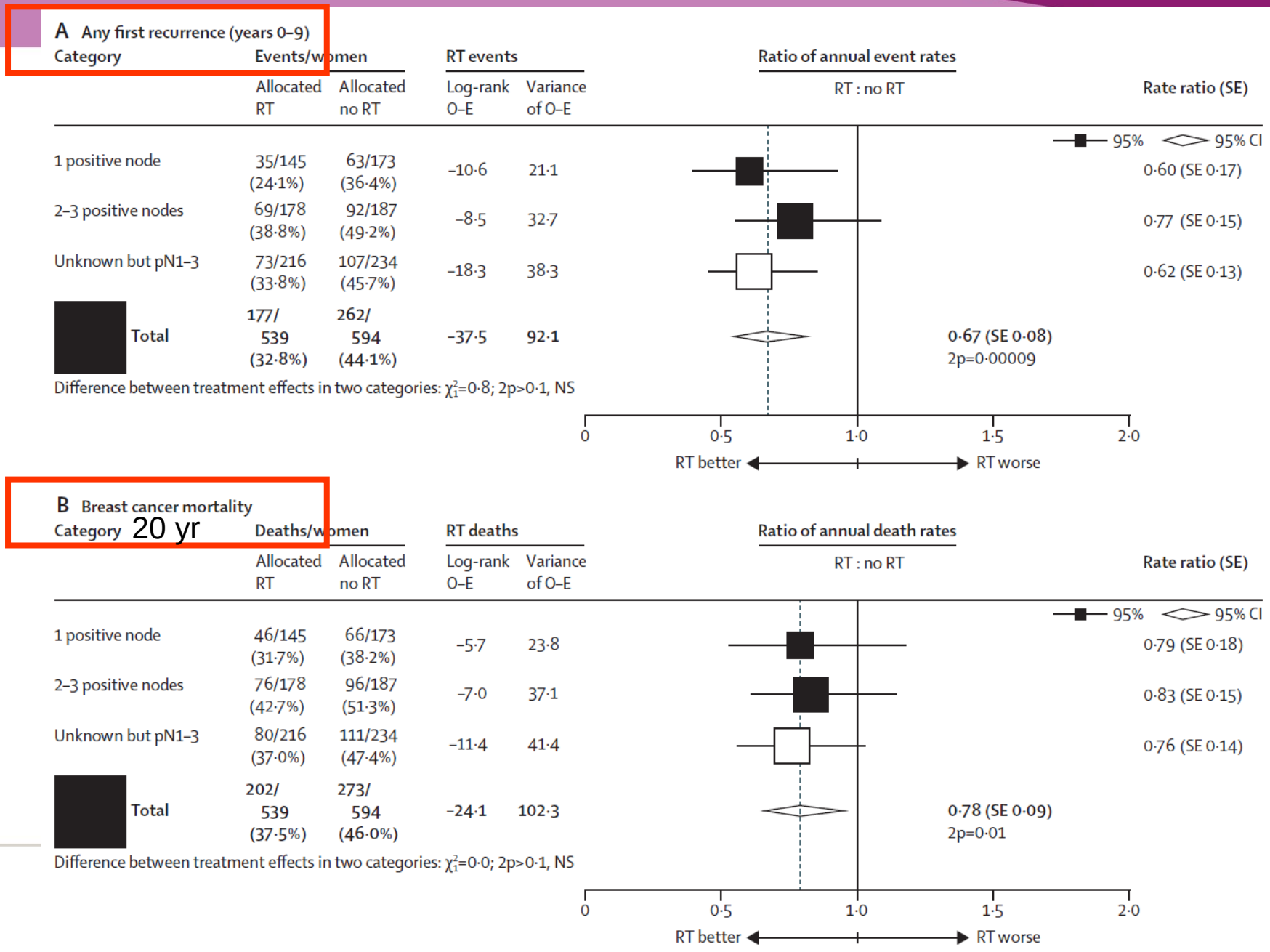
Effect of PMRT in pN1-3 patients treated with systemic therapy



Systemic therapy usually CMF or tamoxifen

ESTRO School

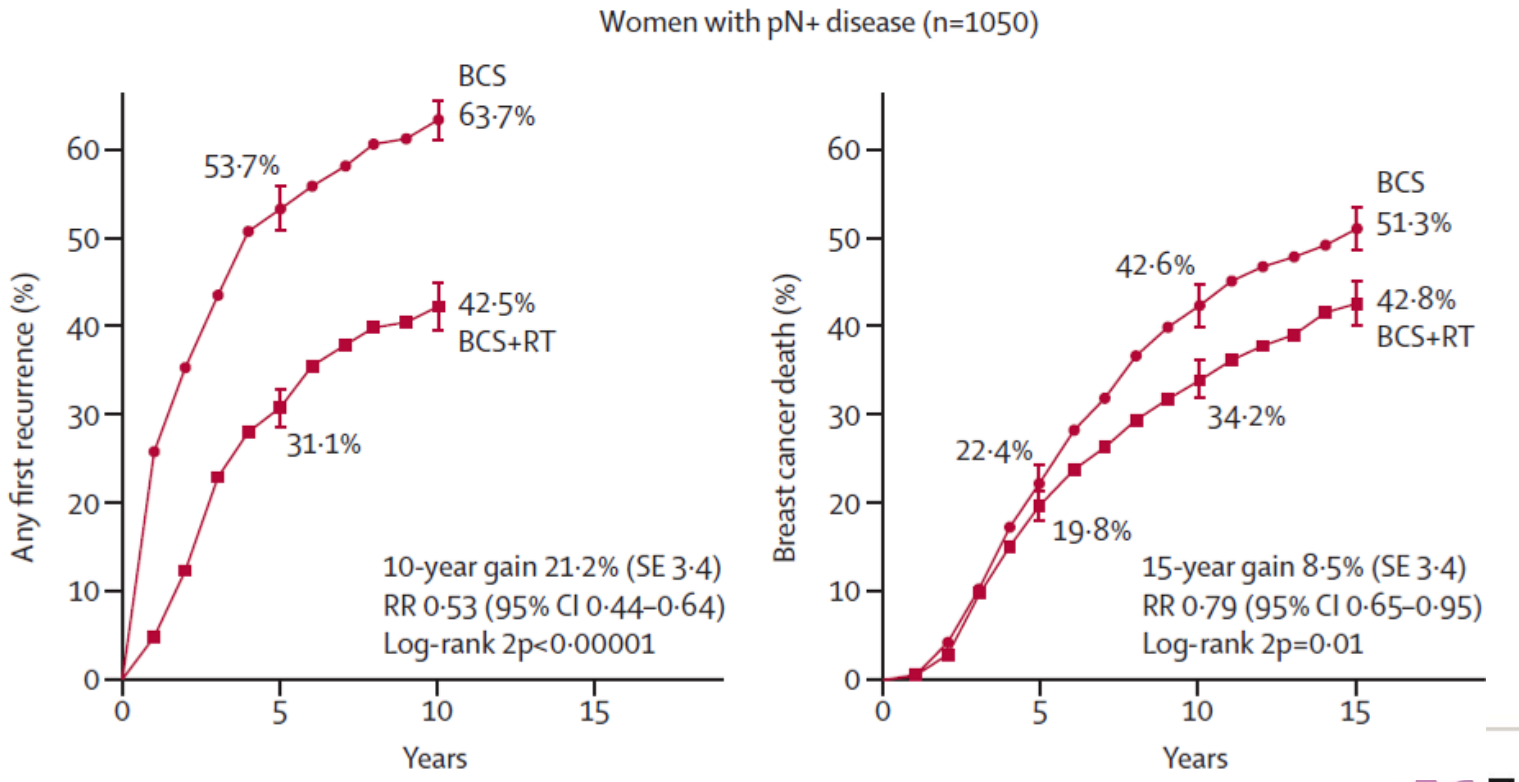
Effect of PMRT in pN1-3 patients treated with systemic therapy



Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Lancet 2011; 378: 1707–16



ESTRO School

EBCTCG´s conclusions

PMRT to pN+ patients:

- LRR ↓ Any first rec ↓ BC mortality ↓

PMRT to pN+ patients is effective

- systemic therapy
- 1 pos node
- pN1-3 nodes
- pN4+ nodes

RT after BCS to pN+ disease

- Any first rec ↓ BC mortality ↓

Are there any guideline recommendations?

VOLUME 34 · NUMBER 36 · DECEMBER 20, 2016

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update

Abram Recht, Elizabeth A. Comen, Richard E. Fine, Gini F. Fleming, Patricia H. Hardenbergh, Alice Y. Ho, Clifford A. Hudis, E. Shelley Hwang, Jeffrey J. Kirshner, Monica Morrow, Kilian E. Salerno, George W. Sledge Jr, Lawrence J. Solin, Patricia A. Spears, Timothy J. Whelan, Mark R. Somerfield, and Stephen B. Edge

Abram Recht, Beth Israel Deaconess Medical Center, Boston, MA; Elizabeth A. Comen, Alice Y. Ho, Clifford A. Hudis, Monica Morrow, Memorial Sloan Kettering Cancer Center; New York; Jeffrey J. Kirshner, Hematology Oncology Associates of Central New York, East

ASCO, ASTRO & SSO recommendation, 2016

Recommendations

The panel unanimously agreed that available evidence shows that PMRT reduces the risks of locoregional failure (LRF), any recurrence, and breast cancer mortality for patients with T1-2 breast cancer with one to three positive axillary nodes. However, some subsets of these patients are likely to have such a low risk of LRF that the absolute benefit of PMRT is outweighed by its potential toxicities. In addition, the acceptable ratio of benefit to toxicity varies among patients and physicians. Thus, the decision to recommend PMRT requires a great deal of clinical judgment. The panel agreed clinicians making such recommendations for individual patients should consider factors that may decrease the risk of LRF, attenuate the benefit of reduced breast cancer–specific mortality, and/or increase risk of complications resulting from PMRT. When clinicians and patients elect to omit axillary dissection after a positive sentinel node biopsy, the panel recommends that these patients receive PMRT only if there is already sufficient information to justify its use without needing to know additional axillary nodes are involved. Patients with axillary nodal involvement after neoadjuvant systemic therapy should receive PMRT. The panel recommends treatment generally be administered to both the internal mammary nodes and the supraclavicular-axillary apical nodes in addition to the chest wall or reconstructed breast.

Thus, tricky to recommend who is not a candidate for PMRT in this group (level 5 evidence=personal experience)

ESTRO School

ESMO recommendations

clinical practice guidelines

Annals of Oncology 26 (Supplement 5): v8–v30, 2015
doi:10.1093/annonc/mdv298

Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

E. Senkus[1], S. Kyriakides[2], S. Ohno[3], F. Penault-Llorca[4,5], P. Poortmans[6], E. Rutgers[7], S. Zackrisson[8] & F. Cardoso[9], on behalf of the ESMO Guidelines Committee*

ESTRO School

ESMO recommendations

radiation after mastectomy: PMRT in node-positive patients reduces the 10-year risk of any recurrence (including locoregional and distant) by 10% and the 20-year risk of breast cancer-related mortality by 8% [75]. The benefits of PMRT are independent from the number of involved axillary lymph nodes and the administration of adjuvant systemic treatment. Therefore, while PMRT was always recommended for high-risk patients, including involved resection margins, four or more involved axillary lymph nodes [I, A], and T3–T4 tumours independent of the nodal status [II, B], we should now also consider routine use of PMRT for patients with one to three positive axillary lymph nodes [I, A] [75, 76].

ESTRO School

International consensus on RT to pN1-3, however…

Old data

Outdated surgical techniques

Outdated systemic therapy

Today´s patients do much better

So do we have new data
on modern treated patients?

International consensus on RT to pN1-3, however…

Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer

P.M. Poortmans, S. Collette, C. Kirkove, E. Van Limbergen, V. Budach, H. Struikmans, L. Collette, A. Fourquet, P. Maingon, M. Valli, K. De Winter, S. Marnitz, I. Barillot, L. Scandolaro, E. Vonk, C. Rodenhuis, H. Marsiglia, N. Weidner, G. van Tienhoven, C. Glanzmann, A. Kuten, R. Arriagada, H. Bartelink, and W. Van den Bogaert, for the EORTC Radiation Oncology and Breast Cancer Groups*

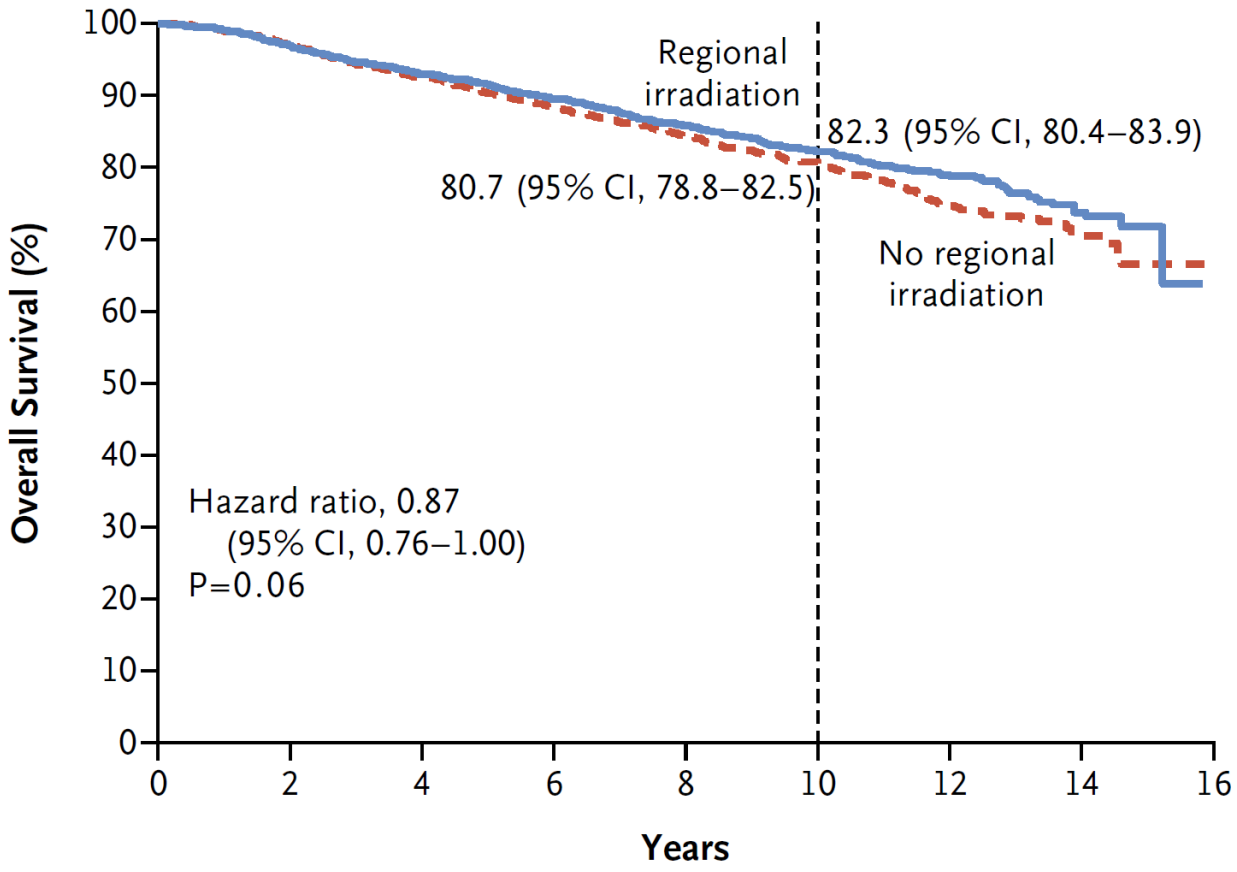
N Engl J Med 2015;373:317-27.
DOI: 10.1056/NEJMoa1415369

ESTRO School

EORTC trial 22922/10925

1996-2004
Eligible: pN0 with centrally/medially tumour or pN+
R to +/- RT to IM-MS, mostly including IC3
Primary endpoint: OS
Secondary endpoints: DFS and BCM
4004 patients, 44% node-negative
Around 25% had mastectomy
Median follow up 10.9 yr

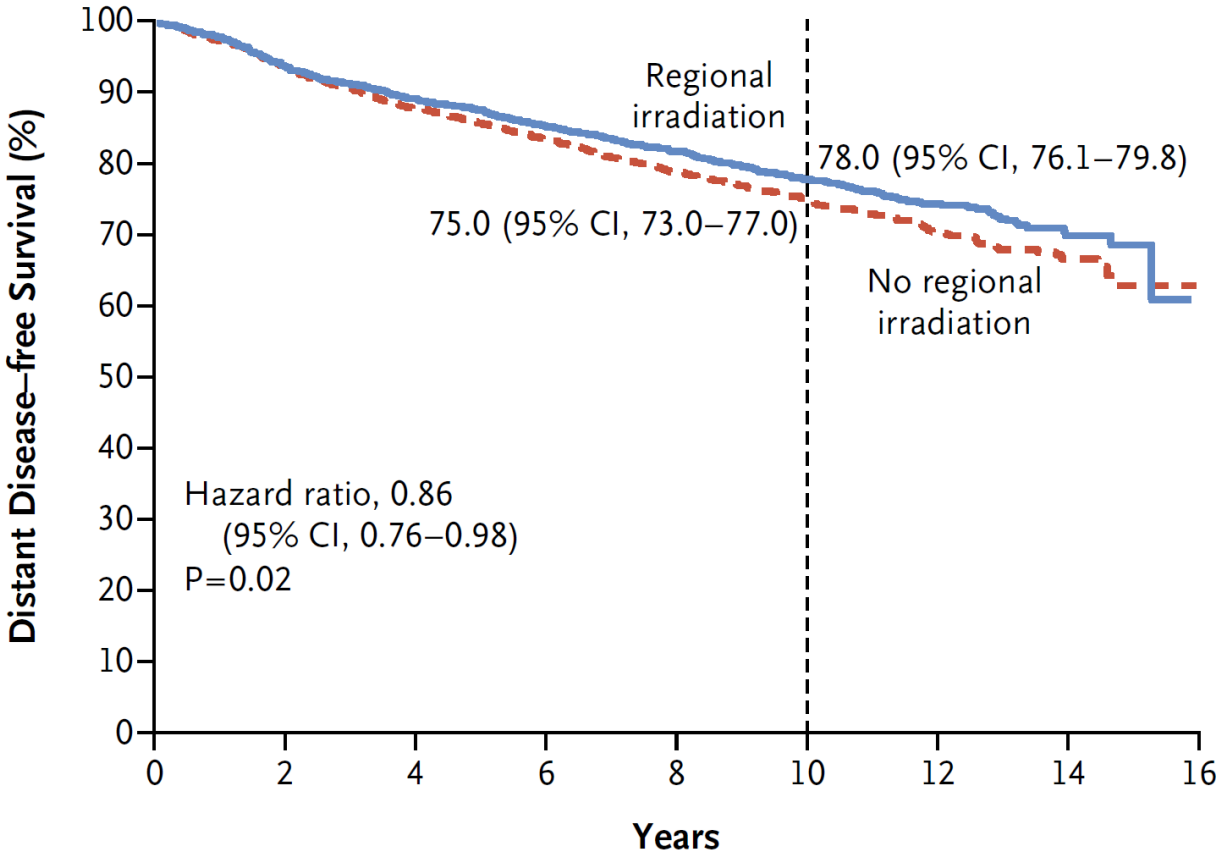
EORTC trial 22922/10925



No. at Risk									No. of Events
No regional irradiation	2002	1926	1819	1698	1475	969	434	119	429
Regional irradiation	2002	1931	1839	1732	1532	988	466	124	382

ESTRO School

EORTC trial 22922/10925

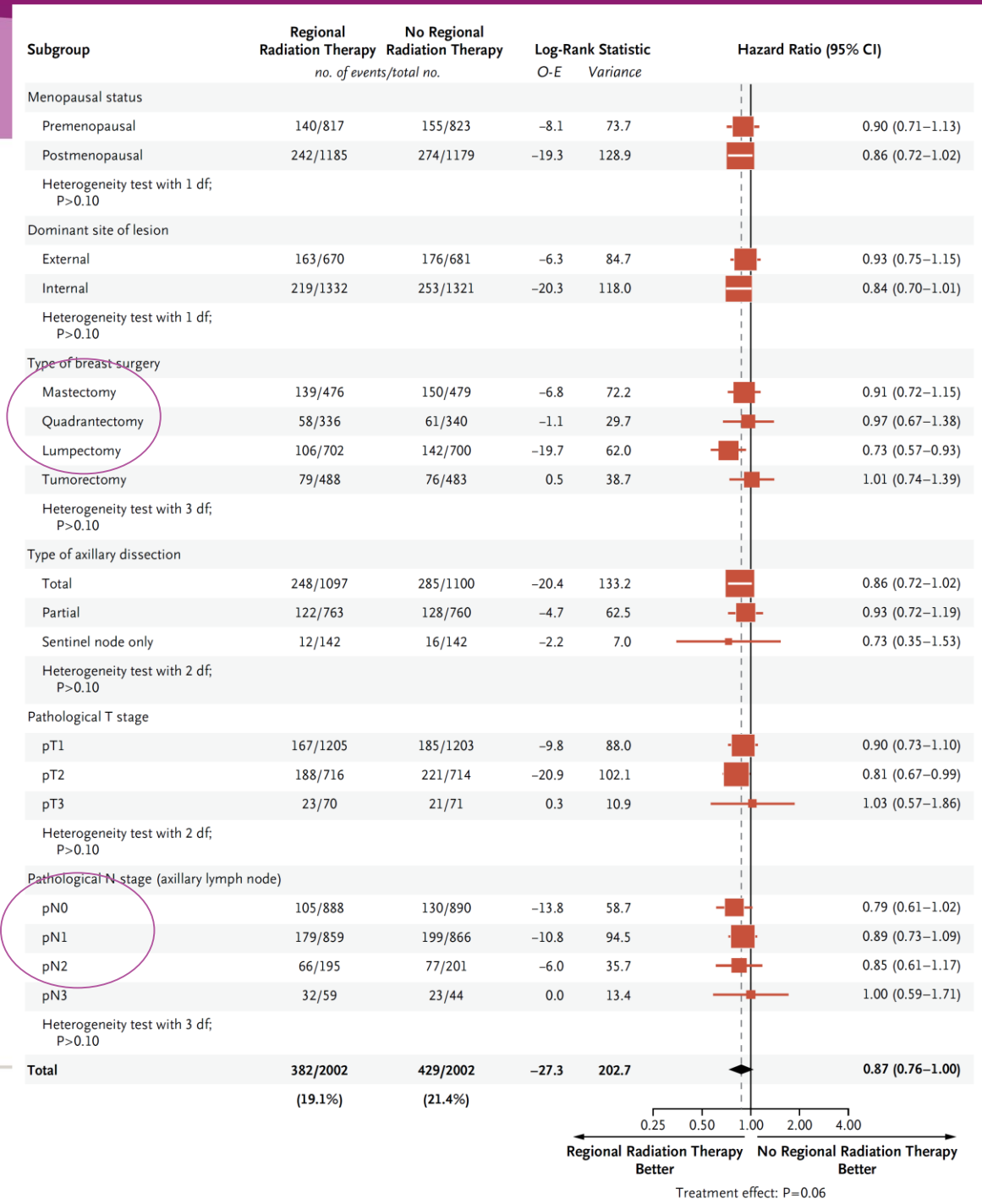


No. at Risk									No. of Events
No regional irradiation	2002	1862	1728	1606	1382	890	403	113	523
Regional irradiation	2002	1866	1764	1650	1464	939	437	117	462

ESTRO School

Forest plot of IM-MS RT effect in relevant subgroups using OS as endpoint

Conclusion: all subgrops appear to gain the same effect



Subgroup	Regional Radiation Therapy	No Regional Radiation Therapy	Log-Rank Statistic		Hazard Ratio (95% CI)
	no. of events/total no.		*O-E*	*Variance*	
Menopausal status					
Premenopausal	140/817	155/823	−8.1	73.7	0.90 (0.71–1.13)
Postmenopausal	242/1185	274/1179	−19.3	128.9	0.86 (0.72–1.02)
Heterogeneity test with 1 df; P>0.10					
Dominant site of lesion					
External	163/670	176/681	−6.3	84.7	0.93 (0.75–1.15)
Internal	219/1332	253/1321	−20.3	118.0	0.84 (0.70–1.01)
Heterogeneity test with 1 df; P>0.10					
Type of breast surgery					
Mastectomy	139/476	150/479	−6.8	72.2	0.91 (0.72–1.15)
Quadrantectomy	58/336	61/340	−1.1	29.7	0.97 (0.67–1.38)
Lumpectomy	106/702	142/700	−19.7	62.0	0.73 (0.57–0.93)
Tumorectomy	79/488	76/483	0.5	38.7	1.01 (0.74–1.39)
Heterogeneity test with 3 df; P>0.10					
Type of axillary dissection					
Total	248/1097	285/1100	−20.4	133.2	0.86 (0.72–1.02)
Partial	122/763	128/760	−4.7	62.5	0.93 (0.72–1.19)
Sentinel node only	12/142	16/142	−2.2	7.0	0.73 (0.35–1.53)
Heterogeneity test with 2 df; P>0.10					
Pathological T stage					
pT1	167/1205	185/1203	−9.8	88.0	0.90 (0.73–1.10)
pT2	188/716	221/714	−20.9	102.1	0.81 (0.67–0.99)
pT3	23/70	21/71	0.3	10.9	1.03 (0.57–1.86)
Heterogeneity test with 2 df; P>0.10					
Pathological N stage (axillary lymph node)					
pN0	105/888	130/890	−13.8	58.7	0.79 (0.61–1.02)
pN1	179/859	199/866	−10.8	94.5	0.89 (0.73–1.09)
pN2	66/195	77/201	−6.0	35.7	0.85 (0.61–1.17)
pN3	32/59	23/44	0.0	13.4	1.00 (0.59–1.71)
Heterogeneity test with 3 df; P>0.10					
Total	**382/2002**	**429/2002**	**−27.3**	**202.7**	**0.87 (0.76–1.00)**
	(19.1%)	**(21.4%)**			

VOLUME 34 · NUMBER 4 · FEBRUARY 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

DBCG-IMN: A Population-Based Cohort Study on the Effect of Internal Mammary Node Irradiation in Early Node-Positive Breast Cancer

Lise Bech Jellesmark Thorsen, Birgitte Vrou Offersen, Hella Danø, Martin Berg, Ingelise Jensen, Anders Navrsted Pedersen, Sune Jürg Zimmermann, Hans-Jürgen Brodersen, Marie Overgaard, and Jens Overgaard

ESTRO School

DBCG IMN study

1980's
Internal mammary node (IMN) RT for all N+ breast cancer patients

2000
Anthracyclines

2003

No evidence for effect of IMN-RT

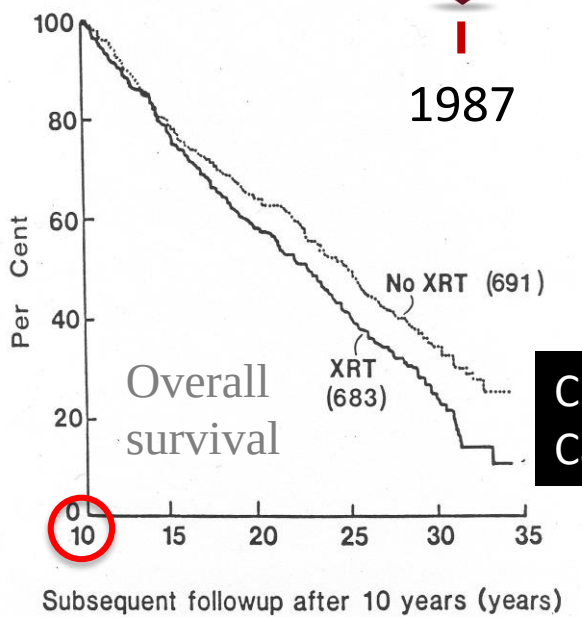
1987

2003

Right side
+ IMN RT

Left side
No IMN-RT

Left side
heart dose high



Cuzick, et al.
Cancer Treat Rep, 1987

Courtesy of Lise Thorsen

ESTRO School

Patient and tumor characteristics

	IMN RT (n=1485)	No IMN RT (n=1586)
Median age (range)	56 (23-70)	57 (27-70)
Pre-menopausal	611 (41%)	646 (40%)
Estrogen receptor positive (%)	1202 (81%)	1274 (80%)
Invasive ductal carcinoma Invasive lobular carcinoma Other	1305 (88%) 134 (9%) 46 (3%)	1346 (85%)* 163 (10%) 77 (5%)
Grade I Grade II Grade III	307 (19%) 710 (48%) 414 (28%)	307 (19%) 743 (47%) 456 (29%)
pT1 pT2 pT3	527 (36%) 830 (56%) 126 (9%)	556 (35%) 905 (57%) 124 (8%)
pN1 pN2 pN3	867 (58%) 396 (27%) 222 (15%)	949 (60%) 412 (26%) 225 (14%)
Lateral Medial/central	904 (61%) 578 (39%)	943 (60%) 640 (40%)

CIRRO

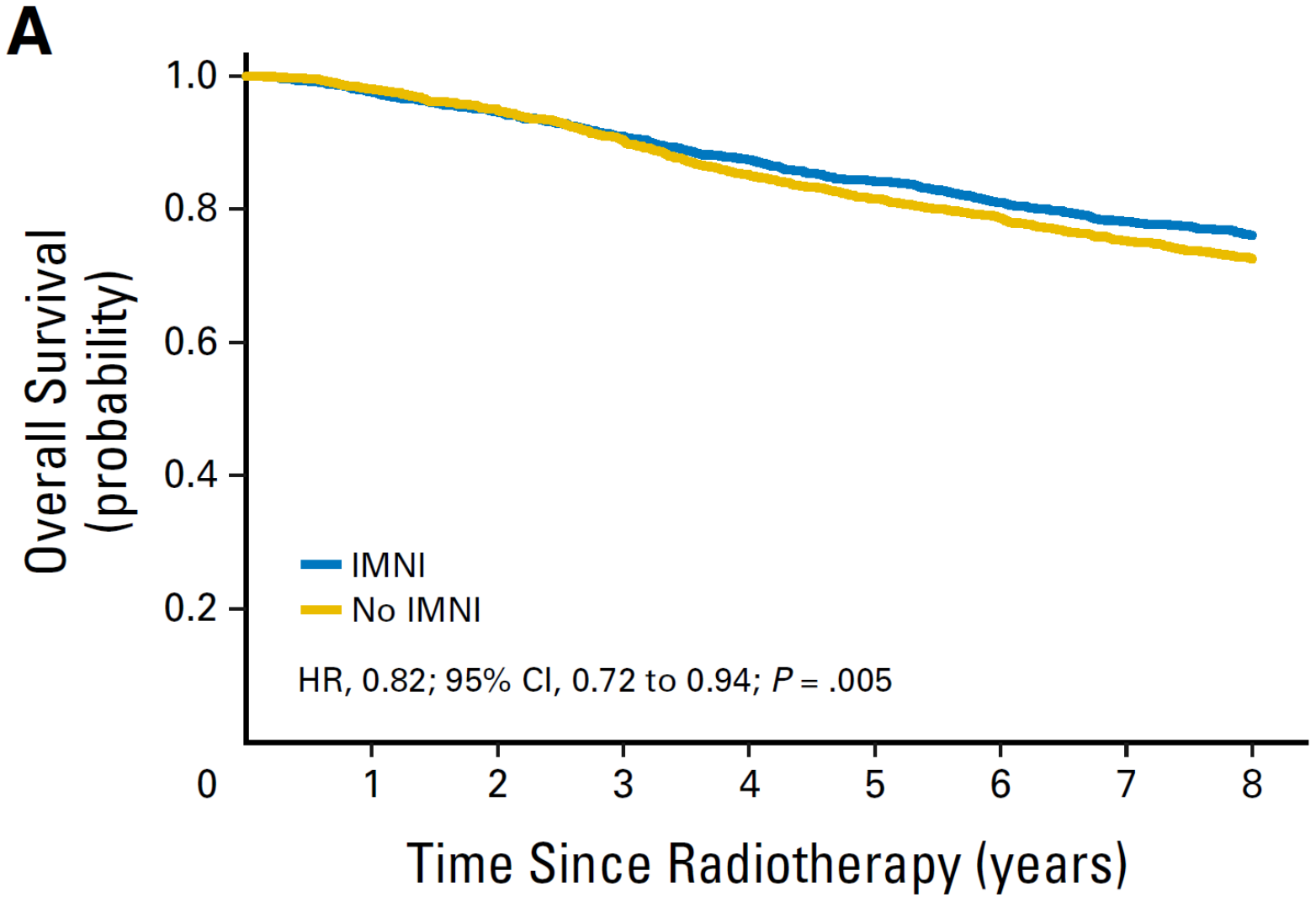
ESTRO School

DBCG-IMN: Treatment

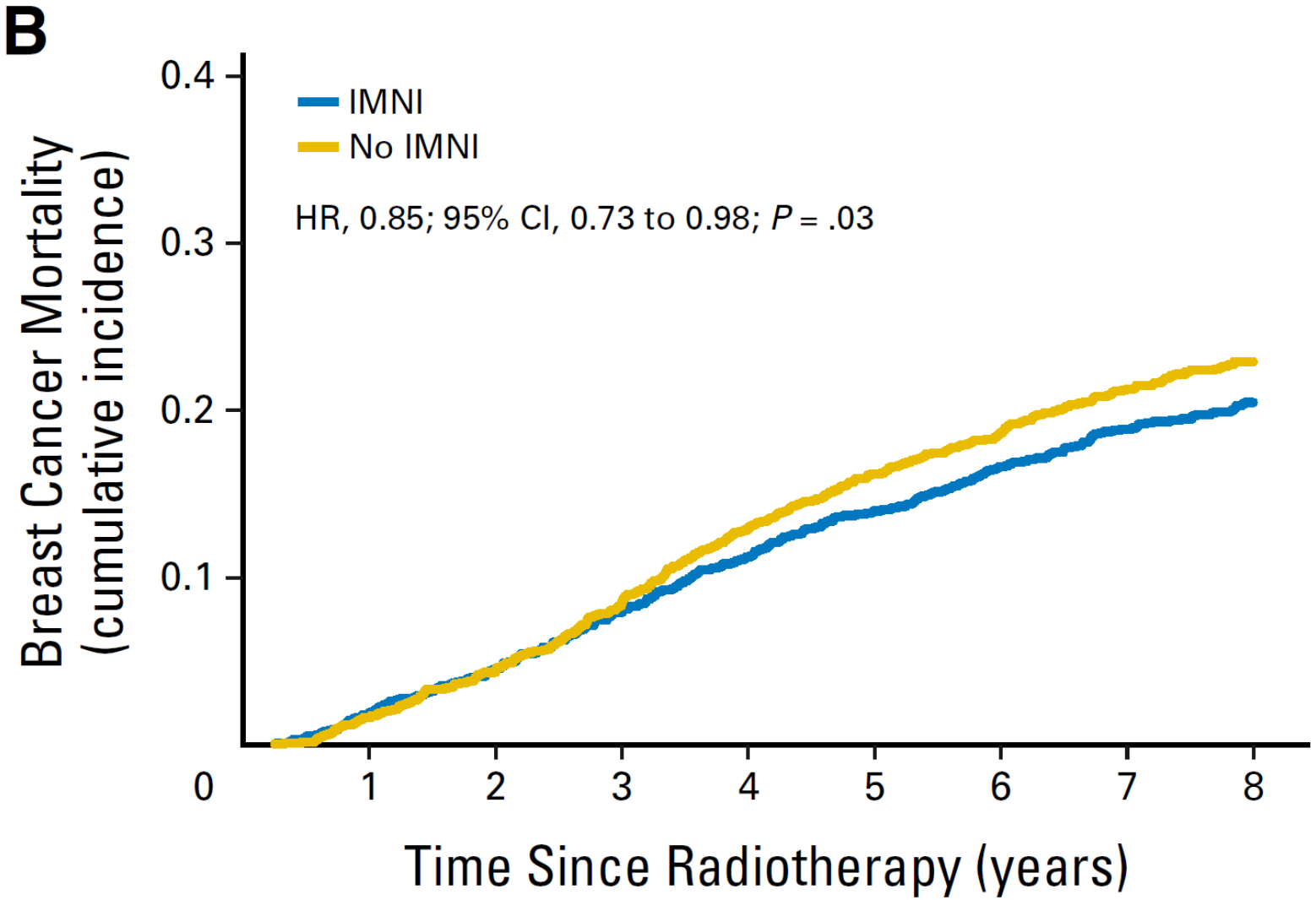
	IMN RT (n=1485)	No IMN RT (n=1586)
Radiotherapy: 48 Gy/24 F IMN-RT (%) Axillary level II-III-IV (%) Axillary level I-II-III-IV (%) Boost after BCS (%)	 1431 (96%) 1213 (82%) 272 (18%) 176 (33%)	 161 (10%) 1294 (82%) 292 (18%) 164 (30%)
Type of surgery Mastectomy + AC(%) Breast conserving +AC(%)	 959 (65%) 526 (35%)	 1048 (66%) 538 (34%)
Systemic treatment Endocrine therapy (%) Chemotherapy (%) Endocrine + chemotherapy (%)	 697 (47%) 274 (19%) 514 (35%)	 741 (47%) 304 (19%) 541 (34%)

CIRRO

ESTRO School



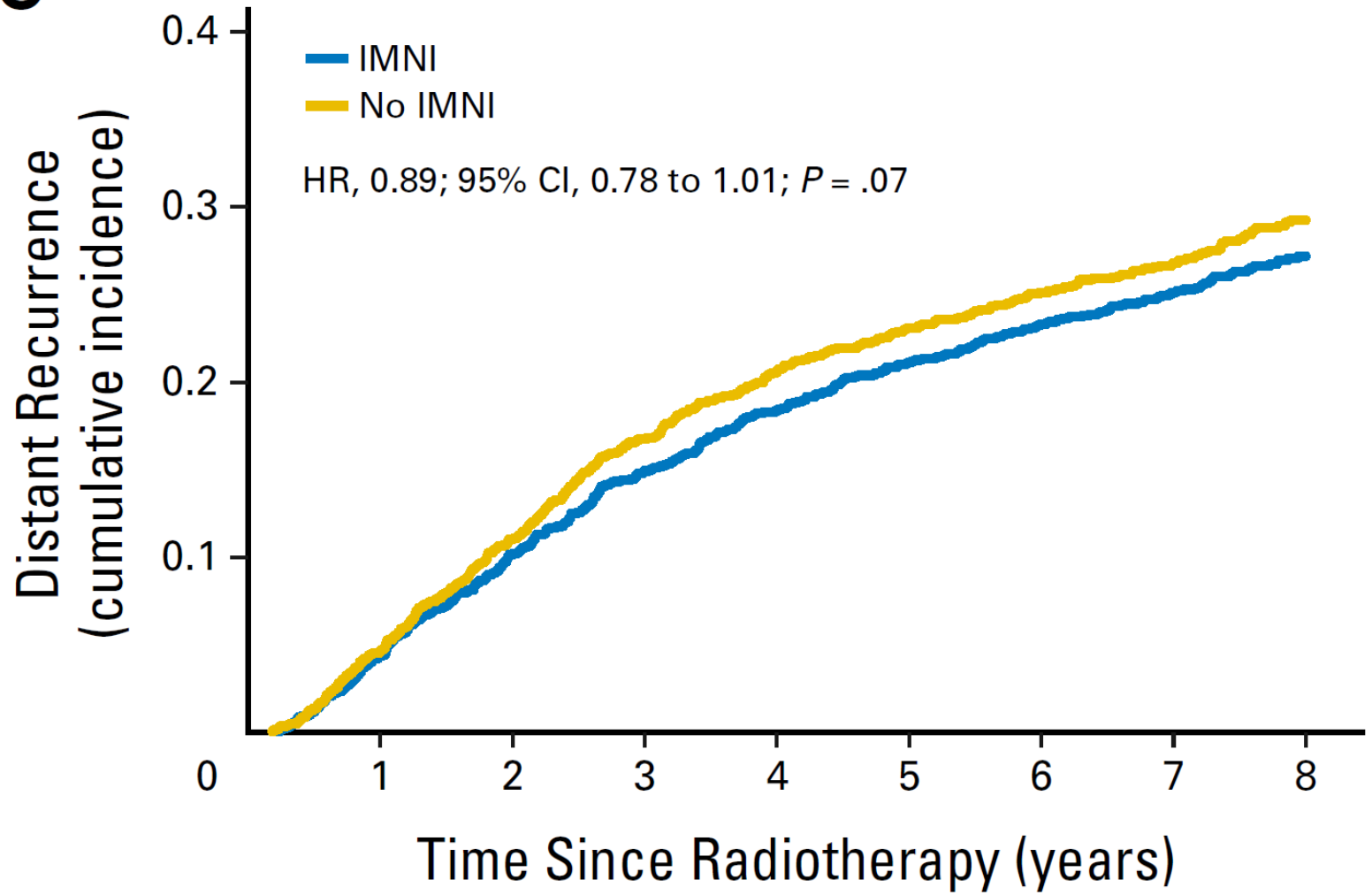
No. at risk					
IMNI	1,492	1,410	1,301	1,205	783
No IMNI	1,597	1,512	1,356	1,248	791



No. at risk					
IMNI	1,492	1,410	1,301	1,205	783
No IMNI	1,597	1,512	1,356	1,248	791

STRO
chool

C

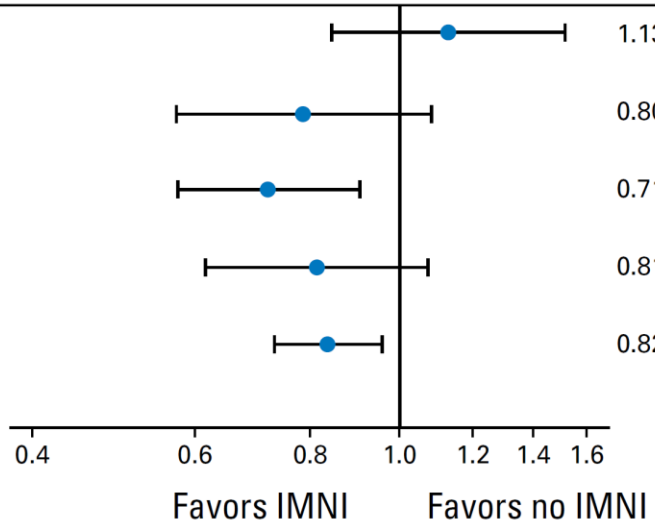


No. at risk					
IMNI	1,492	1,322	1,193	1,066	573
No IMNI	1,597	1,402	1,230	1,103	565

ESTRO
School

Subgroup	IMNI Patients	IMNI Events	No IMNI Patients	No IMNI Events	HR (95% CI)	8-year survival rate (%) IMNI	8-year survival rate (%) No IMNI
Lateral 1–3 nodes	511	91	564	91	1.13 (0.84 to 1.51)	82.9	85.7
Medial/central 1–3 nodes	353	67	382	88	0.80 (0.58 to 1.10)	83.2	78.8
Lateral ≥ 4 nodes	392	137	384	170	0.71 (0.57 to 0.89)	68.0	58.3
Medial/central ≥ 4 nodes	224	86	259	131	0.81 (0.61 to 1.06)	61.9	53.8
All patients	1,480	381	1,589	480	0.82 (0.72 to 0.94)	75.9	72.2

Test for heterogeneity, $P = .10$



PMRT & Reconstruction

PMRT and reconstruction?

The far majority of PMRT is therapy of the chest wall and regional nodes

If the chest wall target is replaced with autologous tissue, then the PMRT may be modified to only include regional nodes, except in cases with locally advanced breast cancer (LABC).

In patients with LABC immediate reconstruction is generally not a good strategy. However, if performed the chest wall is still target for PMRT.

But can we further individualize the use of loco-regional radiation therapy?

Personalized Medicine and Imaging

Development and Validation of a Gene Profile Predicting Benefit of Postmastectomy Radiotherapy in Patients with High-Risk Breast Cancer: A Study of Gene Expression in the DBCG82bc Cohort

Trine Tramm[1], Hayat Mohammed[2], Simen Myhre[3,4,5], Marianne Kyndi[1], Jan Alsner[1], Anne-Lise Børresen-Dale[3,4], Therese Sørlie[3,4], Arnoldo Frigessi[2], and Jens Overgaard[1]

Clin Cancer Res; 20(20); 5272–80. ©2014 AACR.

CIRRO

Aarhus University Hospital

PMRT: Material and Methods

DBCG82bc
Danish Breast Cancer Cooperative Group
3083 high risk pts.

mastectomy
partial axillary lymph node dissection

1708
Pre-meno.
(b)

1375
Post-meno.
(c)

RT+CMF

CMF

RT+TAM

TAM

267
fresh frozen tumor samples

Whole genome arrays
(Applied Biosystem Human Genome Survey Microarray v2.0)

195/267 samples
successful microarray

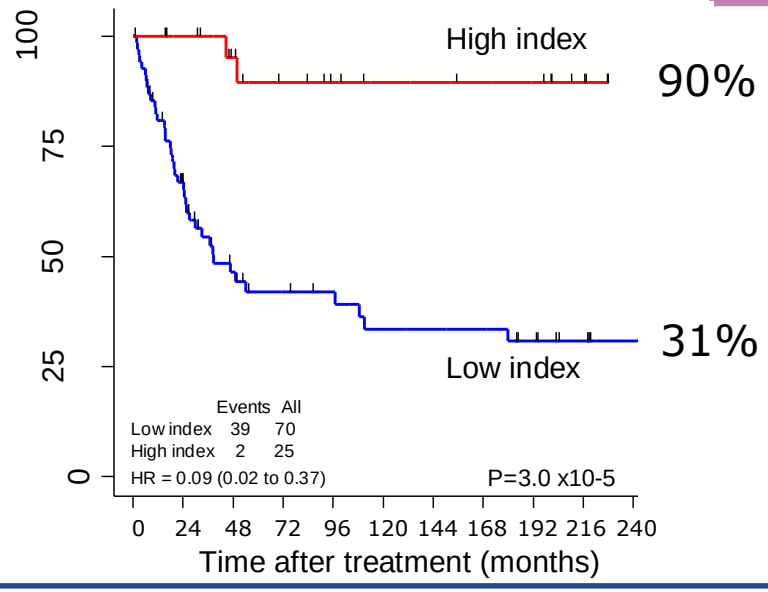
2-step
Cox Proportional Hazard
model with lasso penalty

7 genes identified
7-gene index based on
the combined expression levels

Tramm T et al, Clin Can Res 2014

Results

Prognostic (no PMRT group)

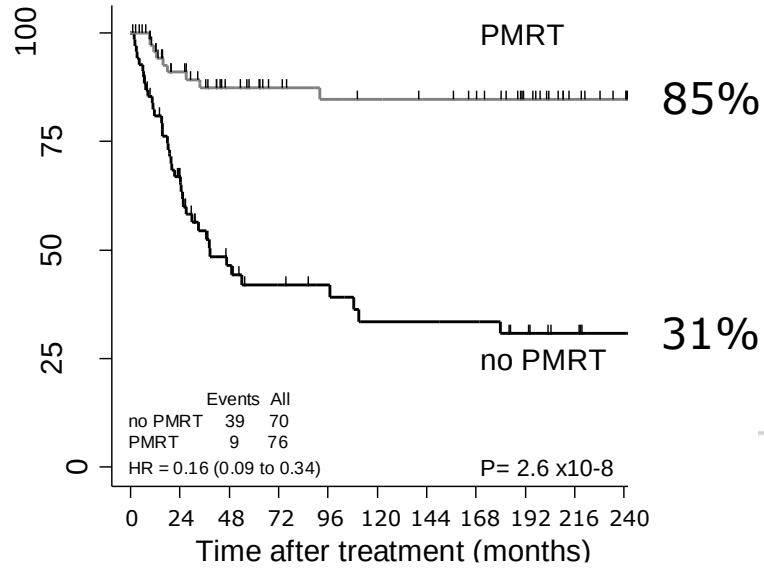


This pattern is seen regardless of
-nodal status
-T status
-menopausal status

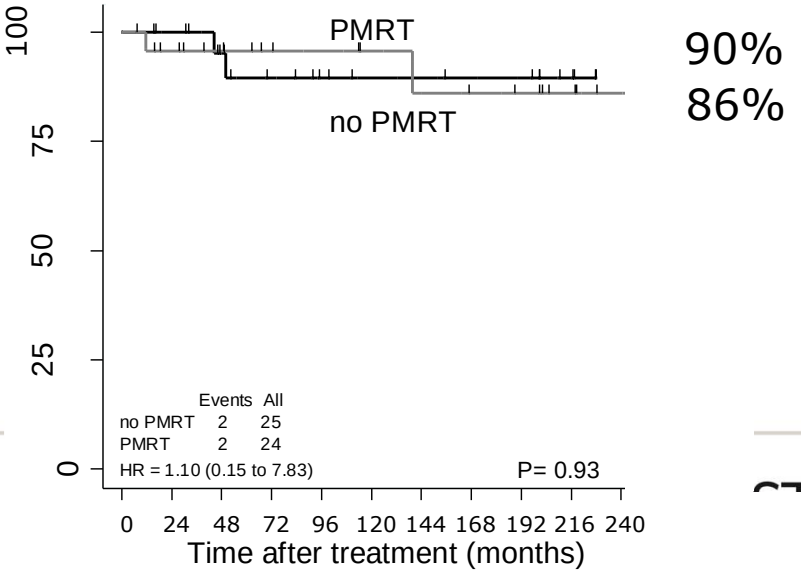
The gene profile has been validated in an independent data set (Tramm et al, Clin Can Res, 2014)

Predictive

Low index



High index

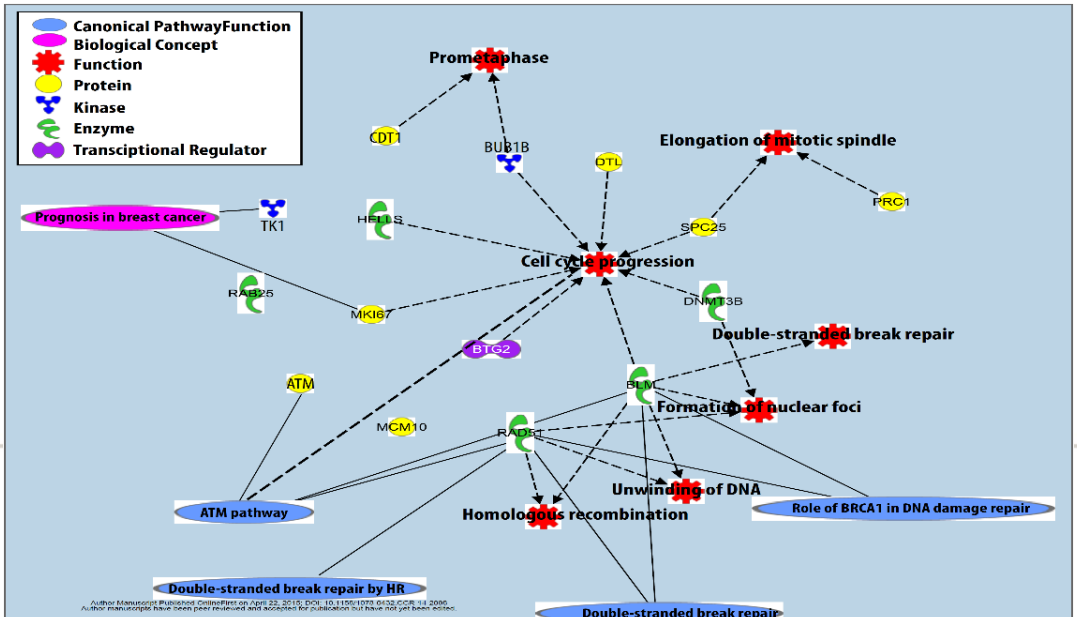


Development and validation of a novel radiosensitivity signature in human breast cancer

Clin Can Res, 2015

Corey Speers[1*], Shuang Zhao[1*], Meilan Liu[1], Harry Bartelink[4], Lori J. Pierce[¥,1,3], Felix Y. Feng[¥,†,1,2,3]

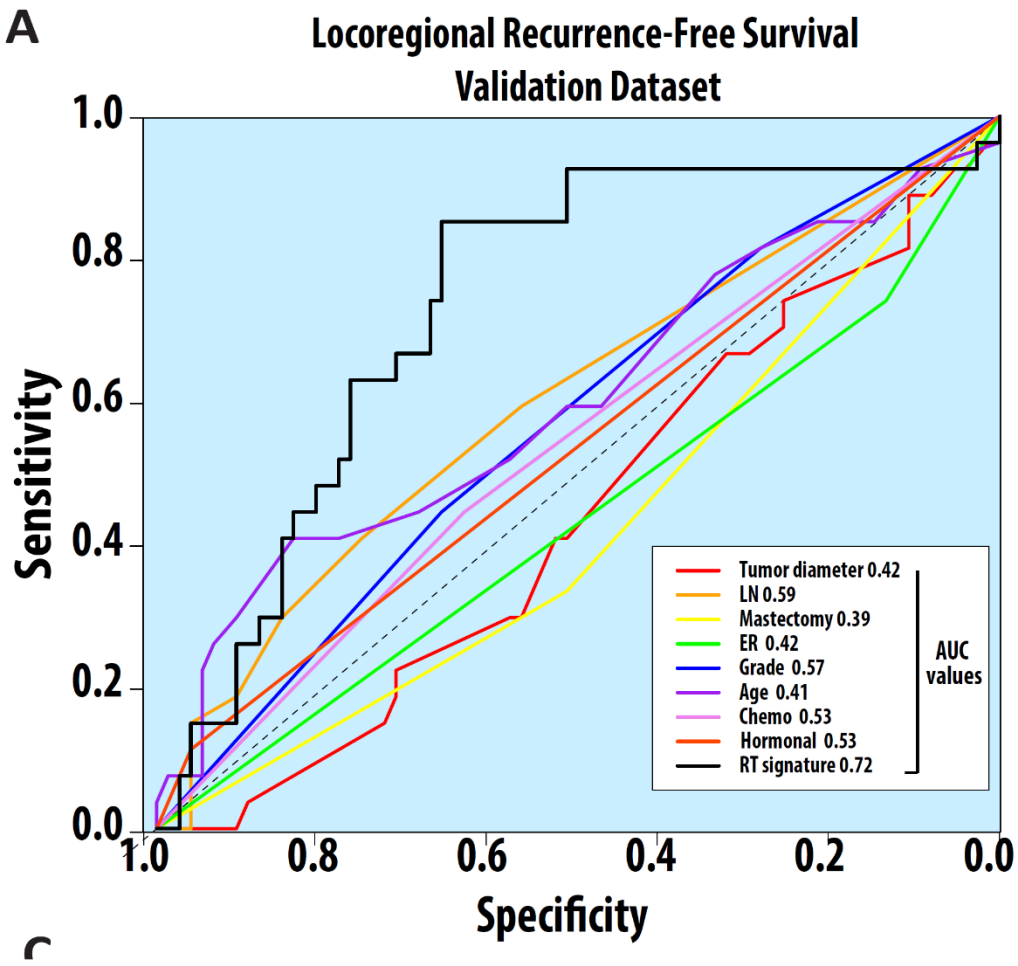
1) In vitro: Clonogenic survival assays to identify the SF-2Gy in 16 BCC lines
2) Surviving fractions (17-77%) independent of intrinsic subtypes
3) Gene expression data from BCC correlated to SF data, 147 genes identified
4) Hierarchical cluster analysis separates genes into radioresistent vs –sensitive
5) In vivo: RSS run in test set of 343 pts with gene analysis data, all treated with BCS+RT and with FU, then RSS further trained and refined to 51 genes.
6) 51 gene profile evaluated on ingenuity.com, tested in a validation set of 295 pts with gene analysis data and with BCS+RT and FU

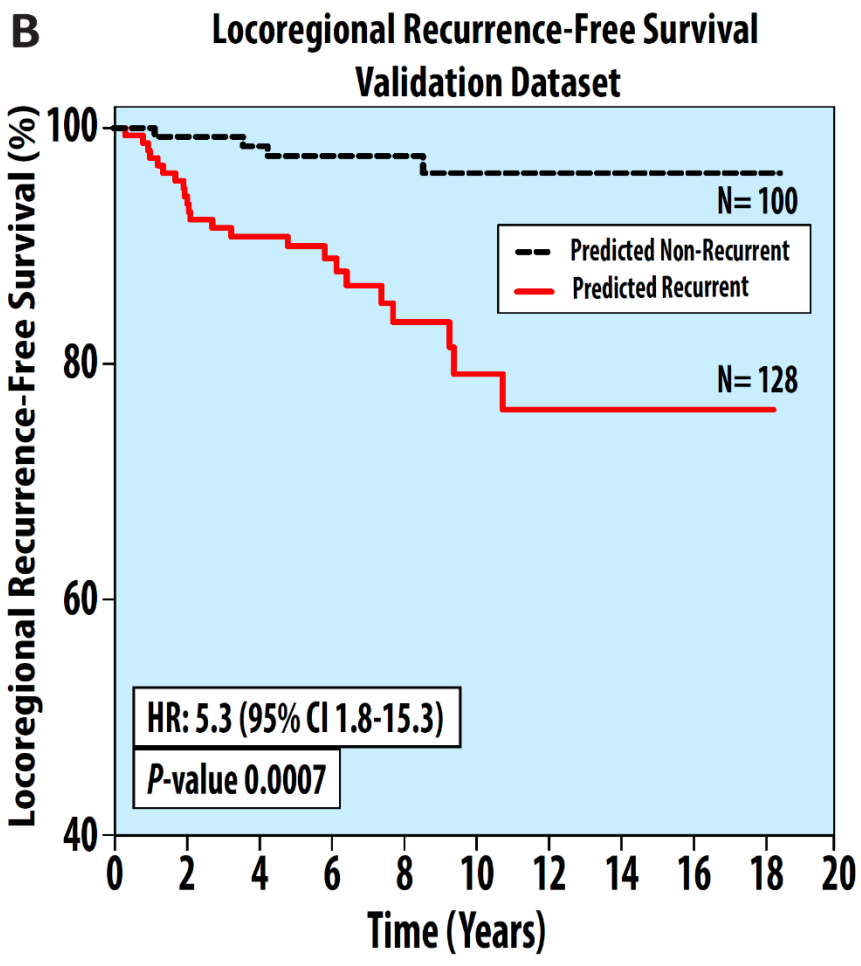


Genes involved in
cell cycle
DNA damage
DNA repair

ESTRO School

Radiation signature tested in the validation set





The RT signature is independent of molecular subtype (luminal A/B….)

ESTRO School

Radiation signature tested in the validation set

Author Manuscript Published OnlineFirst on April 22, 2015; DOI: 10.1158/1078-0432.CCR-14-2898
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

	Univariable Analysis			
	Local Recurrence		Overall Survival	
Covariate	Hazard Ratio (HR)	*P* value	Hazard Ratio (HR)	*P* value
Radiation signature	**5.25 (95% CI 1.80-15.34)**	**0.002**	**2.52 (95% CI 1.52-4.17)**	**<0.0001**
Age	0.95 (95% CI 0.89-1.02)	0.14	**0.96 (95% CI 0.92-0.99)**	**0.02**
Mastectomy	0.54 (95% CI 0.24-1.23)	0.14	1.01 (95% CI 0.65-1.59)	0.95
Tumor diameter	0.73 (95% CI 0.45-1.20)	0.22	**1.46 (95% CI 1.16-1.89)**	**0.001**
ER status	0.66 (95% CI 0.27-1.59)	0.35	**0.31 (95% CI 0.20-0.49)**	**<0.0001**
Grade	1.26 (95% CI 0.76-2.09)	0.37	**2.96 (95% CI 2.05-4.27)**	**<0.0001**
Chemotherapy	1.38 (95% CI 0.63-3.02)	0.42	0.76 (95% CI 0.47-1.23)	0.27
LN status	1.06 (95% CI 0.91-1.23)	0.44	1.03 (95% CI 0.94-1.14)	0.48
Endocrine Therapy	0.76 (95% CI 0.23-2.55)	0.66	0.45 (95% CI 0.20-1.05)	0.06

D

	Multivariable Cox Regression Analysis			
	Local Recurrence		Overall Survival	
Covariate	Hazard Ratio (HR)	*P* value	Hazard Ratio (HR)	*P* value
Radiation signature	**6.12 (95% CI 1.94-19.3)**	**0.002**	**1.80 (95% CI 1.03-3.17)**	**0.04**
Age	0.94(95% CI 0.88-1.01)	0.07	0.97 (95% CI 0.94-1.01)	0.18
Diameter (cm)	0.61(95% CI 0.35-1.05)	0.07	1.22 (95% CI 0.93-1.59)	0.14
LN-positive	1.10 (95% CI 0.90-1.34)	0.34	1.06 (95% CI 0.96-1.18)	0.26
Mastectomy	0.68 (95% CI 0.28-1.67)	0.40	0.98 (95% CI 0.60-1.58)	0.92
ER status	0.77 (95% CI 0.29-2.07)	0.61	**0.57 (95% CI 0.34-0.93)**	**0.03**
Endocrine Therapy	1.12 (95% CI 0.31-4.03)	0.87	0.56 (95% CI 0.24-1.33)	0.19
Chemotherapy	1.05 (95% CI 0.41-2.67)	0.93	0.72 (95% CI 0.40-1.29)	0.27
Grade	0.97 (95% CI 0.53-1.81)	0.94	1.95 (95% CI 1.29-2.96)	0.002

Downloaded from clincancerres.aacrjournals.org on May 30, 2015. © 2015 American Association for Cancer

ESTRO School

Potential of gene analysis studies

The DBCG 7 gene profile can predict gain from loco-regional RT after mastectomy. It identifies 25% of a high-risk cohort where RT may not be of any value. This gene profile is predictive of RT effect.

The Michigan 51 gene profile can discriminate patients treated with BCS+RT who are unlikely to develop local recurrence after RT from those patients with a high likelyhood of recurrence despite RT. Thus it may identify patients who need treatment intensification. This gene profile is prognostic (not predictive).

Further studies are being performed to explore the potential of these profiles.

Conclusion

Results from large randomised trials demonstrate significant gain in recurrence from loco-regional RT in pN+ breast cancer, also in overall survival. The gain is seen also in pN1 patients treated with PMRT

The gain in recurrence from loco-regional RT is (at least) of the same magnitude as for systemic therapy

The morbidity after RT is not higher or more serious than after systemic therapy (lecture later on in this ESTRO course) and now virtually all departments use CT-planning, target delineation, gating techniques, advanced RT technique with field-in-field strategy, so morbidity is likely to be even more limited in the future

Subgroups of pN+ patients may be overtreated with loco-regional RT, but no consensus no how to select these patients

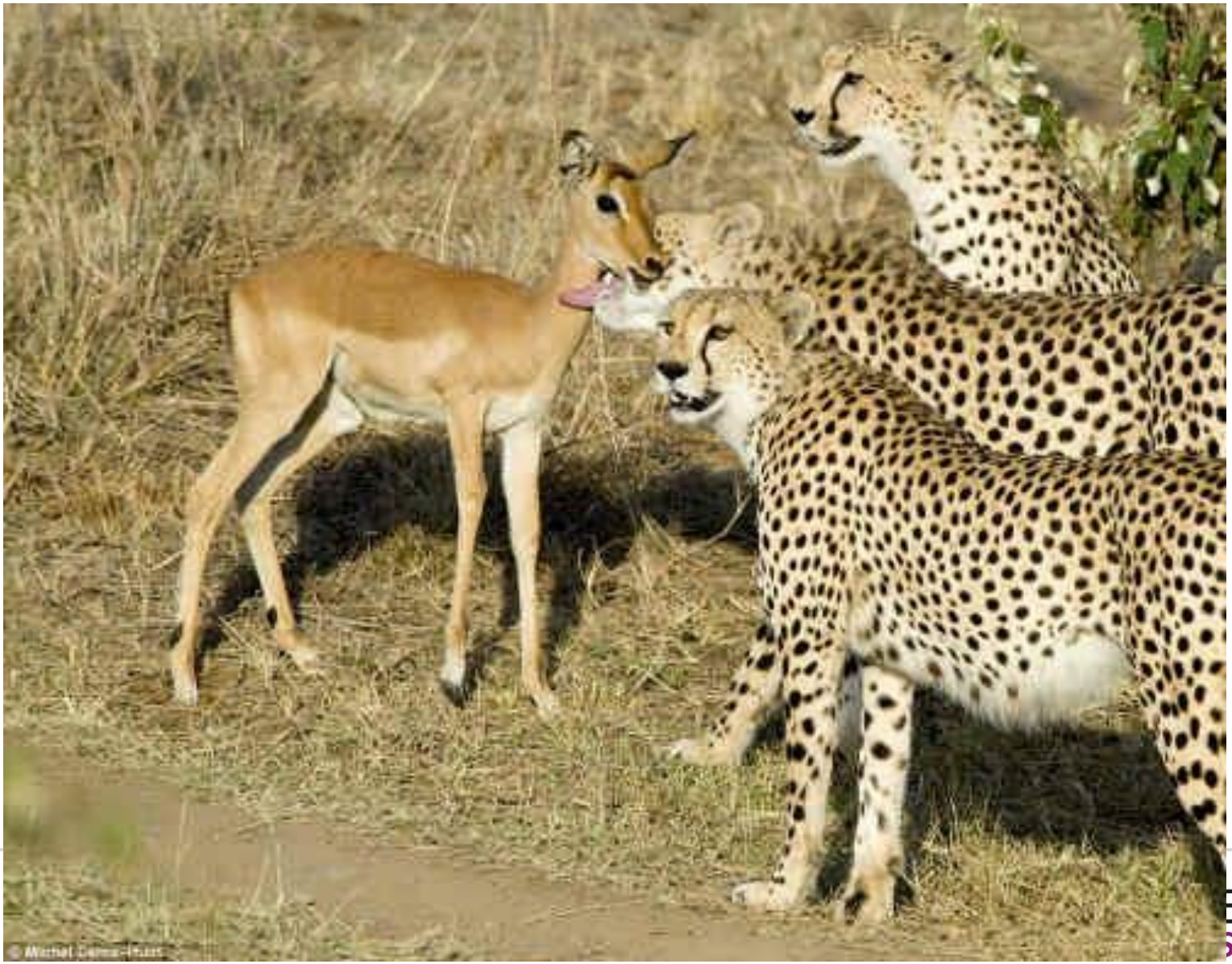
Very promising new strategies involving gene analyses are now underway to help optimal selection of the right therapy to the right patient

BUT, WE STILL DO NOT HAVE THE OPTIMAL SELECTION CRITERIA TO SELECT PATIENTS WITH NODE-POSITIVE DISEASE TO LESS RADIATION THERAPY

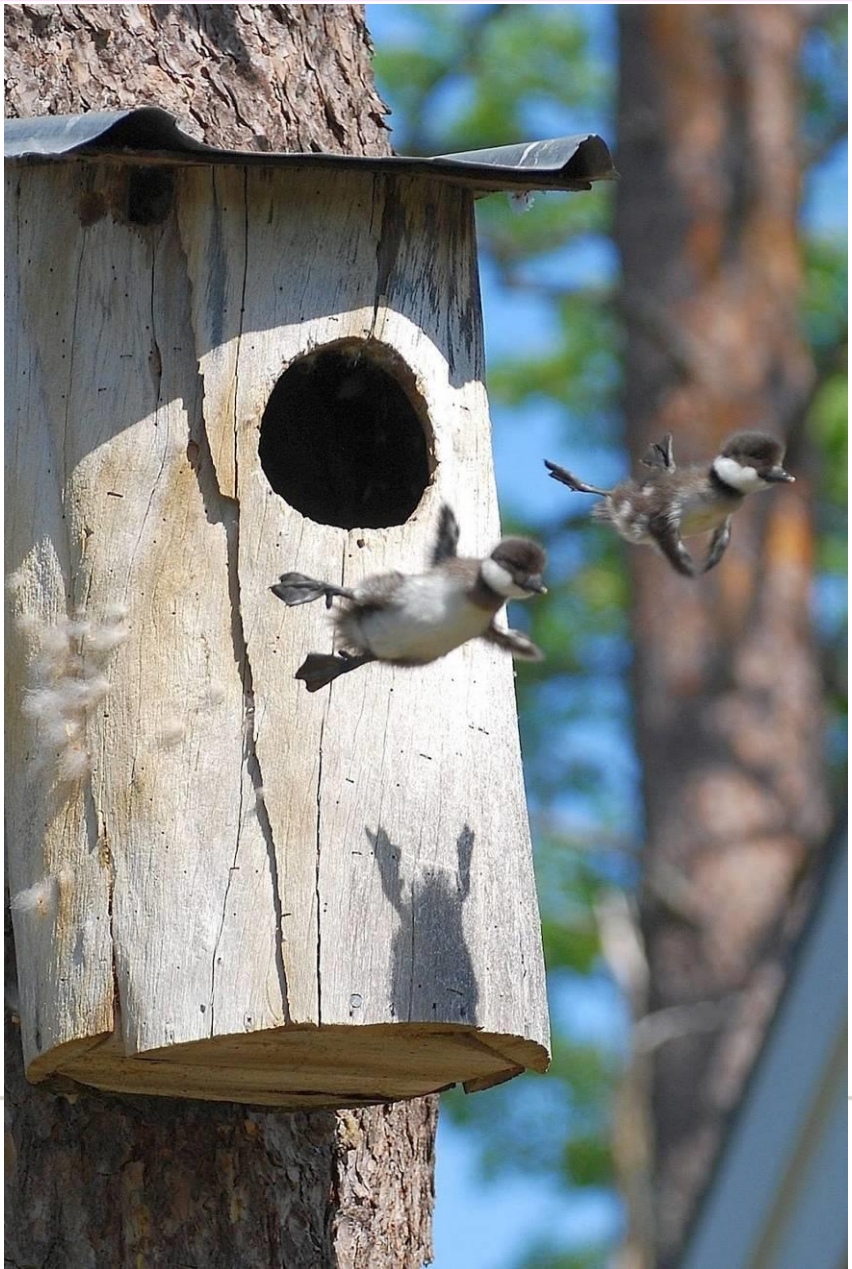
ESTRO School

If you treat node-positive patients with less intensity in the axilla outside trial you must be sure you know what is going to happen…..

….. So you may need to prepare for a surprise!



Everything has a time….. And you can´t turn back time….



So support trials when you have the chance! When RT gene signatures are ready for clinical test, we need to support those trials.

ESTRO School

Target volume delineation: lymph node areas

Liesbeth Boersma, radiation oncologist

Maastro Clinic/ University Hospital Maastricht, The Netherlands

ESTRO Teaching Course on Breast Cancer, Dublin, September 10-13th 2017

Background and aim of the guideline:

- Aim:
  - Guideline which is endorsed by many, that does NOT lead to larger treatment volumes, but DOES lead to uniform delineation in the various studies

- Primarily started with anatomical borders, based on theory.

- But, because of excellent local and regional controls: take care not to increase treatment volumes!

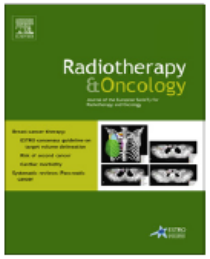
- Made compromises, tried to reconstruct: what is the CTV we apparently have been treating all these years …- does it fit the recurrence rates ?

Radiotherapy and Oncology 114 (2015) 3–10

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



ESTRO consensus guidelines

ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer

Birgitte V. Offersen [a,*], Liesbeth J. Boersma [b], Carine Kirkove [c], Sandra Hol [d], Marianne C. Aznar [e], Albert Biete Sola [f], Youlia M. Kirova [g], Jean-Philippe Pignol [h], Vincent Remouchamps [i], Karolien Verhoeven [j], Caroline Weltens [j], Meritxell Arenas [k], Dorota Gabrys [l], Neil Kopek [m], Mechthild Krause [n], Dan Lundstedt [o], Tanja Marinko [p], Angel Montero [q], John Yarnold [r], Philip Poortmans [s]

[a] Department of Oncology, Aarhus University Hospital, Denmark; [b] Department of Radiation Oncology, Maastricht University Medical Centre – GROW (MAASTRO), The Netherlands [c] Department of Radiation Oncology, Catholic University of Louvain, Belgium; [d] Department of Radiation Oncology, Institute Verbeeten, Tilburg, The Netherlands; [e] Department of Oncology, Rigshospitalet, Copenhagen, Denmark; [f] Department of Radiation Oncology, Hospital Clinic i Provincial, Barcelona, Spain; [g] Department of Radiation Oncology, Institut Curie, Paris, France; [h] Department of Radiation Oncology, Erasmus University Medical Center, Rotterdam, The Netherlands; [i] Department of Radiation Oncology, Clinique Sainte Elisabeth (AMPR), Namur; [j] Department of Radiation Oncology, University Hospitals Leuven, KU Leuven, Belgium; [k] Department of Radiation Oncology, Hospital Universitari Sant Joan, Reus, Spain; [l] Department of Radiation Oncology, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Gliwice, Poland; [m] Department of Oncology, Division of Radiation Oncology, McGill University, Montréal, Canada; [n] German Cancer Consortium (DKTK) Dresden and German Cancer Research Center (DKFZ) Heidelberg, Dept. of Radiation Oncology and OncoRay, University Hospital Carl Gustav Carus, Technische Universität Dresden and Helmholtz-Zentrum Dresden-Rossendorf, Dresden, Germany; [o] Department of Oncology, Sahlgrenska Universitetssjukhuset, Gothenborg, Sweden; [p] Department of Radiation Oncology, Institute of Oncology, Ljubljana, Slovenia; [q] Department of Radiation Oncology, Centro Integral Oncológico Clara Campal, Hospital Universitario Sanchinarro, Madrid, Spain; [r] Division of Radiotherapy and Imaging, Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, UK; [s] Department of Radiation Oncology, Radboud university medical centre, The Netherlands

Radiotherapy and Oncology 114 (2015) 3–10

Contents lists available at ScienceDirect

Radiotherapy and Oncology 118 (2016) 205–208

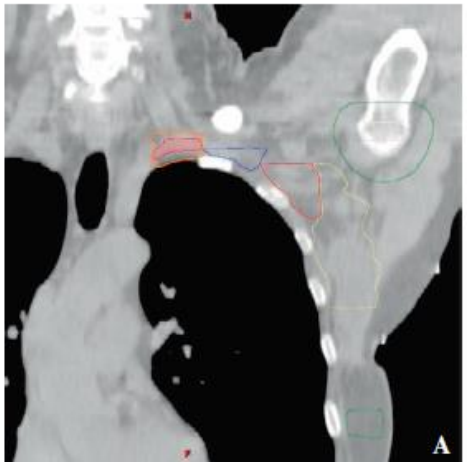
Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ESTRO breast cancer consensus guidelines

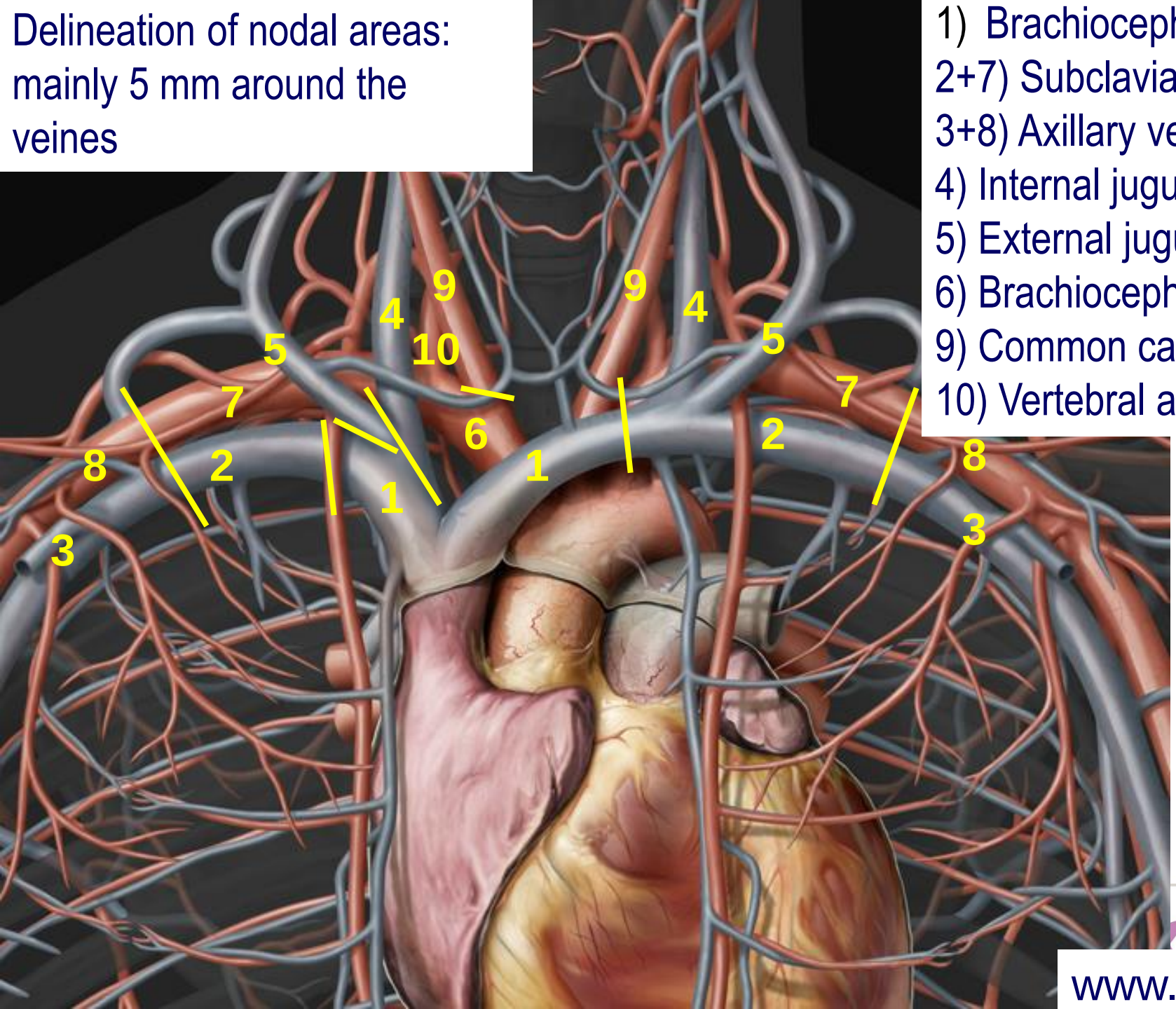
ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer, version 1.1 ☆



To the Editor,

One year ago we presented the ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer [1]. We hereby present an update following the need for modification of the caudal part of CTVn_L4 and the lateral border of CTVn_IMN in the published pdf-files. Also, as a consequence of frequent questions, we provide more information regarding the lateral border of the CTVp_breast and for dose planning in relation to the humeral joint.

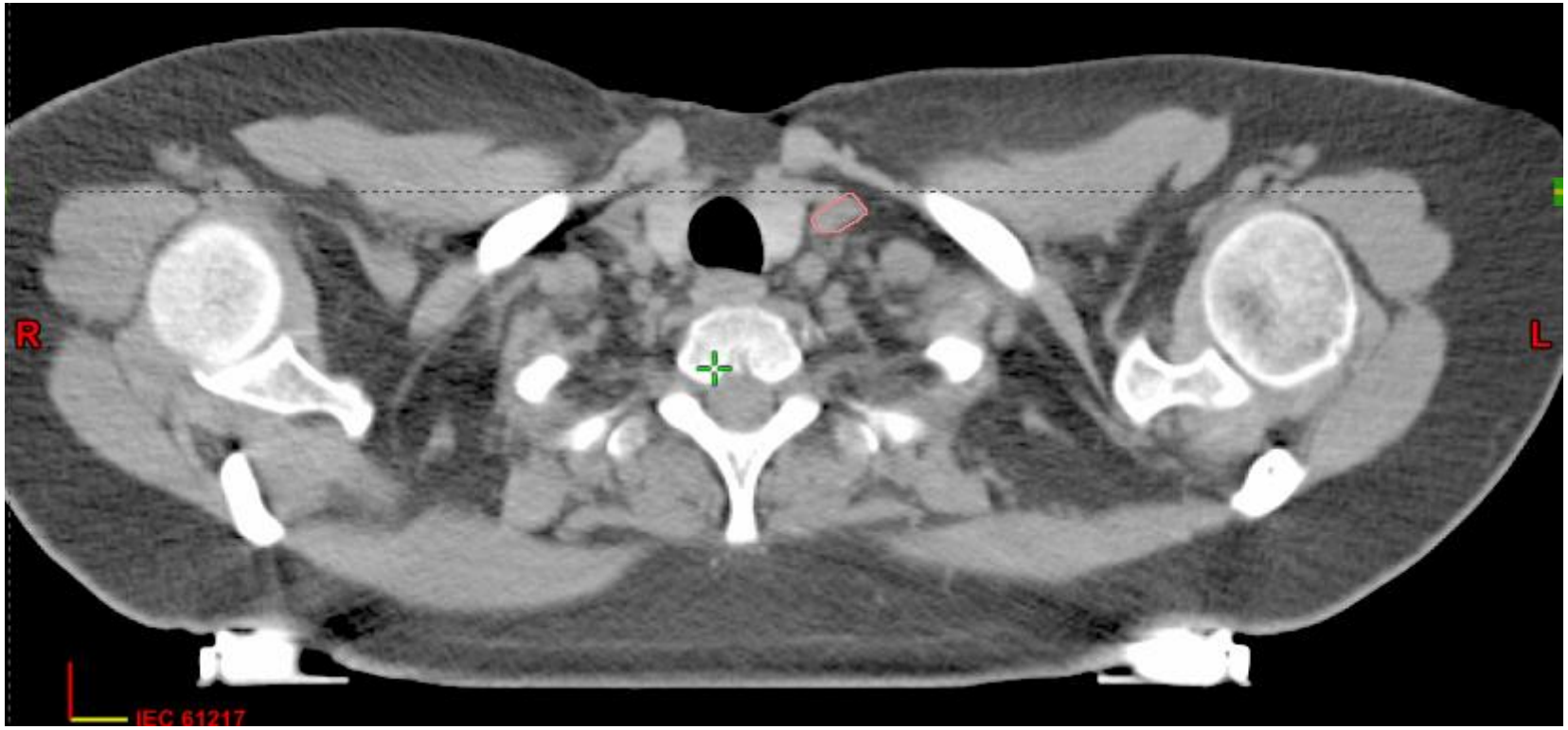
Delineation of nodal areas: mainly 5 mm around the veines



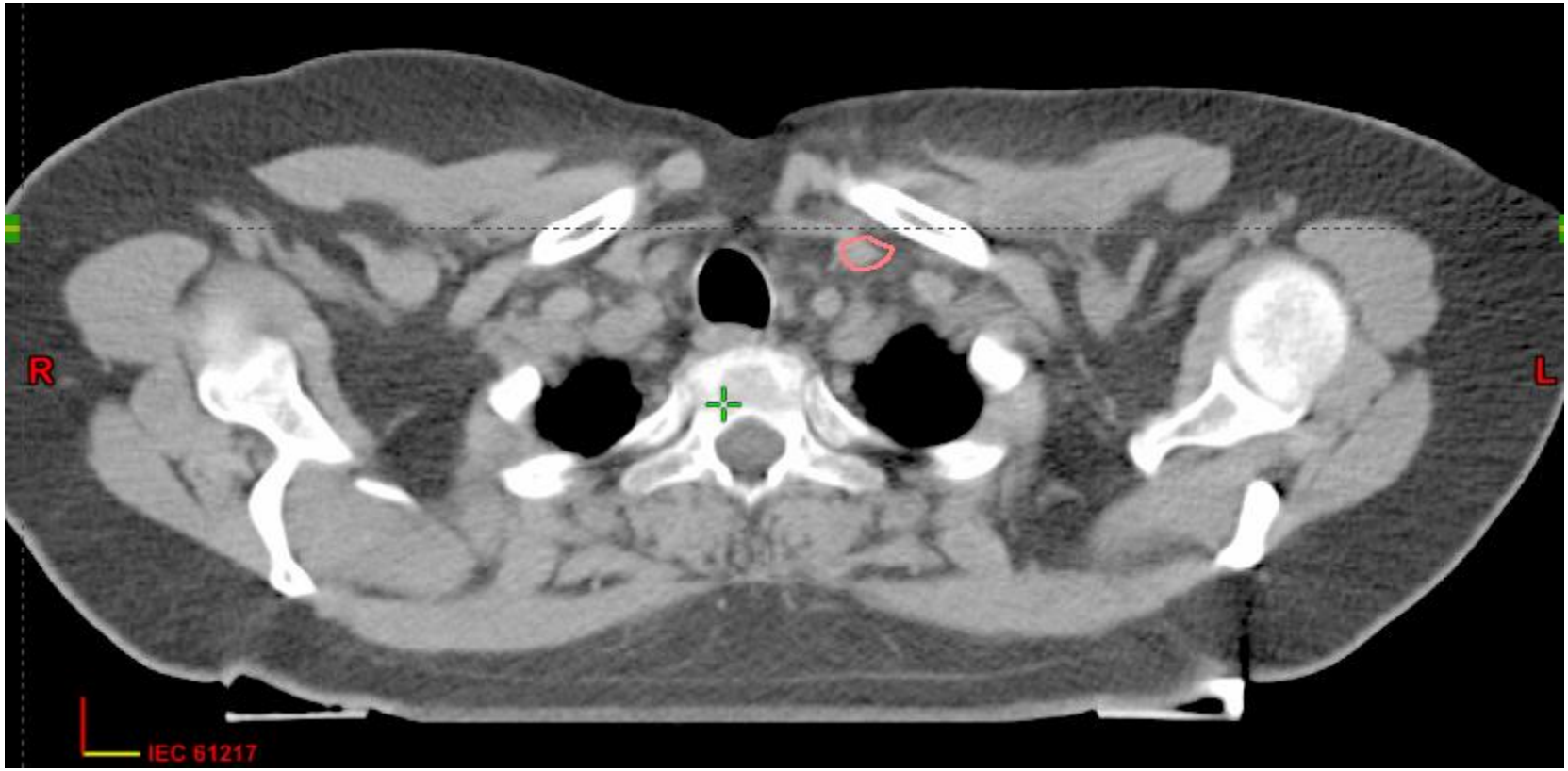
1) Brachiocephalic vein
2+7) Subclavian vessels
3+8) Axillary vessels
4) Internal jugular vein
5) External jugular vein
6) Brachiocephalic trunk
9) Common carotid artery
10) Vertebral artery

ESTRO
www.ikonet.co

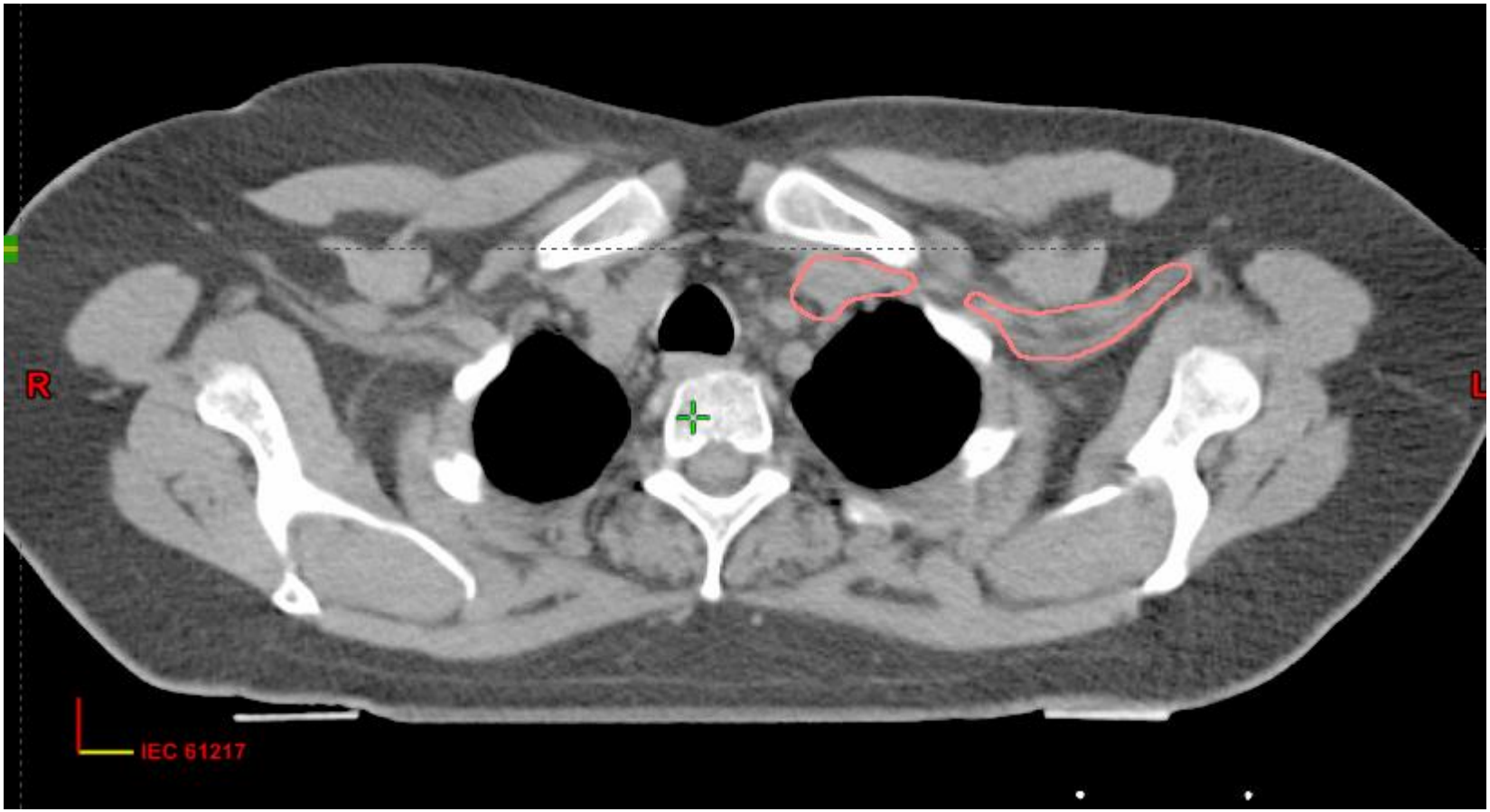
Delineation of the vessels



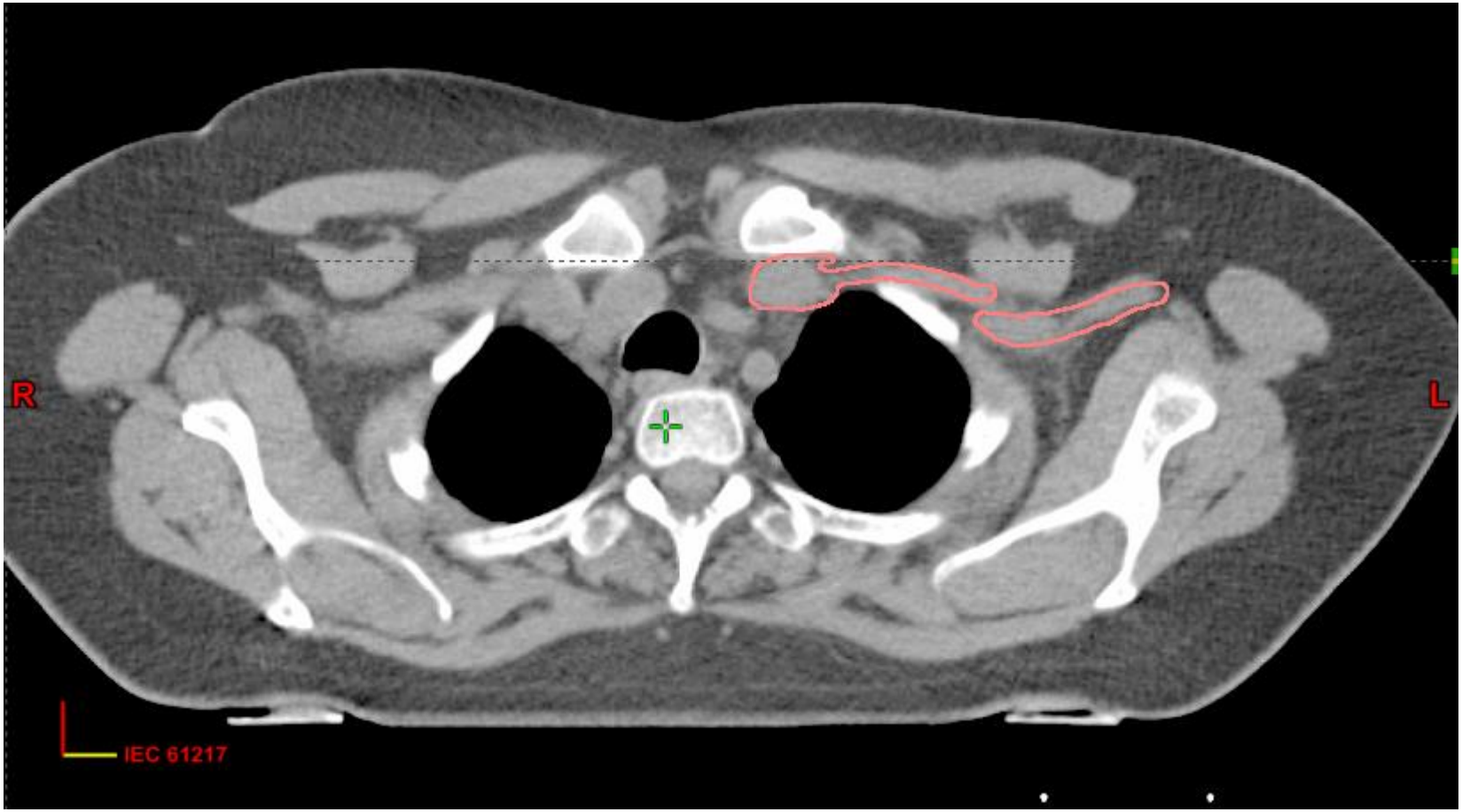
Delineation of the vessels



Delineation of the vessels

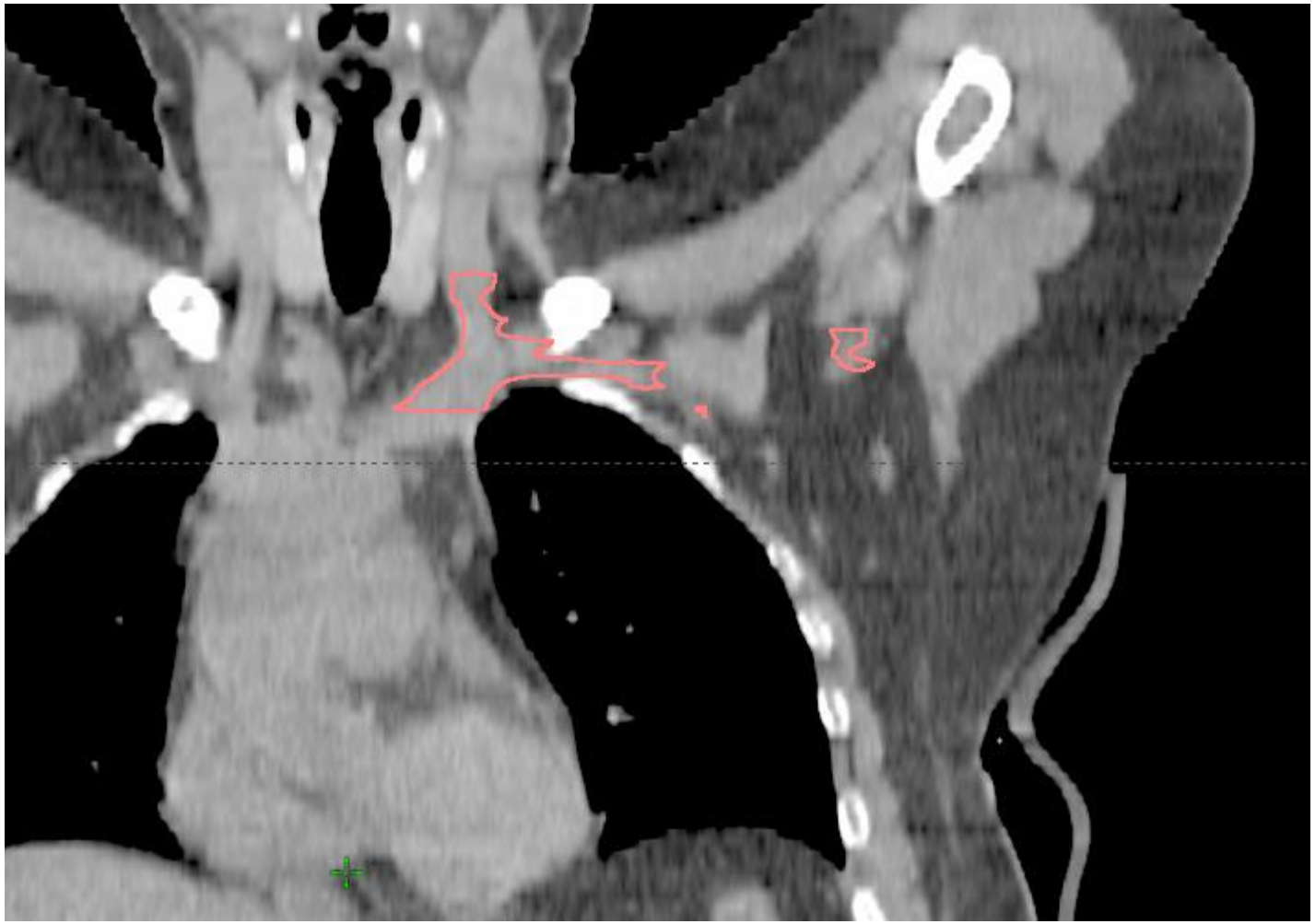


Delineation of the vessels

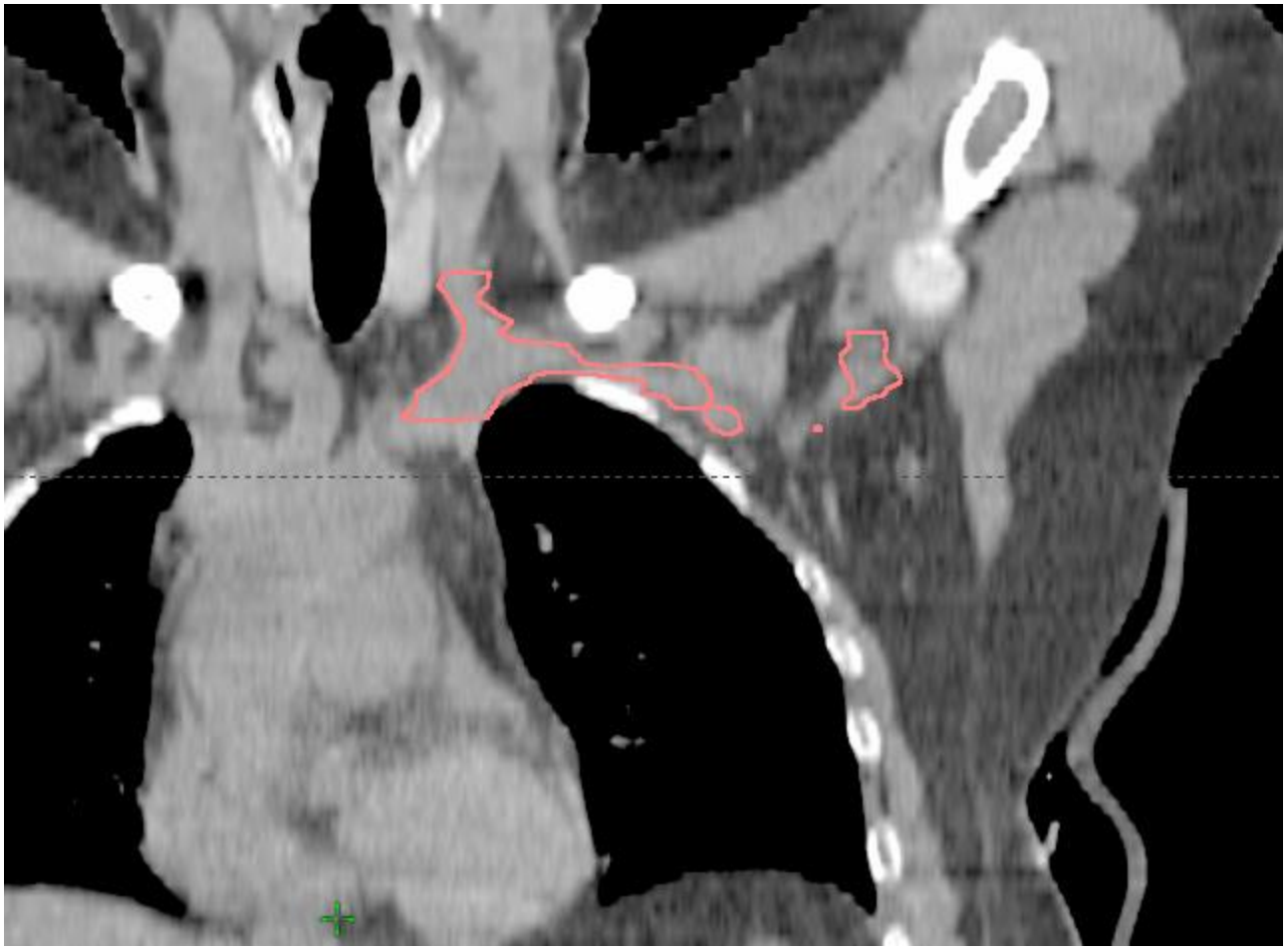


Delineation of the vessels

Delineation of the vessels

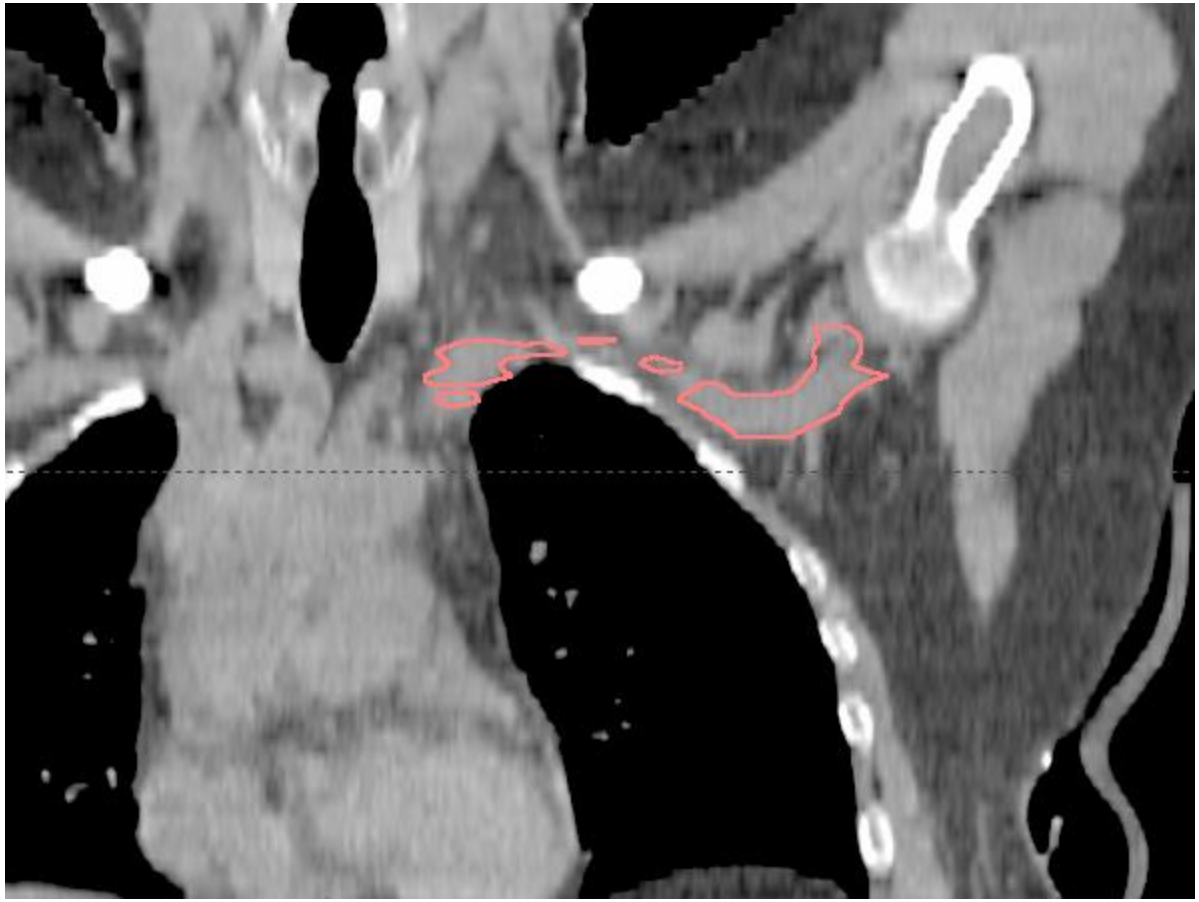


Delineation of the vessels



Delineation of the vessels

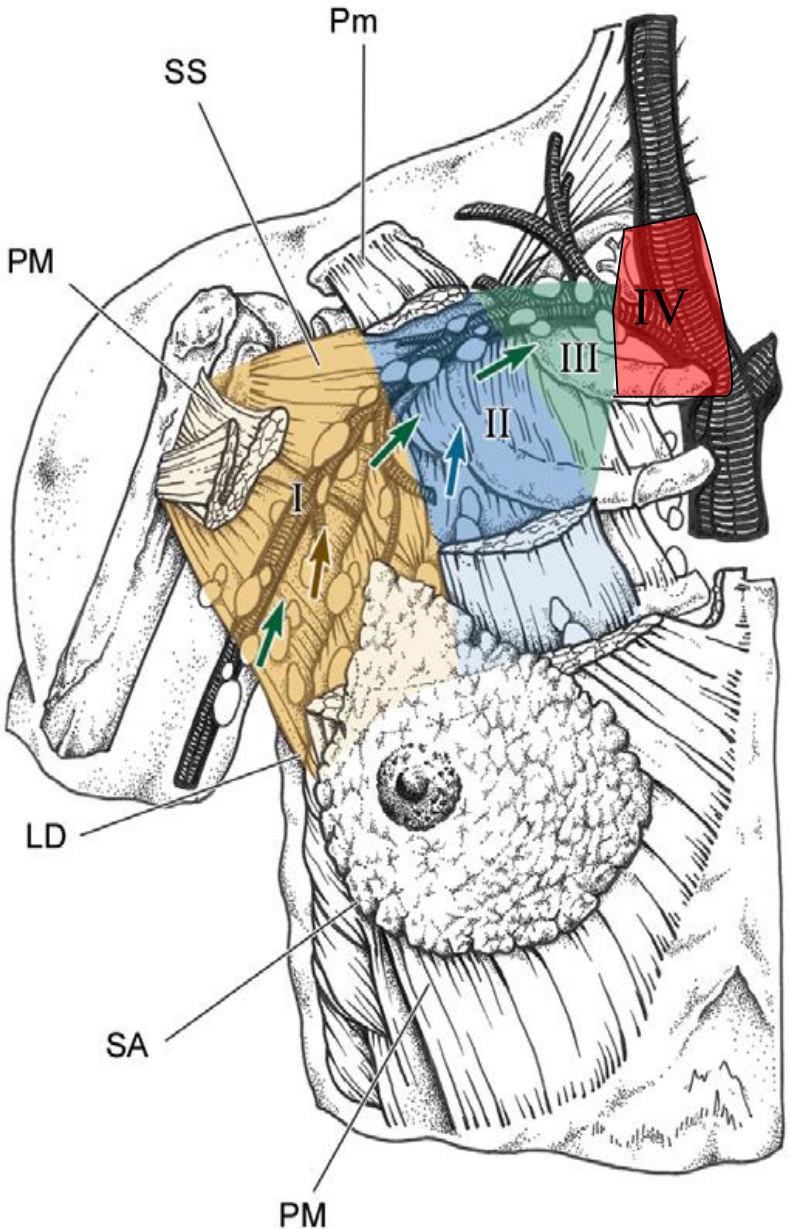
Delineation of the vessels



Delineation of the vessels

Global anatomy of axillary levels

Pm: pectoralis minor

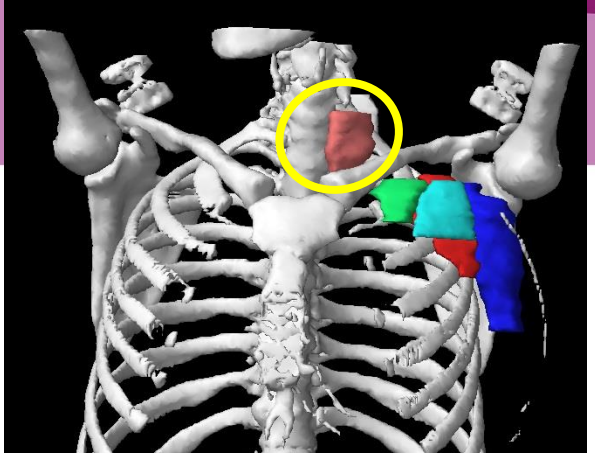


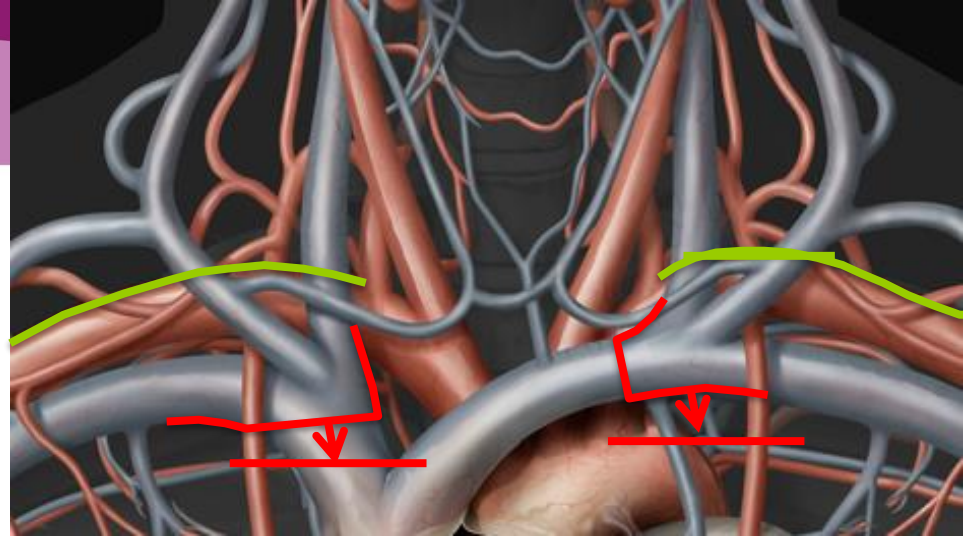
Level I

Level II

Level III

Level IV

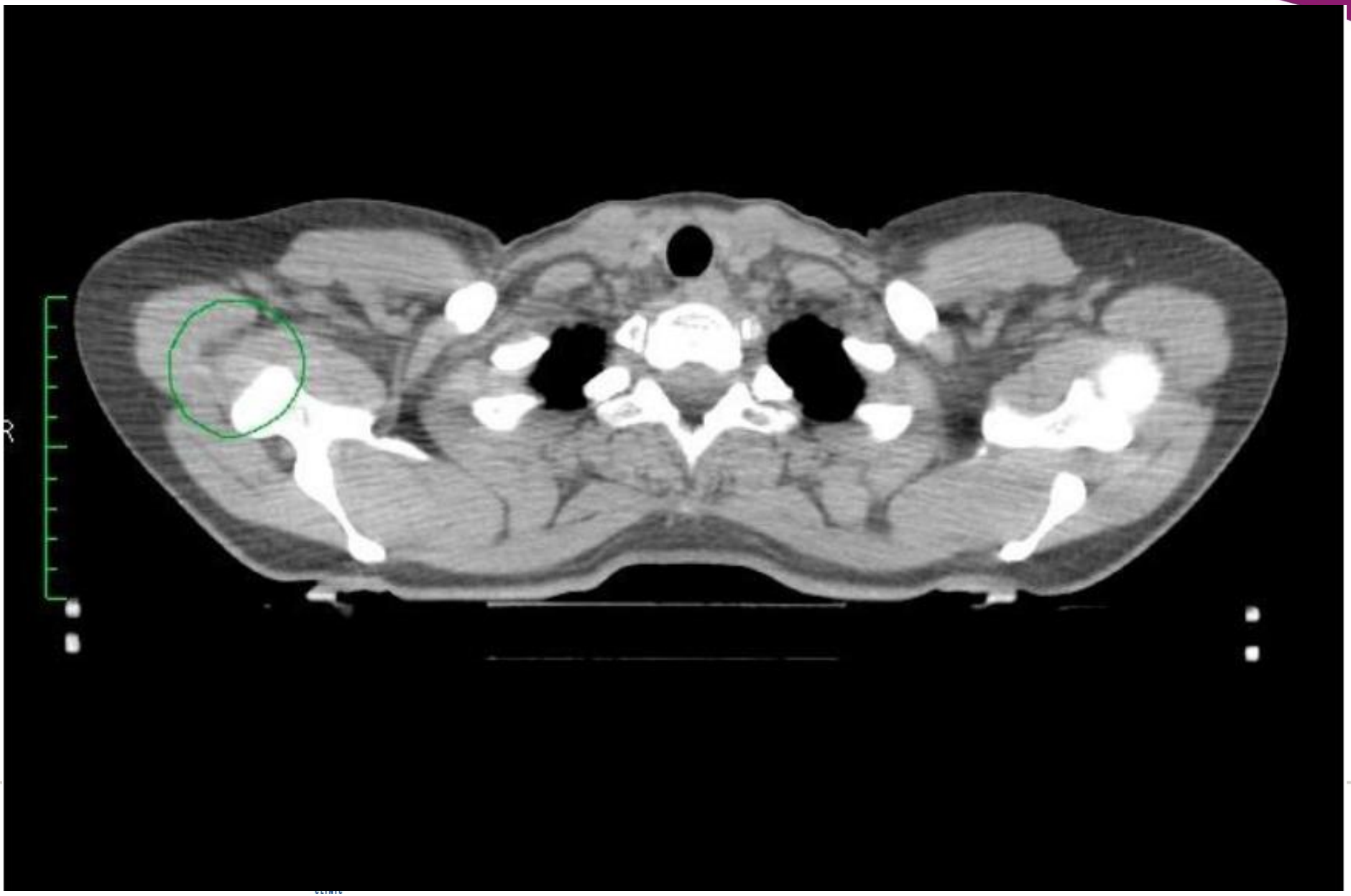




Supraclavicular LN area, CTVn_L4:

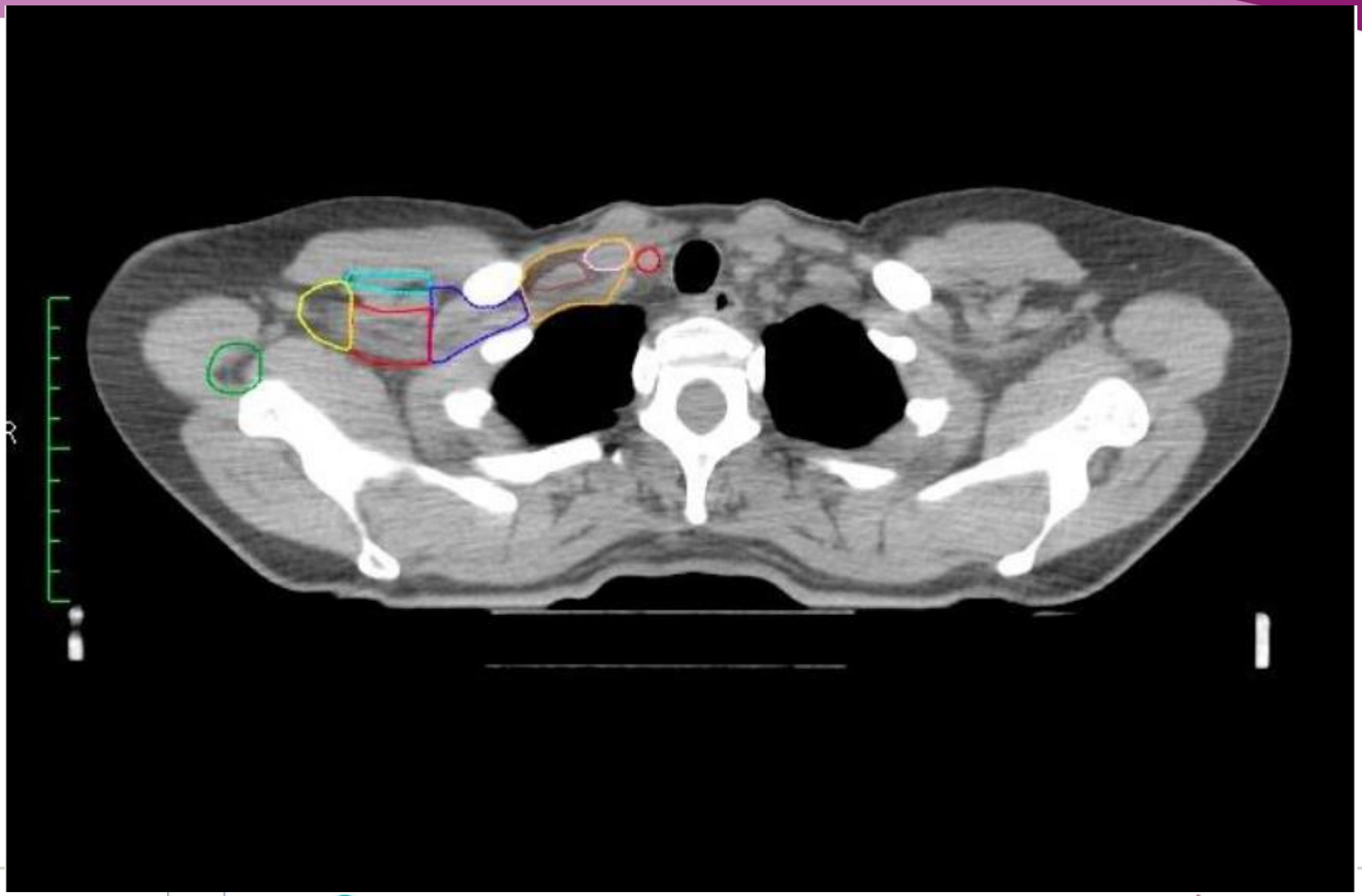
- ✓ Superior border: upper limit of subclavian artery
- ✓ Caudal border: 5mm caudal from junction of subclavian and internal jugular veins
- ✓ Ventral border: sternocleidomastoideus muscle, clavicle
- ✓ Dorsal border: Pleura
- ✓ Medial border: including the jugular vein without margin; excluding the thyroid gland and the common carotid artery
- ✓ Lateral border: includes the anterior scalene muscle, and connects to medial border CTVn L3

CTVn_L4 = orange



CTVn_L4 = orange

CTVn_L4 = orange

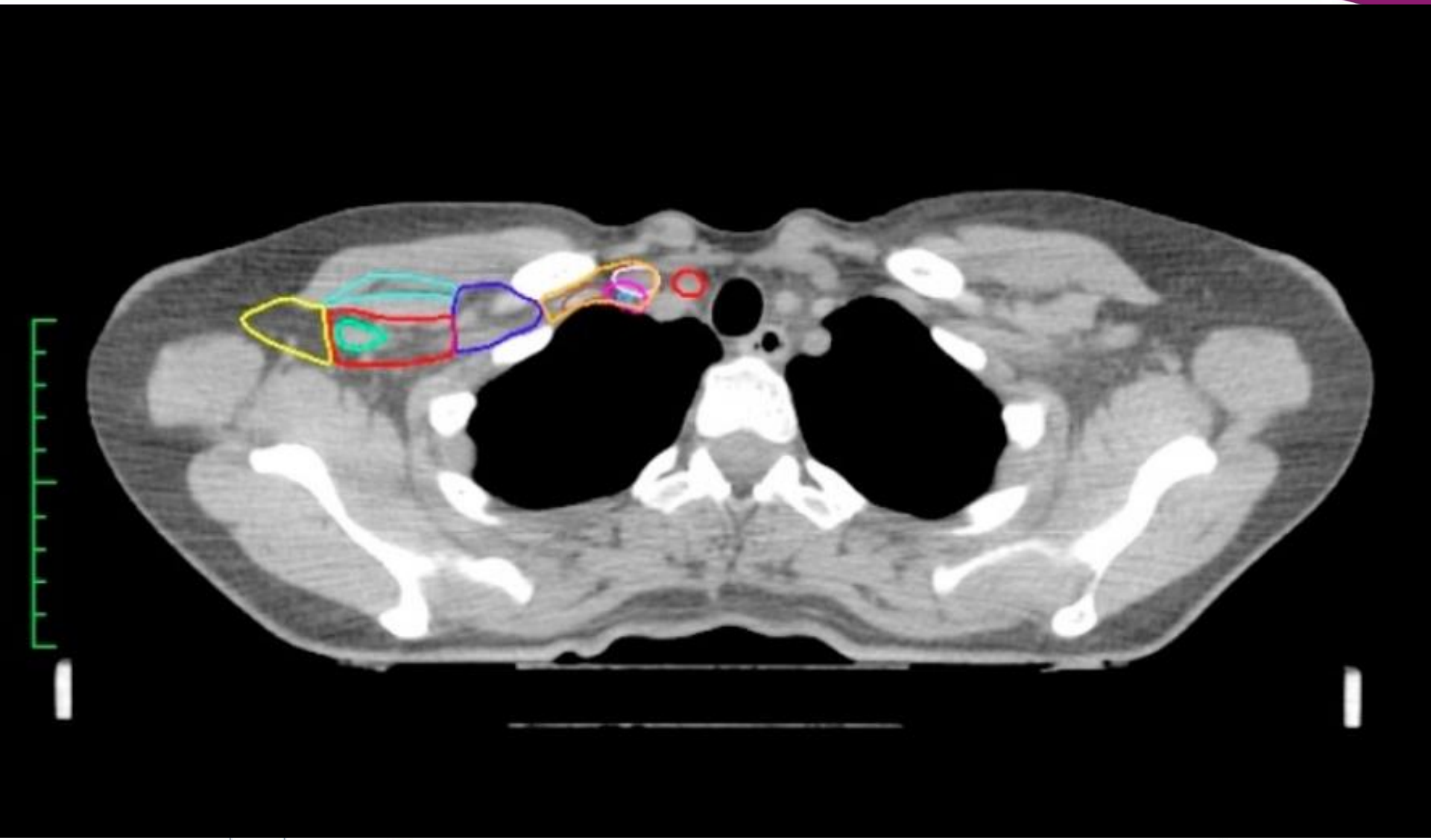


MAASTRO CLINIC

ESTRO School

CTVn_L4 = orange

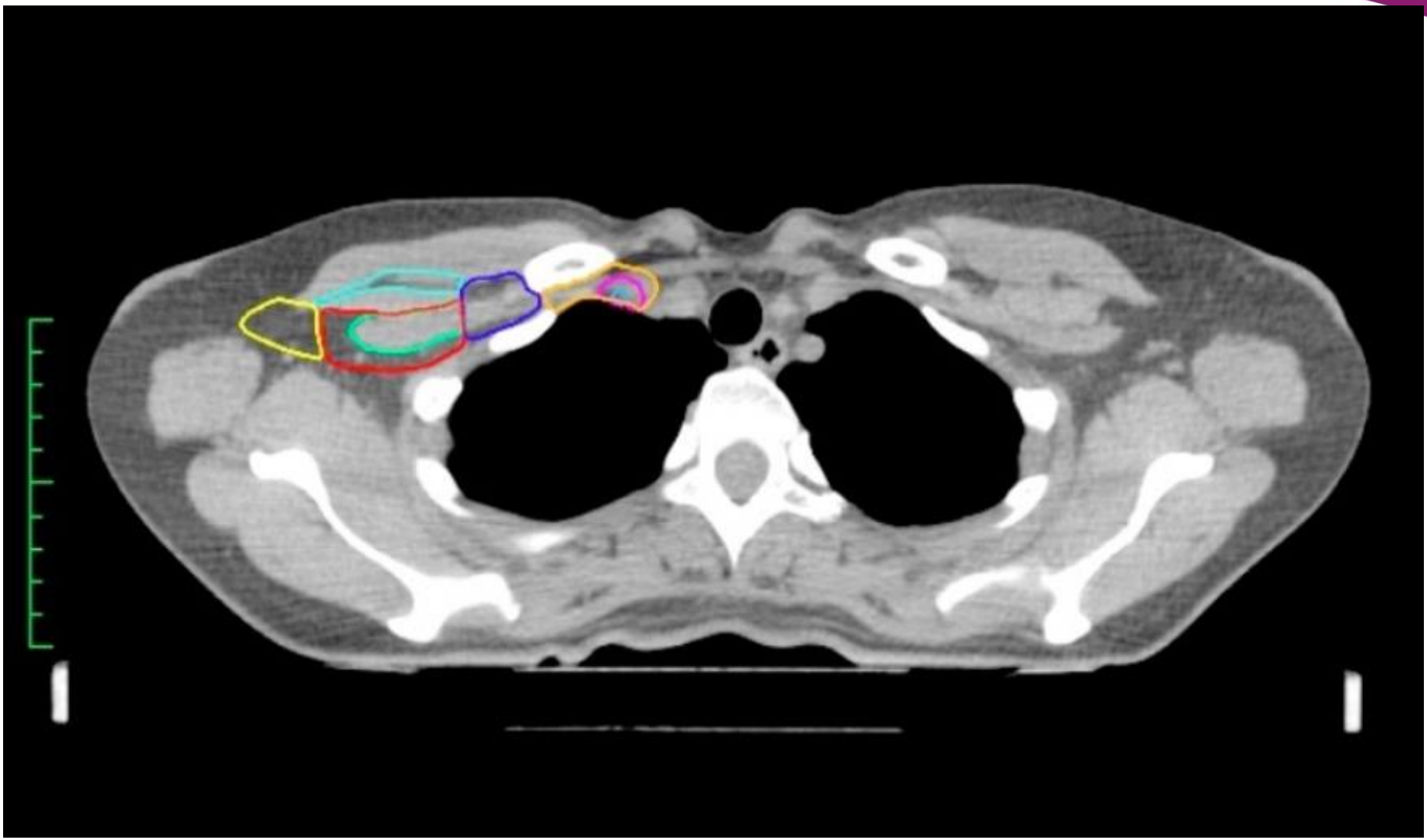
CTVn_L4 = orange



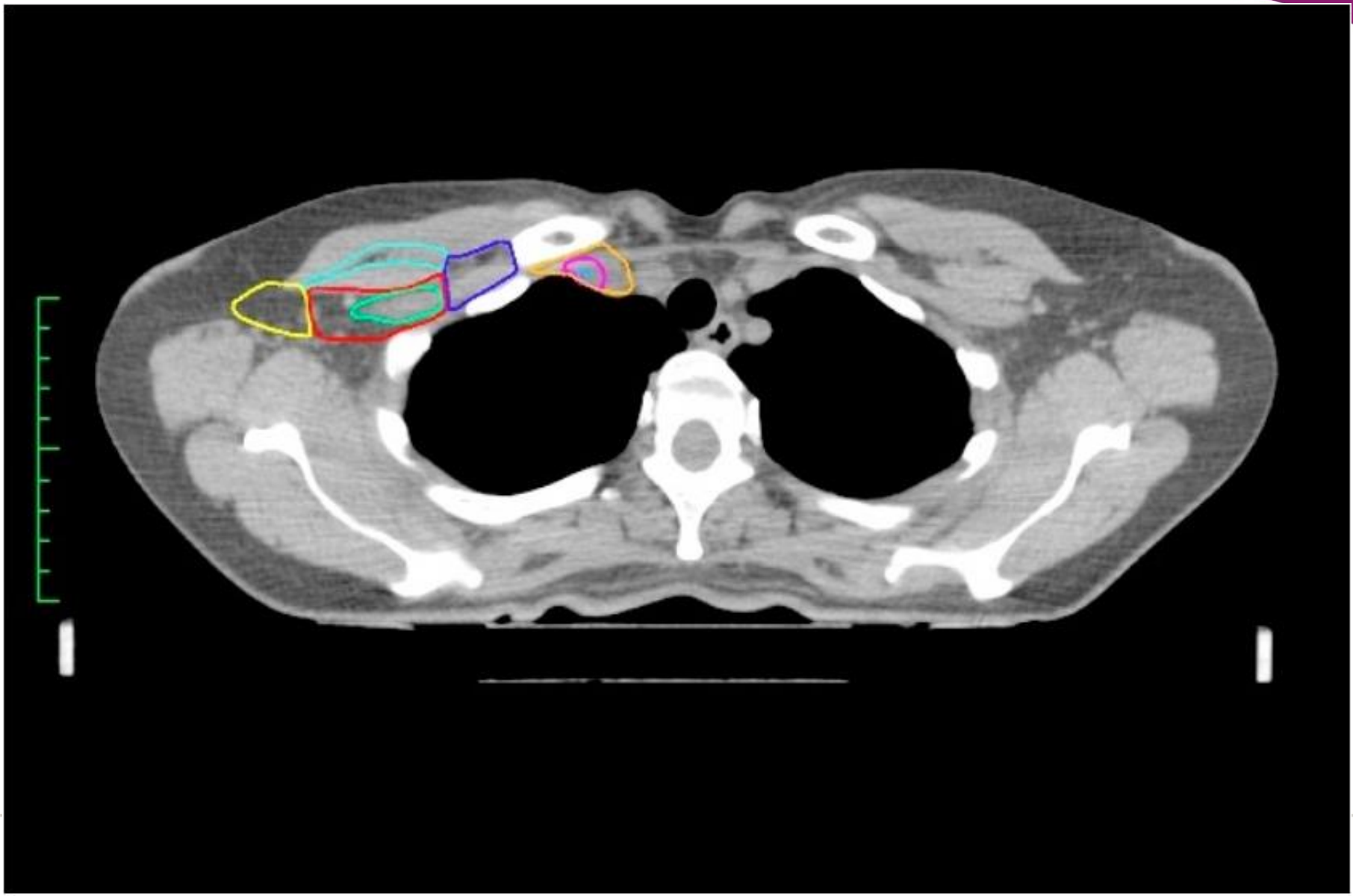
MAASTRO CLINIC

ESTRO School

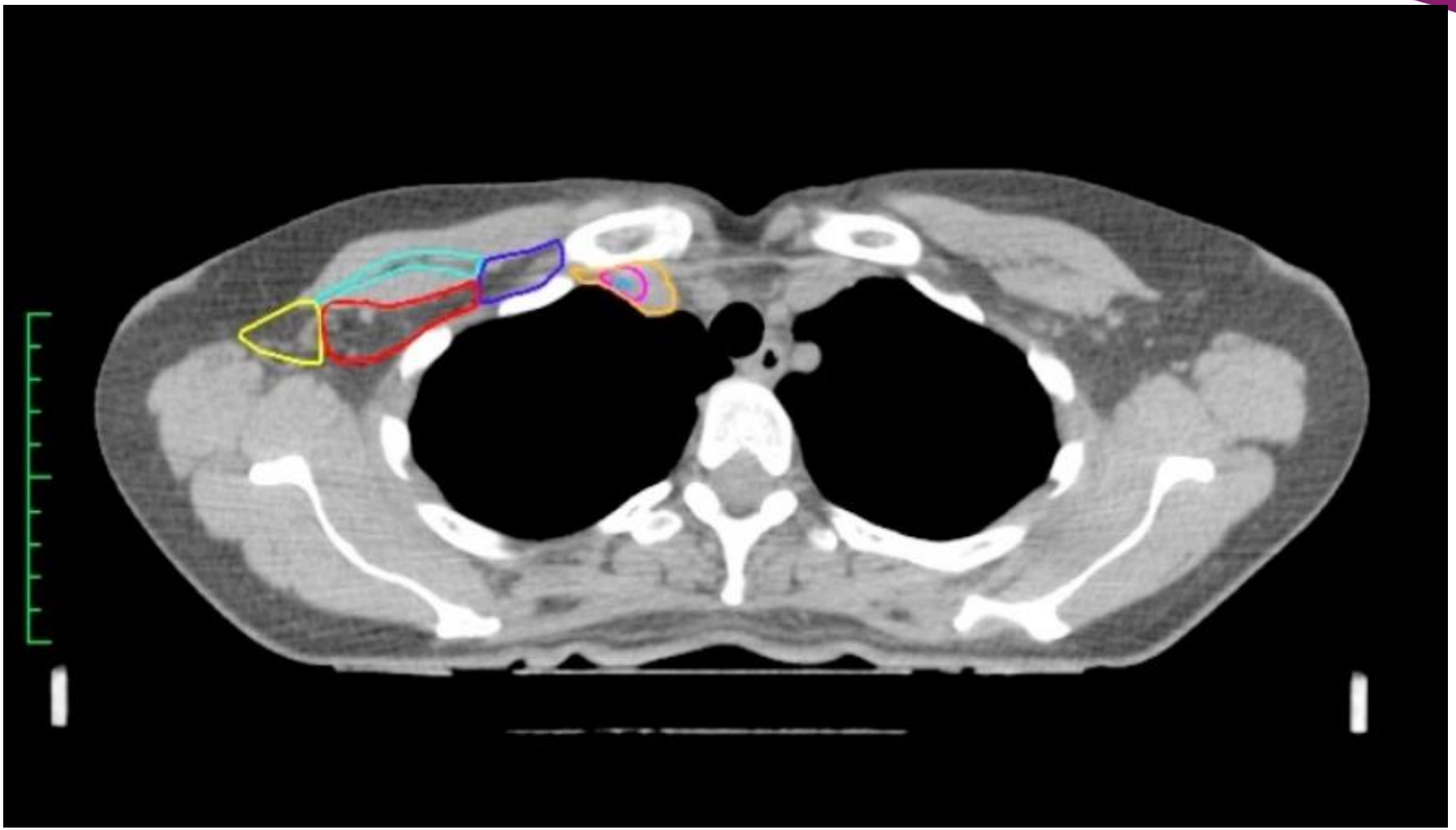
CTVn_L4 = orange



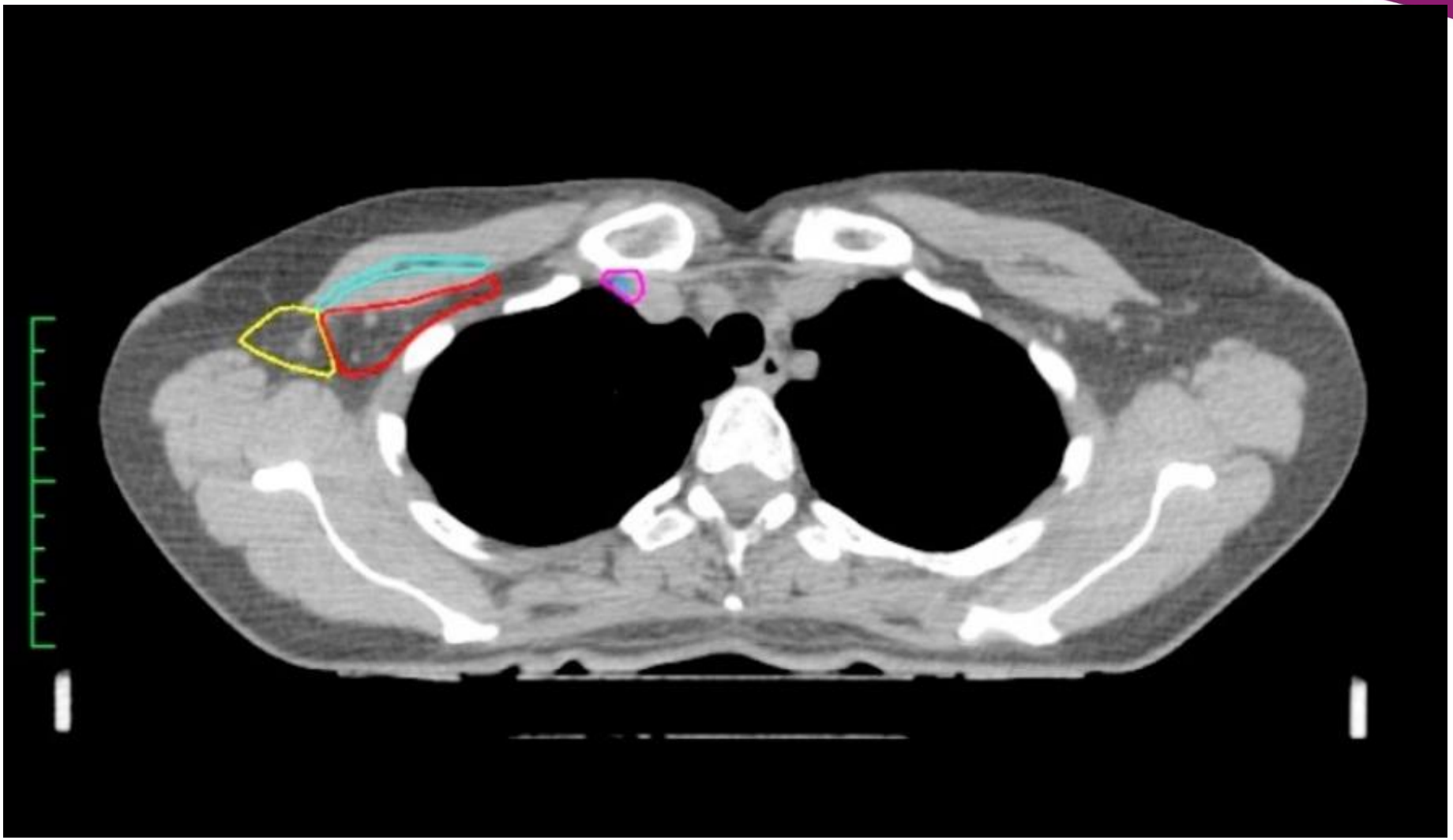
CTVn_L4 = orange



CTVn_L4 = orange



CTVn_L4 = orange

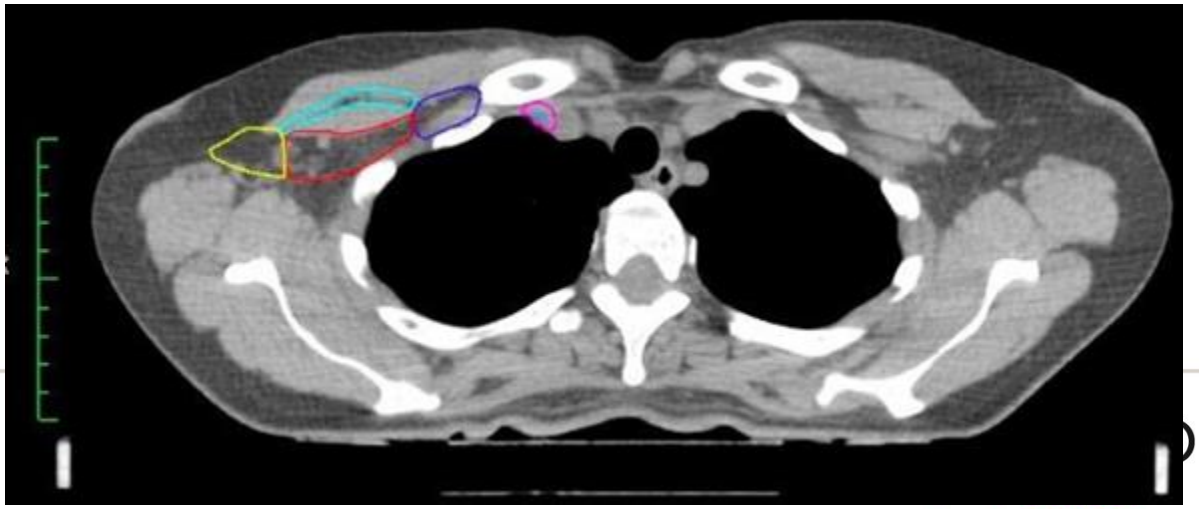


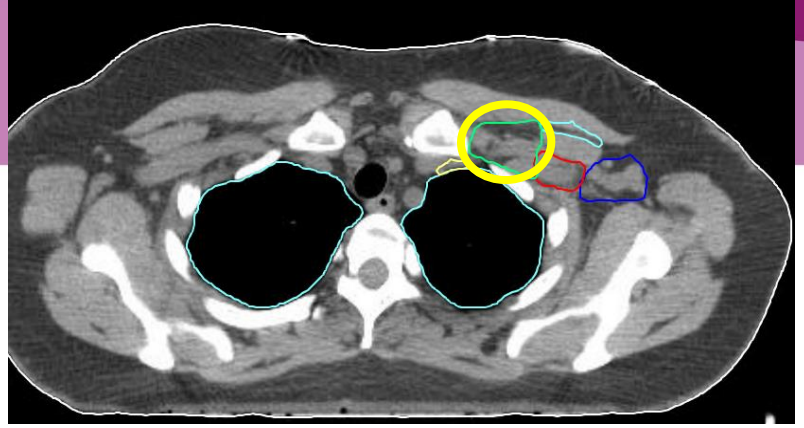
Axillary lymph node areas levels 1-3

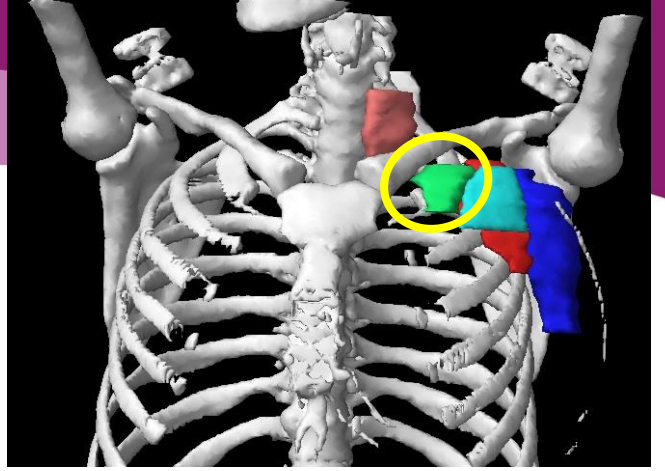
Traditionally ➔ subdivided into 3 subregions:

- **level 1** caudally from lower border of major pectoral muscle
- **level 2** posterior to minor pectoral muscle
- **level 3** located medio-cranially from the pectoral muscles

+ Rotter located between minor and major pectoral muscle

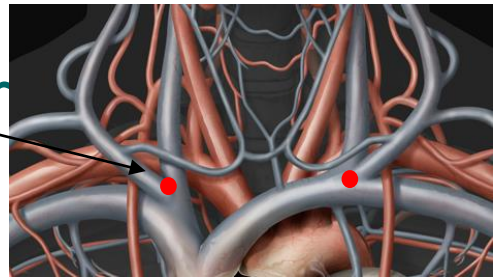






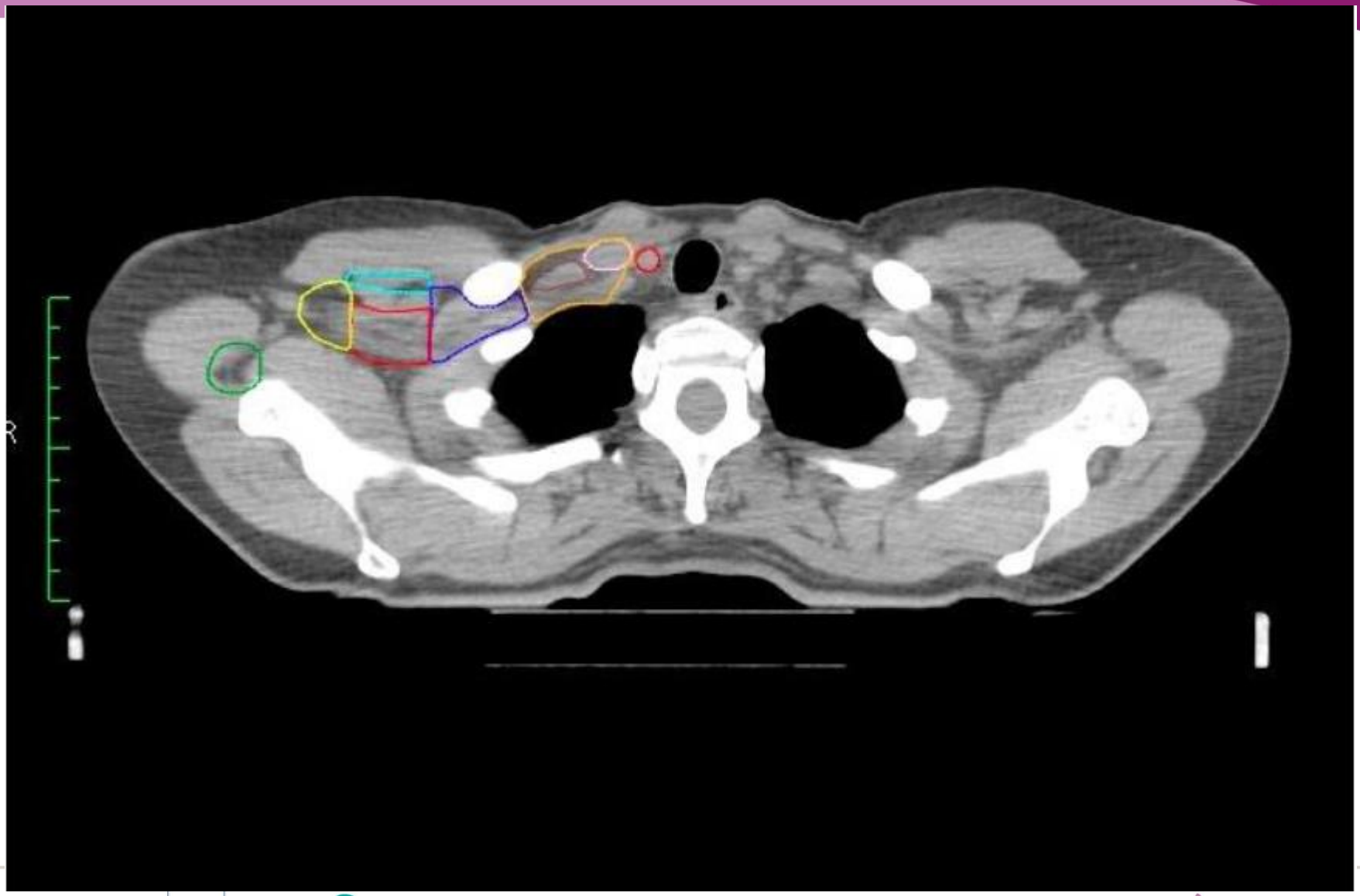
Axilla level 3 (infraclavicular) – CTVn_L3:

- ✓ Cranial border: 5 mm cranial of the subclavian vein. More medially it is the clavicle
- ✓ Caudal border: 5 mm below the subclavian vein
- ✓ Lateral border: medial side of the pectoralis minor muscle
- ✓ Medial border: junction of subclavian and jugular vein
- ✓ Ventral border: pectoralis major muscle
- ✓ Dorsal border: up to 5mm post. of subclavian/axillary vein



CTVn_L3 = dark blue

CTVn_L3 = dark blue

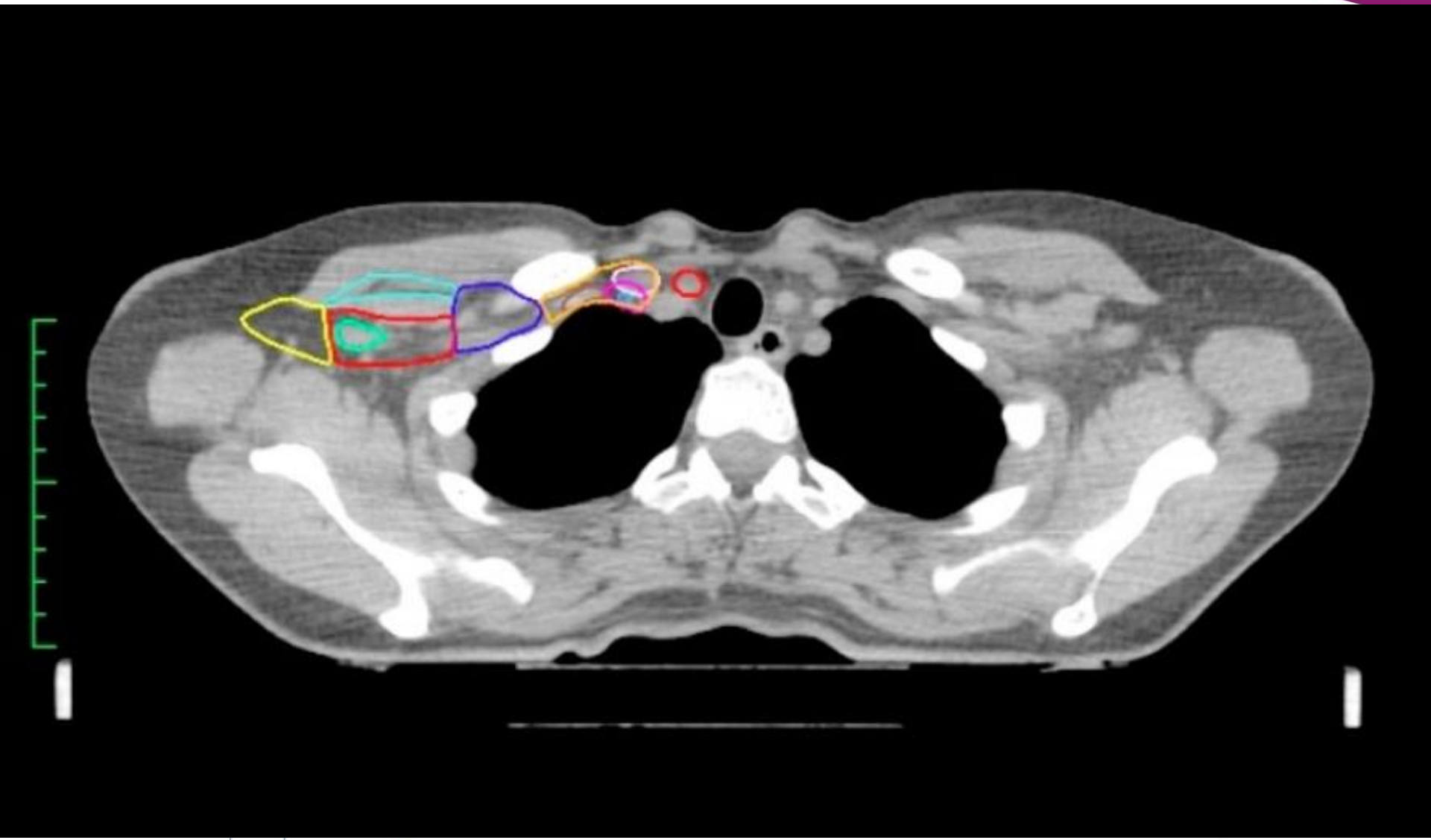


MAASTRO CLINIC

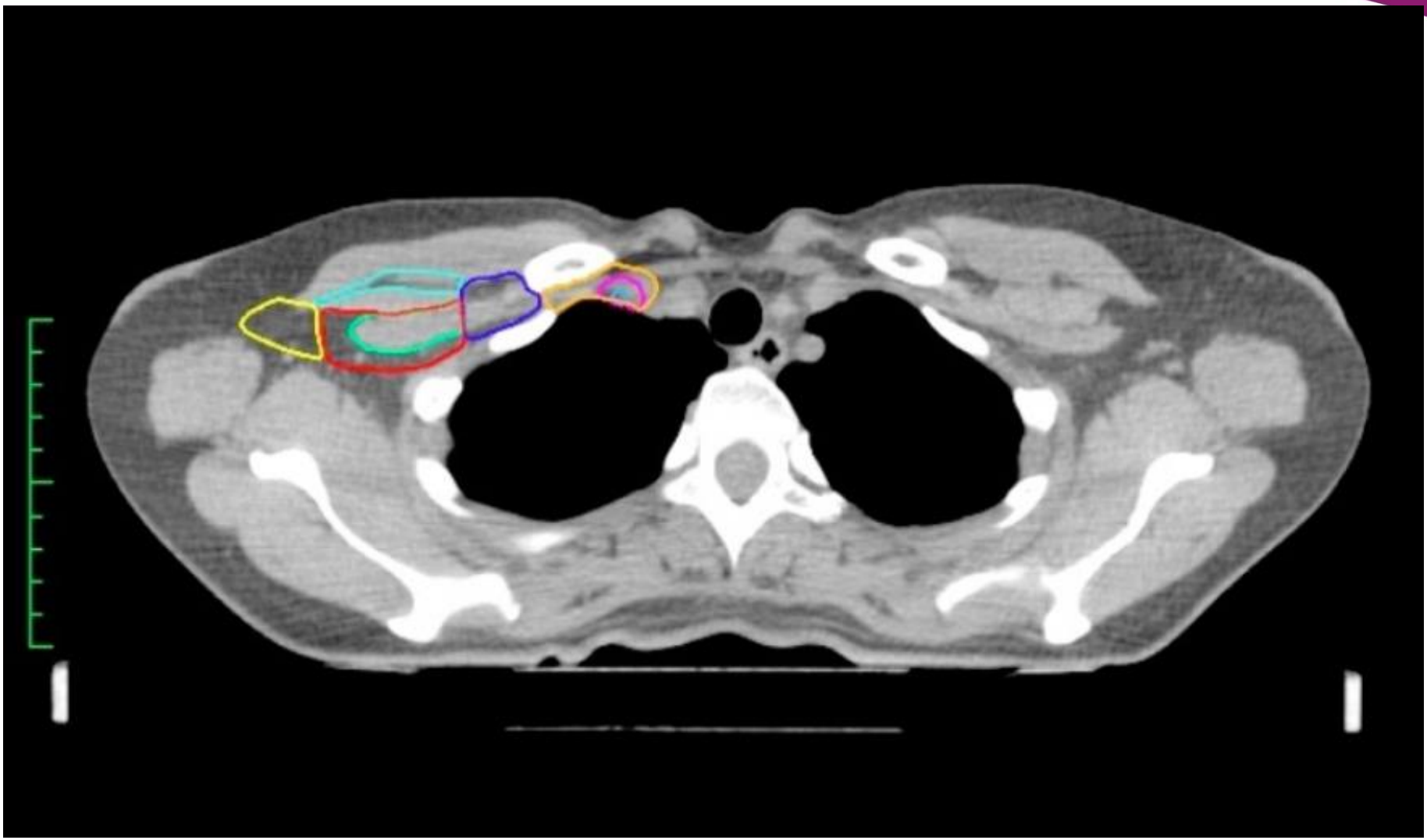
ESTRO School

CTVn_L3 = dark blue

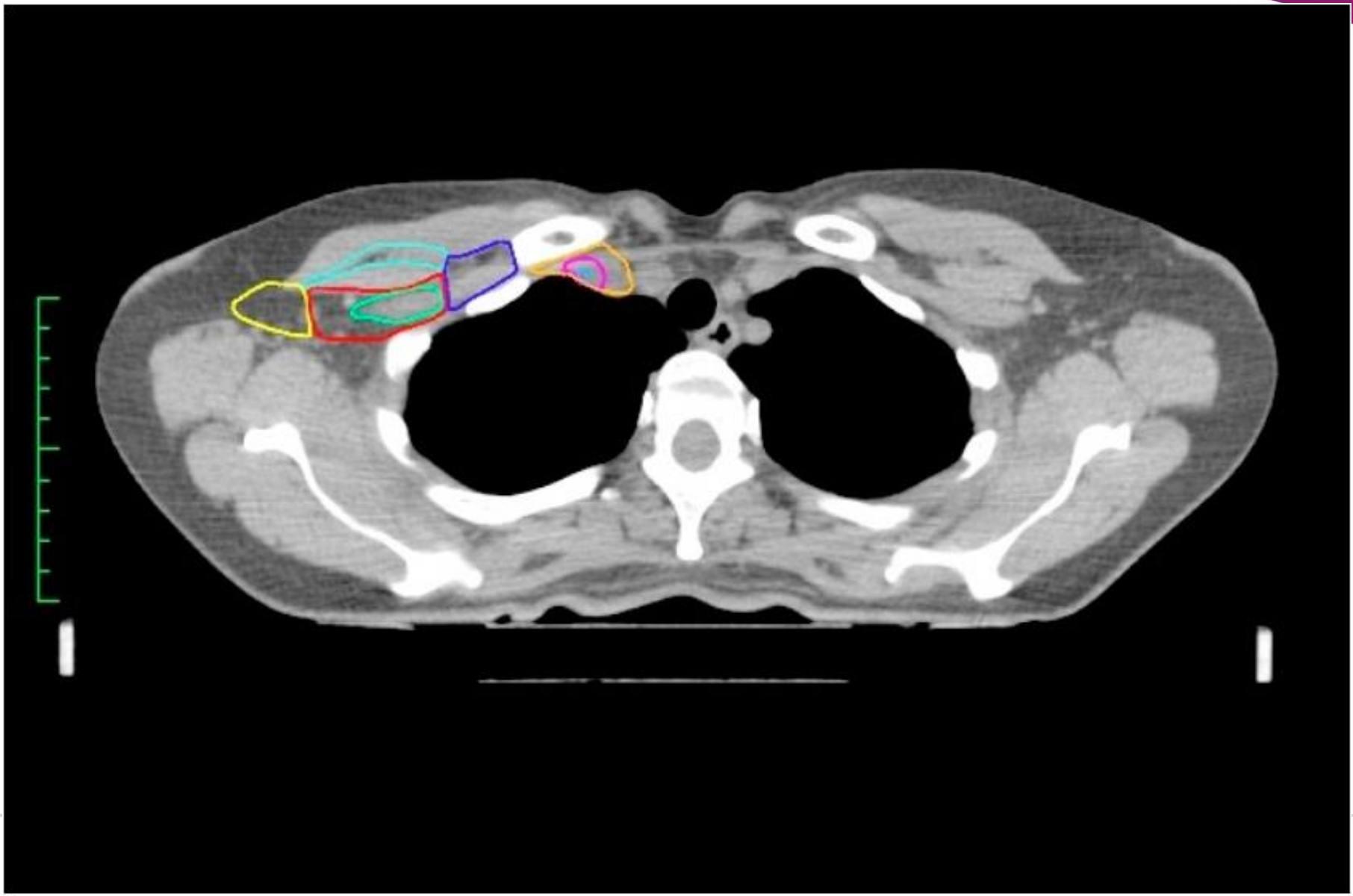
CTVn_L3 = dark blue



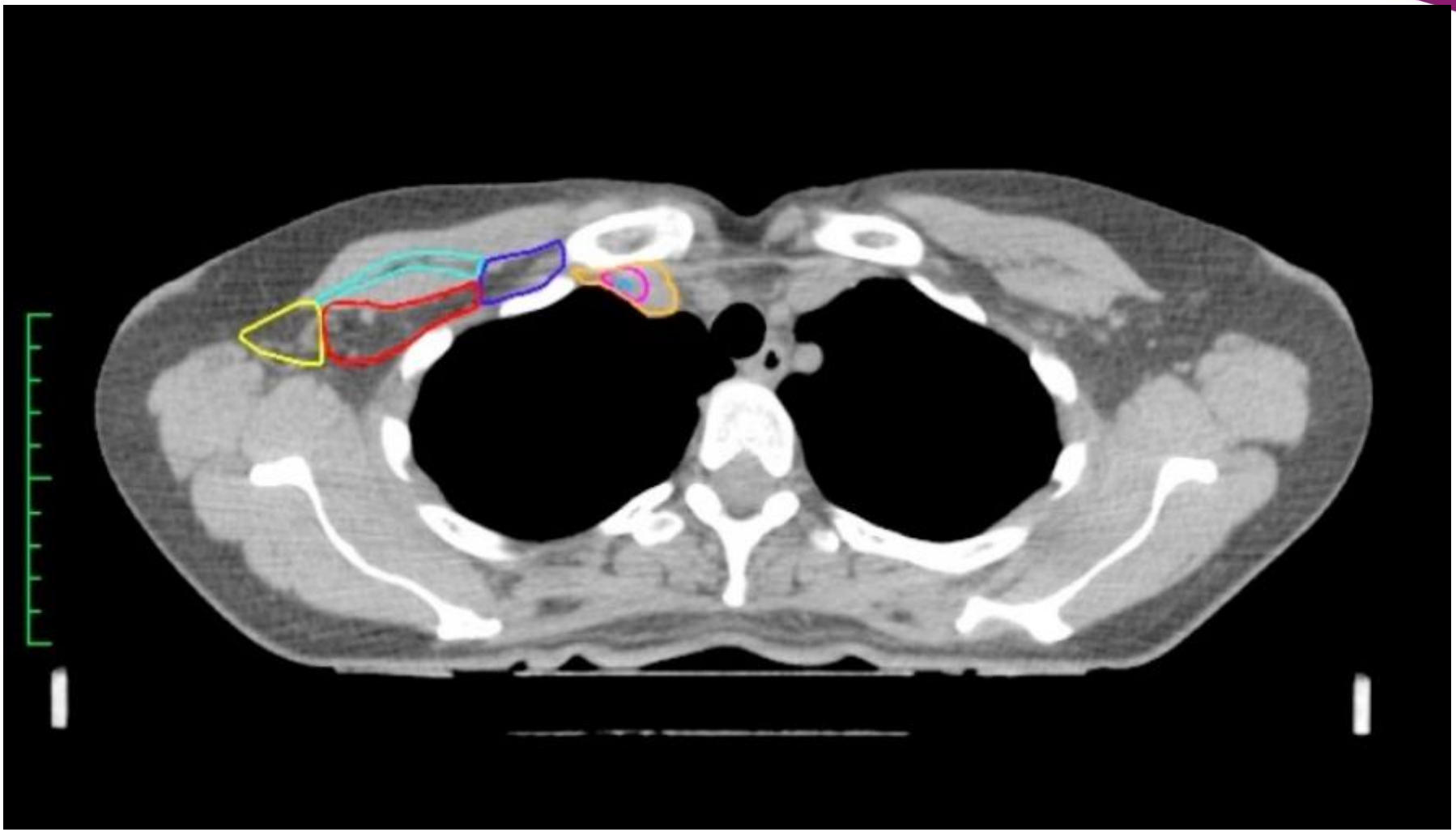
CTVn_L3 = dark blue



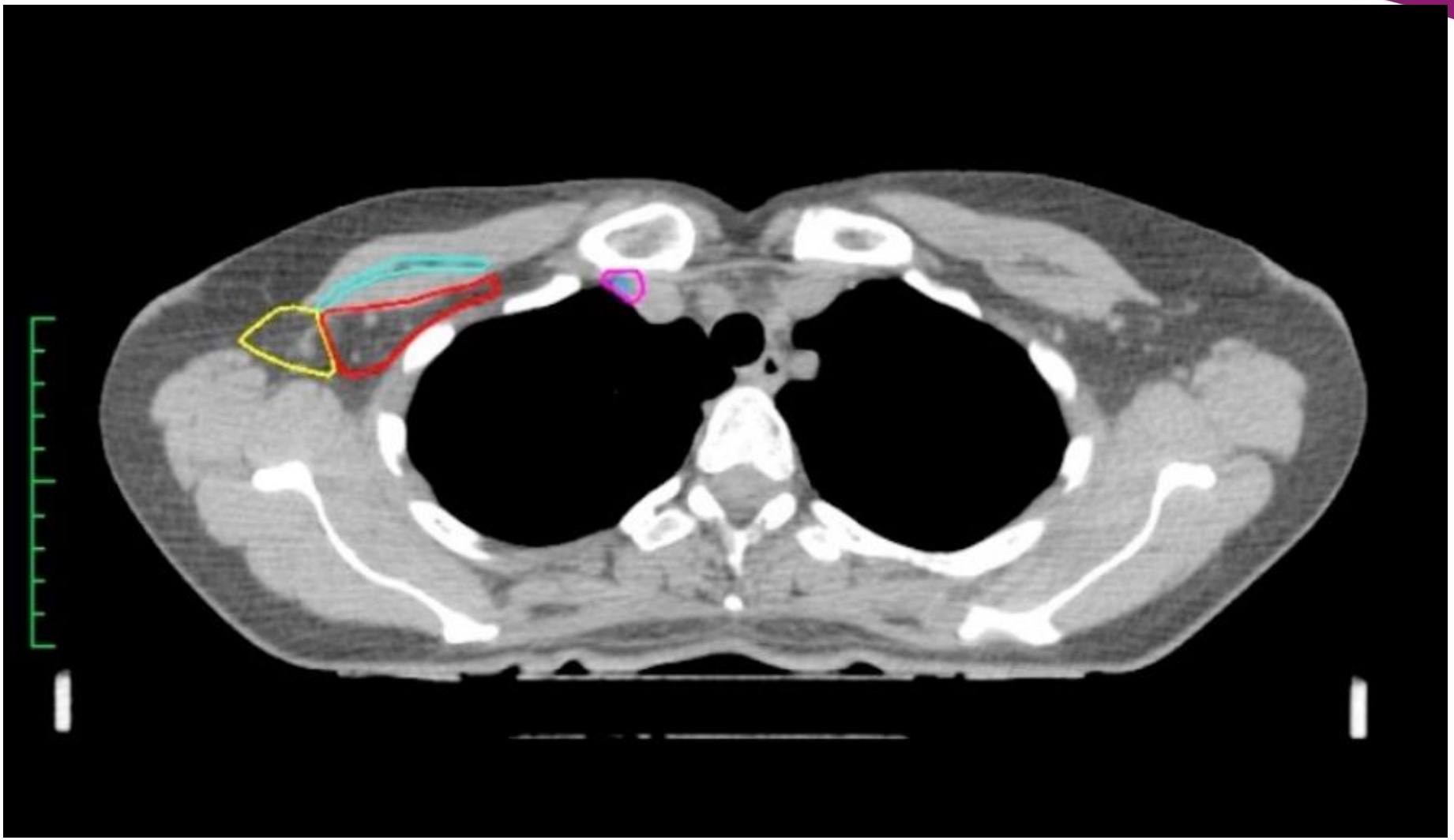
CTVn_L3 = dark blue



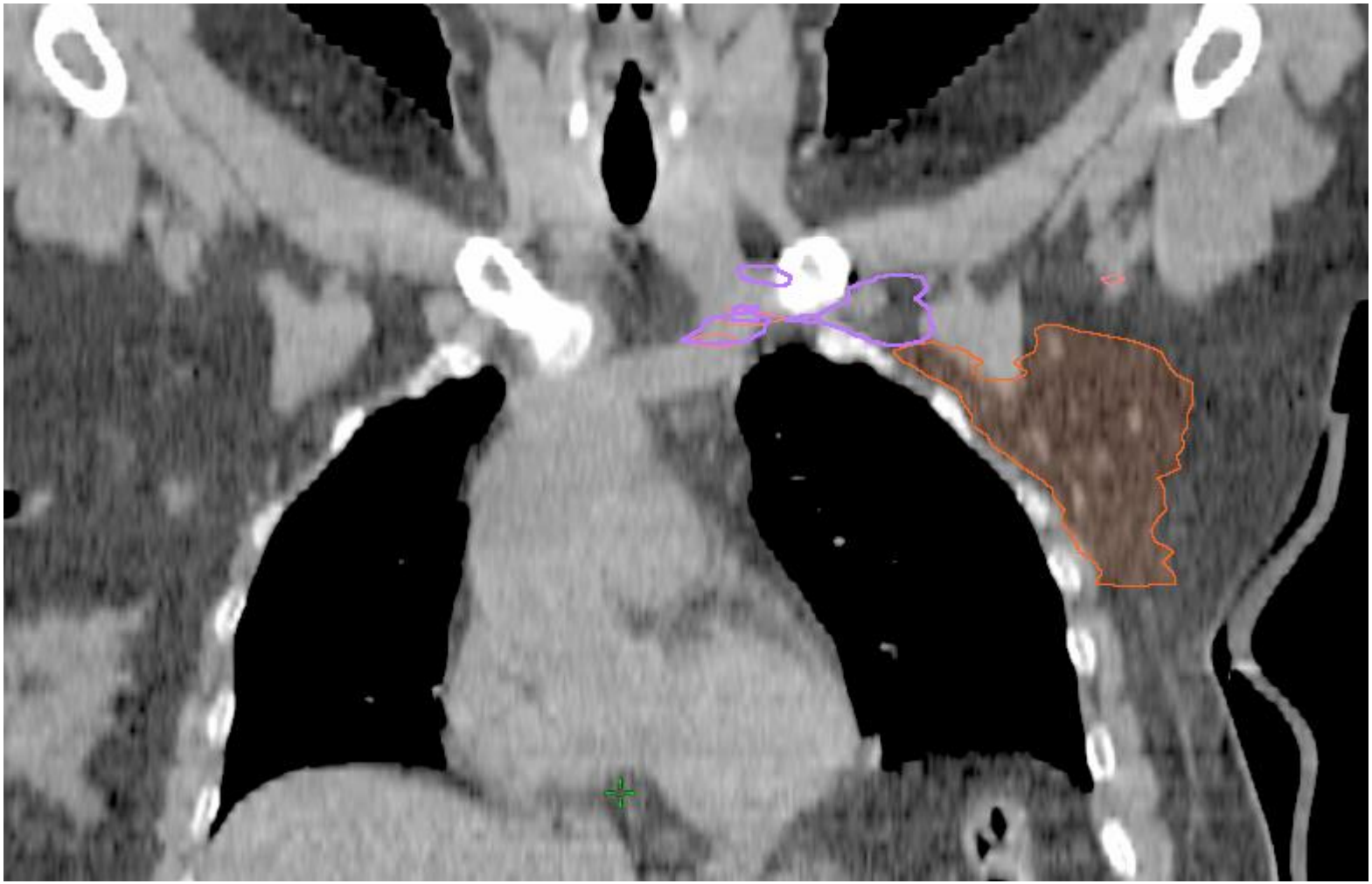
CTVn_L3 = dark blue



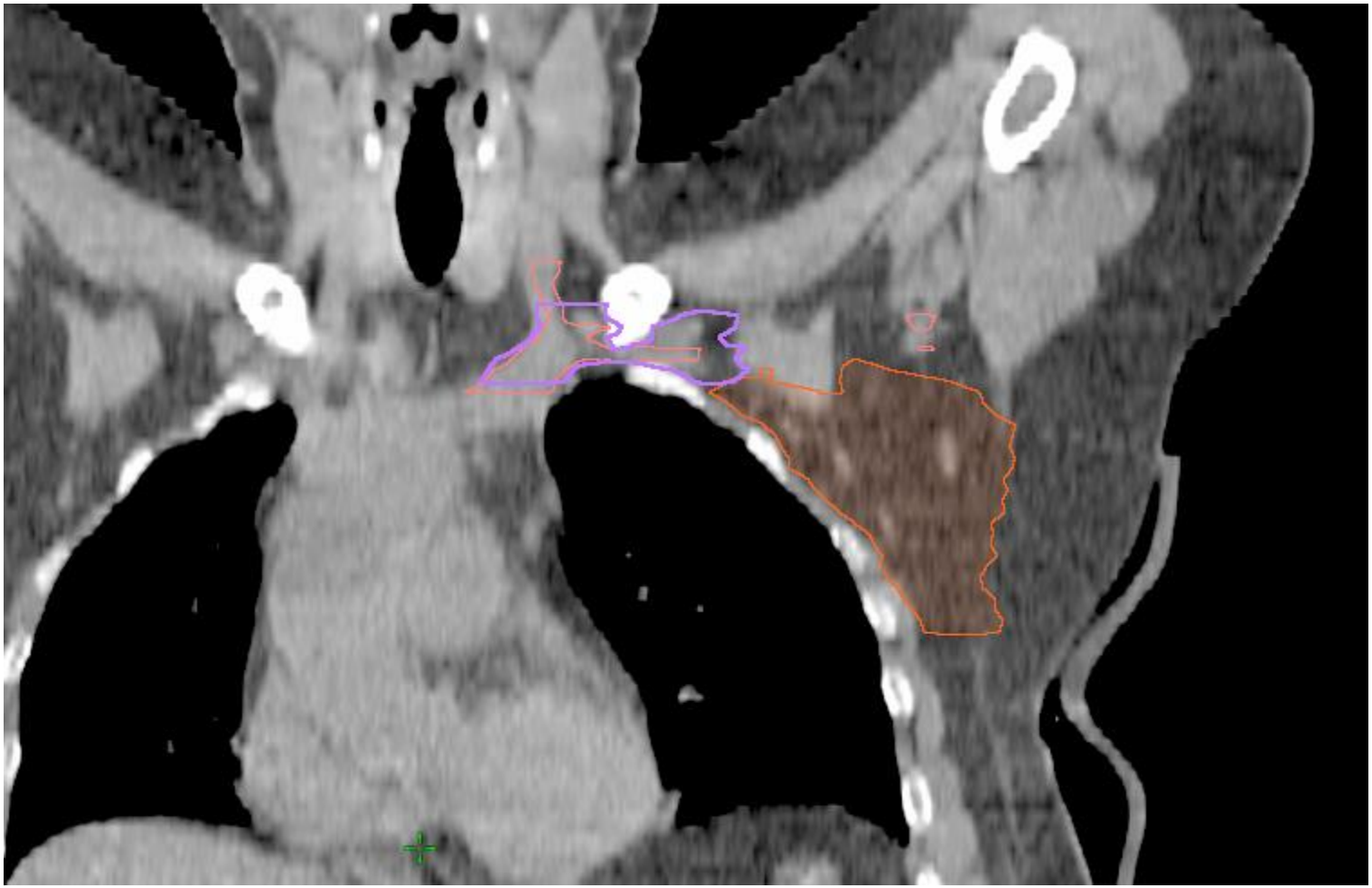
CTVn_L3 = dark blue



Coronal view of Level 3 and 4

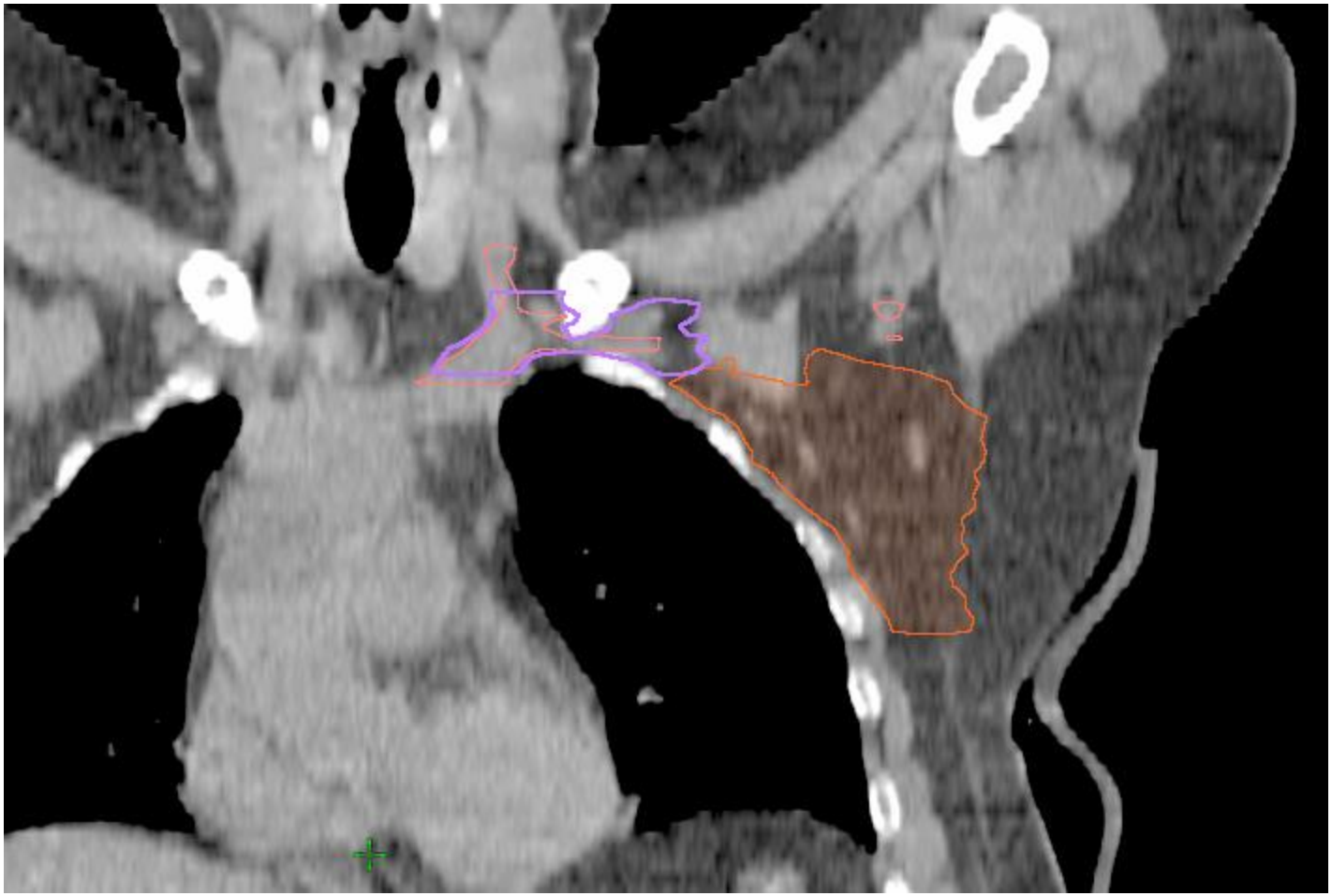


Coronal view of Level 3 and 4



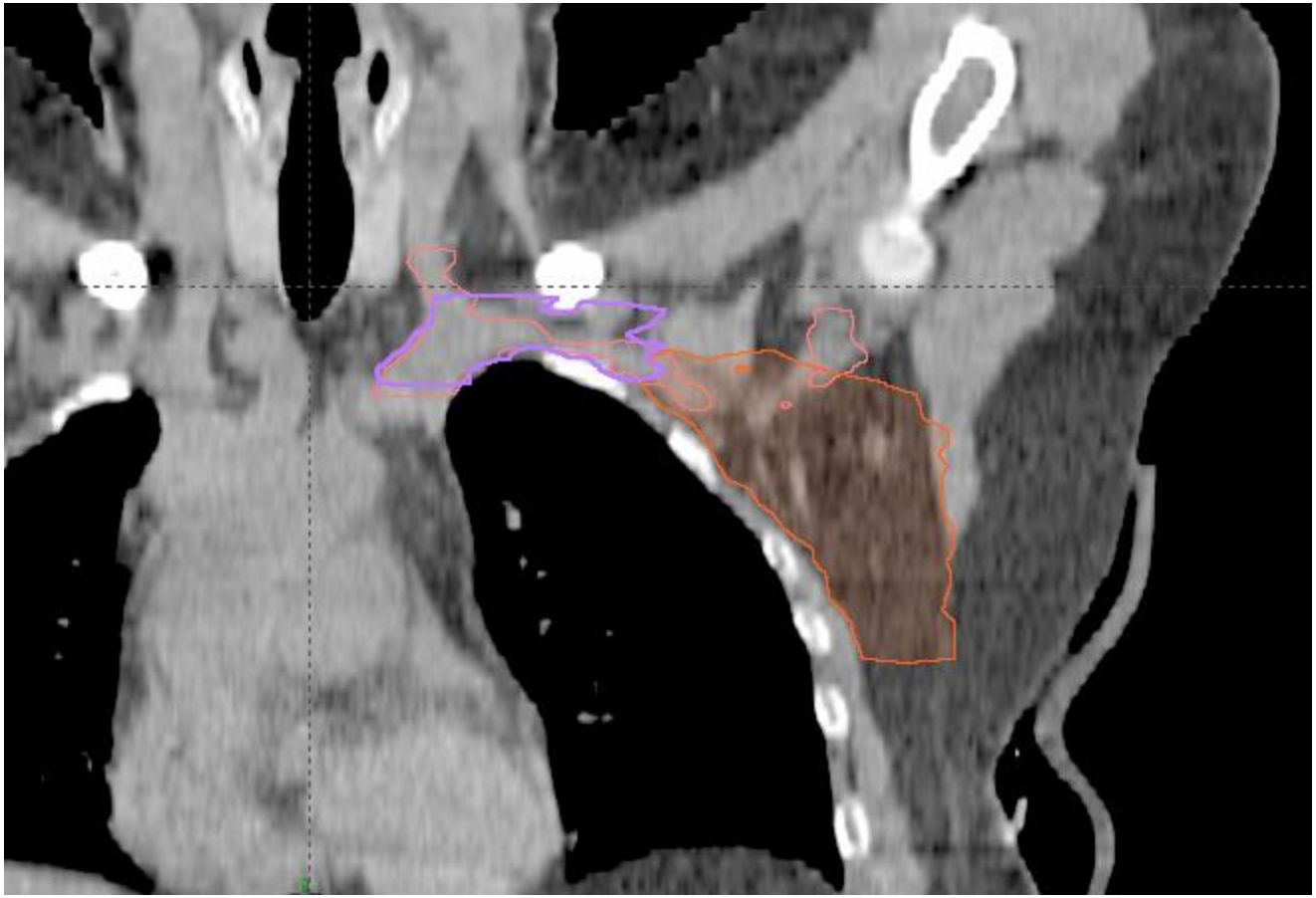
Coronal view of Level 3 and 4

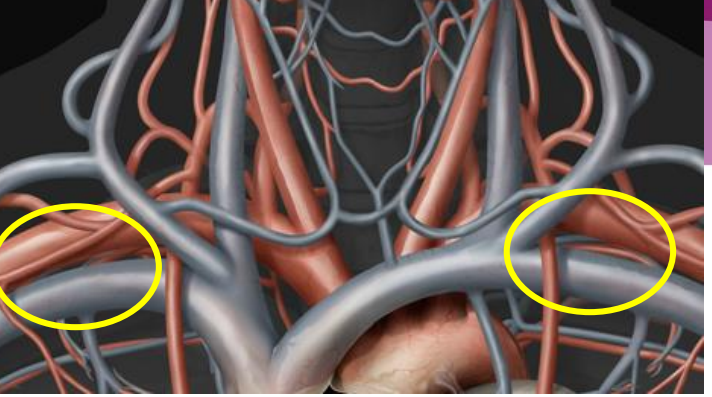
Coronal view of Level 3 and 4

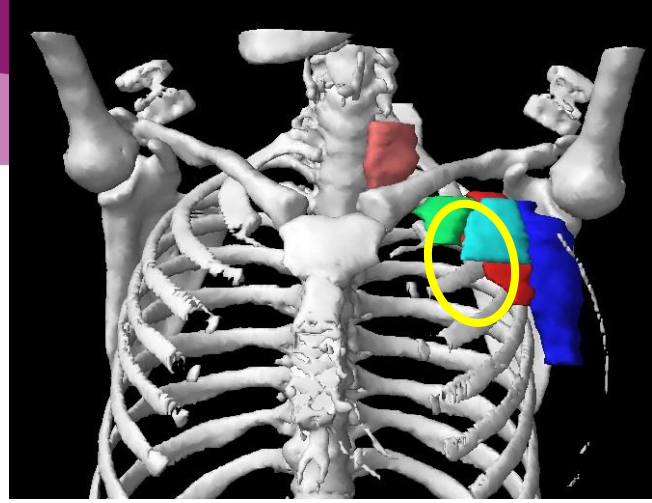


Coronal view of Level 3 and 4

Coronal view of Level 3 and 4

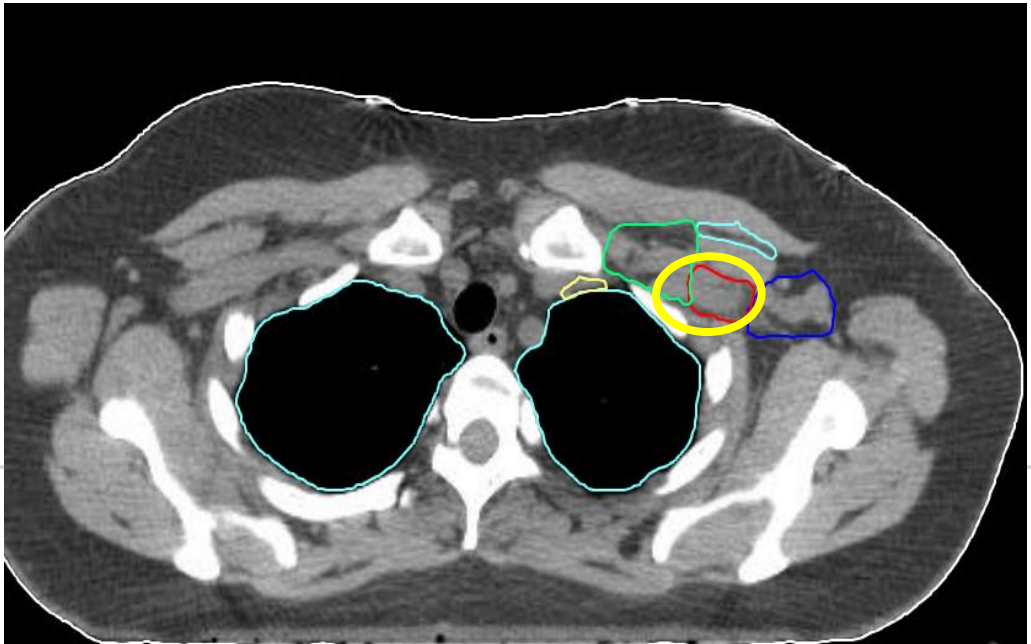




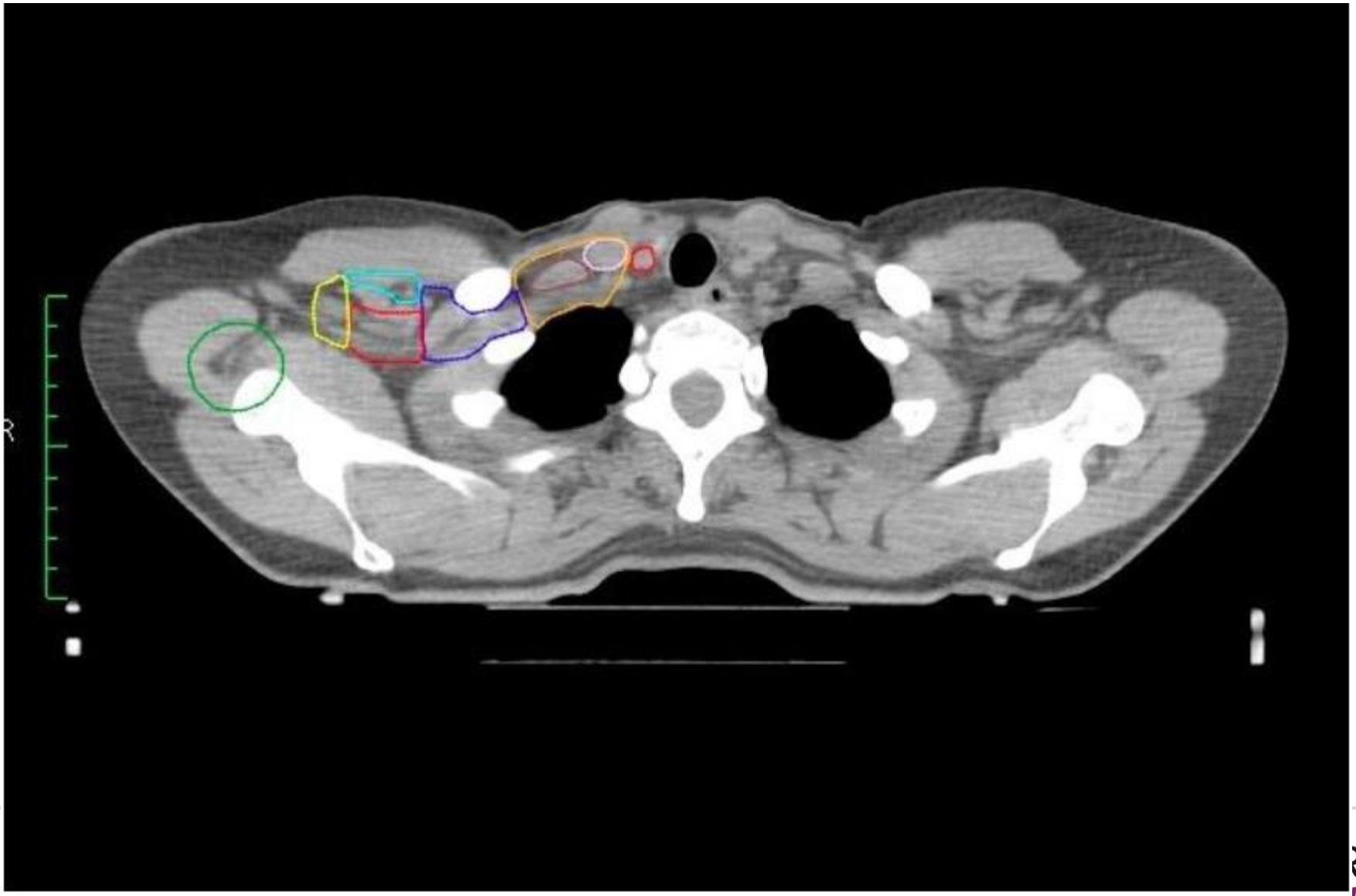


Axilla level 2 – CTVn_L2

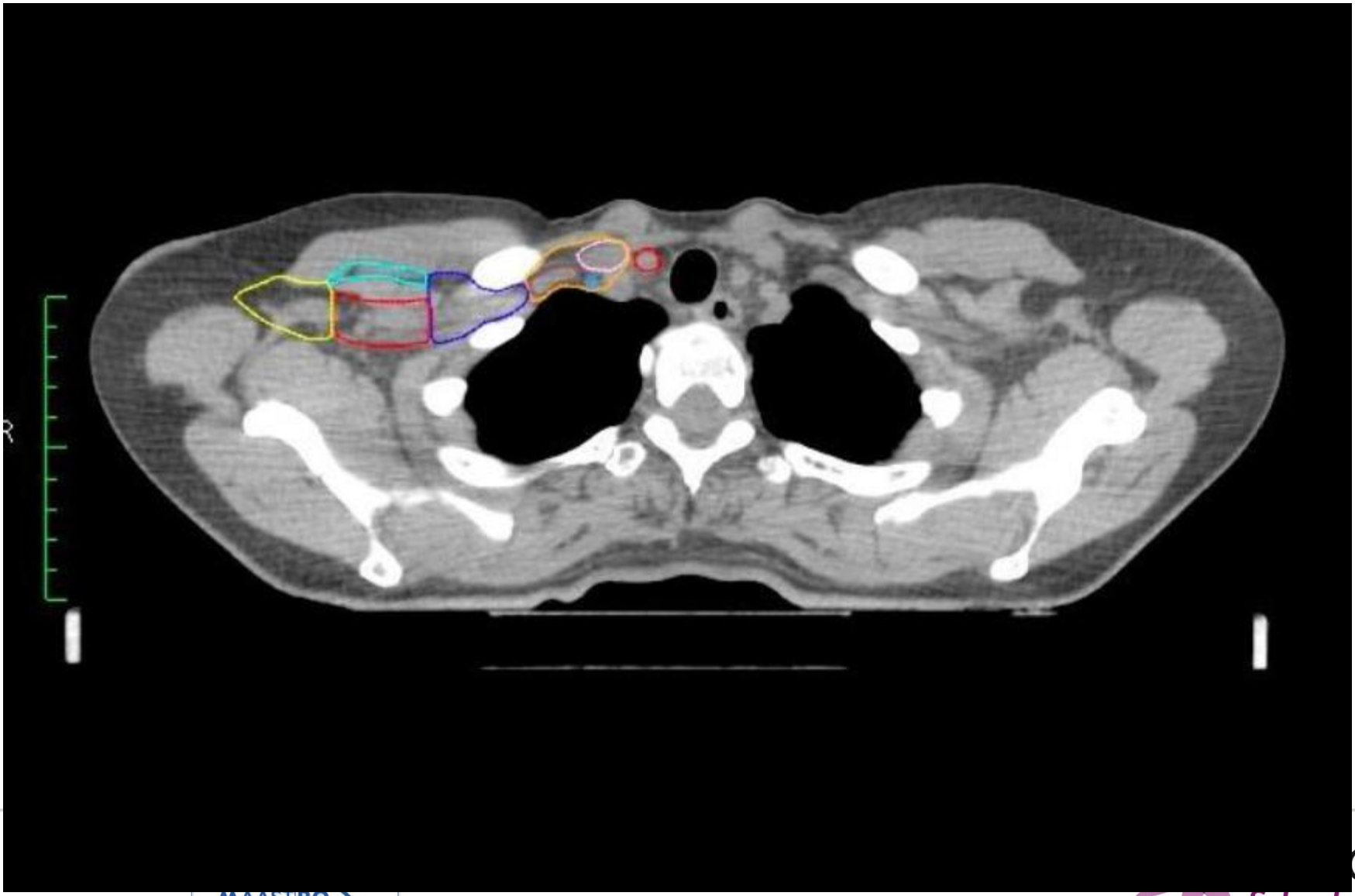
- ✓ In between levels 1 and 3
- ✓ Dorsal of minor pectoral muscle
- ✓ Cranial/Dorsal: 5 mm around axillary vein
- ✓ Caudal: dorsal of minor pectoral muscle



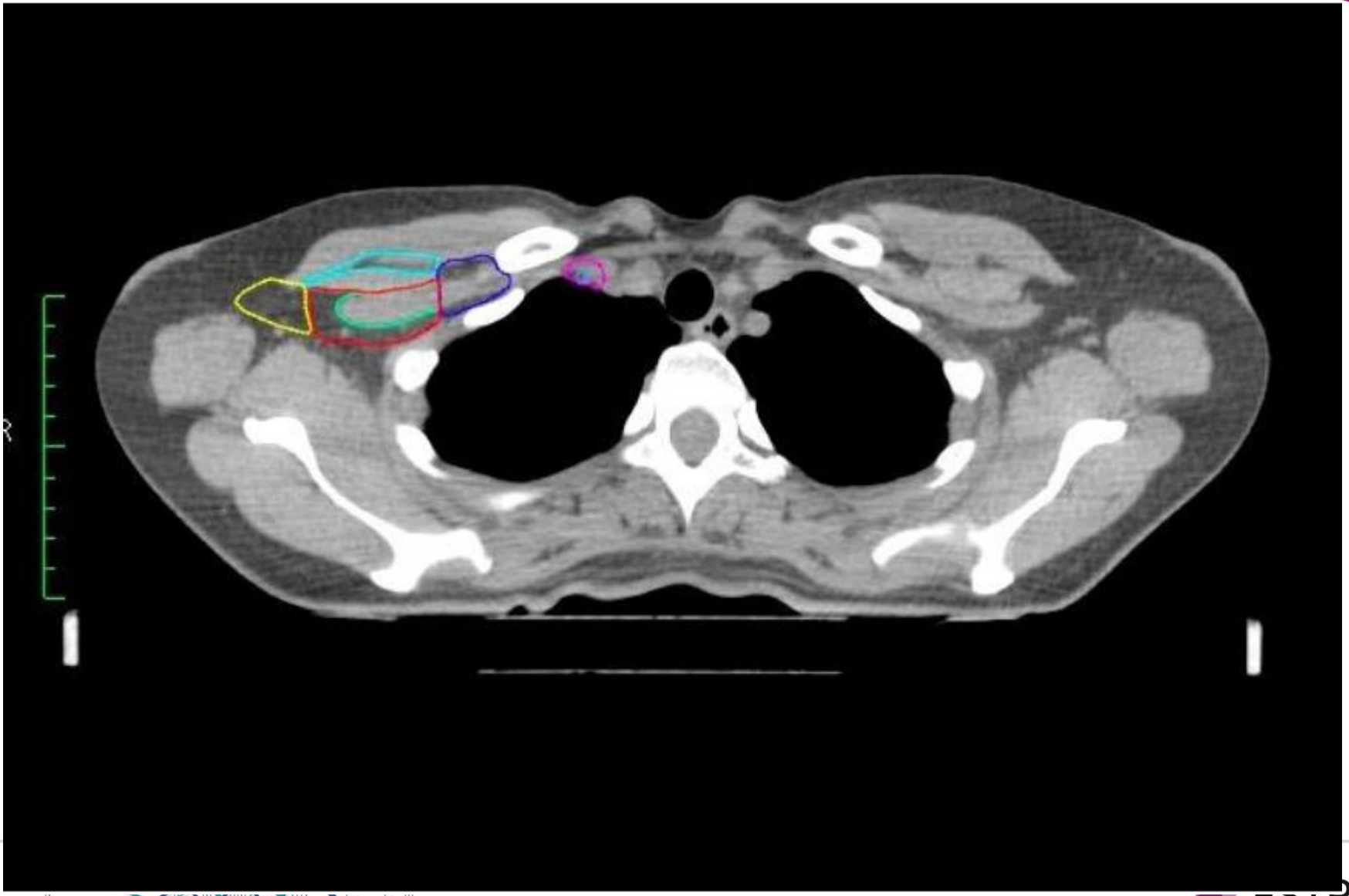
CTVn_L2 = red
Rotter/ Interpectoral nodes = light blue



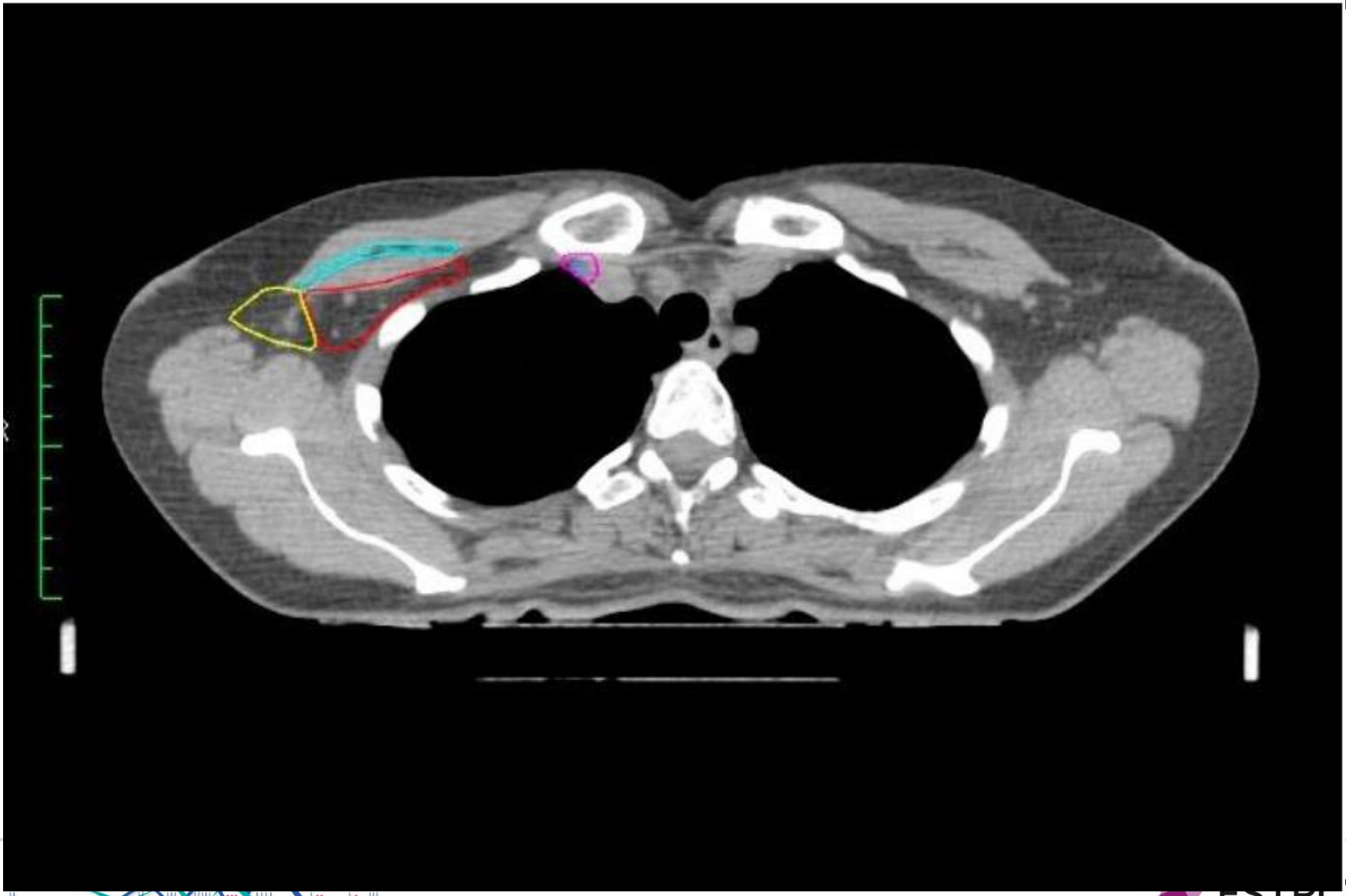
CTVn_L2 = red
Rotter/ Interpectoral nodes = light blue



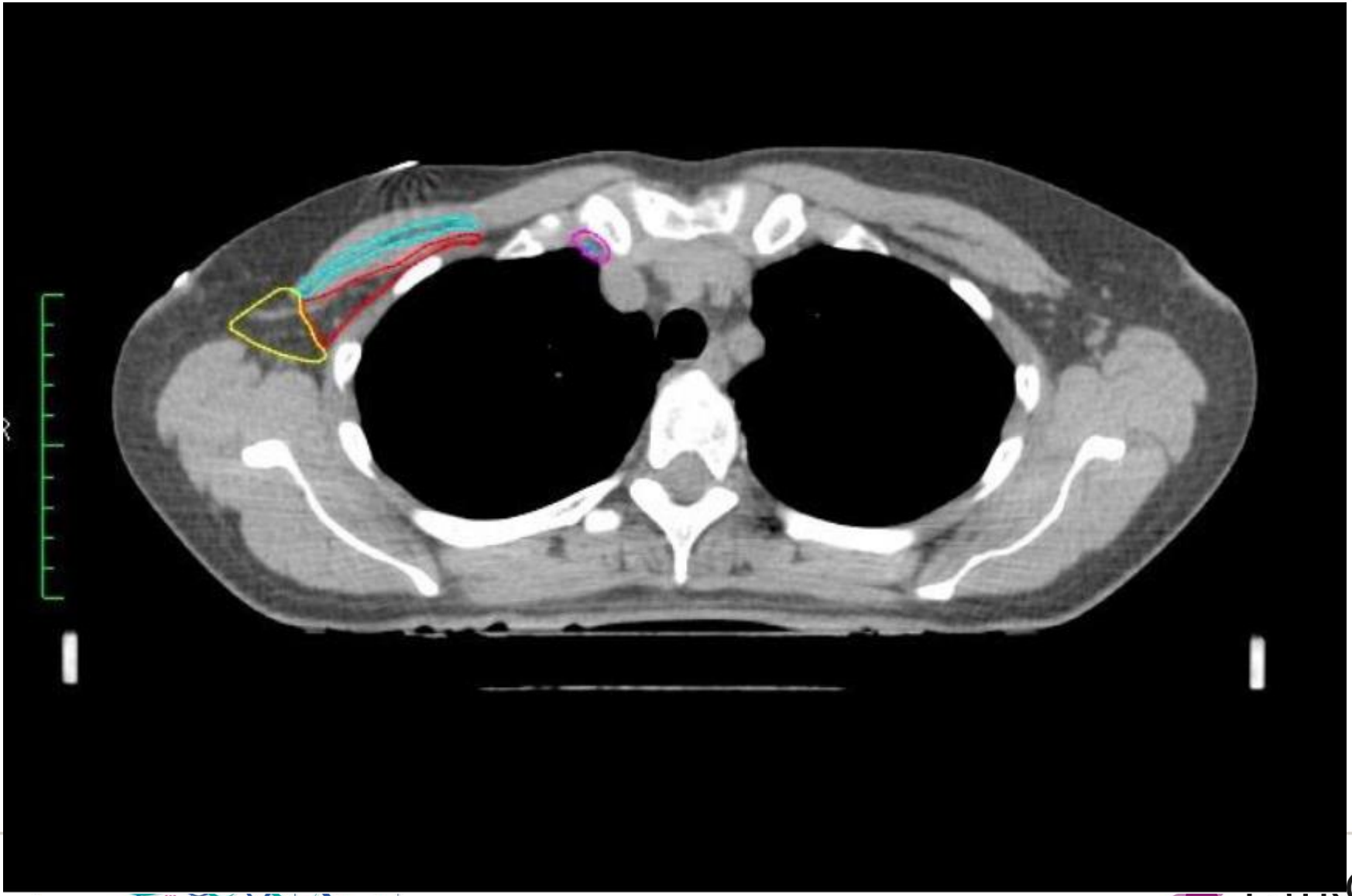
CTVn_L2 = red
Rotter/ Interpectoral nodes = light blue



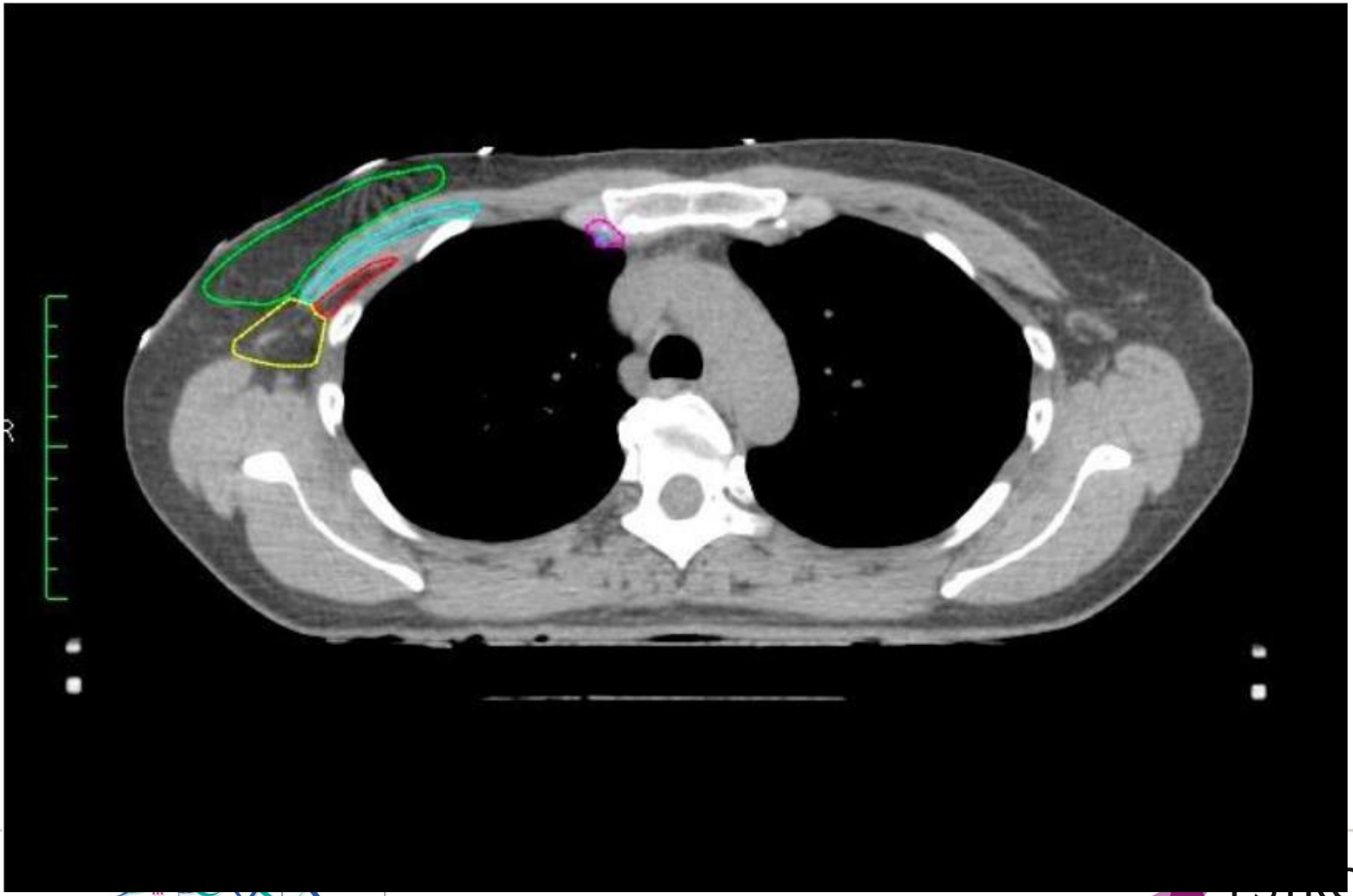
CTVn_L2 = red
Rotter/ Interpectoral nodes = light blue



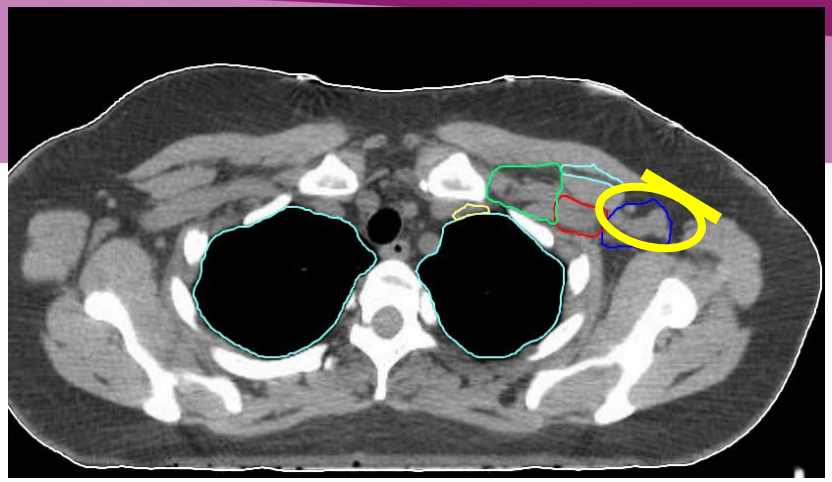
CTVn_L2 = red
Rotter/ Interpectoral nodes = light blue

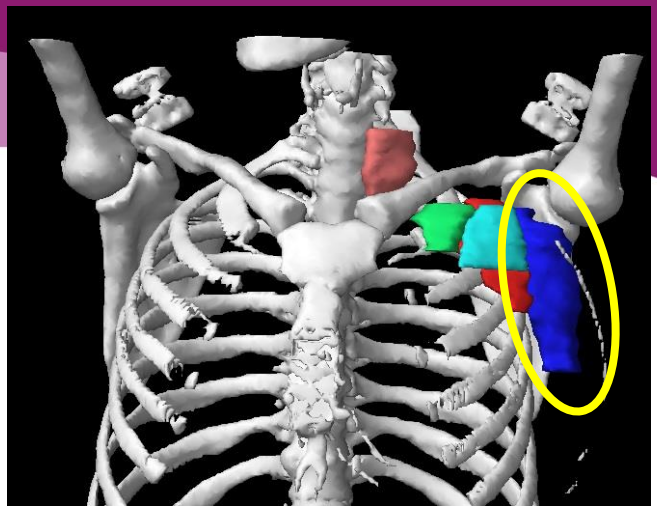


CTVn_L2 = red
Rotter/ Interpectoral nodes = light blue



CTVn_L2 = red
Rotter/ Interpectoral nodes = light blue



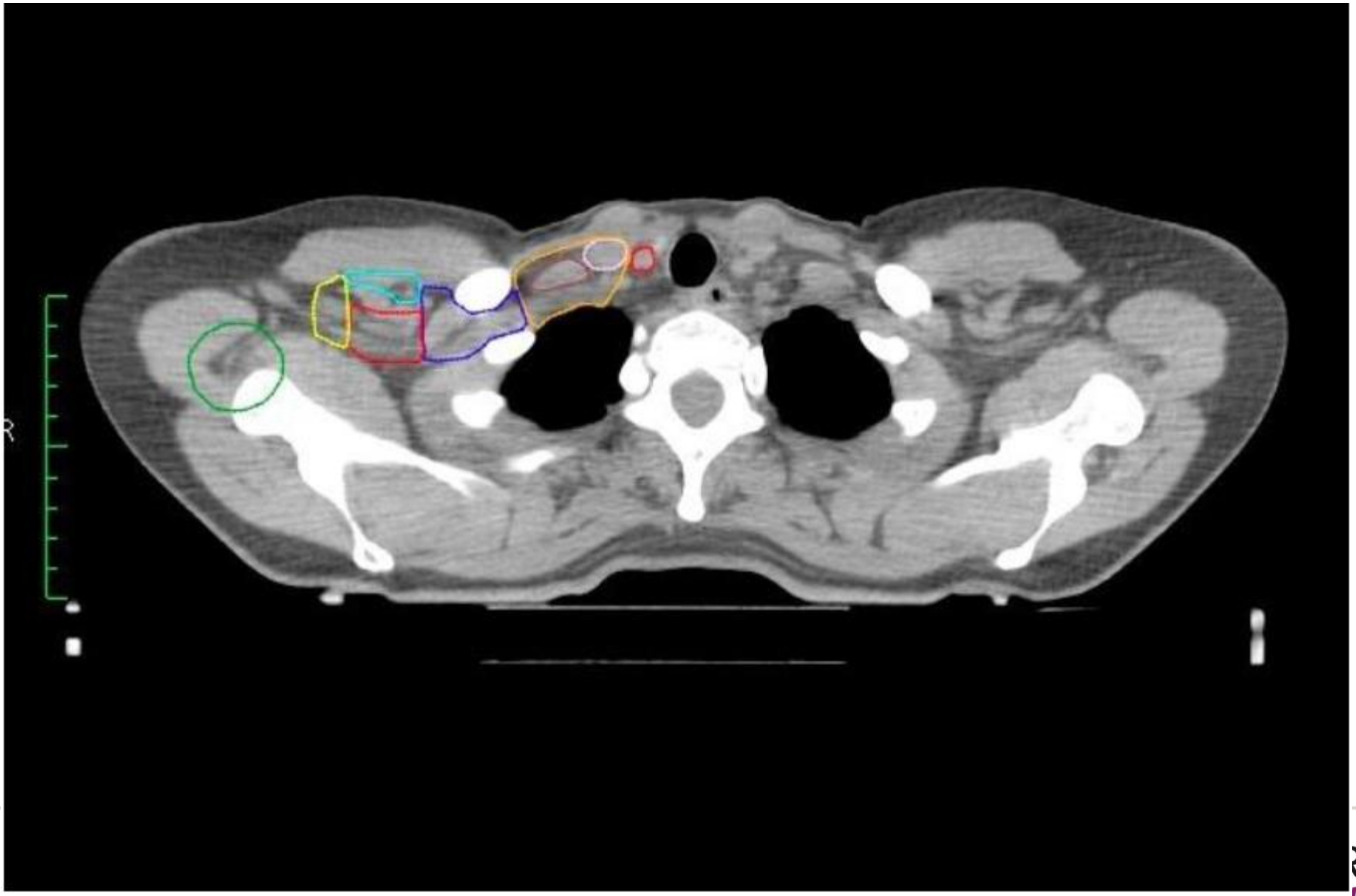


Axilla level 1- CTVn_L1:

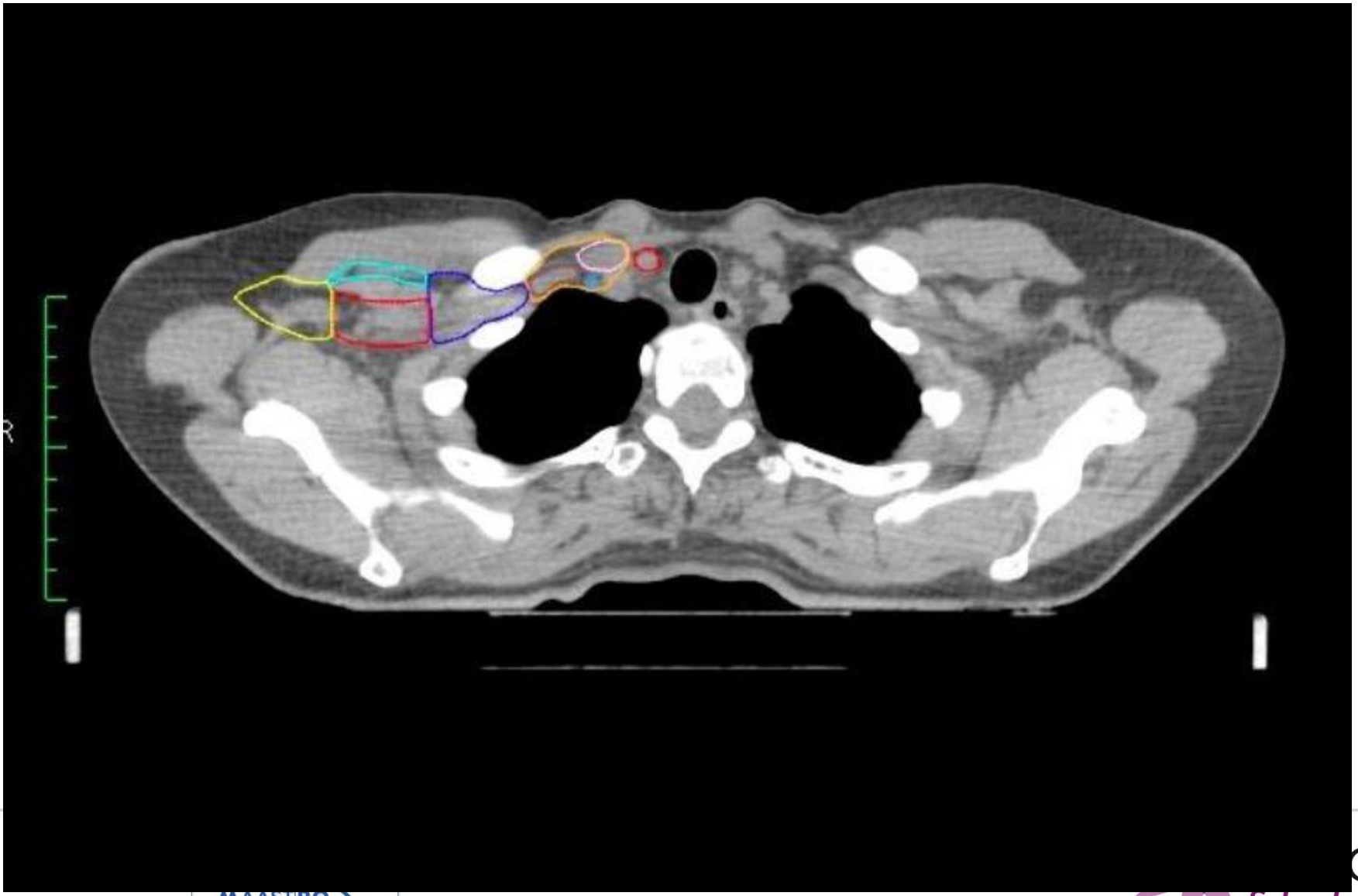
- ✓ General: use surgical effects to guide
- ✓ Cranio-medial: lateral limit of level 2/ interpectoral nodes
- ✓ Cranio-lateral: up to 1 cm below and following edge of caput humeri, OR where axillary vein crosses the minor pectoral muscle; 5mm around axillary vein
- ✓ Caudal border: between the level of ribs 4 – 5
- ✓ Lateral border: up to superficial part of muscles **(line)**
- ✓ Medial border: level 2 and thoracic wall
- ✓ Ventral border: pectoralis major & minor muscles
- ✓ Dorsal border: up to the posterior blood vessels

MAASTRO CLINIC

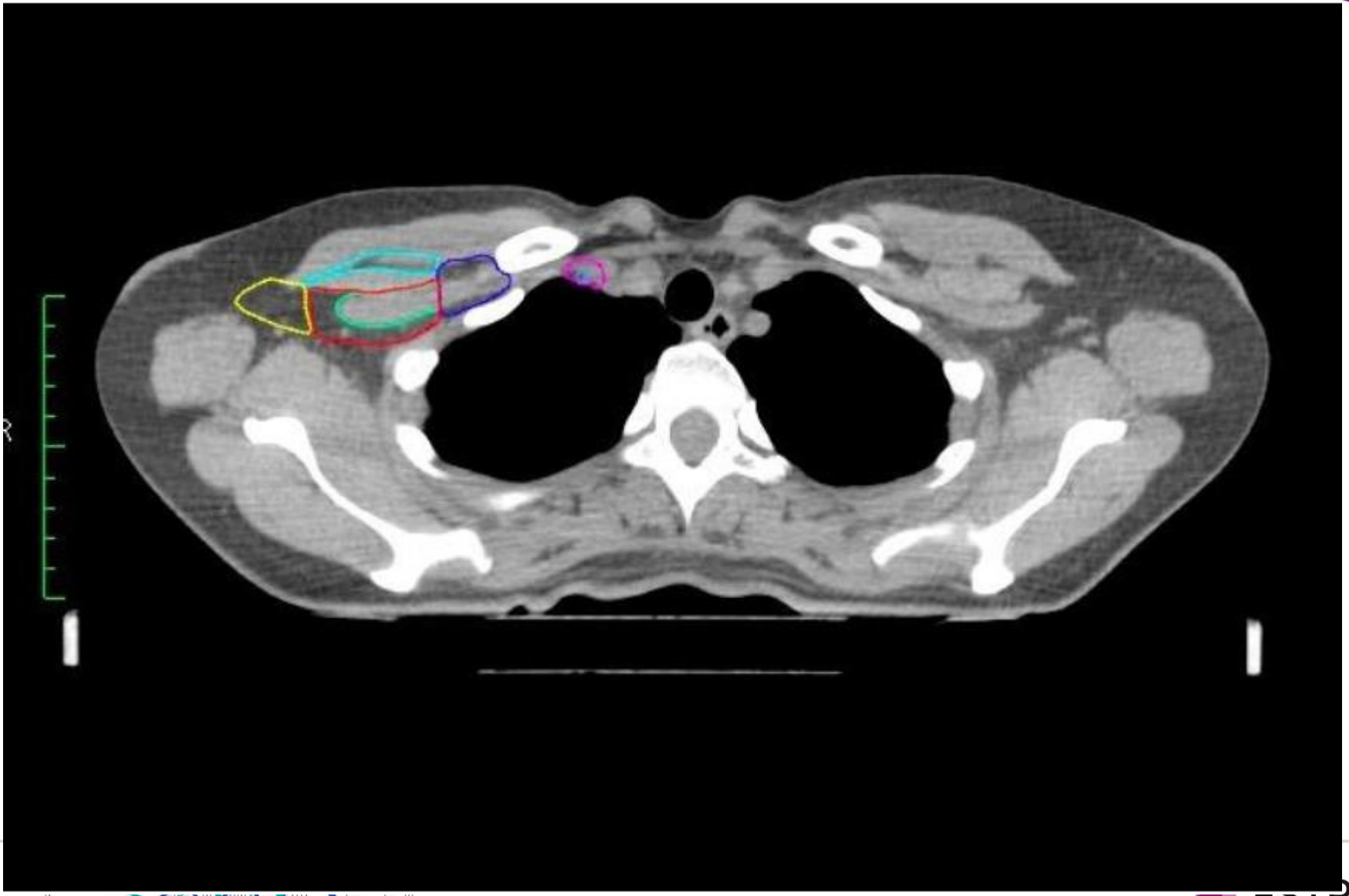
CTVn_L1 = yellow



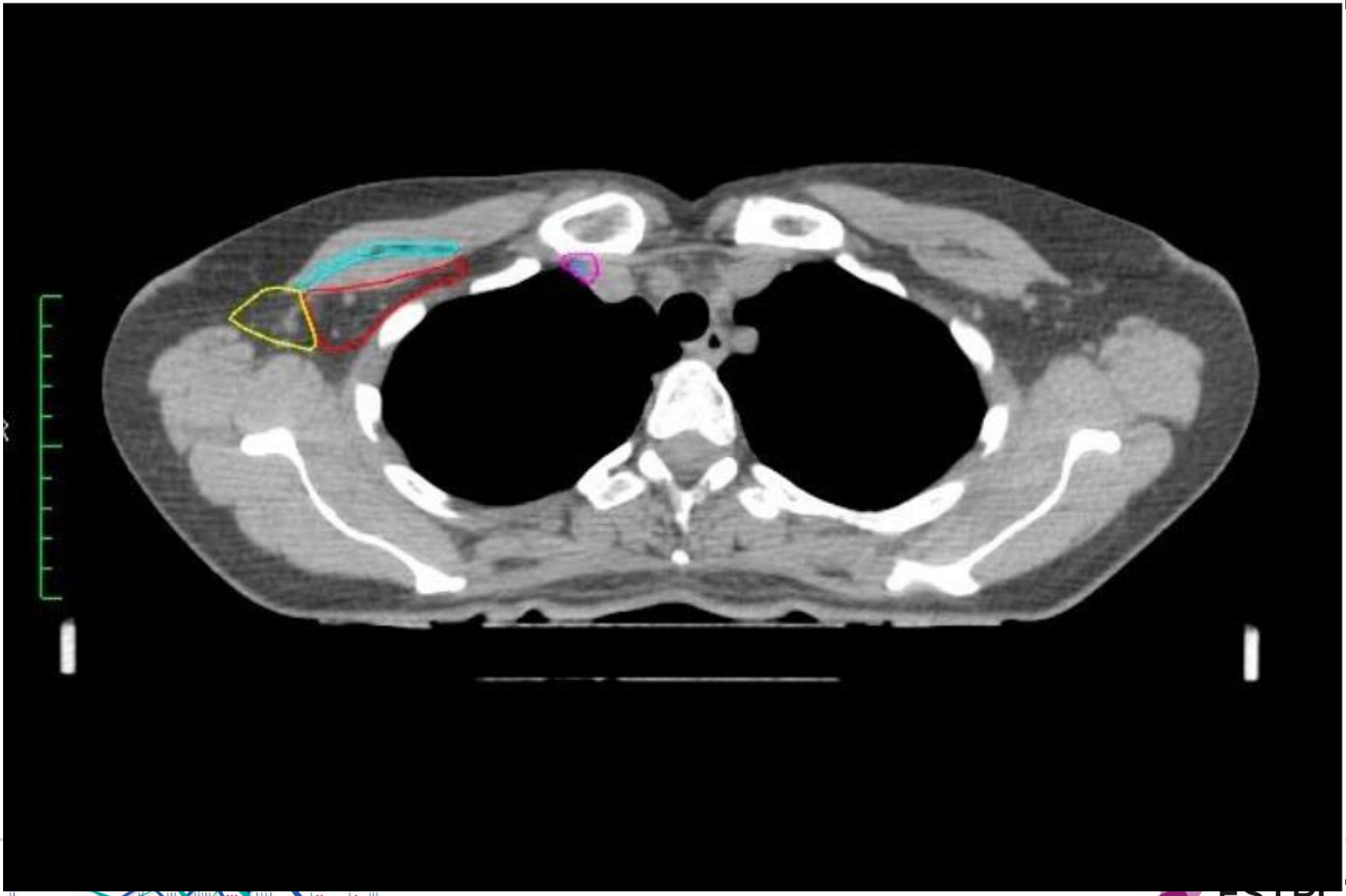
CTVn_L1 = yellow



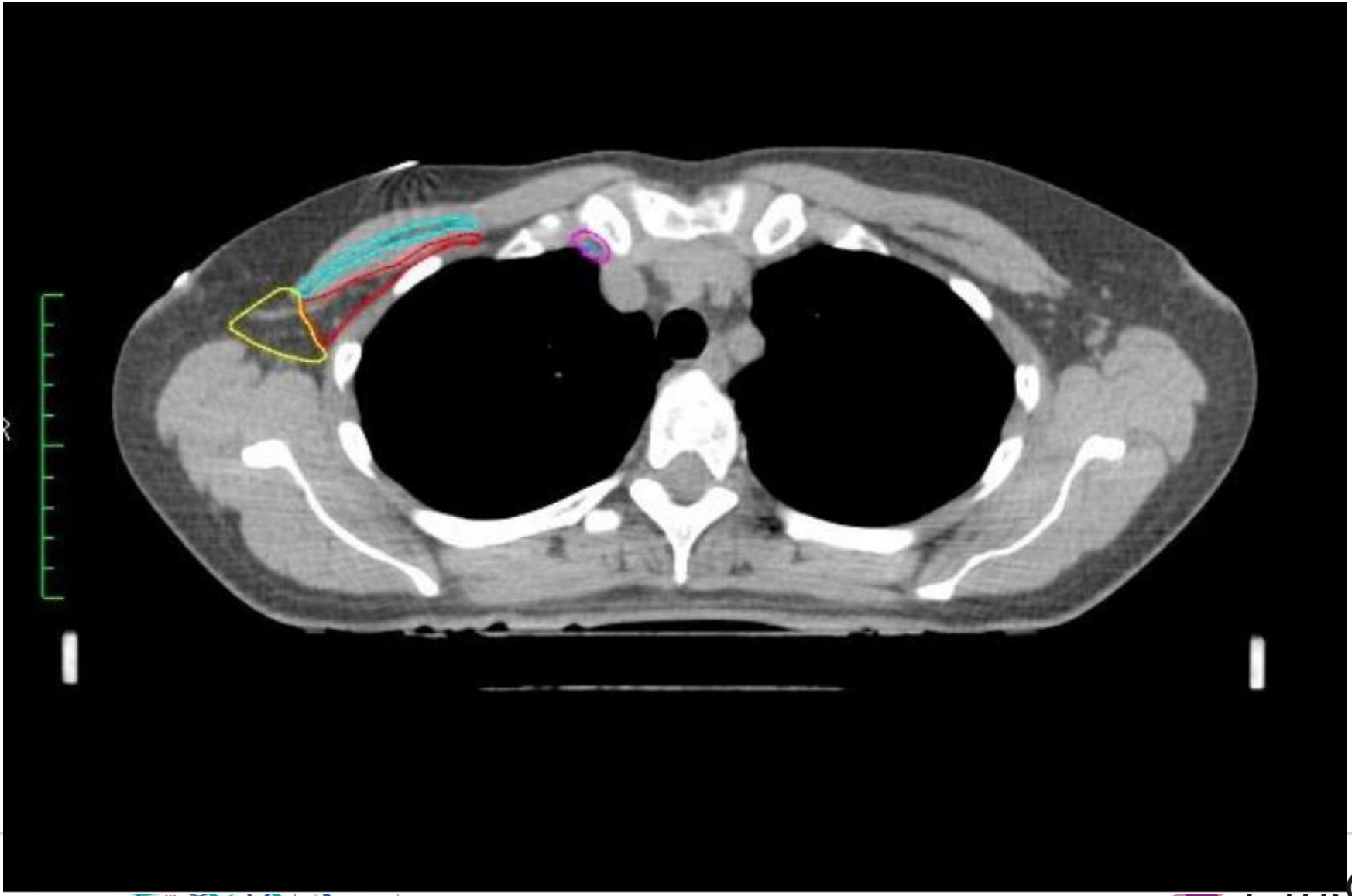
CTVn_L1 = yellow



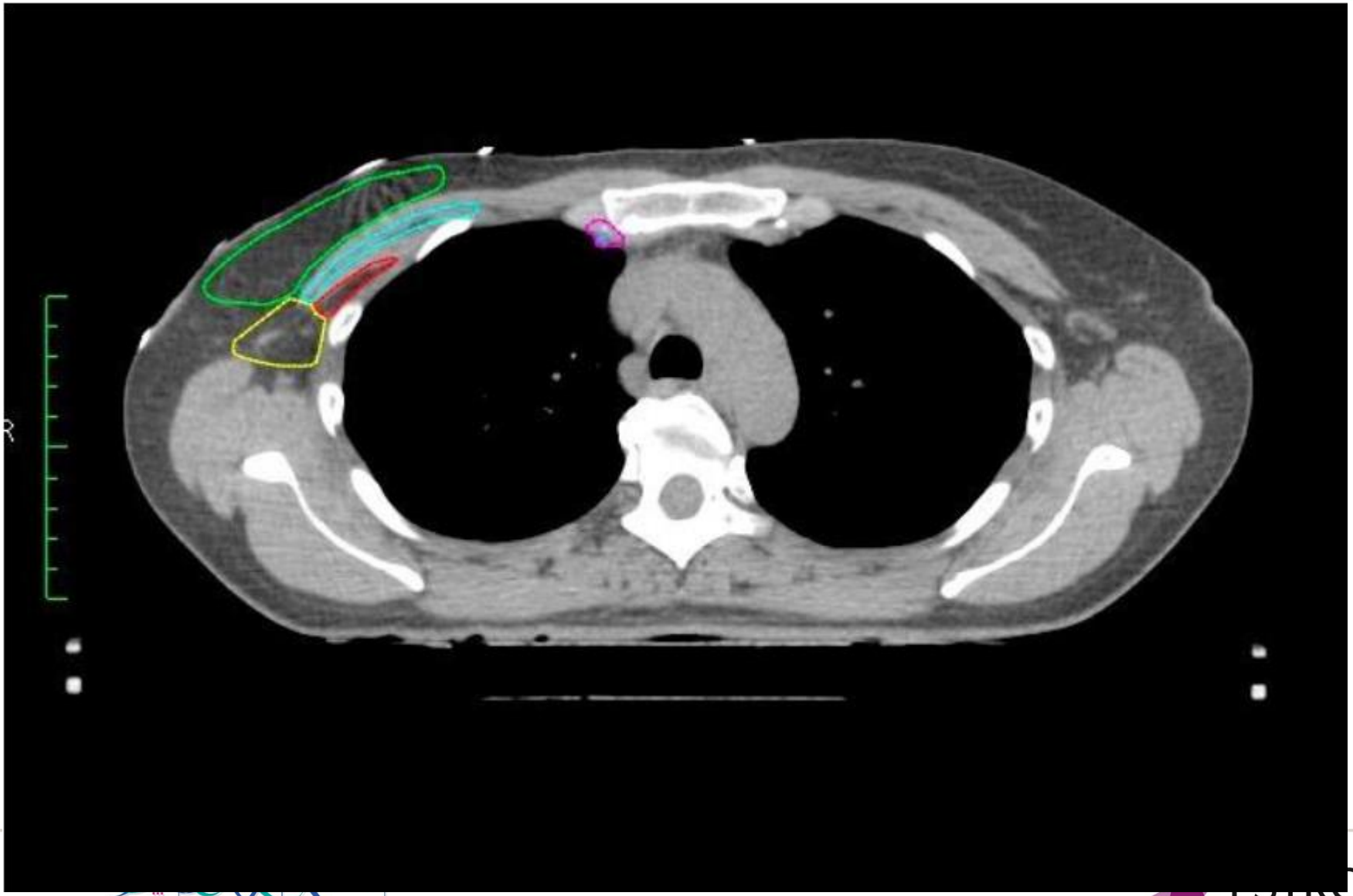
CTVn_L1 = yellow



CTVn_L1 = yellow



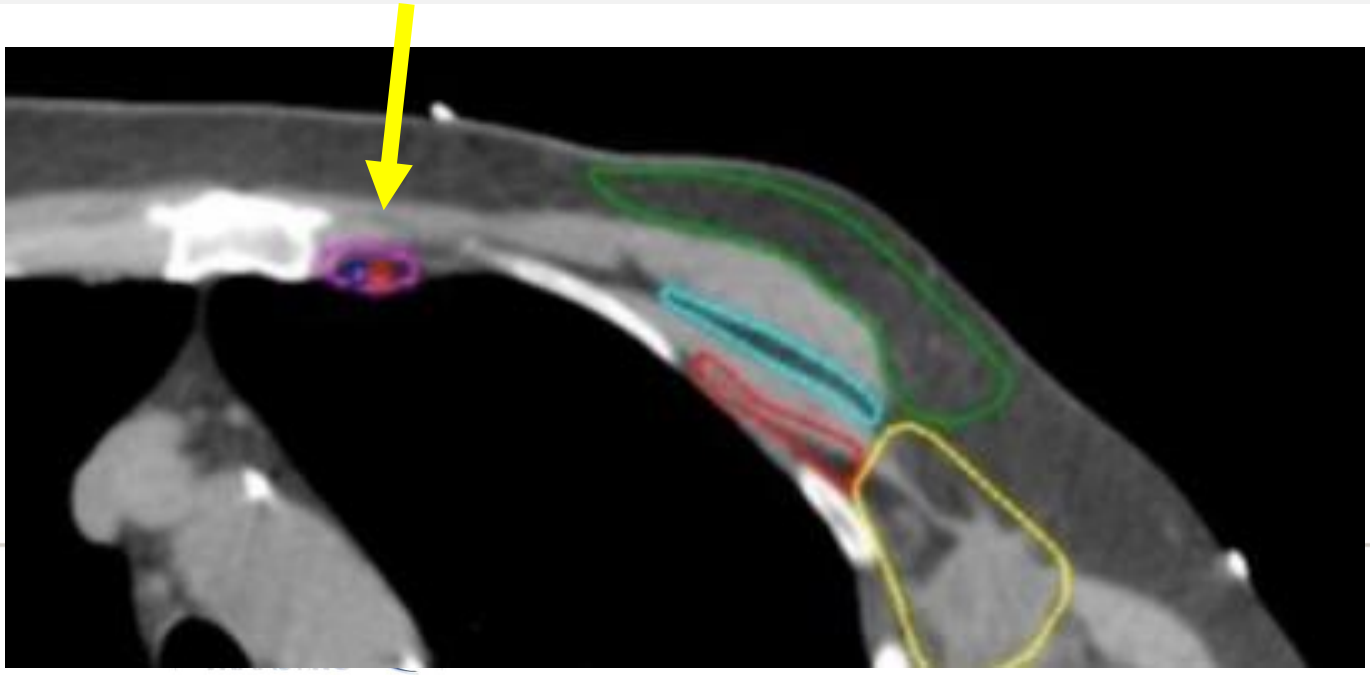
CTVn_L1 = yellow



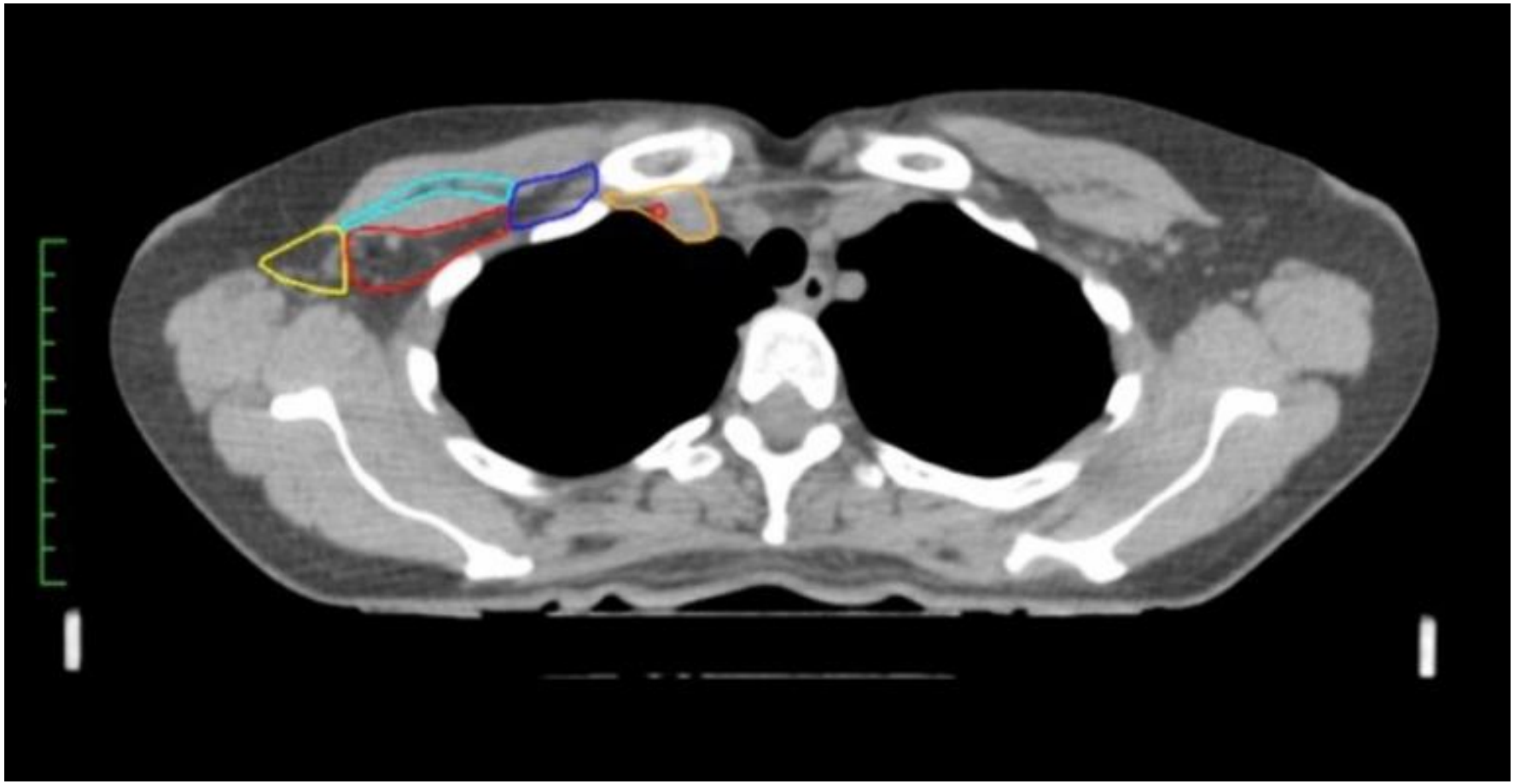
CTVn_L1 = yellow

CTV of internal mammary lymph node area

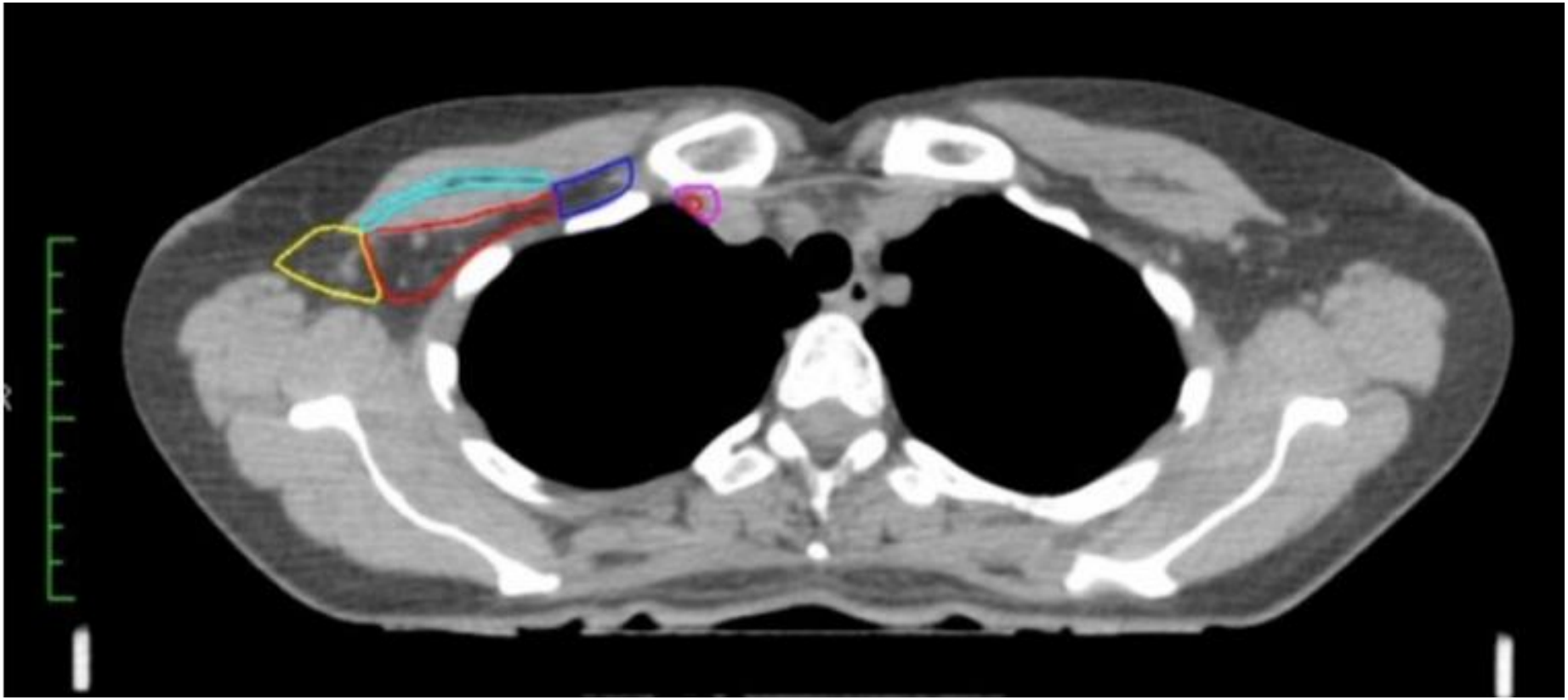
- ✓ Cranial: junction of subclavian and internal jugular veins → *L4*
- ✓ Caudal: superior side of the 4th rib
- ✓ Ventral: anterior limit of the vascular area
- ✓ Medial: 5 mm medial of vessels; edge of the sternal bone
- ✓ Dorsal: pleura
- ✓ Lateral: 5 mm lateral of vessels



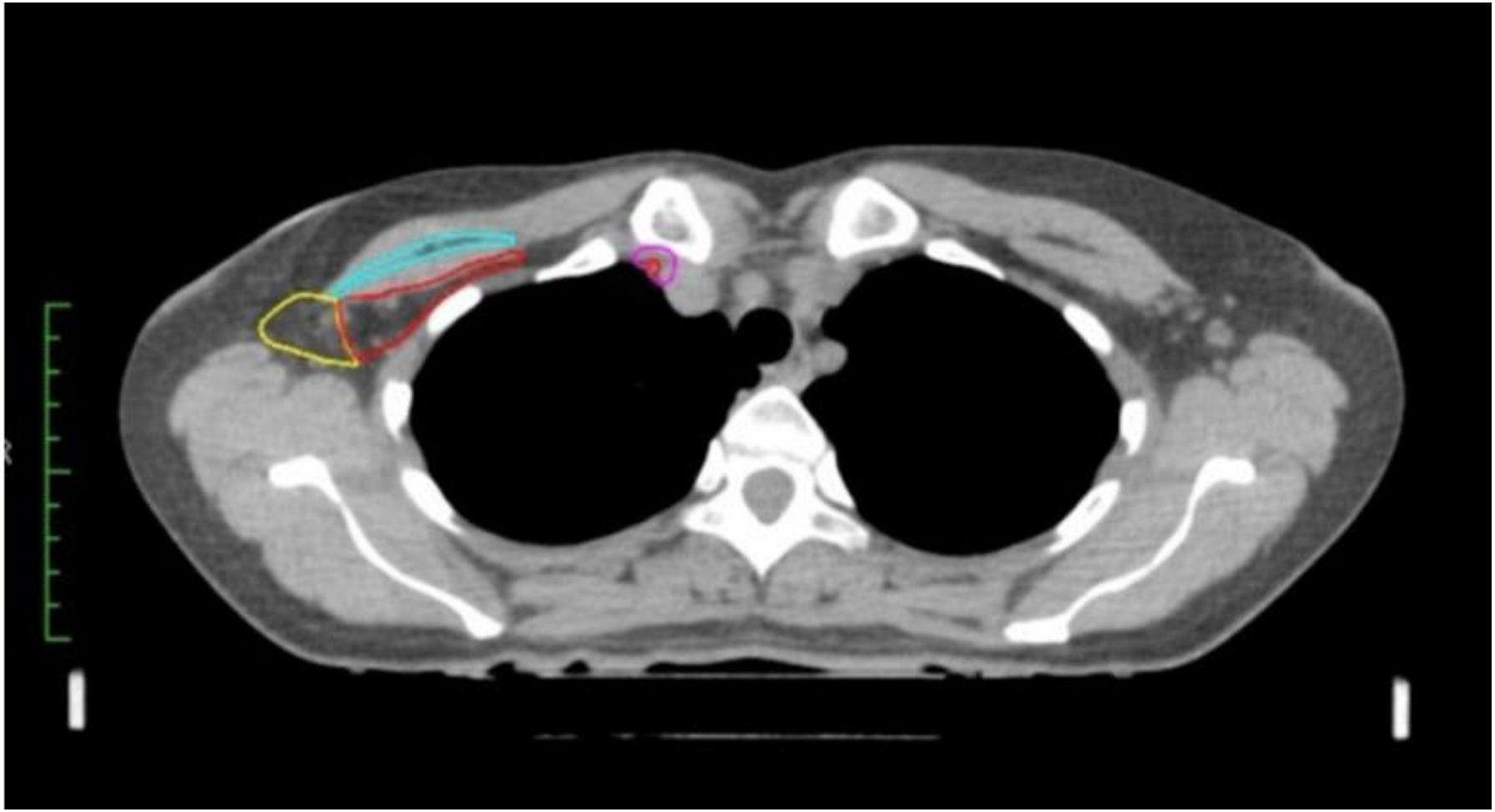
CTVn_IMN = purple



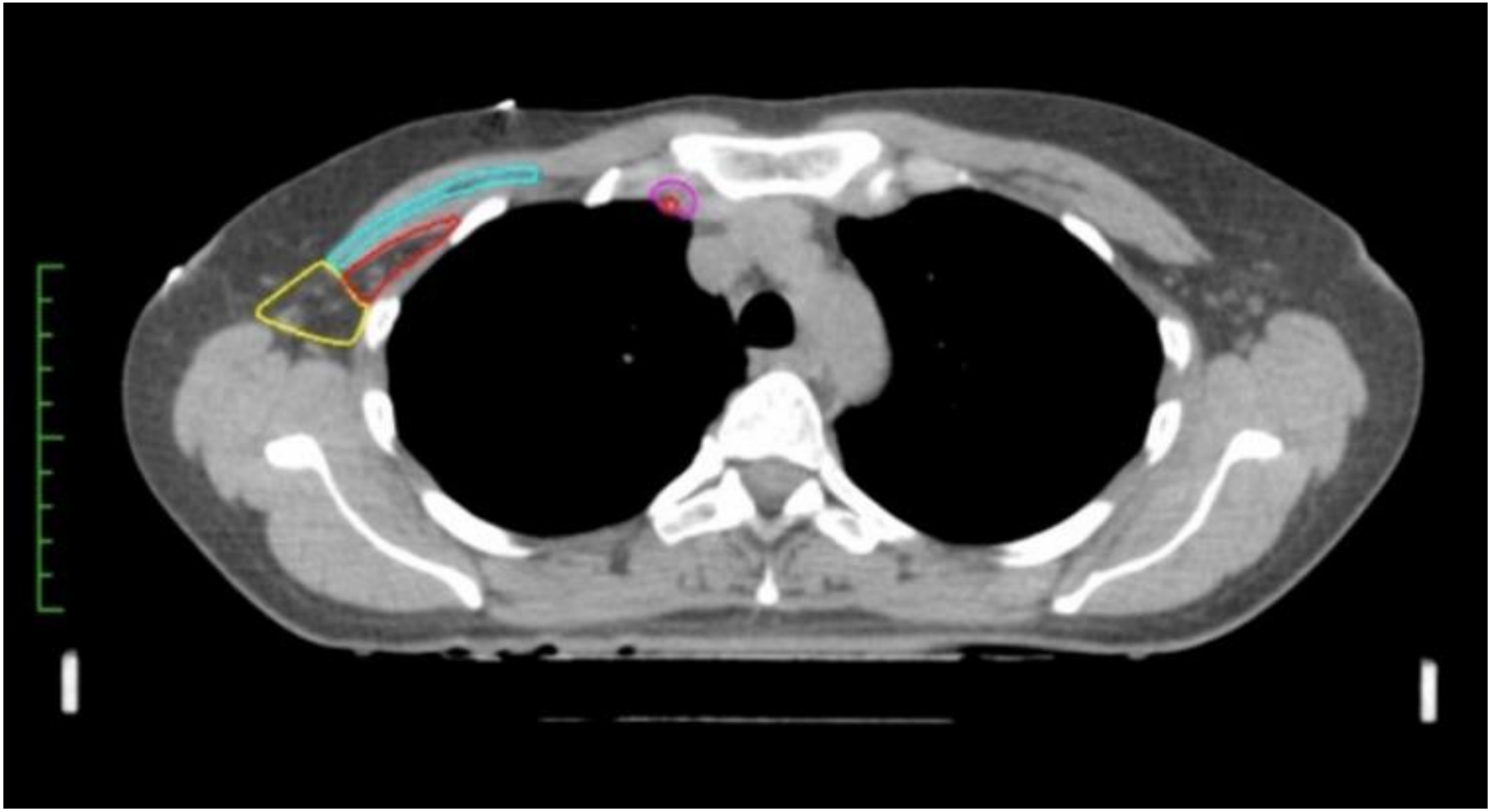
CTVn_IMN = purple



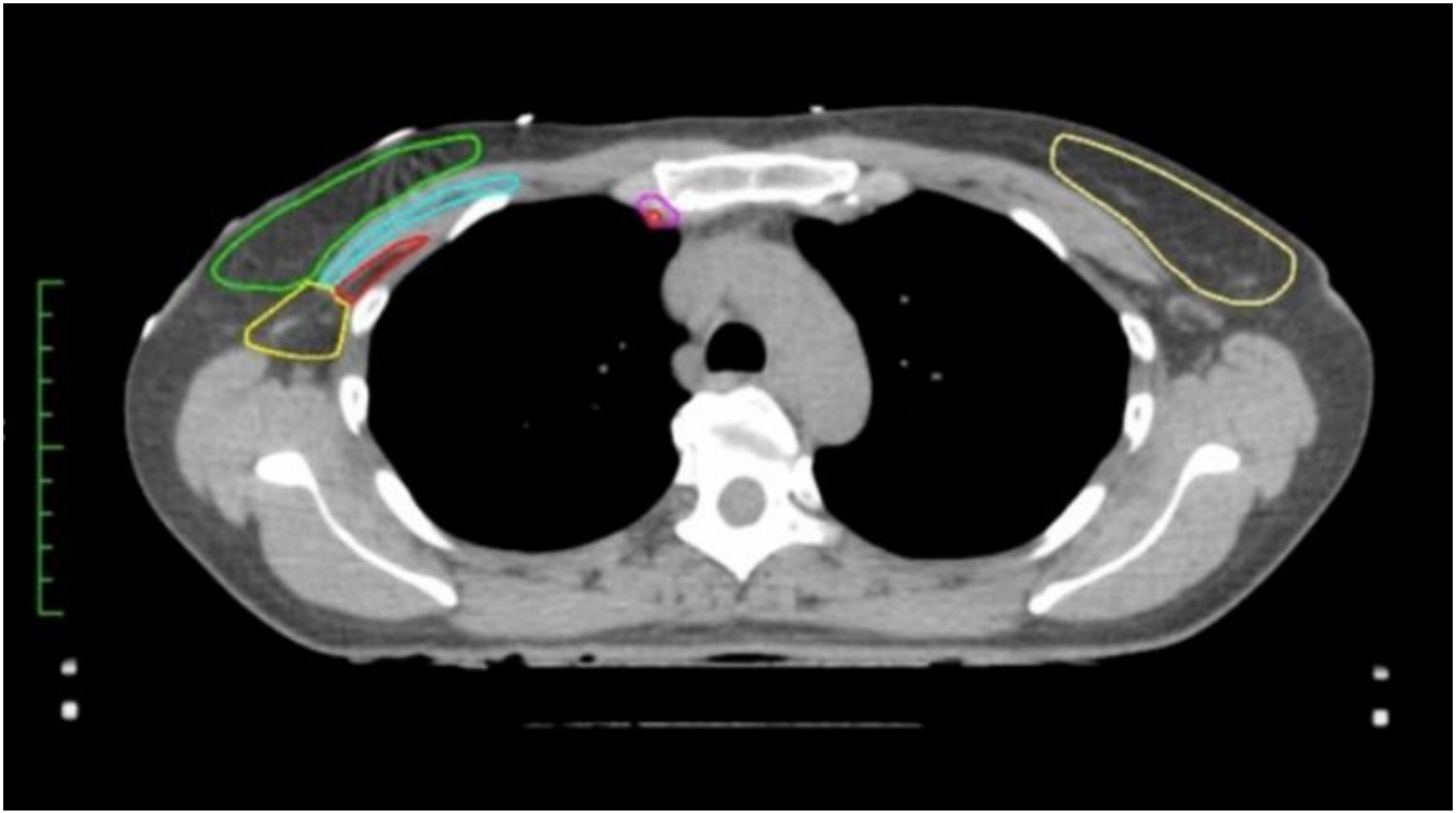
CTVn_IMN = purple



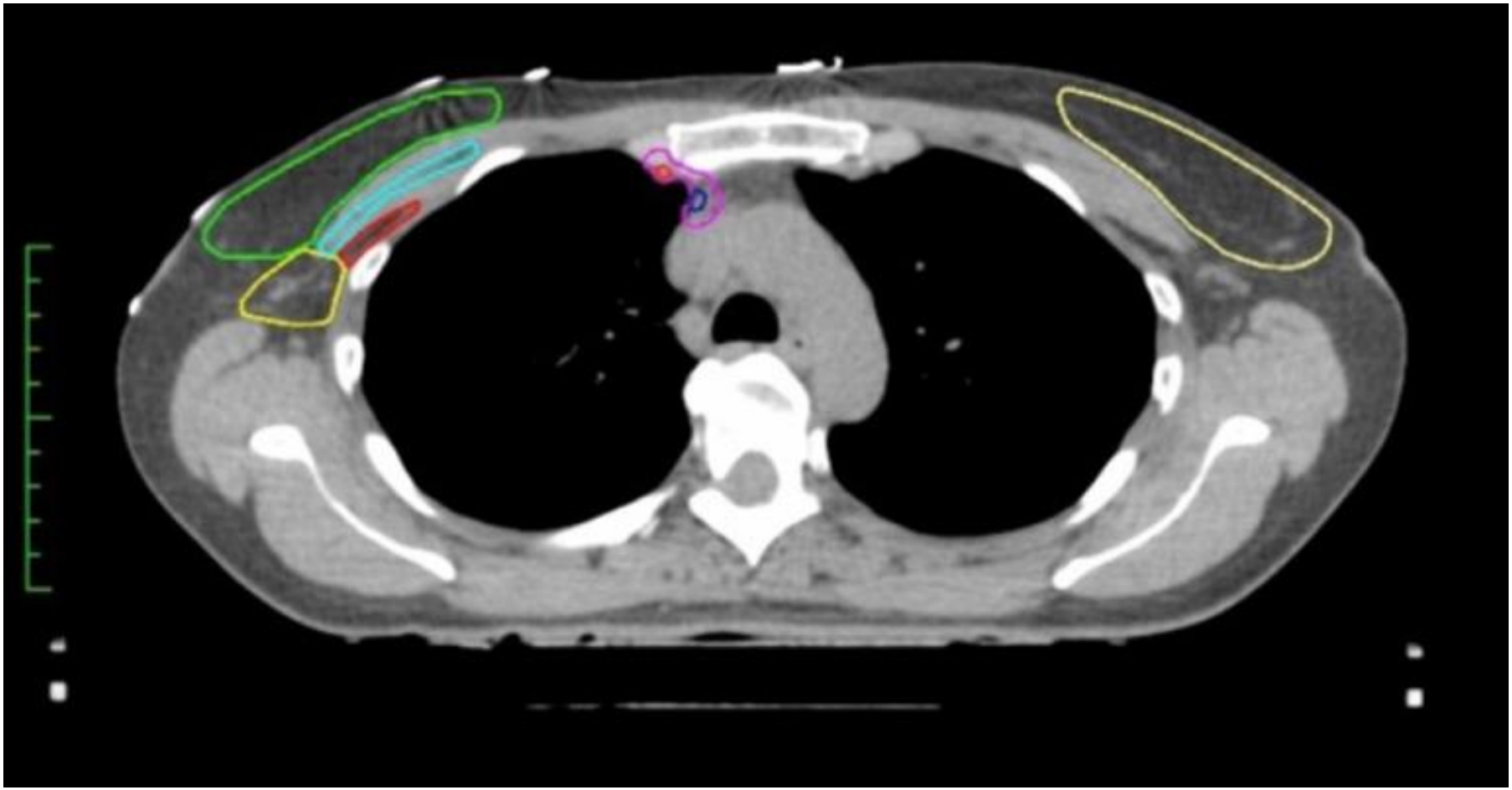
CTVn_IMN = purple



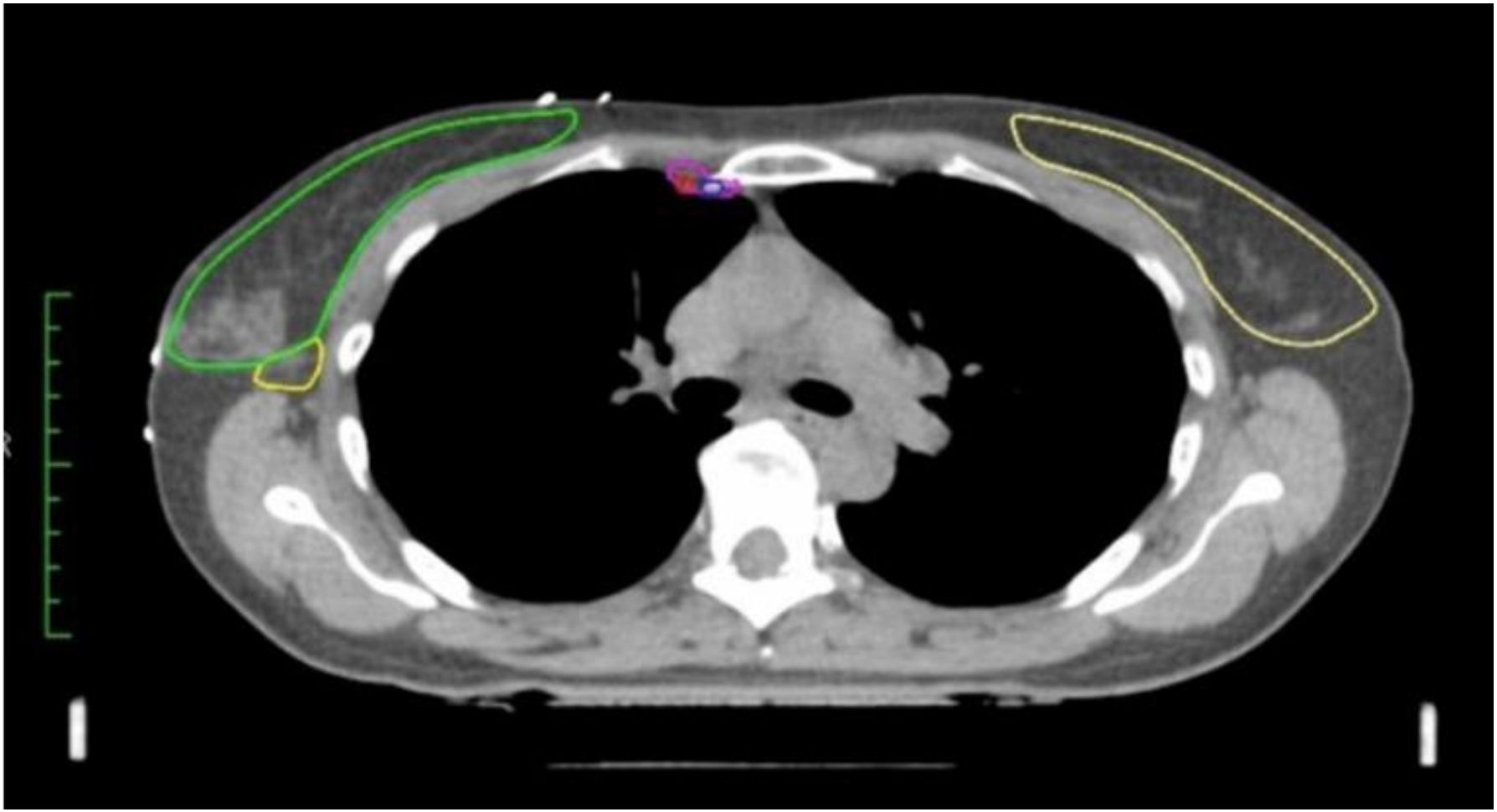
CTVn_IMN = purple



CTVn_IMN = purple



CTVn_IMN = purple

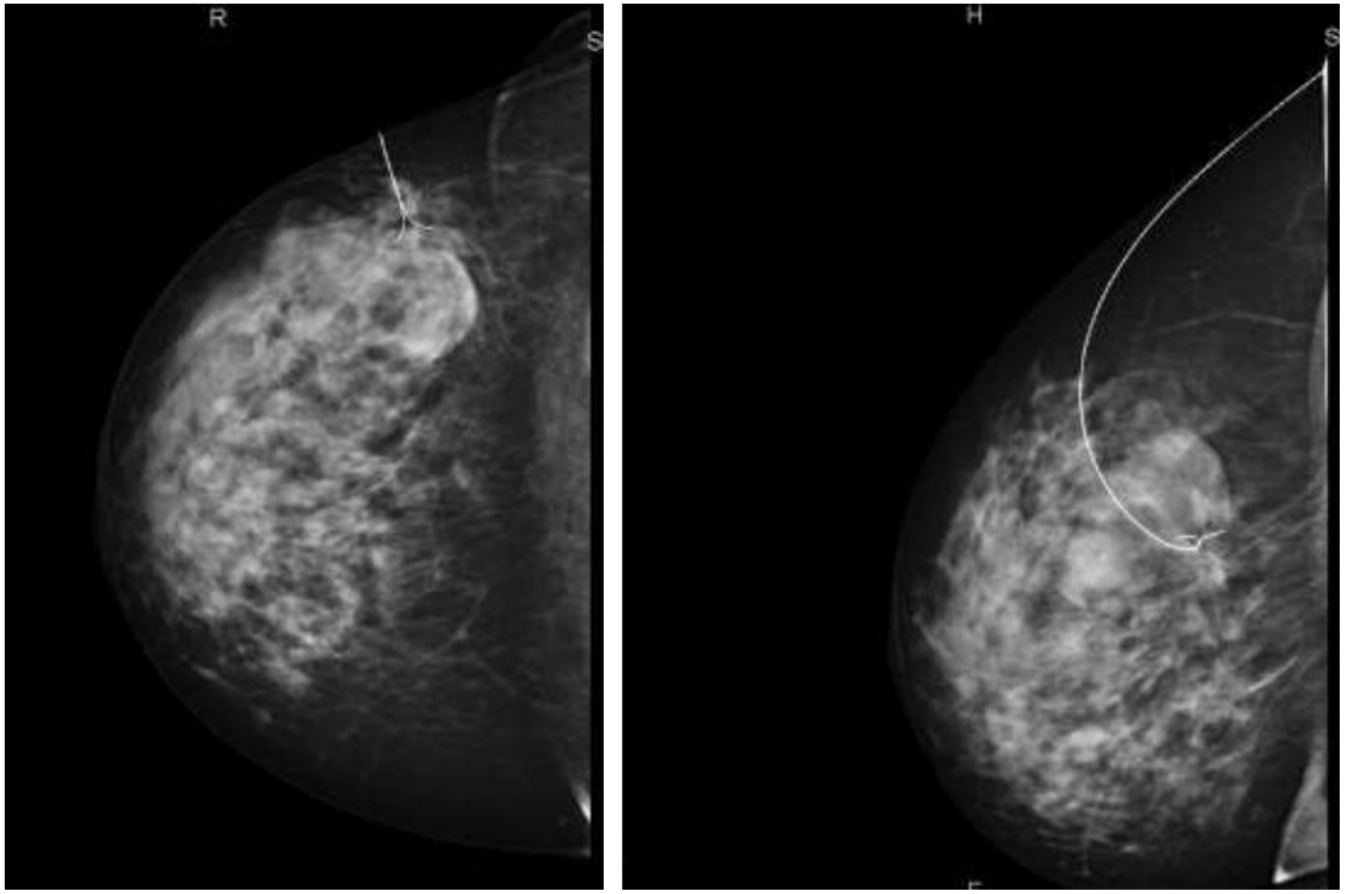


Questions ?

Case for homework – case 2

- Palpable lump in upper outer quadrant of right breast.
- Mammography: cluster of cysts, tumour located amongst the cysts.
- Ultrasound: suspicious lesion: biopsy -> malignant
- Lumpectomy with SN and ALND:
- Pathology:
  - IDC gr 2; 12mm; no LVI, irradical at cranial resection side
  - SLNB: 2+/3 ; ALND:9+/11; total 11+/14
- pT1cpN3M0; ER = ++; PR = ++; Her-2-Neu = -
- Further Treatment:
  - Adjuvant chemotherapy and hormonal treatment and locoregional RT:
  - Breast with boost (!) and all lymph node areas: axilla L1, L2, L3, L4, IMN, Rotter

Case for homework – case 2



Case for homework – case 3

- 53 yr, lump cranially in left breast, slightly red skin and slight edema
- Imaging: 8.2 x 5.7 x 2.8 cm and couple of pathological nodes
- Biopsy: IDC gr 1, ER neg, Her2.neu pos
- → cT3/4 N1 M0 breast cancer left-sided

- Treatment:
  - Primary systemic treatment with immunotherapy --. Clinically near CR
  - MRM left; right preventive mastectomy: ypT0N0 (6/22 nodes with signs of treatment response)
  - Locoregional RT, including 4th ICR 40 Gy/15 fx SKAGEN Trial 1
  - Adj. immunotherapy

Case for homework

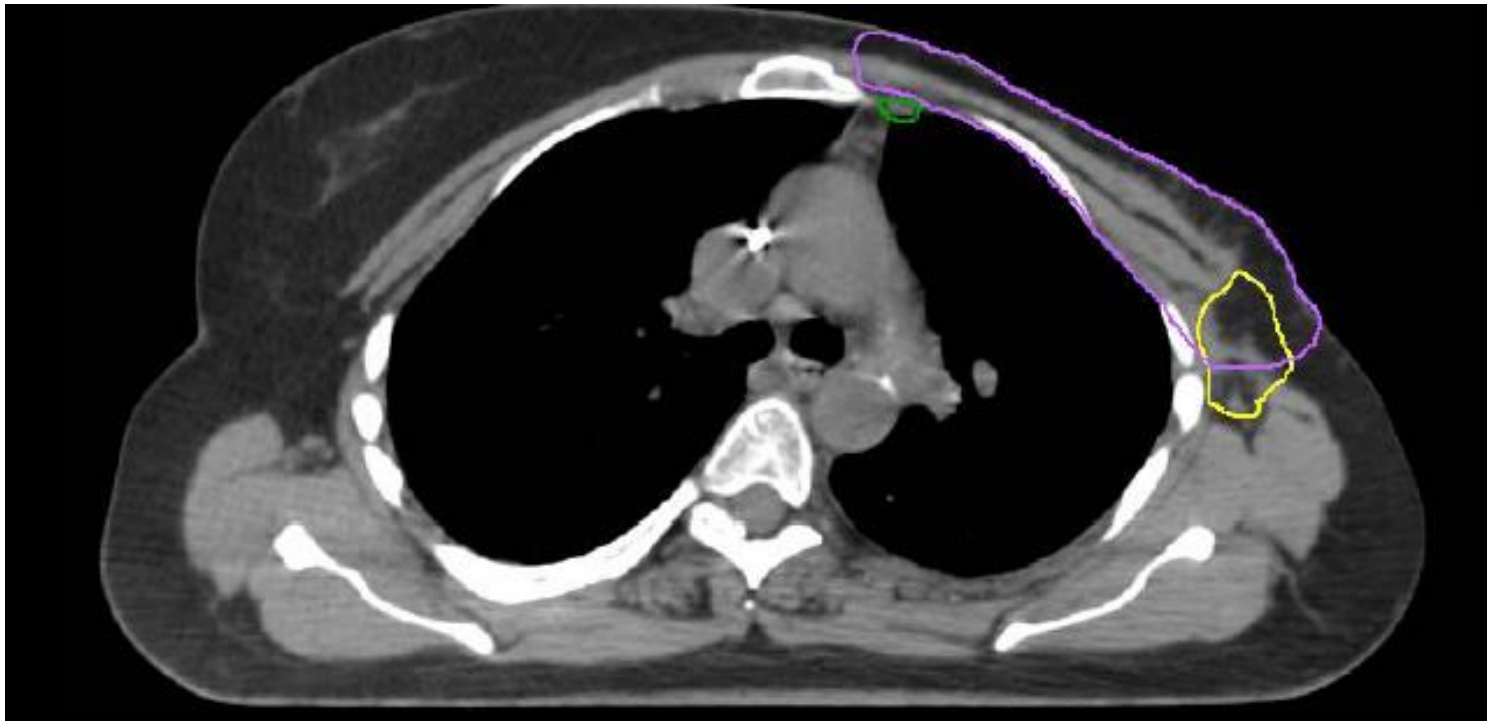
Case for homework

Most important points of discussion…(1)

Dorsal border level 1:

- Sometimes we do see a recurrence dorsally; Dijkema and RTOG atlas more to dorsal
- However, the dorsal border has a large impact on dose to the lungs
- LRR pattern justifies our choice

RTOG atlas axilla level 1 has a different dorsal border



Most important points of discussion…(2)

Cranial border level 4

- Many guidelines use lower border of cricoid
- However, is not logical in view of theory and anatomy
- LRR pattern justifies our choice

Most important points of discussion…(3)

Borders of CTVn_IMN:

- Should we limit CTVn to tissue around the vein only or also around the artery ?
- Since nodes are often seen around both vessels, include both (update 2016)

Localisation of locoregional recurrences

Radiotherapy and Oncology 114 (2015) 1–2

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Editorial

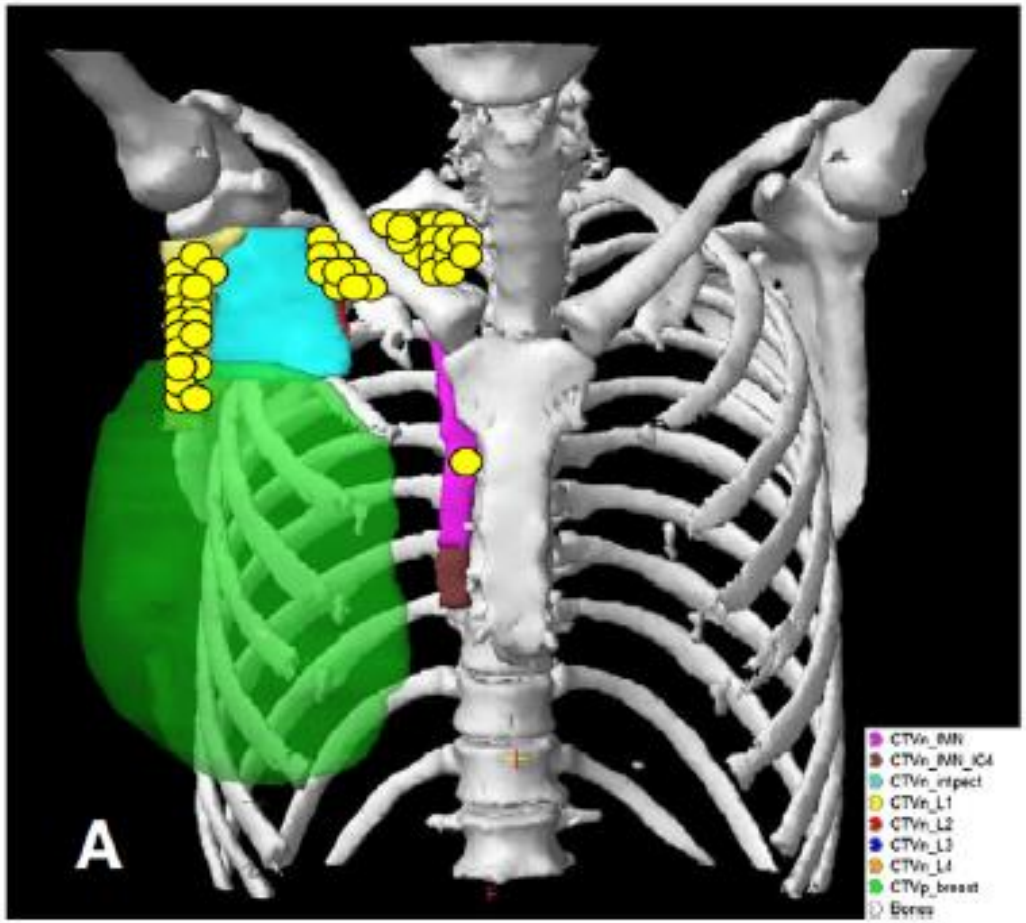
Regional recurrence after adjuvant breast cancer radiotherapy is not due to insufficient target coverage

Hanne Melgaard Nielsen, Birgitte Vrou Offersen *

Department of Oncology, Aarhus University Hospital, Denmark

Anatomical localisation of all RR diagnosed from 2000 to 2013 in Aarhus, analysed in detail:
RR detected inside or outside of the RT fields given to the patients

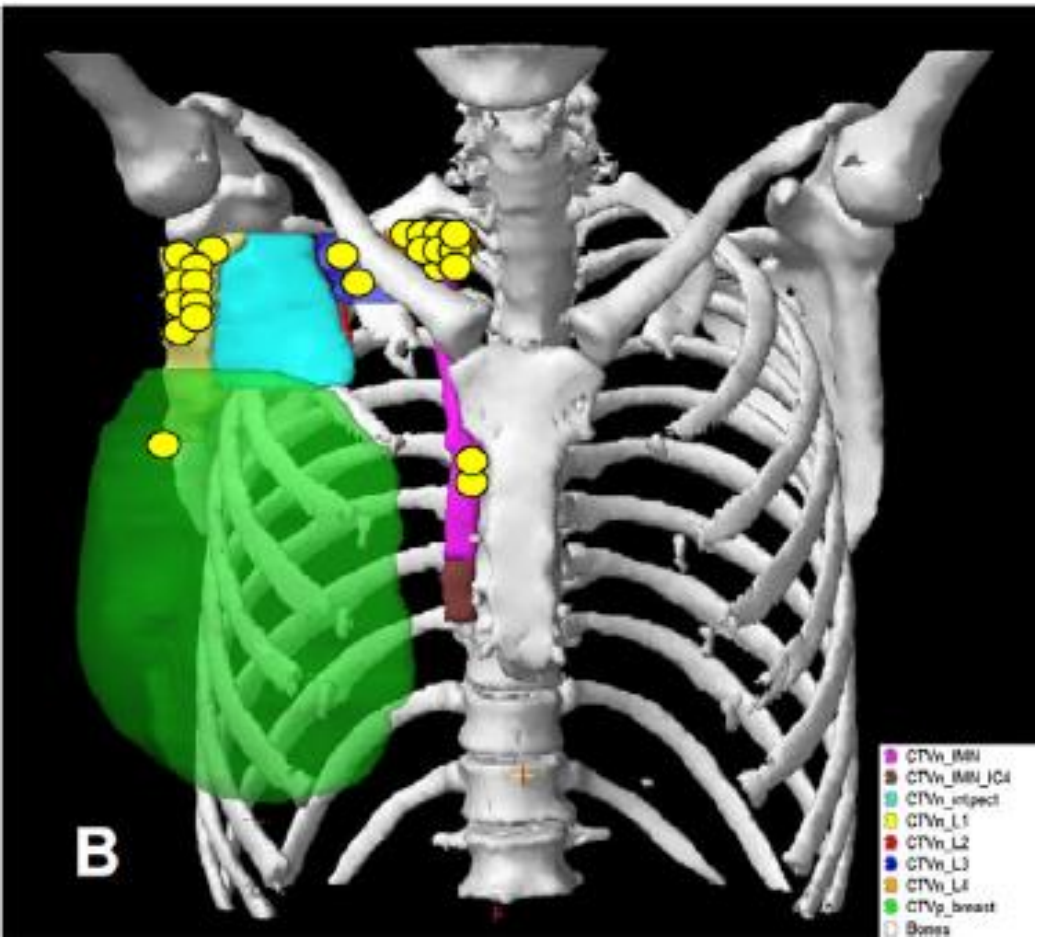
Localisation of RR in patients WITHOUT adjuvant RT



- 38 patients with 53 RR
- Half of the patients had an indication for RT, not given due to patients' refusal or comorbidity
- Most frequent localisations: axilla levels 1, 3, & 4

Nielsen and Offersen 2015

Localisation of RR in patients AFTER adjuvant LR-RT

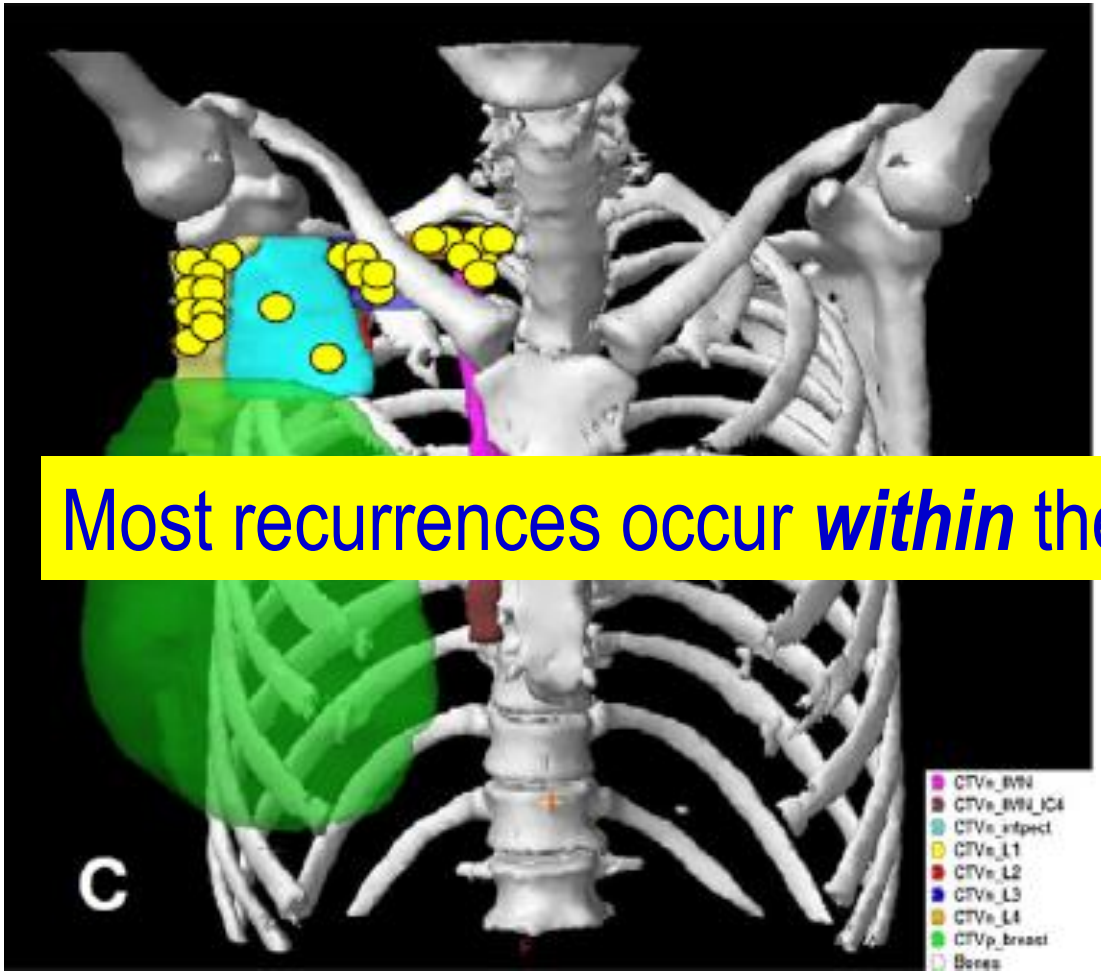


- 21 patients with 25 RR.
- Field border medially of humeral head, just caudally of cricoid, medially of sternocleidomastoid muscle
- Most frequent localisations:

  level 1 & 4
- 1 recurrence very caudal in level 1 (17 positive nodes in ALND)

Nielsen and Offersen 2015

Localisation of RR after ONLY RT breast



- 14 patients with 23 RR.
- Most frequent localisation: level 1.

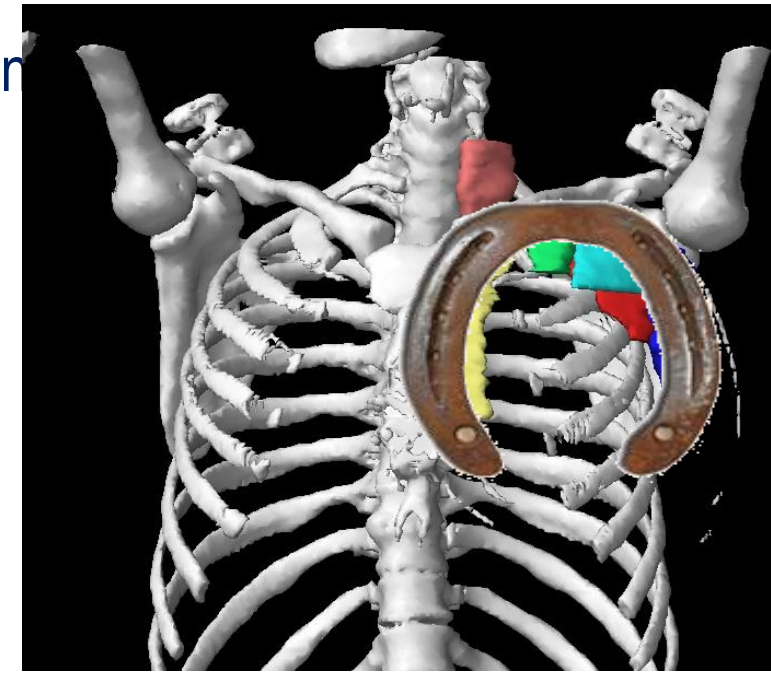
Most recurrences occur ***within*** the delineated volumes

Nielsen and Offersen 2015

General considerations

- General rule for LN areas: veins+ 5mm margin
- IV contrast ➔ facilitates ➔ for learning

  but not required.
- Normal anatomy atlas = more than helpful.
- Coronal views: very helpful as well !
- Lymph node regions should all interconnect.
- Some discussion points left:
  - Are we ready to leave a gap between PTVs of primary tumor and LN areas ?



General considerations

- Recent comments on RTOG atlases (& probably also valid for ESTRO atlas):
  - In case of massive involvement supraclavicular nodes: nodes extend beyond CTVn_L4 → should atlas be adapted ? *(Brown et al, IJRBOP 2015; Jing et al IJRBOP 2015)*
  - To cover 95% of lymph nodes at cranial and anterior borders of level 1, CTVn_L1 should be increased considerably: i.e. take into account nodal involvement seen before surgery/ chemotherapy *(Gentile et al, IJRBOP 2015).*
  - *NB: ESTRO guidelines are meant for elective irradiation of early stage breast cancer; i.e. in case of clinically overt pathological nodes: individualise target volume delineation !*

General considerations

We don't have clinical reason to increase field size compared to the old standard fields.

➔ mind resulting field size/including OAR!

➔ a margin of 5 mm from CTV to PTV should be sufficient (if adequate fixation as well as a carefully designed IGRT procedure are used)

Questions ?

Thanks for your attention

Loco-regional treatments

Marianne Aznar/Sandra Hol

With treatment examples from:

Rigshospitalet, Denmark

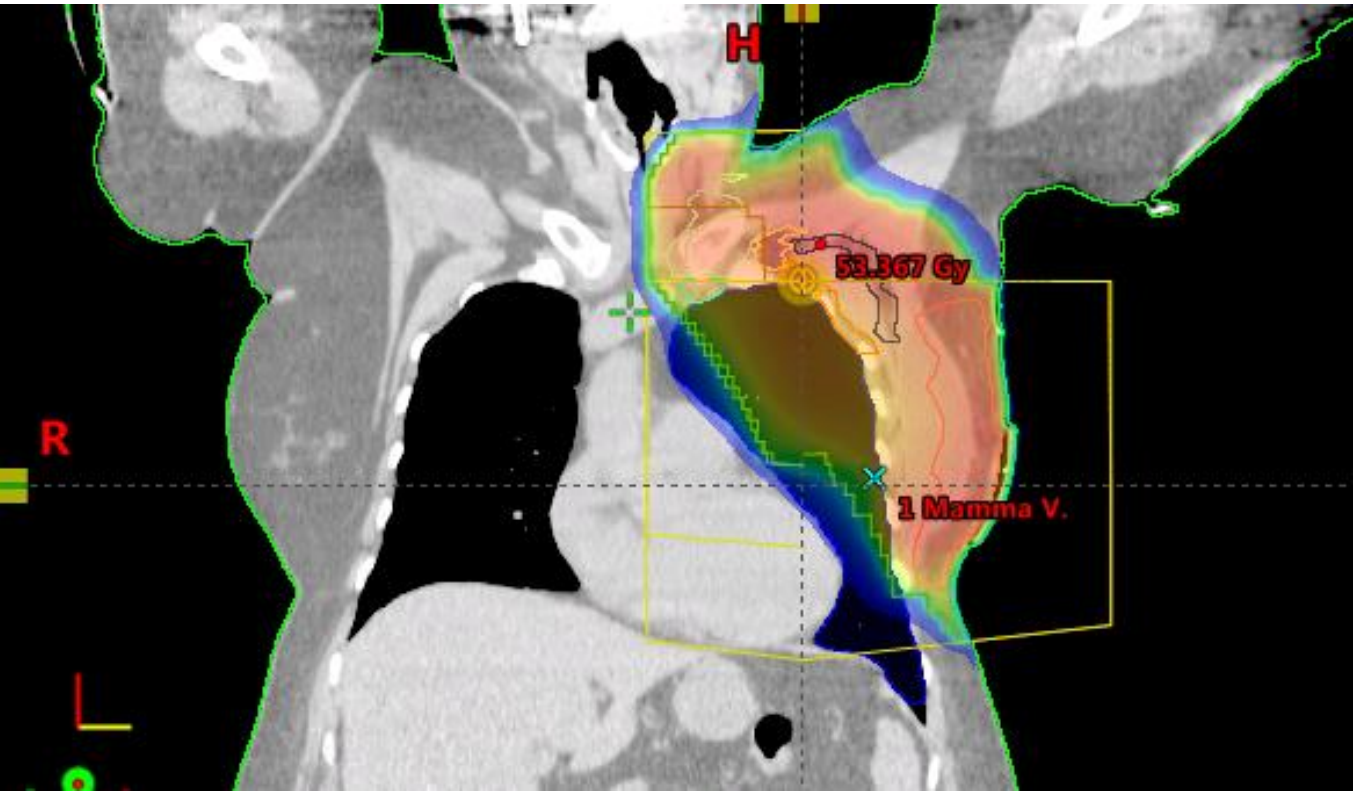
Tilburg, the Netherlands, courtesy of P Poortmans and S Hol

Institut Curie, France, courtesy of Y Kirova

Learning objectives: loco-regional treatments

- To know the most common field arrangements in loco-regional treatments
- To be able to discuss the respective advantages of
  1)DIBH and
  2) IMRT
  in loco-regional treatment
- To understand the challenges of positioning/IGRT in loco-regional versus local treatments

Larger, complex volume



What are we trying to achieve ?

CTV target : minimum **95%** to the breast

CTV nodes (including IMN): minimum **90%** to nodal targets

NB: CTV vs PTV coverage !!!!

Until recently…

compromize the IM nodal coverage if the dose to the heart was too high

But now ????

Example of constraints: the DBCG criteria

For 2 Gy x 25

CTV

CTV breast/CW $\mathbf{V_{95\%}}$>98%, V107% ≤2%, V110%=0

CTV nodes $\mathbf{V_{90\%}}$>98%, V107% ≤2%, V110%=0

Organs at risk

Heart V_{20Gy} ≤ 10 %, V_{40Gy} ≤ 5 %

Ipsi lung V_{20Gy} ≤ 35 % Mean ≤ 18 Gy

Contralateral breast “as low as possible”

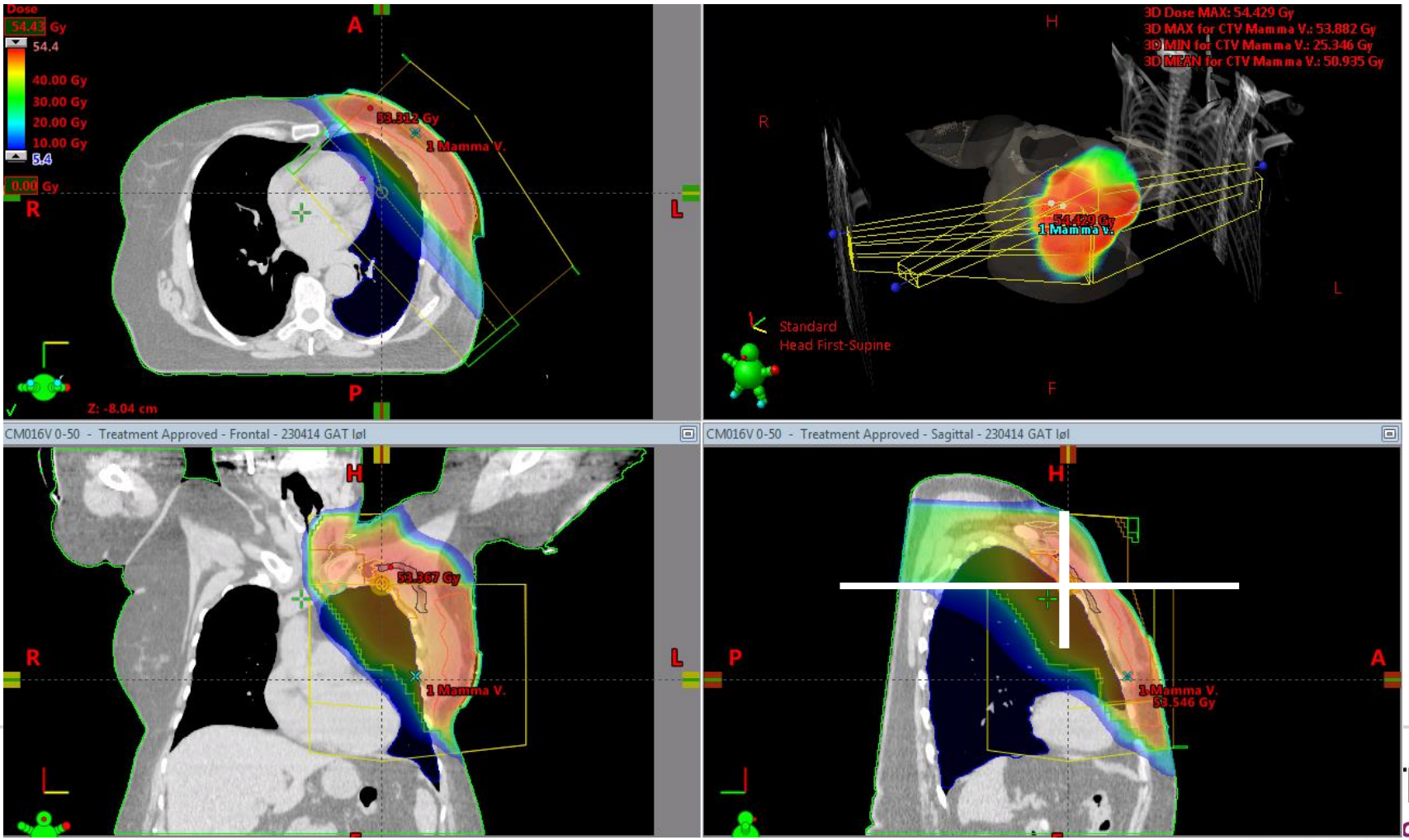
+ spinal cord, brachial plexus, and optimisation constraints

PRIORITIES ??

ESTRO School

Common field arrangements

Isocentric half beam technique

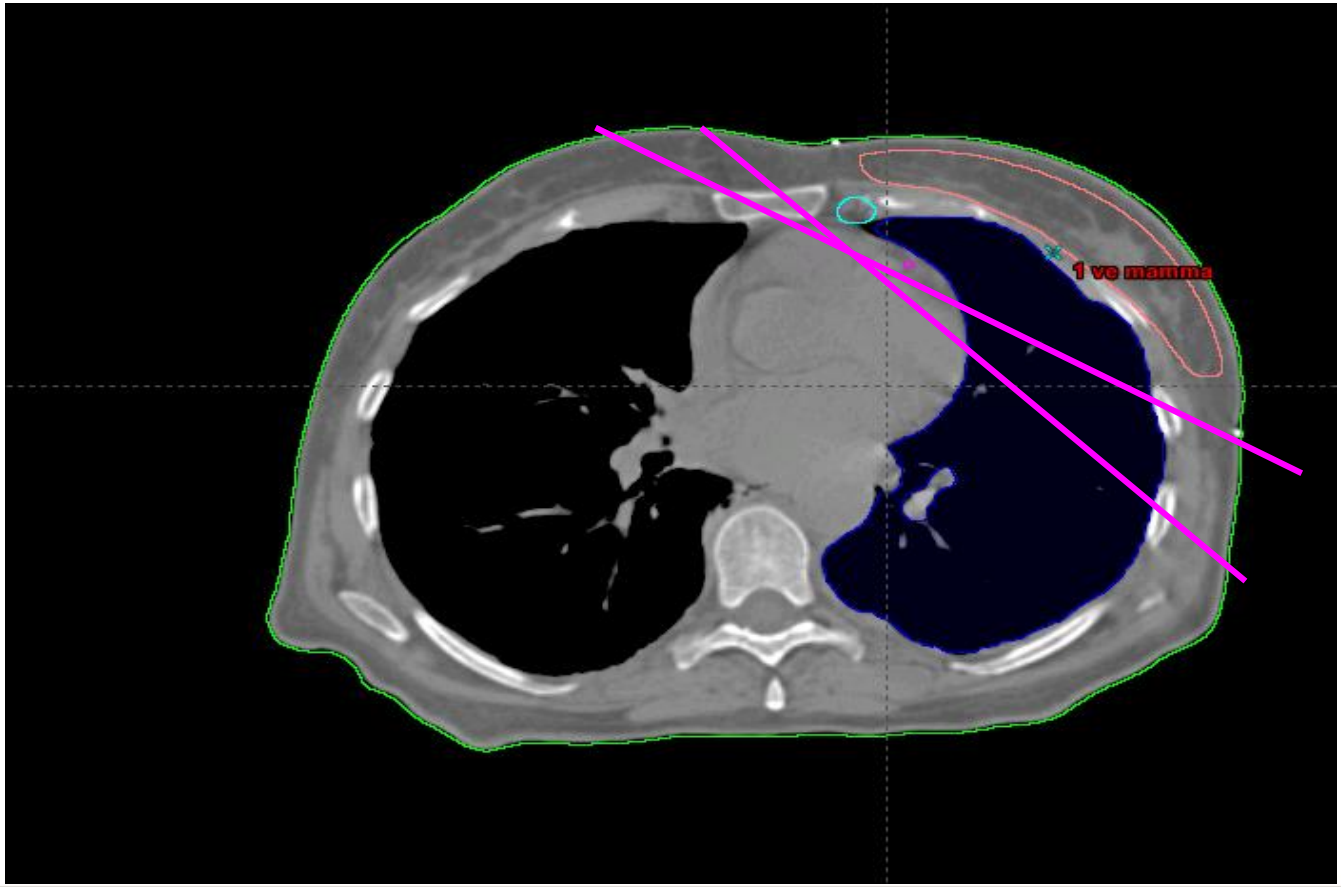


Common field arrangements

Wide tangents for IMN

Simple

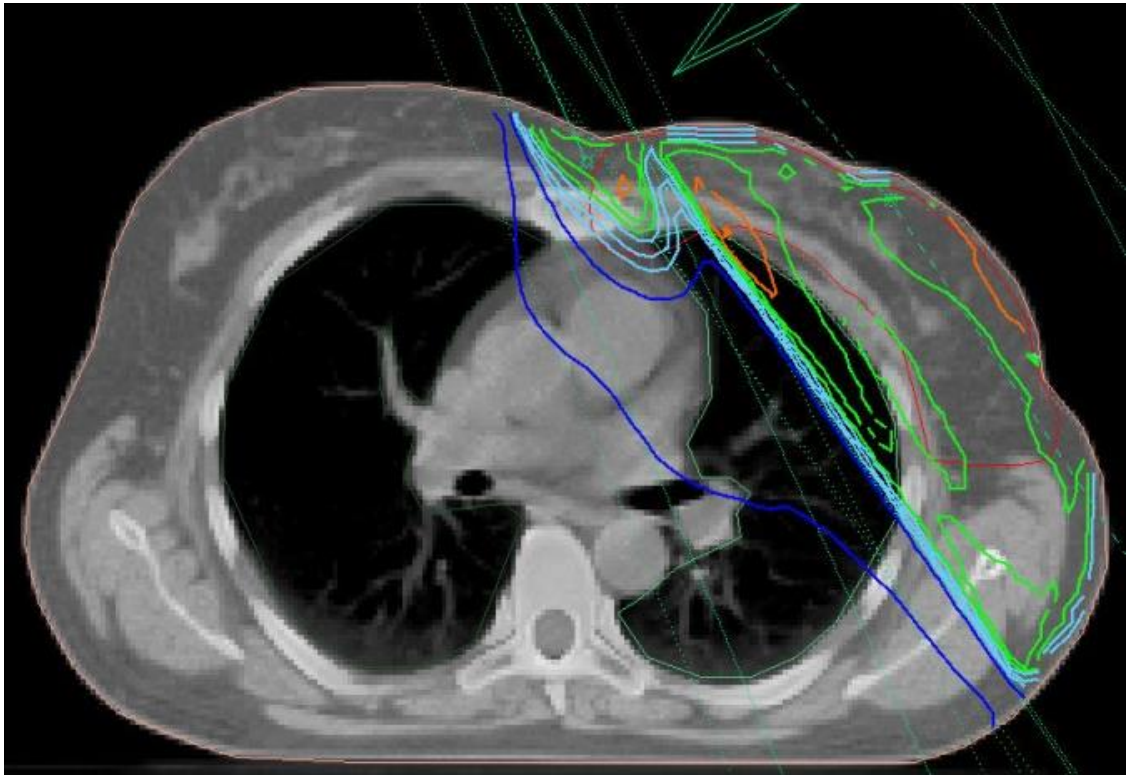
Risk of high dose to OARs (unless…)



Common field arrangements

Field junction for IMN

With electrons + photons

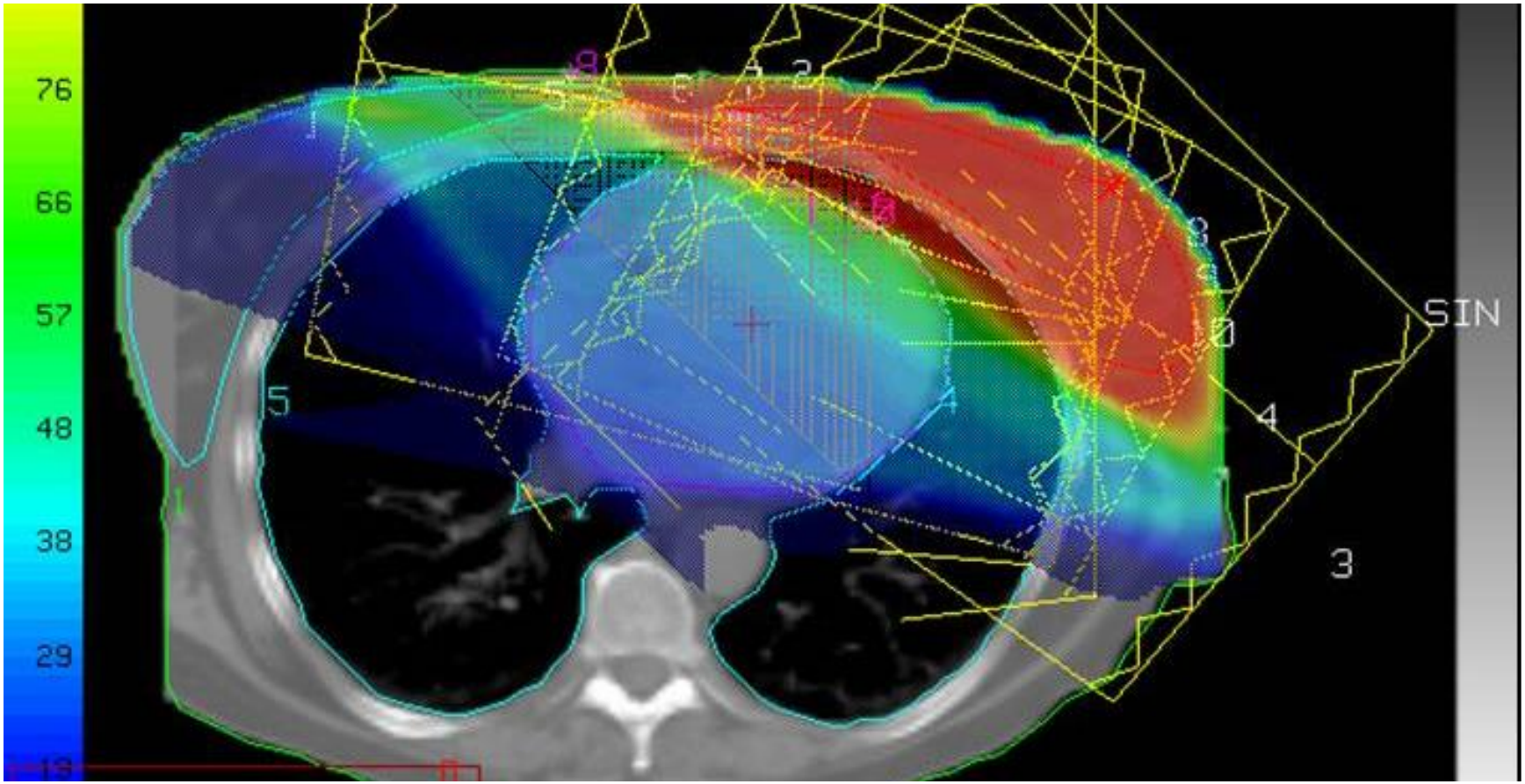


Overlap can be challenging

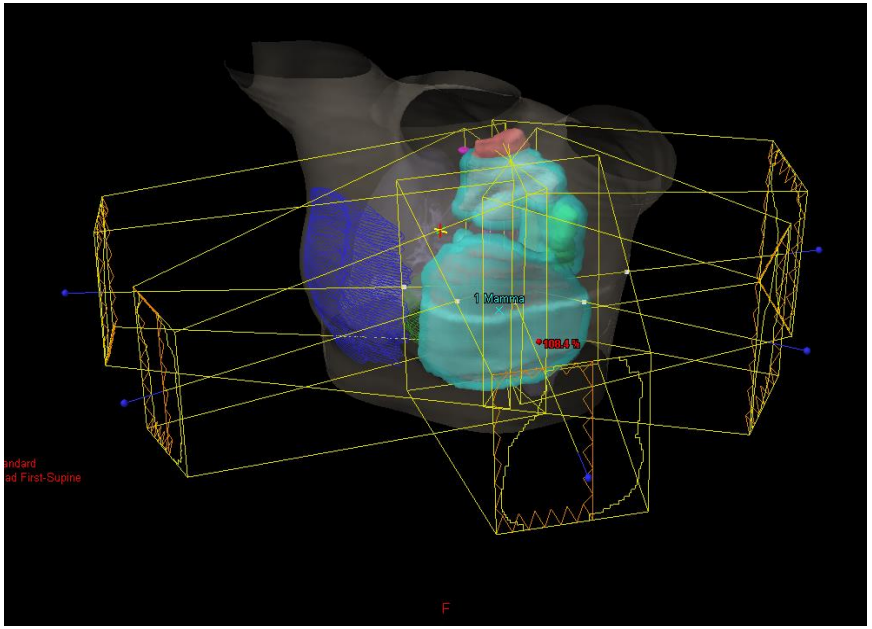
Higher skin dose

Image guidance?

“full” IMRT / VMAT / rotational therapy
= many angles, not only tangents

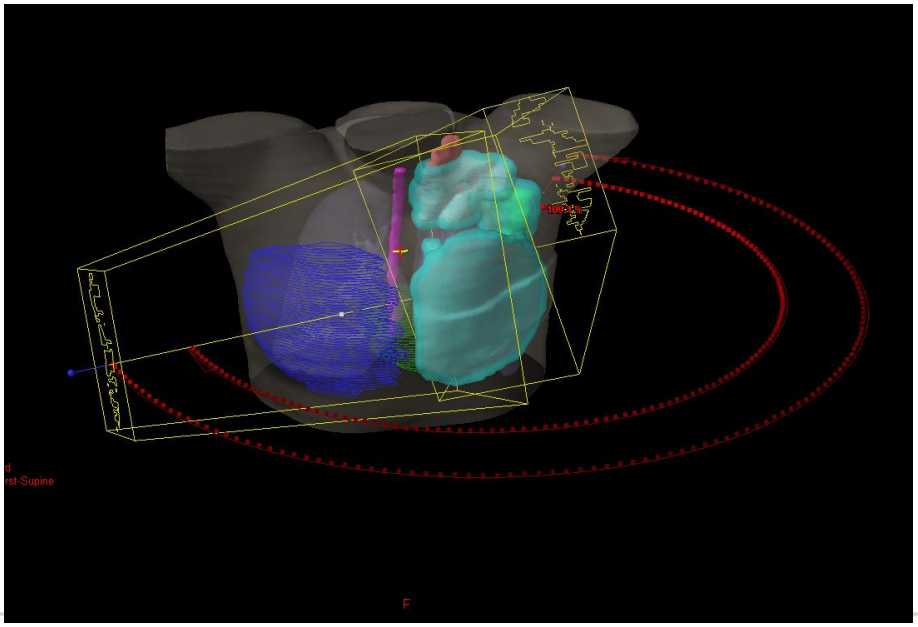


inverse-planned IMRT= more field directions !!



Static field –IMRT: usually 4-5 fields, mostly entering ispilateral side

Step and shoot, sliding window



Rotational IMRT: irradiating through arcs (or portion of arcs)

VMAT, RapidArc, Tomo

ESTRO School

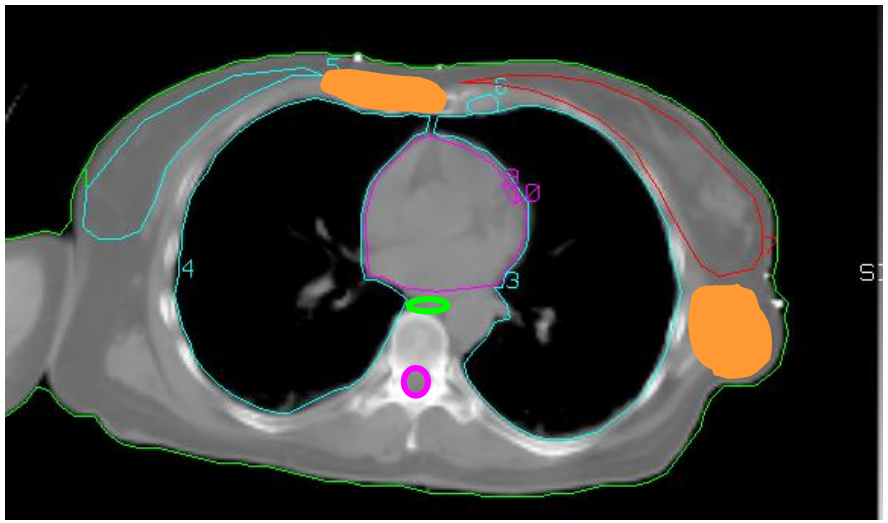
First step when using inverse-planned IMRT

Delineation of Target **PTV** and OAR

heart, LAD, both lungs, contralateral breast, esophagus, spinal cord, liver, brachial plexus, ribs, skin, body?

Dummy contours?

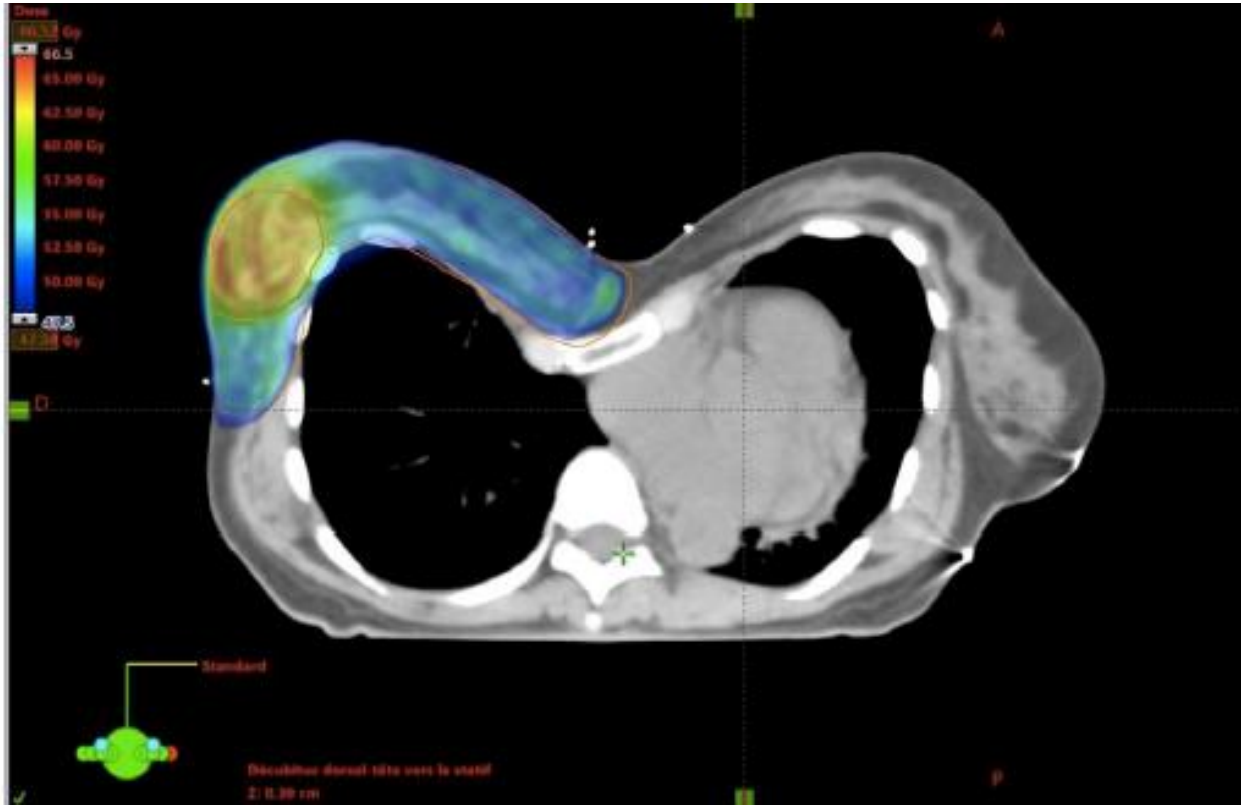
To avoid hotspots outside target



ESTRO School

A no- brainer

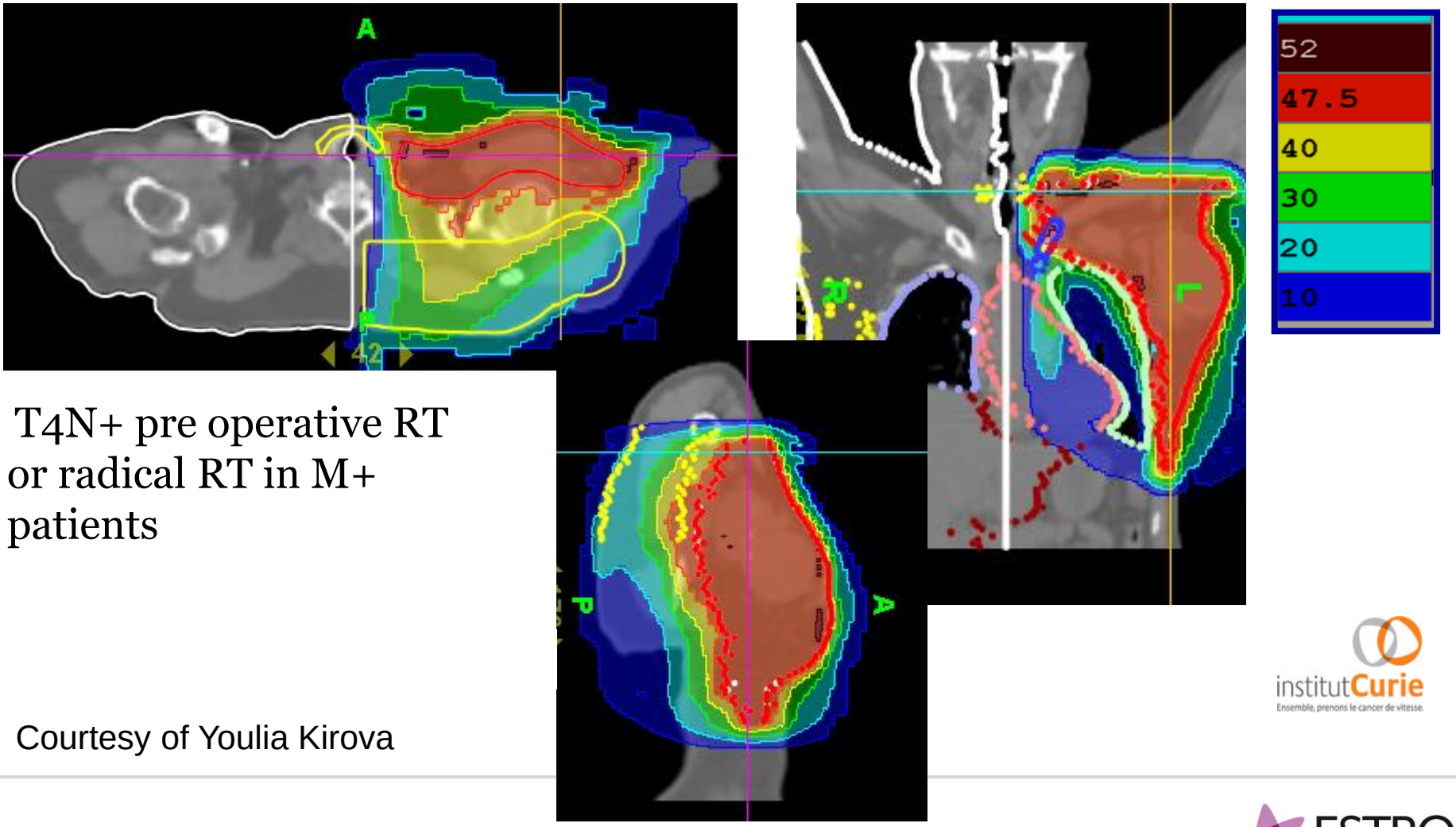
Arsene-Henry R&O 2017



institutCurie
Ensemble, prenons le cancer de vitesse.

ESTRO School

Pre-operative RT (high dose, need for sharp gradients)



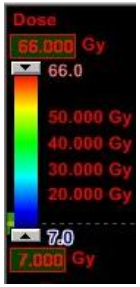
T4N+ pre operative RT or radical RT in M+ patients

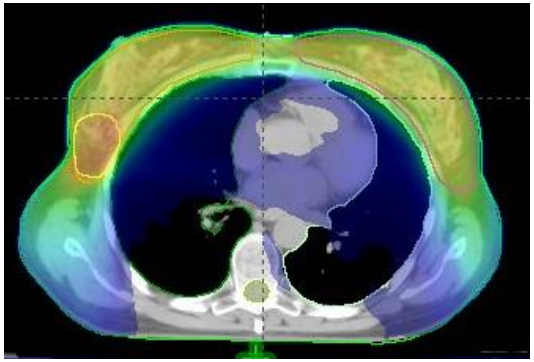
Courtesy of Youlia Kirova

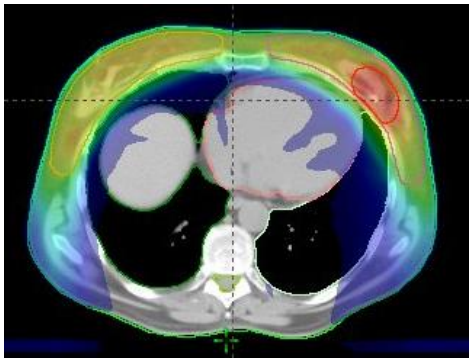
Bilateral treatment with Intensity-modulated arc therapy

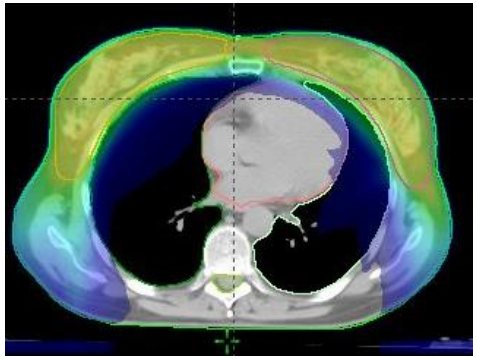
SIB: 25 x 2 Gy = 50 Gy whole bilateral breasts
25 x 2.5 = 62.5 Gy (left boost) & 25 x 2.35 Gy (right boost)

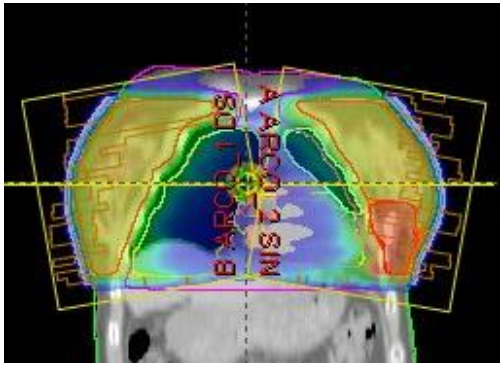
2 isocentric arcs

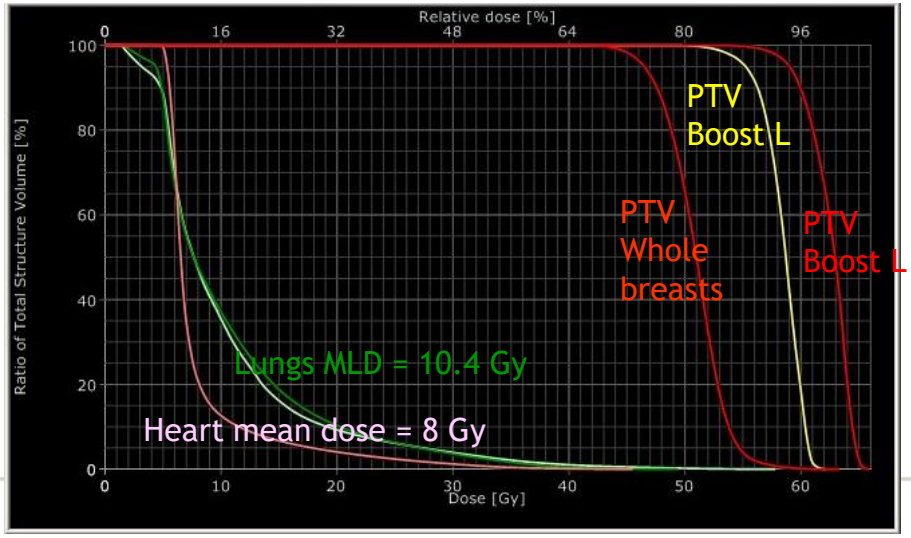












Lbreast: 520 cm^3
Rbreast: 551 cm^3
Lboost: 50 cm^3
Rboost: 32 cm^3

516 + 522 MU
76 + 74 sec

Nicolini et al, Radiation Oncology 2009

ESTRO School

Inverse-planning: you only get what you ask for

- Inverse planning is not a magic bullet: it does not remove dose, it redistributes it

- Talk to your computer:

  - **contour as much as clinically relevant**

  - use constraints on the low dose bath (ex V5Gy for the lung, as low as possible for the heart)

- Be careful when reviewing the literature:

  - what compromise did they accept? (contralateral lung?)

  - what dose level are they looking at? (at V20 or V30, IMRT looks often better than 3D-CRT… but this is not the whole picture!)

  - what is their target coverage criterion (CTV/PTV)

Take home message for IMRT

- Inverse planned IMRT /VMAT clearly has a role for challenging cases
- Be careful about dose to OARs (delineated or not!)
- The computer has no brain: use yours!
- How do you handle breast swelling / breathing motion ??

A (GOLDEN) MIDDLE WAY?

Hybrid technique

Why?

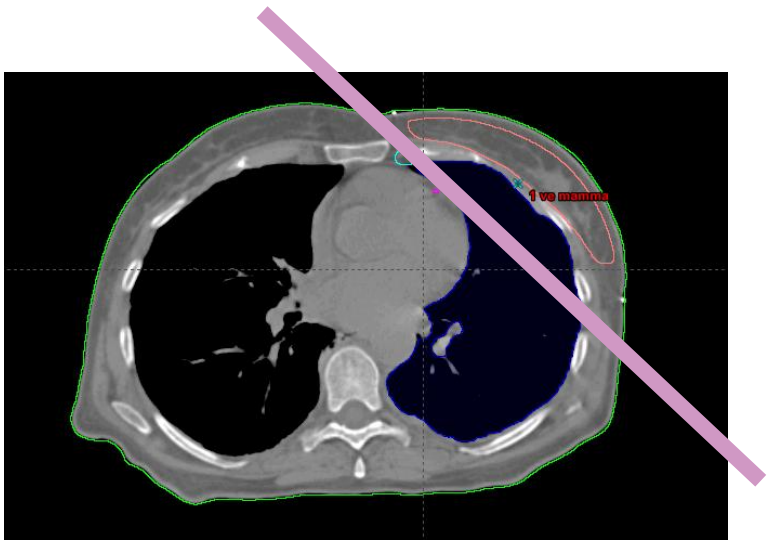
Compromise between

- open fields (very robust to position/volume changes)
- modulated field (re-distribute the dose)

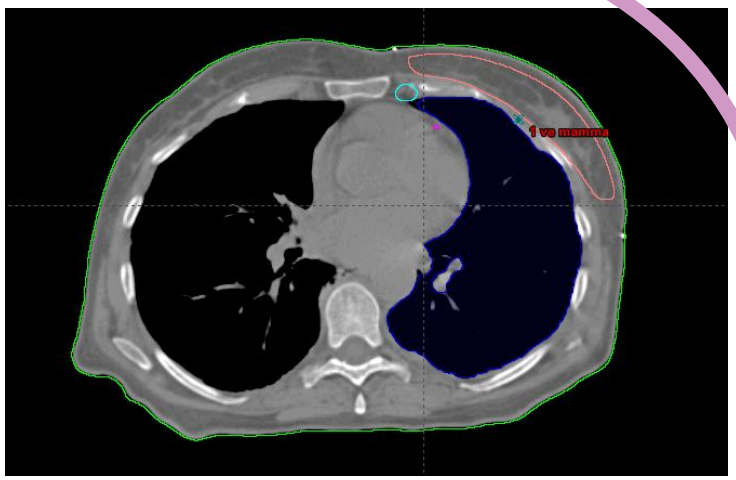
How? (example)

- make plan for 1Gy with open tangents
- input this plan in optimizer and “add” another Gy with VMAT/IMRT

“Hybrid” techniques



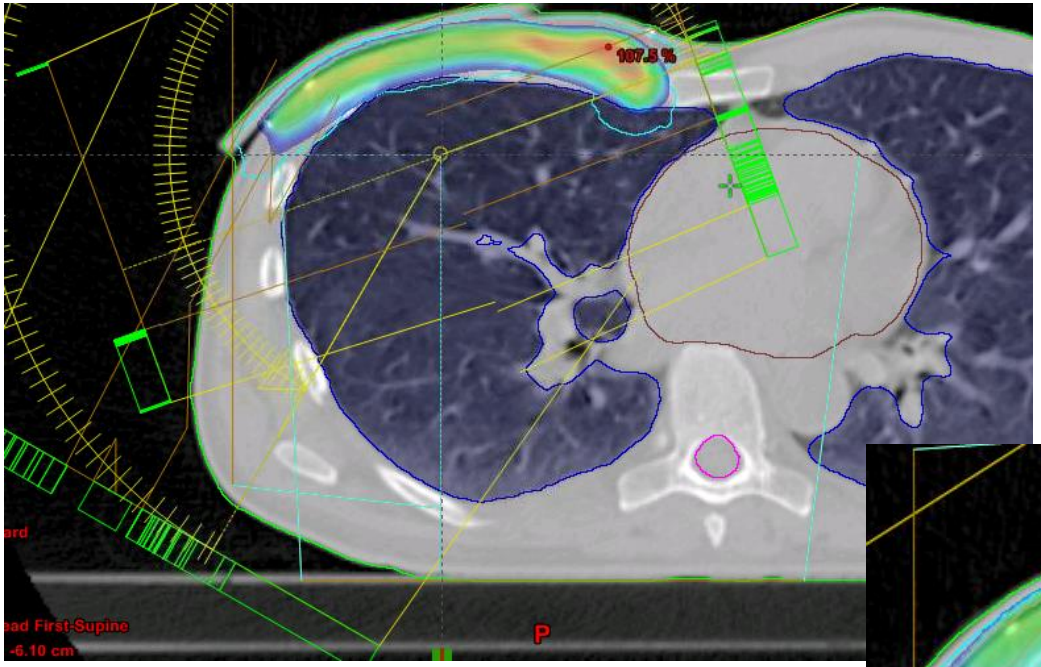
+



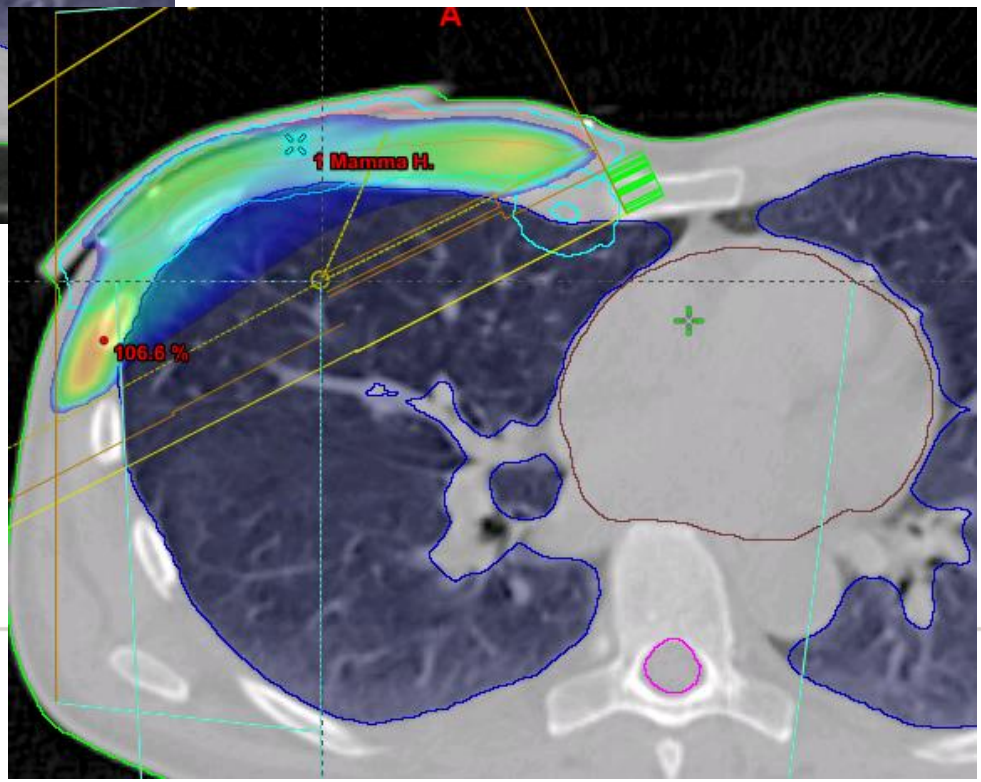
50/50 ? more modulated

80/20 ? more robust

OAR sparing vs target coverage: no free lunch!



3D vs “hybrid technique” (combination of 3D and arc)



Better coverage of IMN, lower V20 for lung
BUT: higher dose to the liver and the heart

Inverse-planning: you only get what you ask for

- Inverse planning is not a magic bullet: it does not remove dose, it redistributes it
- Talk to your computer:

  - contour as much as possible

  - use constraints on the low dose bath (ex V5Gy for the lung, as low as possible for the heart)

- Be careful when reviewing the literature:

  - what compromise did they accept? (contralateral lung?)

  - what dose level are they looking at? (at V20 or V30, iIMRT looks often better than 3D-CRT… but this is not the whole picture!)

  - what is their target coverage criterion (CTV/PTV)

HOW CAN WE EFFICIENTLY REDUCE THE DOSE TO OARS?

How often is IMRT/VMAT/rot therapy used??

Institut Curie: **Tomo 3% 2012 – 10% 2017**
alternative positioning

Tilburg: **3% VMAT, 20% hybrid (all locoregional RT)**
DIBH in all locoregional patients and left sided local

Rigshospitalet: vast majority DIBH,
approx 5% IMRT/hybrid VMAT

- 20-30 breast patients with IMRT or RapidArc /year

ESTRO School

Systematic review of published doses to the heart

Taylor IJROBP 2015

Mean dose to the heart

IMC irradiation ↑ 4 Gy vs 8 Gy

Technique:

Lowest: protons and prone

Highest: IMRT (fixed field or rotational)

Breathing adaptation (DIBH) ↓ 3 Gy vs 1 Gy without IMC (tangents)

9 Gy vs 4 Gy with IMC (tangents)

Systematic review of published doses to the lung

Aznar et al (submitted)

Mean dose to ipsilateral lung

Regions irradiated

Breast/CW < Axilla/SCF <IMC

Breast/CW:	tangents < IMRT
+axilla/SCF + IMC:	IMRT < tangents

Breathing adaptation (DIBH)	20 Gy 16 Gy (wide tangents)
	14 Gy vs 13 Gy (IMRT)

Take home message for loco-regional treatment

- IMRT/VMAT: no magic bullet

- Remember the distinction between

  - forward IMRT (use with no restriction ☺)
  - inverse planned IMRT /VMAT (role for challenging cases, not your “bread and butter” cases)

- If your main challenge is to reduce the dose to the heart and lungs
  - use deep inspiration

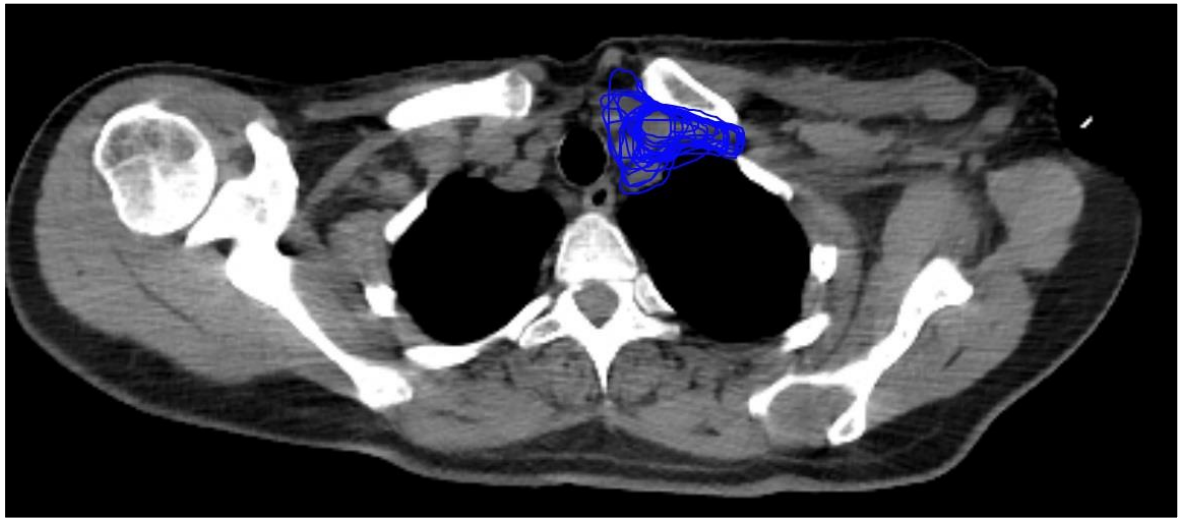
Breast and lymph nodes

Contouring and different techniques

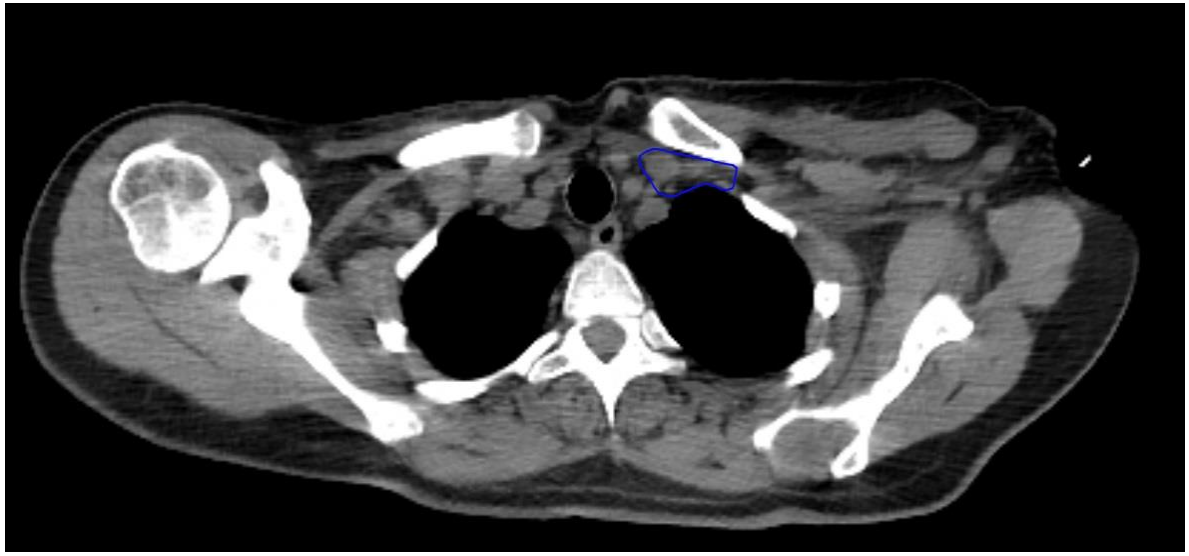
ESTRO School

Contouring

L4 contouring

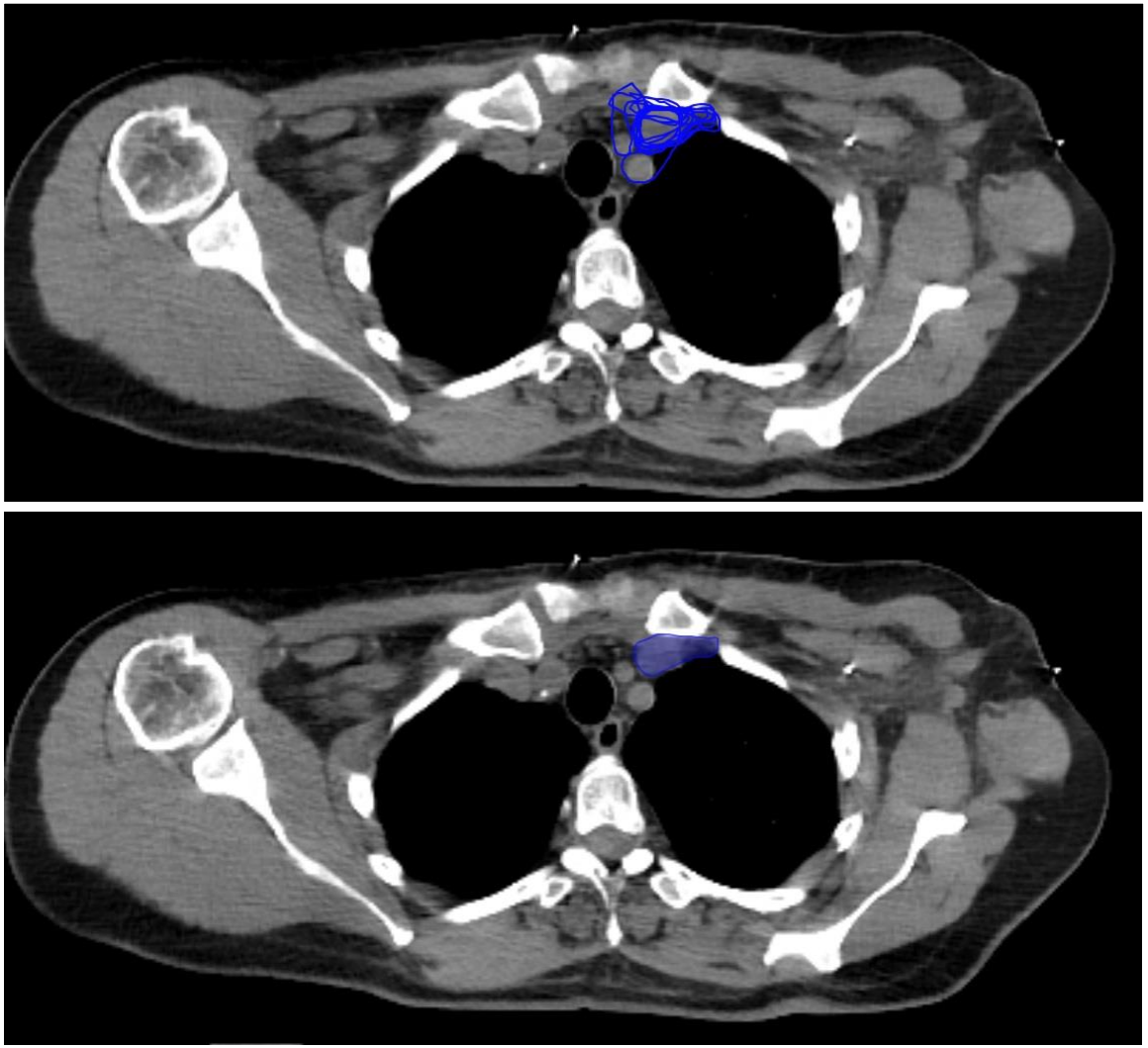


Students



Author

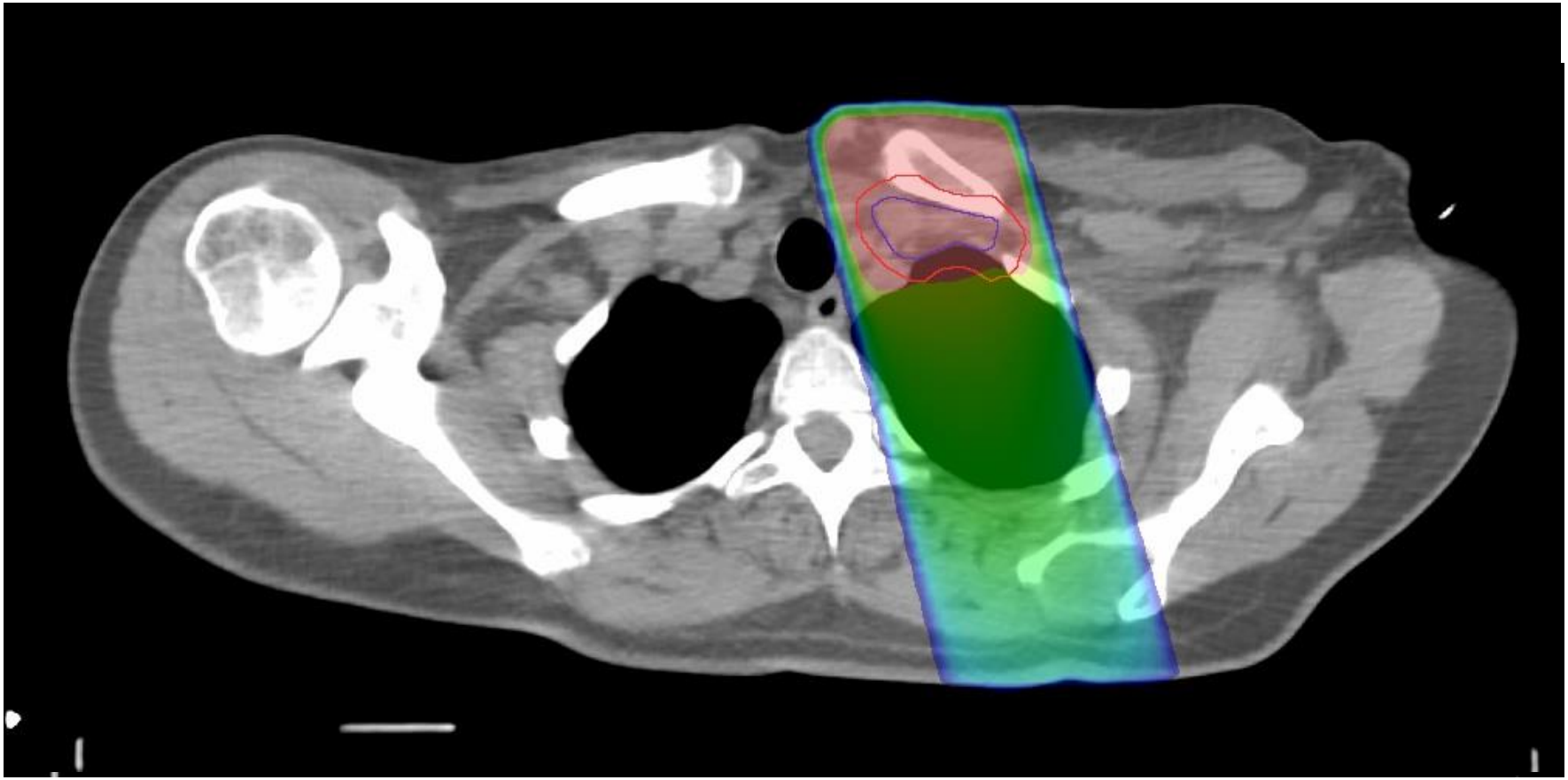
L4 contouring



Students

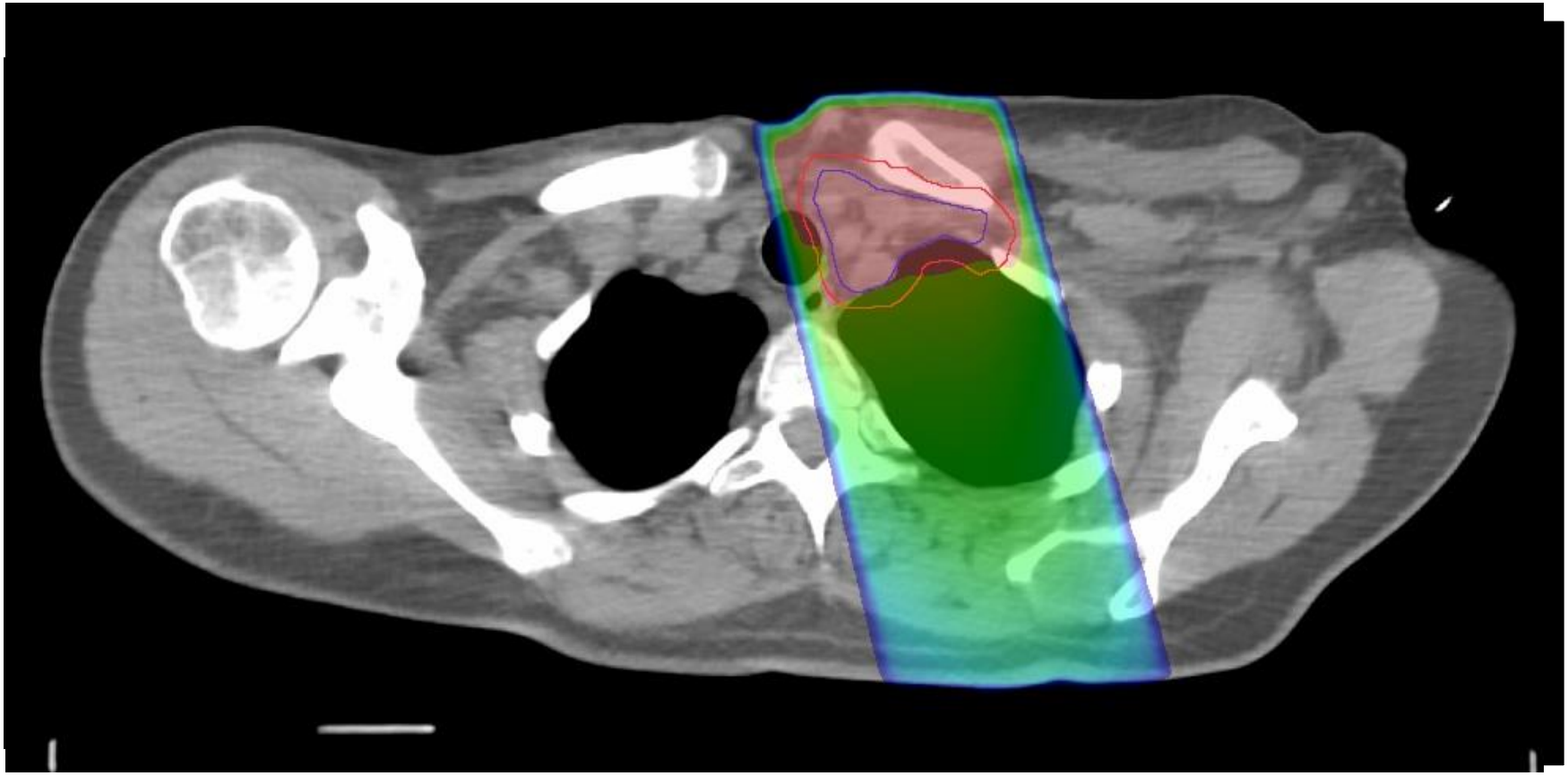
Author

L4 Author’s structure

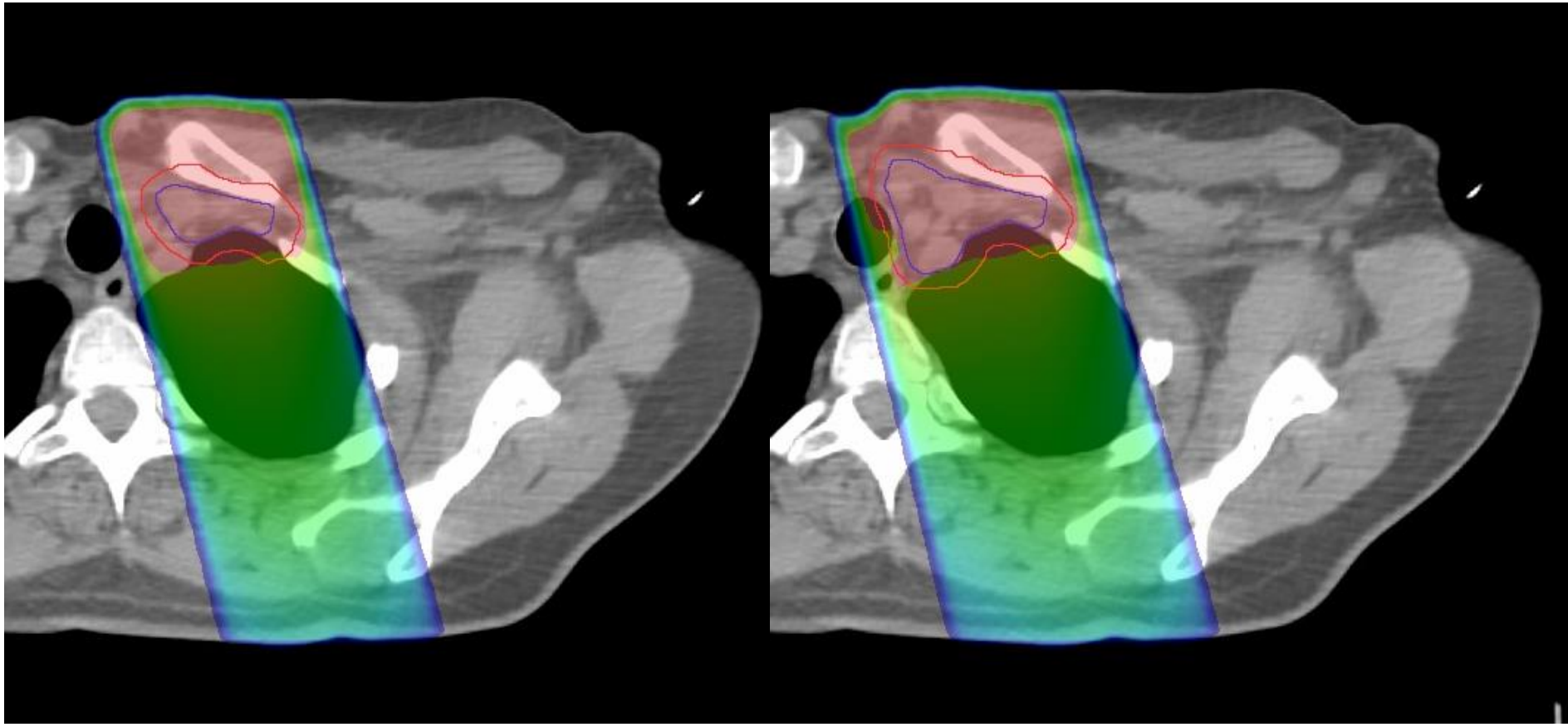


Range 20%-90%

L4 Student’s structure



Range 20%-90%



Range 20%-90%

Comparison of different techniques

Lymph nodes: techniques

- FiF (combined with wedges for lymph nodes)
- Hybrid: 80% open fields for breast combined with 20% VMAT for breast and 100% VMAT for lymph nodes
- Full VMAT

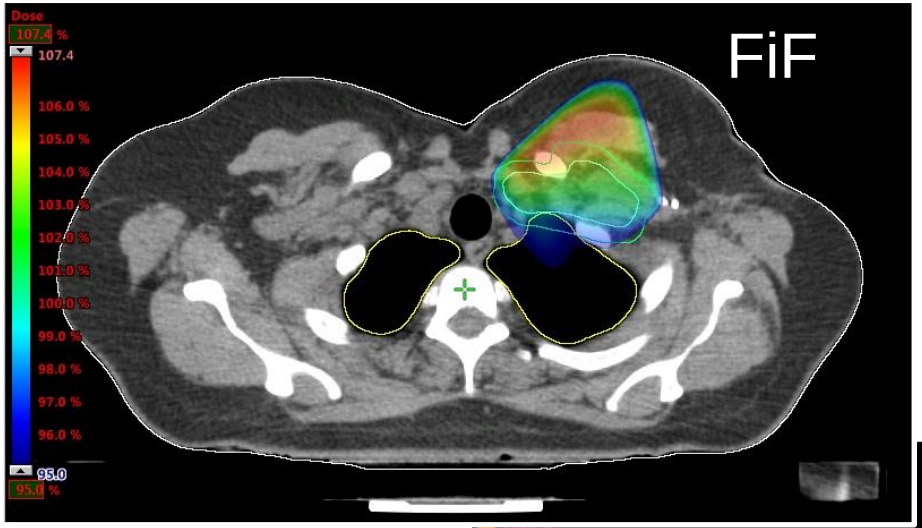
Differences between techniques

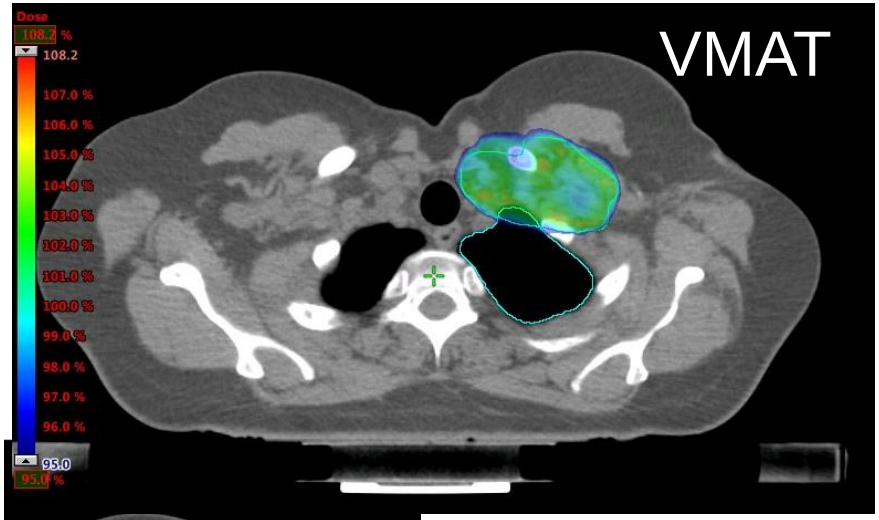
- No strict junction with hybrid and VMAT
- Better coverage lymph nodes with hybrid and VMAT
- Higher MHD if MHD is below 3 Gy with hybrid and VMAT (approximately 0,5 Gy for hybrid and sometimes more for VMAT)

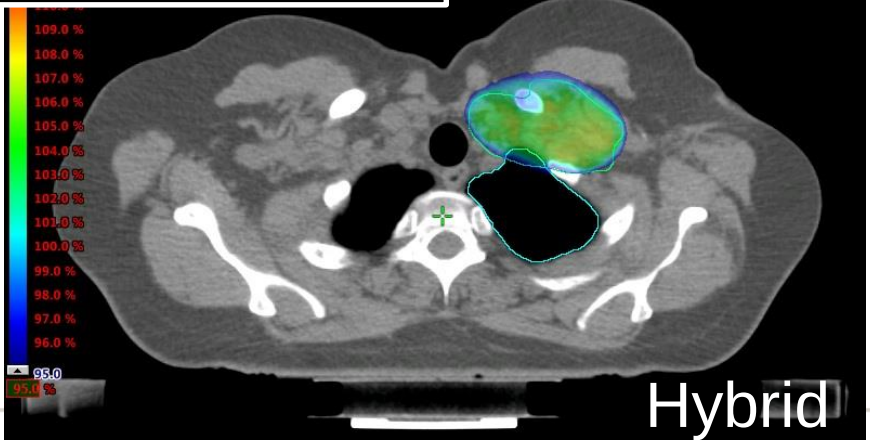
Left Breast and lymph nodes

- 16 x 2,66 Gy

Isodoses

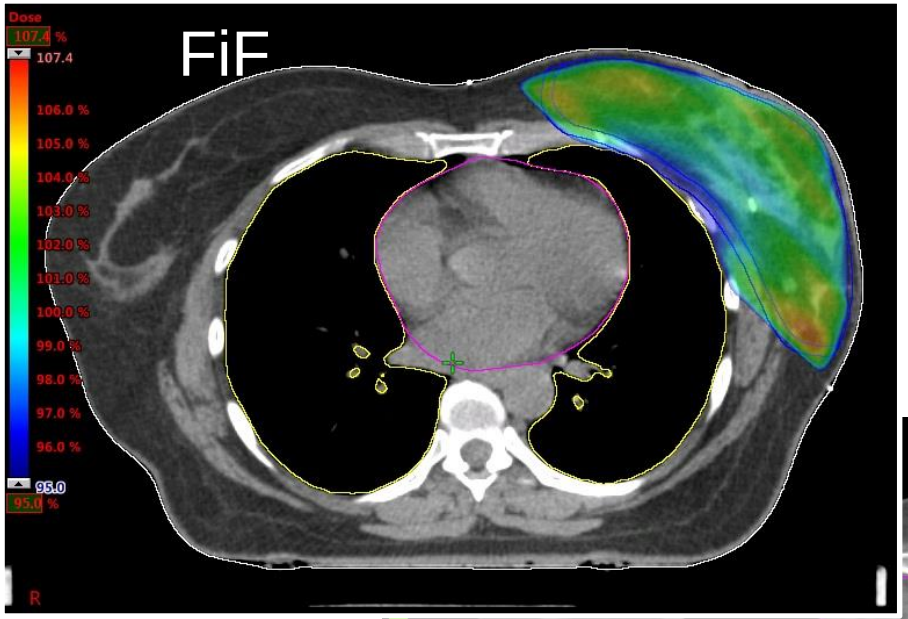




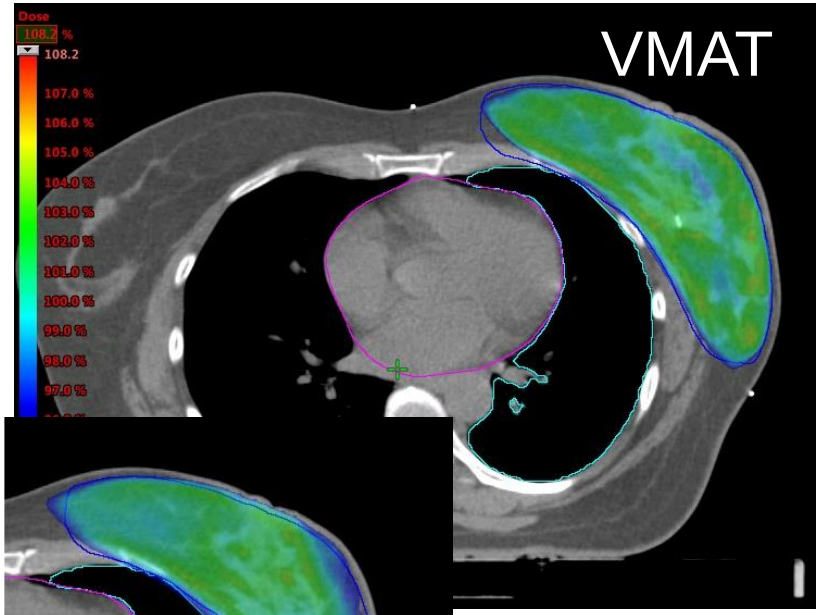


ESTRO School

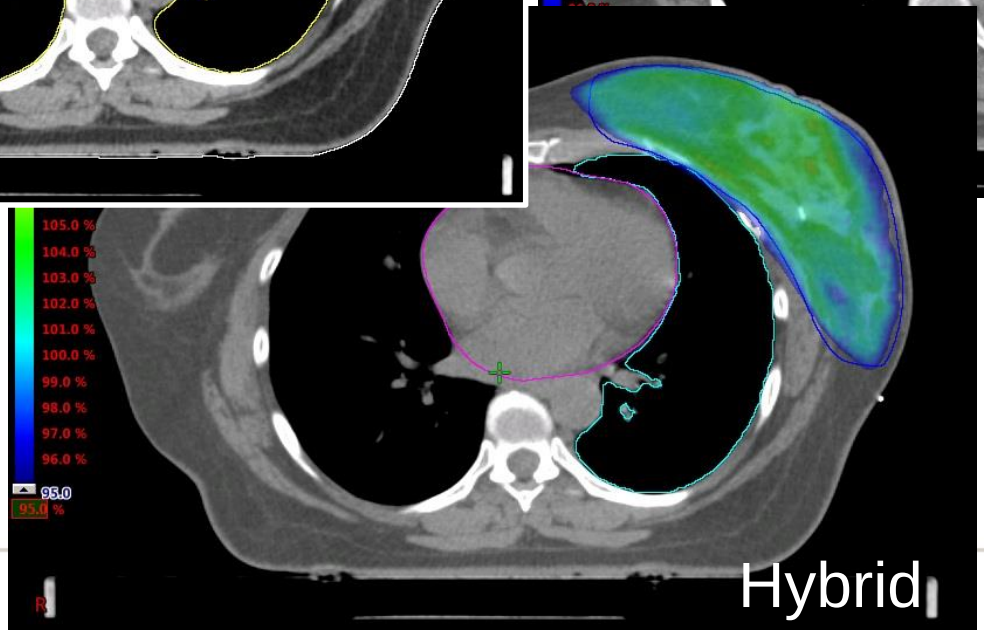
Isodoses



FiF



VMAT



Hybrid

ESTRO School

Isodoses

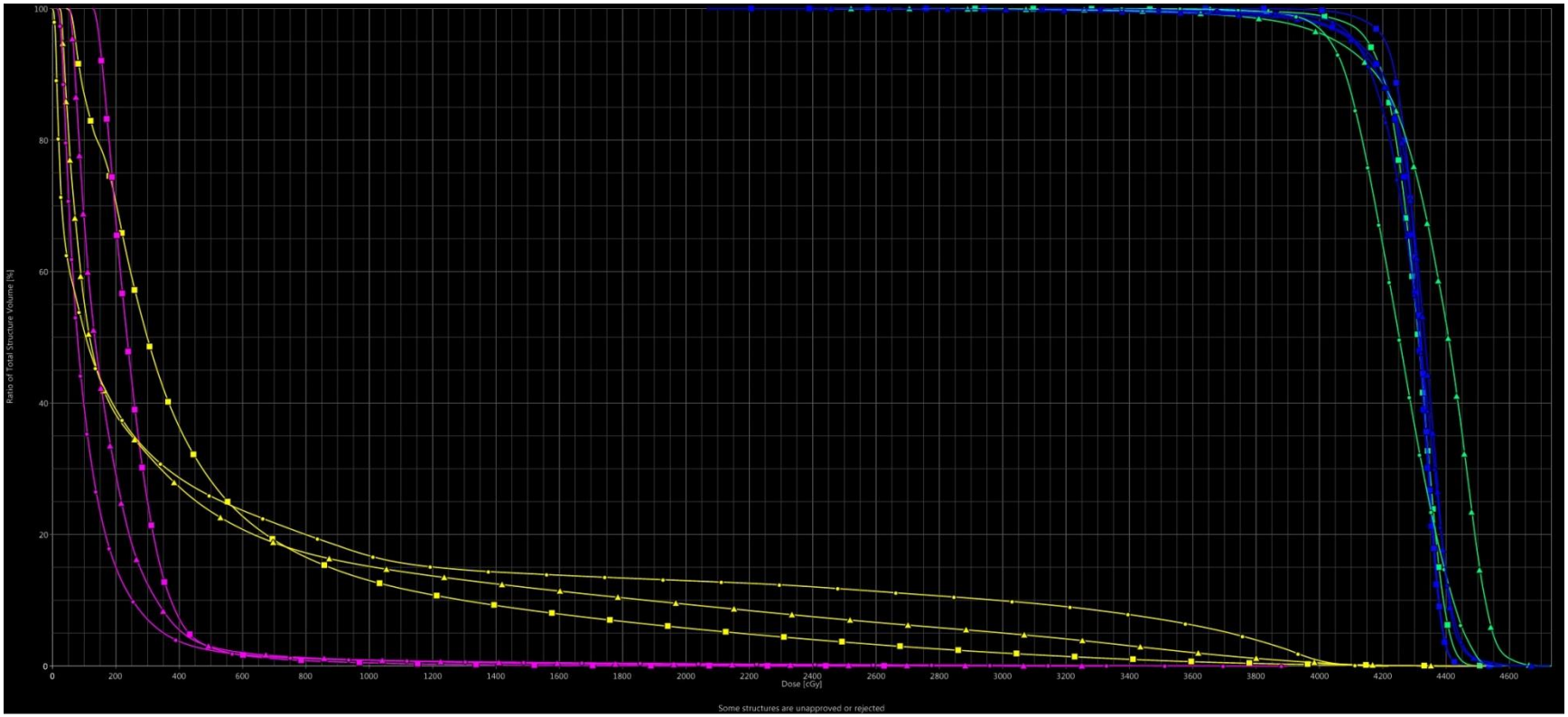
FiF

Hybrid

VMAT

ESTRO School

DVH



- ■ VMAT
- ▲ Hybrid
- ● FiF

ESTRO School

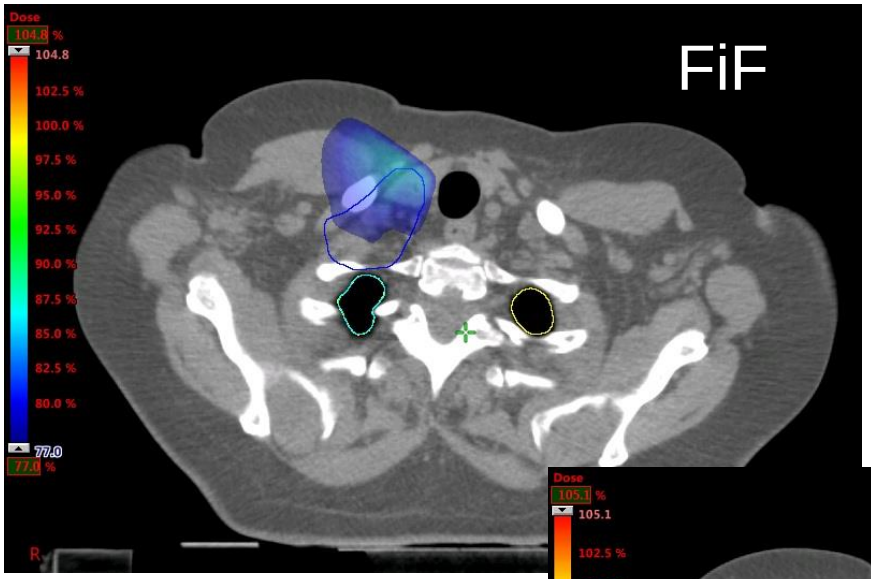
DVH values

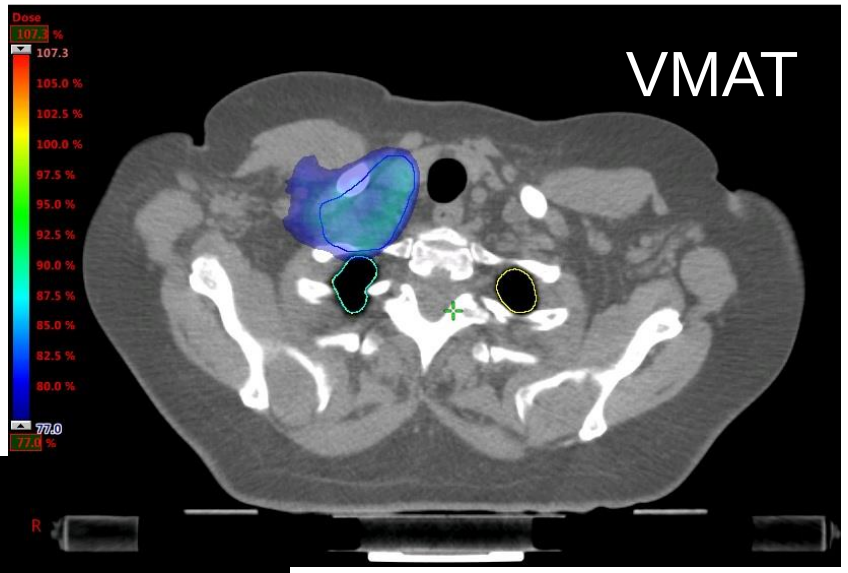
	Lungs		Heart			
	V20	MLD	V20	V10	V5	MHD
FiF	13	634	0,4	0,9	2,4	131
Hybrid	9,4	526	0,2	0,9	2,9	183
RA	5,8	538	0	0,5	2,8	261

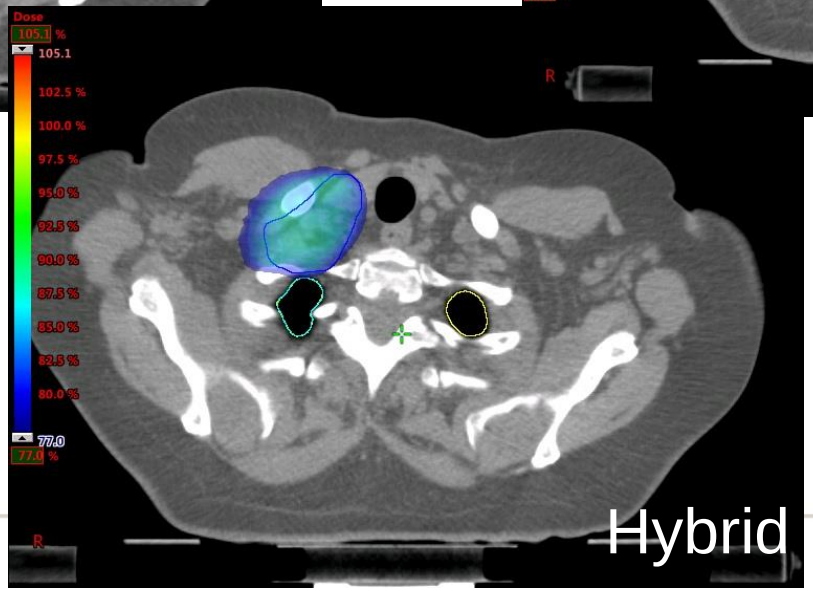
Right Breast and lymph nodes SIB

- 21 x 2,17 Gy on whole breast and lymph nodes
- 21 x 2,66 Gy on primary tumorbed

Isodoses

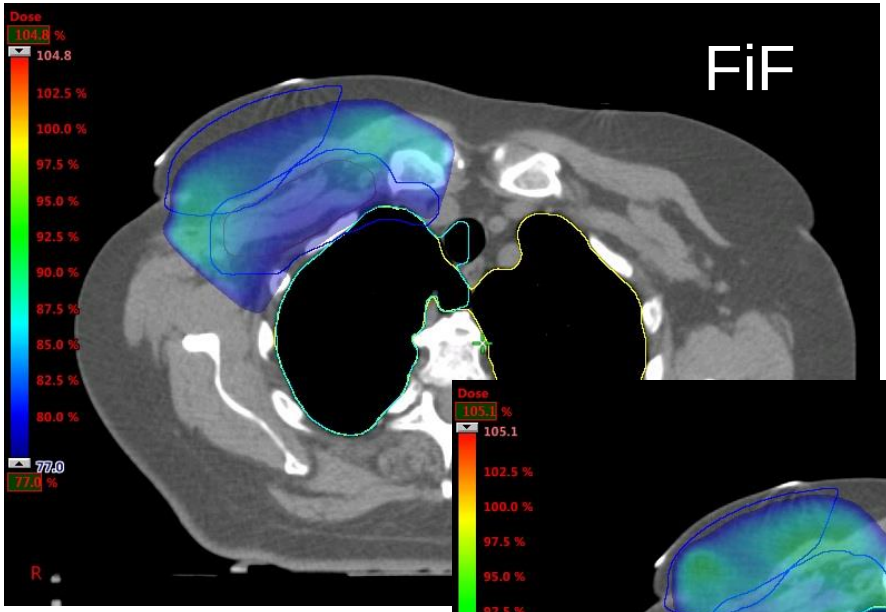


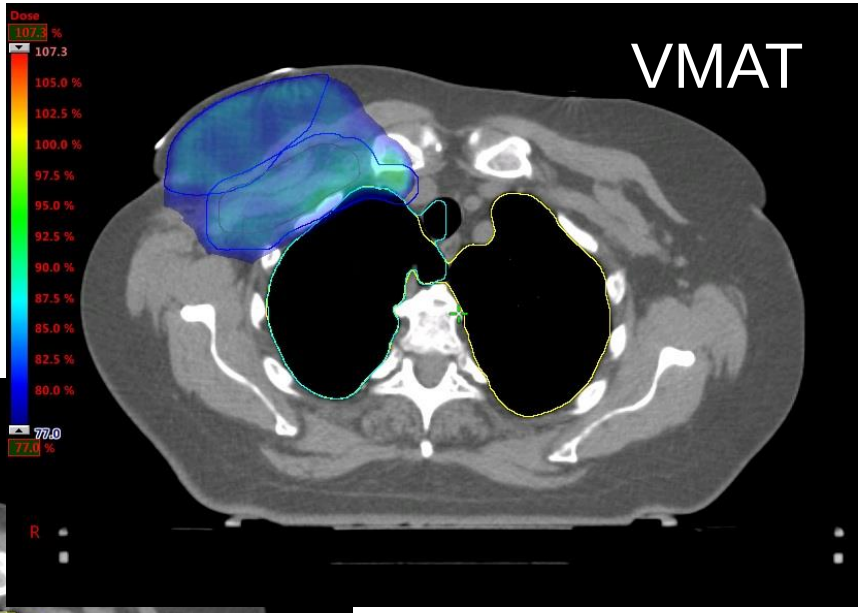


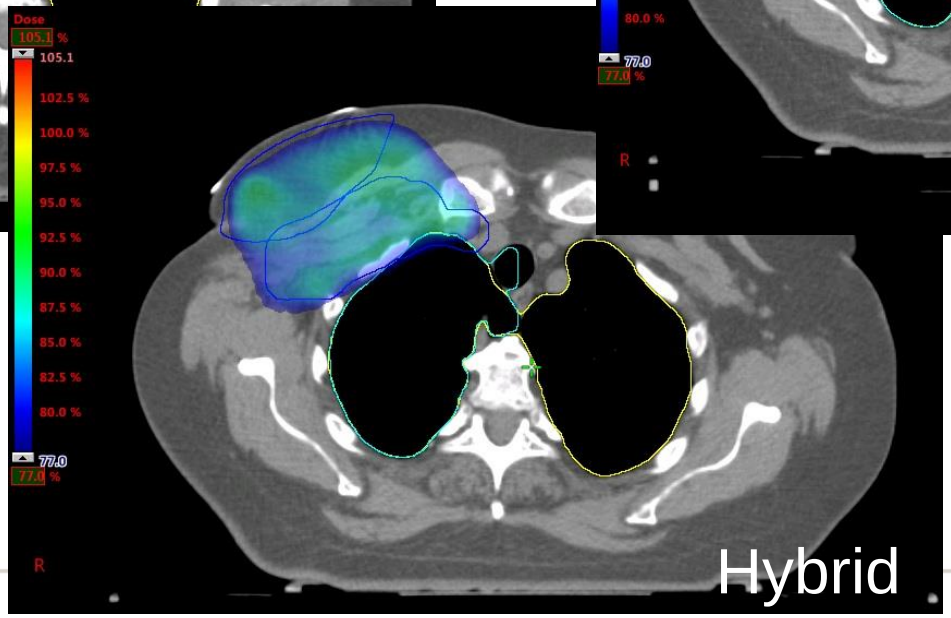


ESTRO School

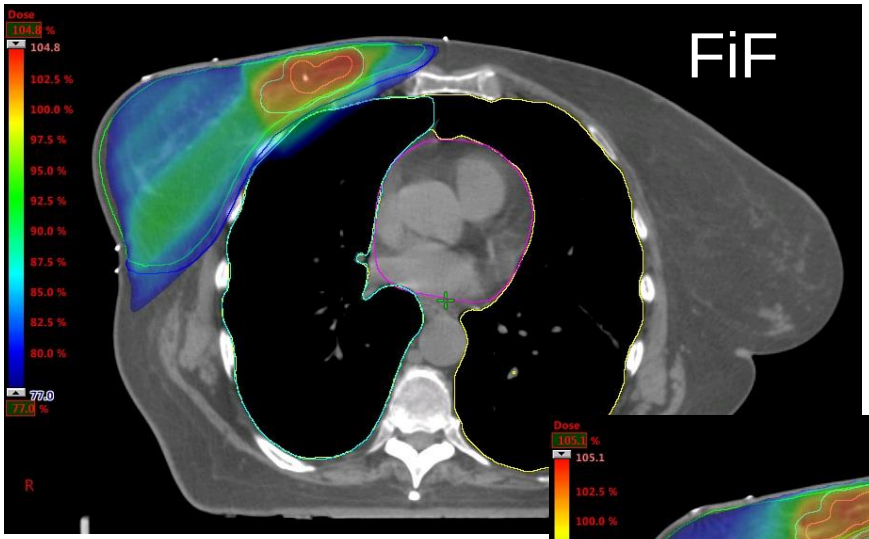
Isodoses

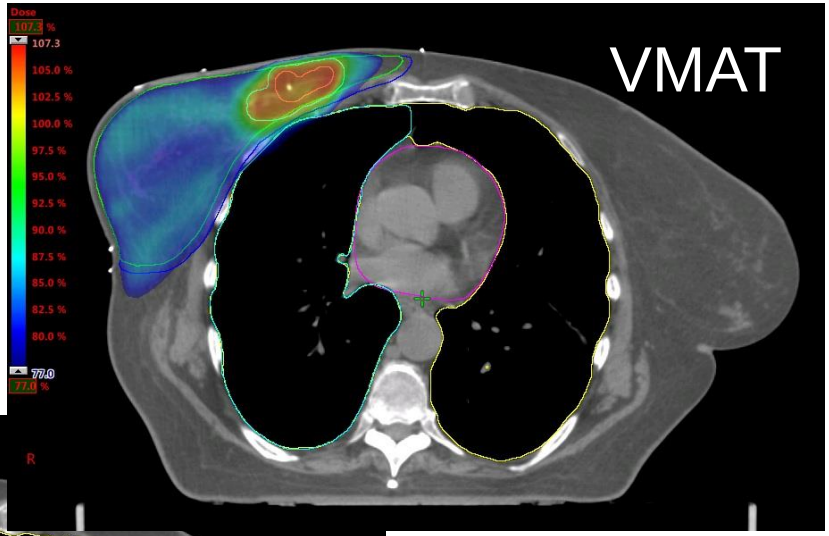


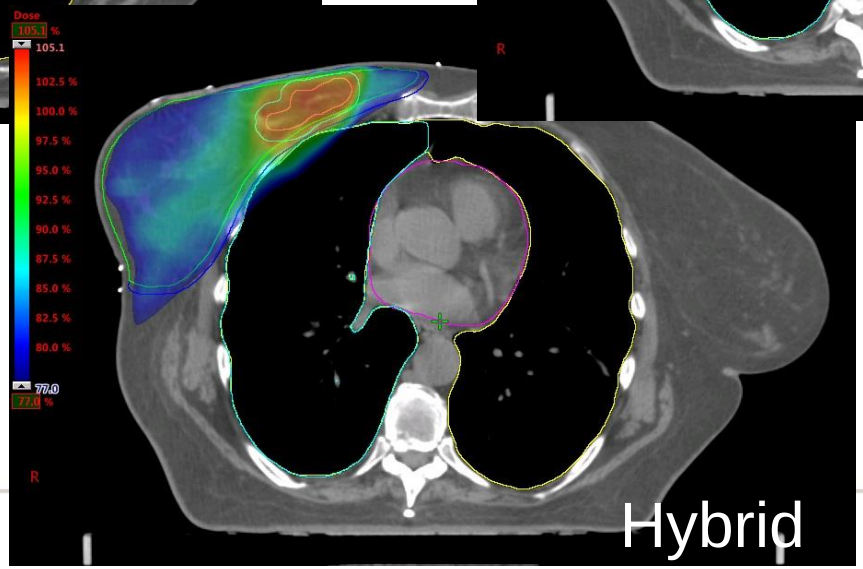




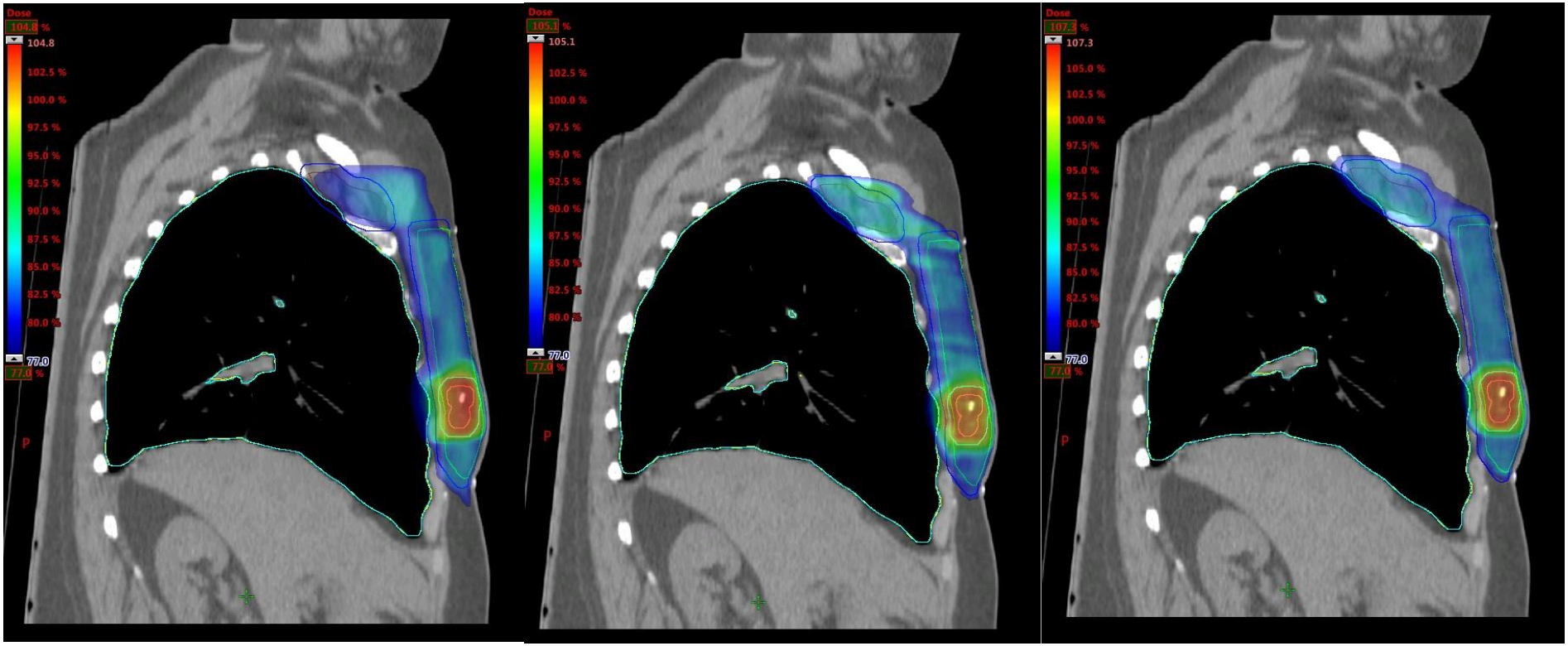
Isodoses







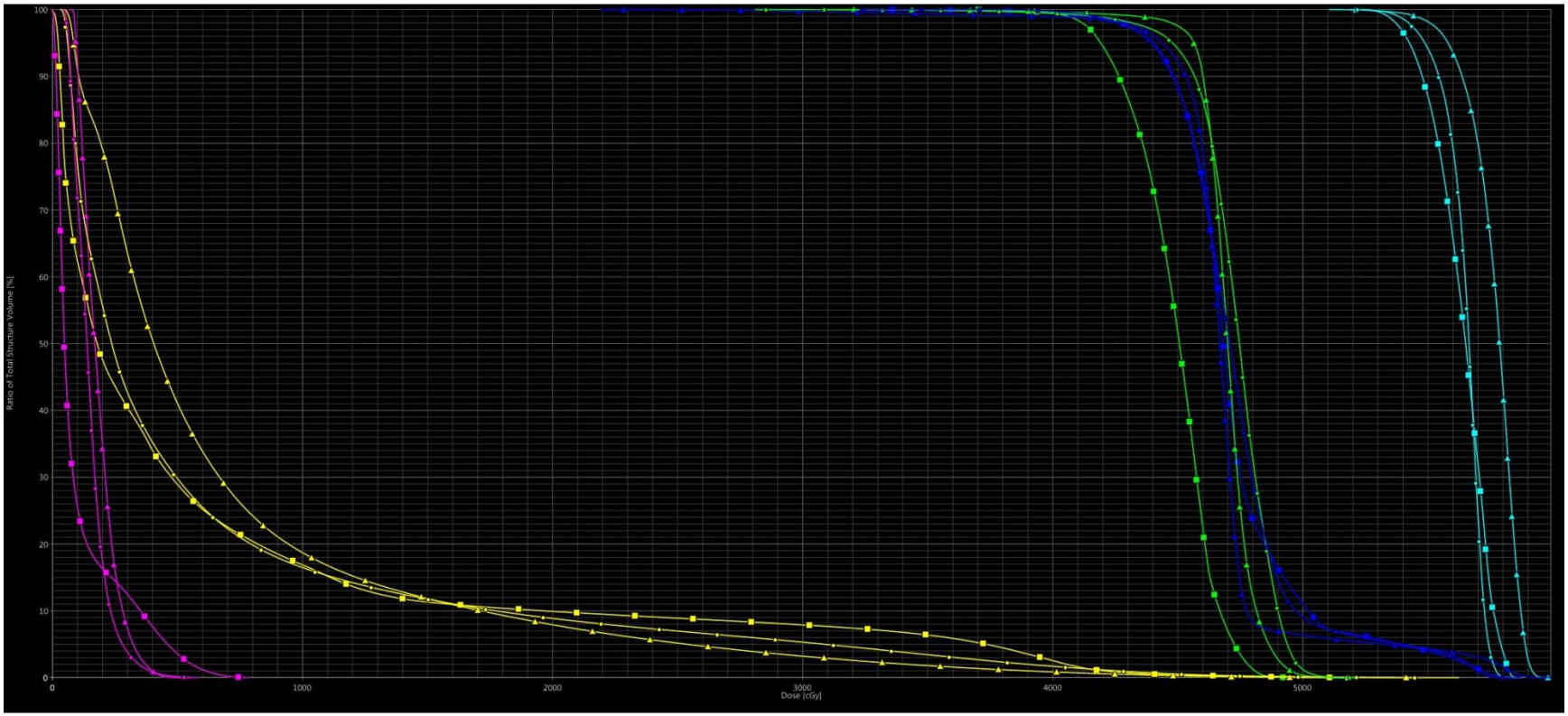
Isodoses



FiF Hybrid VMAT

ESTRO School

DVH



- ■ FiF
- ▲ VMAT
- ● Hybrid

ESTRO School

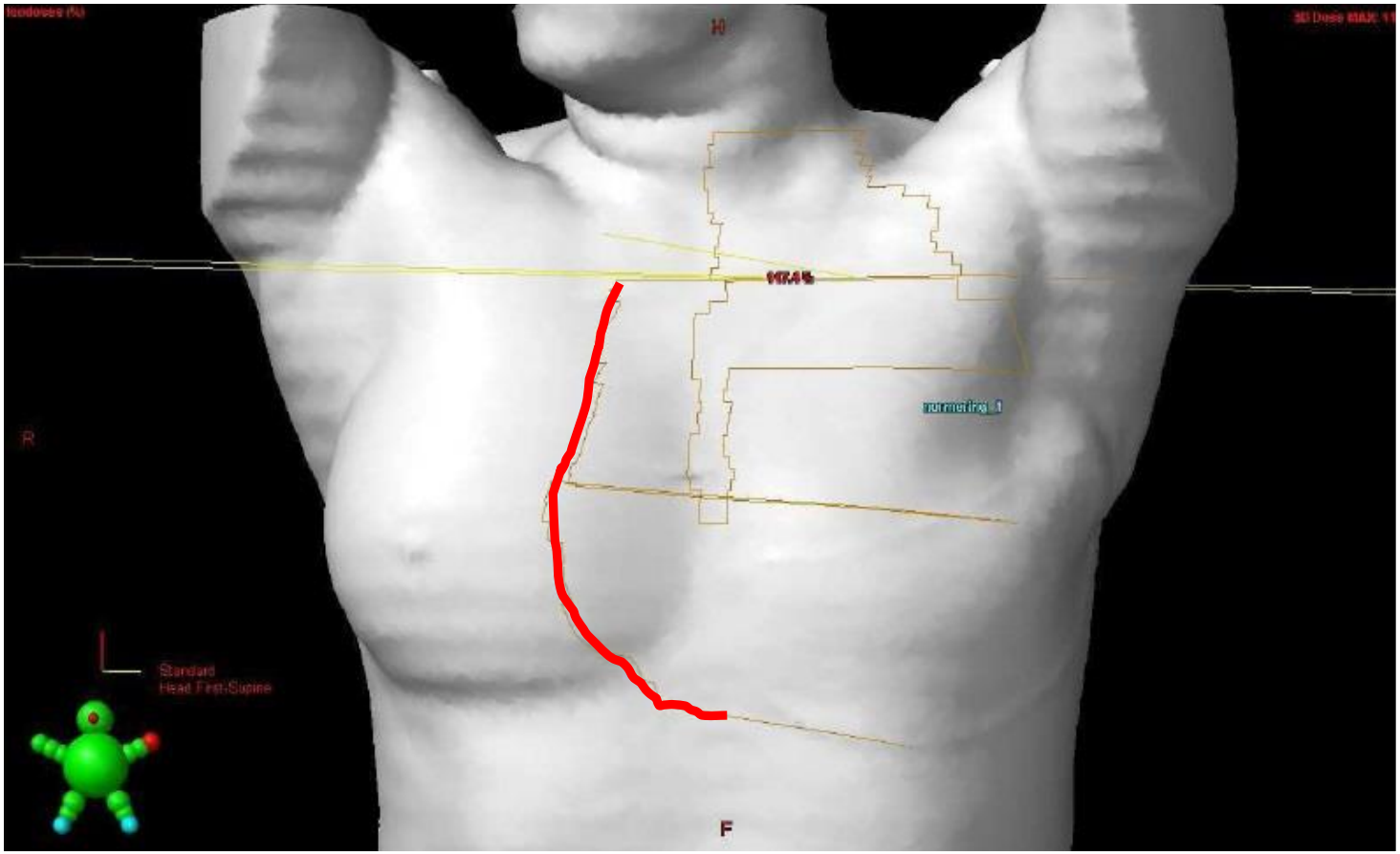
DVH values

	Lungs		Heart			
	V20	MLD	V20	V10	V5	MHD
FiF	9,9	631	0	0	3,5	108
Hybrid	8,9	619	0	0	0,1	148
RA	7,9	691	0	0	0	182

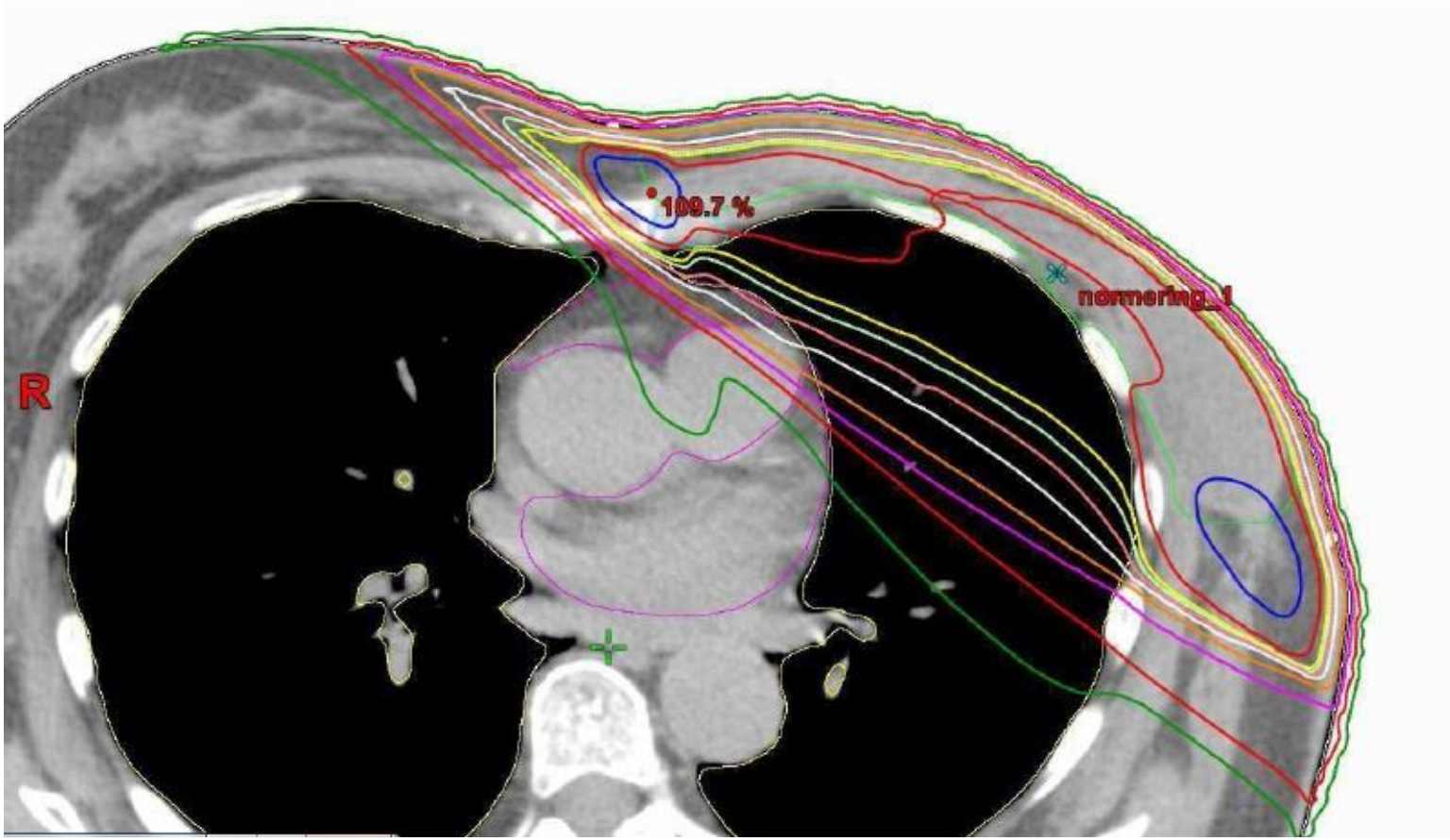
IMN techniques

- Tangents
- VMAT/IMRT
- Hybrid
- Other

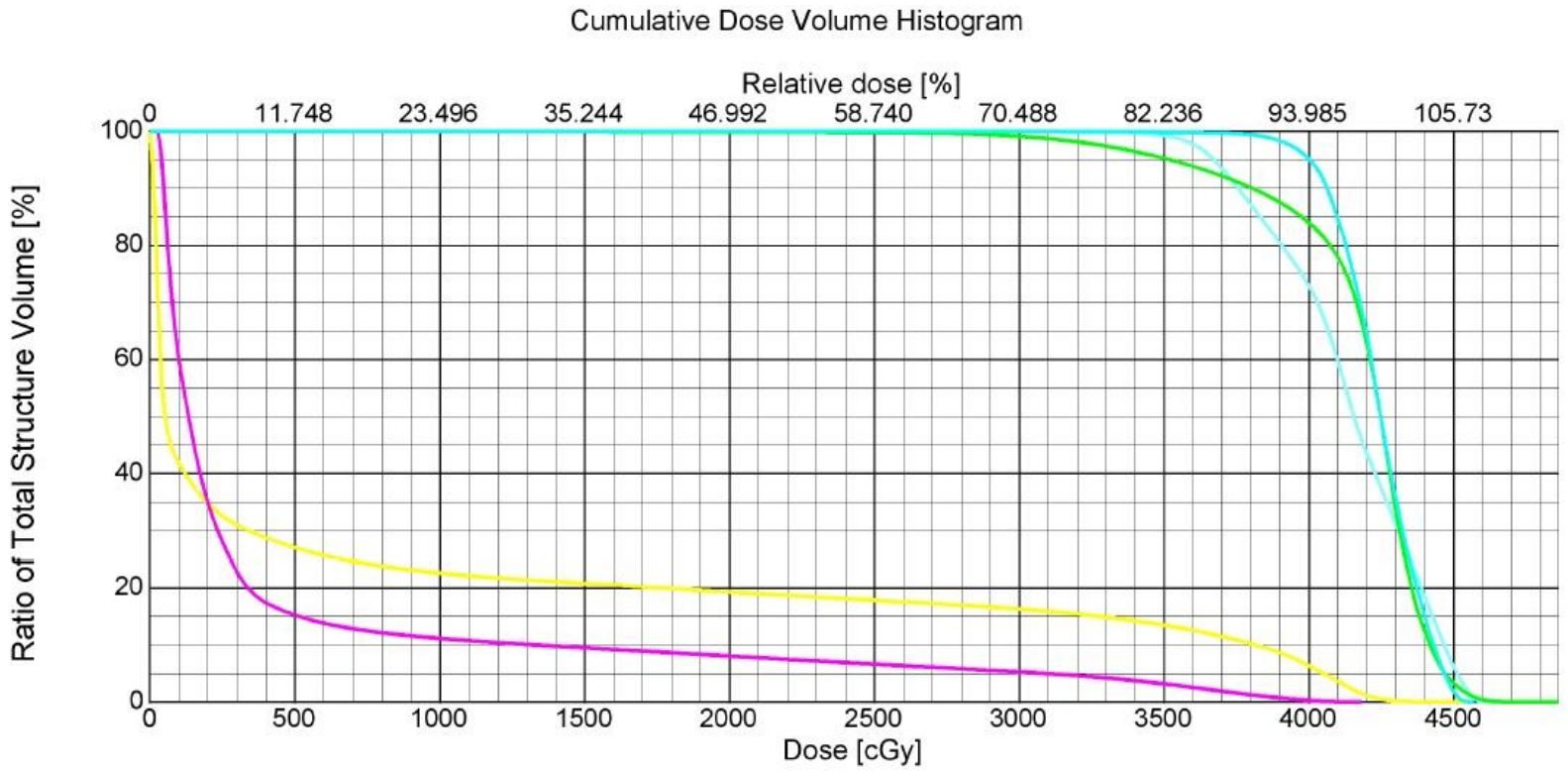
Tangents



ESTRO School

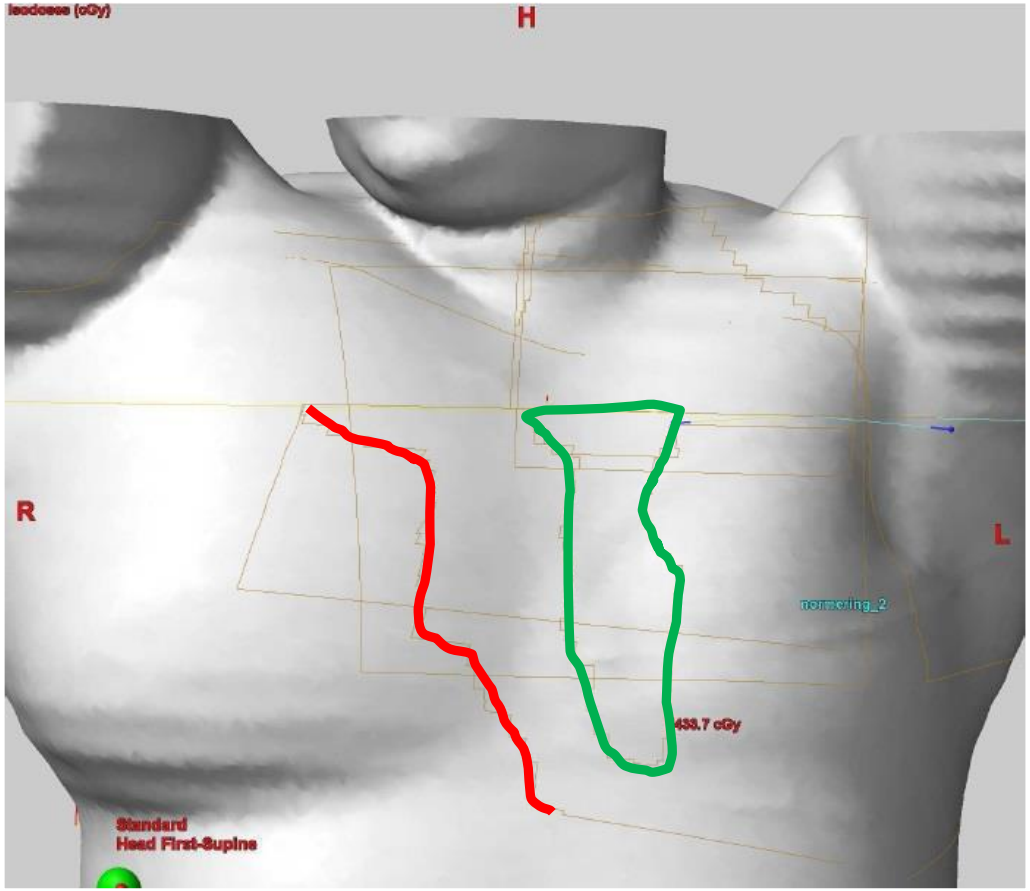


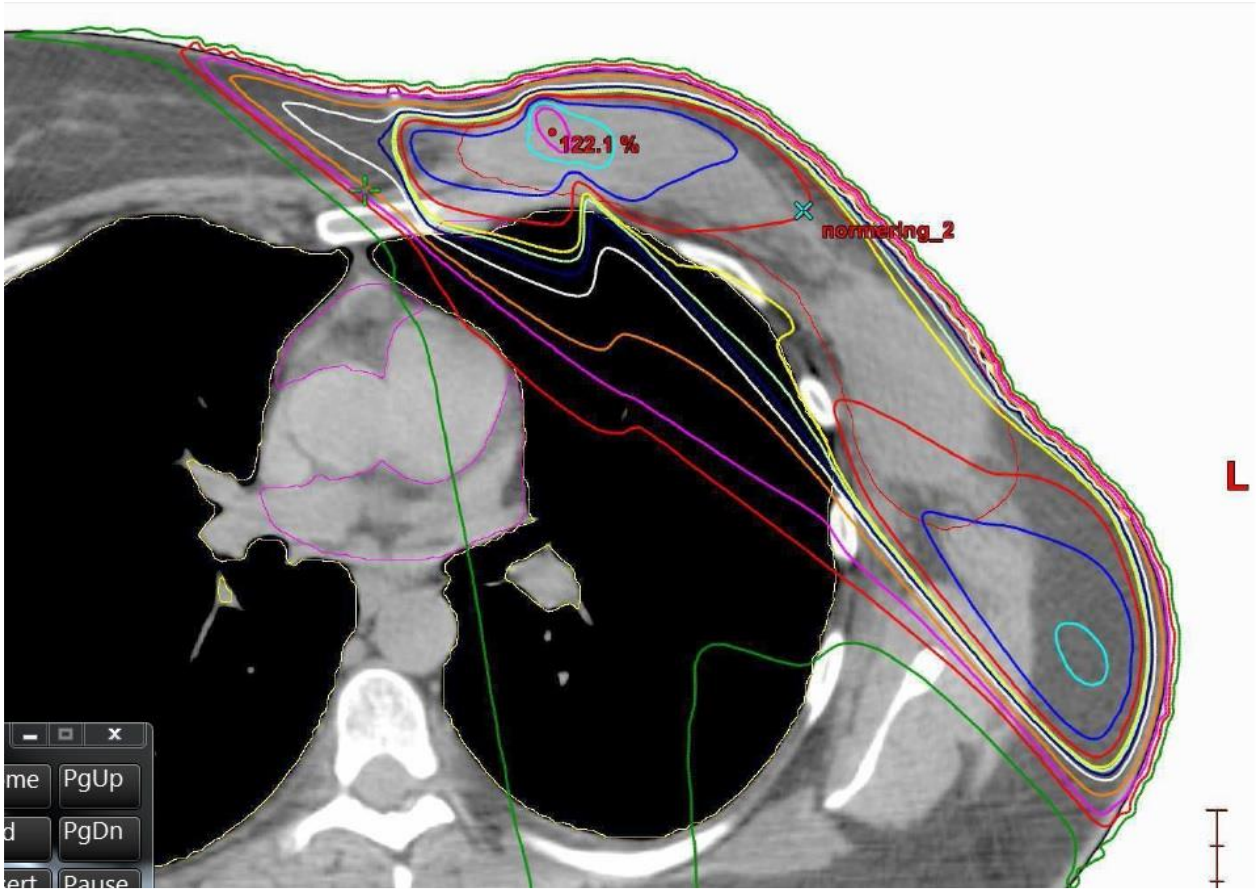
ESTRO School

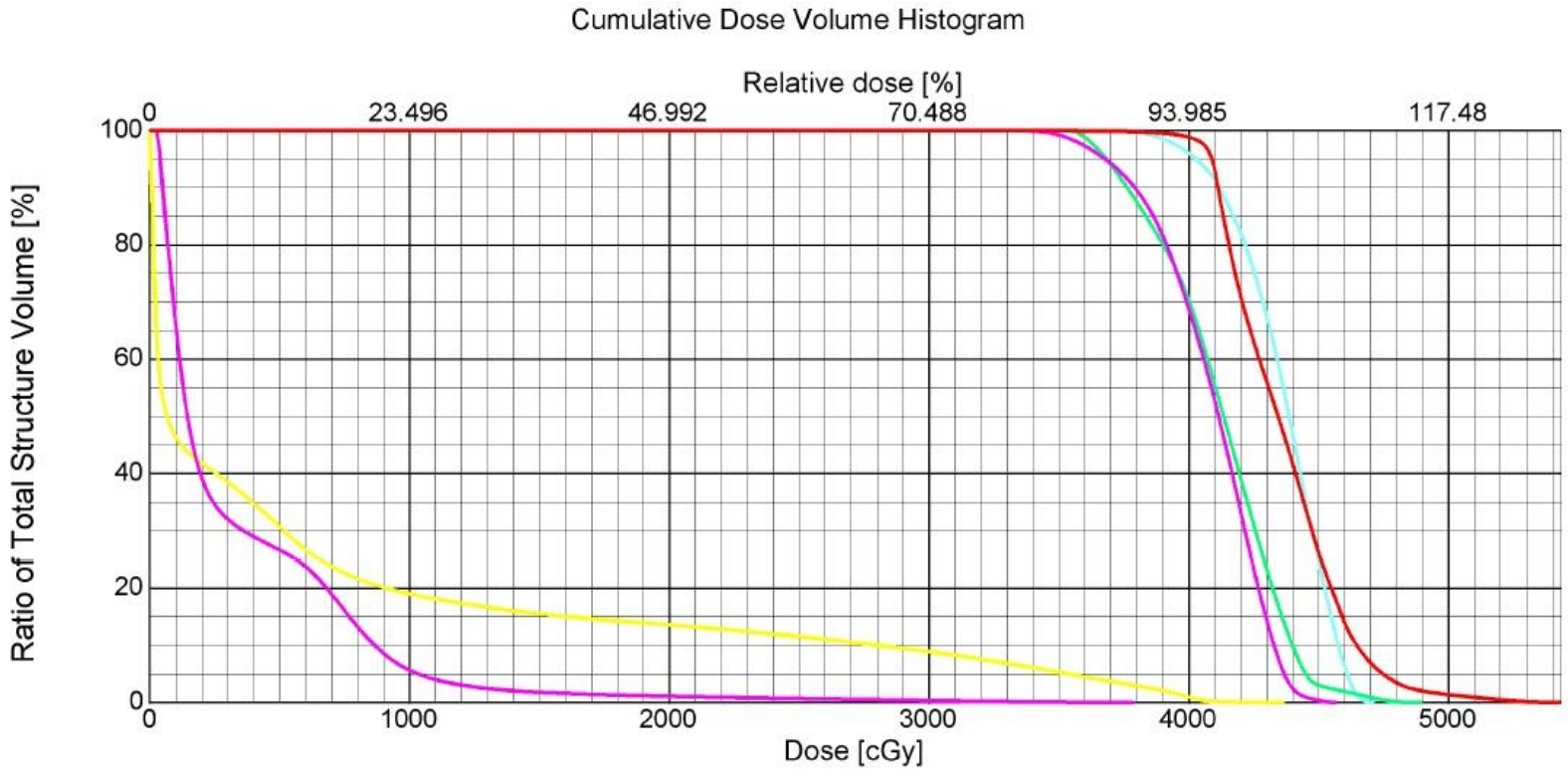


Structure	Structure Status	Coverage [%/%]	Volume	Min Dose	Max Dose	Mean Dose	Modal Dose	Median Dose	Std Dev
hart	Approved	100.0 / 100.0	668.2 cm³	24.4 cGy	4181.4 cGy	450.6 cGy	50.9 cGy	133.3 cGy	874.2 cGy
longen	Approved	100.0 / 100.0	3599.8 cm³	0.0 cGy	4545.9 cGy	833.5 cGy	21.8 cGy	52.2 cGy	1421.4 cGy

Other




122.1 %
normering_2
L
PgUp
PgDn

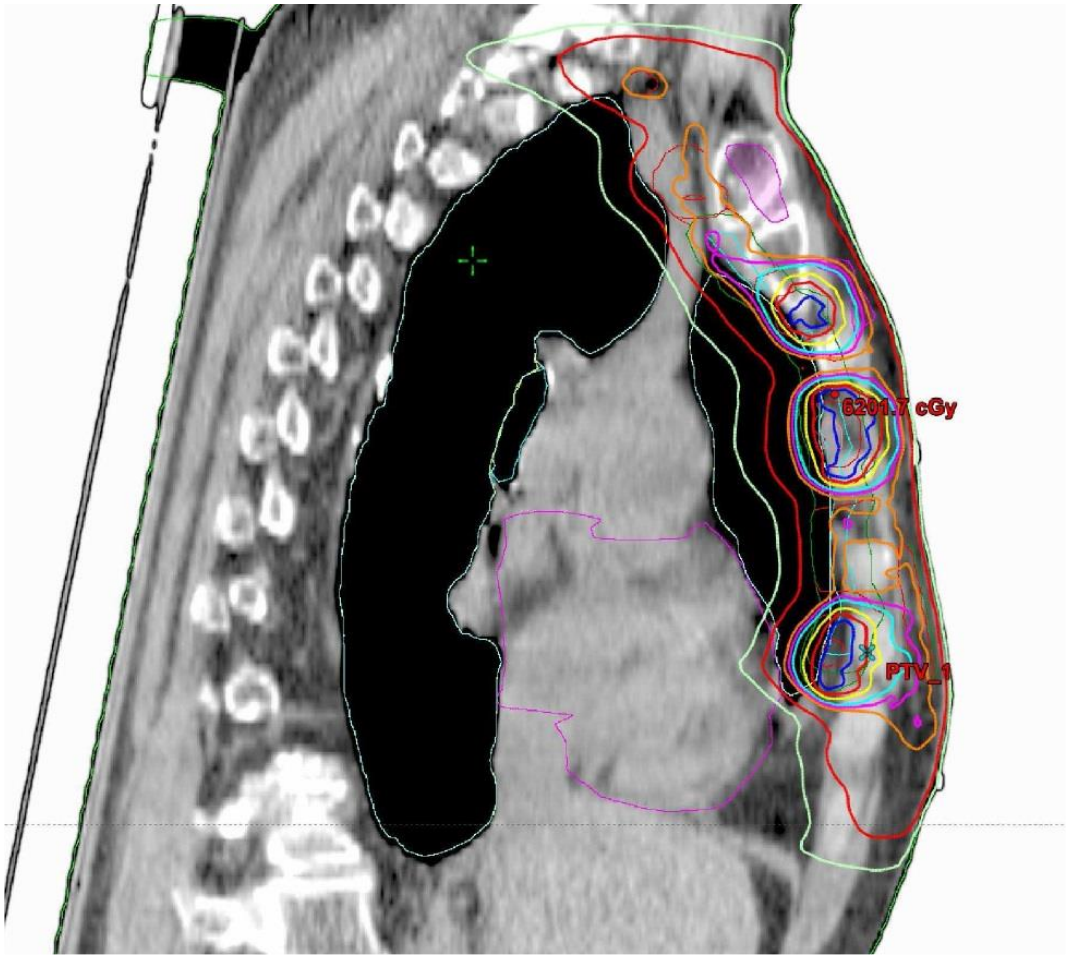


Structure	Structure Status	Coverage [%/%]	Volume	Min Dose	Max Dose	Mean Dose	Modal Dose	Median Dose	Std Dev
hart2	Approved	100.0 / 100.0	696.5 cm³	22.3 cGy	3787.1 cGy	341.0 cGy	49.9 cGy	144.5 cGy	424.9 cGy
longen	Approved	100.0 / 100.0	5623.6 cm³	0.0 cGy	4369.9 cGy	654.9 cGy	0.4 cGy	66.3 cGy	1105.6 cGy

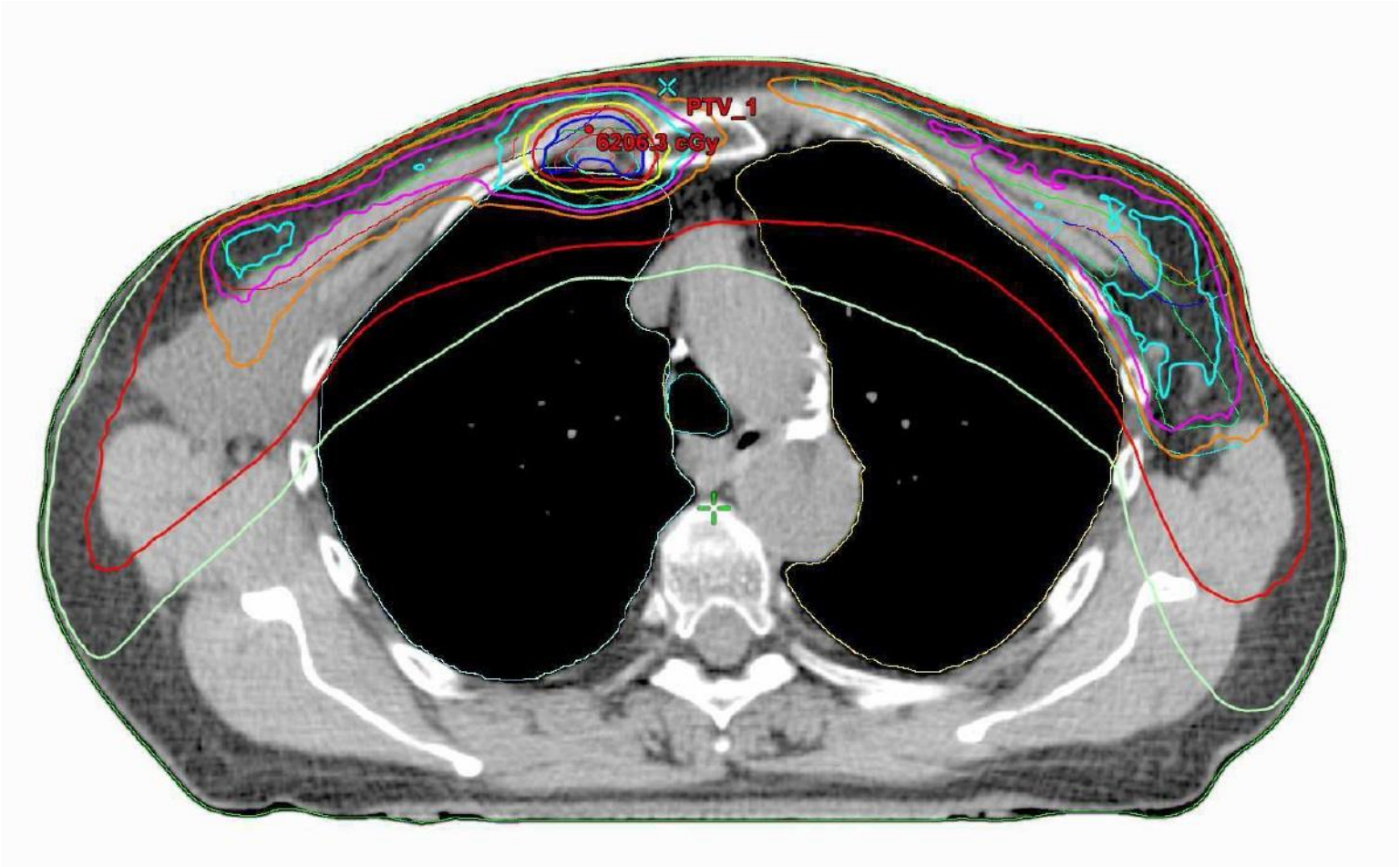
Bilateral thoracic wall + IMN 3 boosts

- 21 x 2,17 Gy to thoracic wall left and right
- 21 x 2,66 Gy to IMN nodes

Isodoses

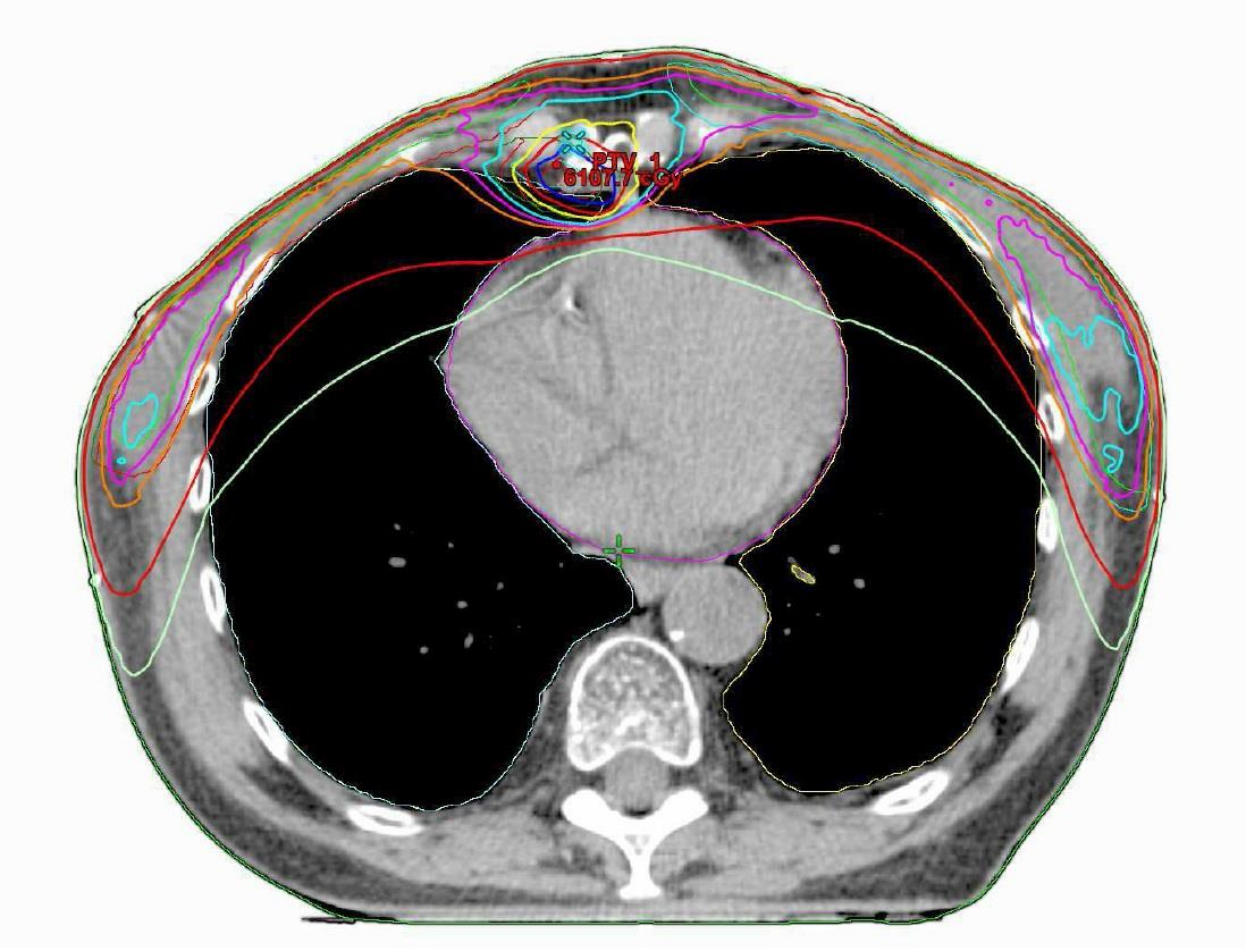


Isodoses



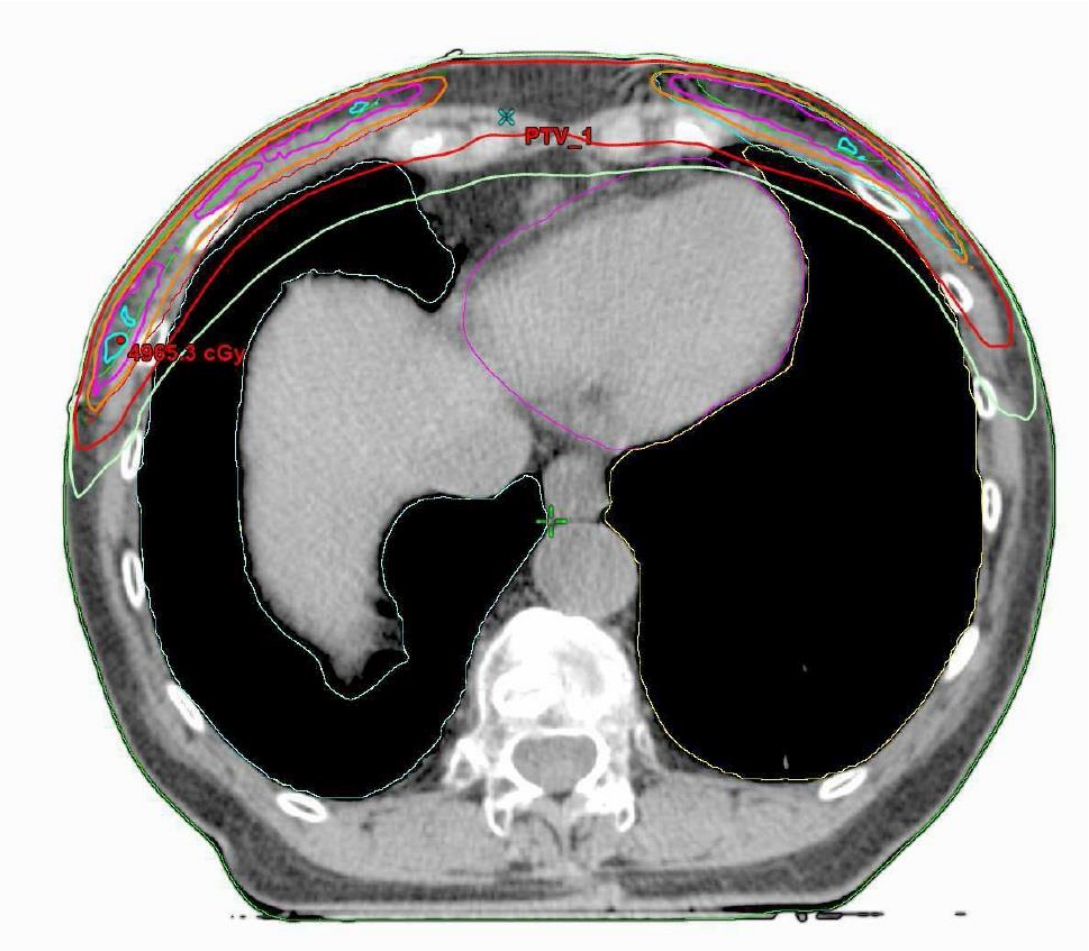
ESTRO School

Isodoses



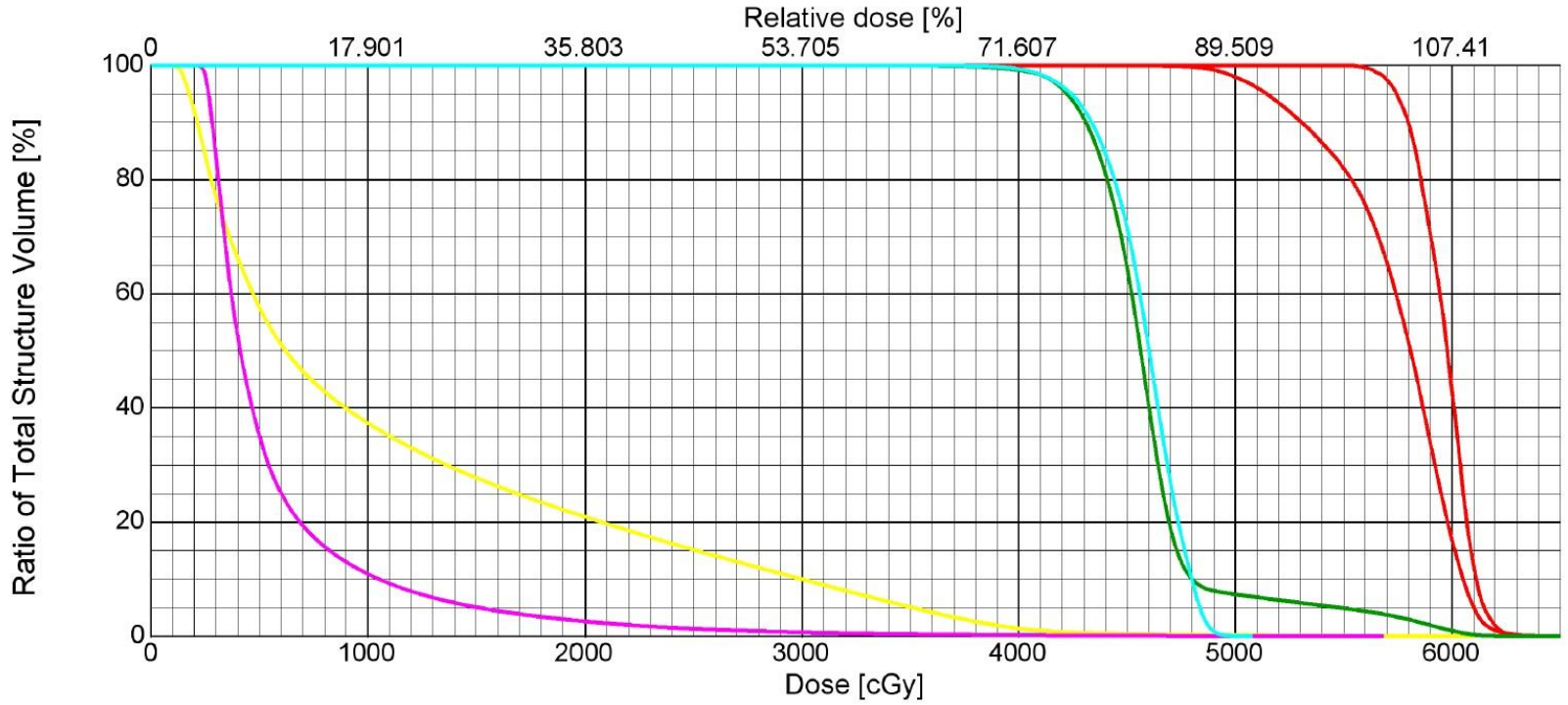
ESTRO School

Isodoses



ESTRO School

DVH



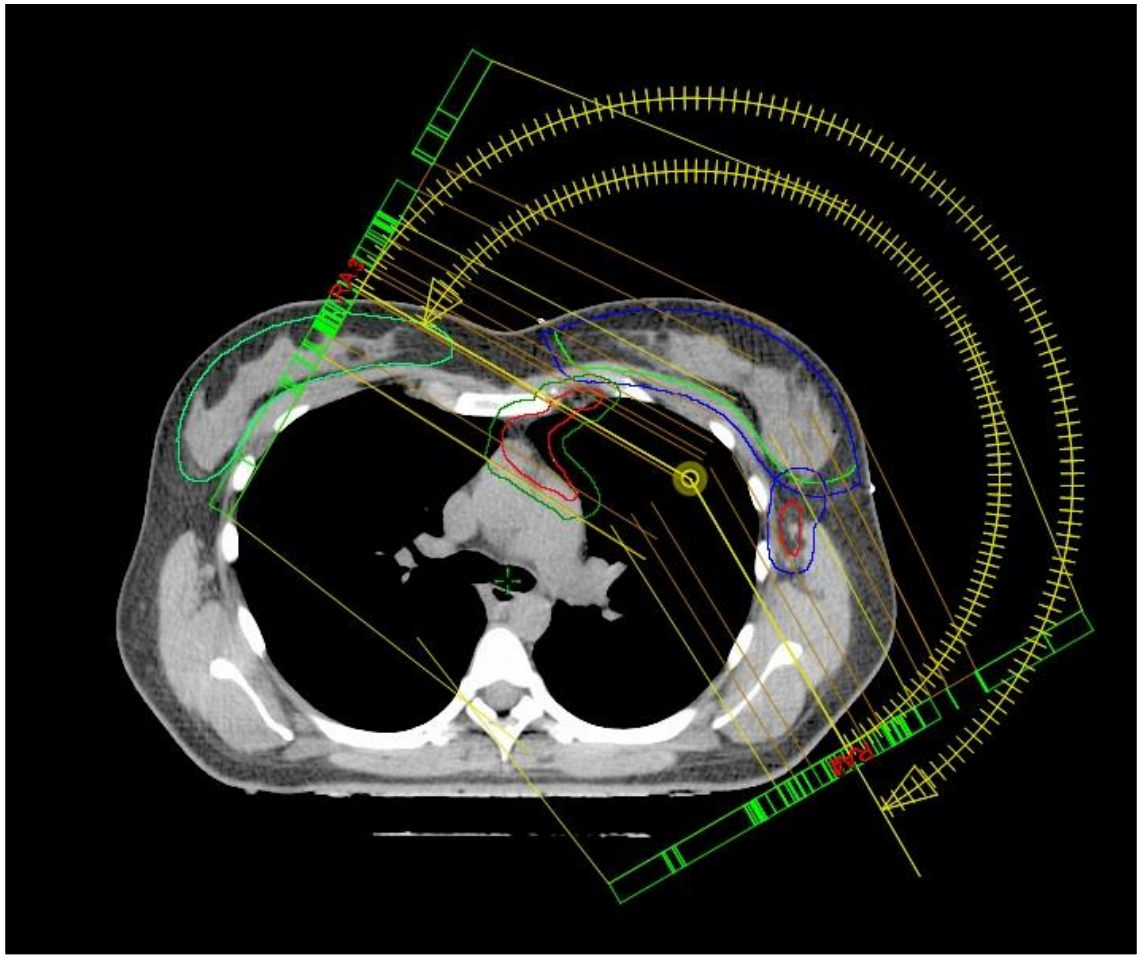
Structure	Structure Status	Coverage [%/%]	Volume	Min Dose	Max Dose	Mean Dose	Modal Dose	Median Dose	Std Dev
CTV_RparaRboos	Approved	100.0 / 99.7	5.3 cm³	5527.3 cGy	6328.0 cGy	5964.5 cGy	5978.2 cGy	5977.9 cGy	124.3 cGy
PTV_paraR_boost	Approved	100.0 / 100.1	28.5 cm³	4555.4 cGy	6500.4 cGy	5744.7 cGy	5851.2 cGy	5808.9 cGy	287.8 cGy
PTVtotaalre	Approved	100.0 / 100.0	499.9 cm³	3375.0 cGy	6500.4 cGy	4607.8 cGy	4576.8 cGy	4562.8 cGy	346.6 cGy
PTVtotaalli	Approved	100.0 / 100.0	577.6 cm³	3444.3 cGy	5078.9 cGy	4588.8 cGy	4617.5 cGy	4602.1 cGy	182.0 cGy
Heart	Approved	100.0 / 100.0	607.1 cm³	205.4 cGy	5683.3 cGy	576.3 cGy	313.5 cGy	411.1 cGy	483.5 cGy
Lungs	Approved	100.0 / 100.0	4051.2 cm³	69.1 cGy	6105.5 cGy	1135.8 cGy	250.9 cGy	621.1 cGy	1096.8 cGy

ESTRO School

Breast left , L1-L4, IMN

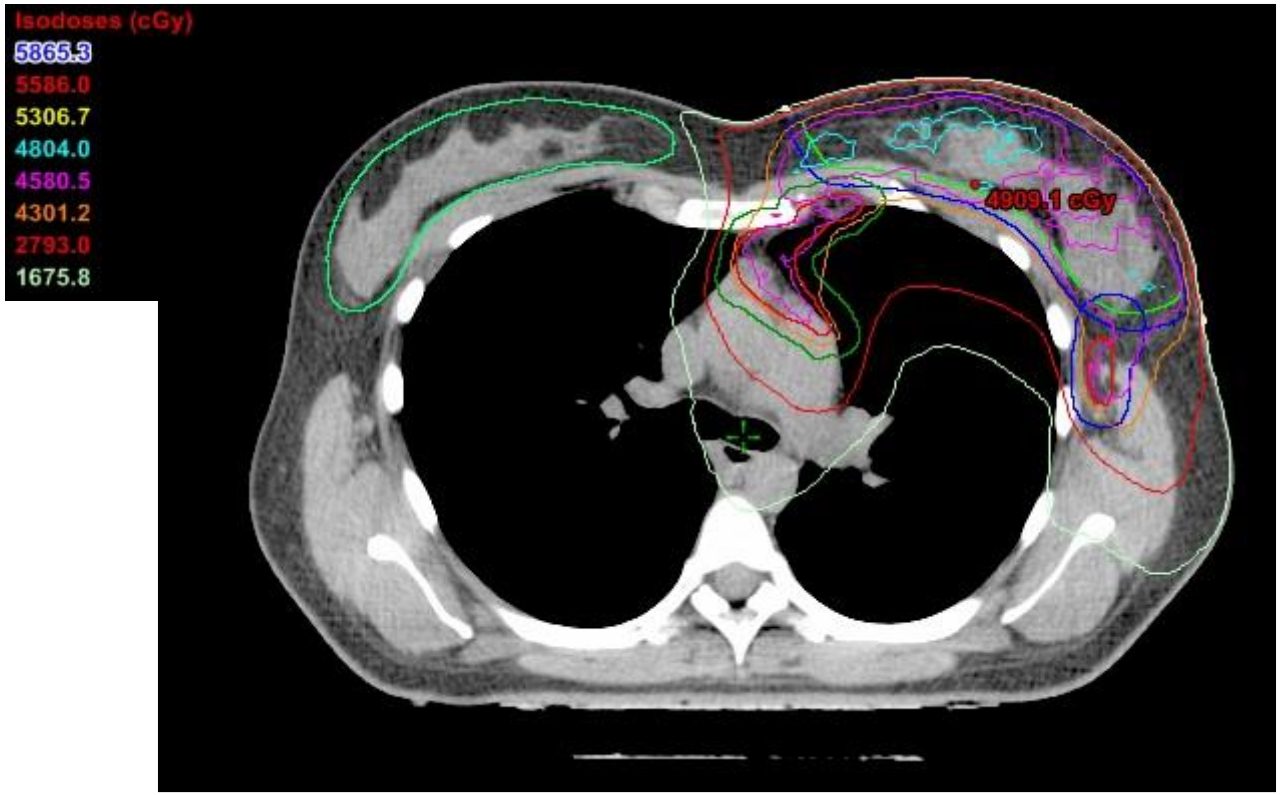
- 21 x 2,17 Gy on whole breast, L1-L4, IMN
- 21 x 2,66 Gy on primary tumorbed

Beams (4 arcs)

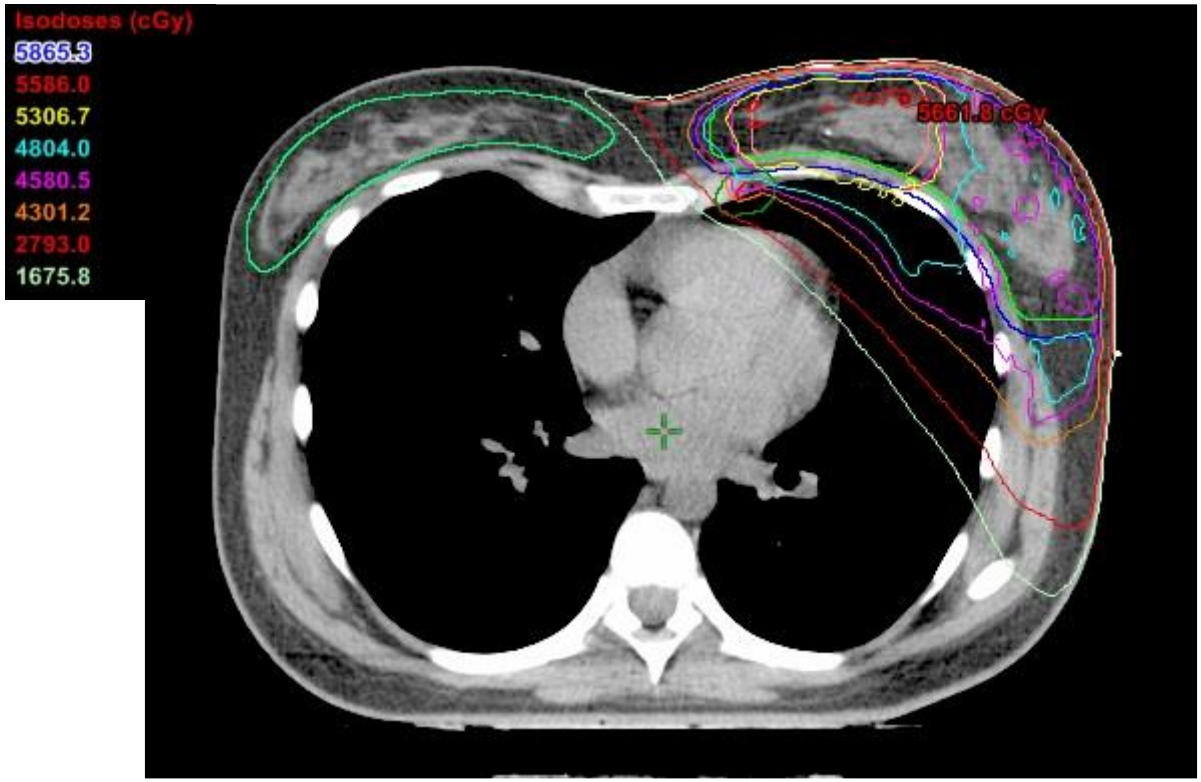


ESTRO School

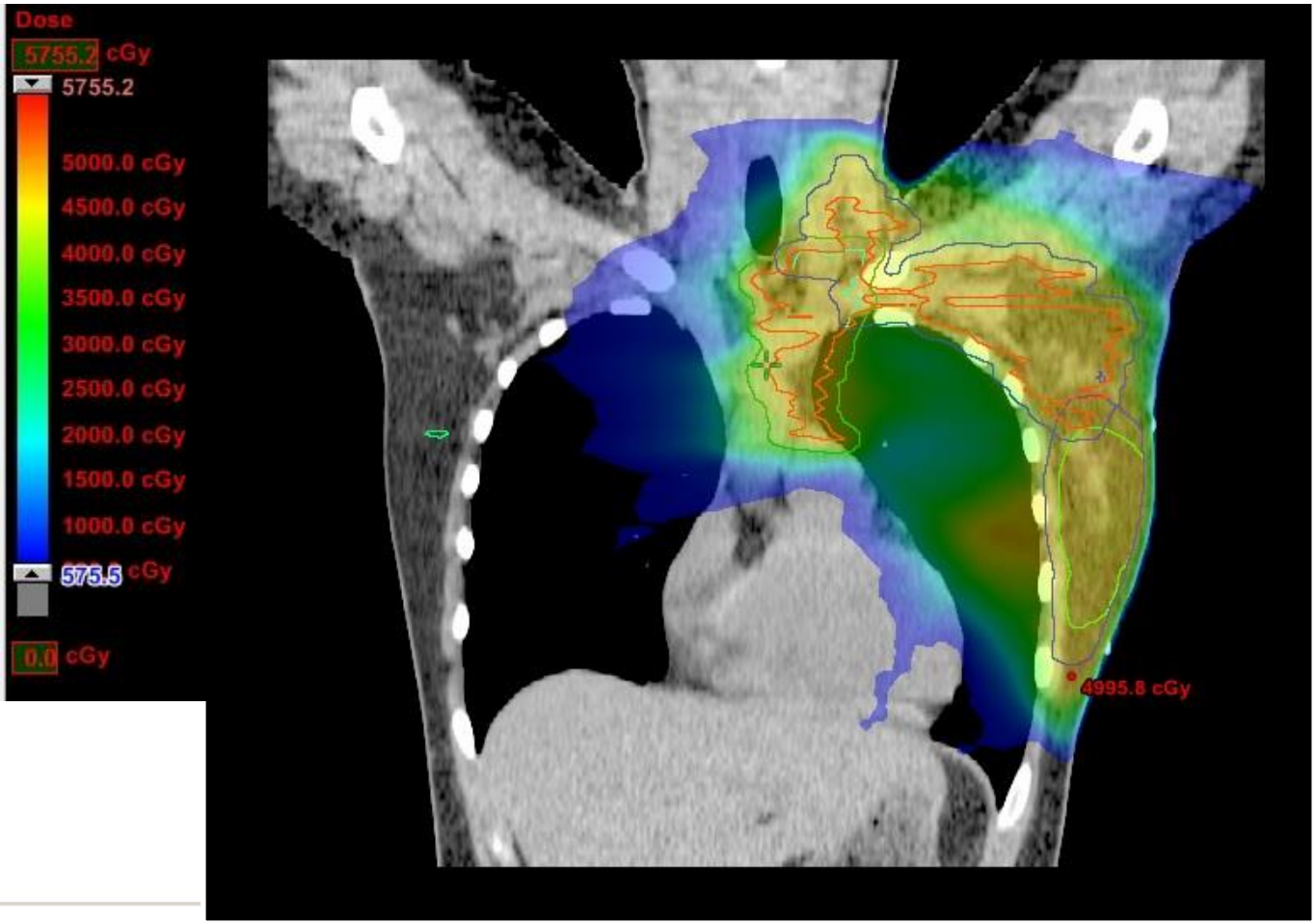
Isodoses


Isodoses (cGy)
5865.3
5586.0
5306.7
4804.0
4580.5
4301.2
2793.0
1675.8
4909.1 cGy

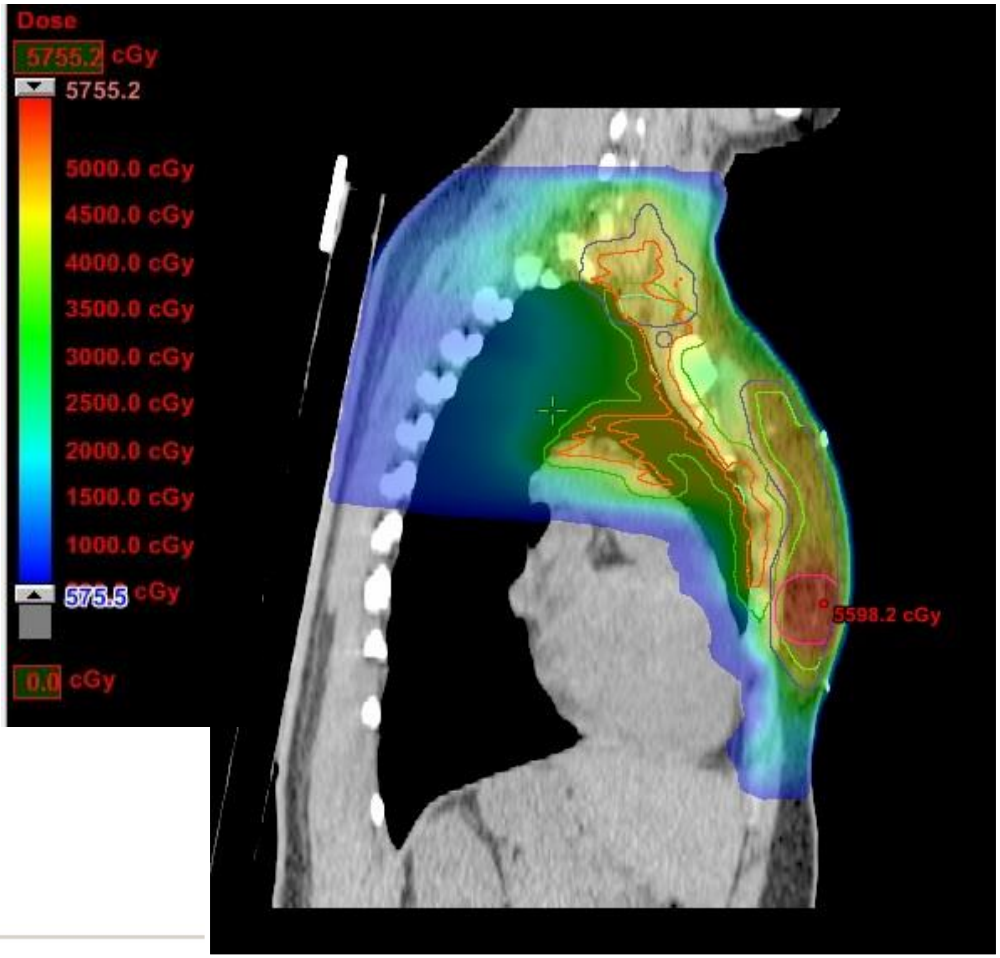
Isodoses


Isodoses (cGy)
5865.3
5586.0
5306.7
4804.0
4580.5
4301.2
2793.0
1675.8
5661.8 cGy

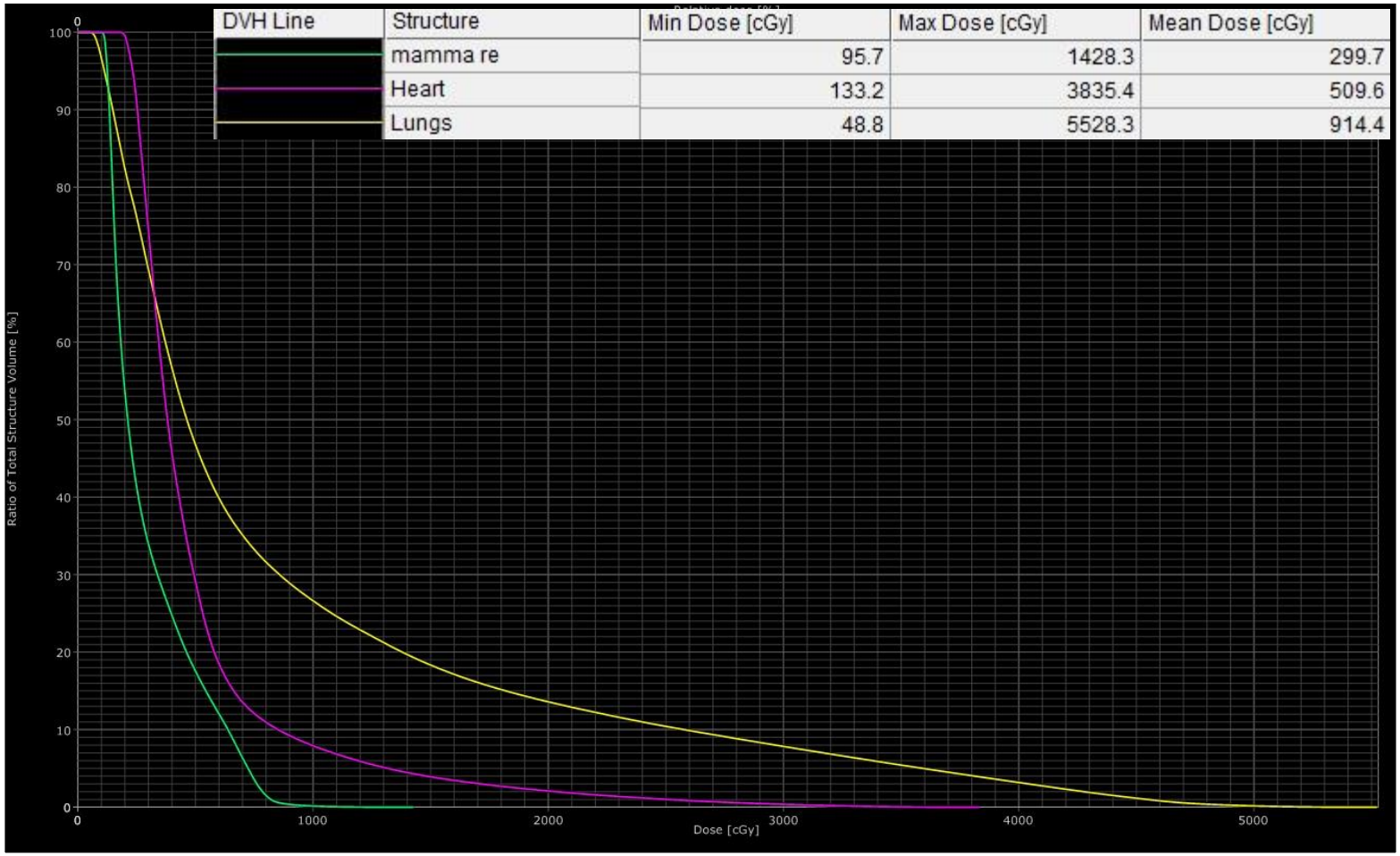
Isodoses


Dose
5755.2 cGy
5755.2
5000.0 cGy
4500.0 cGy
4000.0 cGy
3500.0 cGy
3000.0 cGy
2500.0 cGy
2000.0 cGy
1500.0 cGy
1000.0 cGy
575.5 cGy
0.0 cGy
4995.8 cGy

Isodoses


Dose
5755.2 cGy
5755.2
5000.0 cGy
4500.0 cGy
4000.0 cGy
3500.0 cGy
3000.0 cGy
2500.0 cGy
2000.0 cGy
1500.0 cGy
1000.0 cGy
575.5 cGy
0.0 cGy
5598.2 cGy

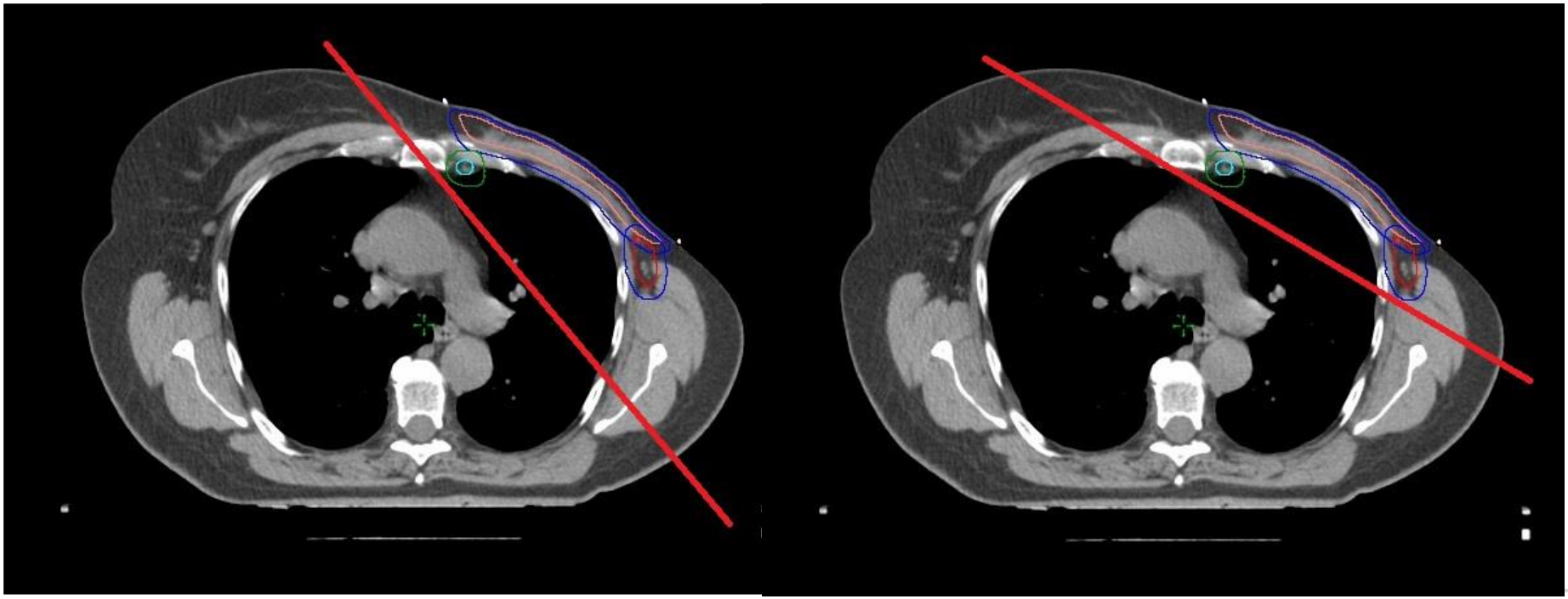
DVH



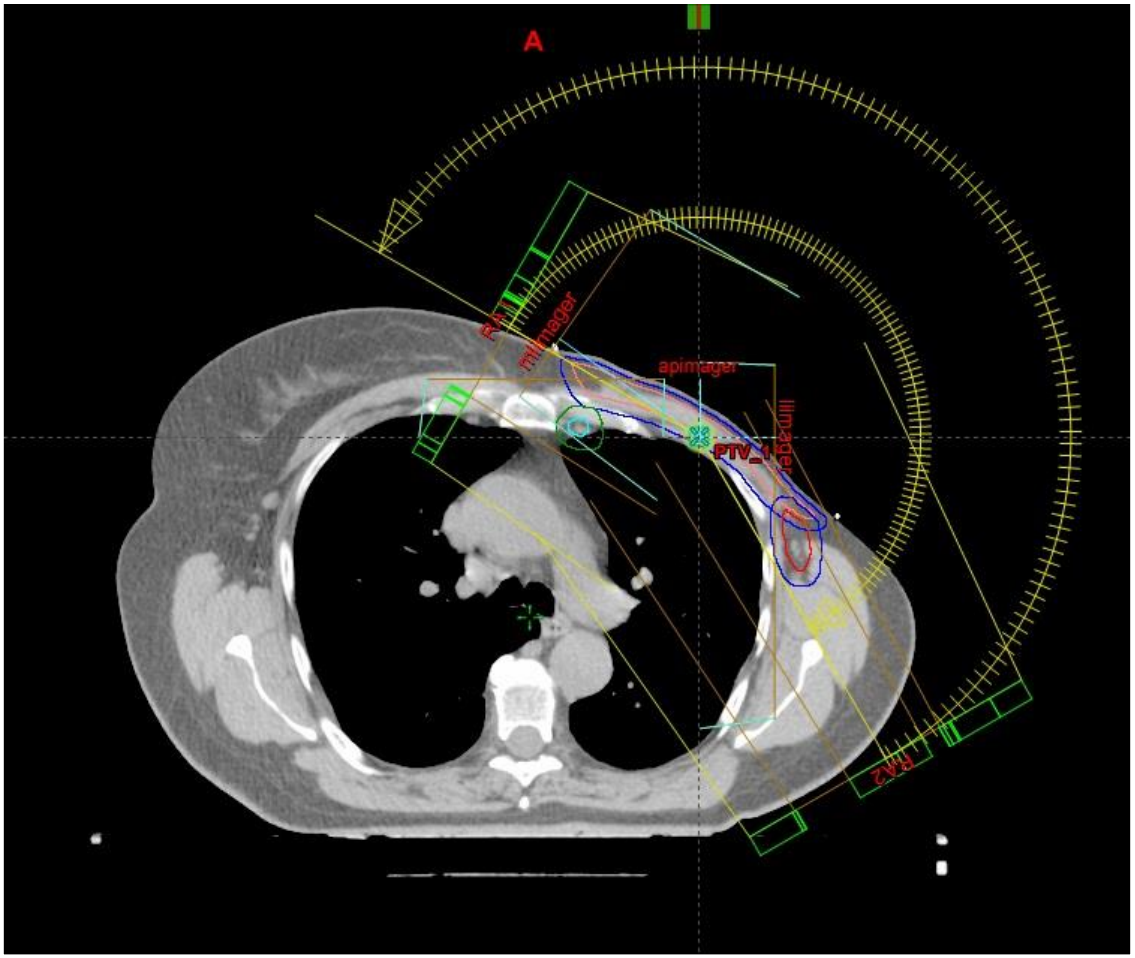
ESTRO School

Breast left IMN

- 23 x 2Gy + hyperthermia

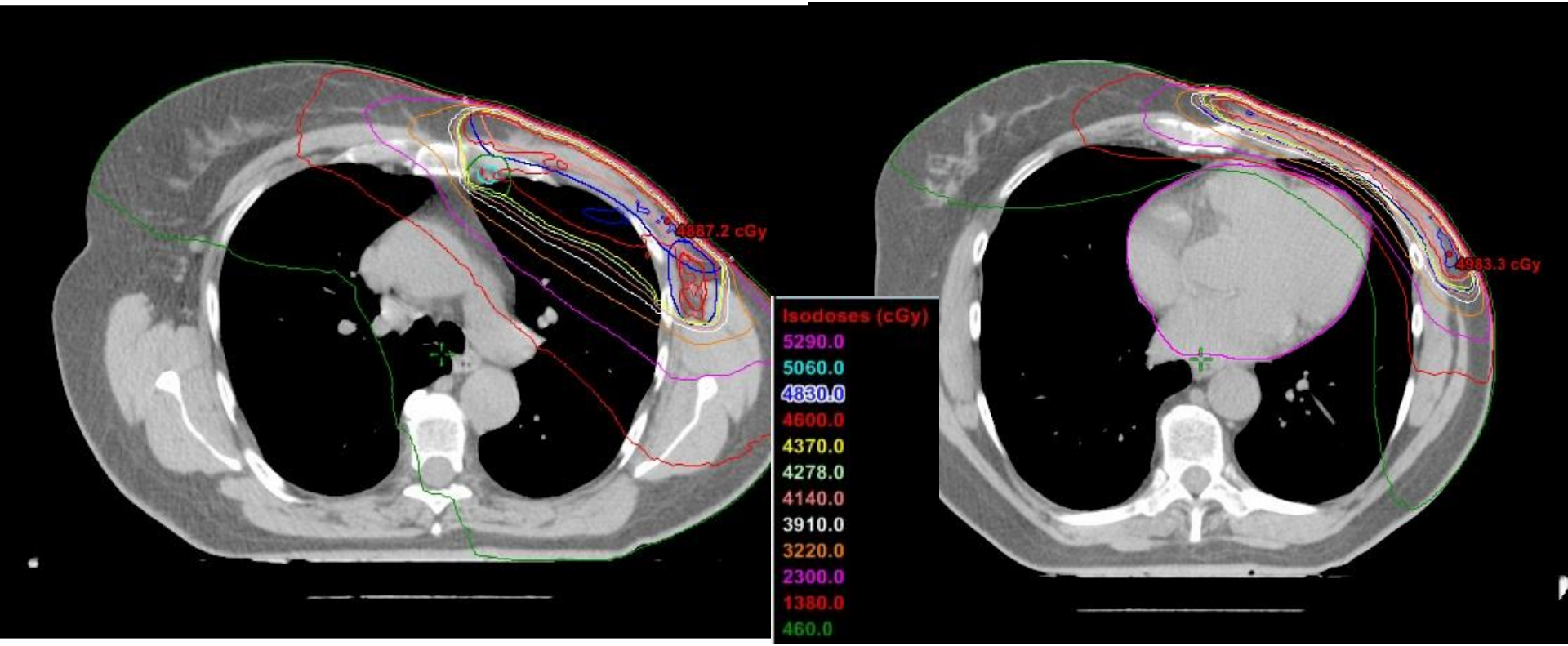


Beams (2 arcs)

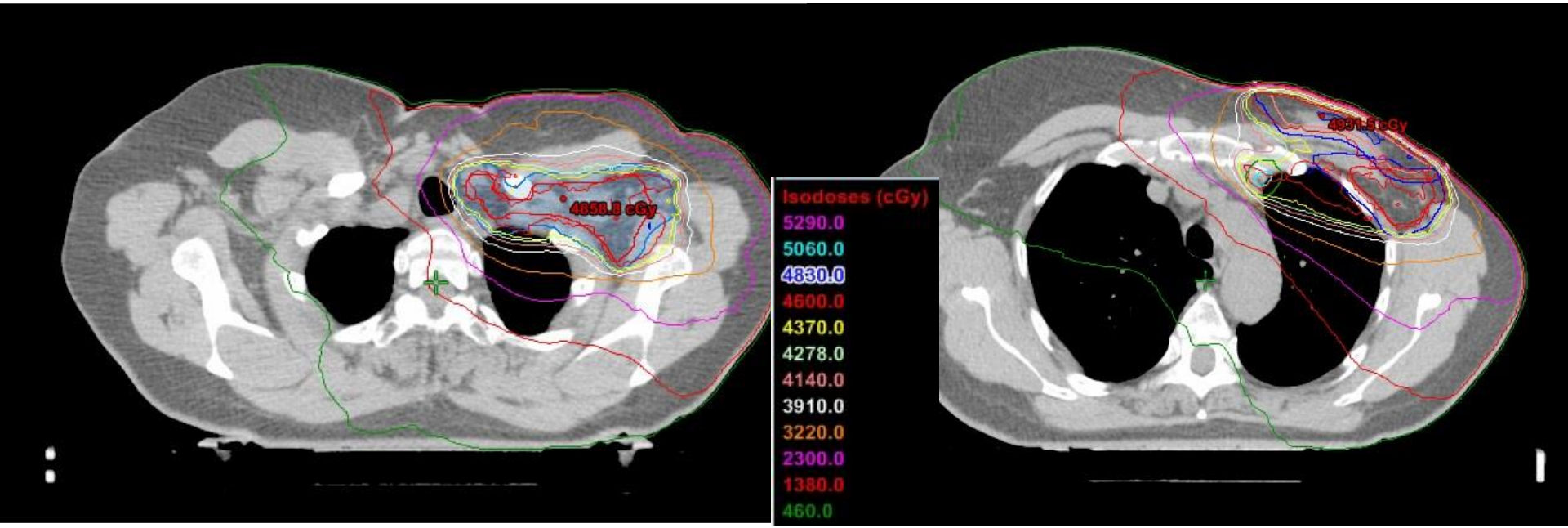


ESTRO School

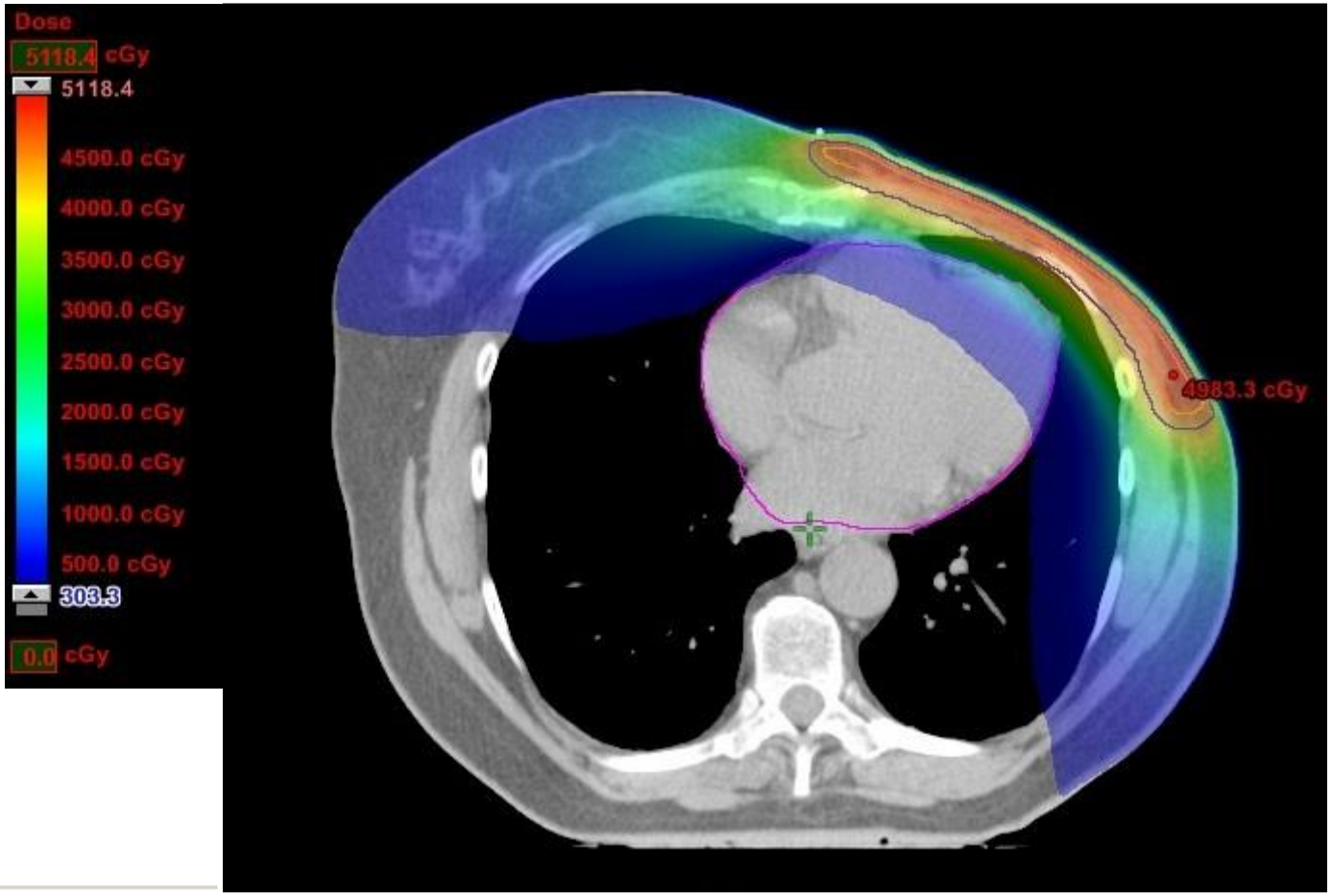
Isodoses


4887.2 cGy
4983.3 cGy
Isodoses (cGy)
5290.0
5060.0
4830.0
4600.0
4370.0
4278.0
4140.0
3910.0
3220.0
2300.0
1380.0
460.0

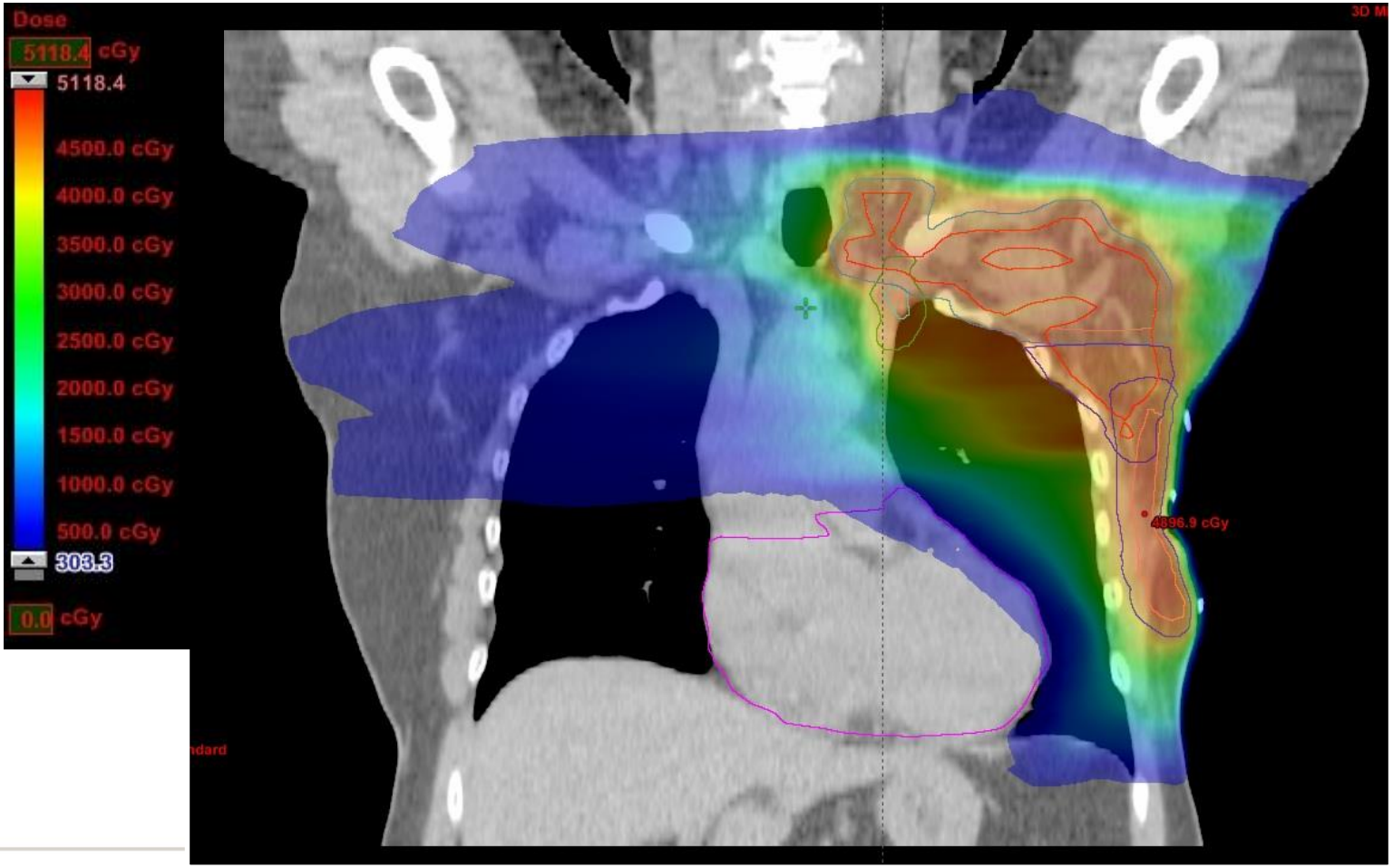
Isodoses


4658.8 cGy
4931.8 cGy
Isodoses (cGy)
5290.0
5060.0
4830.0
4600.0
4370.0
4278.0
4140.0
3910.0
3220.0
2300.0
1380.0
460.0

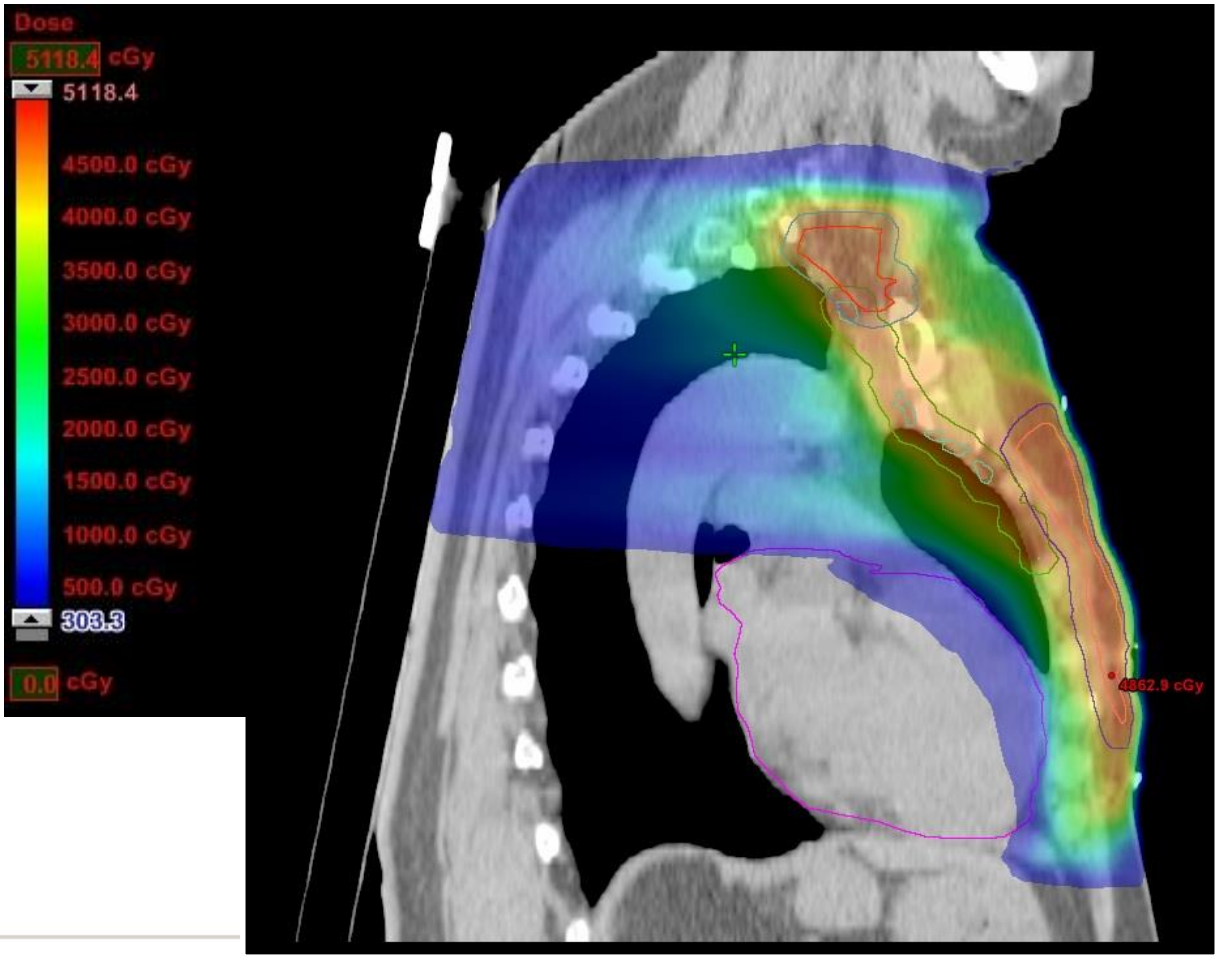
Isodoses


Dose
5118.4 cGy
5118.4
4500.0 cGy
4000.0 cGy
3500.0 cGy
3000.0 cGy
2500.0 cGy
2000.0 cGy
1500.0 cGy
1000.0 cGy
500.0 cGy
303.3
0.0 cGy
4983.3 cGy

Isodoses

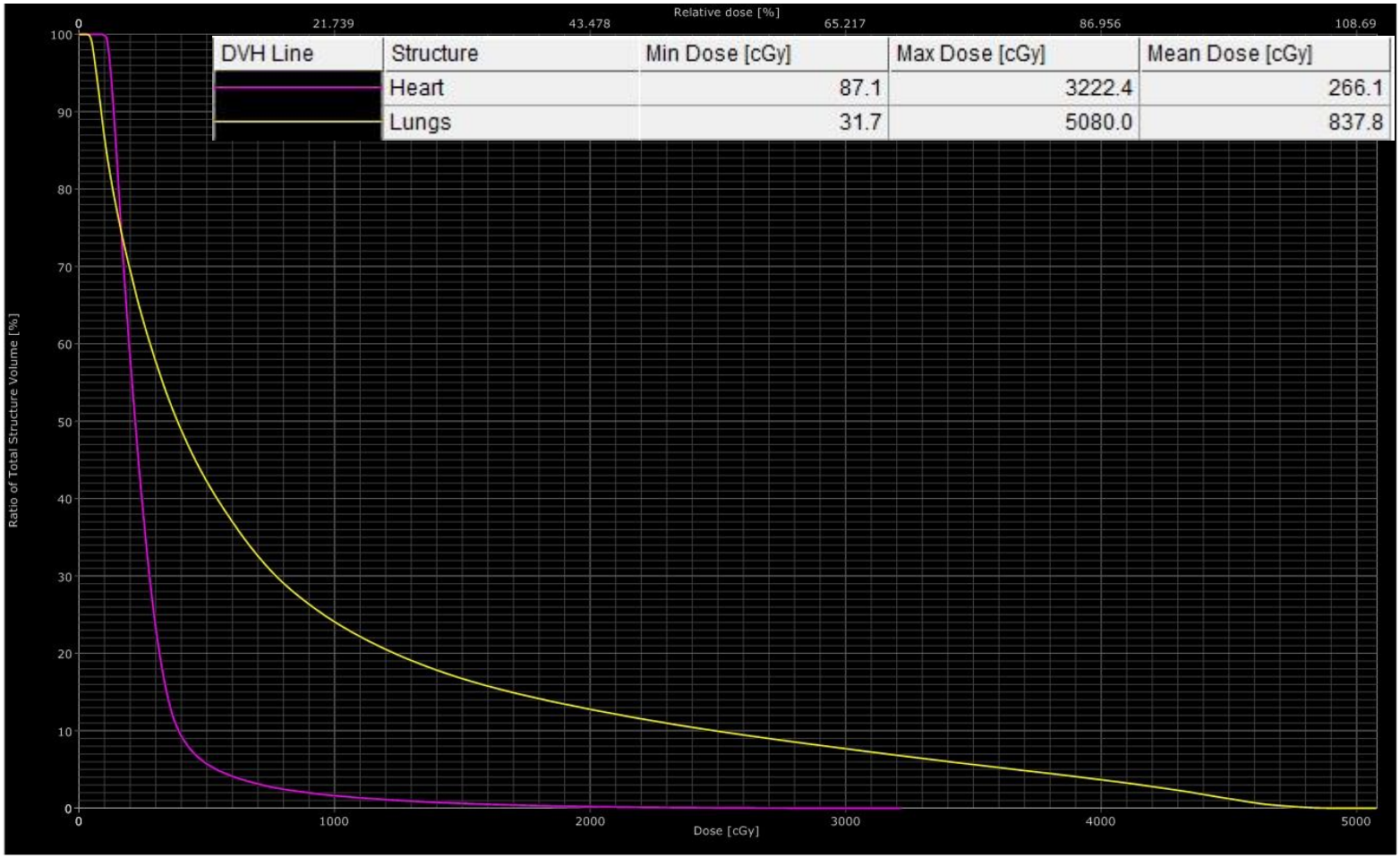

Dose
5118.4 cGy
5118.4
4500.0 cGy
4000.0 cGy
3500.0 cGy
3000.0 cGy
2500.0 cGy
2000.0 cGy
1500.0 cGy
1000.0 cGy
500.0 cGy
303.3
0.0 cGy
4896.9 cGy

Isodoses



ESTRO School

DVH



DVH Line	Structure	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
	Heart	87.1	3222.4	266.1
	Lungs	31.7	5080.0	837.8

ESTRO School

Clinical studies on lymph node treatment: maturing, accruing and nurturing

Birgitte V. Offersen, MD, PhD

Clinical oncologist

Aarhus University Hospital, Denmark

Trials on pN+ disease, *maturing* (accrual finished, (more) results awaited)

EORTC IM-MS trial 22922/10925

MA.20

DBCG IMN study

IBCSB-23-01
AMAROS
ACOSOG Z0011

} These trials were discussed Day 2, not included here

Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer

P.M. Poortmans, S. Collette, C. Kirkove, E. Van Limbergen, V. Budach, H. Struikmans, L. Collette, A. Fourquet, P. Maingon, M. Valli, K. De Winter, S. Marnitz, I. Barillot, L. Scandolaro, E. Vonk, C. Rodenhuis, H. Marsiglia, N. Weidner, G. van Tienhoven, C. Glanzmann, A. Kuten, R. Arriagada, H. Bartelink, and W. Van den Bogaert, for the EORTC Radiation Oncology and Breast Cancer Groups*

N Engl J Med 2015;373:317-27.
DOI: 10.1056/NEJMoa1415369

ESTRO School

EORTC IM-MS trial 22922/10925

1996-2004

Eligible: pN0 with centrally/medially tumour or pN+

R to +/- RT to IM-MS, mostly including IC3

50 Gy/25 fractions

Primary endpoint: OS

Secondary endpoints: DFS and BCM

4004 patients

Median follow up 10.9 yr

IM-MS technique

Basic:

50 Gy/ 25 fractions,

26 Gy/13 fr was photons, 24 Gy /12 fr was electrons

Anterior fields,

Dose prescribed at depth 3 cm

EORTC trial 22922/10925

Table 1. Baseline Characteristics of the Patients, According to Study Group.*

Characteristic	Control Group (N = 2002)	Nodal-Irradiation Group (N = 2002)	Total (N = 4004)
Age — yr			
Median	54.0	54.0	54.0
Range	22.0–75.0	19.0–75.0	19.0–75.0
Type of surgery — no. (%)			
Mastectomy	479 (23.9)	476 (23.8)	955 (23.9)
Breast-conserving surgery	1523 (76.1)	1526 (76.2)	3049 (76.1)
Pathological tumor stage — no. (%)			
pT1: ≤2 cm	1203 (60.1)	1205 (60.2)	2408 (60.1)
pT2: 2–5 cm	714 (35.7)	716 (35.8)	1430 (35.7)
pT3: >5 cm	71 (3.5)	70 (3.5)	141 (3.5)
Pathological nodal stage — no. (%)			
pN0: no axillary lymph nodes involved	890 (44.5)	888 (44.4)	1778 (44.4)
pN1a: 1–3 axillary lymph nodes involved	866 (43.3)	859 (42.9)	1725 (43.1)
pN2a: 4–9 axillary lymph nodes involved	201 (10.0)	195 (9.7)	396 (9.9)
pN3a: >9 axillary lymph nodes involved	44 (2.2)	59 (2.9)	103 (2.6)
Adjuvant treatment — no. (%)			
None	301 (15.0)	324 (16.2)	625 (15.6)
Chemotherapy	500 (25.0)	494 (24.7)	994 (24.8)
Hormonal therapy	599 (29.9)	586 (29.3)	1185 (29.6)
Both chemotherapy and hormonal therapy	602 (30.1)	598 (29.9)	1200 (30.0)

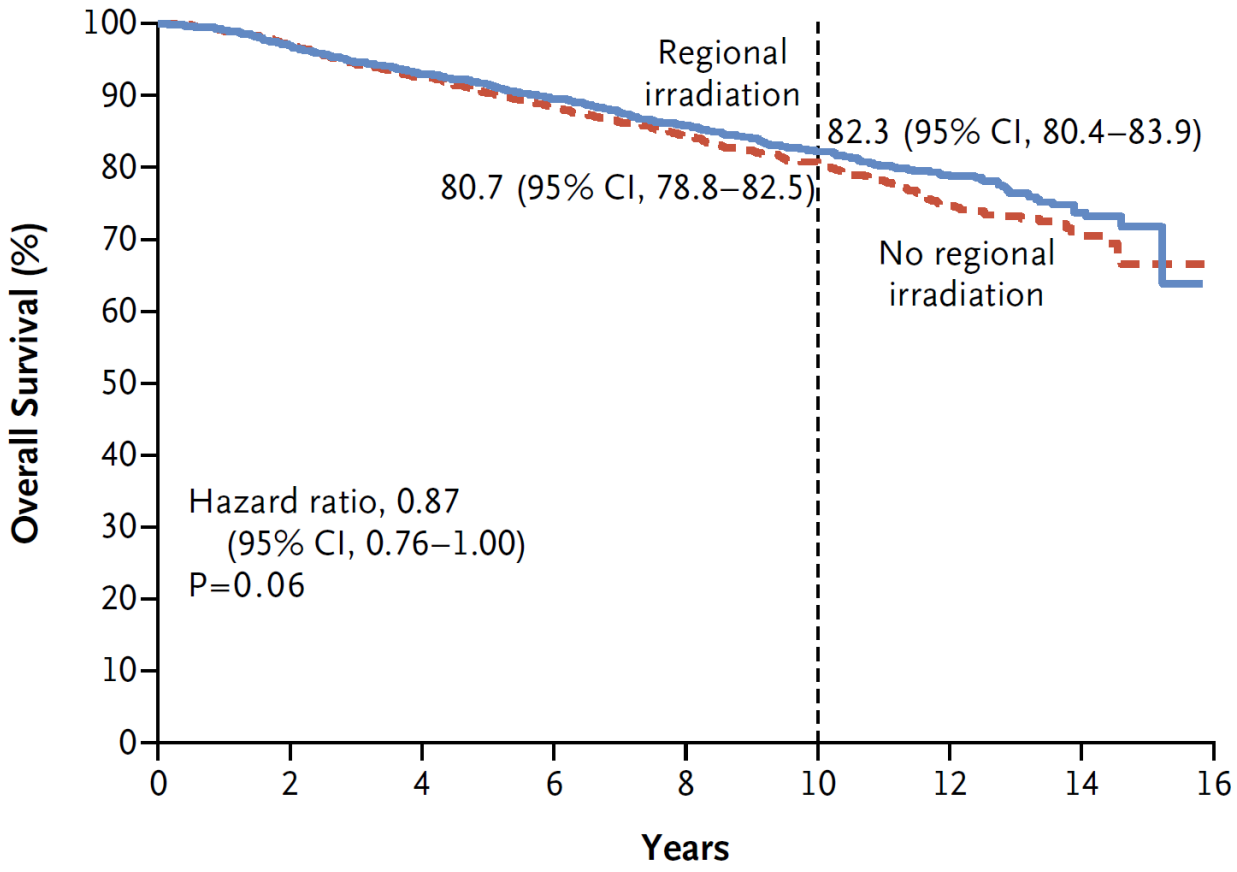
EORTC trial 22922/10925

Table 2. Events in the Intention-to-Treat Population.

Event	Control Group (N = 2002)	Nodal-Irradiation Group (N = 2002)	Total (N=4004)
		no. of patients (%)	
Recurrence			
Local	107 (5.3)	112 (5.6)	219 (5.5)
Regional*	85 (4.2)	54 (2.7)	139 (3.5)
Axillary	38 (1.9)	27 (1.3)	65 (1.6)
Medial supraclavicular	41 (2.0)	30 (1.5)	71 (1.8)
Internal mammary	16 (0.8)	4 (0.2)	20 (0.5)
Distant disease	392 (19.6)	319 (15.9)	711 (17.8)
Second cancer			
Any	222 (11.1)	191 (9.5)	413 (10.3)
Ipsilateral or contralateral breast cancer	105 (5.2)	97 (4.8)	202 (5.0)

* Multiple locations of regional recurrence may have been observed.

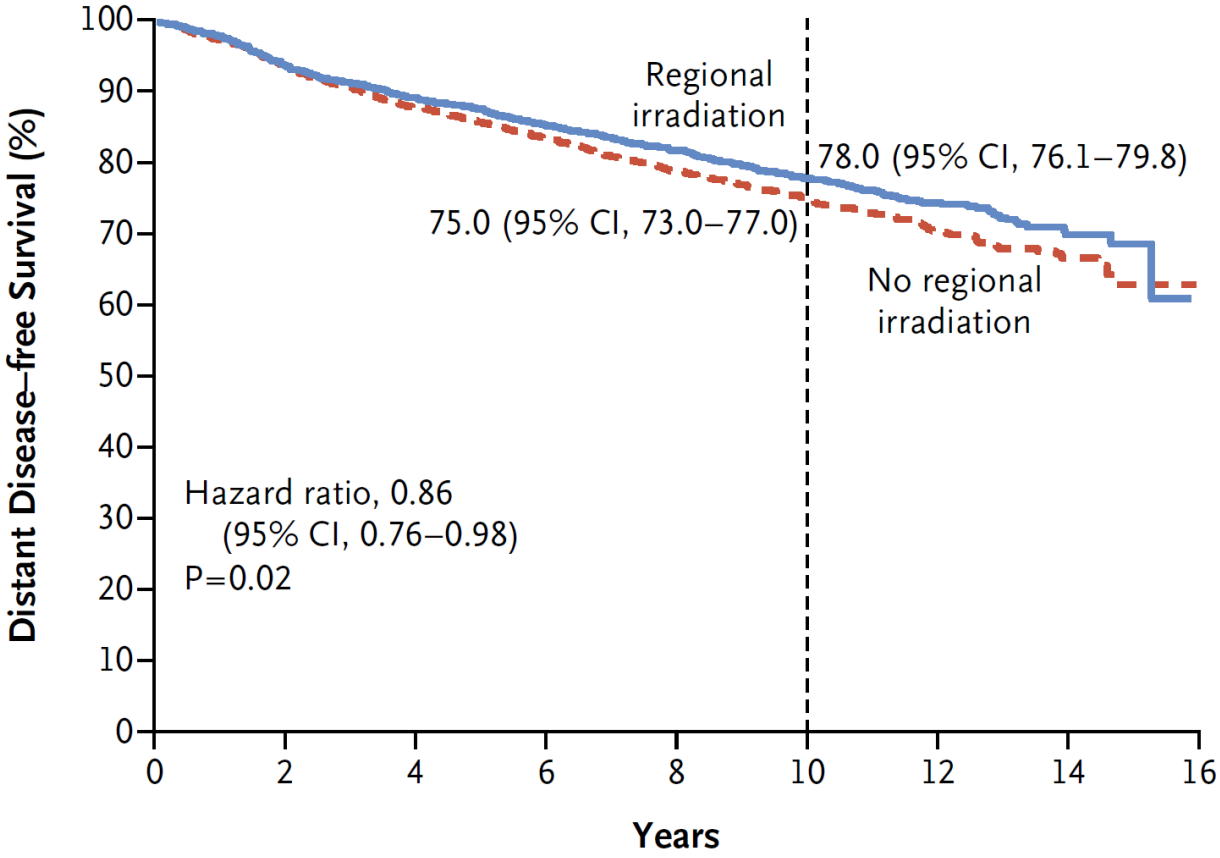
EORTC trial 22922/10925



No. at Risk									No. of Events
No regional irradiation	2002	1926	1819	1698	1475	969	434	119	429
Regional irradiation	2002	1931	1839	1732	1532	988	466	124	382

ESTRO School

EORTC trial 22922/10925

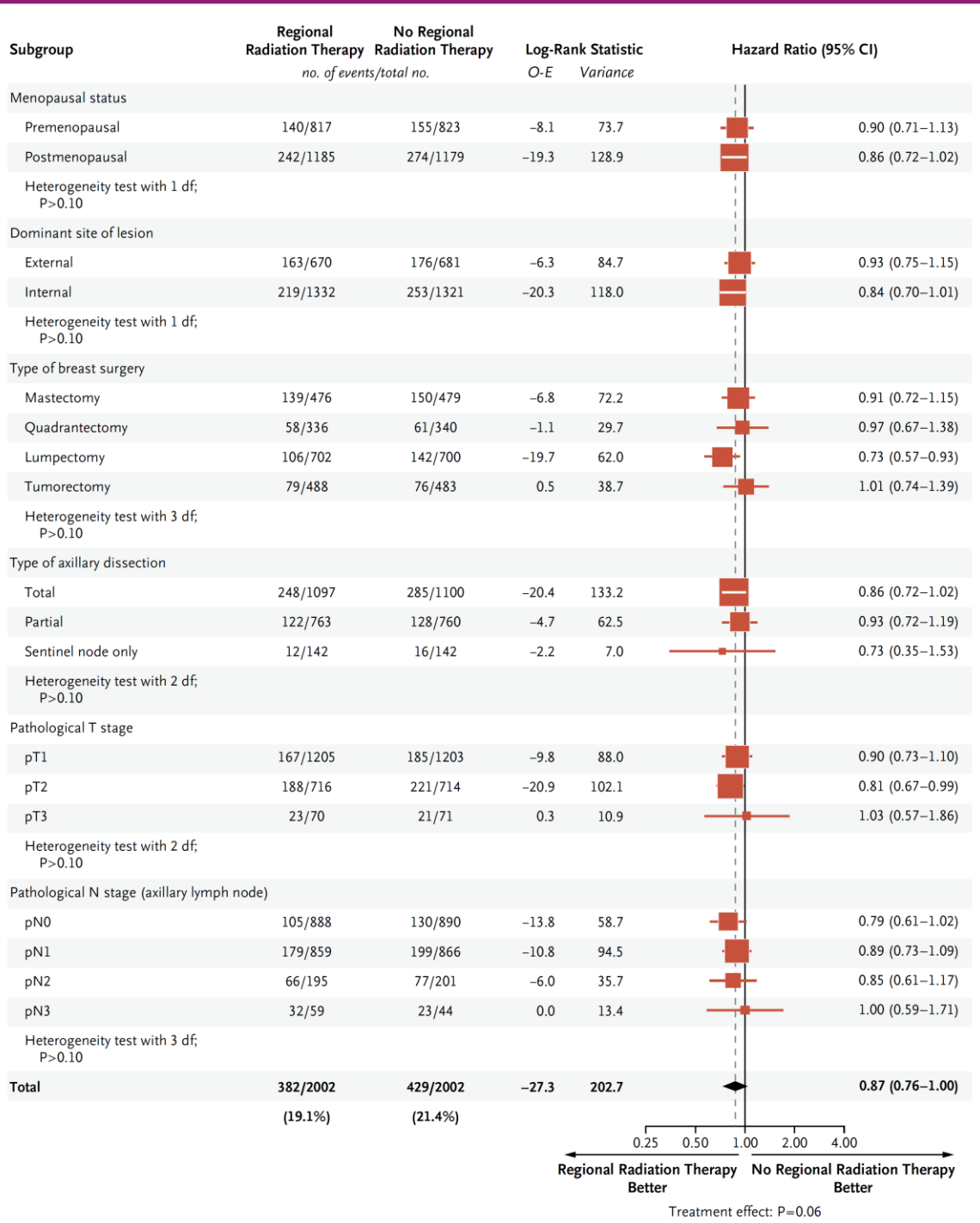


No. at Risk									No. of Events
No regional irradiation	2002	1862	1728	1606	1382	890	403	113	523
Regional irradiation	2002	1866	1764	1650	1464	939	437	117	462

ESTRO School

Forest plot of IM-MS RT effect in relevant subgroups using OS as endpoint

Conclusion: all subgrops appear to gain the same effect



Subgroup	Regional Radiation Therapy (no. of events/total no.)	No Regional Radiation Therapy (no. of events/total no.)	Log-Rank Statistic O-E	Log-Rank Statistic Variance	Hazard Ratio (95% CI)
Menopausal status					
Premenopausal	140/817	155/823	−8.1	73.7	0.90 (0.71–1.13)
Postmenopausal	242/1185	274/1179	−19.3	128.9	0.86 (0.72–1.02)
Heterogeneity test with 1 df; P>0.10					
Dominant site of lesion					
External	163/670	176/681	−6.3	84.7	0.93 (0.75–1.15)
Internal	219/1332	253/1321	−20.3	118.0	0.84 (0.70–1.01)
Heterogeneity test with 1 df; P>0.10					
Type of breast surgery					
Mastectomy	139/476	150/479	−6.8	72.2	0.91 (0.72–1.15)
Quadrantectomy	58/336	61/340	−1.1	29.7	0.97 (0.67–1.38)
Lumpectomy	106/702	142/700	−19.7	62.0	0.73 (0.57–0.93)
Tumorectomy	79/488	76/483	0.5	38.7	1.01 (0.74–1.39)
Heterogeneity test with 3 df; P>0.10					
Type of axillary dissection					
Total	248/1097	285/1100	−20.4	133.2	0.86 (0.72–1.02)
Partial	122/763	128/760	−4.7	62.5	0.93 (0.72–1.19)
Sentinel node only	12/142	16/142	−2.2	7.0	0.73 (0.35–1.53)
Heterogeneity test with 2 df; P>0.10					
Pathological T stage					
pT1	167/1205	185/1203	−9.8	88.0	0.90 (0.73–1.10)
pT2	188/716	221/714	−20.9	102.1	0.81 (0.67–0.99)
pT3	23/70	21/71	0.3	10.9	1.03 (0.57–1.86)
Heterogeneity test with 2 df; P>0.10					
Pathological N stage (axillary lymph node)					
pN0	105/888	130/890	−13.8	58.7	0.79 (0.61–1.02)
pN1	179/859	199/866	−10.8	94.5	0.89 (0.73–1.09)
pN2	66/195	77/201	−6.0	35.7	0.85 (0.61–1.17)
pN3	32/59	23/44	0.0	13.4	1.00 (0.59–1.71)
Heterogeneity test with 3 df; P>0.10					
Total	**382/2002**	**429/2002**	**−27.3**	**202.7**	**0.87 (0.76–1.00)**
	(19.1%)	**(21.4%)**			

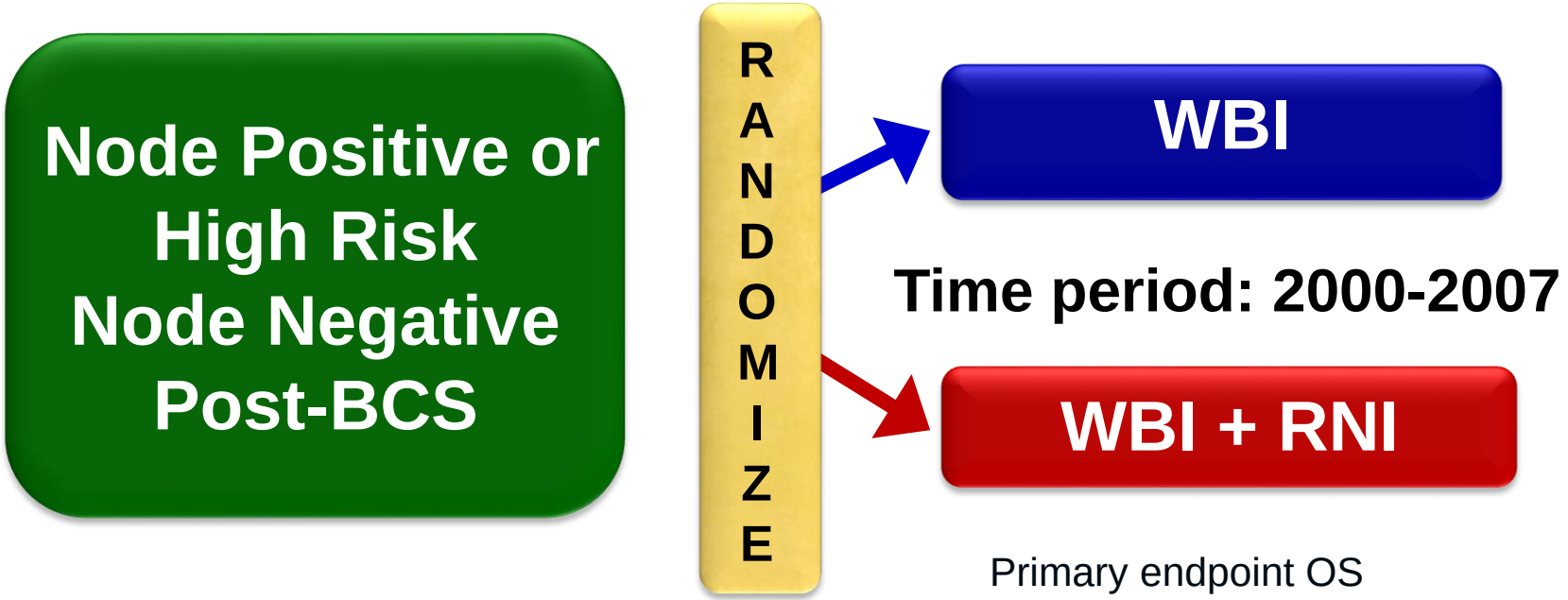
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 23, 2015 VOL. 373 NO. 4

Regional Nodal Irradiation in Early-Stage Breast Cancer

Timothy J. Whelan, B.M., B.Ch., Ivo A. Olivotto, M.D., Wendy R. Parulekar, M.D., Ida Ackerman, M.D., Boon H. Chua, M.B., B.S., Ph.D., Abdenour Nabid, M.D., Katherine A. Vallis, M.B., B.S., Ph.D., Julia R. White, M.D., Pierre Rousseau, M.D., Andre Fortin, M.D., Lori J. Pierce, M.D., Lee Manchul, M.D., Susan Chafe, M.D., Maureen C. Nolan, M.D., Peter Craighead, M.D., Julie Bowen, M.D., David R. McCready, M.D., Kathleen I. Pritchard, M.D., Karen Gelmon, M.D., Yvonne Murray, B.Sc., Judy-Anne W. Chapman, Ph.D., Bingshu E. Chen, Ph.D., and Mark N. Levine, M.D., for the MA.20 Study Investigators*

Study Design



Time period: 2000-2007

Primary endpoint OS
Sec endpoints DFS, locoreg DFS, distant DFS

Stratification

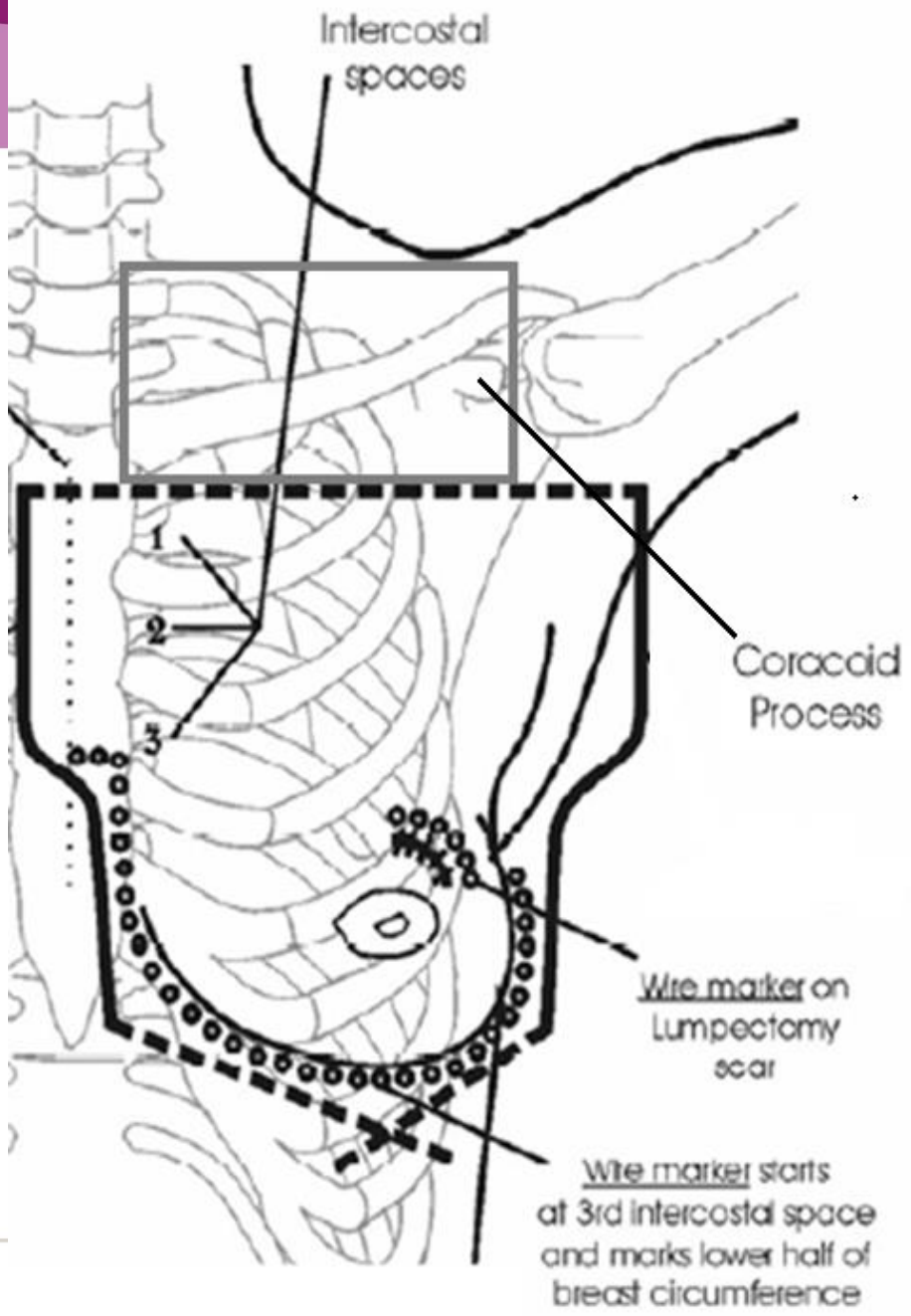
- **Axillary nodes removed (<10, ≥10)**
- **Positive axillary nodes (0, 1-3, >3)**
- **Chemotherapy (anthracycline, other, none)**
- **Endocrine therapy (yes, no)**

ESTRO School

Methods

WBI + RNI

- Treat breast + upper 3 intercostal IM, SC and level 3 AX nodes
- IMN volume treated with a modified wide tangent technique or direct field matched to tangent fields
- Aim to include IMN + 1cm with the 80% isodose, 50 Gy
- SC and level 3 AX nodes treated with an anterior field
- Dose to the breast and boost irradiation 50 Gy/25 fr + 10-16 Gy boost
- Dose to the periclavicular nodes: 45 Gy/25 fractions



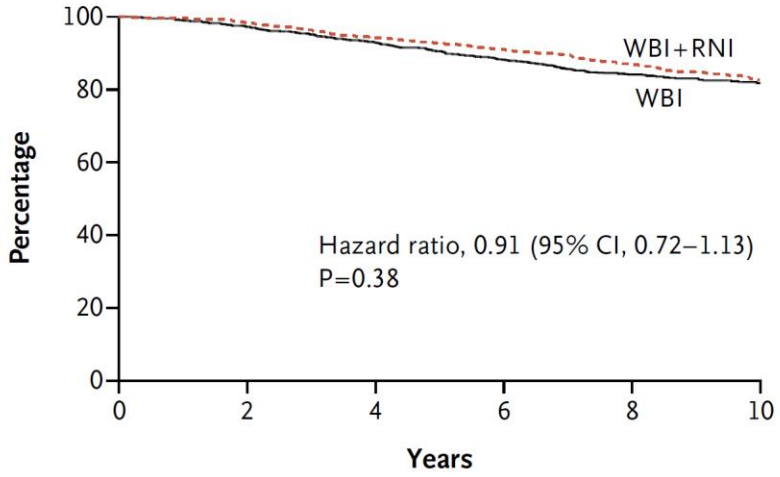
Baseline Characteristics, N=1832 patients

	WBI N=916	WBI+RNI N=916
Age *(mean)*	53	54
Axillary nodes removed *(mean)*	12	12
Node Negative	10%	10%
Node Positive (1-3)	85%	85%
Tumor size > 2cm	45%	50%
Grade III	42%	43%
ER Negative	26%	25%
Adjuvant chemotherapy	91%	91%
Adjuvant endocrine therapy	77%	77%
Boost irradiation	35%	32%

Median follow up 9.5 years

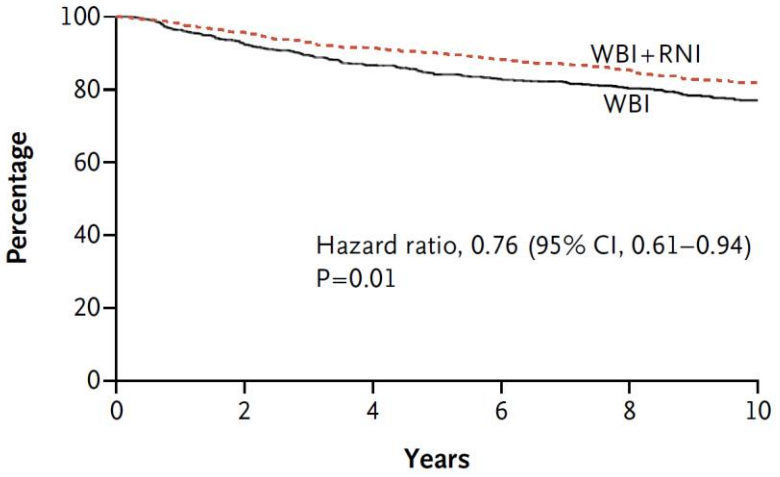
ESTRO School

A Overall Survival



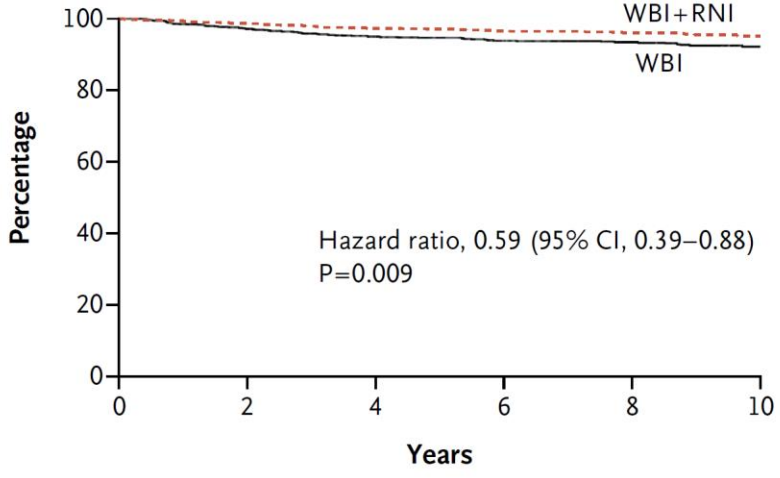
No. at Risk						
WBI	916	879	828	773	602	317
WBI+RNI	916	890	841	806	635	331

B Disease-free Survival



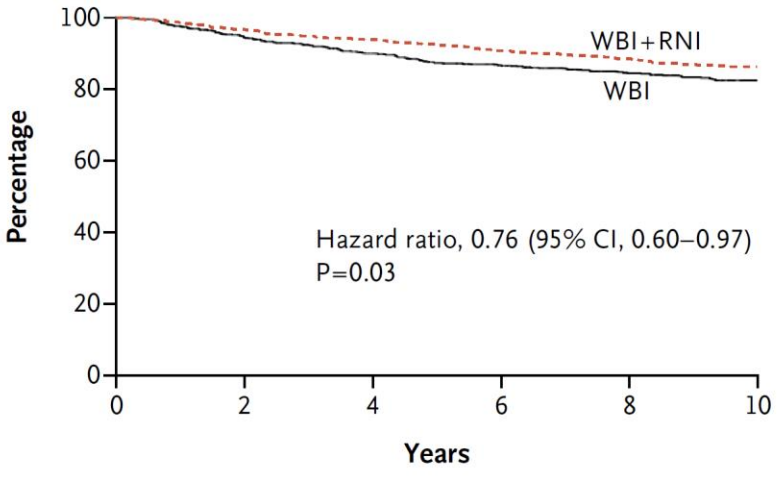
No. at Risk						
WBI	916	833	764	710	553	279
WBI+RNI	915	861	800	758	592	297

C Isolated Locoregional Disease-free Survival



No. at Risk						
WBI	916	836	769	720	563	288
WBI+RNI	915	863	806	764	602	307

D Distant Disease-free Survival



No. at Risk						
WBI	916	851	793	743	579	304
WBI+RNI	916	871	823	781	617	318

MA.20, Forest plot using DFS as endpoint

Subgroup	WBI	WBI+RNI	WBI	WBI+RNI	Hazard Ratio (95% CI)	WBI	WBI+RNI	P Value for Interaction
	no. of patients		*no. of patients with events*			*10-yr DFS (%)*		
All patients	916	916	195	154	0.76 (0.61–0.94)	77.0	82.0	
Positive nodes								0.65
0	89	88	23	13	0.55 (0.28–1.09)	72.4	83.7	
1	447	460	76	68	0.85 (0.61–1.18)	80.9	83.5	
2–3	333	318	80	60	0.74 (0.53–1.04)	67.6	74.8	
>3	47	50	16	13	0.71 (0.34–1.48)	60.3	69.8	
Nodes removed								0.29
<10	303	294	63	55	0.88 (0.62–1.27)	74.0	76.6	
≥10	612	622	132	99	0.70 (0.54–0.90)	74.2	81.2	
ER status								0.04
Negative	234	231	78	48	0.56 (0.39–0.81)	61.6	76.2	
Positive	682	685	117	106	0.88 (0.68–1.15)	78.6	80.8	
PR status								0.03
Negative	365	360	91	55	0.57 (0.41–0.80)	70.5	81.9	
Positive	549	553	104	98	0.91 (0.69–1.20)	76.7	78.5	
Tumor location								0.63
Medial	136	125	34	20	0.60 (0.35–1.05)	72.5	82.3	
Central	202	227	39	37	0.83 (0.53–1.30)	78.7	82.0	
Lateral	578	564	122	97	0.77 (0.59–1.01)	73.0	78.4	

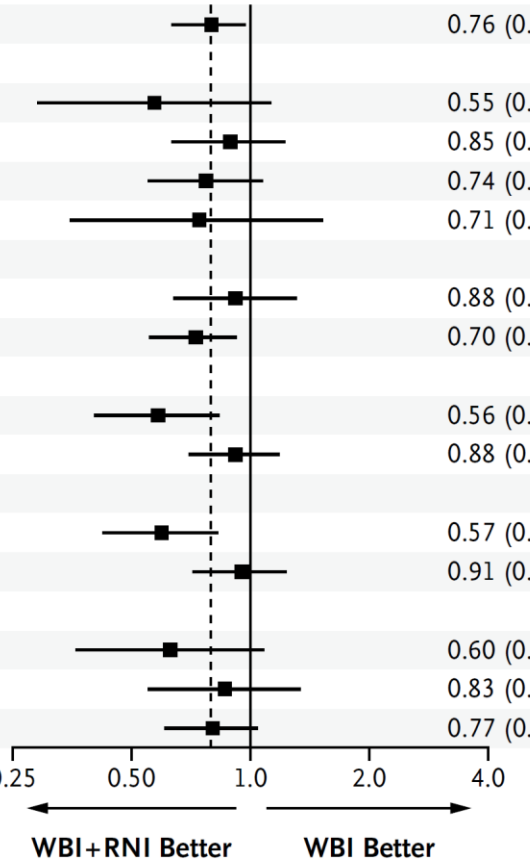


Table 3. Adverse Events of Grade 2 or Higher.*

Adverse Event	WBI (N=927)				WBI+RNI (N=893)				P Value†
	Grade 2	Grade 3	Grade 4	Total	Grade 2	Grade 3	Grade 4	Total	
	no. of patients with event (%)								
Acute									
Fatigue	156	13	0	169 (18.2)	154	16	0	170 (19.0)	0.67
Pain‡	35	5	0	40 (4.3)	46	7	0	53 (5.9)	0.14
Pneumonitis§	2	0	0	2 (0.2)	11	0	0	11 (1.2)	0.01
Radiation dermatitis	349	23	0	372 (40.1)	397	45	0	442 (49.5)	<0.001
Delayed									
Cardiac¶	2	2	0	4 (0.4)	0	6	2	8 (0.9)	0.26
Lymphedema‖	38	4	0	42 (4.5)	65	10	0	75 (8.4)	0.001
Neuropathy**	16	1	0	17 (1.8)	16	5	1††	22 (2.5)	0.42
Pneumonitis or fibrosis§‡‡	2	1	0	3 (0.3)	4	0	0	4 (0.4)	0.72
Joint	12	2	0	14 (1.5)	21	0	0	21 (2.4)	0.23
Skin§§	38	2	0	40 (4.3)	51	11	0	62 (6.9)	0.02
Subcutaneous tissue	19	0	0	19 (2.0)	34	3	0	37 (4.1)	0.01
Second cancer¶¶	NA	NA	NA	93 (10.0)	NA	NA	NA	98 (11.0)	0.54

VOLUME 34 · NUMBER 4 · FEBRUARY 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

DBCG-IMN: A Population-Based Cohort Study on the Effect of Internal Mammary Node Irradiation in Early Node-Positive Breast Cancer

Lise Bech Jellesmark Thorsen, Birgitte Vrou Offersen, Hella Danø, Martin Berg, Ingelise Jensen, Anders Navrsted Pedersen, Sune Jürg Zimmermann, Hans-Jürgen Brodersen, Marie Overgaard, and Jens Overgaard

ESTRO School

DBCG IMN study

1980's
Internal mammary node (IMN) RT for all N+ breast cancer patients

2000
Anthracyclines

2003

No evidence for effect of IMN-RT

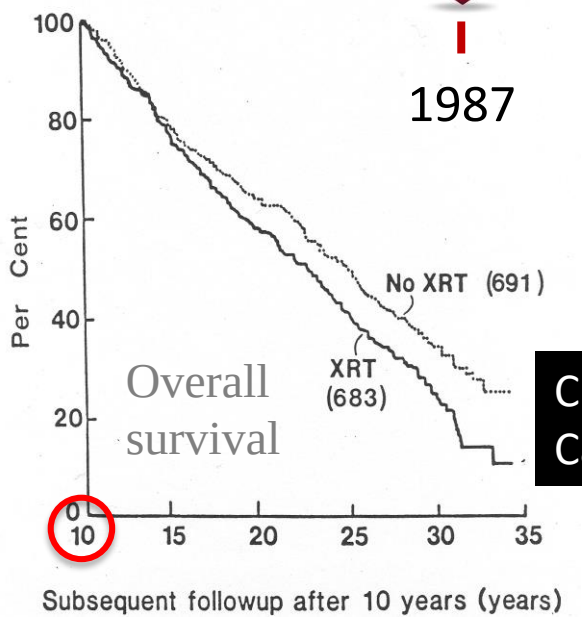
1987

2003

Right side
+ IMN RT

Left side
No IMN-RT

Left side
heart dose high



Cuzick, et al.
Cancer Treat Rep, 1987

ESTRO School

Patient and tumor characteristics

	IMN RT (n=1485)	No IMN RT (n=1586)
Median age (range)	56 (23-70)	57 (27-70)
Pre-menopausal	611 (41%)	646 (40%)
Estrogen receptor positive (%)	1202 (81%)	1274 (80%)
Invasive ductal carcinoma Invasive lobular carcinoma Other	1305 (88%) 134 (9%) 46 (3%)	1346 (85%)* 163 (10%) 77 (5%)
Grade I Grade II Grade III	307 (19%) 710 (48%) 414 (28%)	307 (19%) 743 (47%) 456 (29%)
pT1 pT2 pT3	527 (36%) 830 (56%) 126 (9%)	556 (35%) 905 (57%) 124 (8%)
pN1 pN2 pN3	867 (58%) 396 (27%) 222 (15%)	949 (60%) 412 (26%) 225 (14%)
Lateral Medial/central	904 (61%) 578 (39%)	943 (60%) 640 (40%)

CIRRO

School

DBCG-IMN: Treatment

	(IMN RT n=1485)	No IMN RT (n=1586)
Radiotherapy: 48 Gy/24 F IMN-RT (%) Axillary level II-III-IV (%) Axillary level I-II-III-IV (%) Boost after BCS (%)	 1431 (96%) 1213 (82%) 272 (18%) 176 (33%)	 161 (10%) 1294 (82%) 292 (18%) 164 (30%)
Type of surgery Mastectomy + AC(%) Breast conserving +AC(%)	 959 (65%) 526 (35%)	 1048 (66%) 538 (34%)
Systemic treatment Endocrine therapy (%) Chemotherapy (%) Endocrine + chemotherapy (%)	 697 (47%) 274 (19%) 514 (35%)	 741 (47%) 304 (19%) 541 (34%)

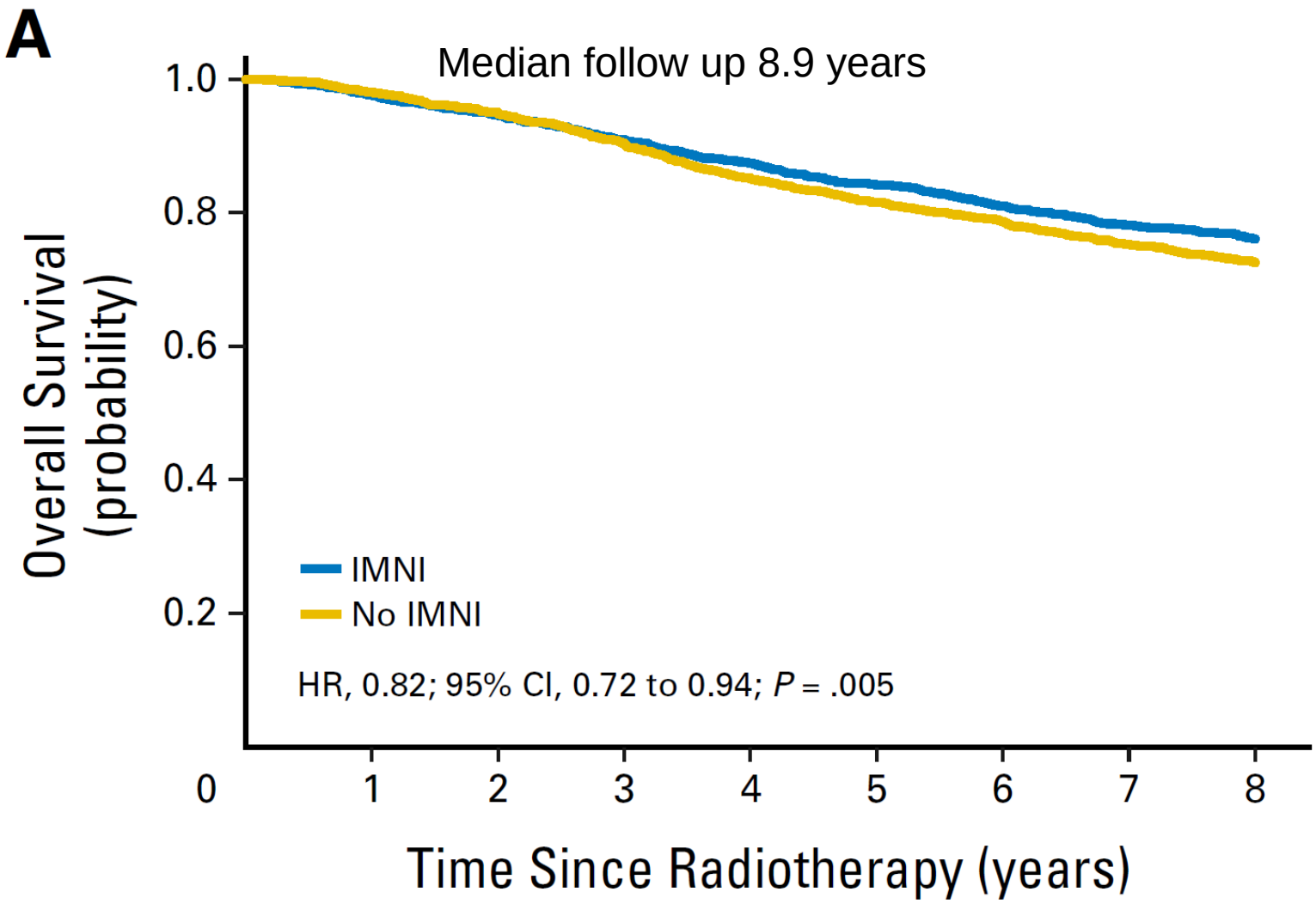
CIRRO

ESTRO School

Results

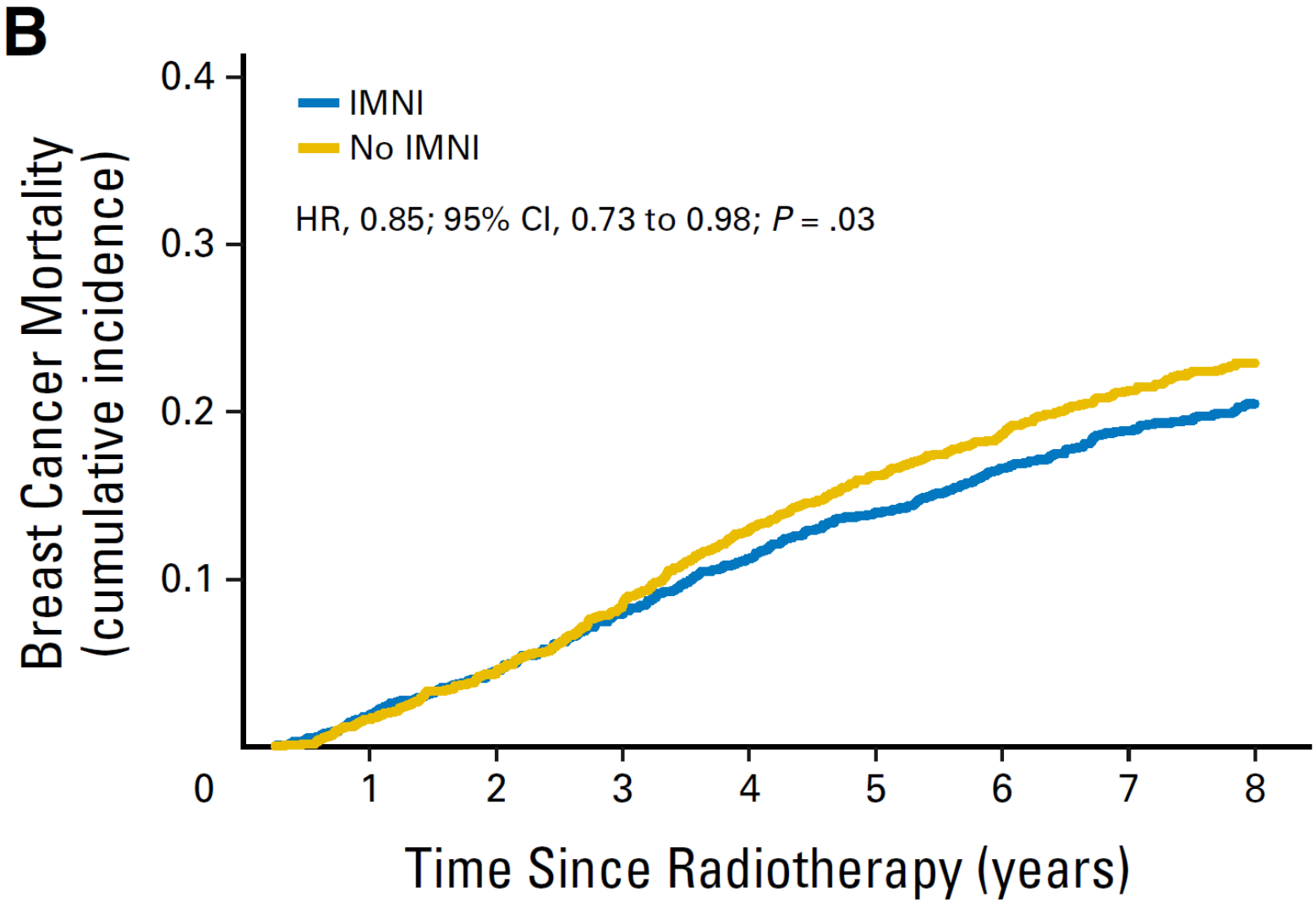
Pattern of recurrence Median FU= 8.0 years	IMN RT (n=1485)	No IMN RT (n=1586)
Local recurrence	**29 (2.0 %)**	**21 (1.3 %)**
Regional lymph node recurrence	**10 (0.7 %)**	**15 (0.9 %)**
Contralateral breast cancer	**39 (2.6 %)**	**36 (2.3 %)**

DBCG IMN study, OS



No. at risk					
IMNI	1,492	1,410	1,301	1,205	783
No IMNI	1,597	1,512	1,356	1,248	791

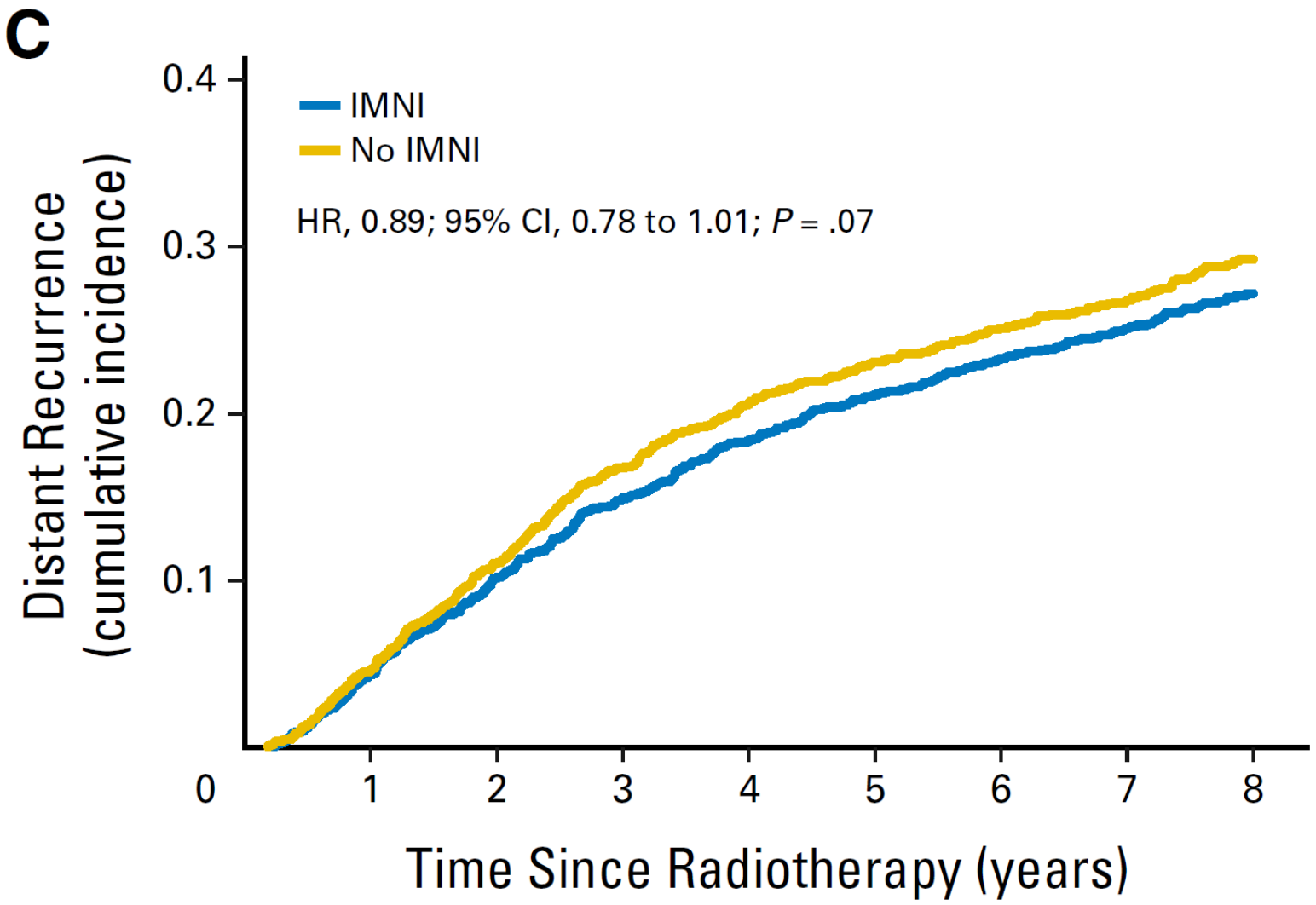
DBCG IMN study, BCM



No. at risk					
IMNI	1,492	1,410	1,301	1,205	783
No IMNI	1,597	1,512	1,356	1,248	791

ESTRO
School

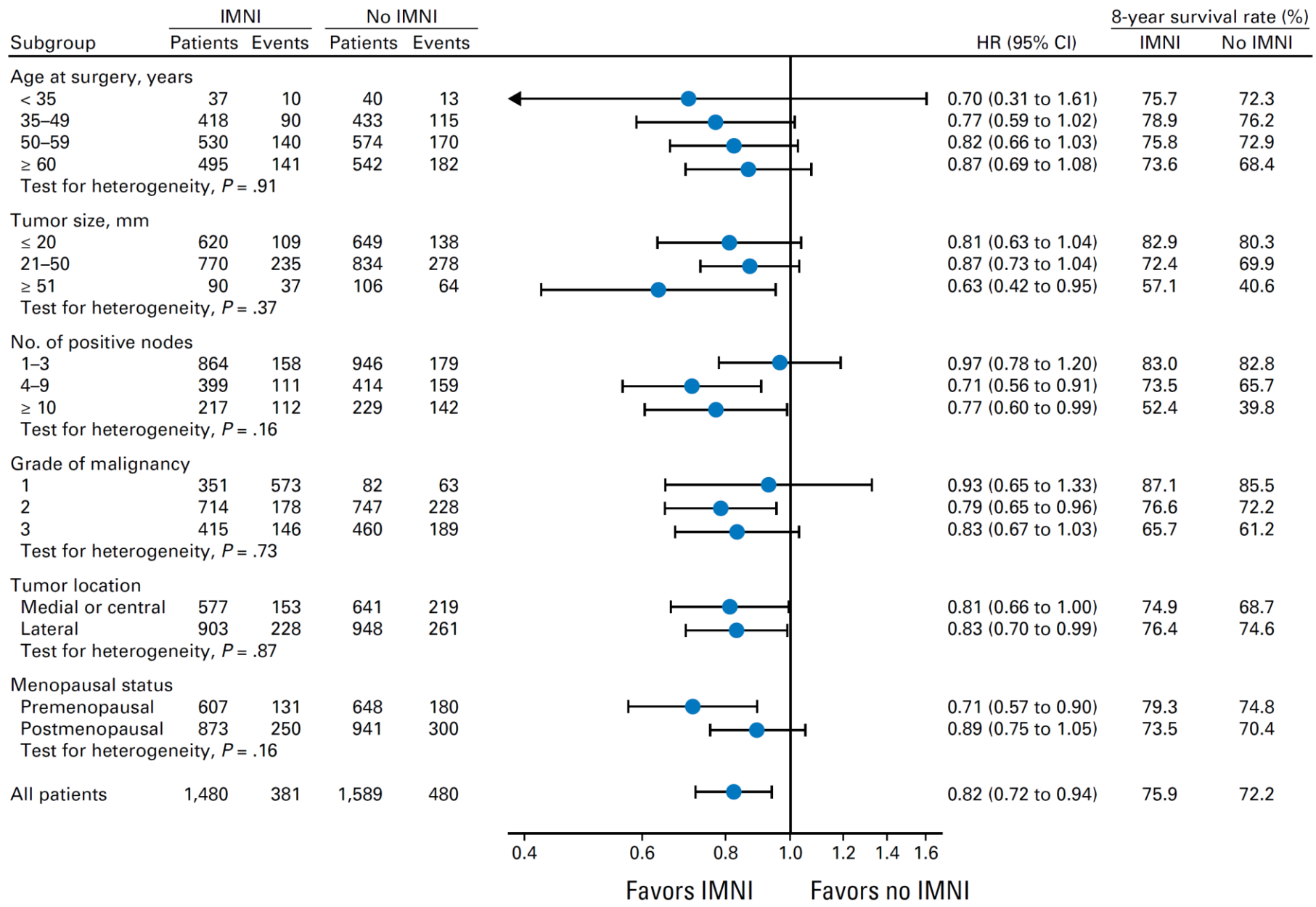
DBCG IMN study, Distant recurrence



No. at risk					
IMNI	1,492	1,322	1,193	1,066	573
No IMNI	1,597	1,402	1,230	1,103	565

ESTRO School

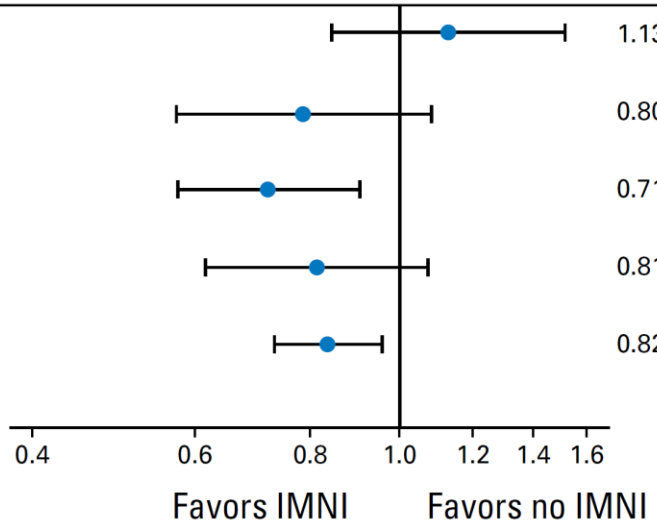
DBCG IMN study, Forest plot using OS as endpoint



Subgroup	IMNI Patients	IMNI Events	No IMNI Patients	No IMNI Events	HR (95% CI)	8-year survival rate (%) IMNI	8-year survival rate (%) No IMNI
Age at surgery, years							
< 35	37	10	40	13	0.70 (0.31 to 1.61)	75.7	72.3
35–49	418	90	433	115	0.77 (0.59 to 1.02)	78.9	76.2
50–59	530	140	574	170	0.82 (0.66 to 1.03)	75.8	72.9
≥ 60	495	141	542	182	0.87 (0.69 to 1.08)	73.6	68.4
Test for heterogeneity, $P = .91$							
Tumor size, mm							
≤ 20	620	109	649	138	0.81 (0.63 to 1.04)	82.9	80.3
21–50	770	235	834	278	0.87 (0.73 to 1.04)	72.4	69.9
≥ 51	90	37	106	64	0.63 (0.42 to 0.95)	57.1	40.6
Test for heterogeneity, $P = .37$							
No. of positive nodes							
1–3	864	158	946	179	0.97 (0.78 to 1.20)	83.0	82.8
4–9	399	111	414	159	0.71 (0.56 to 0.91)	73.5	65.7
≥ 10	217	112	229	142	0.77 (0.60 to 0.99)	52.4	39.8
Test for heterogeneity, $P = .16$							
Grade of malignancy							
1	351	573	82	63	0.93 (0.65 to 1.33)	87.1	85.5
2	714	178	747	228	0.79 (0.65 to 0.96)	76.6	72.2
3	415	146	460	189	0.83 (0.67 to 1.03)	65.7	61.2
Test for heterogeneity, $P = .73$							
Tumor location							
Medial or central	577	153	641	219	0.81 (0.66 to 1.00)	74.9	68.7
Lateral	903	228	948	261	0.83 (0.70 to 0.99)	76.4	74.6
Test for heterogeneity, $P = .87$							
Menopausal status							
Premenopausal	607	131	648	180	0.71 (0.57 to 0.90)	79.3	74.8
Postmenopausal	873	250	941	300	0.89 (0.75 to 1.05)	73.5	70.4
Test for heterogeneity, $P = .16$							
All patients	1,480	381	1,589	480	0.82 (0.72 to 0.94)	75.9	72.2

Subgroup	IMNI Patients	IMNI Events	No IMNI Patients	No IMNI Events	HR (95% CI)	8-year survival rate (%) IMNI	8-year survival rate (%) No IMNI
Lateral 1–3 nodes	511	91	564	91	1.13 (0.84 to 1.51)	82.9	85.7
Medial/central 1–3 nodes	353	67	382	88	0.80 (0.58 to 1.10)	83.2	78.8
Lateral ≥ 4 nodes	392	137	384	170	0.71 (0.57 to 0.89)	68.0	58.3
Medial/central ≥ 4 nodes	224	86	259	131	0.81 (0.61 to 1.06)	61.9	53.8
All patients	1,480	381	1,589	480	0.82 (0.72 to 0.94)	75.9	72.2

Test for heterogeneity, $P = .10$



Maturing of these trials?

All trials will provide up-dates of results with longer follow up

A meta-analysis is in process

Regarding the DBCG-IMN study, the rigth/left guideline was used 2003-2014, but the DBCG IMN study reported data only from 2003-2007. Thus outcome from >5000 patients treated 2008-2014 will be published (including taxans, trastuzumab, letrozole)

What do we need? Biological information to identify subgroups who do not need MS-IMN RT

Accruing: open trials accruing pN+ patients

FRACTIONATION

The DBCG RT Skagen Trial 1
The HYPOG-01 trial
Trials from Colorado/Kansas/Virginia/Egypt
Ghent trial
FAST forward trial, nodal substudy

TARGET FOR REGIONAL RT AFTER PST

NSABP-B51 trial
Alliance A011202 trial

MANAGEMENT OF THE AXILLA WITH MACROMET IN SN

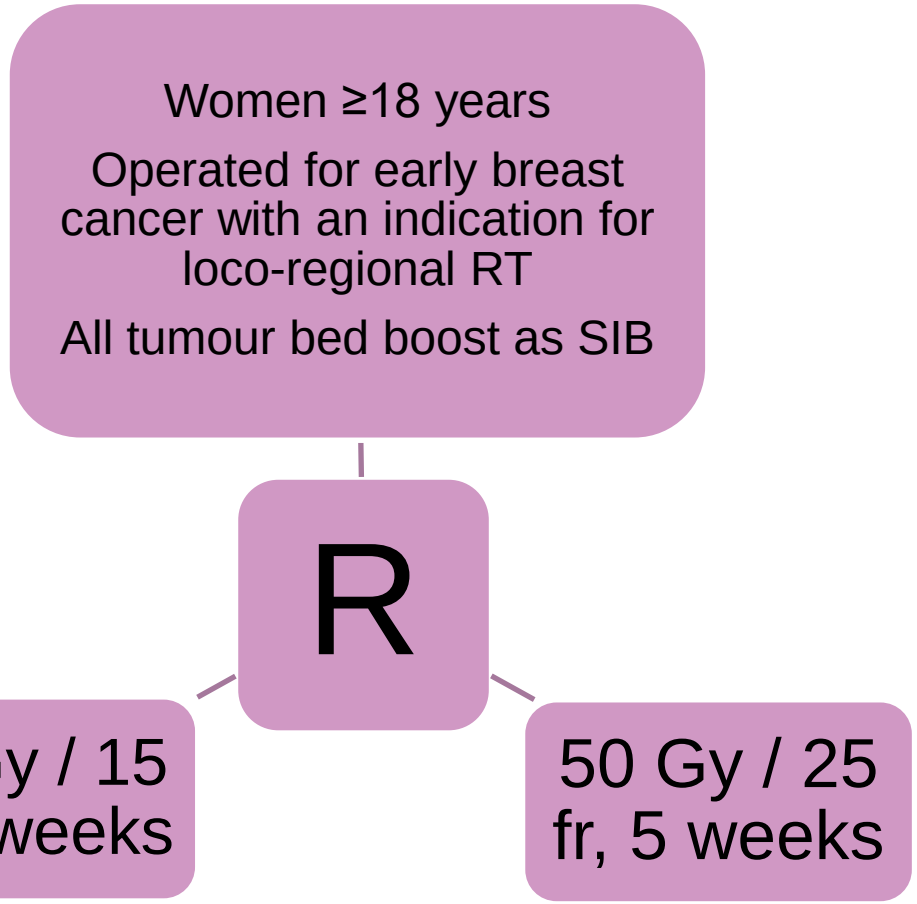
POSNOC
SENOMAC

FRACTIONATION

The DBCG RT Skagen Trial 1
The French HYPOG-01 trial

DBCG trial: open since 2015
Active in 6/7 DK centres and centres in Norway, Germany, Belgium, Poland, Slovenia and soon in Finland and Australia/New Zealand. Now 1000 pts accrued. Continues until 1012 pts have 3 yr morbidity results.
PI: Birgitte Offersen

HYPOG-01 trial: open since 2016
Active in 6 centres now, a total of 28 French centres will start. Now ~ 100 pts accrued. Continues until 1012 pts have 3 yr morbidity results.
PI: Sofia Rivera



mph oedema
ROMs, pattern of recurrences

Follow up yearly for 5 years then at 10 years

Skagen Trial: www.dbcg.dk, Nielsen et al 2016, Francolini et al 2017, Eldesoky et al 2017

ESTRO School

FRACTIONATION

Similar trials from Colorado/Kansas/Virginia/Egypt

General: Patients with indication for loco-regional RT, BCS/mast, morbidity is primary endpoint

Randomised trials:

Colorado: 40 Gy/15 fr versus 50 Gy/25 fr, target accrual 112 pts
Kansas: 40 Gy/15 fr versus 50 Gy/25 fr, target accrual 296 pts
Egypt: 42.5 Gy/16 fr versus 50 Gy/25 fr, target accrual 500 pts

Single arm study:

Virginia: 42.5 Gy/16 fr, target accrual 145 pts

FAST-Forward Trial

Randomised clinical trial testing a 1-week course of curative whole breast radiotherapy against a standard 3-week schedule in terms of local cancer control and late adverse effects in patients with early breast cancer.

Courtesy Professor Murray Brunt, Cambridge, UK

START Trial B –

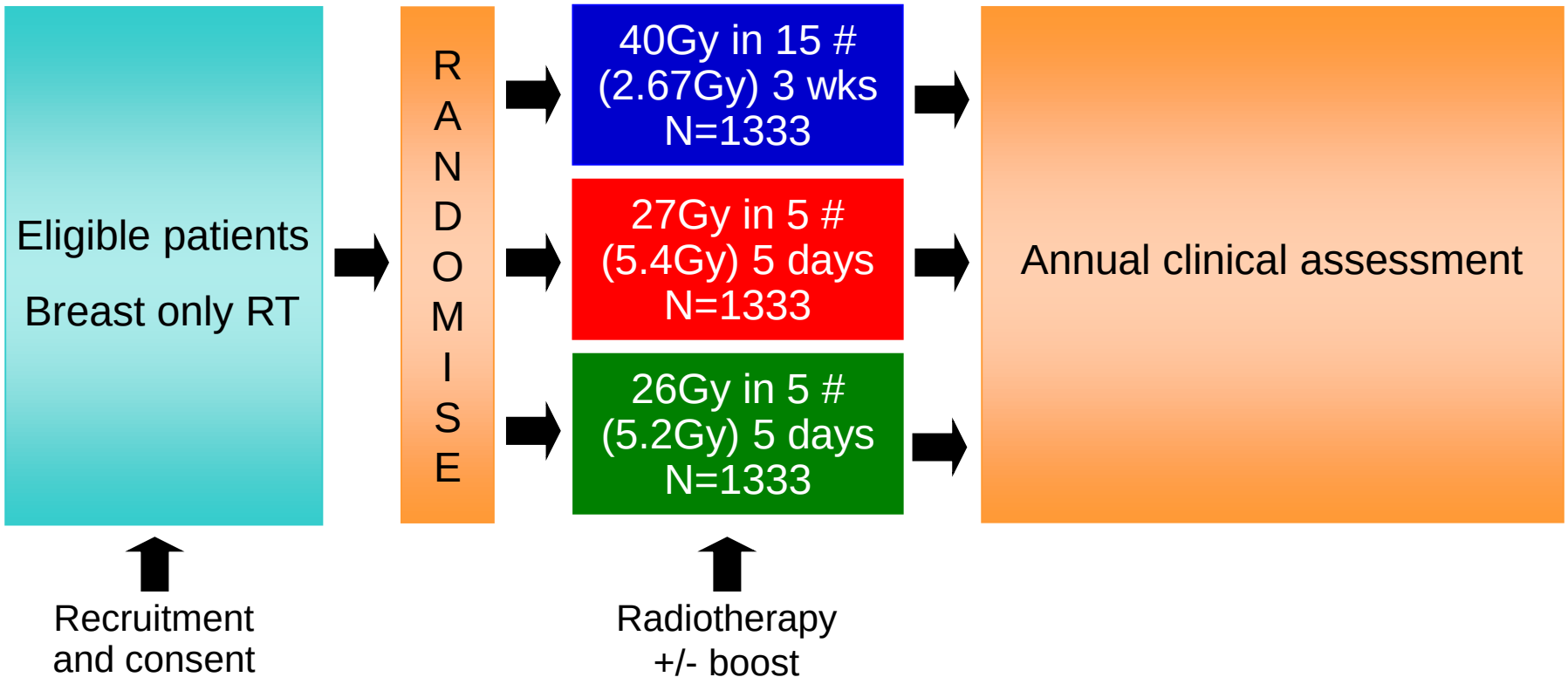
40Gy in 15# of 2.67Gy was as effective in terms of tumour control & adverse effects as 50Gy in 25# of 2Gy.

FAST trial

28.5Gy in 5# of 5.7Gy appears equivalent to 50Gy/25F in terms of change in breast appearance at 2 years and late adverse effects in breast at a median of 3.1 years.

This is unlikely to be the limit of hypofractionation – how far can we go?

Trial Design



Primary endpoint:

- ipsilateral local tumour control

Secondary endpoints:

- early and late adverse effects in normal tissues,
- quality of life,
- contralateral primary tumours,
- regional and distant metastases
- survival.

ESTRO School

Current Status

Trial opened to recruitment on 23rd Nov 2011

103 centres open to recruitment

4110 patients recruited by March 2014

- 3903 blood, 1798 PROMS, 1737 photographs

Nodal Radiotherapy Sub-study
-Start April 2016

Aim:

To show that a 5-fraction schedule of adjuvant radiotherapy to levels 1-3 axilla and/or level 4 axilla is non-inferior to a 15-fraction standard in terms of patient reported arm swelling and function and to contribute additional information to the endpoints of the main trial

Primary endpoint: Ipsilat tumour control (personal communication, M Brunt)

Sec endpoints: PROMs

Sample size: 627 patients randomised 1:1:1 to 3 arms

August 2017: 202 patients accrued

ESTRO School

Nodal Radiotherapy Sub-study - endpoints

Patient-reported outcomes*:*

- arm swelling
- shoulder stiffness
- upper limb pain
- sensorimotor symptoms
- arm function

Clinical-reported outcomes:

- upper limb sensorimotor symptoms

Nodal Radiotherapy Sub-study - inclusion criteria

Inclusion Criteria: as for the main trial plus

- pT1-3, pN1-2, M0 disease
- histological involvement of axillary lymph nodes
- indication for radiotherapy to level I-III axilla and/or level IV axilla (SCF) (NO IMN RT)

(combinations)

Sub-studies: PROMS are mandatory

Other sub-studies as per main trial

FRACTIONATION, severe hypofractionation cont.

HAI-5-III trial: partially randomised patient preference trial, comparing adjuvant hypofractionated RT in 15 versus 5 fractions after breast conservation or mastectomy for early or locally advanced breast cancer in women above 65 years
Boost provided as SIB

Pts can accept randomisation or choose treatment

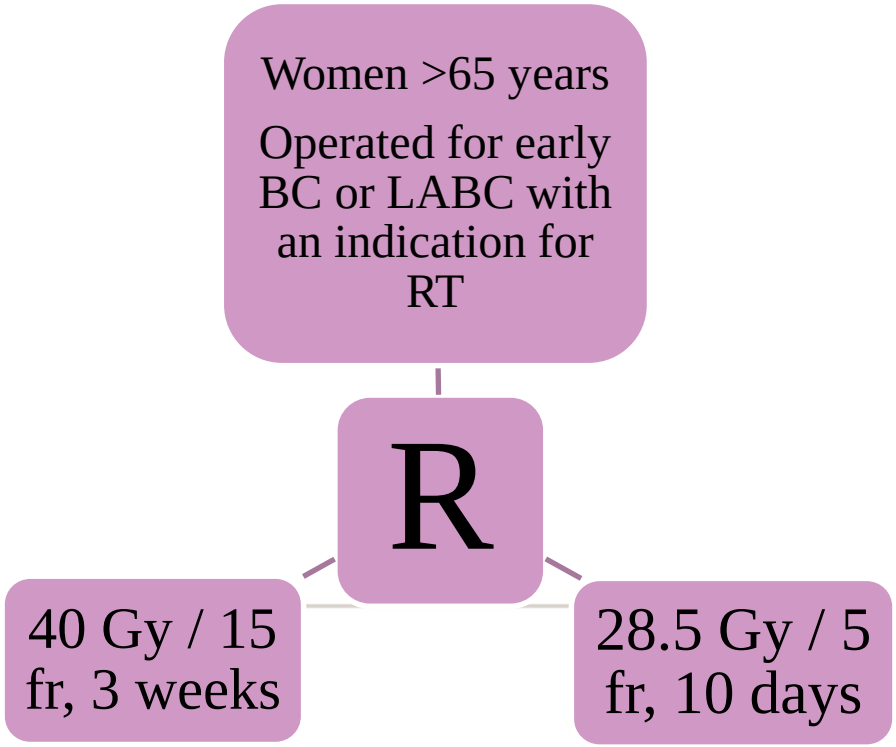
Primary endpoint:
breast retraction 2-5 years, BCCT core

Start Febr 2017

Expected accrual 798 patients

PI: Liv Veldeman, Ghent

(If regional nodes RT: 27 Gy/5 fr)



Accruing: open trials accruing pN+ patients

FRACTIONATION
The DBCG RT Skagen Trial 1
The HYPOG-01 trial
Trials from Colorado/Kansas/Virginia/Egypt
Ghent trial
FAST forward trial, nodal substudy

TARGET FOR REGIONAL RT AFTER PST
NSABP-B51 trial
Alliance A011202 trial

MANAGEMENT OF THE AXILLA WITH MACROMET IN SN
POSNOC
SENOMAC

Molecular subtypes and residual disease

Ann Surg Oncol (2015) 22:S495–S501
DOI 10.1245/s10434-015-4697-7

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

The Effect of Molecular Subtype and Residual Disease on Locoregional Recurrence in Breast Cancer Patients Treated with Neoadjuvant Chemotherapy and Postmastectomy Radiation

T. Jonathan Yang, MD[1], Monica Morrow, MD[2], Shanu Modi, MD[3], Zhigang Zhang, PhD[4], Kate Krause, BS[1], Chun Siu, BS[1], Beryl McCormick, MD[1], Simon N. Powell, MD, PhD[1], and Alice Y. Ho, MD[1]

233 pts (from MSKCC) with stages 2-3 BC, NAC, mastectomy, PMRT 2000-2009 (50 Gy/25f, chest wall+supraclav, 40% axillary boost, 20% IMN boost, 14% scar boost)
NAC: Anthracycline 10%, Taxane 6%, both 86%
99% had ALND, 36% had ypN2-3
HR+: 53%
HER2+: 23% (74% had trastuzumab)
TN: 24%
pCR: 14% (T and N site)

ESTRO School

Molecular subtypes, residual disease

Median follow up 62 months

5-yr LRR 8% overall cohort

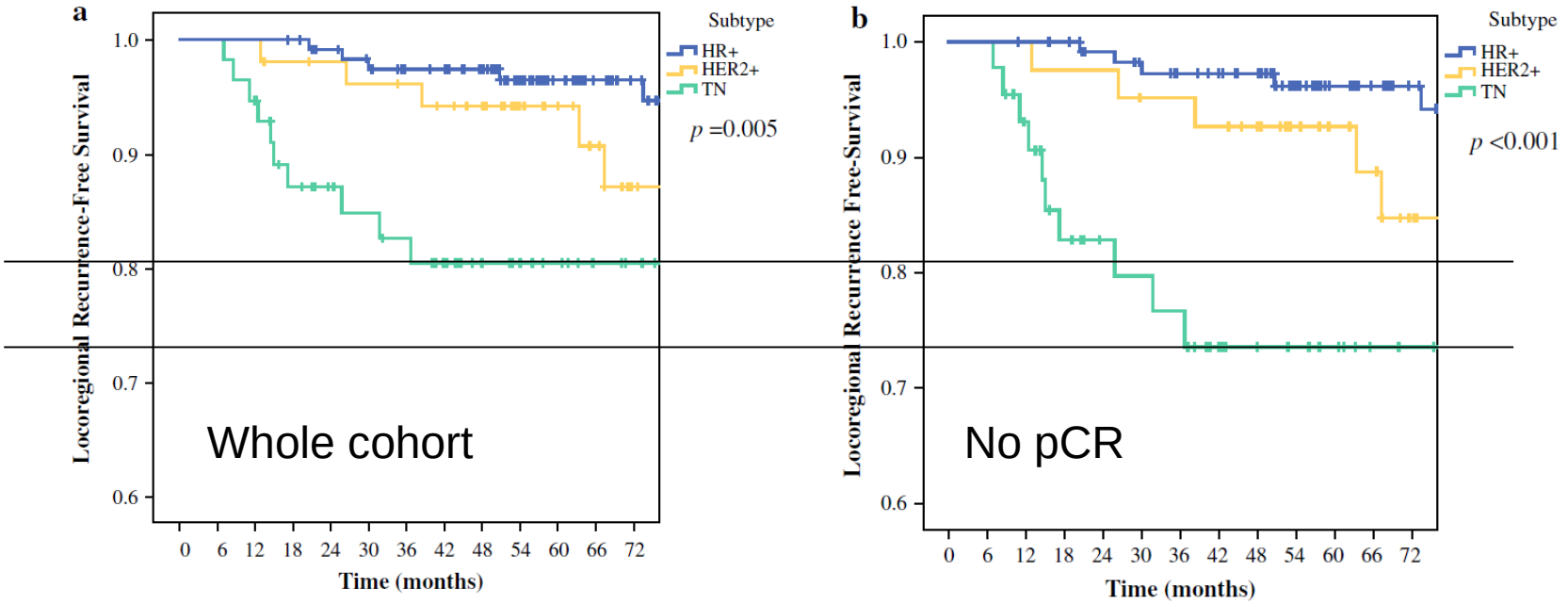
pCR *vs* no pCR: 0% vs 9%, p=0.05

Endpoint LRR: HR (TN) 4.4, p=0.003 and HR (ypN+) 9.8, p=0.03

	All patients, n=233		Patients with no pCR, n=201	
	5-yr LRR	p	5-yr LRR	p
TN	20%	0.005	26%	<0.001
HER2+	6%		7%	
HR+	4%		4%	

Molecular subtypes, residual disease and 5-yr LRR

In addition: the National Comprehensive Cancer Network (NCCN) and St. Gallen consensus statements advise to use the pre-NAC staging and risk factors



Conclusion:

TN breast cancer pts have a poor prognosis, and in particular patients with no pCR have a very high LRR risk

Patients with HR+ or HER2+ breast cancer had favourable LRR rates regardless of NAC response

ESTRO School

Target for RT after PST, ongoing trials

cN1 → NAC → ypN0

NSABP B-51

Standard versus comprehensive radiotherapy in treating patients with no residual nodal disease after NAC

- cT1-3N1M0
- Needle biopsy demonstrating nodal disease before NAC
- NAC
- Surgery + ALND/SNB with nodal pCR
- Randomisation
  - BCS: WBI vs WBI + RNI
  - Mastectomy: PMRT (chest wall + RNI) vs no PMRT
- N=1636
- Start 2013, estimated end of accrual 2023
- Primary endpoint: any event (LR, RR, DM, death)

Target for RT after PST, ongoing trials

cN1 → NAC → ypN+

Alliance trial A011202

Comparison of ALND with axillary RT for pts with node-positive BC treated with NAC

- cT1-3N1M0
- Needle biopsy proving nodal disease before NAC
- NAC
- Residual nodal disease after NAC (>0.2mm)
- Randomisation
  - ALND + RNI (undissected axilla + level III, supraclav fossa+IMN I-III)
  - RNI (full axilla level I-III + supraclav fossa + IMN I-III
- Primary endpoint: invasive breast cancer recurrence-free interval
- Start 2014, expected closure 2024
- Accrual 2918 pts

Notice:

In the retrospective MSKCC study the risk of 5-yr LRR in triple neg pts with ypN+ was 26% (all had ALND + PMRT, however, clinical stages 2/3)

Accruing: open trials accruing pN+ patients

FRACTIONATION
The DBCG RT Skagen Trial 1
The French HYPOfractionated nodal trial
Ghent trial
FAST forward trial, nodal substudy
HeNRIetta

TARGET FOR REGIONAL RT AFTER PST
NSABP-B51 trial
Alliance A011202 trial

MANAGEMENT OF THE AXILLA WITH MACROMET IN SN
POSNOC
SENOMAC *Thorsten presented these trials yesterday*

Nurturing (resulted in clinical guidelines)

Strategies from ACOSOG Z0011 & AMAROS trials are used in some institutions and countries

IMN RT is international standard in most patients treated with regional nodes RT

Future trials pN+

ATNEC Trial, UK trial in planning phase

DBCG RT Recon trial (later today)

Breast P1

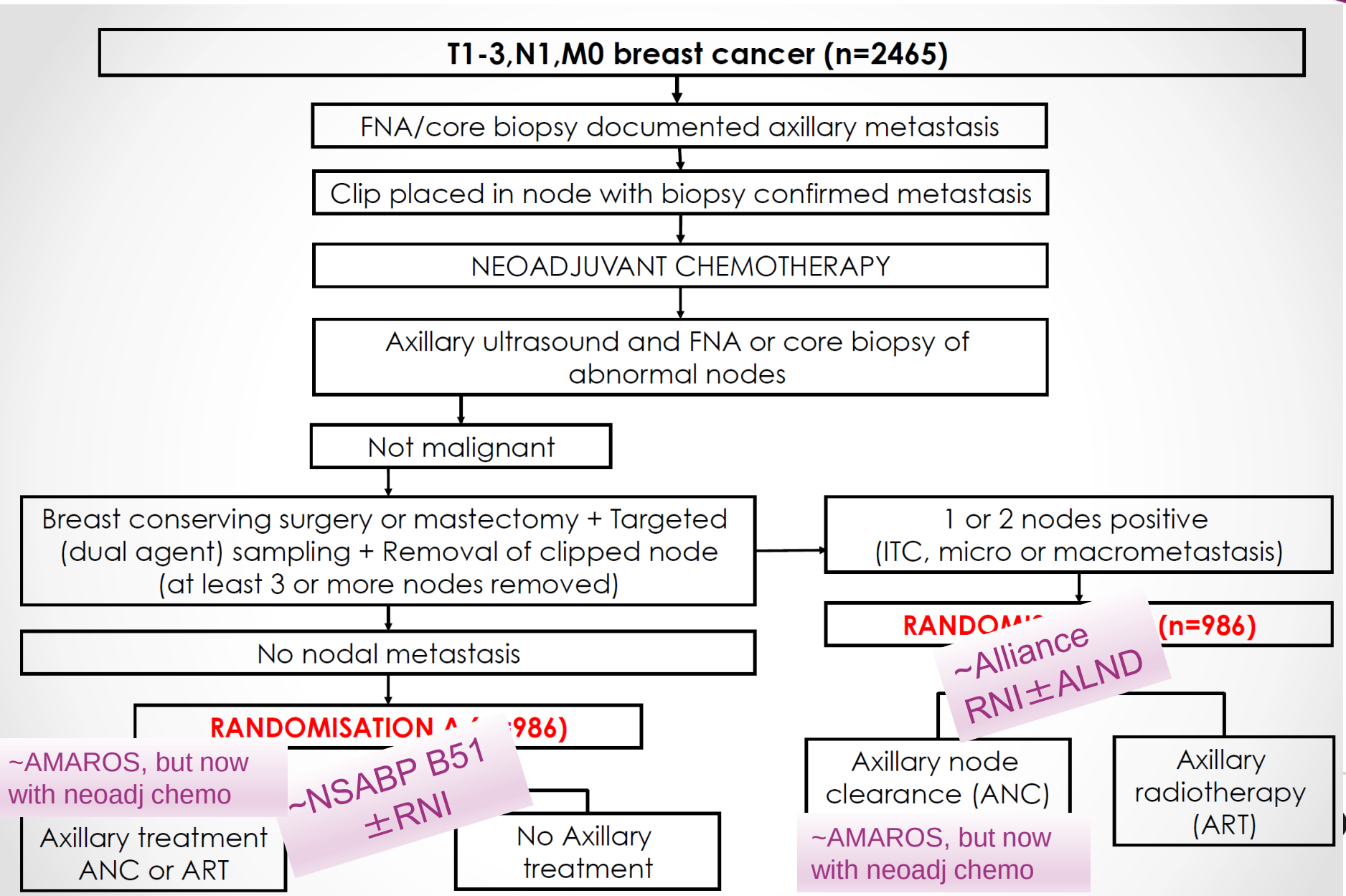
Derby Hospitals NHS
NHS Foundation Trust

ATNEC trial

A randomised trial evaluating the role of **A**xillary **T**reatment in patients with T1-3N1M0 breast cancer after **NE**oadjuvant **C**hemotherapy

Amit Goyal
Consultant Oncoplastic Breast Surgeon & Associate Professor
Royal Derby Hospital, Derby, United Kingdom

ESTRO School


T1-3,N1,M0 breast cancer (n=2465)
FNA/core biopsy documented axillary metastasis
Clip placed in node with biopsy confirmed metastasis
NEOADJUVANT CHEMOTHERAPY
Axillary ultrasound and FNA or core biopsy of abnormal nodes
Not malignant
Breast conserving surgery or mastectomy + Targeted (dual agent) sampling + Removal of clipped node (at least 3 or more nodes removed)
No nodal metastasis
RANDOMISATION A (n=986)
~AMAROS, but now with neoadj chemo
~NSABP B51 ±RNI
Axillary treatment ANC or ART
No Axillary treatment
1 or 2 nodes positive (ITC, micro or macrometastasis)
RANDOM (n=986)
~Alliance RNI±ALND
Axillary node clearance (ANC)
Axillary radiotherapy (ART)
~AMAROS, but now with neoadj chemo

Outcomes

- **Primary**
  - Disease free survival at 5 years
- **Secondary**
  - Arm morbidity and quality of life
  - local (breast or chest wall) recurrence
  - regional (nodal) recurrence
  - distant metastasis, overall survival
  - contralateral breast cancer
  - non-breast malignancy

Tissue Collection

- Primary breast cancer tissue

- Residual breast cancer tissue(after neoadjuvant chemotherapy)
  - gene expression profiles in residual tumour tissue and to develop predictors of disease progression

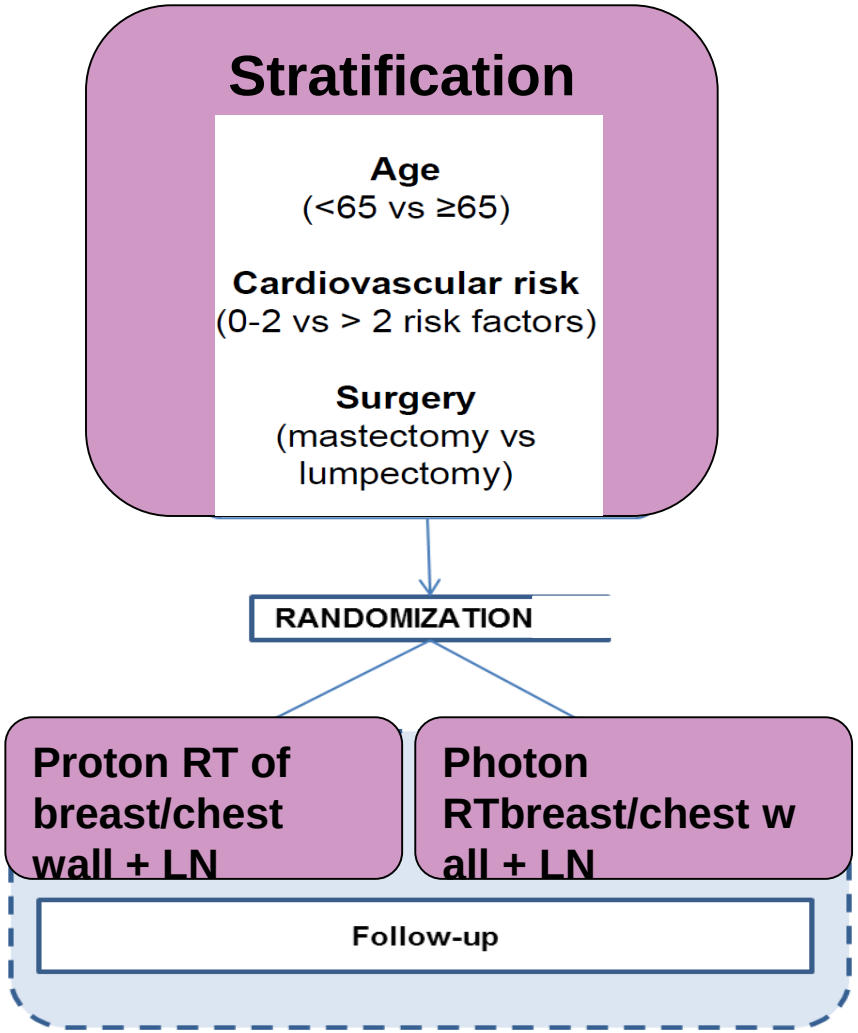
BREAST P1: Multicenter European Randomized Phase III trial comparing protons *vs.* optimal photon radiotherapy in breast cancer with an indication for regional lymph node irradiation in terms of cardiac and other long term toxicities

Youlia M. Kirova, M.D.,

youlia.kirova@curie.fr

- To assess the superiority of the proton locoregional radiotherapy to currently used photon-electrons 3D conformal or IMRT radiotherapy in term of cardiac toxicity at 10 years (reduction of 50% in 10 yrs).
- Evaluation strict by ultrasound but also blood tests, MRI in population at risk.
- ESTRO Guidelines for volume definition
- Translational research

Woman ≥ 18 years who had radical surgery for invasive breast cancer pT1-3, pN0-N3, M0 with either mastectomy or breast conservation.



ESTRO School

Statistics

We estimated that among patients treated with normofractionated radiotherapy in EORTC IMN vs no IMN study, the cardiac disease rates were 6.5% at 10 years after radiation therapy. If we want to show 50% decrease of this cardiac toxicity using protons;
With this total of 1310 patients, we will be able to show this difference at 10 years if it exists with a power of 87%.

To assess the non-inferiority to proton versus photon therapy in reducing ipsilateral breast cancer loco-regional recurrence, 1310 patients in total are needed. There is 80% power for a 5-year non-inferiority not higher than 3 % for local-regional recurrence assuming local-regional recurrence in the photon arm of 5% at 5 years with a type one error equal to 5% (unilateral).

Conclusion: Recent trials in pN+ patients

TARGET FOR NODAL RT

EORTC trial

MA.20

DBCG IMN study

FRACTIONATION

The DBCG RT Skage

The HYPOG-01 trial

Other fractionation tri

Ghent trial

FAST forward trial, n

TARGET FOR REGI

NSABP-B51 trial

Alliance A011202 tria

MANAGEMENT OF THE AXILLA WITH MACROMET IN SN

POSNOC

SENOMAC

ESTRO School

A little remark on biology and RT (because the debate on nodal RT was cancelled yesterday)

Personalized Medicine and Imaging

Development and Validation of a Gene Profile Predicting Benefit of Postmastectomy Radiotherapy in Patients with High-Risk Breast Cancer: A Study of Gene Expression in the DBCG82bc Cohort

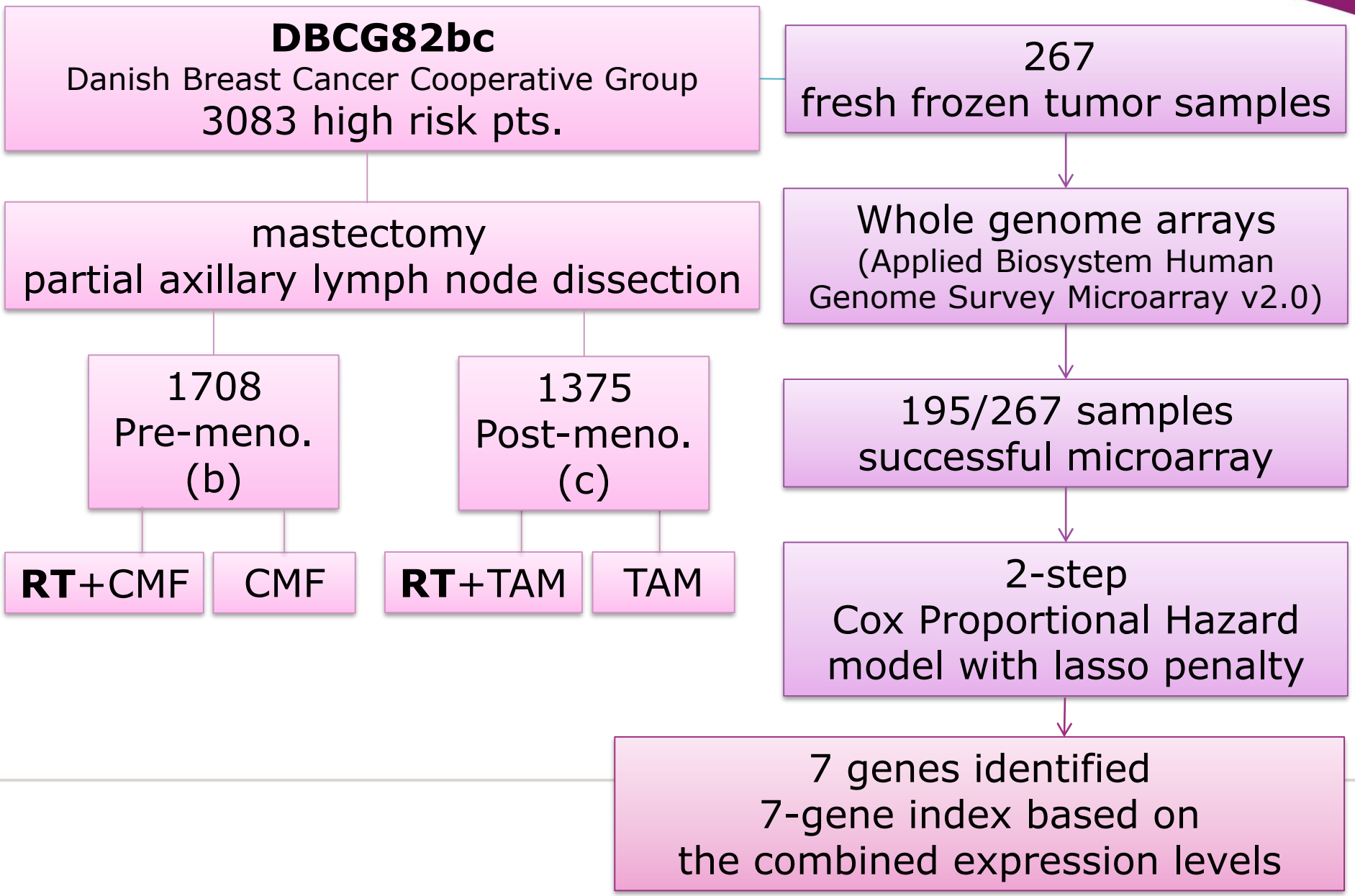
Trine Tramm[1], Hayat Mohammed[2], Simen Myhre[3,4,5], Marianne Kyndi[1], Jan Alsner[1], Anne-Lise Børresen-Dale[3,4], Therese Sørlie[3,4], Arnoldo Frigessi[2], and Jens Overgaard[1]

Clin Cancer Res; 20(20); 5272–80. ©2014 AACR.

CIRRO

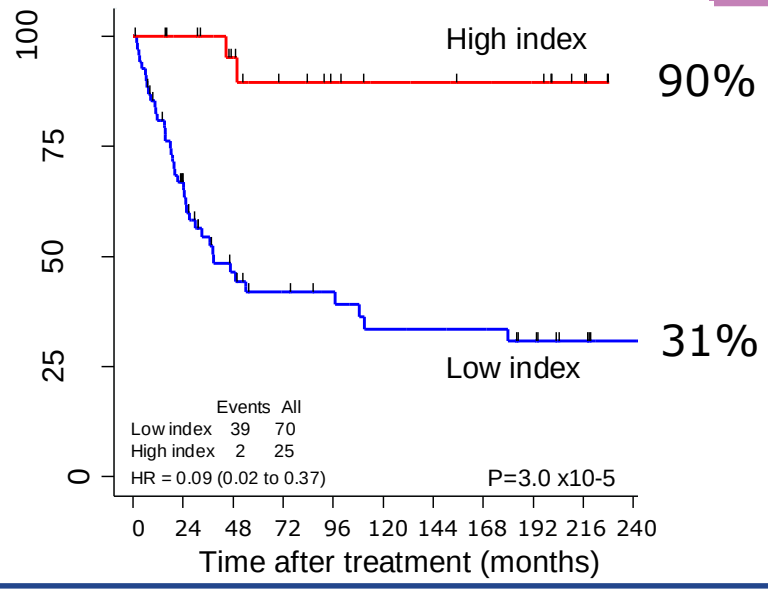
Aarhus University Hospital

PMRT: Material and Methods



Results

Prognostic (no PMRT group)

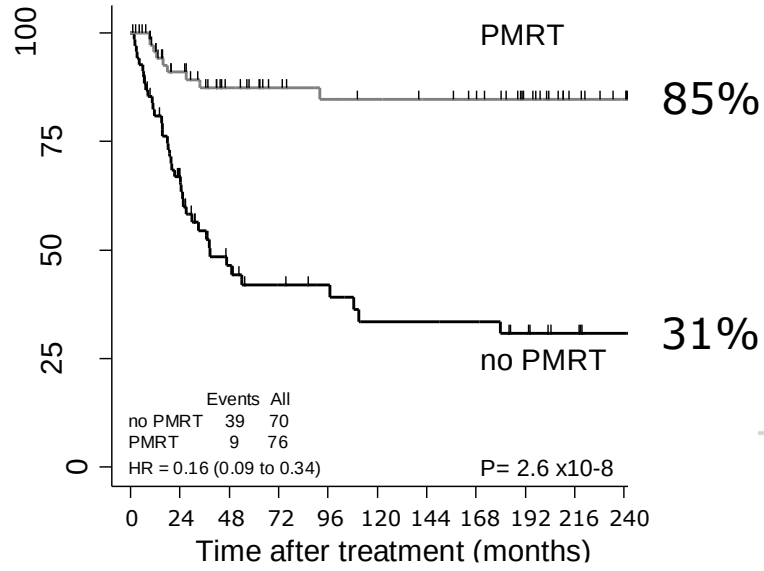


This pattern is seen regardless of
-nodal status
-T status
-menopausal status

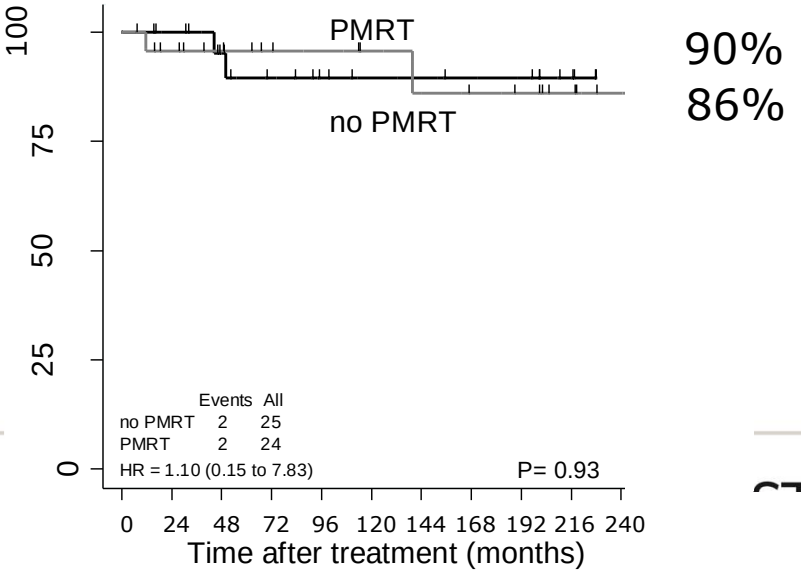
The gene profile has been validated in an independent data set (Tramm et al, Clin Can Res, 2014)

Predictive

Low index



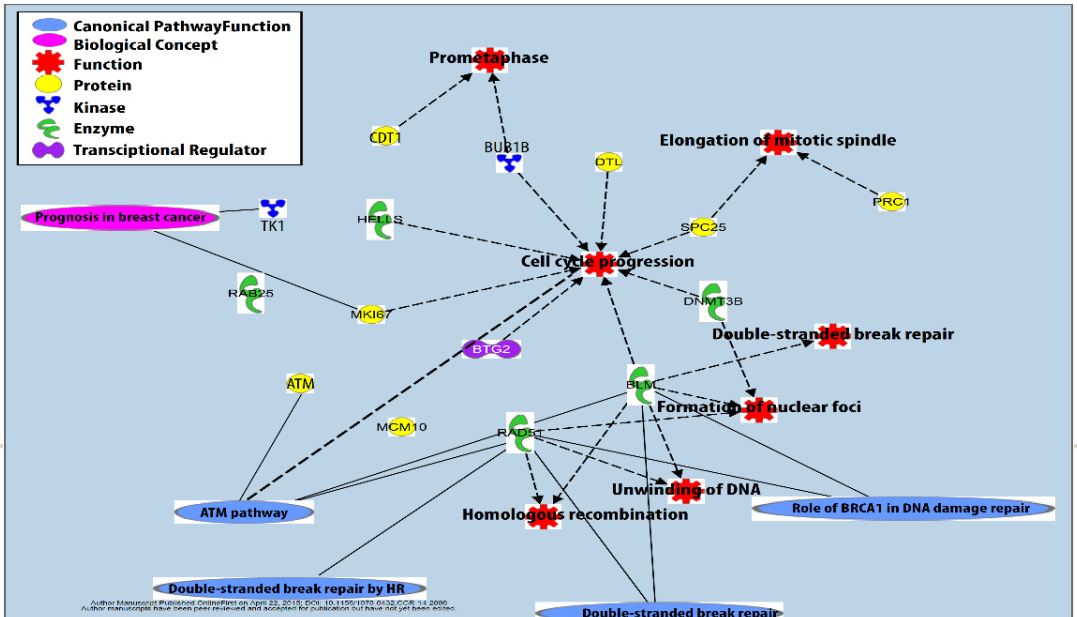
High index



Development and validation of a novel radiosensitivity signature in human breast cancer

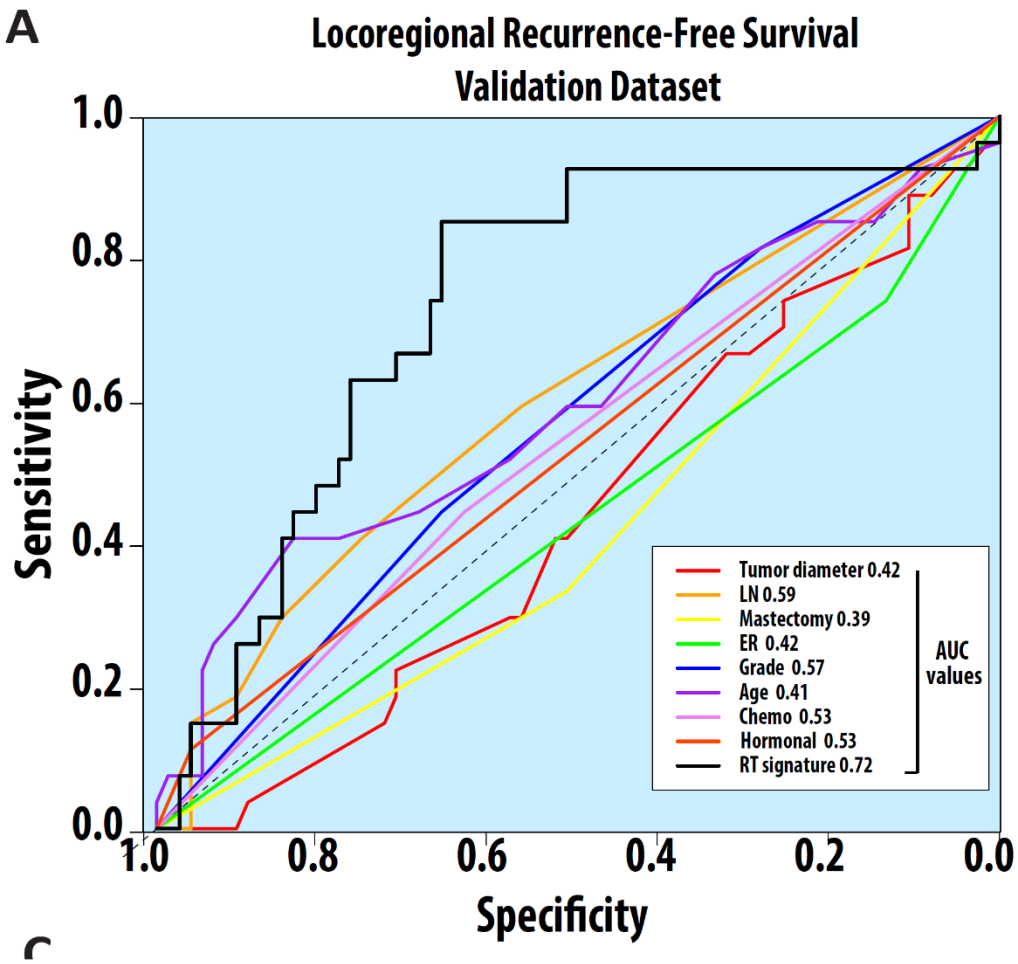
Corey Speers[1*], Shuang Zhao[1*], Meilan Liu[1], Harry Bartelink[4], Lori J. Pierce[¥,1,3], Felix Y. Feng[¥,†,1,2,3]

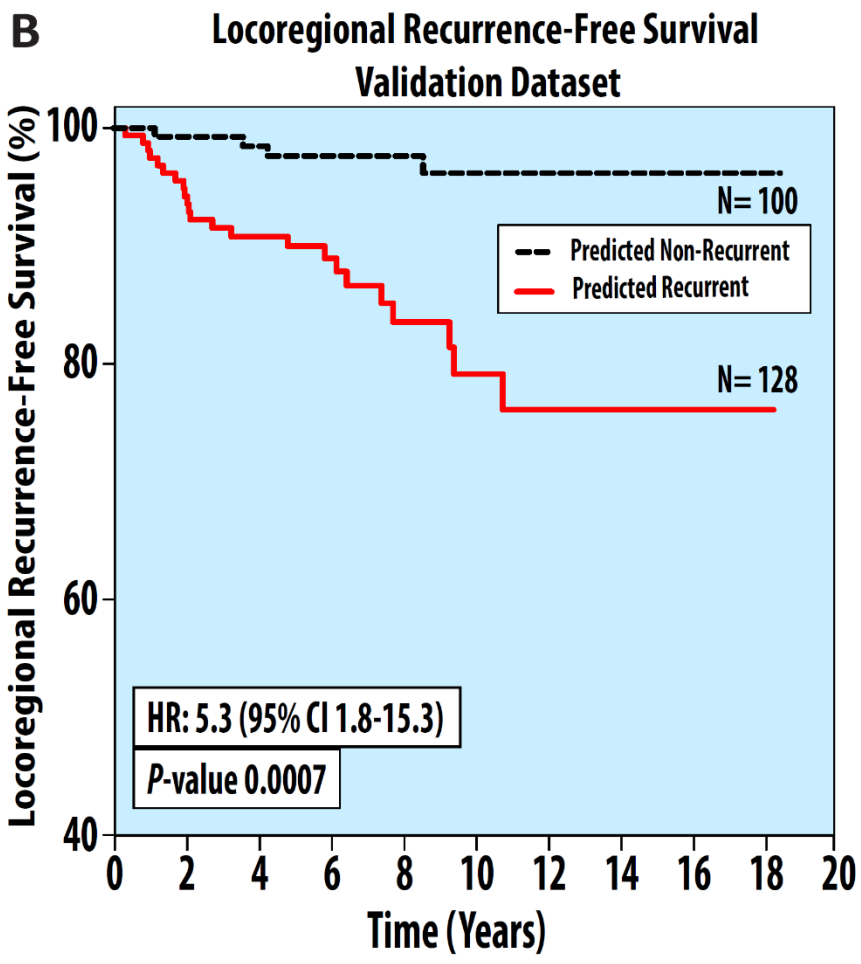
1) In vitro: Clonogenic survival assays to identify the SF-2Gy in 16 BCC lines
2) Surviving fractions (17-77%) independent of intrinsic subtypes
3) Gene expression data from BCC correlated to SF data, 147 genes identified
4) Hierarchical cluster analysis separates genes into radioresistent vs –sensitive
5) In vivo: RSS run in test set of 343 pts with gene analysis data, all treated with BCS+RT and with FU, then RSS further trained and refined to 51 genes.
6) 51 gene profile evaluated on ingenuity.com, tested in a validation set of 295 pts with gene analysis data and with BCS+RT and FU



ESTRO School

Radiation signature tested in the validation set





Radiation signature tested in the validation set

Author Manuscript Published OnlineFirst on April 22, 2015; DOI: 10.1158/1078-0432.CCR-14-2898
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

	Univariable Analysis			
	Local Recurrence		Overall Survival	
Covariate	Hazard Ratio (HR)	*P* value	Hazard Ratio (HR)	*P* value
Radiation signature	**5.25 (95% CI 1.80-15.34)**	**0.002**	**2.52 (95% CI 1.52-4.17)**	**<0.0001**
Age	0.95 (95% CI 0.89-1.02)	0.14	**0.96 (95% CI 0.92-0.99)**	**0.02**
Mastectomy	0.54 (95% CI 0.24-1.23)	0.14	1.01 (95% CI 0.65-1.59)	0.95
Tumor diameter	0.73 (95% CI 0.45-1.20)	0.22	**1.46 (95% CI 1.16-1.89)**	**0.001**
ER status	0.66 (95% CI 0.27-1.59)	0.35	**0.31 (95% CI 0.20-0.49)**	**<0.0001**
Grade	1.26 (95% CI 0.76-2.09)	0.37	**2.96 (95% CI 2.05-4.27)**	**<0.0001**
Chemotherapy	1.38 (95% CI 0.63-3.02)	0.42	0.76 (95% CI 0.47-1.23)	0.27
LN status	1.06 (95% CI 0.91-1.23)	0.44	1.03 (95% CI 0.94-1.14)	0.48
Endocrine Therapy	0.76 (95% CI 0.23-2.55)	0.66	0.45 (95% CI 0.20-1.05)	0.06

D

	Multivariable Cox Regression Analysis			
	Local Recurrence		Overall Survival	
Covariate	Hazard Ratio (HR)	*P* value	Hazard Ratio (HR)	*P* value
Radiation signature	**6.12 (95% CI 1.94-19.3)**	**0.002**	**1.80 (95% CI 1.03-3.17)**	**0.04**
Age	0.94(95% CI 0.88-1.01)	0.07	0.97 (95% CI 0.94-1.01)	0.18
Diameter (cm)	0.61(95% CI 0.35-1.05)	0.07	1.22 (95% CI 0.93-1.59)	0.14
LN-positive	1.10 (95% CI 0.90-1.34)	0.34	1.06 (95% CI 0.96-1.18)	0.26
Mastectomy	0.68 (95% CI 0.28-1.67)	0.40	0.98 (95% CI 0.60-1.58)	0.92
ER status	0.77 (95% CI 0.29-2.07)	0.61	**0.57 (95% CI 0.34-0.93)**	**0.03**
Endocrine Therapy	1.12 (95% CI 0.31-4.03)	0.87	0.56 (95% CI 0.24-1.33)	0.19
Chemotherapy	1.05 (95% CI 0.41-2.67)	0.93	0.72 (95% CI 0.40-1.29)	0.27
Grade	0.97 (95% CI 0.53-1.81)	0.94	1.95 (95% CI 1.29-2.96)	0.002

Downloaded from clincancerres.aacrjournals.org on May 30, 2015. © 2015 American Association for Cancer

ESTRO School

Potential of gene analysis studies

The DBCG 7 gene profile can predict gain from loco-regional RT after mastectomy. It identifies 25% of a high-risk cohort where RT may not be of any value. This gene profile is both prognostic and predictive of RT effect.

The Michigan 51 gene profile can discriminate patients treated with BCS+RT who are unlikely to develop local recurrence after RT from those patients with a high likelyhood of recurrence despite RT. Thus it may identify patients who need treatment intensification. This gene profile is prognostic (not predictive).

Further studies are being performed to explore the potential of these profiles.

The role of adjuvant systemic treatment in the 21st – screening – patient population

B.Vriens

Medical oncologist

Catharina Hospital Eindhoven

The Netherlands

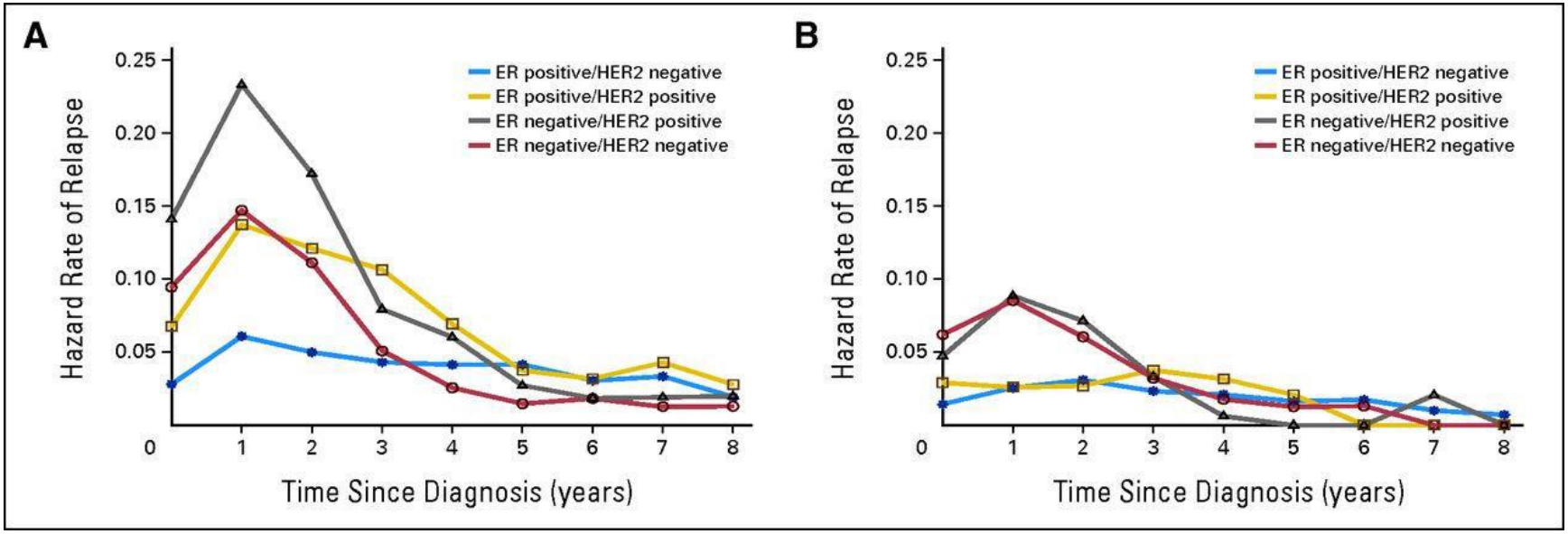
ESTRO Breast Cancer 2017

ESTRO School

Prognosis of early breast cancer has been greatly improved in the last four decades

1986 to 1992

2004 to 2008



Hazard rate of relapse according to tumor subtype and year of diagnosis (breast)

Cossetti R J et al. JCO
J Clin Oncol 2015:33(1):65-73

ESTRO School

Improved survival by treatment escalation
Systemic treatment

- in terms of number of drugs
- dose (sometimes)
- duration of therapy

Increasing number of breast cancer survivors

Focus on quality of life, limiting morbidity

Trials addressing de-escalation of treatment to reduce morbidity without significantly compromising survival are of increasing importance.

It seems unlikely that further escalation of adjuvant chemotherapy will improve survival, except in selected subgroups

Escalation or De-escalation?

Therapeutic escalation has also brought about significant problems.

- For patients: increasing burden of treatment-related toxicities, which can cause important emotional, social and economic issues.
- Healthcare systems: enormous financial strain as treatment costs soar ever higher.

Determining which patient will benefit from therapeutic escalation has proven to be a scientific challenge.

Failure to de-escalate systemic treatments contrasts starkly with successful de-escalation that come from breast cancer SURGERY and RADIOTHERAPY.

Who needs more or less treatment?

Treatments (neo)-adjuvant setting

Chemotherapy (e.g.)

- Taxanes
- Anthracyclines
- Cyclophosphamide
- Carboplatin

Endocrine therapy (ER+ and/or PR+ tumors)

- Tamoxifen
- Aromatase-inhibitors

Trastuzumab +/- Pertuzumab (HER2+ tumor)

Prognosis of early breast cancer has been greatly improved in the last four decades

- Landmark trials of adjuvant tamoxifen
- 1970s and 1980s; combination chemotherapy
- Since then, ever more intense and complex regimens, containing a combination of cytotoxic agents, endocrine agents and/or targeted agents have become the norm for hundreds of thousands of women.

(Neo)adjuvant Chemotherapy

Anthracyclines

Chemotherapy – Antracycline based

6 months of anthracycline-based polychemotherapy (eg, with FAC or FEC) reduces the annual breast cancer death rate

- by 38% (SE 5) age <50y
- by 20% (SE 4) age 50–69y

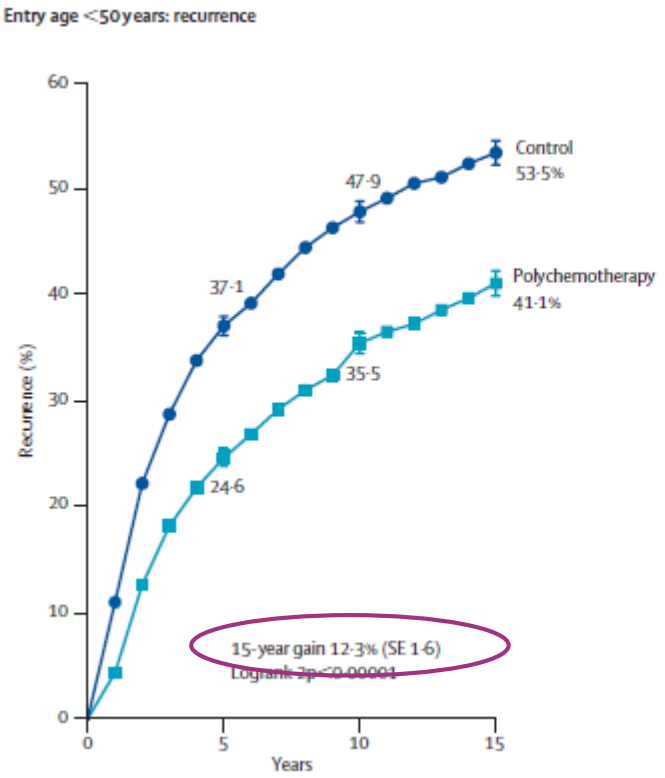
Irrespective of the use of tamoxifen, oestrogen receptor (ER) status, nodal status, or other tumour characteristics.

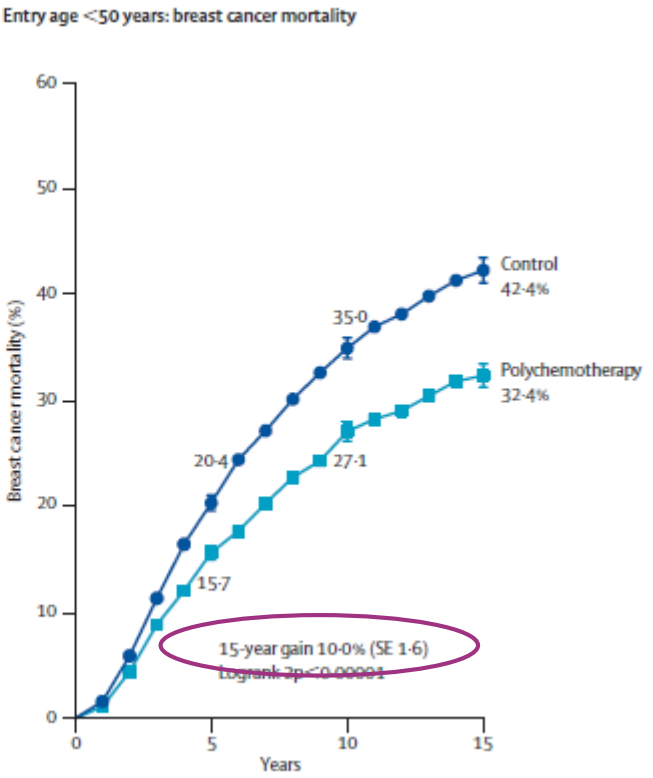
Systemic adjuvant treatment and age at diagnosis (years)	Proportional effect on annual breast cancer mortality rate (treatment vs control): Ratio of rates (R)	Proportional reduction
Chemotherapy only in ER-poor or ER-positive disease*		
None (any age)	1·0	–
Anthracycline (age <50 years)	0·62	38%
Anthracycline (50–69 years)	0·80	20%
Anthracycline (≥70 years)	?	?
Endocrine, or chemoendocrine, therapy in ER-positive disease*		
None (any age)	1·0	–
Tamoxifen (any age)	0·69	31%
Anthracycline+tamoxifen (age <50 years)	0·62×0·69	57%
Anthracycline+tamoxifen (50–69 years)	0·80×0·69	45%
Anthracycline+tamoxifen (≥70 years)	?×0·69	?

EBCTCG 2005

ESTRO School

Chemotherapy – Antracyline based



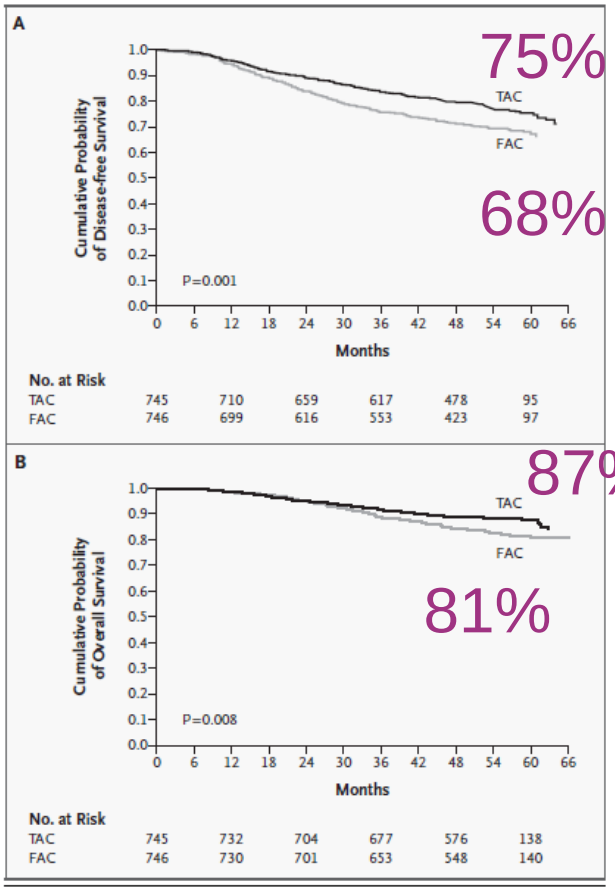


EBCTCG 2005

ESTRO School

Chemotherapy TAC vs FAC

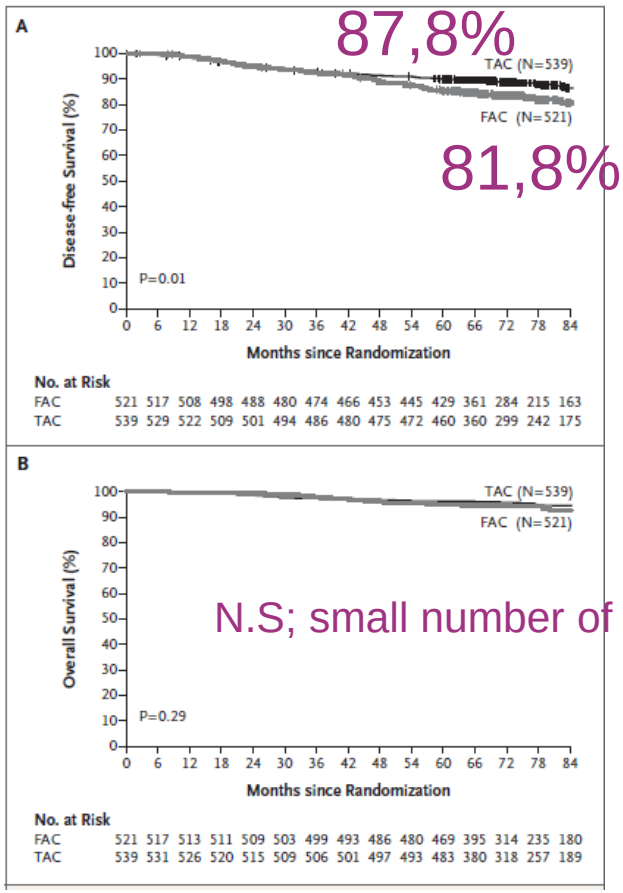
Node positive



Median FU 55m – 5y DFS/5y OS

Martin M; 2005 & 2010

Node Negative



N.S; small number of events

Median FU 77m DFS and OS

ESTRO School

De-escalation anthracyclines

DOSE:

Escalation of doxorubicin dose did not improve the DFS and OS (stage II BC)

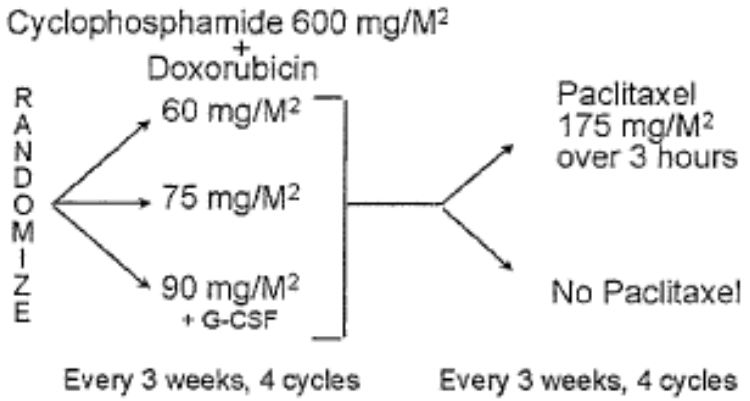


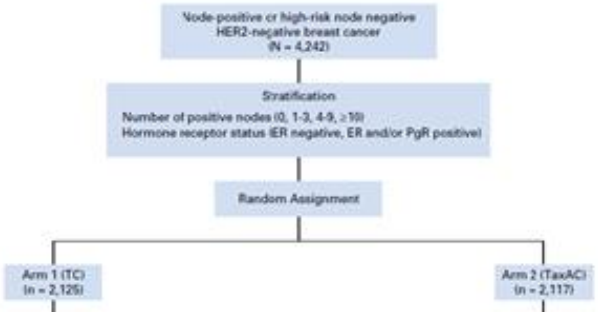
Fig 1. Protocol schema; 3 × 2 factorial design. After completion of chemotherapy, radiation therapy was administered if patient was treated with lumpectomy or at discretion of physician if patient was treated with masectomy, and tamoxifen 20 mg/d was administered for 5 years if the tumor was receptor positive.

Henderson, JCO 2003

ESTRO School

De-escalation anthracyclines

ABC-trials: TaxAC versus TC



Timeline and Accrual of ABC Trials

Trial	Arms	Accrual	Dates of Accrual	Median F/U, yrs	Funding
USOR 06-090	TC TaxAC	1295	MAY 2007 to JUN 2009	6.3	Sanofi
NSABP B-46I USOR 07132	TC TaxAC	1077	MAY 2009 to JAN 2012	4.8	Genentech
	*TC-BV	556			
NSABP B-49	TC TaxAC	1870	APR 2012 to NOV 2013	2.2	CTEP

*not included in ABC Trials analysis

ABC Trials
Patient Characteristics % all Patients

	06-090 N=1286	B-46I/07132 N=1051	B-49 N=1819	Total N=4156
Positive Nodes				
0	35	38	46	41
1-3	51	43	40	44
4-9	11	14	11	11
10+	3	5	4	4
Hormone Receptor				
ER+ or PgR+	71	67	68	69
ER– and PgR–	29	33	32	31

Blum JCO 2017

ESTRO School

Results Invasive free survival

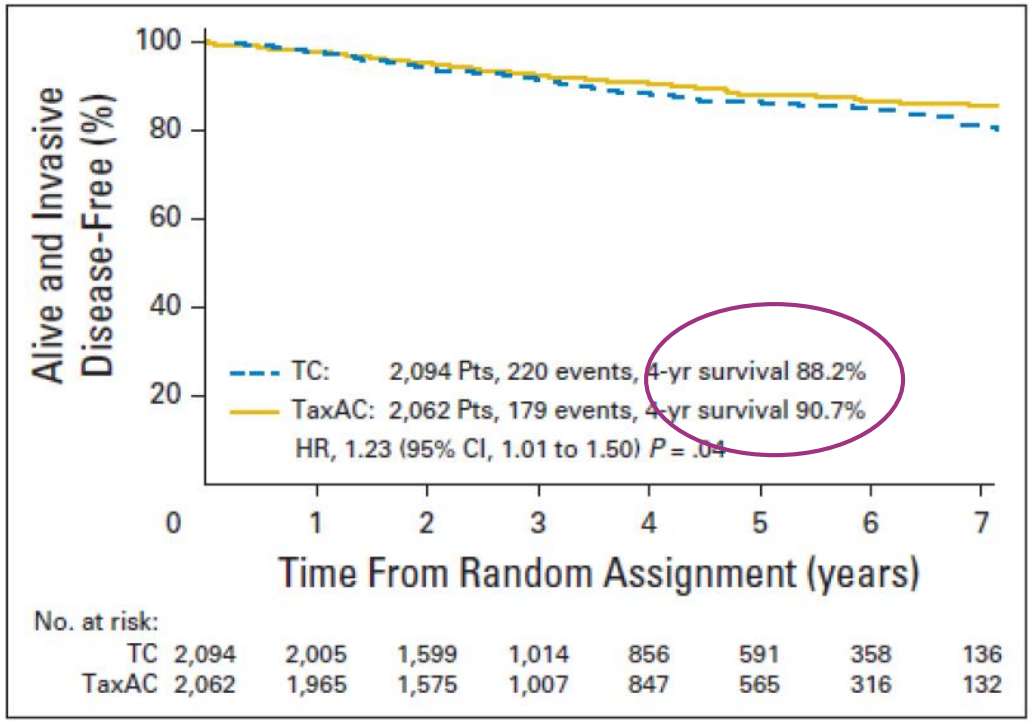
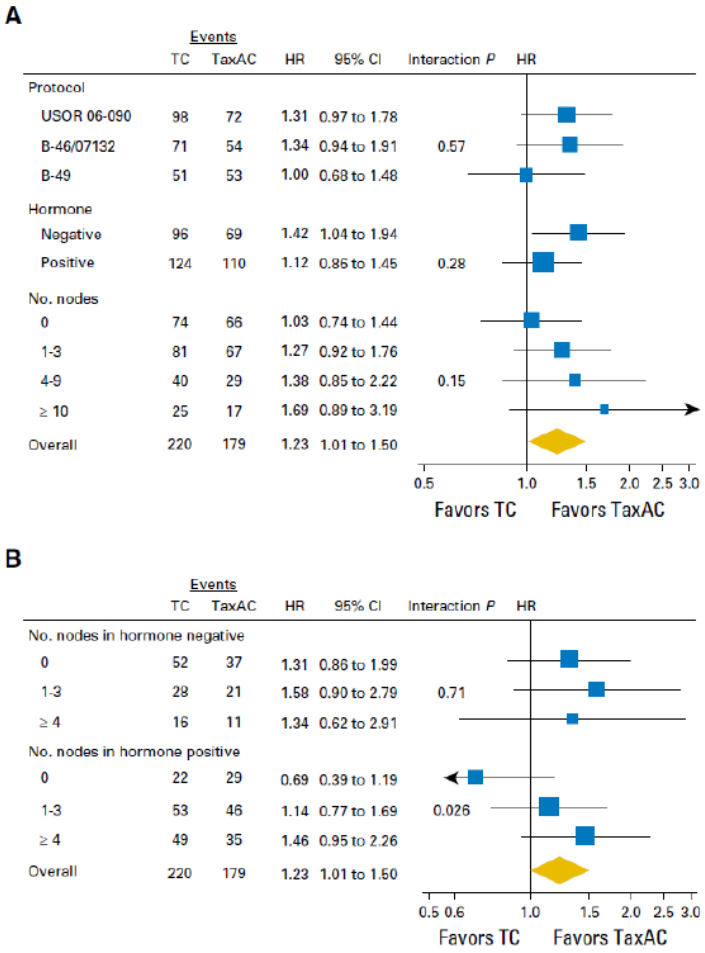


Fig 2. Kaplan-Meier plots of invasive disease-free survival. HR, hazard ratio; TaxAC, doxorubicin and cyclophosphamide regimens with a taxane; TC, docetaxel and cyclophosphamide.

ESTRO School

Explorative analysis



Minimal/No benefit anthracylines

ER+N0 High risk group

Benefit anthracyclines

- Triple negative N0/N+
- ER+/N+

- Waiting for data longer FU!!

ESTRO School

Conclusions ABC trials

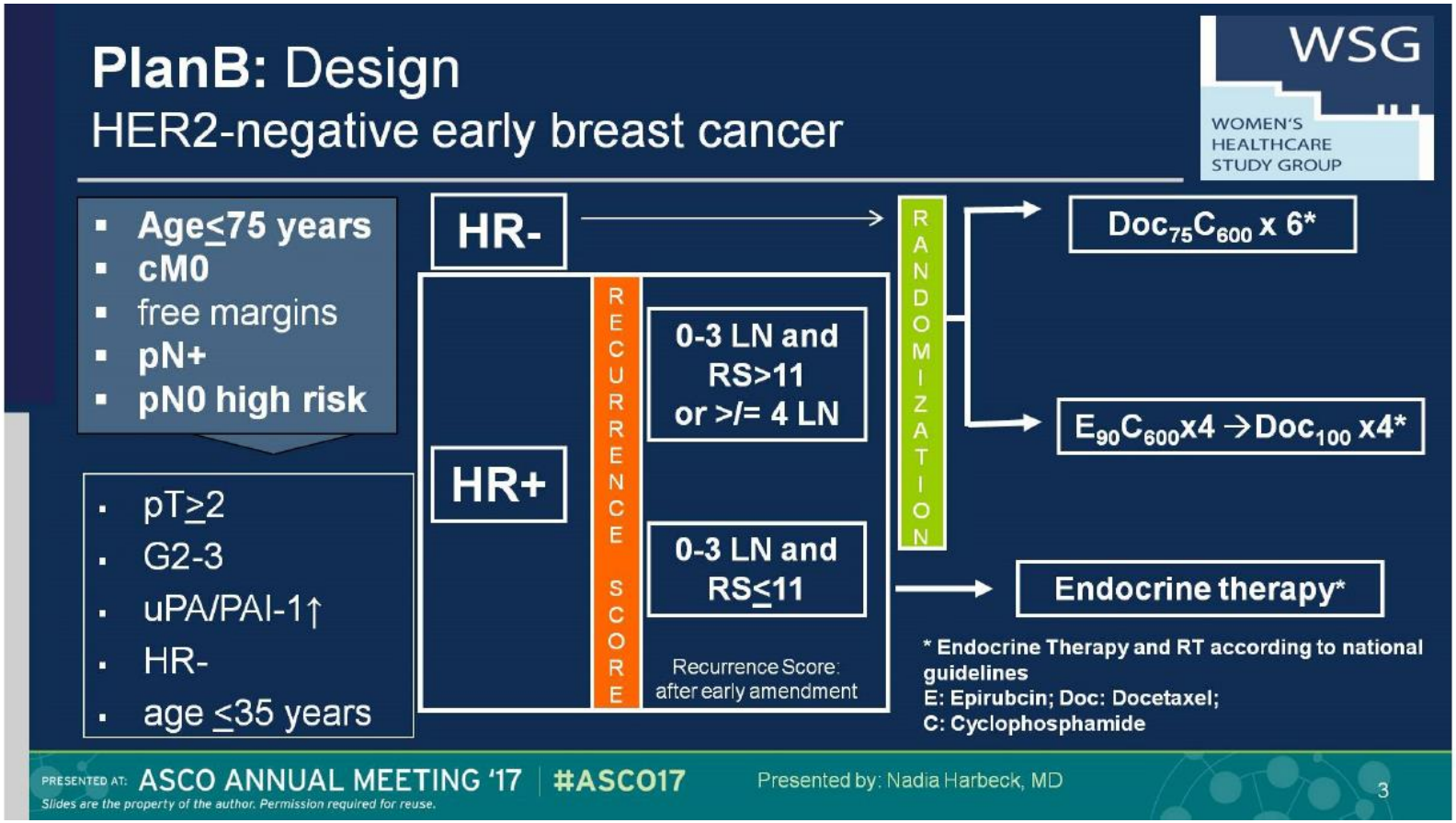
IDFS was significant for superiority of TaxAC relative to TC

4 year OS was high in both groups

Exploratory subgroup analyses suggest TaxAC provides

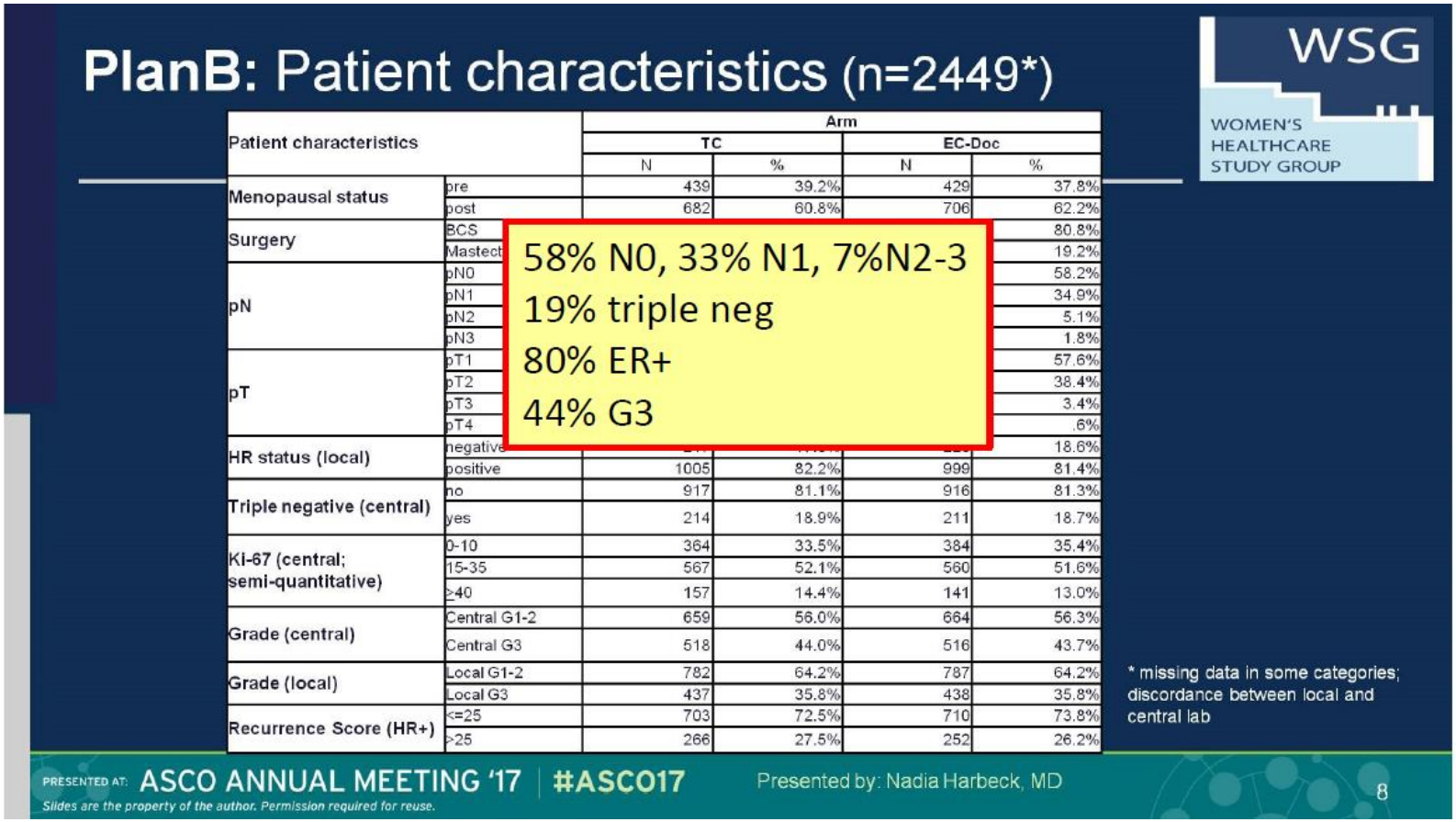
- Minimal, if any benefit in ER+/Node negative cohorts

TC versus EC-D



ESTRO School

Patient characteristics

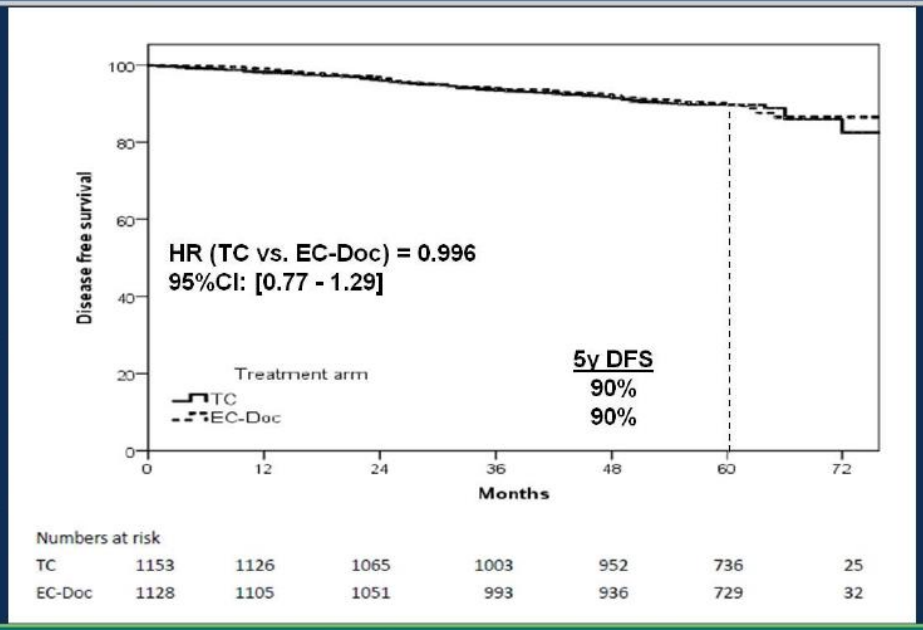


Patient characteristics		Arm			
		TC		EC-Doc	
		N	%	N	%
Menopausal status	pre	439	39.2%	429	37.8%
	post	682	60.8%	706	62.2%
Surgery	BCS				80.8%
	Mastect				19.2%
pN	pN0				58.2%
	pN1				34.9%
	pN2				5.1%
	pN3				1.8%
pT	pT1				57.6%
	pT2				38.4%
	pT3				3.4%
	pT4				.6%
HR status (local)	negative				18.6%
	positive	1005	82.2%	999	81.4%
Triple negative (central)	no	917	81.1%	916	81.3%
	yes	214	18.9%	211	18.7%
Ki-67 (central; semi-quantitative)	0-10	364	33.5%	384	35.4%
	15-35	567	52.1%	560	51.6%
	≥40	157	14.4%	141	13.0%
Grade (central)	Central G1-2	659	56.0%	664	56.3%
	Central G3	518	44.0%	516	43.7%
Grade (local)	Local G1-2	782	64.2%	787	64.2%
	Local G3	437	35.8%	438	35.8%
Recurrence Score (HR+)	<=25	703	72.5%	710	73.8%
	>25	266	27.5%	252	26.2%

ESTRO School

PlanB: Disease-free survival (DFS) by chemotherapy arm (ITT population)

WSG
WOMEN'S HEALTHCARE STUDY GROUP



Numbers at risk

TC	1153	1126	1065	1003	952	736	25
EC-Doc	1128	1105	1051	993	936	729	32

TC not inferior to EC-D

Slides are the property of the author. Permission required for reuse.

ESTRO School

Anthracyclines

The role of non-anthracycline chemotherapy needs further investigation in lesser risk cancers

Additional follow up and correlative studies to identify biomarkers of anthracycline benefit will be crucial for fully determining the utility of anthracyclines

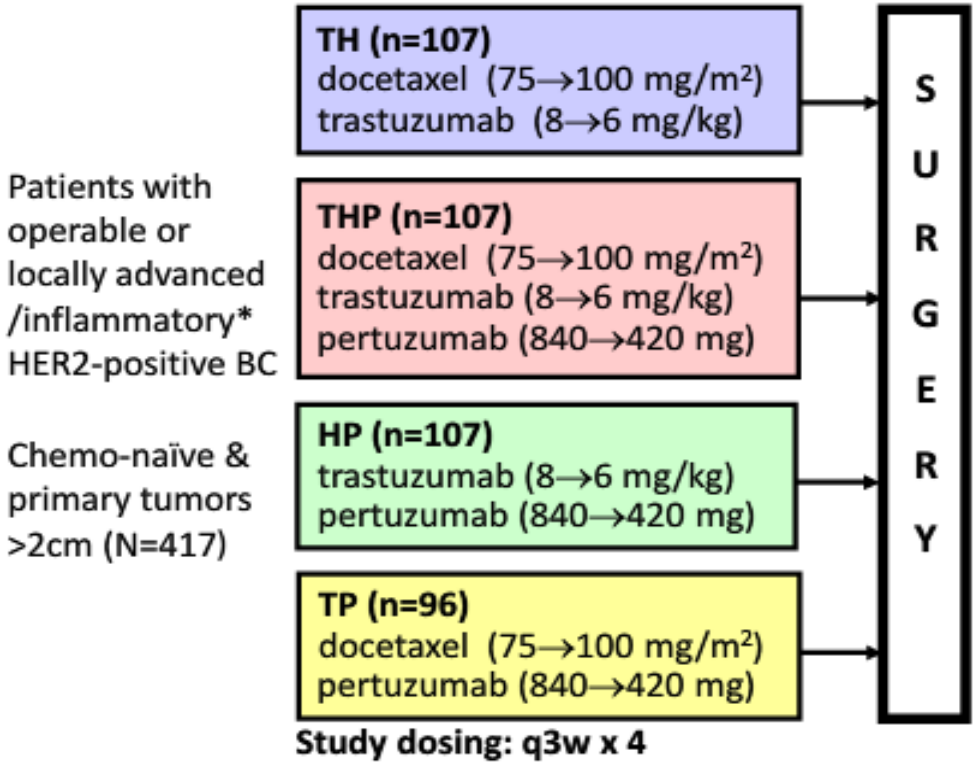
The use of neoadjuvant chemotherapy for larger cancers with pathological Complete Remission as a surrogate end point might identify more patients who do not require more intensive anthracycline-containing regimens.

Treatment HER2+ Breast Cancer

ESTRO School

HER2+ breastcancer; NeoSphere

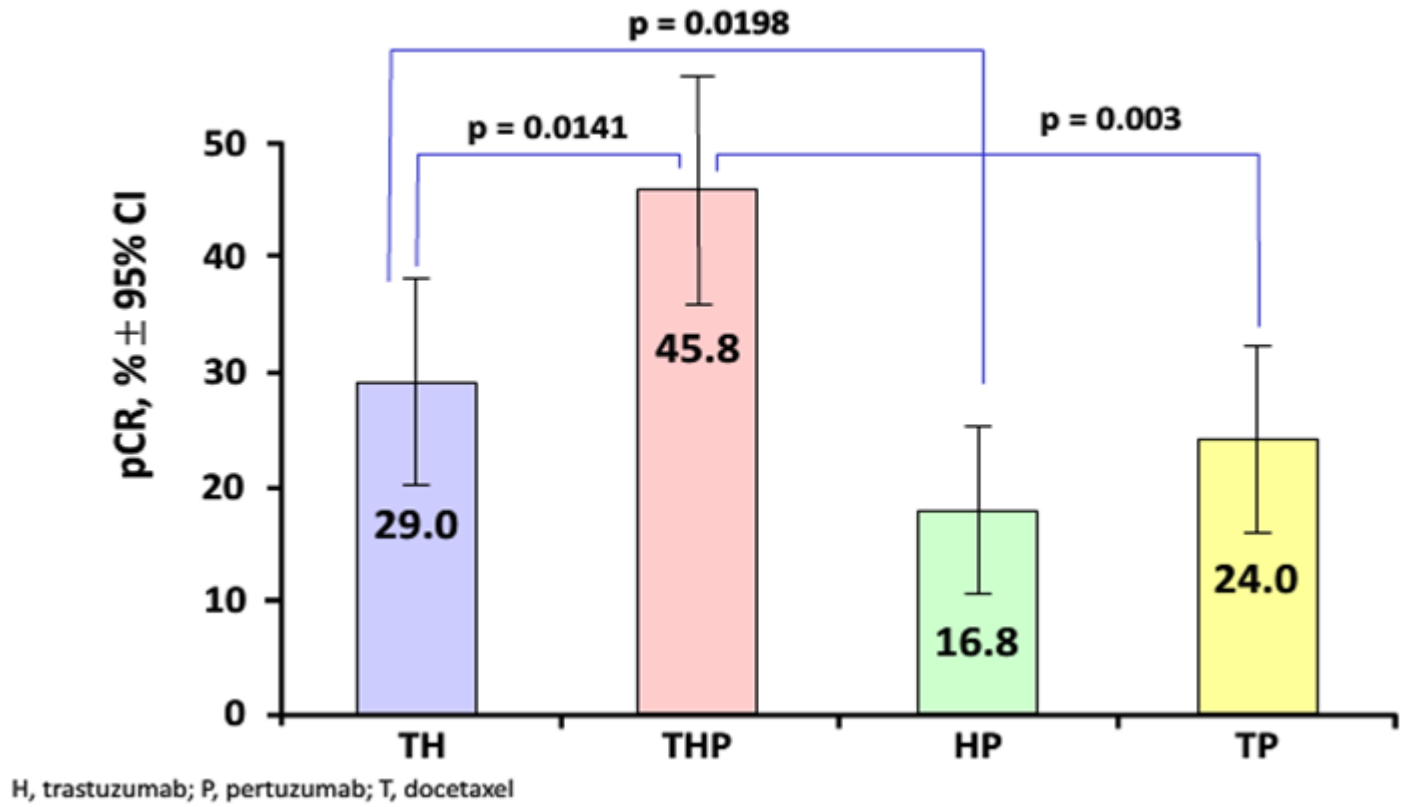
NeoSphere: study design and objectives



- **Phase II design**
- **Primary endpoint:**
  - comparison of pCR rates
    - TH vs THP
    - TH vs HP
    - THP vs TP
- **Secondary endpoints:**
  - Clinical response
  - DFS
  - Breast conservation rate
  - Biomarker evaluation

BC, breast cancer; FEC, 5-fluorouracil, epirubicin and cyclophosphamide
*Locally advanced=T2–3, N2–3, M0 or T4a–c, any N, M0; operable=T2–3, N0–1, M0; inflammatory = T4d, any N, M0
H, trastuzumab; P, pertuzumab; T, docetaxel

NeoSphere pCR rates



H, trastuzumab; P, pertuzumab; T, docetaxel

- Significant increase pCR rate THP population
- Substantial antitumor effect with trastuzumab en pertuzumab without chemotherapie

ESTRO School

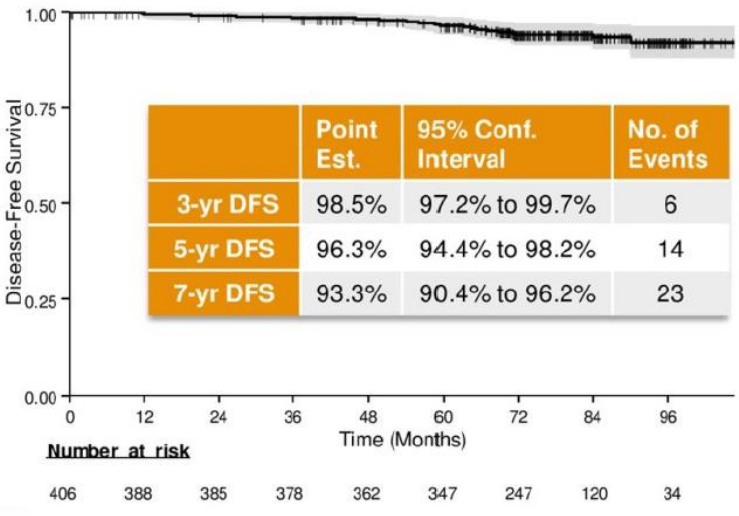
HER2+ patients

Paclitaxel 12 wkly + trastuzumab 1 yr: 7 year FU of APT trial

HER2+
ER+ or ER-
T ≤ 3 cm
Node neg

12 x q1wk paclitaxel 80 mg/m2 + trastuzumab 2 mg/kg → trastzumab 6 mg/kg q3wk or 2 mg/kg q1wk for 40 weeks

	N	%
Age		
<50	132	33
50-70	233	57
≥70	41	10
Size of Primary Tumor		
T1a ≤0.5 cm	77	19
T1b >0.5 - ≤1.0	124	31
T1c >1.0 - ≤2.0	169	42
T2 >2.0 - ≤3.0	36	9
Histologic Grade		
I Well differentiated	44	11
II Moderately differentiated	131	32
III Poorly differentiated	228	56
HR Status (ER and/or PR)		
Positive	272	67
Negative	134	33



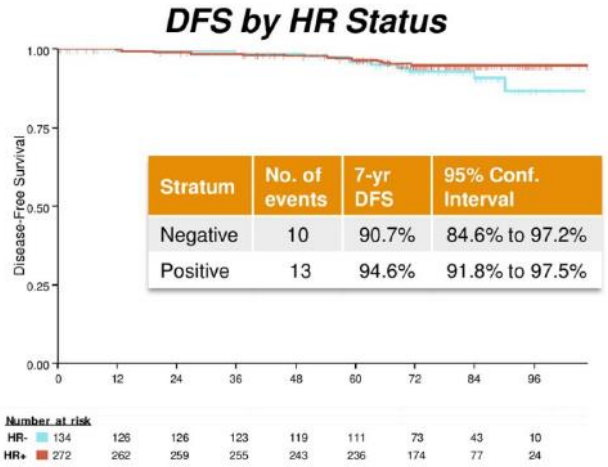
	Point Est.	95% Conf. Interval	No. of Events
3-yr DFS	98.5%	97.2% to 99.7%	6
5-yr DFS	96.3%	94.4% to 98.2%	14
7-yr DFS	93.3%	90.4% to 96.2%	23

Tolaney et al, ASCO 2017

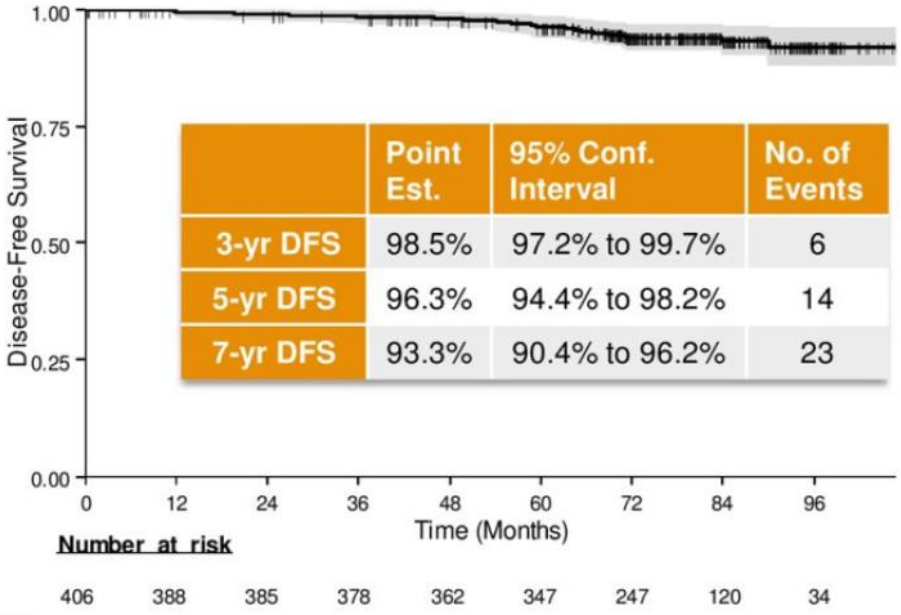
ESTRO School

Paclitaxel 12 wkly + trastuzumab 1 yr: 7 year FU

DFS Event	N (%)	Time to event [months; mean (range)]
Any recurrence or death	23 (5.7)	
Local/Regional Recurrence*	5 (1.2)	
Ipsilateral axilla (HER2+)	3	29 (12-54)
Ipsilateral breast (HER2+)	2	51 (37-65)
New Contralateral Primary Breast Cancer	6 (1.5)	
HER2+	1	56
HER2-	3	26 (12-59)
Unknown	2	87 (84-90)
Distant Recurrence	4 (1.0)	49 (27-63)
Death		
Non-breast cancer related	8 (2.0)	58 (13-71)



Stratum	No. of events	7-yr DFS	95% Conf. Interval
Negative	10	90.7%	84.6% to 97.2%
Positive	13	94.6%	91.8% to 97.5%



	Point Est.	95% Conf. Interval	No. of Events
3-yr DFS	98.5%	97.2% to 99.7%	6
5-yr DFS	96.3%	94.4% to 98.2%	14
7-yr DFS	93.3%	90.4% to 96.2%	23

Excellent survival with paclitaxel-trastuzumab in stage I HER2-positive breast cancer

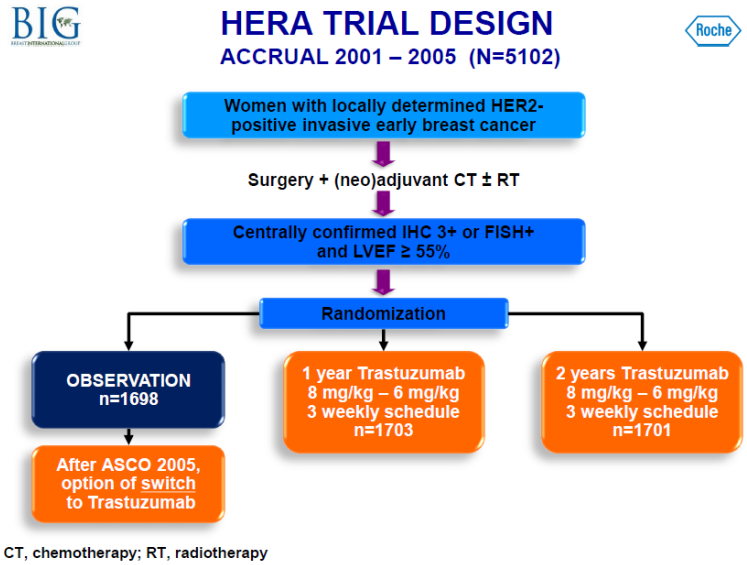
Tolaney et al, ASCO 2017

ESTRO School

Treatment duration trastuzumab

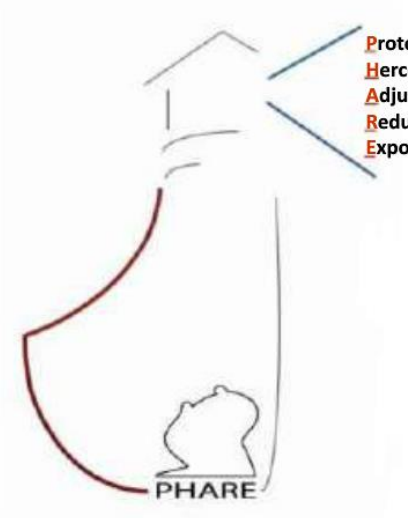
2 vs 1 year trastuzumab after adjuvant chemotherapy

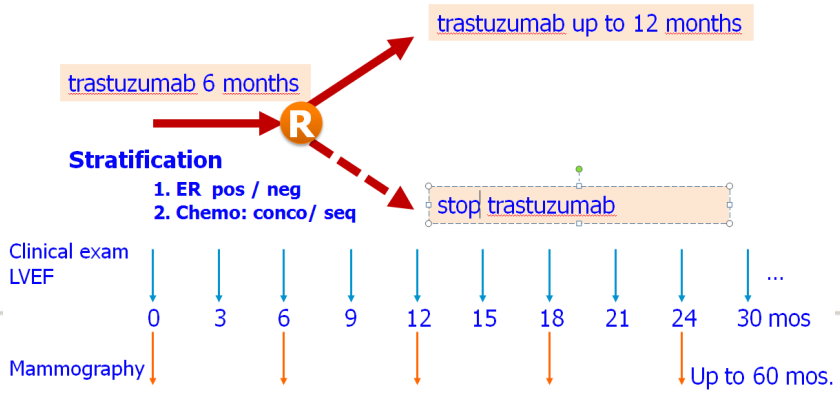
HERA



CT, chemotherapy; RT, radiotherapy

6 vs 12 months trastuzumab after adjuvant chemotherapy

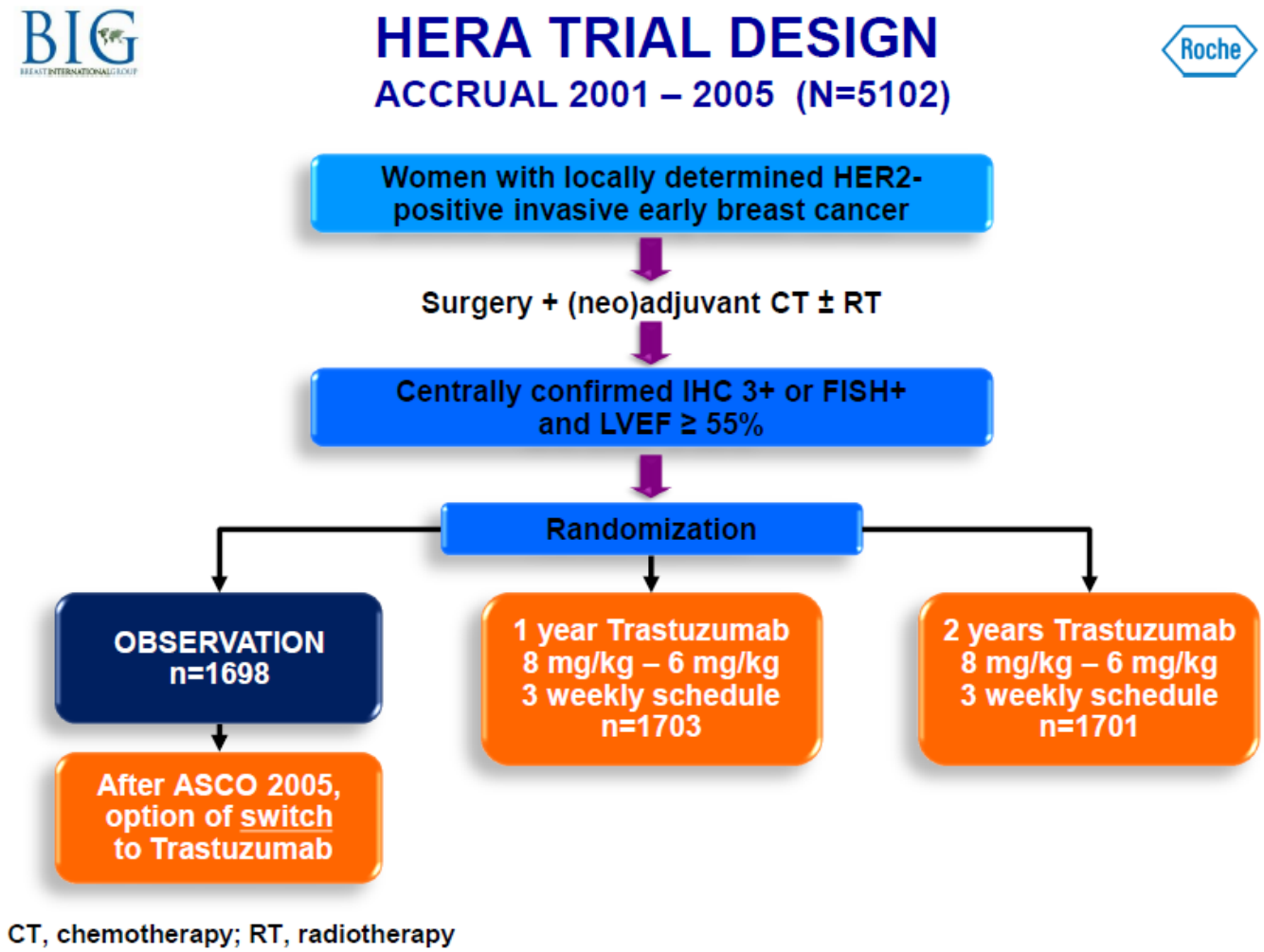




R: Randomization after informed consent

ESTRO School

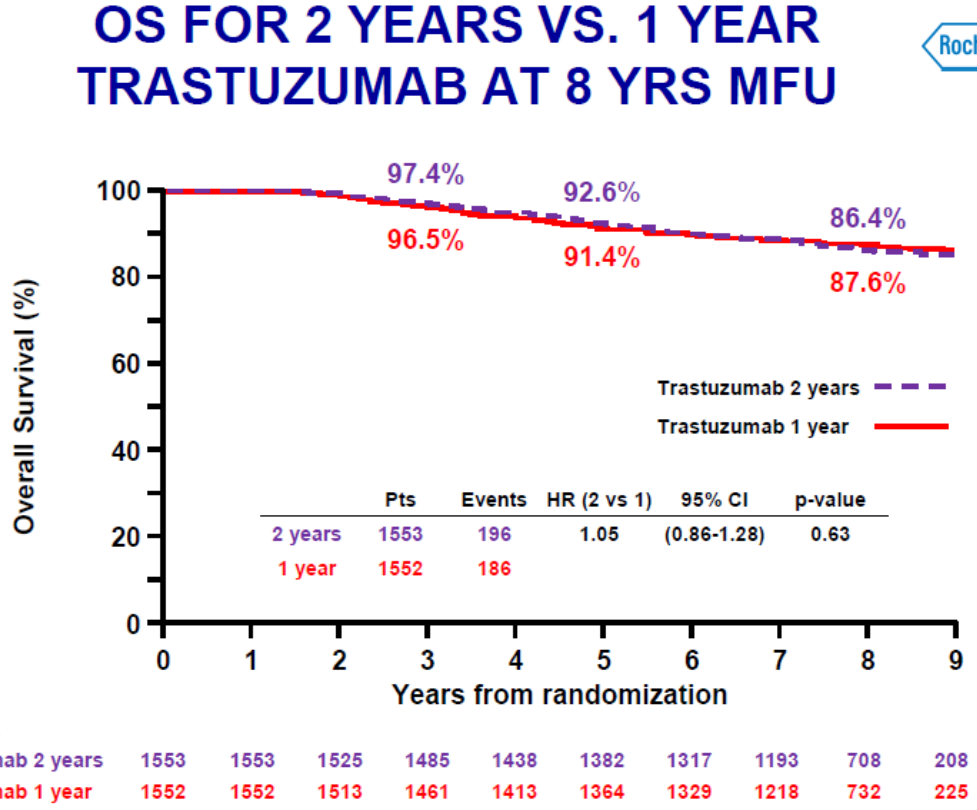
HERA Trial Design



CT, chemotherapy; RT, radiotherapy

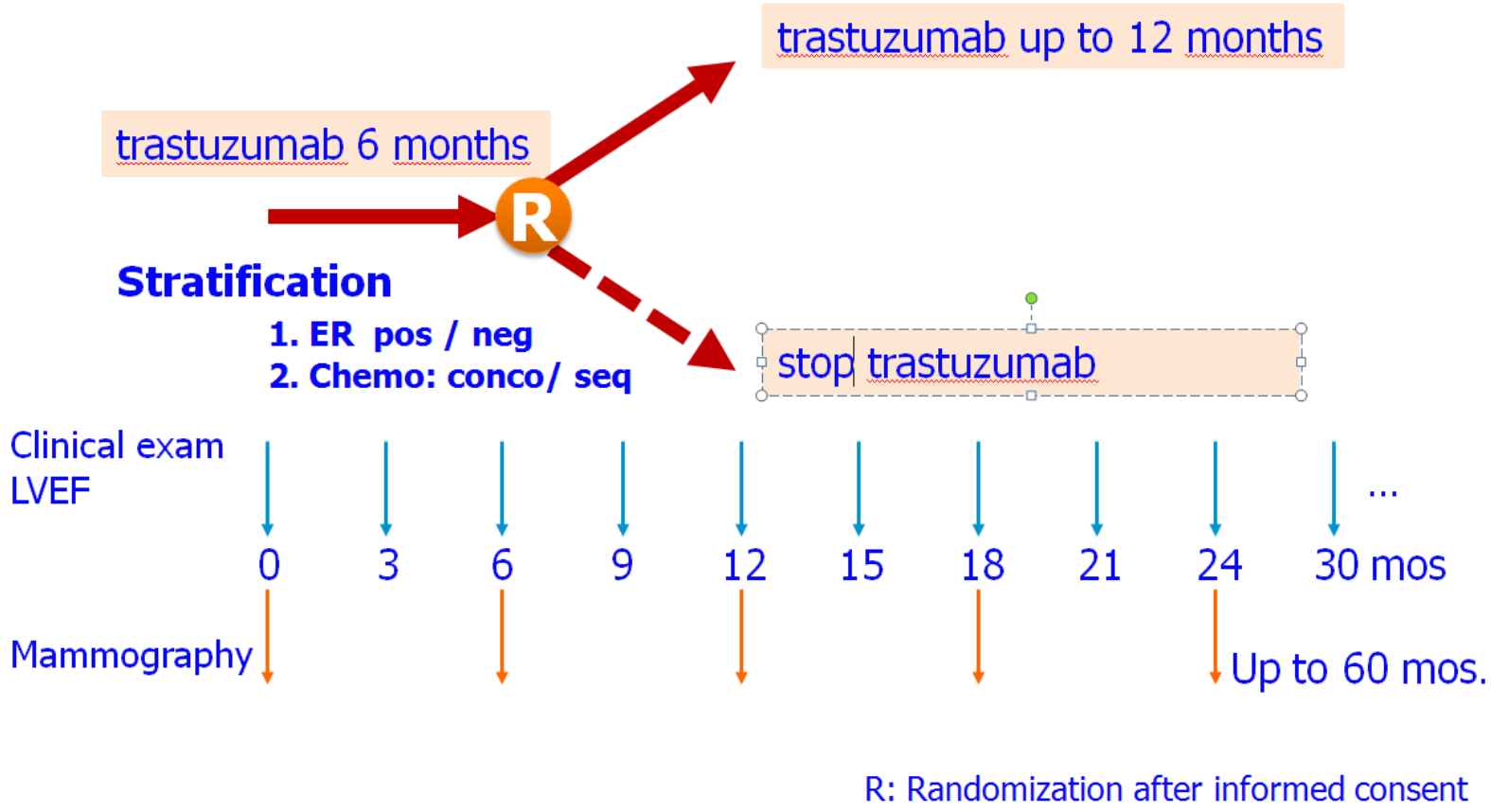
ESTRO School

HERA: Overall survival

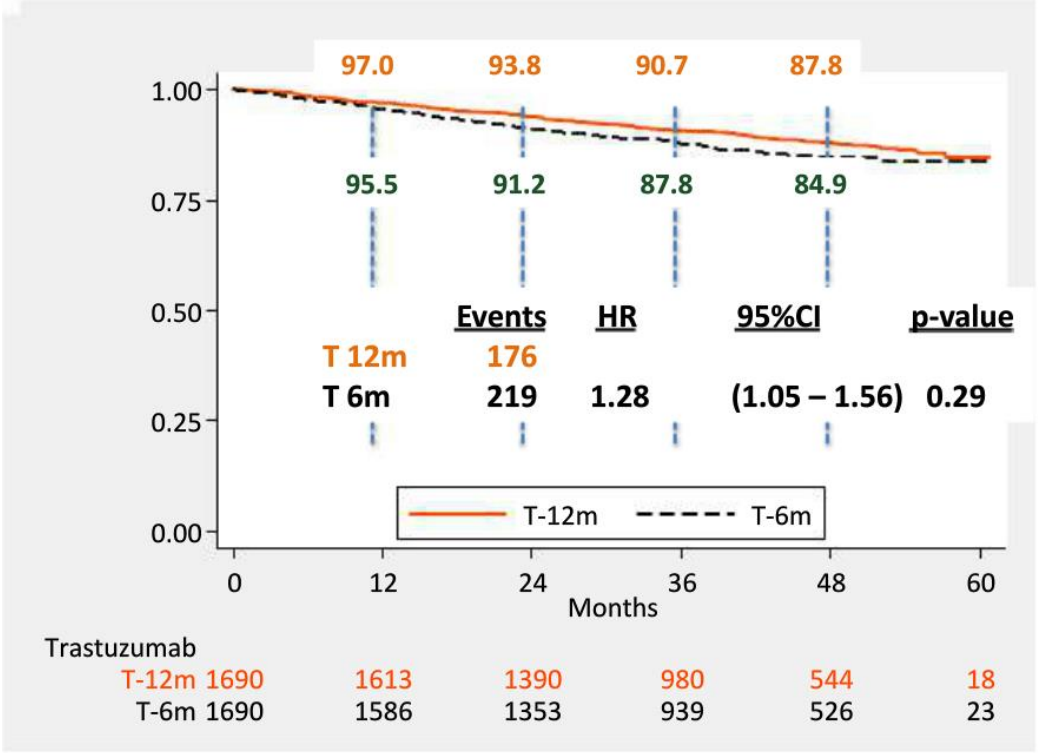


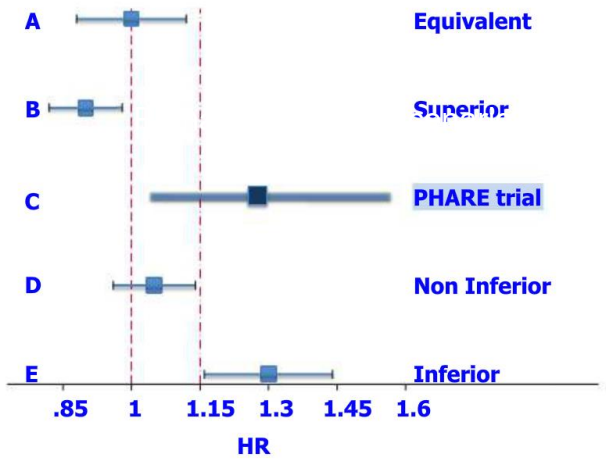
- No evidence of long-term benefit of 2 years compared to 1 year trastuzumab
- Secondary cardiac endpoints and other adverse events are increased in the 2 years trastuzumab arm
- The majority of cardiac endpoints occurred during trastuzumab administration and are reversible

Phare studie design



R: Randomization after informed consent





Non-inferiority trial

- PHARE failed to show that 6 m of trastuzumab is non inferior to 12 months
- Longer follow up is needed
- Other trial results are expected (shorther & SOLD trial)

1 year trastuzumab adjuvant will be daily practice

ESTRO School

HER2 + patients

Weekly paclitaxel with anti-HER2 therapy is as effective as standard chemotherapy for small cancers.

Available data shows, that only a fraction of patients benefit from any particular instance of therapeutic escalation.

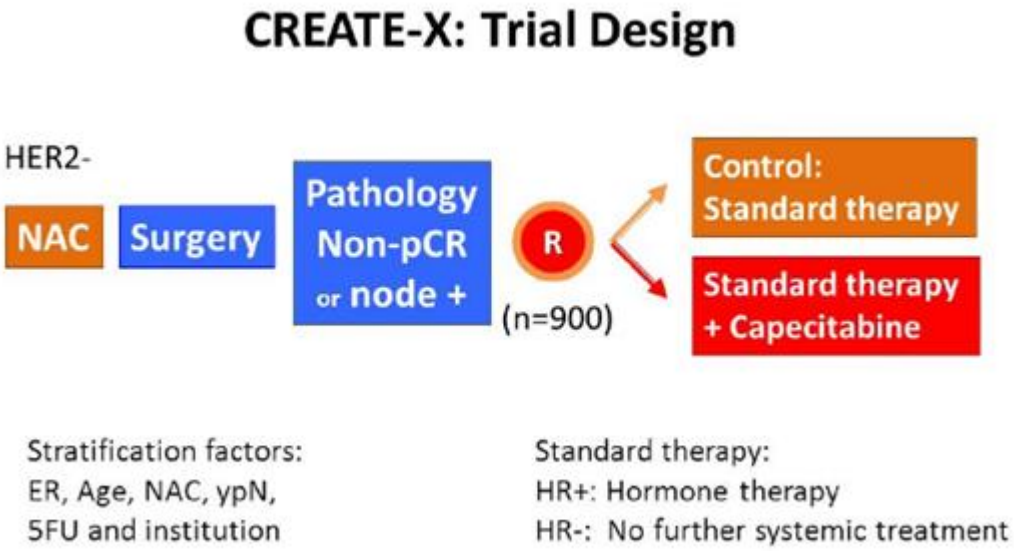
Evidence suggests that some patients with HER2-positive cancers may be curable with anti-HER2 antibody therapy alone, and the challenge is to identify these.

At this moment 1 year trastuzumab adjuvant will be daily practice

Escalation

Escalation in specific populations

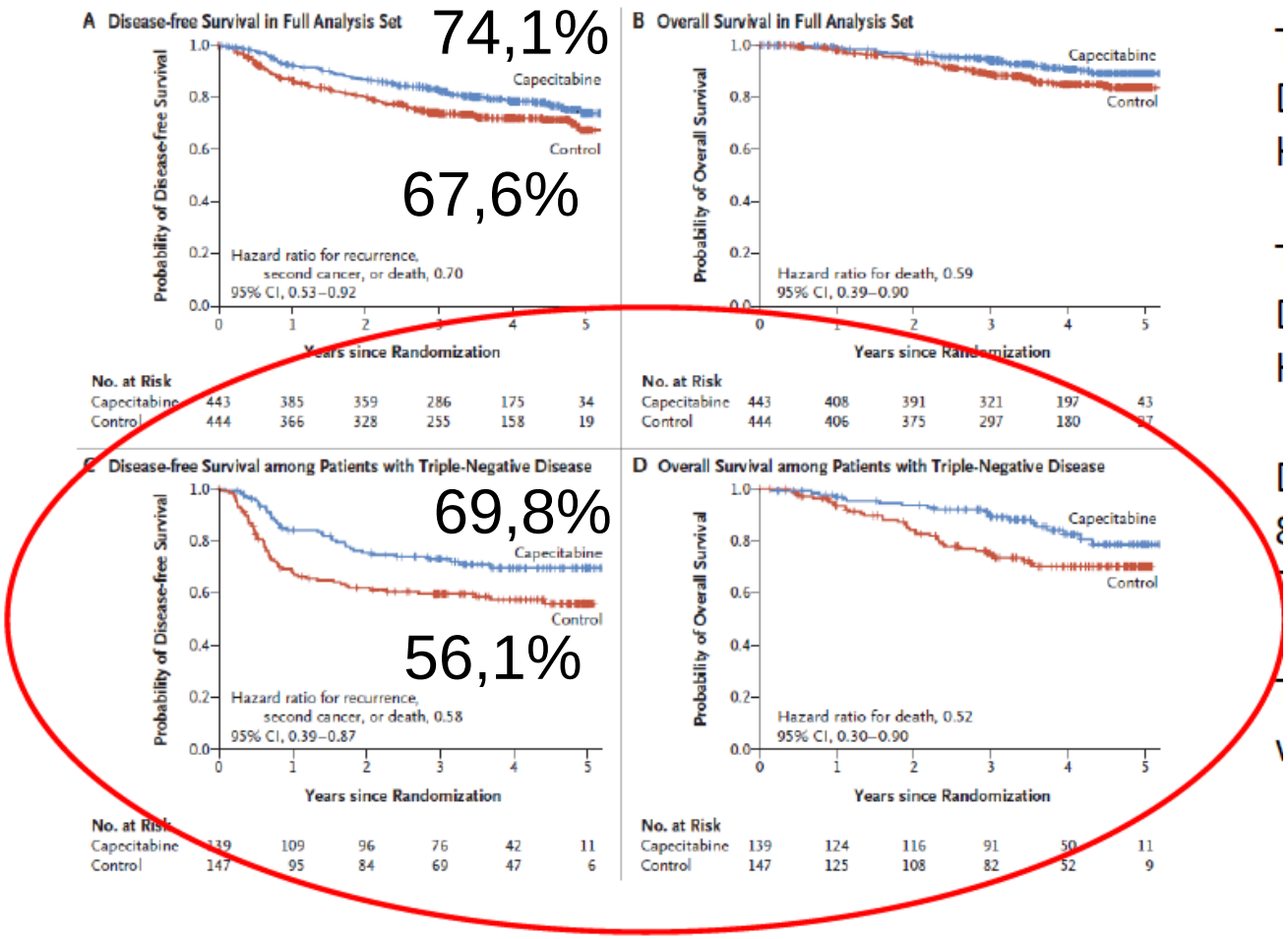
. E.g. post-neoadjuvant study design show that it is possible to target very specific populations for escalation based even on conventional pathologic criteria.



Asian
32% triple negative

6 – 8 cycles
capecitabine 1250 mg/m2 twice daily d1-d14 q 3wk

Create X trial



Masuda, 2017

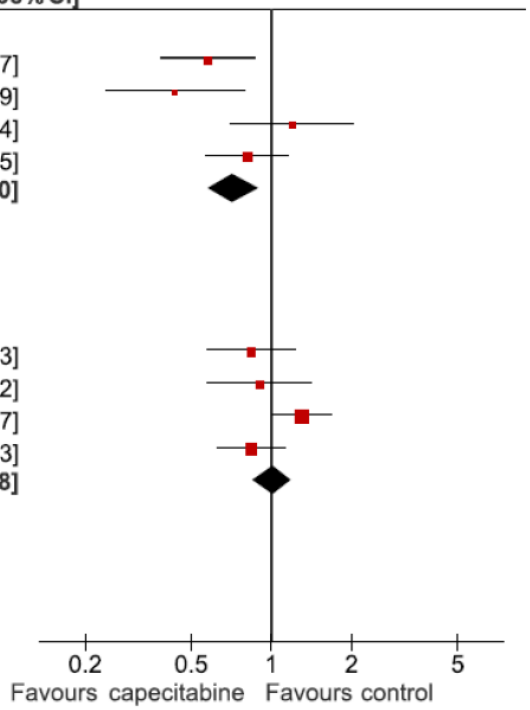
Capecitabine in EBC: A meta-analysis of RCT

Note: unselected + combined with 'standard' AdjCT

More effective in TNBC, but more toxic when added

Study or Subgroup	Weight	Hazard Ratio [95% CI]
Triple Negative		
CREATE-X	10.1%	0.58 [0.39, 0.87]
FinXX	4.7%	0.43 [0.24, 0.79]
GEICAM 2003-10	5.9%	1.19 [0.70, 2.04]
US Oncology 01062	13.6%	0.81 [0.57, 1.15]
Subtotal	**34.2%**	**0.72 [0.58, 0.90]**
Non-Triple Negative		
CREATE-X	11.5%	0.84 [0.57, 1.23]
FinXX	8.3%	0.90 [0.58, 1.42]
GEICAM 2003-10	26.3%	1.30 [1.01, 1.67]
US Oncology 01062	19.6%	0.84 [0.63, 1.13]
Subtotal	**65.8%**	**1.01 [0.86, 1.18]**

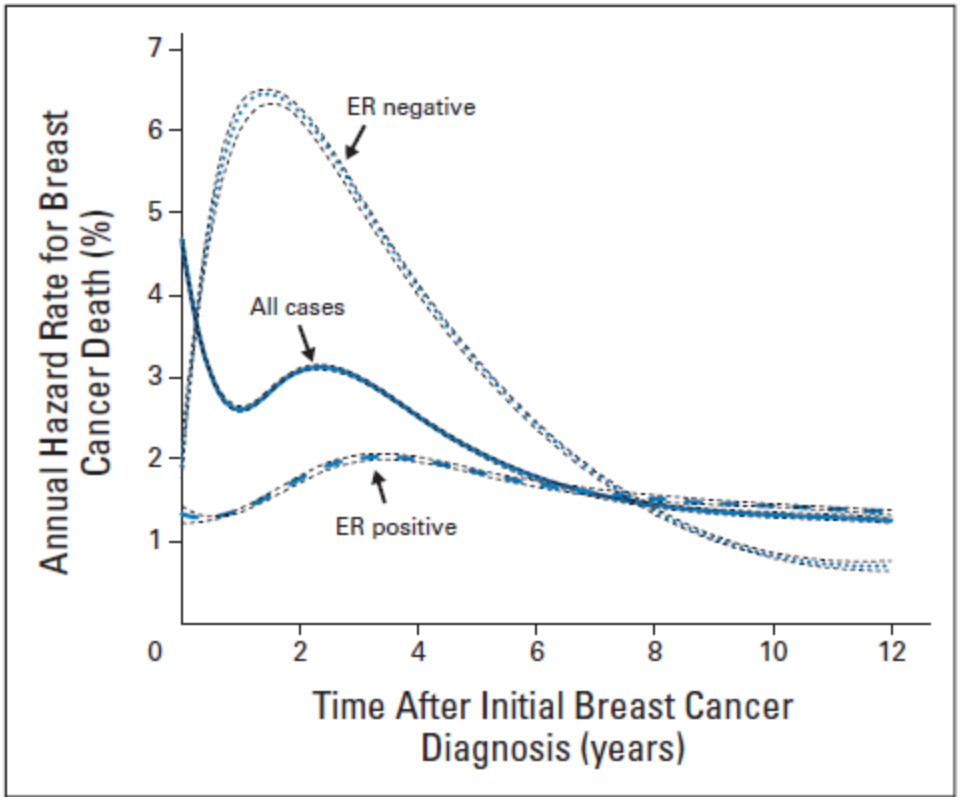
Test for subgroup differences: P = 0.02, I^2 = 82.9%



Endocrine therapy

ESTRO School

HR for Breast Cancer Death ER+/ER- patients



A substantial proportion of breast cancer recurrences occur >5 years post-surgery

The annual risk of late recurrence is higher in ER+ tumors

Jatoi, et al;JCO 2011

ESTRO School

Questions in endocrine therapy

- What is the optimal duration of endocrine therapy?
- What is the optimal treatment for premenopausal women?
- What is the impact of adherence/ compliance?
- What is next in endocrine therapy?

ER-positive disease and tamoxifen

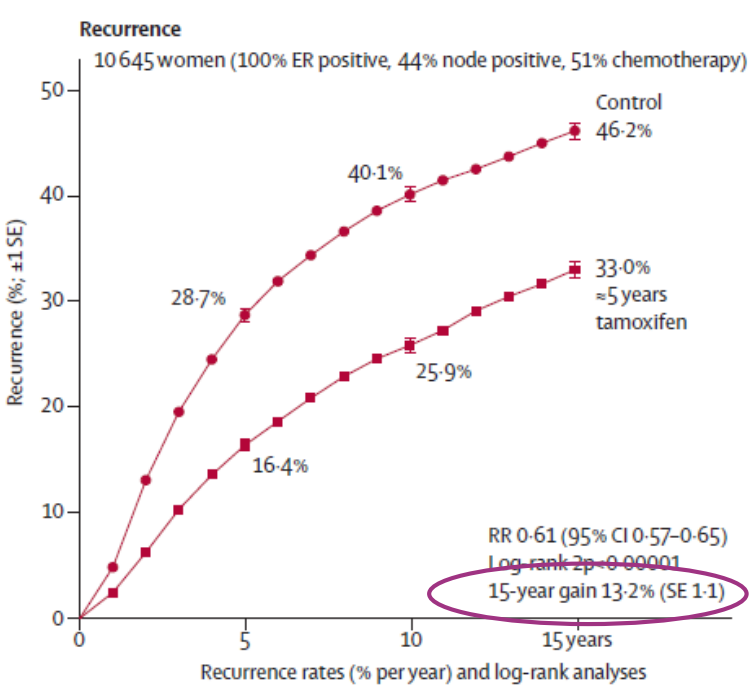
- Tamoxifen for 1-2 years is significantly more effective than no treatment
  - Recurrence rate 5,8% vs 7,1%/year
- Tamoxifen for 5 years is significantly more effective than just 1–2 years of tamoxifen.
- 5 year of adjuvant tamoxifen reduces the annual breast cancer death rate by 31% (SE 3)
  - Irrespective of the use of chemotherapy and of age, progesterone receptor status, or other tumor characteristics.

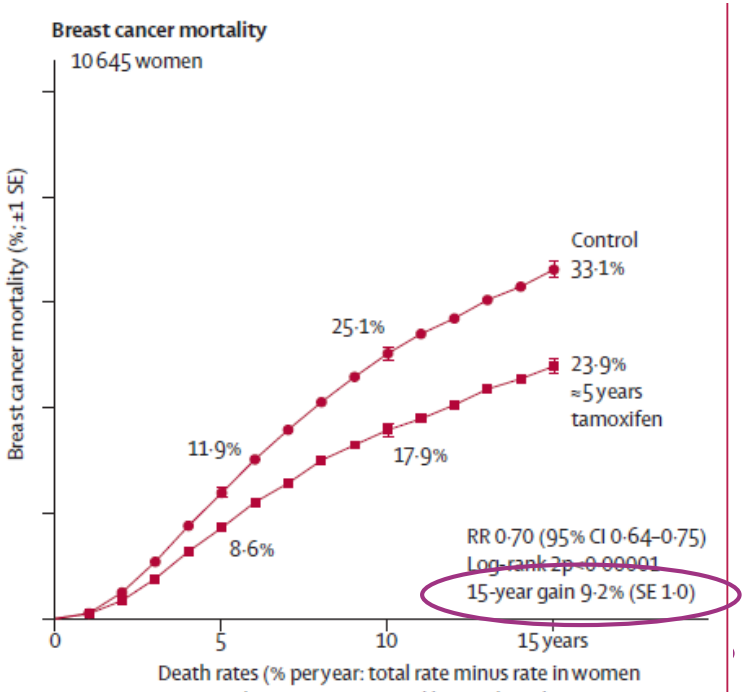
Systemic adjuvant treatment and age at diagnosis (years)	Proportional effect on annual breast cancer mortality rate (treatment vs control)	
	Ratio of rates (R)	Proportional reduction
Endocrine, or chemoendocrine, therapy in ER-positive disease*		
None (any age)	1·0	–
Tamoxifen (any age)	0·69	31%
Anthracycline + tamoxifen (age <50 years)	0·62×0·69	57%
Anthracycline + tamoxifen (50–69 years)	0·80×0·69	45%
Anthracycline + tamoxifen (≥70 years)	?×0·69	?

EBCTCG 2005 & 2011

ESTRO School

ER-positive disease; 5y Tamoxifen vs no Tamoxifen





	Years 0–4	Years 5–9	Years 10–14	Year 15+
Tamoxifen	3·74 (891/23 819)	2·62 (454/17 315)	2·06 (220/10 657)	1·75 (88/5034)
Control	6·71 (1466/21 862)	3·46 (499/14 420)	2·11 (182/8620)	1·76 (71/4045)
Rate ratio	0·53 (SE 0·03)	0·68 (SE 0·06)	0·97 (SE 0·10)	0·88 (SE 0·16)
(O–E)/V	−343·3/535·1	−82·5/217·5	−3·3/93·3	−4·4/35·5

Years 0–4	Years 5–9	Years 10–14	Year 15+
1·79 (SE 0·08)	2·25 (SE 0·11)	1·54 (SE 0·11)	1·48 (SE 0·16)
2·46 (SE 0·10)	3·23 (SE 0·13)	2·28 (SE 0·14)	1·89 (SE 0·19)
0·71 (SE 0·05)	0·66 (SE 0·05)	0·68 (SE 0·08)	0·88 (SE 0·14)
−84·4/244·8	−95·8/233·2	−38·6/99·4	−5·7/42·6

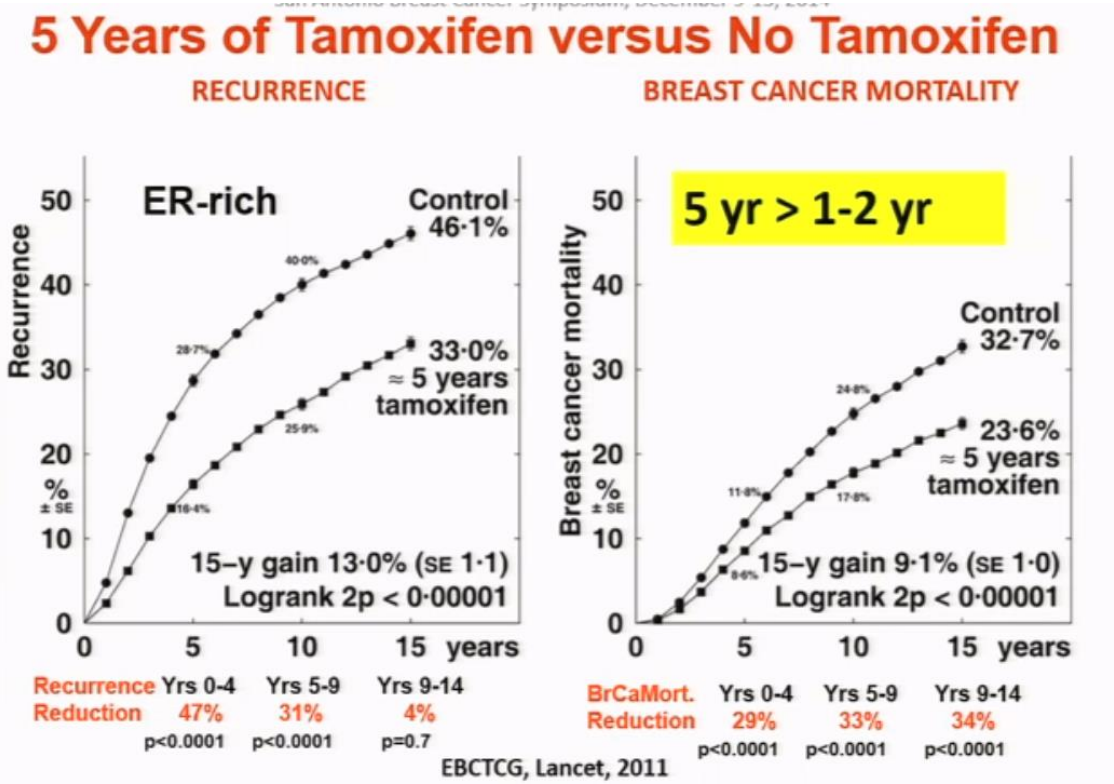
***Figure 5*: Effects of about 5 years of tamoxifen on the 15-year probabilities of recurrence and of breast cancer mortality, for ER-positive disease**
Outcome by allocated treatment in trials of about 5 years of adjuvant tamoxifen. Event rate ratio (RR) is from summed log-rank statistics for all time periods. Gain (and its SE) is absolute difference between ends of graphs. ER=oestrogen receptor. O–E=observed minus expected, with variance V.

EBCTCG 2011

ESTRO School

ER-positive disease and Tamoxifen

- The annual breast cancer mortality rates are similar during years 0 - 4 and 5 - 14
- The cumulative reduction in mortality is more than twice as big at 15 years as at 5 years after diagnosis



EBCTCG 2005 & 2011

ESTRO School

Aromatase inhibitors (AI)

Upfront studies: AI versus tamoxifen (5 year)

ATAC; BIG 1-98; ABCSG-12

Sequential studies

2-3 y tamoxifen followed by 3-2y AI vs 5y tamoxifen or 5y AI

2-3 y AI followed by 3-2y tamoxifen vs 5y tamoxifen or 5y AI

IES; ITA; ARNO-95 Randomisation after 2-3y tamoxifen

TEAM; ABCSG-8

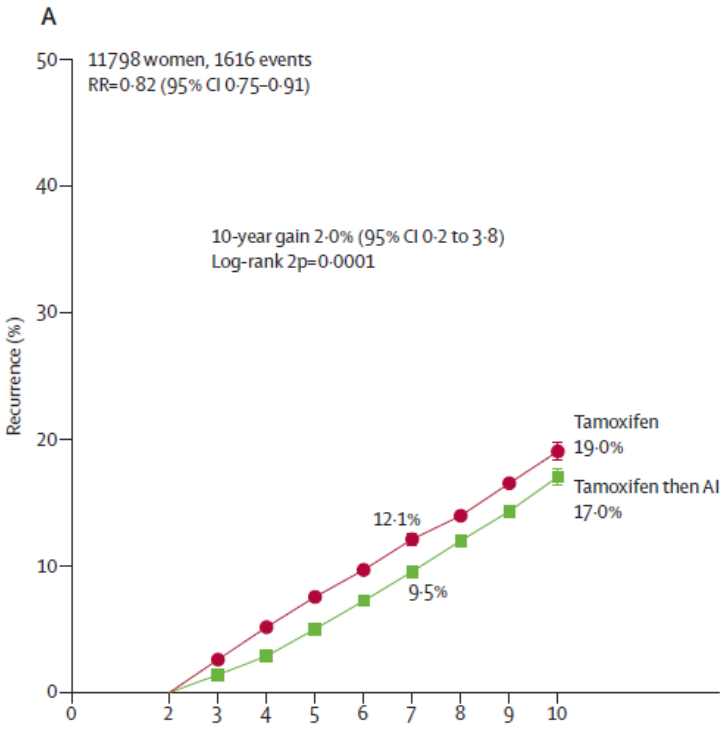
Extension studies

AI after 5y tamoxifen

AI after 5y tamoxifen/AI

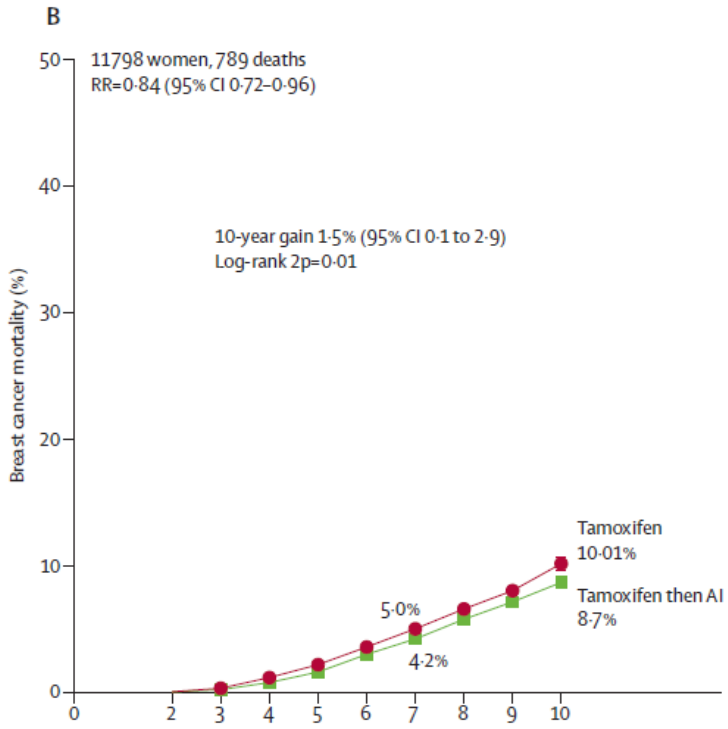
MA.17; ABCSG-6A; NSABP B-33; DATA; LEAD

Tamoxifen vs Tamoxifen then AI



Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 2–4	Years 5–9	Year 10+
Tamoxifen then AI	1·48 (170/11515)	2·48 (495/19920)	3·26 (88/2696)
Tamoxifen	2·64 (300/11360)	2·51 (479/19101)	3·35 (84/2505)
Rate ratio (95% CI)	0·56 (0·46–0·67)	0·97 (0·86–1·11)	0·92 (0·68–1·25)
from (O-E)/V	−65·3/111·5	−5·9/234·0	−3·3/40·8



Death rates (%/year: total rate minus rate in women without recurrence) and log-rank statistics

Allocation	Years 2–4	Years 5–9	Year 10+
Tamoxifen then AI	0·37 (0·25–0·48)	1·28 (1·12–1·44)	1·68 (1·63–1·72)
Tamoxifen	0·56 (0·43–0·70)	1·40 (1·26–1·56)	2·54 (2·45–2·59)
Rate ratio (95% CI)	0·65 (0·44–0·96)	0·91 (0·77–1·08)	0·69 (0·48–1·00)
from (O-E)/V	−11·0/25·8	−11·9/132·0	−10·6/28·9

EBCTCG

ESTRO School

Recommendations endocrine therapy

Premenopausal women

5 years of tamoxifen +/- ovarian suppression

Caution against longer durations of treatment when neither safety nor efficacy data were available.

ASCO guideline

Soft and Text trial

Additional benefit of ovarian suppression?

Two important questions

- Tamoxifen + Ovarian suppression vs. Aromatase inhibitor + Ovarian suppression ?
- Tamoxifen + Ovarian suppression vs Tamoxifen

Conclusions Pre-menopausal ER+ BC

Effectivity aromatase inhibitor + ovarian suppression not convincing

Trend worser overall survival

•Impact ovarian suppression + TAM vs TAM:

–Trend better DFS and OS

–Young age

–Higher risk (initial chemotherapy)

•Don’t forget large influence Qol:

–AR / OFS > TAM + OFS > TAM

Consider Pre-menopausal ER+ BC

Low risk: Tam 5 y

Intermediair risk: TAM + ovarian suppression 5-10 y

- –Young age
- –Higher risk (initial chemotherapy)

High risk: TAM + ovarian suppression 10 y

- –Young age
- –Higher risk (initial chemotherapy)

Depending on tolerance and co-morbidity

ESTRO School

Recommendations endocrine therapy

Postmenopausal women

- A minimum of 5 years of adjuvant therapy using either an AI or a sequence of tamoxifen followed by an AI.
- Women who are postmenopausal who receive tamoxifen as initial treatment are candidates for extended adjuvant endocrine treatment either by continuing tamoxifen for a total of 10 years, or by switching to an AI.
- As there are no data for the efficacy or safety of AI therapy in excess of 5 years, 5 years remains the appropriate duration of AI treatment, whether begun as initial therapy or after prior tamoxifen.

Caution against longer durations of treatment when neither safety nor efficacy data were available.

How can we select for candidates for shorter or longer therapy today?

Use of extended adjuvant endocrine therapy

- Higher stage at diagnosis
- Limited or absent toxicity
- Absence of life-threatening co-morbidities
- Younger age
- Patient preference
- Biomarkers for late recurrence?

Prognostic signatures for the predictions of late distant recurrence

Test	Information included	Development population
Oncotype RS	21 genes (oestrogen, proliferation genes)	Pre- and postmenopausal, node negative, tamoxifen or placebo
PAM50 ROR	50 genes, proliferation score, tumour size included	Pre- and postmenopausal, some chemotherapy, and pre- and post-menopausal, oestrogen receptor positive, tamoxifen
BCI	H/I and 5 proliferation genes (molecular grade index) (BUB1B, CENPA, NEK2, RACGAP1, RRM2)	Postmenopausal, node negative, oestrogen receptor positive, tamoxifen Pre- and postmenopausal, node negative, oestrogen receptor positive, chemotherapy, tamoxifen
EPclin	12 genes (proliferation, differentiation, oestrogen), nodal status and tumour size included	Postmenopausal, oestrogen receptor positive, HER2 negative, tamoxifen

RS = Recurrence Score, PAM50 ROR = Prosigna PAM50 risk of recurrence, BCI = Breast Cancer Index, EPclin = EndoPredict.

These markers combine expression profiles of a panel of cancer-related genes
Mostly been developed and validated in ER+/HER2- and Node- patients
Prognostic information or recurrence-free survival independent of traditional clinical markers (TNM)
They were not developed to specifically predict late (distant) recurrences

I Sestak Breast Care 2017;12:146–151

ESTRO School

Prognostic signatures for the predictions of late distant recurrence

Test	Information included	Development population
Oncotype RS	21 genes (oestrogen, proliferation genes)	Pre- and postmenopausal, node negative, tamoxifen or placebo
PAM50 ROR	50 genes, proliferation score, tumour size included	Pre- and postmenopausal, some chemotherapy, and pre- and post menopausal, oestrogen recept positive, tamoxifen
BCI	H/I and 5 proliferation genes (molecular grade index) (BUB1B, CENPA, NEK2 RACGAP1, RRM2)	Postmen pa l no negative, o trog n r ptor positive, ta en Pre- and postmenopausal, n de negative, oestrogen r ep r positive, h r p tamoxifen
EPclin	genes (proliferation, differentiation, o trogen) nodal status an tumor s included	Postm on usal, oestrogen receptor positive, HER2 negative, tam xif

RS = Recurren Sc e, AM50 ROR = Prosigna PAM5 sk f recurrence, BCI = Breast Cancer Index, EPclin = EndoP d t.

It is unkown if they predict benefit for extended therapy

These markers combine expression profiles of a panel of cancer-related genes
Mostly been developed and validated in ER+/HER2- and Node- patients
Prognostic information or recurrence-free survival independent of traditional clinical markers (TNM)
They were not developed to specifically predict late (distant) recurrences

I Sestak Breast Care 2017;12:146–151

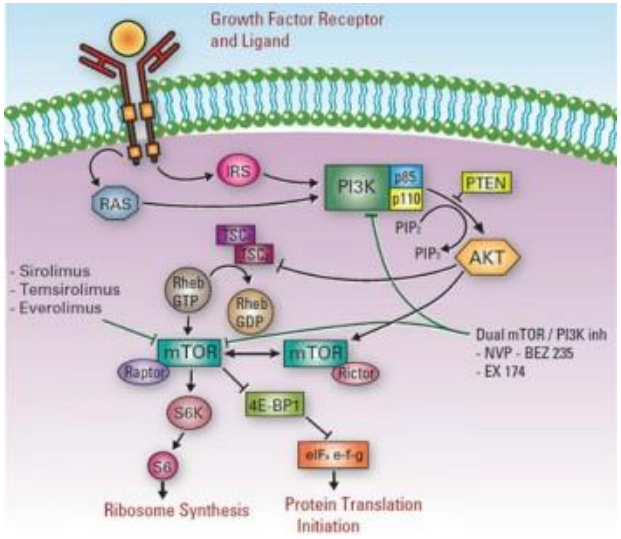
Challenges in Optimal Endocrine therapy

- Predictive markers beyond ER,PR
- Understanding pathways of resistance
- Optimizing host environment (BMI?)
- Monitoring long term benefit & toxicity
- Compliance of patient
- Dissemination of endocrine prevention strategies for high risk women
- New treatment combinations targeting both ER and growth factor receptor signaling to block the crosstalk between these pathways and eliminate escape routes

Targeting both ER and growth factor receptor signaling

PI3K/mTOR inhibitors

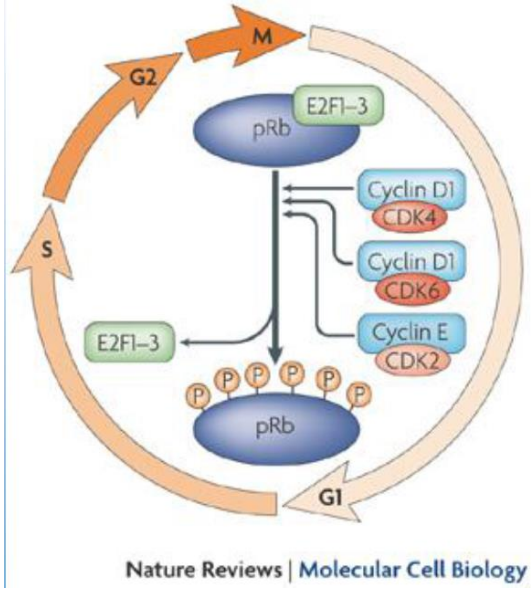
Everolimus



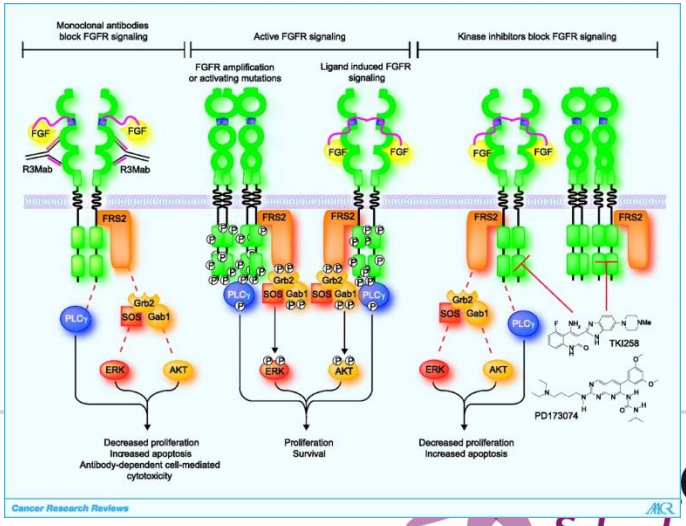
CDK4/6 inhibition

Palbociclib

Ribociclib



Fibroblast growth factor (FGFR) inhibitors



Usefulness of endocrine therapy is limited by common intrinsic and acquired resistance.

Gene expression profiling

Gene expression profiling

Gene expression profiling including Oncotype DX and Mammaprint

- a substantial reduction in the number of patients receiving chemotherapy
- so far without any suggestion of impaired outcome

Take home message

There may be opportunities for de-escalation without compromising Outcome

Major efforts must be made to further refine “personalised” treatment approach.

Questions??

Possible interaction between systemic treatment and radiation therapy

Youlia M. Kirova, M.D.,

Institit Curie, Paris, France

institutCurie
youlia.kirova@curie.fr

…or survival of the radiation oncologist in the world of new systemic treatments…

institutCurie

Introduction

Widespread use of systemic treatments in breast cancer

-Hormone therapy

-Chemotherapy

-Targeted therapy (Trastuzumab, Avastin, Pertuzumab, TDM1, immunotherapy)

All these treatments have an impact on local control and survival

In the adjuvant setting, they are usually delivered sequentially

Few studies have evaluated the delivery of concurrent radiotherapy and systemic treatments

institutCurie

Concurrent radiotherapy and systemic treatments

Theoretical benefit:

- **Reduction of delay of initiation of each modality**
- **« Supra-additive » effect on tumor control**

Theoretical risk

- **Toxicity and sequelae**
- **Decreased radiosensitivity**

Concurrent radiotherapy and endocrine treatment

TAMOXIFEN

institutCurie

Interactions anti-estrogens/RT: clinical results

	No increased toxicity	Increased toxicity
Lung toxicity	Malher et al., *ESTRO* 2002	Bentzen et al., JNCI, 1996 Koc et al., Radiother Oncol, 2002
Skin toxicity	Wazer er al., *JCO*, 1992 Fowble et al., *IJROBP*, 1993 Taylor et al. *IJROBP*, 1995	Christensen et al., *ASCO* 2003 Azria et al., *BJC,* 2004

institutCurie

RT + Tam : similar tolerance

	Med FU	Seq	Conco.		
	yrs.	No.	No.	Tox.	Cosm.
Pierce * SWOG	10.3	107	202	ns	-
Ahn U.Yale	10	241	254	-	-
Harris U.Penn	8.6	104	174	ns	ns

** RH+ : 64% et 50%*

J Clin Oncol 2005

institutCurie

Table 3. Complications and Cosmesis According to Tamoxifen Sequence

Variable	Concurrent Tamoxifen		Sequential Tamoxifen		*P*
	No. of Patients	%	No. of Patients	%	
Breast edema, grade					
0-2	162	95	98	95	.96
3-4	8	5	5	5	
Arm edema, grade					
0-2	168	98	101	97	.53
3-4	3	2	3	3	
Rib fracture					
Absent	174	100	103	99	.31
Present	0		1	1	
Pneumonitis					
Absent	172	99	104	100	.53
Present	2	1	0		
Cosmesis at 3 years					
Excellent or good	122	95	76	95	.92
Fair	6	5	4	5	
Cosmesis at 5 years					
Excellent or Good	87	94	51	94	.83
Fair	6	6	3	6	

Harris, U.Penn

J Clin Oncol 2005, 23 (1)

institutCurie

Aromatase Inhibitors and RT

CO HO RT phase II study

Breast-conserving surgery, HR+, post-menopause

Radiation-induced lymphocyte apoptosis (RILA) test

No adjuvant CT | **Adjuvant CT**

Stratification ⟵ **2nd RILA test**

Center, RILA, Adjuvant CT, Boost

Randomization

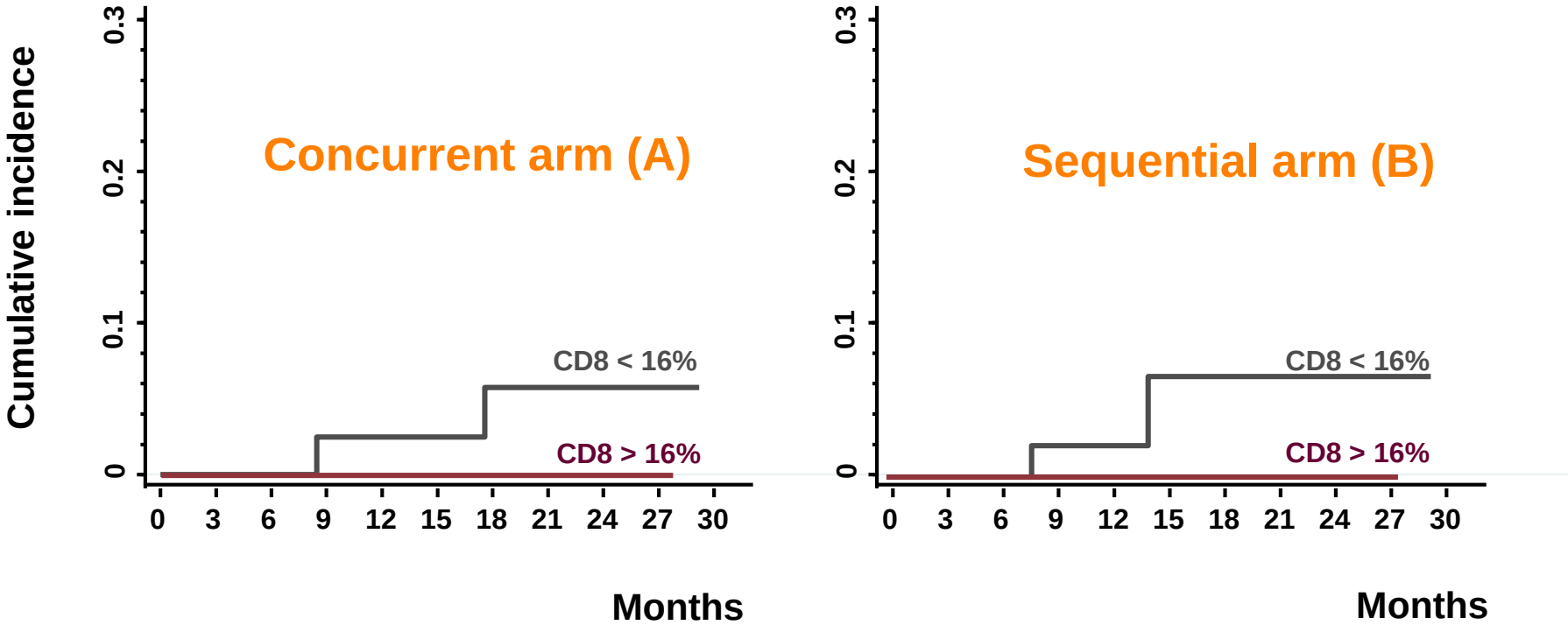
Arm A → **Adjuvant RT** — **Letrozole 2.5 mg/day 5 years**

Arm B → **Adjuvant RT** → **Letrozole 2.5 mg/day 5 years**

Azria et al. Lancet Oncol 2010

institutCurie
Ensemble, prenons le cancer de vitesse.

Subcutaneous fibrosis and RILA



Azria et al. Lancet Oncol 2010

institutCurie
Ensemble, prenons le cancer de vitesse.

Conclusions

• COHORT is the first randomized trial evaluating RT and HT (letrozole) concurrently or sequentially

• In both arms,
No difference of acute and late skin toxicity

• Interestingly, late subcutaneous fibrosis is strongly influenced by intrinsic radiosensitivity evaluated by RILA

Longer F-up is warranted for:
- Skin toxicity evaluation
- Lung fibrosis evaluation (CT Scan, functional tests)
- Cardiac events (3D planning dosimetry, Heart DVH)
- SNP screening

institutCurie
Ensemble, prenons le cancer de vitesse.

Azria et al. Lancet Oncol 2010

Research Article

Radiation-induced CD8 T-lymphocyte Apoptosis as a Predictor of Breast Fibrosis After Radiotherapy: Results of the Prospective Multicenter French Trial☆

EBioMedicine 2 (2015) 1965–1973

Contents lists available at ScienceDirect

EBioMedicine

David Azria [a,*], Olivier Riou [a], Florence Castan [a], Tan Dat Nguyen [b], Karine Peignaux [c], Claire Lemanski [a], Jean-Léon Lagrange [d], Youlia Kirova [e], Eric Lartigau [f], Yazid Belkacemi [d], Céline Bourgier [a], Sofia Rivera [g], Georges Noël [h], Sébastien Clippe [i], Françoise Mornex [j], Christophe Hennequin [k], Andrew Kramar [f], Sophie Gourgou [a], André Pèlegrin [a], Pascal Fenoglietto [a], Esat Mahmut Ozsahin [l]

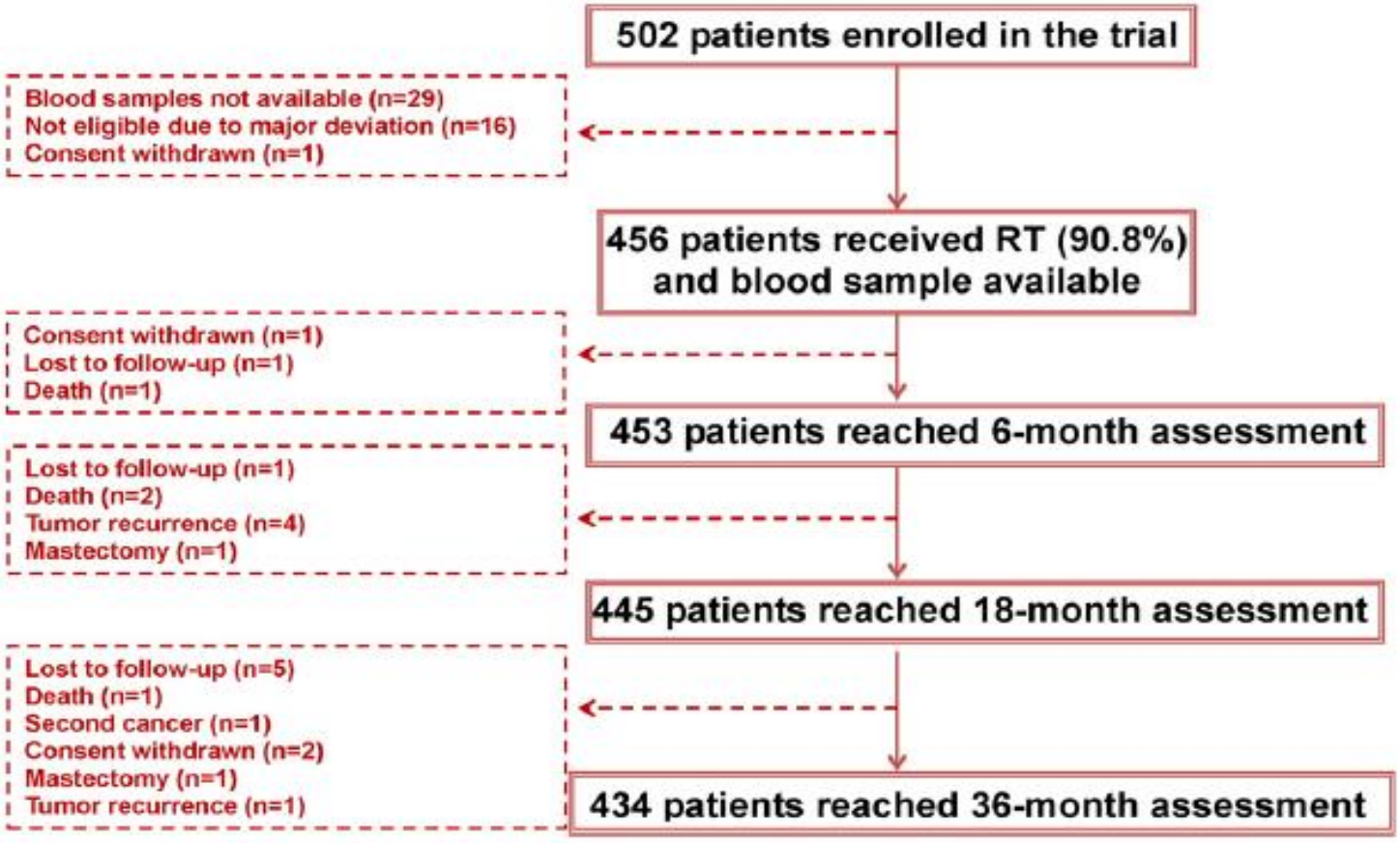


Fig. 1. Trial profile.

institutCurie
Ensemble, prenons le cancer de vitesse.

Biological factors

Table 6
Multivariate regression analysis for CRFS and competing risk analysis.

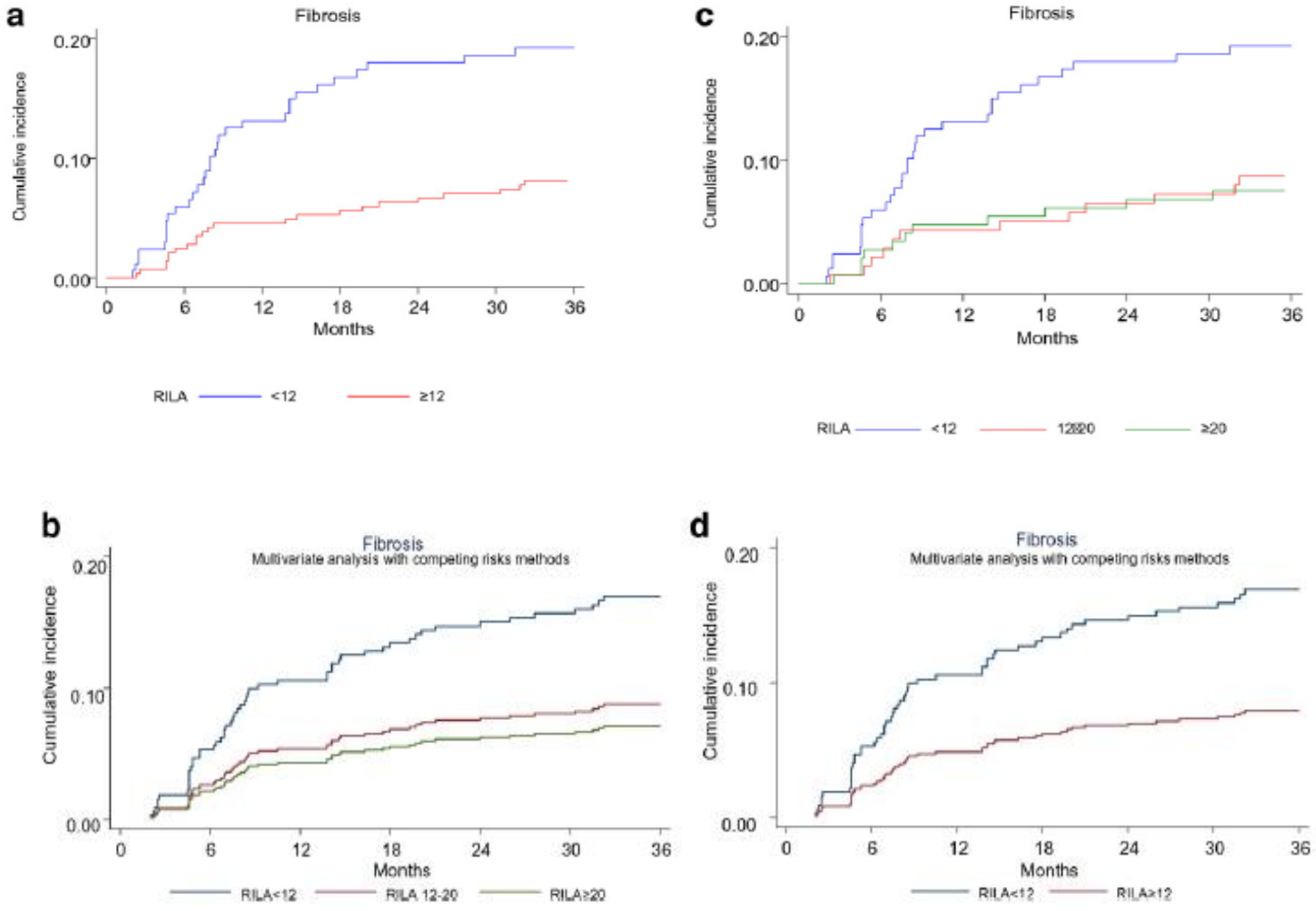
	Fibrosis and relapse (Cox regression)			Fibrosis and relapse (competing risks)		
	HR	95%CI	p value	sHR	95%CI	p value
RILA in subclasses						
RILA						
<12	1			1		
≥12	0.45	0.27–0.74	0.002	0.45	0.27–0.75	0.002
Tobacco Smoking						
No	1			1		
Active/former	1.61	0.97–2.68	0.068	1.60	0.96–2.69	0.074
Hormonotherapy						
No	1			1		
Yes	3.17	1.36–7.40	0.008	3.21	1.37–7.53	0.007
RILA as continuous variable						
RILA	0.96	0.93–0.99	0.012	0.96	0.92–0.99	0.025
Tobacco Smoking						
No	1			1		
Active/former	1.56	0.93–2.06	0.091	1.56	0.93–2.61	0.093
Hormonotherapy						
No	1			1		
Yes	3.17	1.36–7.39	0.008	3.18	1.36–7.44	0.008

HR = hazard ratio estimated by Cox regression. sHR = subdistribution hazard ratio estimated by competing risk method. RILA = radiation-induced CD8 T-lymphocyte apoptosis. CRFS = complication-relapse-free survival.

institutCurie
Ensemble, prenons le cancer de vitesse.

Azria et al. EBM 2015

Biological factors for fibrosis



institutCurie
Ensemble, prenons le cancer de vitesse.

Azria et al. EBM 2015

Concurrent RT-Chemotherapy (CT)

institutCurie

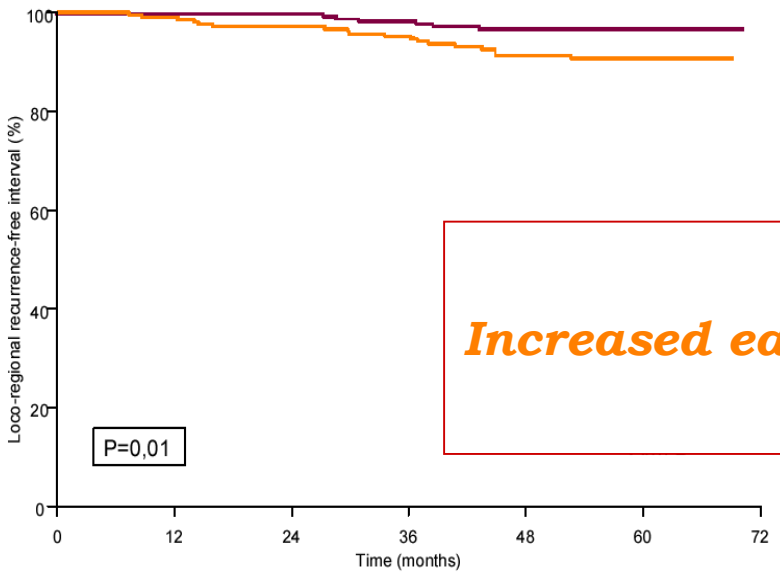
Adjuvant studies

	N	FU	Surgery	CT	
Arcangeli IJROBP 2006	206	5	T+AD	CMFx6	
Rouësse IJROBP 2006	638	5	T/M-AD	FEC60x4 FNCx4	Sequential Concurrent
Toledano JCO 2006	695	5	T+AD	FNCx6	

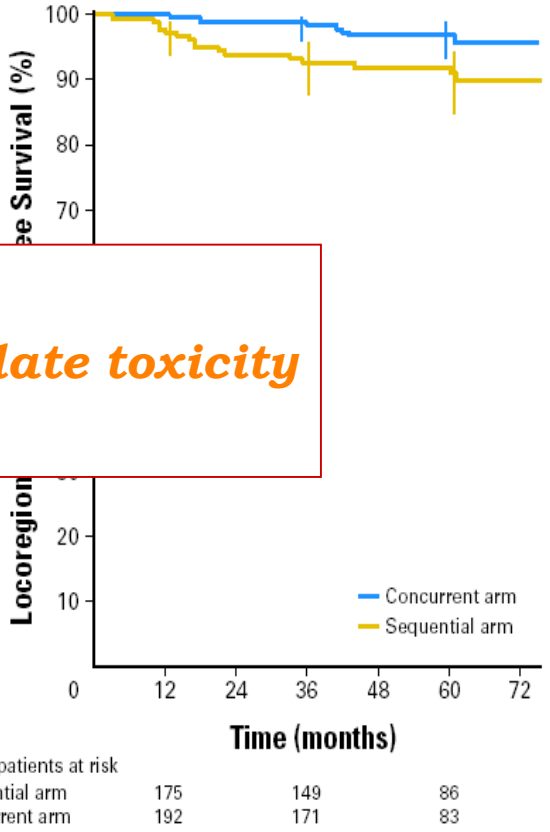
institutCurie

Loco regional control, conserving treatment, pN+

Figure 2: Loco-regional recurrence-free interval in patients with lumpectomy



Increased early and late toxicity



Ptes à risque				
Conc	210	208		155
Seq	206	204		141

No. of patients at risk

Sequential arm	175	149	86
Concurrent arm	192	171	83

99200A
At 5 years
97% Arm A Conc
91% Arm B Seq
Logrank test; p=*0.01*

ARCOSEIN
At 5 years
97% Conc
91% Seq
Logrank test; p=*0.02*

Rouesse, de la Lande et al. IJROBP 2006

Toledano, Azria et al. JCO 2007

institutCurie

Early toxicity

	Rouesse				Arcosein			
		Seq	Conc	p		Seq	Conc	p
Epidermitis	Grade ≥2	21%	29%	0.03	Grade ≥1	37%	41%	NS
Fever	Febrile Neutropenia	<1	1	0.007	Fever	5	7	NS
Cardiac	LVEF ↓15%	2	6	0.02	Grade ≥1	1	1	NS
Neutropenia	Grade ≥3	<1	14	0.0001	Grade ≥1	36	37	NS
Esophagitis					Grade ≥1	13	17	0.02

Rouesse, de la Lande et al. IJROBP 2006

Calais Cancer Radiothérapie 2004

institutCurie

Late toxicity

	Seq	Conc	*p*
Fibrosis (grade >=2)	5	25	*0.003*
Teleangectasia (grade >=2)	7	25	*0.001*
Atrophy (grade >=2)	20	44	*0.0006*
Hyperpigmentation (grade >2)	15	30	*0.02*
Deformation of breast(>moderate)	14	29	*0.0015*
Pain (grade >=2)	12	22	*0.07*
Edema (grade >=2)	0	1	
Lymphoedema (Grade >=2)	7	5	

Toledano et al. IJROBP 2006

institutCurie

Neo adjuvant RT-CT

	No.	Stage	ChT	RT*	pCR %	Epidermatitis Grade 3 %
Formenti et al IJROBP 1997	35	T3-4 Neaoadj	5FU-ci 200mg/m2	50 Gy	20	26
Formenti et al. JCO 2003	44	IIB-III Neoadj.	Paclitaxel	45 Gy	16	7
Kao et al. IJROBP 2004	16	IIIB-C Neoadj	VB + P or P	60 Gy	46	50
Bollet et al. EJC 2006	60	T2-3, N0-1	5FU-ci +VB	50 Gy	27	14

* RT Breast+LN

* RT Breast+LN

institutCurie

Concurrent RT-targeted treatments

institutCurie

Concurrent RT-targeted treatments,

WHY?

- Radiosensibilisation = additive and/or supra-additive effect
- Spatial cooperation = action to the micro-metastases
- Protection of the healthy tissues = radioprotection

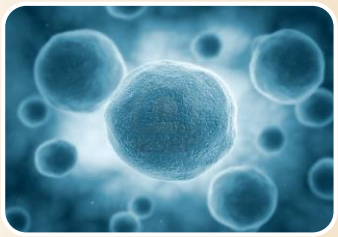
institutCurie

Concurrent RT-targeted treatments,

HOW?

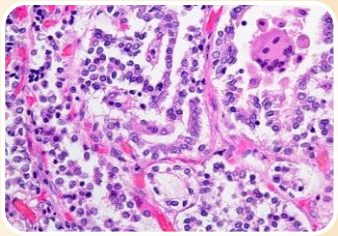
Molecular mechanisms

- Inhibition of the reparation



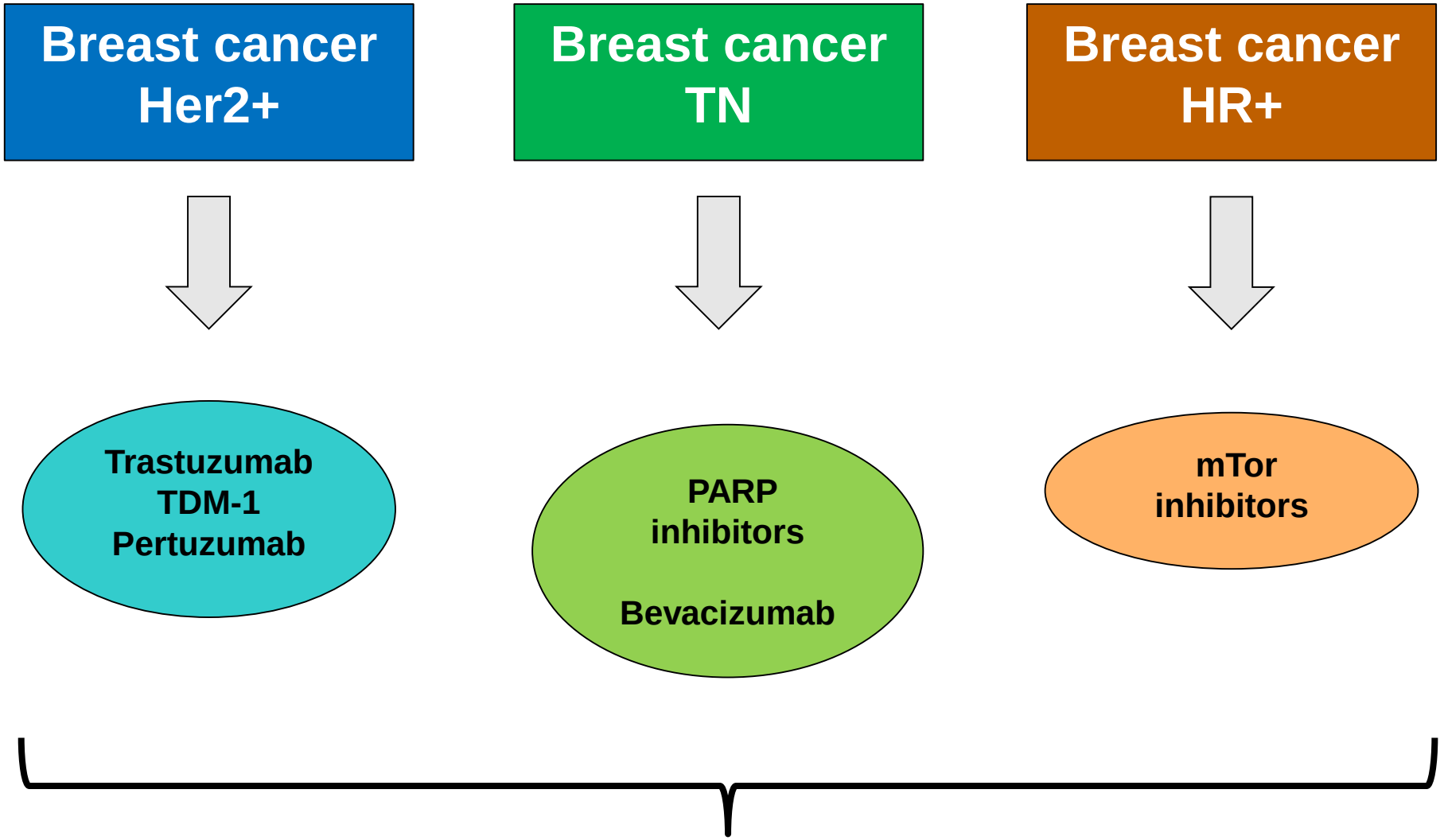
Cellular mechanisms

- Cytokinetic cooperation
- Action to the hypoxic cells
- Promotion of the apoptosis



Tissular mechanisms

- Tumoral re-oxygenation
- Decreasing the tumor repopulation
- Angiogenesis



institutCurie

HER2 POSITIVE BREAST CANCER

institutCurie

➢ **HER2**

- Surexpression in 20-25% of BC

(Spector et al., J Clin Oncol 2009)

- Trastuzumab

(Piccart-Gebhart et al., N Engl J Med 2005,

Halyard et al., J Clin Oncol 2009)

- Association RT & Trastuzumab

> radio sensibilisation *(Pietras et al., Cancer Res 1999)*

Toxicity?

VOLUME 27 · NUMBER 16 · JUNE 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Radiotherapy and Adjuvant Trastuzumab in Operable Breast Cancer: Tolerability and Adverse Event Data From the NCCTG Phase III Trial N9831

Michele Y. Halyard, Thomas M. Pisansky, Amylou C. Dueck, Vera Suman, Lori Pierce, Larry Solin, Larry Marks, Nancy Davidson, Silvana Martino, Peter Kaufman, Leila Kutteh, Shaker R. Dakhil, and Edith A. Perez

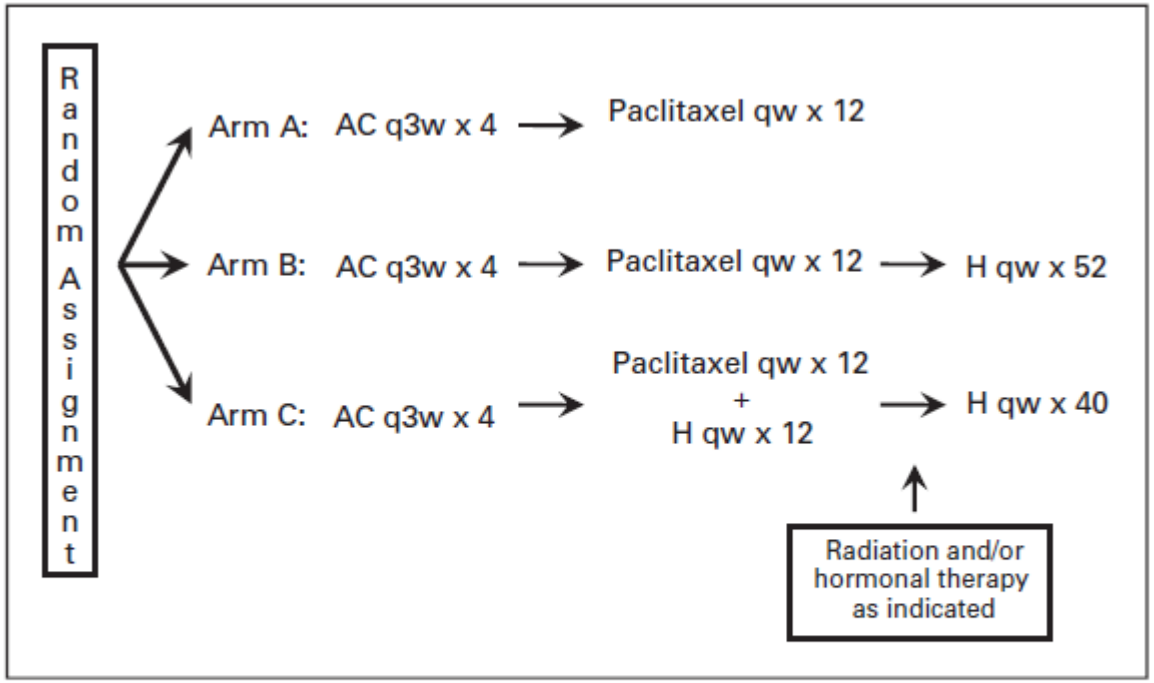


Fig 1. N9831 random assignment schema: H, trastuzumab in 4 mg/kg loading dose followed by 2 mg/kg; A, doxorubicin 60 mg/m^2; C, cyclophosphamide 600 mg/m^2; T, paclitaxel 80 mg/m^2; HRT, hormone replacement therapy; RT, radiotherapy; qw, every week; q3w, every 3 weeks.

institutCurie

Cardiac toxicity in case of IMN RT

- **Only 44 patients with IMN irradiation**

Table 4. Cardiac Events After Completion of T for Patients Receiving IMN RT

	AC-T (RT only)		AC-T-H (RT only)		AC-TH-H (RT only)		All RT Patients		
Cardiac Event	IMN RT	No IMN RT	IMN RT	No IMN RT	IMN RT	No IMN RT	IMN RT	No IMN RT	All RT Patients
Patients, No.	15	468	14	508	15	398	44	1,374	1,418
Confirmed CHF, No.	0	1	1	13	0	7	1	21	22
Cardiac deaths, No.	1	0	0	0	0	0	1	0	1
Cardiac events, No.	1	1	1	13	0	7	2	21	23

NOTE. Three-year cumulative incidence rates were as follows: AC-T: IMN RT, 0%; no IMN RT, 0.2%; AC-T-H: IMN RT, 7.1%; no IMN RT, 2.6%; and AC-TH-H: IMN RT, 0%; no IMN RT, 1.8%.

Abbreviations: T, paclitaxel; IMN, internal mammary nodes; RT, radiotherapy; AC, doxorubicin and cyclophosphamide; H, trastuzumab; CHF, congestive heart failure.

institutCurie

Other studies

Table 8 Comparison of the toxicity rates reported in patients exposed to concurrent trastuzumab with locoregional breast radiotherapy

Grade[a]	*n*	Median follow-up	Acute epithelitis (%)			Acute esophagitis (%)			Late skin reactions (%)		Late esophagitis (%)		LVEF decrease	CHF
			1	2	3	1	2	3	<2	≥2	<2	≥2		
Series														
Belkacémi et al. [10]	146	16 months	37[b]	35	6	64[b]	24	11	48[c]	51	88[c]	12	Grade 2 and greater: 10 %[f]; 5 %[g]	–
Shaffer et al. [11]	44	15 months	–	–	–	–	–	–	–	–	–	–	Mean absolute decrease: 4 %[h]	4.5 %
Meattini et al. [13]	95	4.3 years	20	13.7	0	1.1	0	0	F: 18.9; T: 4.2[d]		–	–	Median decrease: 2 %[i]	1.1 %
Halyard et al. [26]	935	3.7 years	–	–	–	–	–	–	–	–	–	–	–	1.7 %[j]; 2.7 %[k]
Jacob et al.	308	52 months	73.4[d]	21.7	3.9	8.5[d]	1.3	0.1	F: 18.6; T: 4.9[e]	F:7.0; T: 3.5	0.4[e]	0	Grade 2 and greater: 2.9 %[f]	1 %

Jacob et al., 2014

institutCurie

Conclusions Herceptin-RT

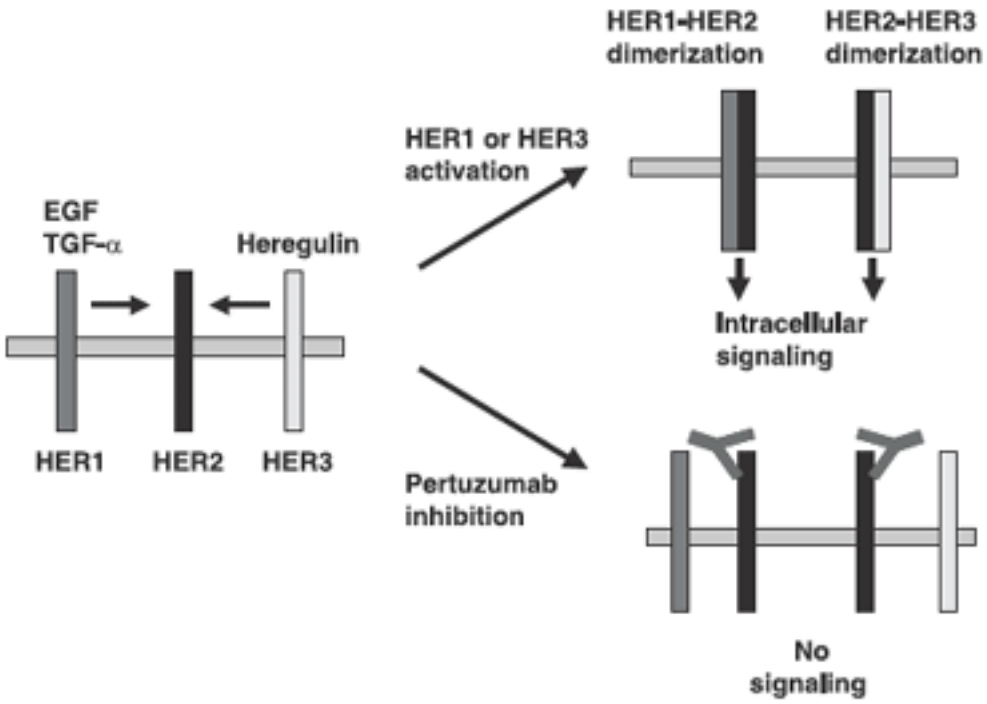
Trastuzumab can be administered concurrently with locoregional breast radiotherapy

Tailored irradiation techniques are required

Long-term follow-up is warranted

institutCurie

- **Trastuzumab-Pertuzumab and radiotherapy: no preclinical data**

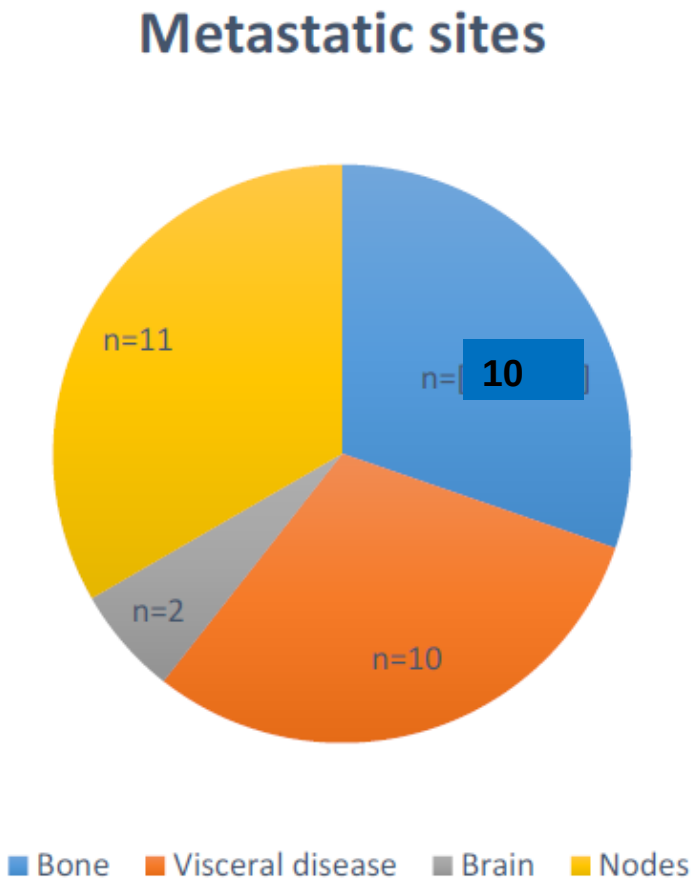


- Autorisation in Her2+ metastatic BC

- No published clinical data

Table 1. Patients' clinical and histological characteristics (n=23)

	n patients	%
Age		
<40 years	2	(9)
40-60 years	14	(61)
>60 years	7	(30)
Treated breast side		
Right	16	(70)
Left	6	(26)
Bilateral treatment	1	(4)
Histology		
IDC	20	(87)
ILC	2	(9)
Adenocarcinoma	1	(4)
Hormone receptor status		
HR+	12	(52)
HR-	11	(48)
Histoprognostic grade (Eston Ellis classification)		
I	0	(0)
II	9	(39)
III	12	(52)
na	2	(9)
Metastatic disease	23	(100)
At diagnosis	15	(65)
Relapse after local treatment	8	(35)
Sites of metastases		
Bone	10	(43)
Visceral disease	10	(43)
Brain	2	(9)
Nodes	11	(48)
Locoregional tumor associated	22	(96)



Ajgal Z et al,CanRad 2016

institutCurie

Table 4. Type of surgery performed

	n	(%)
Locoregional surgery performed in responding metastatic disease	15	(65)
Breast conserving surgery	3	(13)
Radical mastectomy	11	(48)
Axillary node dissection	14	(61)

Table 5. Radiotherapy

		n	%	Prescribed dose (Gy)/fractions
Area				
	Breast	8	(35)	50/25
	Chestwall	9	(39)	50/25
	IMC	9	(39)	46/23
	Axillary area	9	(39)	46/23
	Supra clavicular area	16	(70)	46/23
	WBRT	1	(4)	30/10
	Vertebra	3	(13)	15/5
	Scapula	1	(4)	15/5
	Pelvis	1	(4)	20/10
Irradiation technique				
	Tomotherapy	7	(30)	
	Conformationnal 3D	16	(70)	

Toxicity (n,%)

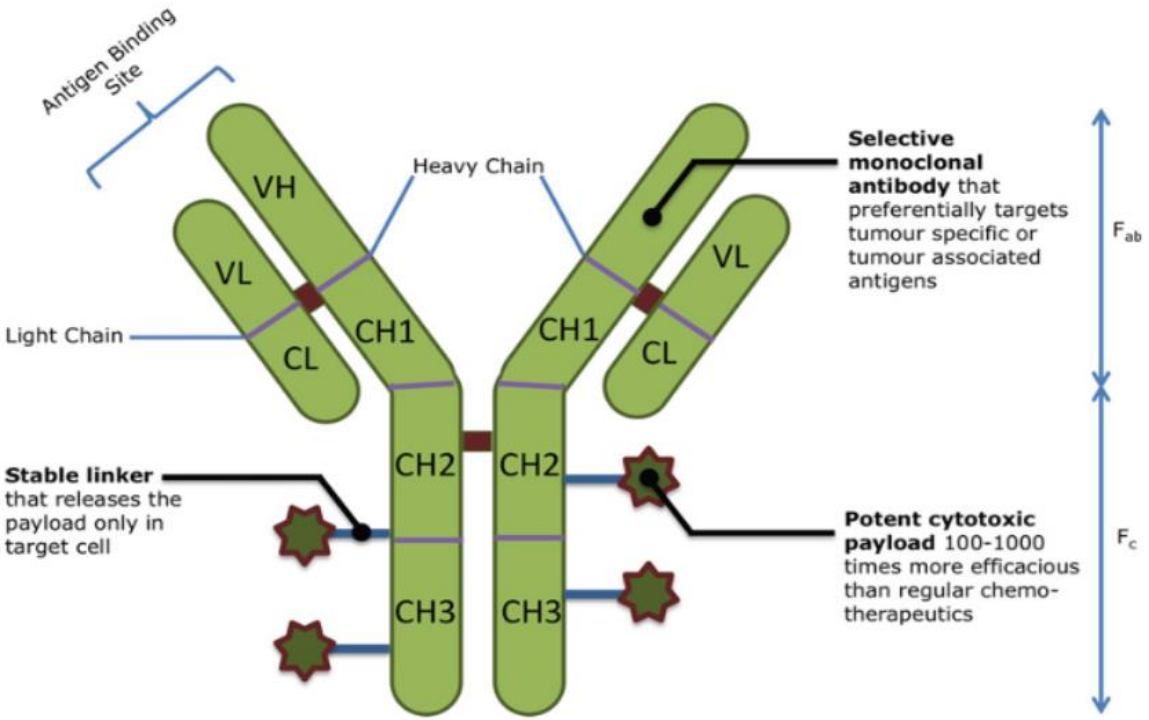
	Grade 0		Grade 1		Grade 2		Grade 3	
	n	%	n	%	n	%	n	%
Diminution of LVEF	0	**0**	0	**0**	2	**9**	1	**4**
Radiodermatitis	11	**48**	5	**22**	6	**26**	1	**4**
Esophagitis	23	**100**	0	**0**	0	**0**	0	**0**
Radiation pneumonitis	0	**0**	1	**4**	1	**4**	0	**0**

Conclusions: Acceptable toxicity comparable with Herceptin-RT, but very preliminary results, have to be confirmed in prospective trials.

Ajgal Z et al, EBCC 2016

institutCurie

TDM1-RT



Bioscience Reports (2015) **35**, e00225, doi:10.1042/BSR20150089

institutCurie

Trastuzumab emtansine and stereotactic radiosurgery: an unexpected increase in clinically significant brain edema

Julie A. Carlson, Zohra Nooruddin, Chad Rusthoven, Anthony Elias, Virginia F. Borges, Jennifer R. Diamond, Brian Kavanagh, and Peter Kabos

Department of Radiation Oncology, University of Colorado Denver, Aurora, Colorado (J.A.C., C.R., B.K.); Department of Medicine, Division of Medical Oncology, University of Colorado Denver, Aurora, Colorado (Z.N., A.E., V.F.B., J.R.D., P.K.)

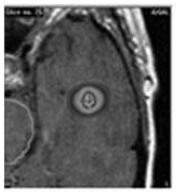
Corresponding authors: Julie Carlson, MD, University of Colorado Anschutz Medical Campus, Mail Stop F706, 1665 Aurora Court, Suite 1032, Aurora, CO 80045 (julie.a2.carlson@ucdenver.edu); Peter Kabos, MD, University of Colorado Anschutz Medical Campus, 12801 E 17th Ave, Aurora, CO 80045 (peter.kabos@ucdenver.edu).

-7 patients association TDM1- RS

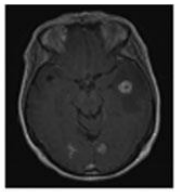
-4 cases of radio necrosis

2 immediately after TDM1 perfusion,
1 after 5 cycles,
1 after 2 cycles.

-3 patients: ARRET et 1 presented the sequels

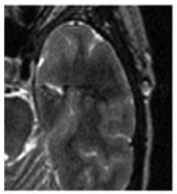


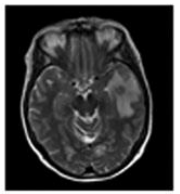
SRS plan to left temporal lesion 15 months prior to T-DM1; T2 images below



15 months post-SRS prior to 1st T-DM1 infusion

SRS plan to left occipital lesion delivered 3 days prior to 2nd T-DM1 infusion





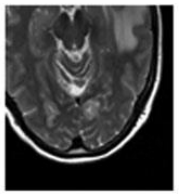


Table 1. Clinical and treatment characteristics for 7 patients with HER2+ breast cancer treated with SRS and T-DM1 over a 2-year period

Patient	Age (years)	CSRN	Prior Systemic Therapy	Total no. Cycles T-DM1	T-DM1 On-Trial	Total no. Treated BM	SRS Dose (Gy)	Maximum Size of Treated Lesion (cm^3)	Interval to CSRN From T-DM1 (days)
1	37	Yes	T, S	1	No	4	24	1.1	10
2	56	Yes	AC, ET	7	Yes	1	18	1.6	7
3	57	Yes	APx, XT, TV, GTCaL	5	No	5	16-20	0.9	35
4	57	Yes	ACPx, T, S	2	No	5	24	4.5	3
5	49	No	TPx, AC, DPT	4	No	3	20	0.5	N/A
6	46	No	TaPT, CaL	2	Yes	2	20	0.9	N/A
7	57	No	AC,TPx, PTPx, V, L	31	Yes	2	18	5.0	N/A

Abbreviations: A, Doxorubicin; C, cyclophosphamide; Ca, capecitabine; CSRN, clinically significant radiation necrosis; D, docetaxel; E, eribulin; G, gemcitabine; L, lapatinib; no., number; P, carboplatin; S, study; Px, Paclitaxel; T, trastuzumab; V, vinorelbine; X. abraxane

institutCurie

TN BREAST CANCER

ANTI-ANGIOGENIC TREATMENT + RT

institutCurie

4 possible mechanisms:

- Vascular normalization
- Apoptosis of endothelial cells provoking the radio sensibility of the tumor cells
- Reduction of the radio resistance of the tumor cells
- Reduction of the number of tumor stem cells

Early toxicity in breast cancer therapy

Goyal et al., IJROBP, 2011

14 patients with bevacizumab –RT mached to 14 controls (RT alone).

	Bevacizumab + RT		RT alone	
Locoregional toxicity	Grade 1–2 *n* affected (total)	Grade 3–5 *n* affected (total)	Grade 1–2 *n* affected (total)	Grade 3–5 *n* affected (total)
Nausea	1 (14)	0 (14)	0 (14)	0 (14)
Fatigue	13 (14)	0 (14)	14 (14)	0 (14)
Pneumonitis	1 (14)	0 (14)	0 (14)	0 (14)
Radiation Dermatitis	14 (14)	0 (14)	11 (14)	3 (14)
Radiation fibrosis	0 (14)	0 (14)	0 (14)	0 (14)
Lymphedema	0 (14)	0 (14)	0 (14)	0 (14)

institutCurie

Tolerance of the Radiotherapy of BC associated or not with Bevacizumab
ToleRAB: National retrospective case-controls study

- **Patients includes in the adjuvant studies with bevacizumab as BEATRICE or neo adjuvant (BEVERLY) associated with radiotherapy (RT) in the breast cancer (BC) treatment**
- **Follow-up of two cohorts: +/- Bevacizumab during 5 years after the end of the RT**
- **65 patients included in the cohort bevacizumab**
- **62 patients evaluated at 1 year**

institutCurie

Tolerance of the Radiotherapy of BC associated or not with Bevacizumab

ToleRAB n= 65 (B+RT): National retrospective case-controls study

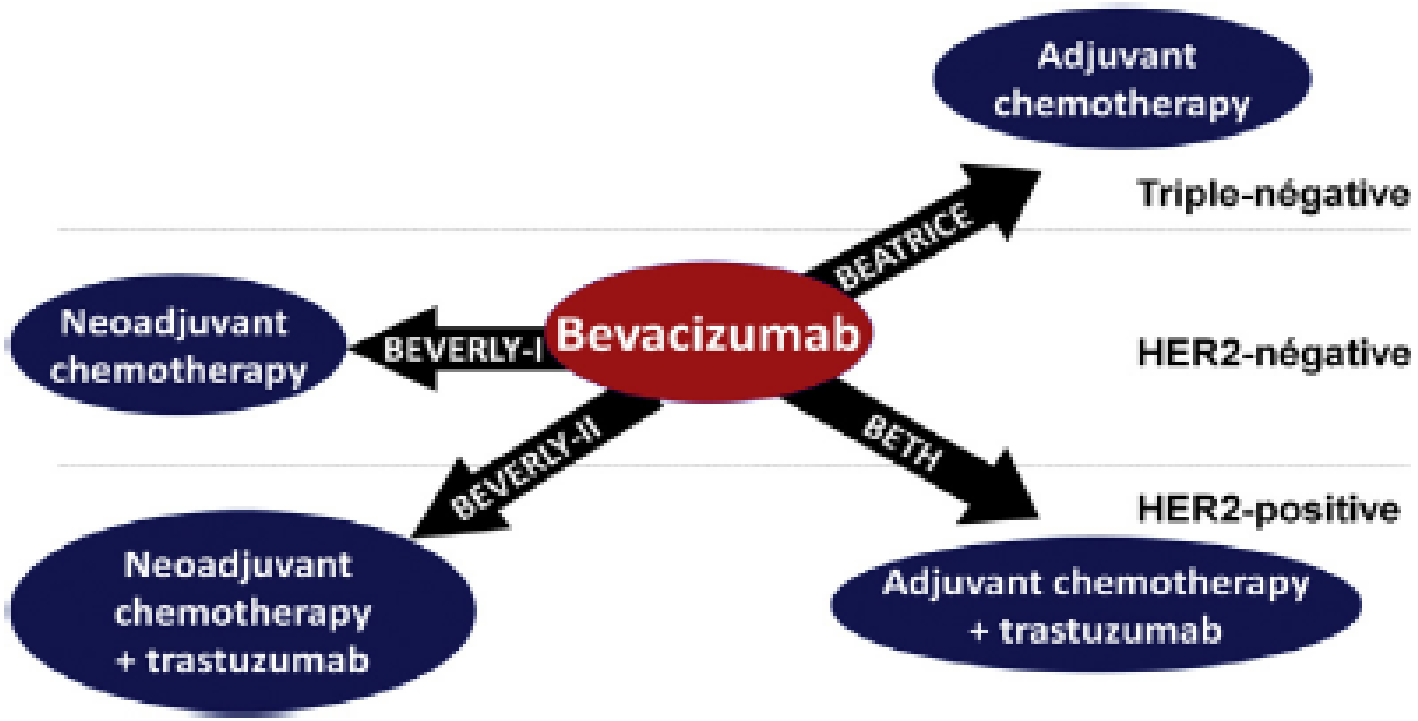


Fig. 1. Presentation of clinical trials: bevacizumab with concurrent radiotherapy or description of the patient population.

Pernin, et al, The Breast 2014

institutCurie

ToleRAB: Acute toxicity (CTCAE v3)

	Bevacizumab + RT				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Radiodermatitis	27 (62)	17 (62)	4 (62)	0 (62)	48 (62)
Œsophagitis	0 (62)	1 (62)	0 (62)	0 (62)	1 (62)

Pernin et al, 2014

institutCurie

ToleRAB: Late toxicity at 1 year

	Bevacizumab + RT				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Pain	3 (62)	4 (62)	0 (62)	0 (62)	7 (62)
Lymphedema	4 (62)	1 (62)	0 (62)	0 (62)	5 (62)
Fibrosis	3 (62)	0 (62)	0 (62)	0 (62	3 (62)
Ulceration	0 (62	0 (62	0 (62	0 (62	0 (62)
Telangiectasias	1 (62)	1 (62)	0 (62)	0 (62)	2 (62)

2 cardiovascular events: 1 case of grade 1 hypertension et 1 case of grade 1 ventricular extrasystolas

institutCurie

ToleRAB: Early toxicity: cosmesis, *Pernin, et al, The Breast 2014*

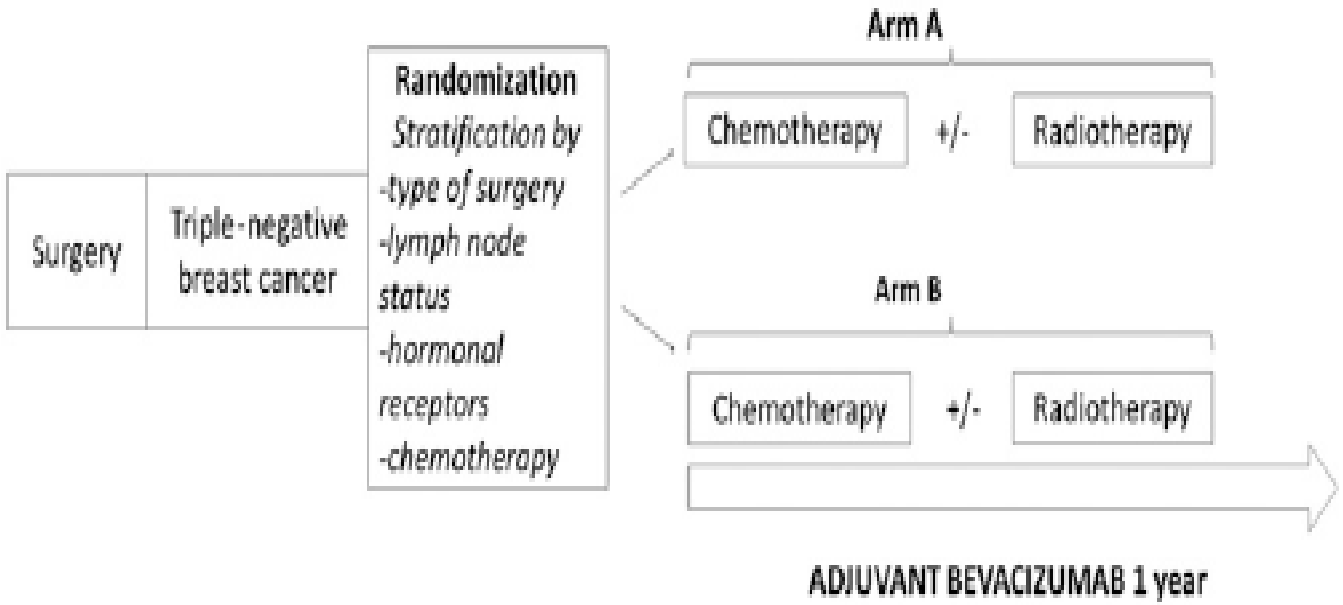
Cosmetic results.

Cosmetic results		N (n = 63)	%
Cosmetic evaluation	Yes	25	40
	No	23	40
	No evaluation (mastectomy)	15	22
Cosmetics results	Grade 0 (no change)	13	21
	Grade 1 (minor changes)	9	14
	Grade 2 (operated breast deformed)	3	5
	Grade 3 (operated breast seriously deformed)	0	0

institutCurie

ToleRAB: randomized part, *Pernin, et al, Br J Radiol 2015*

Figure 1. BEATRICE trial study plan.



institutCurie

ToleRAB: Conclusions, *Pernin, et al, The Breast 2014, BJR 2015*

Concurrent bevacizumab and locoregional radiotherapy for breast cancer did not induce any severe acute and late toxicities after one year of follow-up. However, this combination cannot be recommended in clinical practice until longer term survival data are available. Determination of late toxicity at 3-year and 5-year follow-up after completion of radiotherapy is currently underway.

At 3 years: no increased toxicity found

Dautruche et al, in press

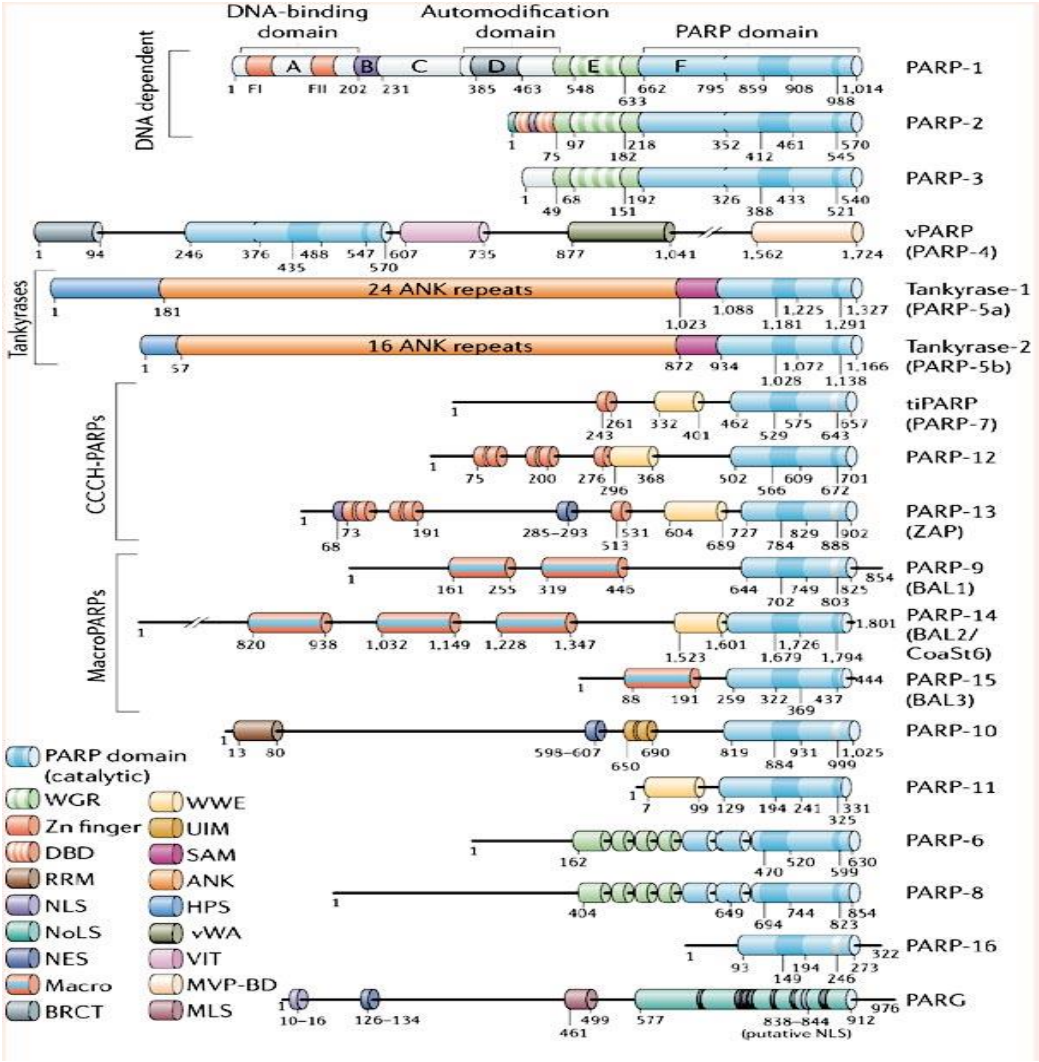
institutCurie

PARP inhibitors and RT

institutCurie

PARPs: poly(ADP-ribose) polymerases

- Superfamily of 16 members.
- 6 have poly(ADP-ribosyl)ating activity
- PARP-1 accounts for more than 90% of this activity.
- Share a common catalytic site
- Inhibitors are often analogues of its substrate NAD> will inhibit many PARPs



Schreiber et al. Nature Reviews Molecular Cell Biology **7**, *517–528 (July 2006)*

institutCurie

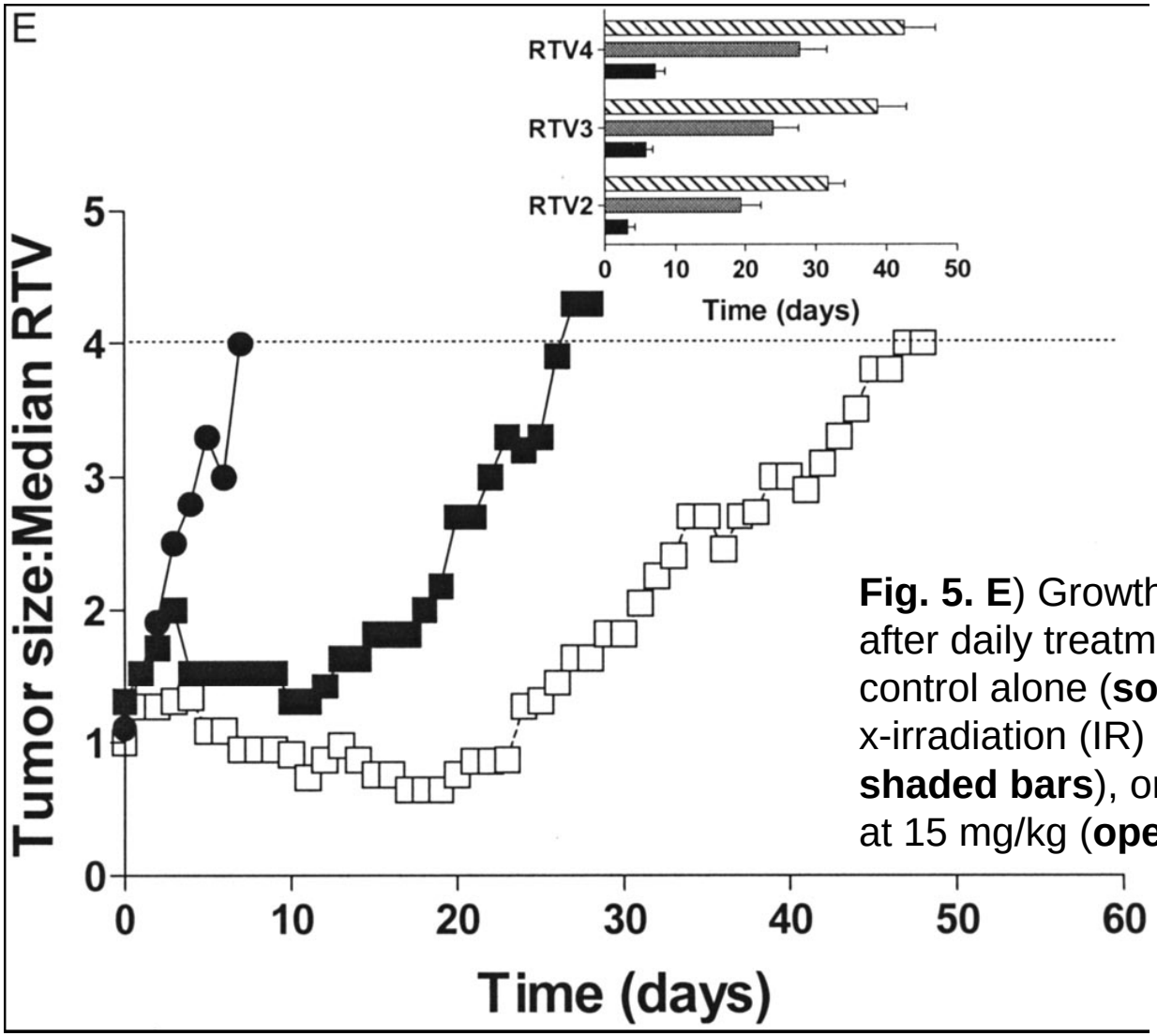
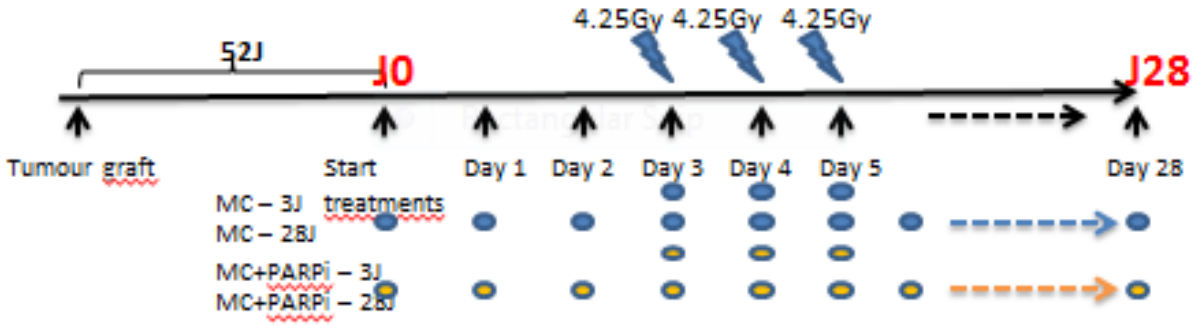
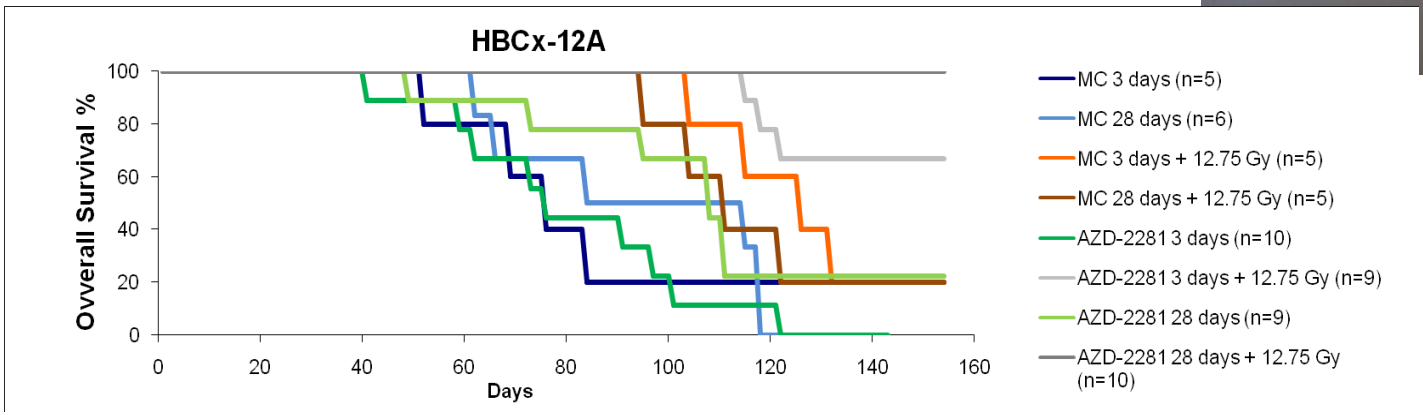


Fig. 5. E) Growth of SW620 tumor xenografts after daily treatment for 5 days with vehicle control alone (**solid circles, solid bars**), 2 Gy of x-irradiation (IR) vehicle (**solid squares, shaded bars**), or 2 Gy of x-irradiation AG14361 at 15 mg/kg (**open squares, hatched bars**).

PRE-CLINICAL STUDIES OF THE THERAPEUTIC EFFECT OF A PARP INHIBITOR COMBINED WITH RADIOTHERAPY FOR BREAST CANCER TREATMENT, *Pouzoulet et al, AACR 2013*





Our preclinical results confirm the susceptibility of TNBC to ionizing radiation and the impact of *BRCA2* mutations on this sensitivity. Such a characterization of highly relevant preclinical models supports their use for pharmacological assessments that will combine both radiotherapy and new therapeutic approaches to improve the outcome of TNBC patients

institutCurie

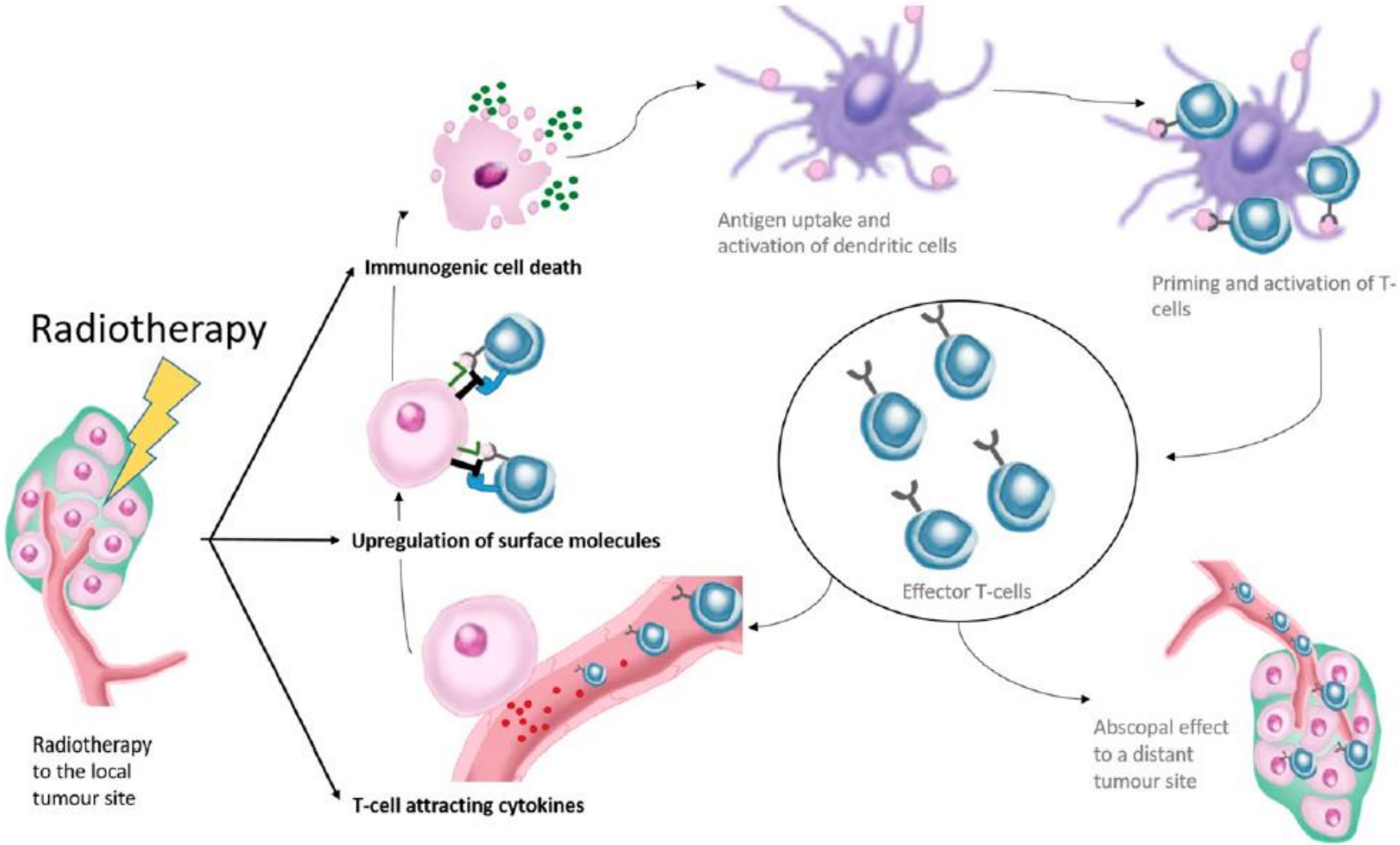
Phase I studies currently running:

Differences, similarities	NKI/AVL	Inst Curie
Pat population	Metast breastca, also ER pos	Mets and loc adv breast ca, TN
Dose esc schedule	50, 100, 200, 300	50, 100, 150,200, 300
RT dose	46.69/23 fr, 14.49Gy SIB	50 Gy, 16 Gy boost sequ
Additional treatment	no surgery	Surgery in some cases
Translational res	HRD, par assay	HRD, ctDNA, parp1 IHS
Tite CRM	DLT period 12 weeks	DLT period 12 weeks
Late tox	Evaluated in the protocol	Evaluated in the protocol
Pat with bolus on skin/WEM	Separate groups in protocol	Depends

Immunotherapy and RT

coming

Radiotherapy and immunity

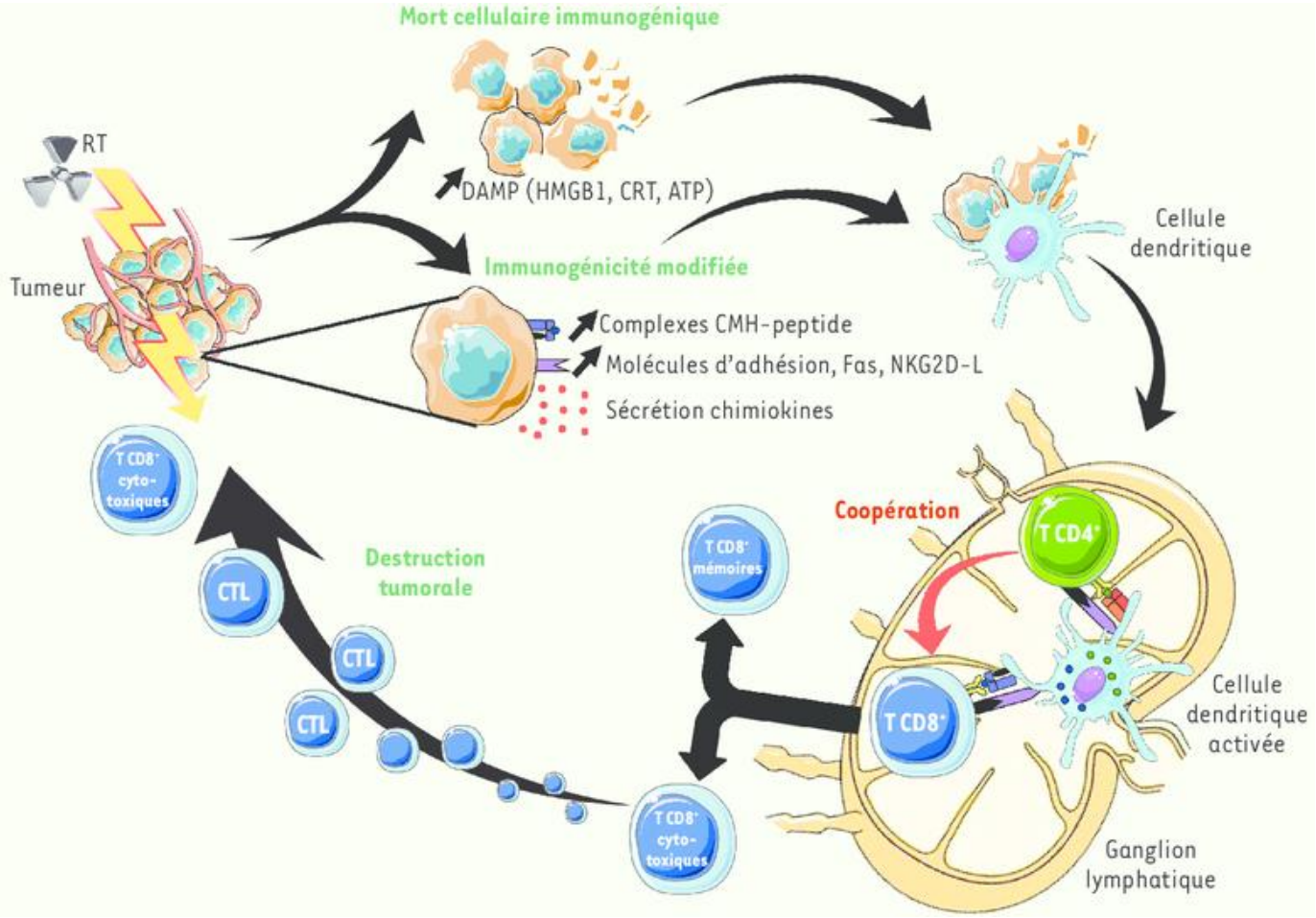


VAN LIMBERGEN, et al, BJR 2017

institutCurie

Immunity and radiotherapy

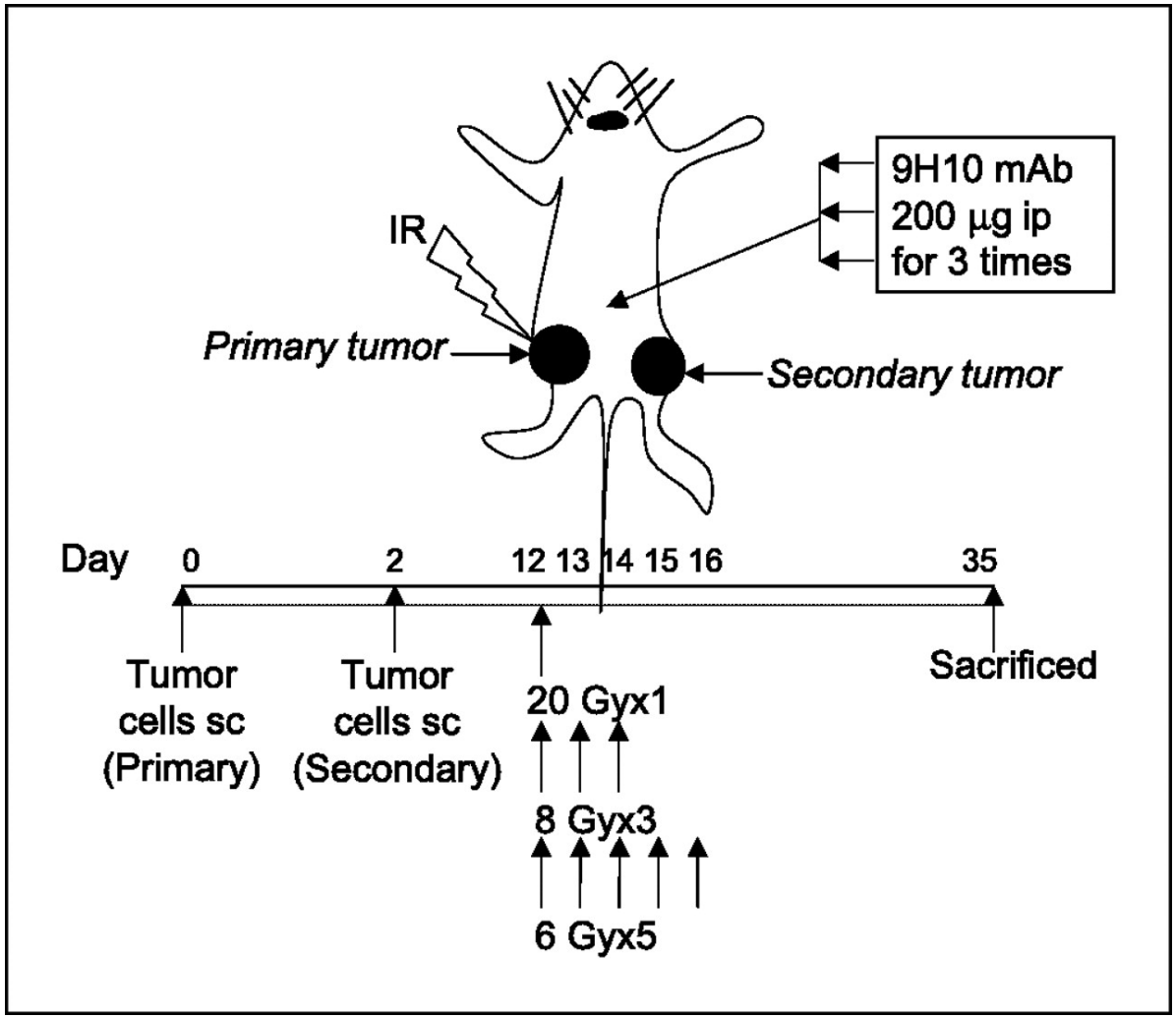
Abscopal Effect



Sharabi et al, 2015

institutCurie

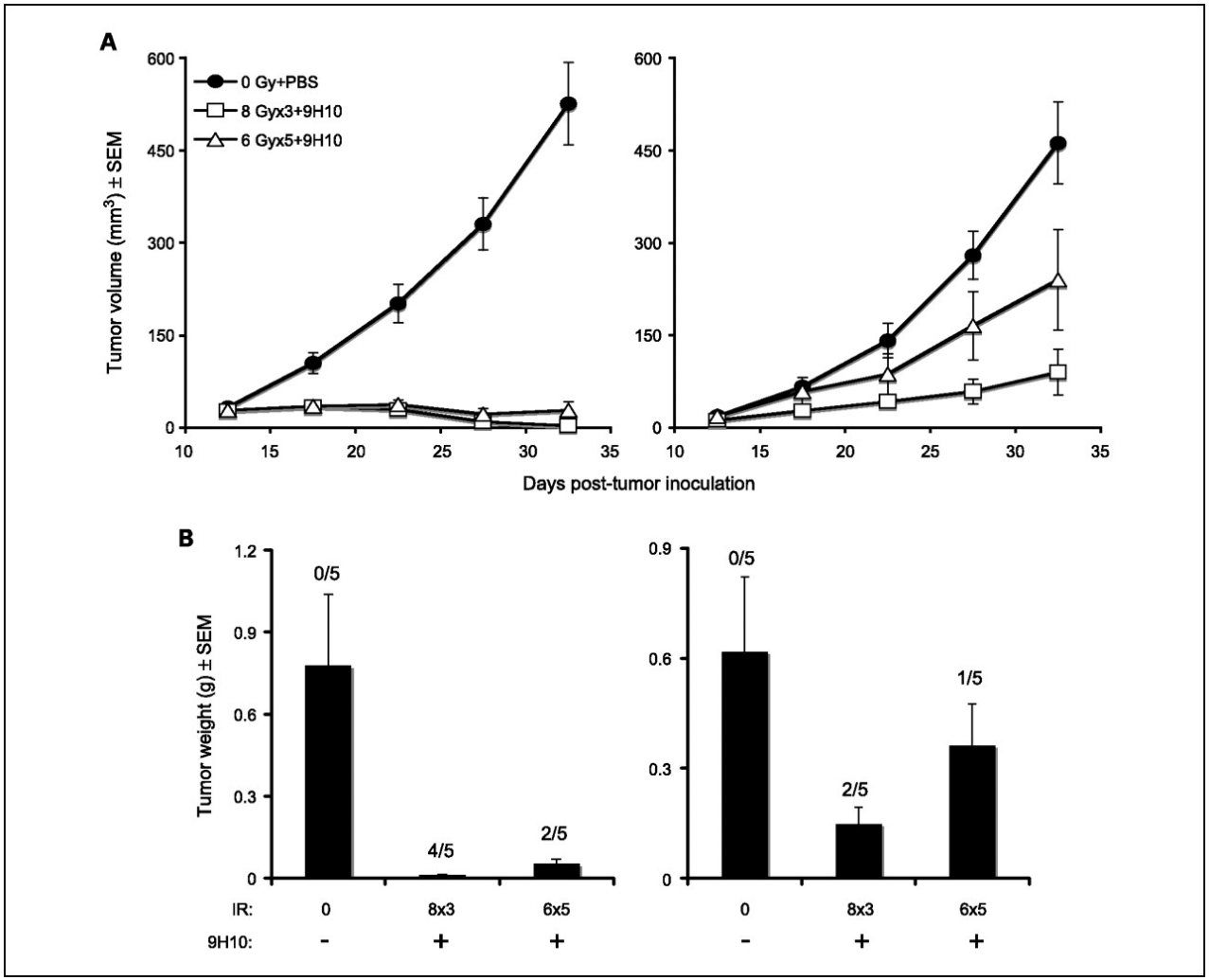
Tumor model and treatment schedule.



M. Zahidunnabi Dewan et al. Clin Cancer Res 2009;15:5379-5388

©2009 by American Association for Cancer Research

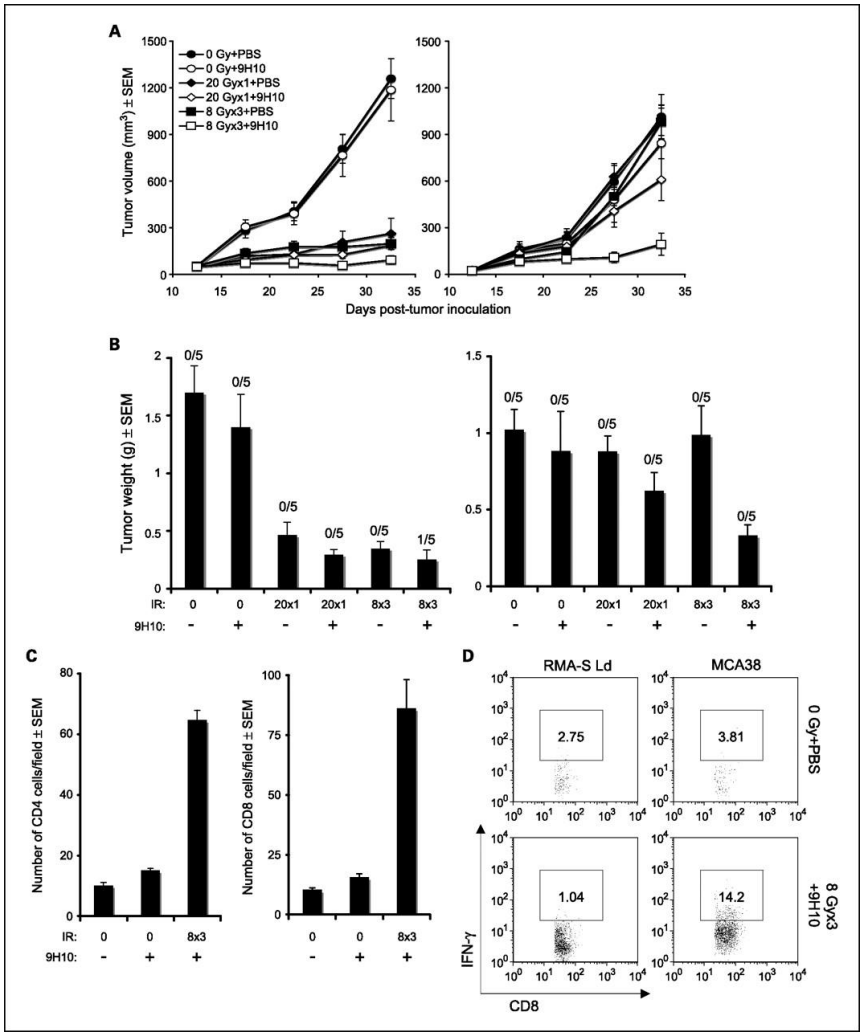
Fractionated radiotherapy given to TSA tumor-bearing mice in three doses of 8 Gy is more effective than five doses of 6 Gy at synergizing with anti–CTLA-4 antibody.



M. Zahidunnabi Dewan et al. Clin Cancer Res 2009;15:5379-5388

©2009 by American Association for Cancer Research

The abscopal effect is induced in MCA38 tumor-bearing mice by fractionated radiation in combination with anti–CTL-4 antibody.



M. Zahidunnabi Dewan et al. Clin Cancer Res 2009;15:5379-5388

©2009 by American Association for Cancer Research

Clinical Cancer Research
AACR American Association for Cancer Research
institutCurie

Conclusions - I

1. Concurrent radiotherapy with Tamoxifen is probably safe
2. Limited clinical data on radiotherapy and AI, but also probably safe
3. Concomitant radiotherapy with current chemotherapy protocols should be evaluated in trials
4. There is an urgent need to evaluate the concurrent use of new targeted therapy and radiotherapy in breast cancer!

Conclusions-II- new targeted treatments

5. More and more new studies with new targeted treatments in association with RT without solid pre clinical data in breast cancer

6. It is important to continue to improve the RT techniques and decrease the toxicity to be sure that these associations will be safe for the patients

7. A lot of work for the radiation oncologist

8. It is important to assess prospectively the early and late toxicities of these associations

Thank you for your attention.

Questions?

youlia.kirova@curie.fr

institutCurie

Systemic treatment: how to advise to most appropriate treatment for your patient: Adjuvant!Online; molecular prediction tools

B.Vriens

Medical oncologist

Catharina Hospital Eindhoven

The Netherlands

ESTRO Breast Cancer 2017

ESTRO School

To identify those who will benefit from adjuvant chemotherapy remains a challenge, leading to the overtreatment of some patients

The biology and behavior of breast cancer affects the treatment plan.

Treatment options and recommendations are very personalized and depend on several factors, including:

The tumor's subtype, including hormone receptor status (ER, PR) and HER2 status

The stage of the tumor

Genomic markers, such as Oncotype DX™/ 70-gene signature (if appropriate)

The patient's age, general health, menopausal status, and preferences

The presence of known mutations in inherited breast cancer genes, such as *BRCA1* or *BRCA2*

Treatments (neo)-adjuvant setting

Chemotherapy (e.g)

- Taxanes
- Anthracyclines
- Cyclophosphamide

Endocrine therapy (ER+ and/or PR+ tumors)

- Tamoxifen
- Aromatase-inhibitors

Trastuzumab +/- Pertuzumab (HER2+ tumor)

Planning adjuvant treatment is complex and incorporates a variety of prognostic and predictive factors

Prognostic & predictive markers utilized in breast cancer

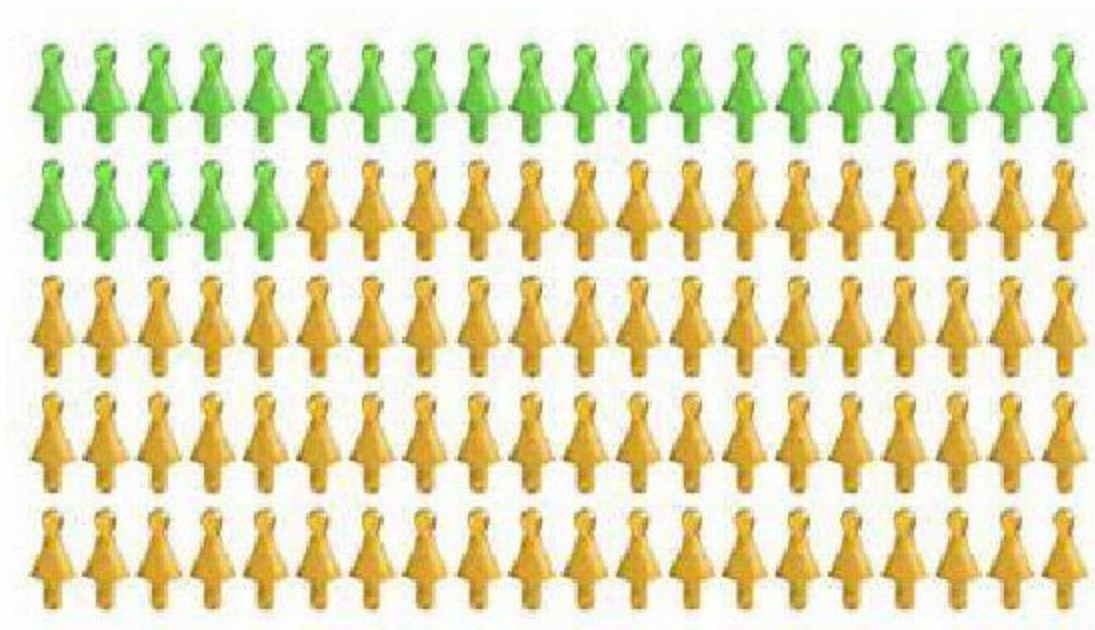
Prognostic (recurrence risk)	Predictive (treatment benefit)
Axillary node status	ER/PR status
Histologic type/grade/proliferation index	HER2 neu status
Tumor size	
Patient age	
Performance status	
Lymphatic/Vascular invasion	
ER/PR status	
HER2 neu status	
Oncotype DX test	
70 gene signature (mammaprint)	

ESTRO School

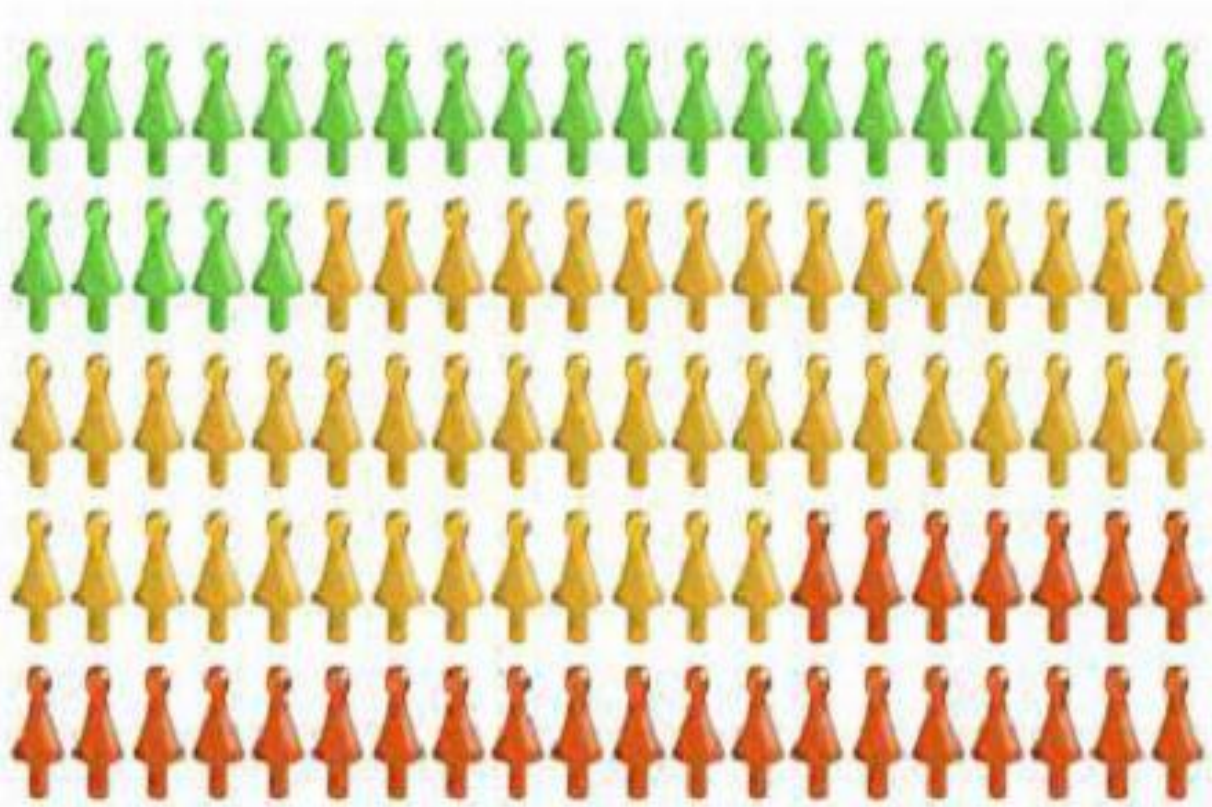
25% will develop distant metastases

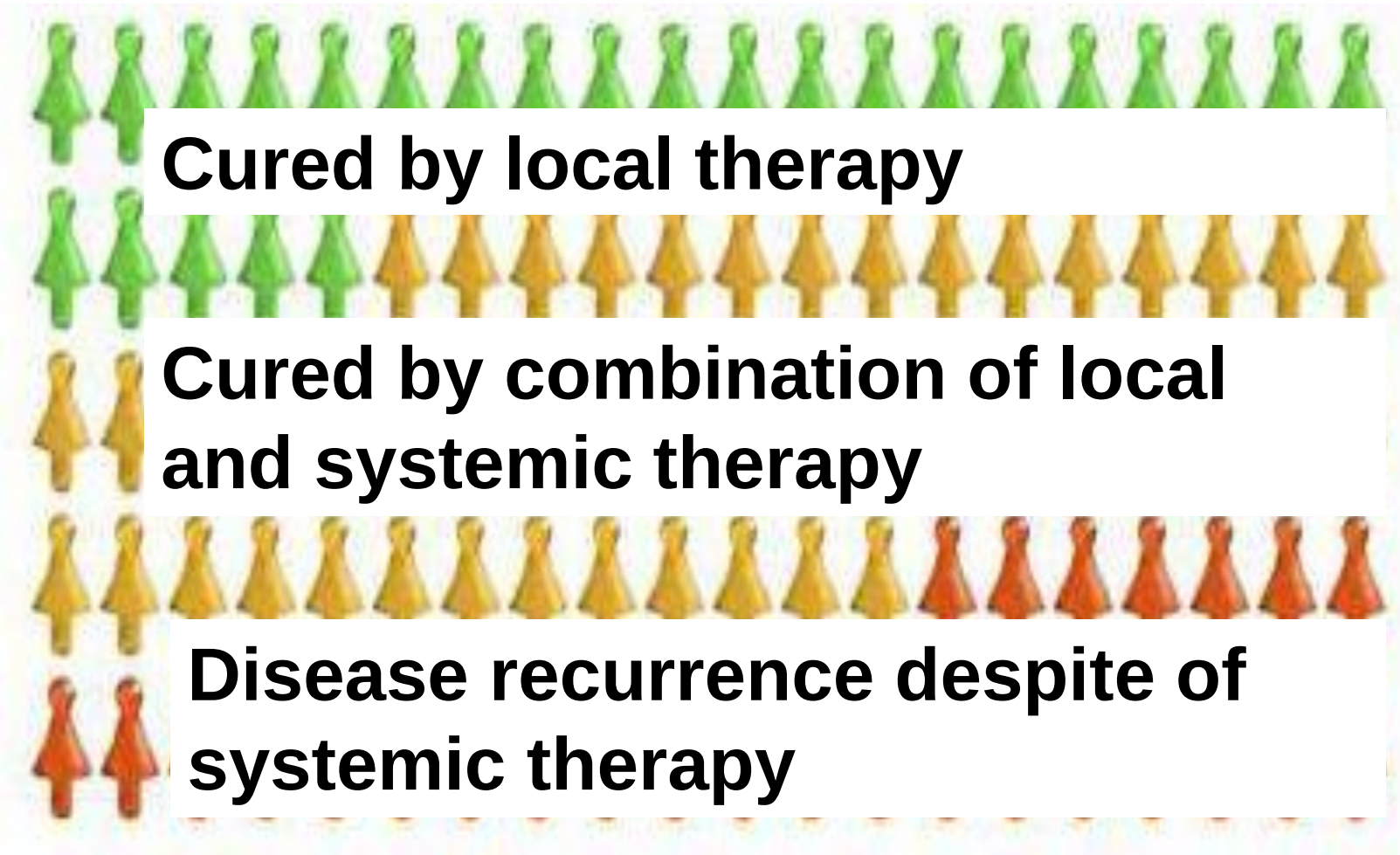
Systemic therapy will reduce development of distant metastases

We treat almost *75%* of the patients



50% of all patients had no benefit of systemic therapy

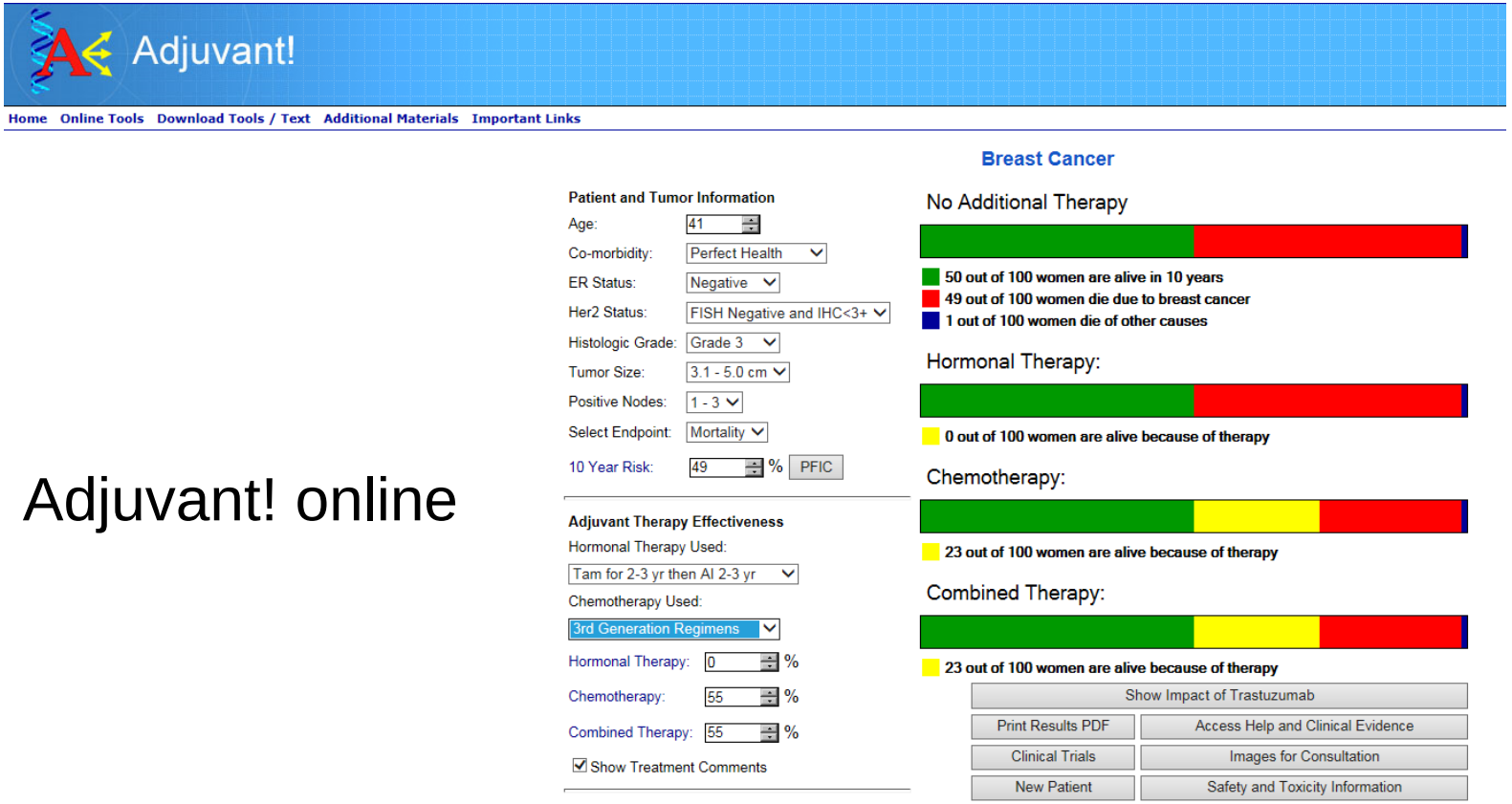



Cured by local therapy
Cured by combination of local and systemic therapy
Disease recurrence despite of systemic therapy

Systemic therapy yes or no

- Prognostic markers
- Better prognosis→absolute advantage is less
- Minimal absolute overall survival benefit of 4 - 5% in 10 years
- Individual consideration
- Use of NewAdjuvant Online! or Predict

Adjuvant! online



How to use Adjuvant! Online

- **Introduction**
- Examples
- Discussion
- Conclusions

Adjuvant! Online

- Adjuvant! Online tools
- Professionals and patients with early cancer
- Discuss the risks and benefits of getting additional therapy after surgery.

Welcome to NewAdjuvant.com

At this time this site is being modified and during this process should not be used for clinical decision making.

Access to Adjuvant! Online is temporarily disabled while we update the tools to reflect the most recent information. Updating Adjuvant! has been a more complex and slower task than planned and it is not yet ready.
During this period other similar tools have also evolved. An updated version of the tool Predict has just become available. This tool has some of the features that the Adjuvant! will soon have. http://www.predict.nhs.uk/predict.html is the web address of Predict.
We encourage you to use Predict and similar tools. You should know that Adjuvant! and Predict teams are completely independent and we have no agreements, financial or otherwise.
If you use that tool, or other similar tools, we encourage you to read their associated documentation as all tools are based on assumptions, some of which might be debated.

http://www.newadjuvant.com/

Adjuvant! Online

- A version of Adjuvant! Online that will include HER2 status and the potential benefit of trastuzumab is in development

- Information about the efficacy of different therapy options are derived from Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analyses in order to provide estimates of reduction in risk at 10 years of breast cancer related death or relapse for selected treatments

The basic format of an early version of Adjuvant! was described by Ravdin
Ravdin, Siminoff, Davis, et al. JCO 2001;19(4):980-991

How to use Adjuvant! Online: introduction

Adjuvant! online provides estimates:

➔ Of the risk of negative outcome (cancer related mortality or relapse) without systemic adjuvant therapy

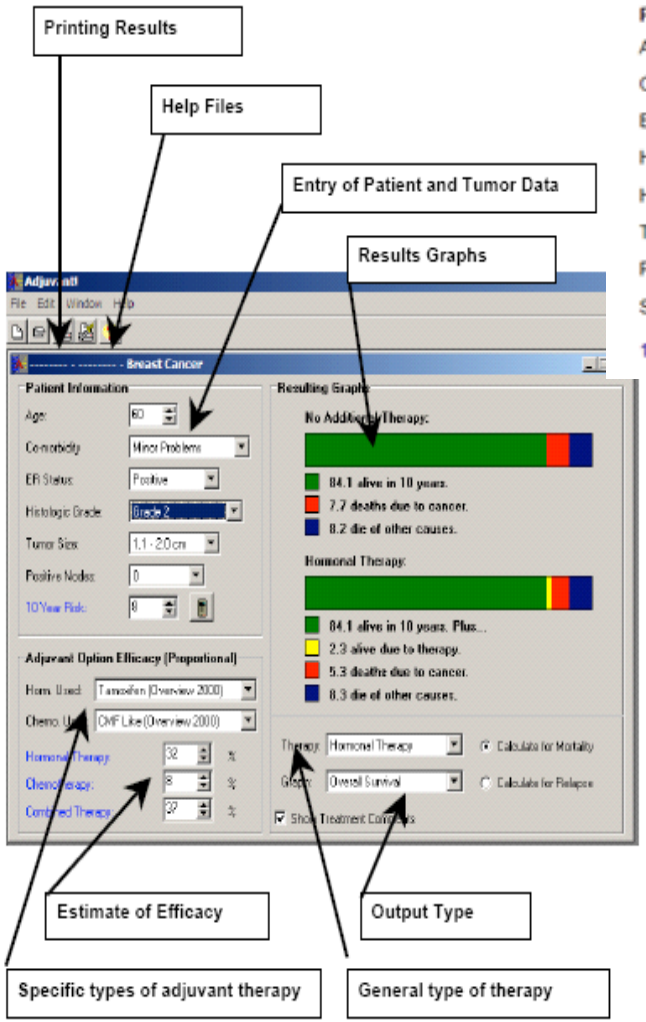
➔ Of the reduction of these risks afforded by therapy

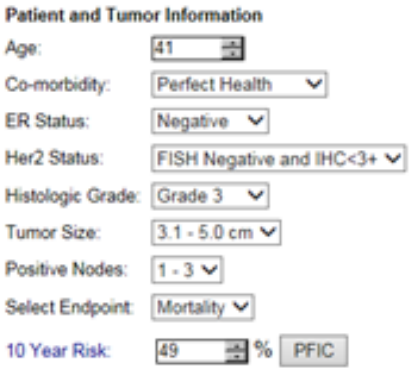
Epply this effect to the baseline risk

-direct comparisons can be made of the estimated risks of mortality or relapse between treatments and with no treatment.

How to use Adjuvant! Online: introduction

Entering patient, tumor and treatment related information





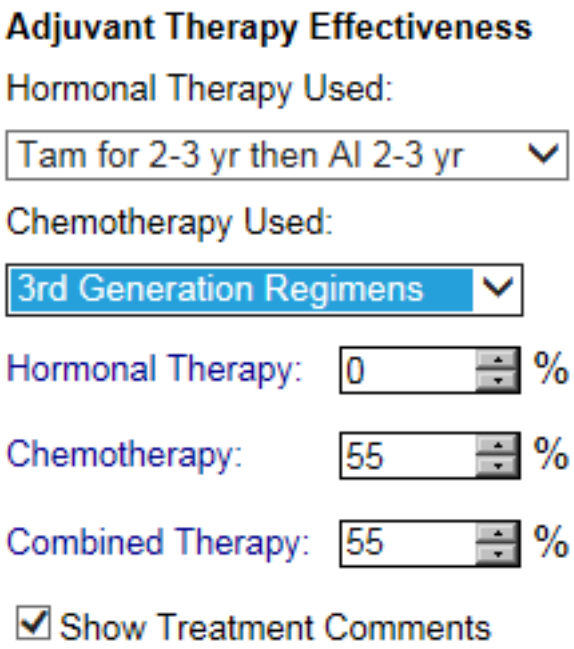
- Age
- Tumor size
- Nodal involvement
- Histologic grade

- Provides an estimate of the baseline risk of mortality or relapse for patients without adjuvant therapy.
- Results may be displayed in graphical form

ESTRO School

How to use Adjuvant! Online: introduction

Effectiveness estimate from a given adjuvant therapy.



In blue: the estimates produced by the program

5 preset selections for adjuvant hormonal therapy:

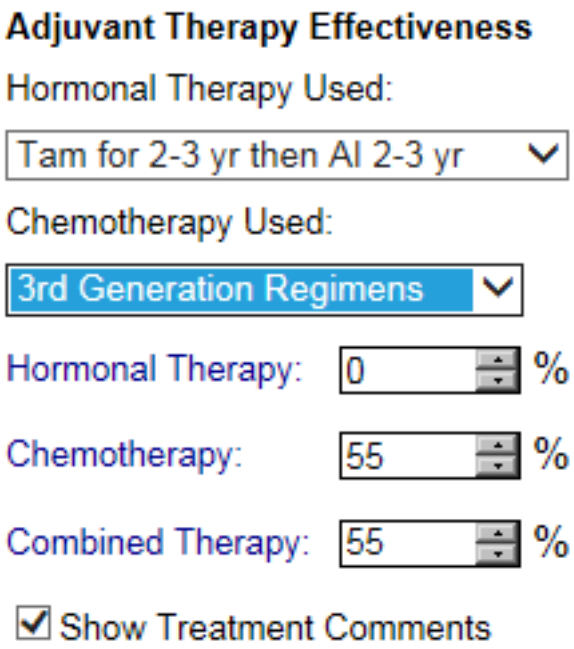
- Tamoxifen (Overview 2000)
- Aromatase Inhibitor for 5 years
- Tam for 2-3 yr then AI 2-3 yr
- Ovarian Ablation
- Ov.Abl. + Tam. (or other horm.)

9 preset selections for adjuvant chemotherapy:

- CMF Like (Overview 2000)
- Anthra. (Overview 2000)
- 1st Generation Regimens
  - CA * 4, CMF, FE(50)*6
- 2nd Generation Regimens
  - Anthra.>4cycles >2 agents
  - CA*4 then T*4 (q3w)
- 3rd Generation Regimens
- Adjusted By User

How to use Adjuvant! Online: introduction

Effectiveness estimate from a given adjuvant therapy.



In blue: the estimates produced by the program

5 preset selections for adjuvant hormonal therapy:

- Tamoxifen (Overview 2000)
- Aromatase Inhibitor for 5 years
- Tam for 2-3 yr then AI 2-3 yr
- Ovarian Ablation
- Ov.Abl. + Tam. (or other horm.)

9 preset selections for adjuvant chemotherapy:

- CMF Like (Overview 2000)
- Anthra. (Overview 2000)
- 1st Generation Regimens
  - CA * 4, CMF, FE(50)*6
- 2nd Generation Regimens
  - Anthra.>4cycles >2 agents
  - CA*4 then T*4 (q3w)
- 3rd Generation Regimens
- Adjusted By User

ESTRO School

How to use Adjuvant! Online

- Introduction
- **Examples**
- Discussion
- Conclusions

How to use Adjuvant! Online: examples

Log In to Use Adjuvant!

Please enter your registered email address and password below.

Email:

Password:

Login

Why do we require a registered email and password? Primarily, the reason is to ensure the information on this site is used by well trained and informed personnel.

How to use Adjuvant! Online: examples

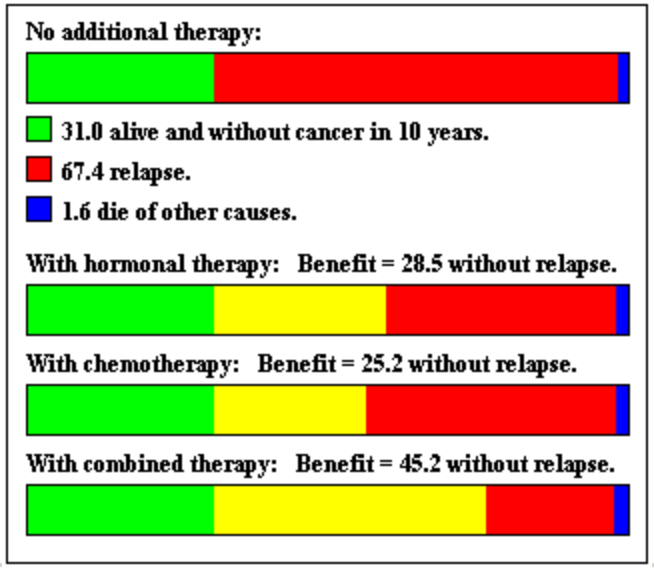
RELAPSE

Age 50, perfect health

ER: positive, tumorgrade III, tumorsize 2.1-3.0 cm, positive nodes 1-3

Horm used: tam -> AI

Chemo used: 3nd regimen



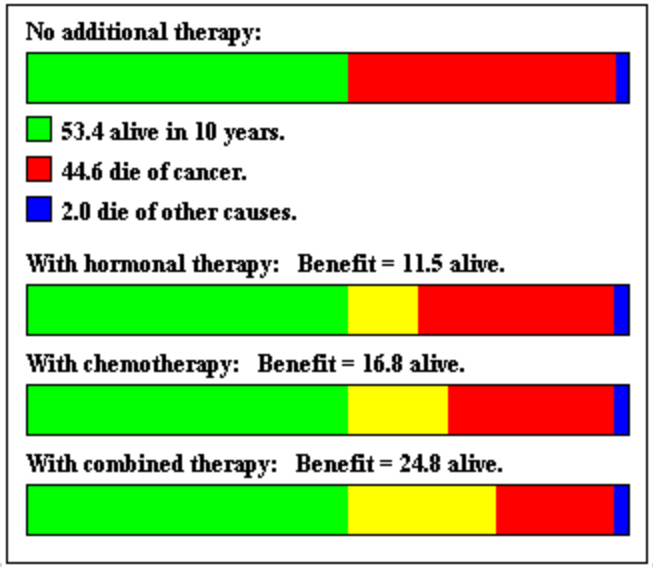
SURVIVAL

Age 50, perfect health

ER: positive, tumorgrade III, tumorsize 2.1-3.0 cm, positive nodes 1-3

Horm used: tam -> AI

Chemo used: 3nd regimen



ESTRO School

How to use Adjuvant! Online: examples

PROGNOSTIC FACTORS & SURVIVAL

pT2G2N0 **50y, ER+/PR+/HER2-** **pT2G3N1**

No Additional Therapy

82 out of 100 women are alive in 10 years
16 out of 100 women die due to breast cancer
2 out of 100 women die of other causes

Hormonal Therapy:

5 out of 100 women are alive because of therapy

Chemotherapy:

7 out of 100 women are alive because of therapy

Combined Therapy:

10 out of 100 women are alive because of therapy

No Additional Therapy

56 out of 100 women are alive in 10 years
42 out of 100 women die due to breast cancer
2 out of 100 women die of other causes

Hormonal Therapy:

11 out of 100 women are alive because of therapy

Chemotherapy:

16 out of 100 women are alive because of therapy

Combined Therapy:

23 out of 100 women are alive because of therapy

ESTRO School

How to use Adjuvant! Online

- Introduction
- Examples
- **Discussion**
- Conclusions

How to use Adjuvant! Online: discussion

Controversies and questions:

Prognostic estimates are absolutely precise? No, and they will never be …

1. Number of events needed to measure with great precision ➔ estimates.
2. Precision of staging changes with time: sentinel node biopsy; CT scanning and other staging techniques.
3. Improvements in local therapy: chest wall irradiation post mastectomy node positive patients may improve survival ➔ cause of drift in the survival statistics for patients with a given pathological stage.
4. Improvement of salvage therapy ➔ 10 year mortality rates will fall even if adjuvant therapy becomes no more effective.

… but:

- Numerical estimates are better then using terms like low, moderate, and high risk that are vague.
- The data is robust enough to give some meaning to the terms low, moderate and high risk.
- Staging, local therapy, and salvage therapy are changing, but not yet in so revolutionary way that makes outcome estimates based on cases from the late 1980's and 1990's irrelevant.

How to use Adjuvant! Online: discussion

Controversies and questions:

Prognostic estimates are absolutely precise? No, and they will never be …

1. Number of events needed to measure with great precision ➔ estimates.
2. Precision of staging changes with time: sentinel node biopsy; CT scanning and other staging techniques.
3. Improvements in local therapy: chest wall irradiation post mastectomy node positive patients may improve survival ➔ cause of drift in the survival statistics for patients with a given pathological stage.
4. Improvement of salvage therapy ➔ 10 year mortality rates will fall even if adjuvant therapy becomes no more effective.

… but:

- Numerical estimates are better then using terms like low, moderate, and high risk that are vague.
- The data is robust enough to give some meaning to the terms low, moderate and high risk.
- Staging, local therapy, and salvage therapy are changing, but not yet in so revolutionary way that makes outcome estimates based on cases from the late 1980's and 1990's irrelevant.

How to use Adjuvant! Online: discussion

- Estimates are based on older data ➔ updates required on regular base.
- It should be noted that the user does not need to accept the preset values, but can enter their own estimates.

How to use Adjuvant! Online

- Introduction
- Evaluation
- Discussion
- **Conclusions**

How to use Adjuvant! Online: conclusions

- Adjuvant! Online is intended as a practical and educational tool for health care professionals.
- It is not designed to be used by patients directly.
- Outcome estimates are estimates and projections.
- Information about toxicity can be found in the help files.
- Supplementary illustrations are available.
- Print a copy of the graphs ➔ supplement in discussion.

How to use Adjuvant! Online: conclusions

- Adjuvant! Online is for sure a handy tool to objectivise our “educated guesses” for:
  - Overall survival.
  - Disease free survival.
  - Breast cancer related mortality.
  - The influence of adjuvant systemic treatments.
- But it does not show the influence and interaction of optimising loco regional treatments.

PREDICT http://www.predict.nhs.uk

predict

Google™ Custom Search Search

Home
Information for Patients and Public
Information for Professionals
PREDICT
What's New
FAQs
Disclaimer
Acknowledgements
Press
Publications
Contact
Privacy Policy

PREDICT is a mathematical model, accessed by the internet and has been designed for patients and doctors to help them decide on the ideal course of treatment following breast cancer surgery. It is the first model of this type to include tumour HER2 and KI67 status.

The **PREDICT** website only needs to know about the histopathology of your cancer. No personal information is collected or stored.

PREDICT tool

Information for Patients and Public

Information for Professionals

Download our information leaflet (pdf, 305kb)

© Eastern Cancer Registry and Information Centre and Cambridge University Contact: info@predict.nhs.uk

ESTRO School

Predict

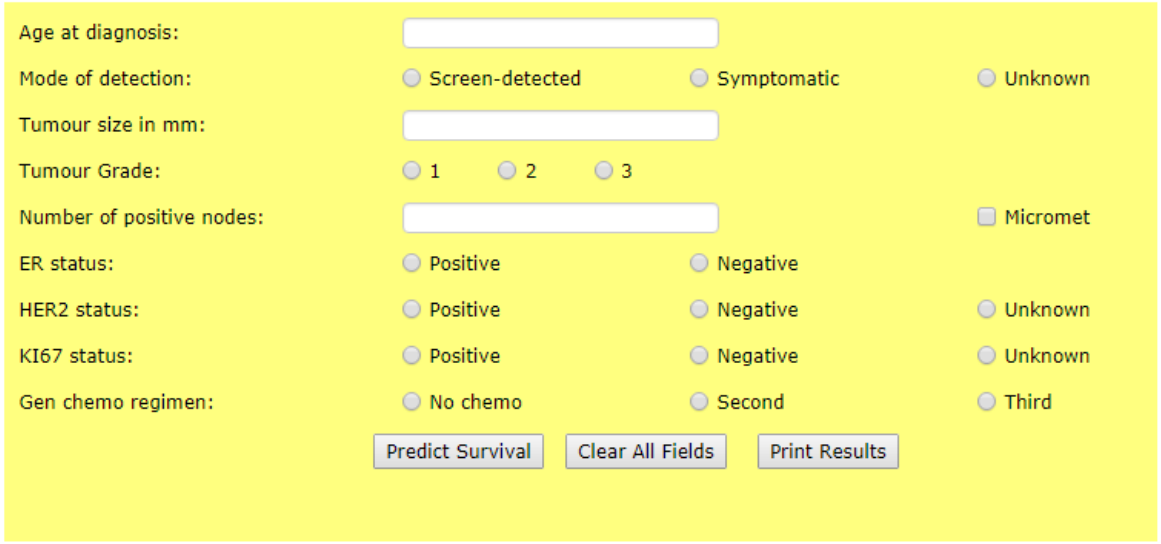
- Statistical model
- Accessed by the internet
- Designed for patients and doctors to help them decide on the ideal course of treatment following breast cancer surgery.
- It is the first model of this type to include tumor HER2 and KI67 status.

http://www.predict.nhs.uk/

ESTRO School

PREDICT

The **PREDICT** website only needs to know about the histopatology of your cancer.



PREDICT has been developed by a partnership between The Breast Unit at Cambridge University NHS Hospital, the University of Cambridge Department of Oncology and the NHS Eastern Cancer Registry and Information Centre (ECRIC).

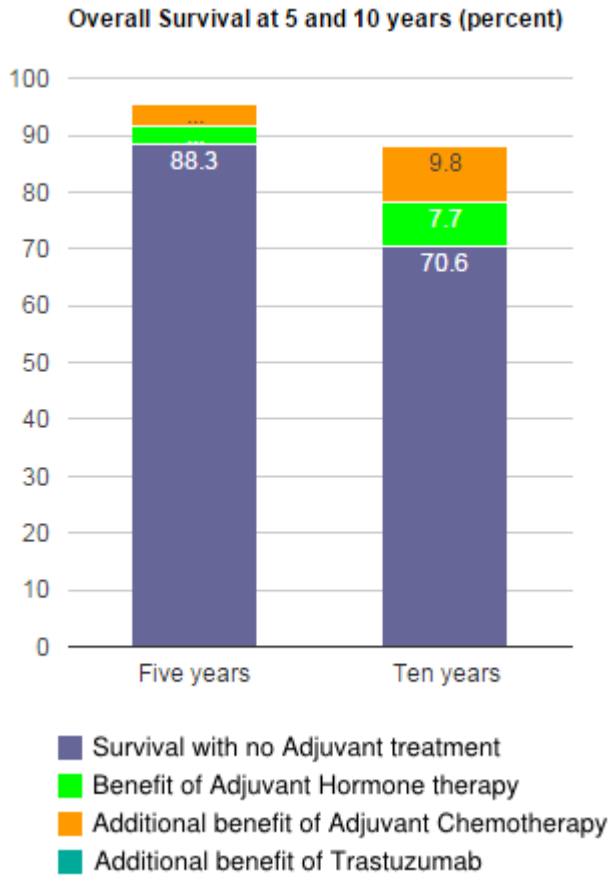
Wishart GC et al, Breast Cancer research 2010
Wishart GC et al, EJSO 2011
Wishart GC et al, Britsh J Cancer 2012

ESTRO School

PREDICT Tool: Breast Cancer Survival; Input

Age at diagnosis:	45		
Mode of detection:	◉ Screen-detected	○ Symptomatic	○ Unknown
Tumour size in mm:	25 (blank if unknown)		
Tumour Grade:	○ 1 ○ 2 ◉ 3	○ Unknown	
Number of positive nodes:	1 (blank if unknown)		
ER status:	◉ Positive	○ Negative	
HER2 status:	○ Positive	◉ Negative	○ Unknown
KI67 status:	○ Positive	○ Negative	◉ Unknown
Gen chemo regimen:	○ No chemo	○ Second	◉ Third

Predict Survival | Clear All Fields | Print Results



PREDICT Tool: Breast Cancer Survival; Results

Five year survival

88 out of 100 women are alive at 5 years with no adjuvant therapy after surgery
An extra 3 out of 100 women treated are alive because of hormone therapy
An extra 7 out of 100 women treated are alive because of hormone therapy & chemotherapy

Ten year survival

71 out of 100 women are alive at 10 years with no adjuvant therapy after surgery
An extra 8 out of 100 women treated are alive because of hormone therapy
An extra 17 out of 100 women treated are alive because of hormone therapy & chemotherapy

To view the numbers in bars hover pointer over each bar-segment
(Or tap segment if using a mobile device)

ESTRO School

Gene expression profiling

Gene expression profiling

Advances in molecular medicine have substantially improved the accuracy of gene-expression profiling of breast tumors, resulting in improvements in the ability to predict a patient's risk of breast cancer recurrence and likely response to therapy

Gene expression profiles

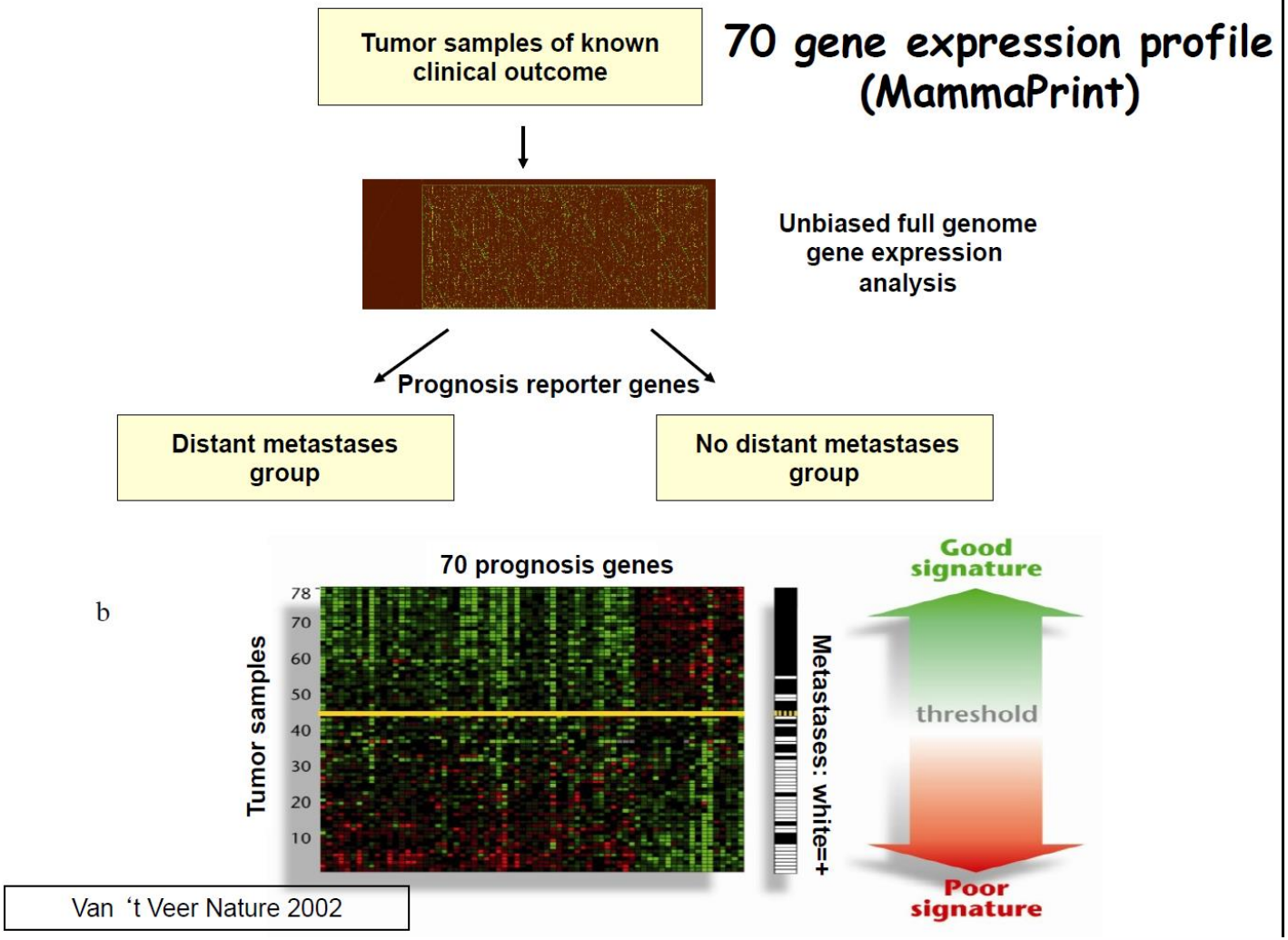
Gene expression profiles: Mammaprint™ or Oncotype Dx Recurrence Score™

Patients with intermediate risk

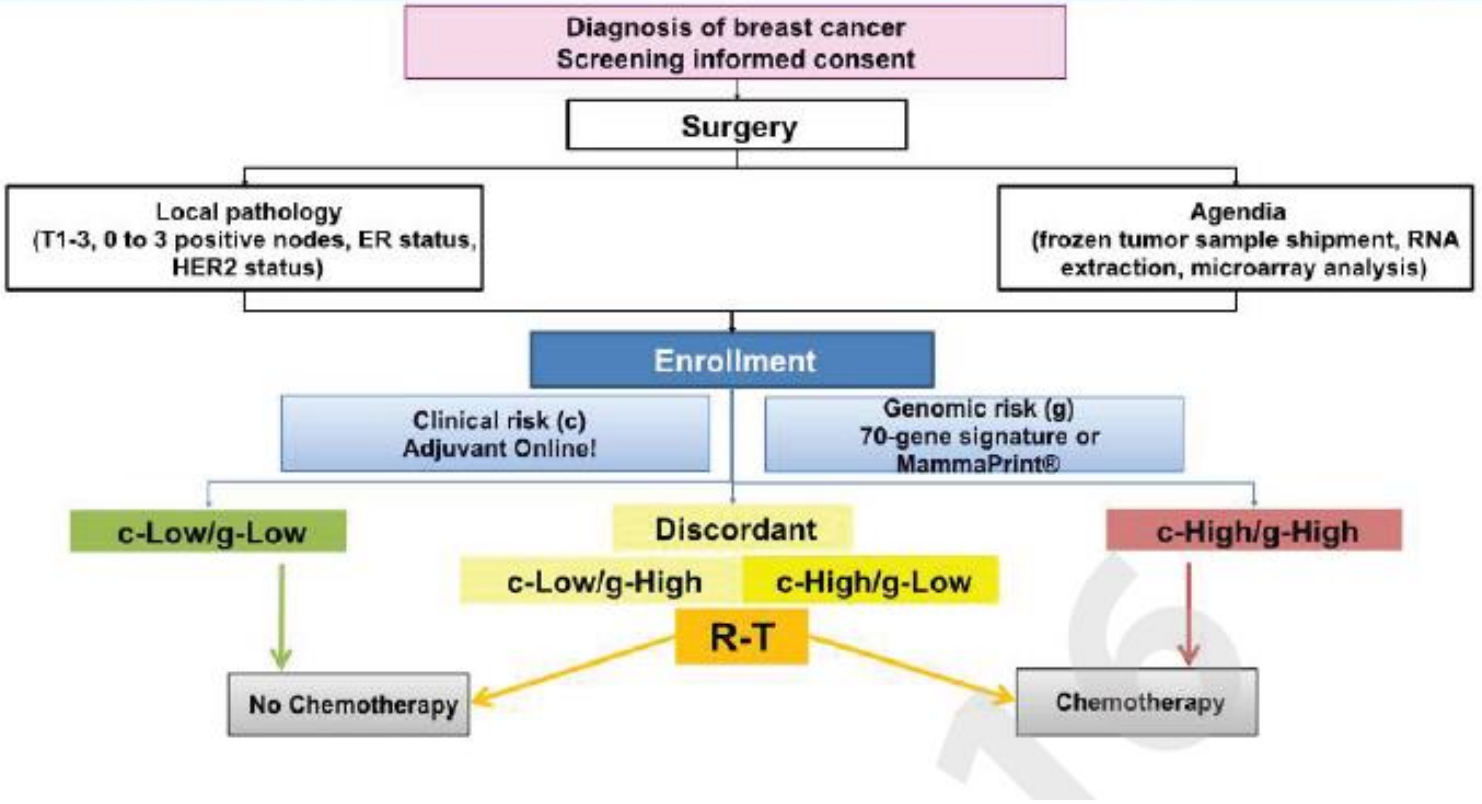
- more accurately identifying patients who will gain the most benefit
- to gain additional prognostic and/or predictive information to complement pathology assessment
- to predict response to adjuvant chemotherapy, in particular in patients with ER-positive early breast cancer

The accurate integration of these new genomic tools into current clinical practice and their added value is evaluated in two large prospective phase III trials (MINDACT and TAILORx).

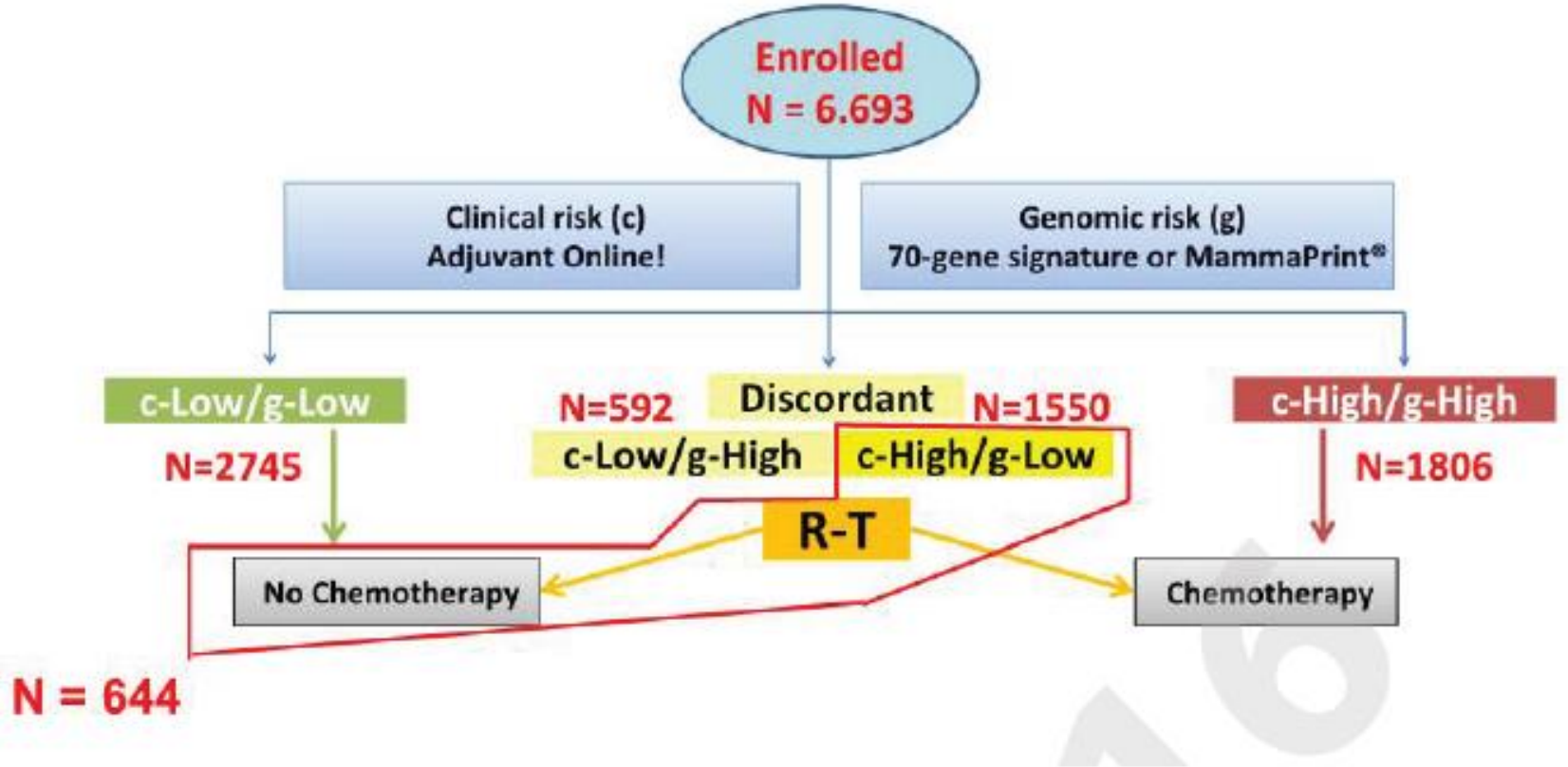
Mammaprint 70 gene expression profile



The MINDACT study design

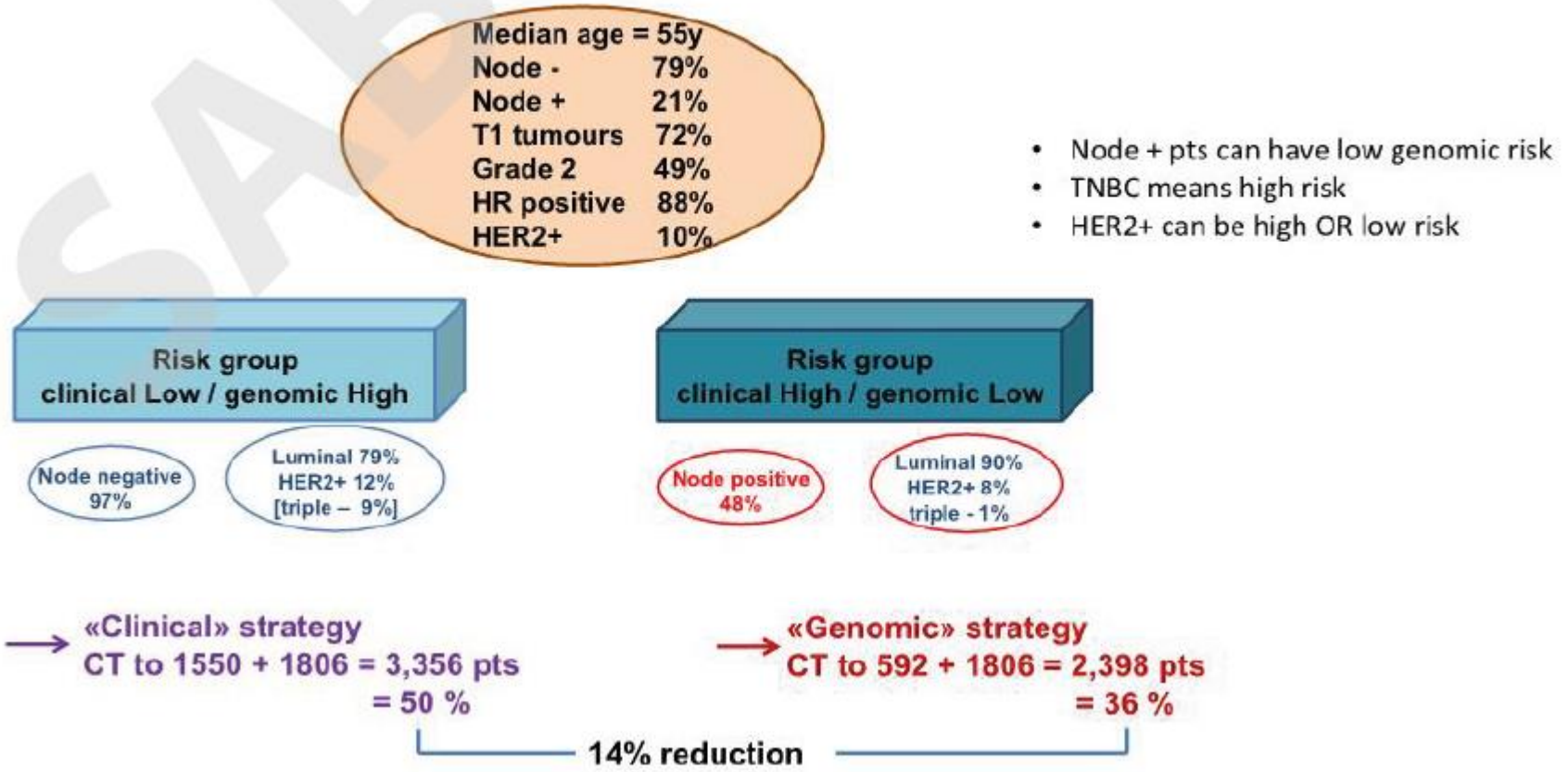


Mindact NEJM 2016
SABCS 2016



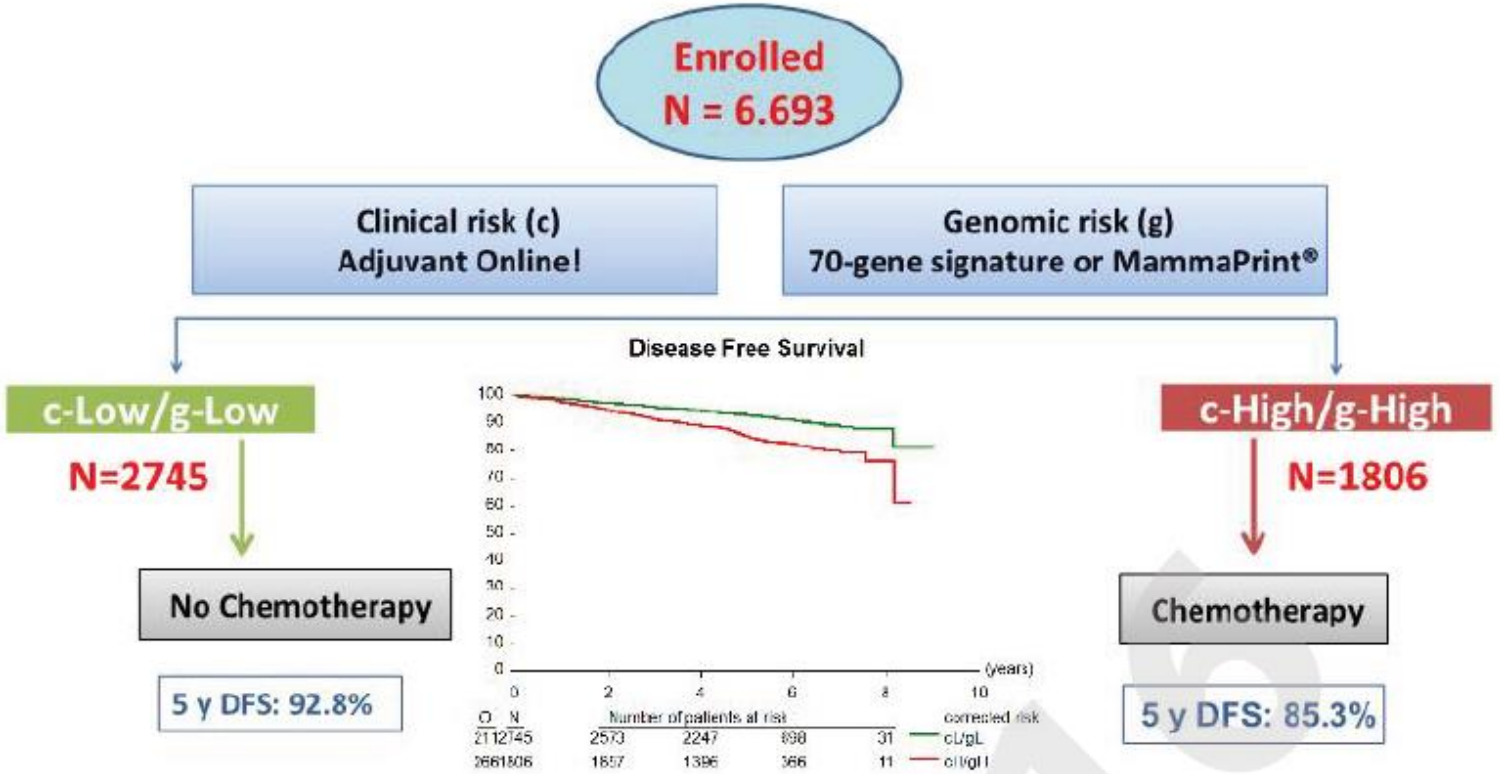
Mindact NEJM 2016 SABCS 2016

Results from MINDACT



Mindact NEJM 2016 SABCS 2016

The primary analysis population



Mindact NEJM 2016 SABCS 2016

ESTRO School

Clinical outcome 5y median FU

The primary analysis population

Discordant risks

c-Low /g-High

c-High/g-Low

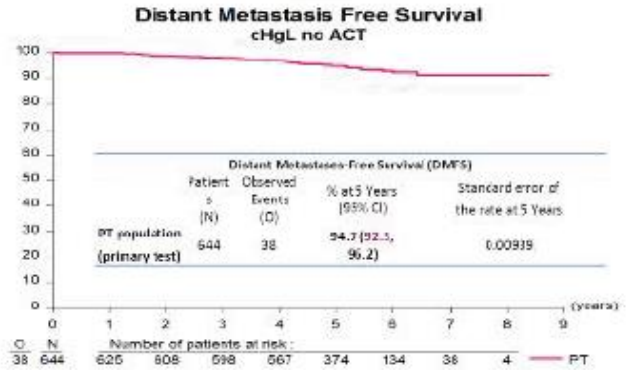
RANDOMIZATION

No chemotherapy N = 748

CT

No change in risk post enrollement and no CT received N = 644

The primary statistical test (DMFS at 5Y)



Null Hypothesis: set at 92%

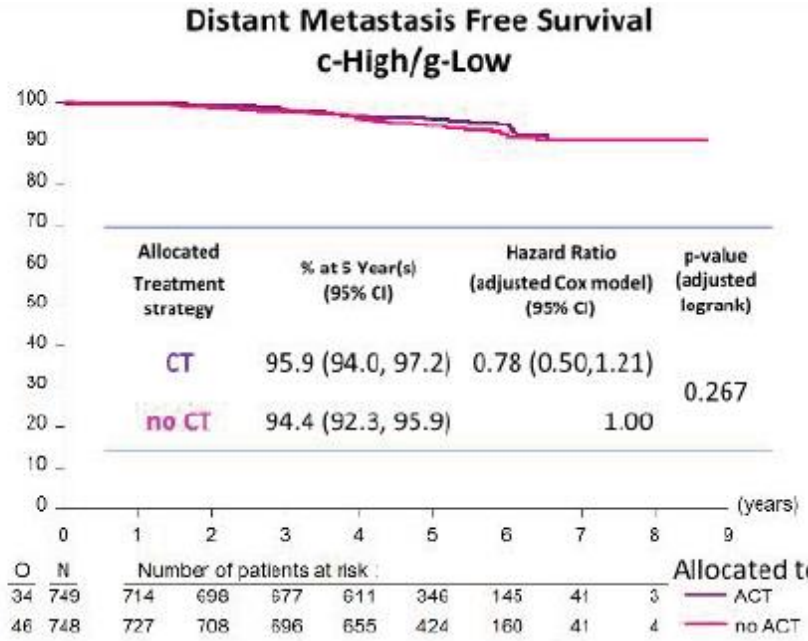
Observed 5Y DMFS = 94.7%

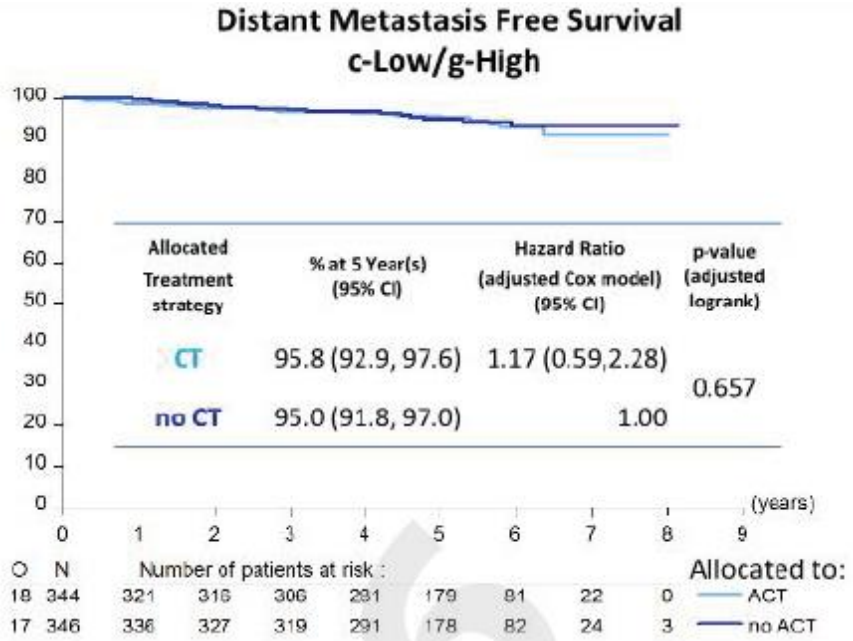
95% CI ≈ 92.5 – 96.2% excludes 92% !!!

Mindact NEJM 2016 SABCS 2016

ESTRO School

Efficacy CT vs no CT (discordant risk groups)





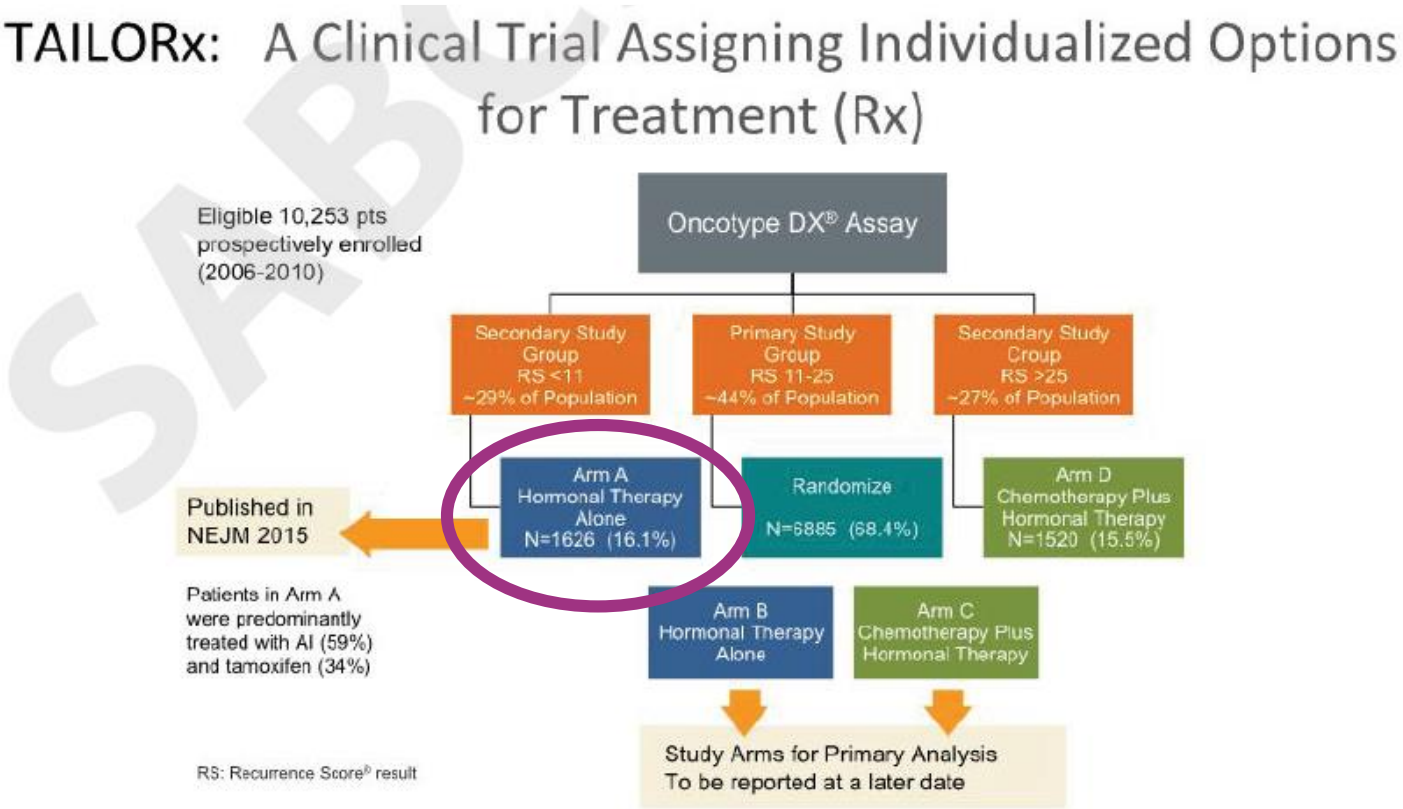
Mindact NEJM 2016 SABCS 2016

Recurrence Score

Early-Stage Invasive Breast Cancer Recurrence Score Result

Recurrence Score Result	What the Score Means
Lower than 18	The breast cancer has a low risk of recurrence with hormonal therapy. The benefit of chemotherapy is likely to be small and will not outweigh the risks of side effects.
Between 18 and 30	The breast cancer has an intermediate risk of recurrence with hormonal therapy. It is unclear whether the benefits of chemotherapy outweigh the risks of side effects.
Greater than 30	The breast cancer has a high risk of recurrence with hormonal therapy, and the benefits of chemotherapy are likely to be greater than the risks of side effects.

Design TAILORx

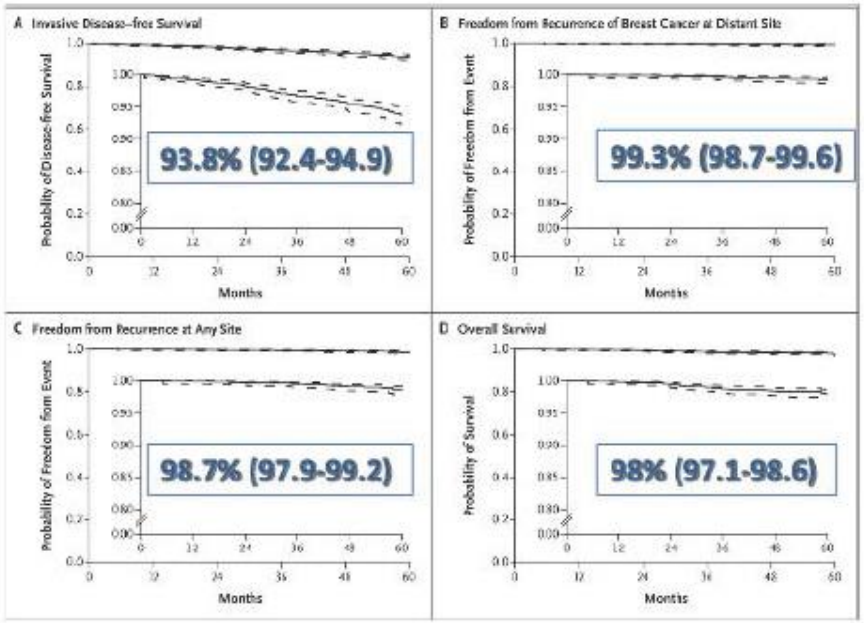


Sparano et al. *N Engl J Med*. 2015.

SABCS 2016

ESTRO School

Results from TAILORx and Conclusions



- Genomic Assays are prognostic of a group of patients with very low risk of recurrence
- In this group of patients the addition of chemotherapy is unlikely to be of benefit.

SABCS 2016

ESTRO School

Take home message

Classical prognostic factors of breast cancer are the patient's age and performance status, in addition to tumor related factors such as tumor size, lymph node status, hormone receptor status, HER2 status, tumor grade and proliferation index

Adjuvant! and Predict are validated for prediction prognosis of the individual patient and predictive for absolute risk reduction because of adjuvant treatment

If there is doubt about the indication of adjuvant chemotherapy based on the classical prognostic factors, a gene expression profile may be used in addition to the classic prognostic factors (eg. in patients> 35 years with pT1-2N0 ER positive and HER2 negative invasive ductal breast cancer)

Gene expression profiles have prognostic significance in addition to the known classical clinical and pathological factors. They can not replace the classical clinical and pathological factors.

Questions??

How to use Adjuvant! Online: introduction

Using prognostic factors to modify the 10-y mortality estimate.

Adjuvant! allows you to take into account prognostic information and to modify Adjuvant!'s prognostic estimate for outcome (based on tumor size, number of nodes, histologic grade, and estrogen receptor status) in 3 basic ways.

1. Using a prognostic calculator to adjust for impact of additional prognostic information ➔ requires estimate of the prevalence of a positive test and a relative risk estimate.
2. By directly entering a prognostic estimate from a literature source into the 10 Year Risk box.
3. By simply toggling the number in the 10 Year Risk Box until it seems about right *(guessing)*.

How to use Adjuvant! Online: introduction

Using prognostic factors to modify the 10-y mortality estimate.

Adjuvant! allows you to take into account prognostic information and to modify Adjuvant!'s prognostic estimate for outcome (based on tumor size, number of nodes, histologic grade, and estrogen receptor status) in 3 basic ways.

1. Using a prognostic calculator to adjust for impact of additional prognostic information ➔ requires estimate of the prevalence of a positive test and a relative risk estimate.
2. By directly entering a prognostic estimate from a literature source into the 10 Year Risk box.
3. By simply toggling the number in the 10 Year Risk Box until it seems about right *(guessing)*.

How to use Adjuvant! Online: introduction

Using prognostic factors to modify the 10-y mortality estimate.

Adjuvant! allows you to take into account prognostic information and to modify Adjuvant!'s prognostic estimate for outcome (based on tumor size, number of nodes, histologic grade, and estrogen receptor status) in 3 basic ways.

1. Using a prognostic calculator to adjust for impact of additional prognostic information ➔ requires estimate of the prevalence of a positive test and a relative risk estimate.
2. By directly entering a prognostic estimate from a literature source into the 10 Year Risk box.
3. By simply toggling the number in the 10 Year Risk Box until it seems about right *(guessing)*.

How to use Adjuvant! Online: introduction

Using prognostic factors to modify the 10-y mortality estimate.

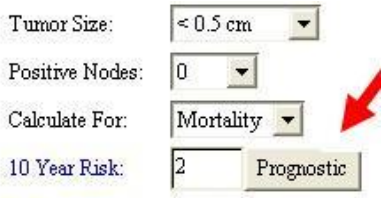
Adjuvant! allows you to take into account prognostic information and to modify Adjuvant!'s prognostic estimate for outcome (based on tumor size, number of nodes, histologic grade, and estrogen receptor status) in 3 basic ways.

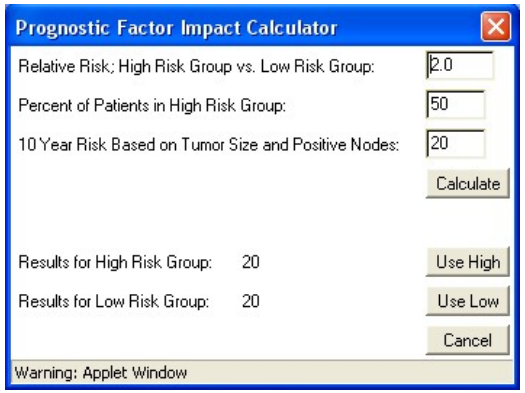
1. Using a prognostic calculator to adjust for impact of additional prognostic information ➔ requires estimate of the prevalence of a positive test and a relative risk estimate.
2. By directly entering a prognostic estimate from a literature source into the 10 Year Risk box.
3. By simply toggling the number in the 10 Year Risk Box until it seems about right *(guessing)*.

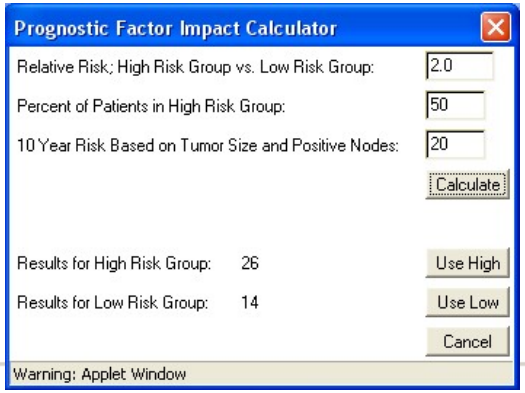
ESTRO School

How to use Adjuvant! Online: introduction

Using prognostic factors to modify the 10-y mortality estimate.







Using the Prognostic Factors Calculator

- Press "Prognostic" button to the right of the 10 yr Risk.
- The user enters:
  1. Relative risk of high risk vs low risk group.
  2. Percentage of patients in high risk group.
- Press calculate button ➔ results high & low risk group.
- Press appropriate button ➔ number in the "10 yr Risk Estimate" box on the main screen.

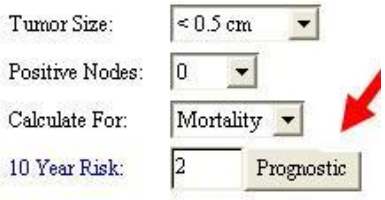
Note:

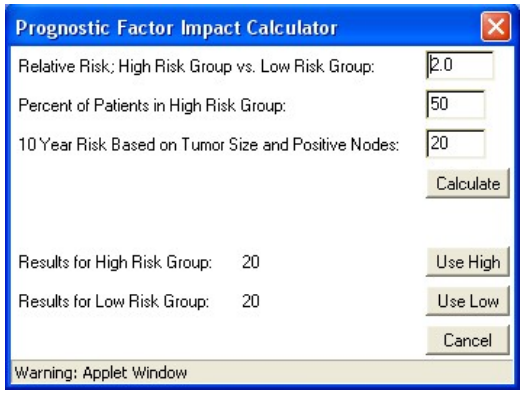
- Standard "10 year Risk Estimate" will be overridden.
- After changing values of grade, ER, size, nodes, or method of calculation ➔ reset to default ➔ repeat the above steps to customize the risk estimate again.

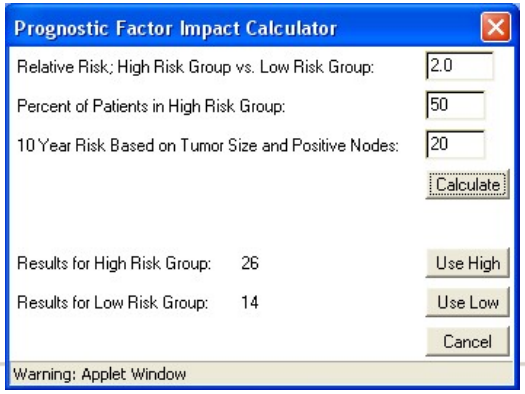
ESTRO School

How to use Adjuvant! Online: introduction

Using prognostic factors to modify the 10-y mortality estimate.







Using the Prognostic Factors Calculator

- Press "Prognostic" button to the right of the 10 yr Risk.
- The user enters:
  1. Relative risk of high risk vs low risk group.
  2. Percentage of patients in high risk group.
- Press calculate button ➔ results high & low risk group.
- Press appropriate button ➔ number in the "10 yr Risk Estimate" box on the main screen.

Note:

- Standard "10 year Risk Estimate" will be overridden.
- After changing values of grade, ER, size, nodes, or method of calculation ➔ reset to default ➔ repeat the above steps to customize the risk estimate again.

ESTRO School

Indications for neoadjuvant systemic treatment

B.Vriens

Medical oncologist

Catharina Hospital Eindhoven

The Netherlands

ESTRO Breast Cancer 2017

Timing of treatment

Indication for systemic therapy

Timing systemic treatment:

before or after surgery?

Neo-adjuvant/Primary chemotherapy (=NAC)

- Concept developed concurrently with adjuvant chemotherapy in the 1970s

- Neoadjuvant systemic treatment is an established part of the management of large, potentially operable, and **locally advanced breast cancers**
  - Converts a previously unresectable, locally advanced breast cancer to an operable tumor
- Has evolved since to use in operable breast tumours

Sequence of treatment primary breast cancer

Diagnosis and staging

↓

Surgical resection

↓

Radiotherapy

↓

Adjuvant systemic treatments

(chemotherapy, hormone therapy and/or targeted therapy)

Diagnosis and staging

↓

Neoadjuvant systemic treatments

(chemotherapy, hormone therapy and/or targeted therapy)

↓

Surgical resection

↓

Radiotherapy

↓

Adjuvant hormonal therapy

Neoadjuvant chemotherapy

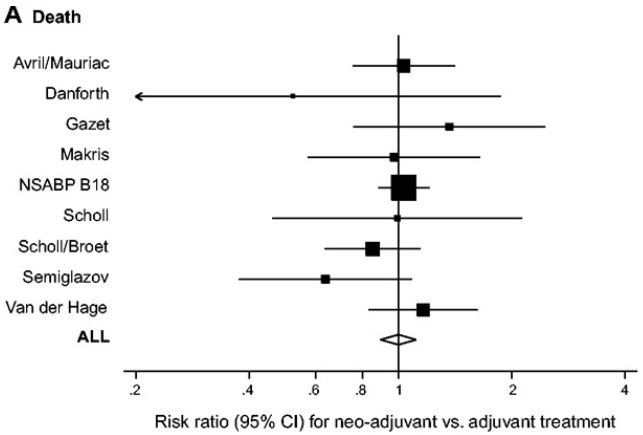
Why neoadjuvant chemotherapy

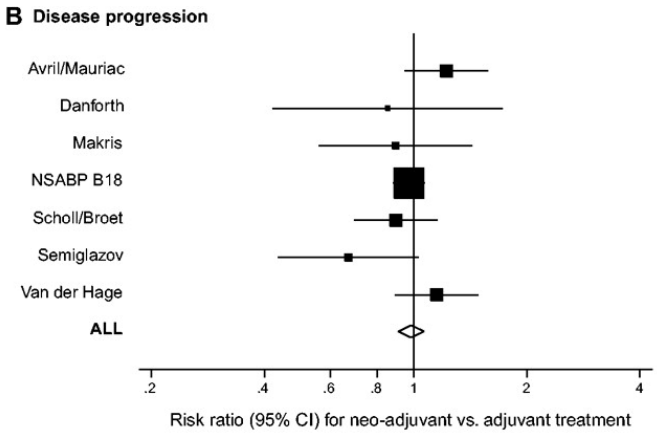
- Improve resectability
- Breast conserving surgery
- Nodal downstaging
- Improved cosmesis
- Adapt treatment to response
- *More time for genetic testing*
- *More time for patient to decide about type of breast surgery/reconstruction*

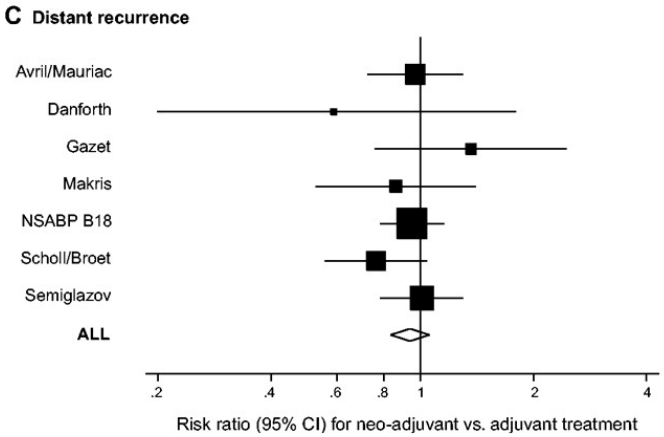
Adjuvant systemic therapy is a “blind” procedure: It is administered after the only opportunity for monitoring for effectiveness has been eliminated

G.N.Hortobagyi, SABCS 2012

Neoadjuvant vs. adjuvant chemotherapy: a meta-analysis







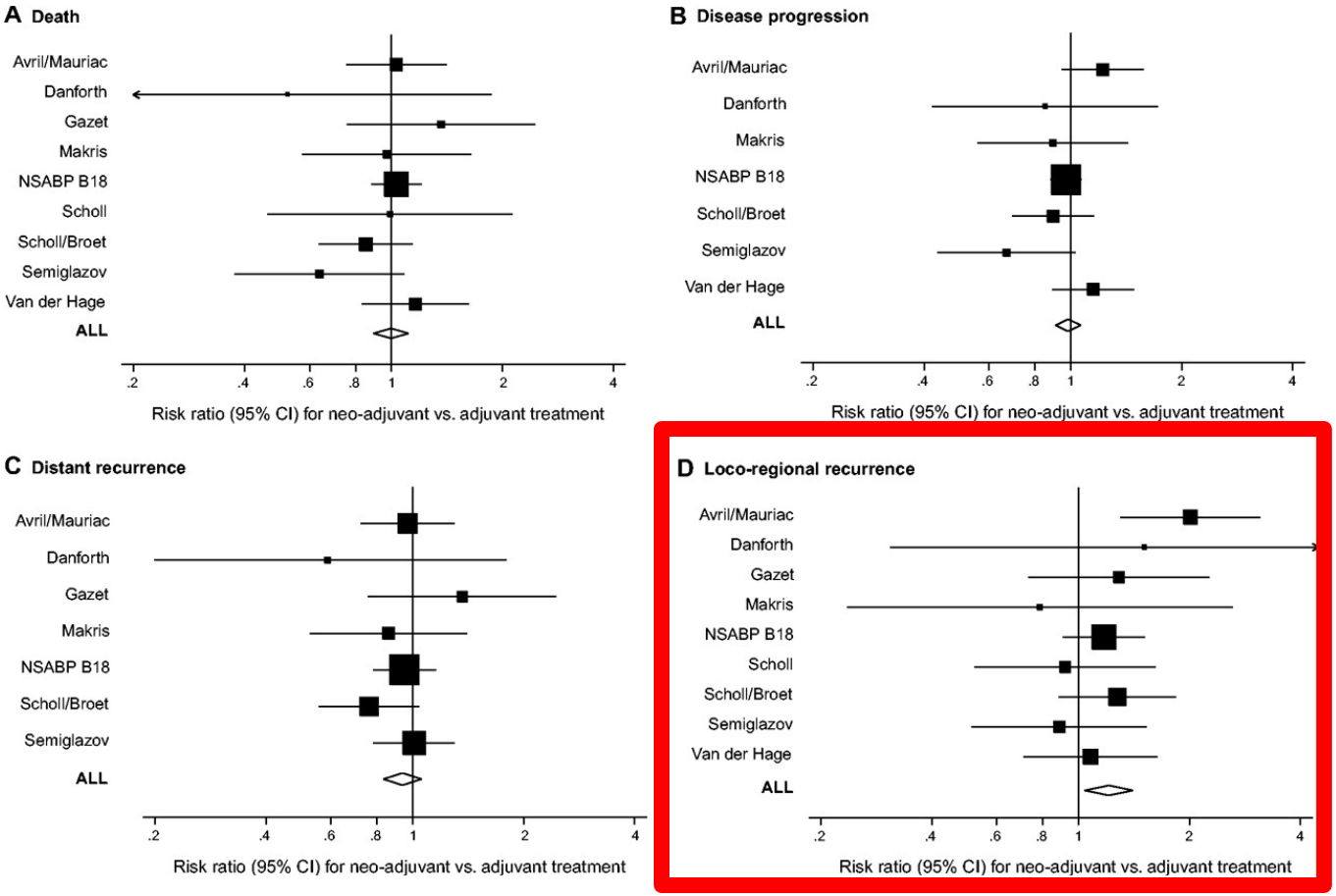
- Survival is <u>as good as</u> with adjuvant therapy
- Selection for neo adjuvant = adjuvant

Recommendations from an international expert panel.
Kaufmann et al. JCO April 20th 2006

Mauri, D. et al. J Natl Cancer Inst 2005;97:188-194
<9 phase III studies, Total +/- 4000 pt, T1-4N0-2>

ESTRO School

Neoadjuvant vs. adjuvant chemotherapy: a meta-analysis



Mauri, D. et al. J Natl Cancer Inst 2005;97:188-194

ESTRO School

The increase in relative risk of LRR in the meta-analysis is mainly due to 3 trials without surgery in case of cCR

Rel. risk of locoregional relapse in the 3 studies was 1.53 (1.17-2.00)

Cochrane review

No increase in local-regional recurrence rates if surgery is part of treatment (HR=1.112; 0.92 – 1.37)*

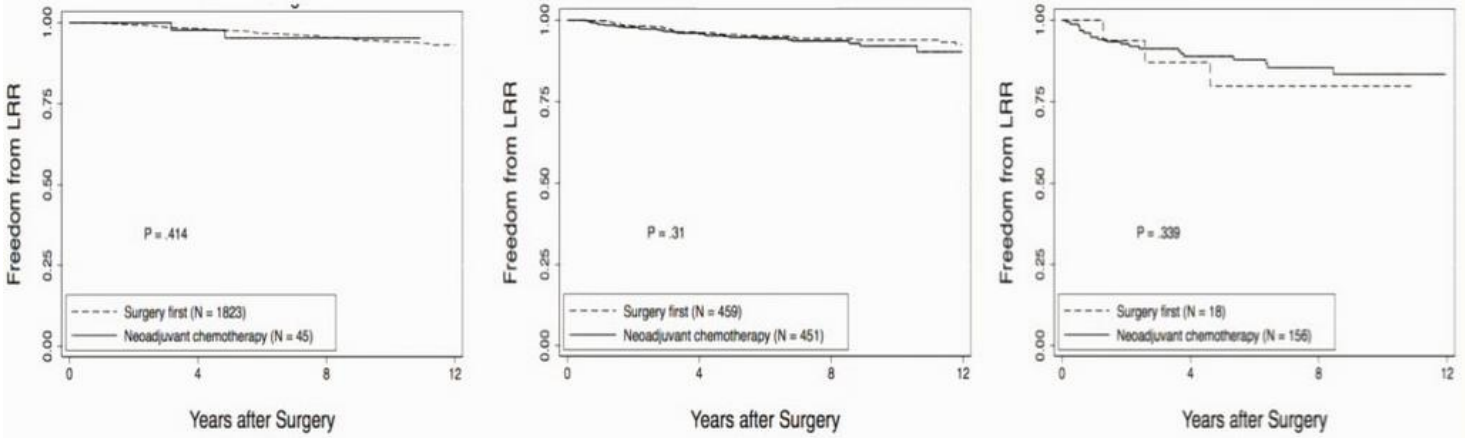
*vd Hage, Cochrane 2007

LRR-Free Survival rates

LRR-Free Survival Rates

- 1589 patients who underwent conservative surgery at MDACC
- 72% had initial surgery and 28% received neoadjuvant chemotherapy

Clinical Stage I	Clinical Stage II	Clinical Stage III



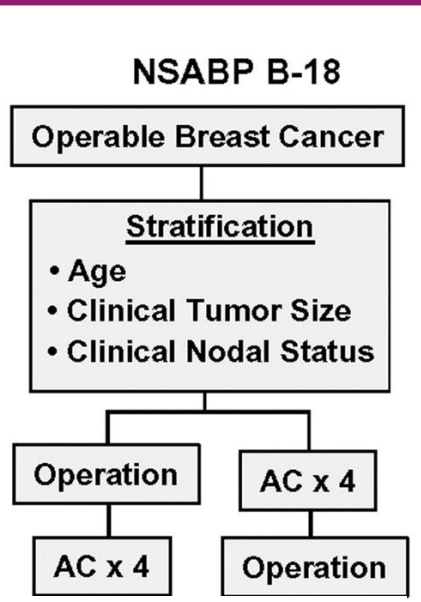
Conservative Surgery Achieved Without Higher Local Recurrence Rate
In Multivariate Model, Neoadjuvant Chemotherapy Was Not Associated With High Local Recurrence

Mittendorf E et al. Ann Surg 2013;257:173-179

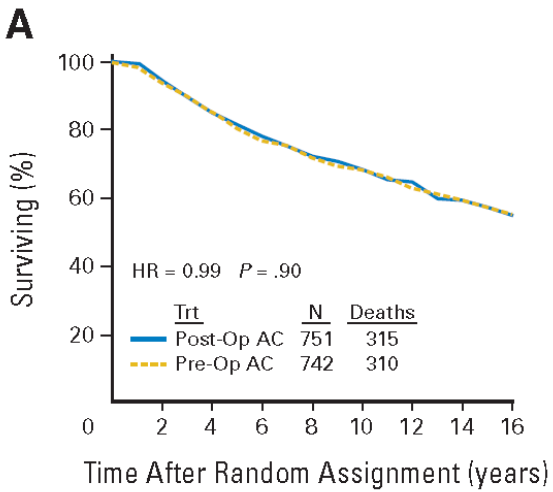
The ability to do less surgery after NAC does not seem to be associated with any risk for te patient

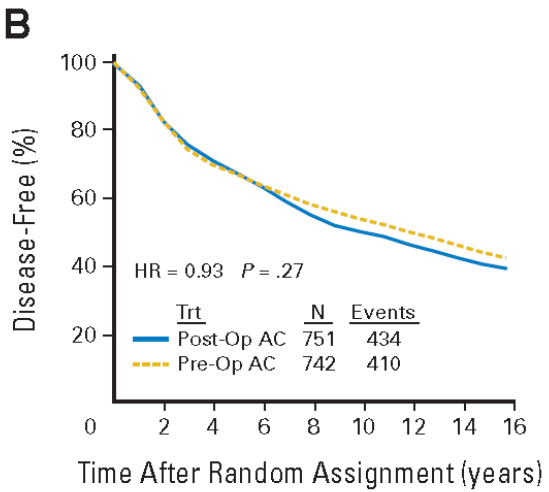
ESTRO School

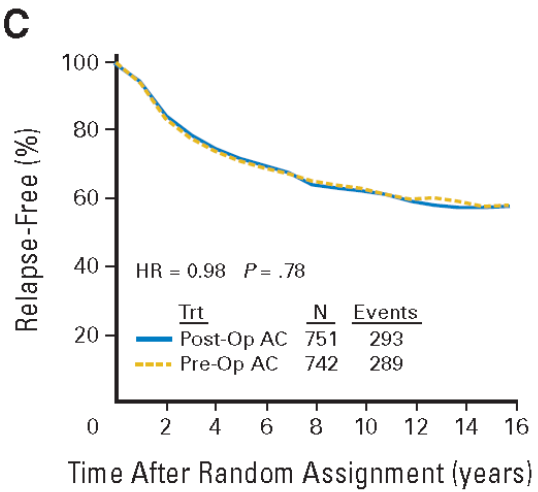
Neoadjuvant vs. adjuvant chemotherapy: OS, DFS and RFS



B-18



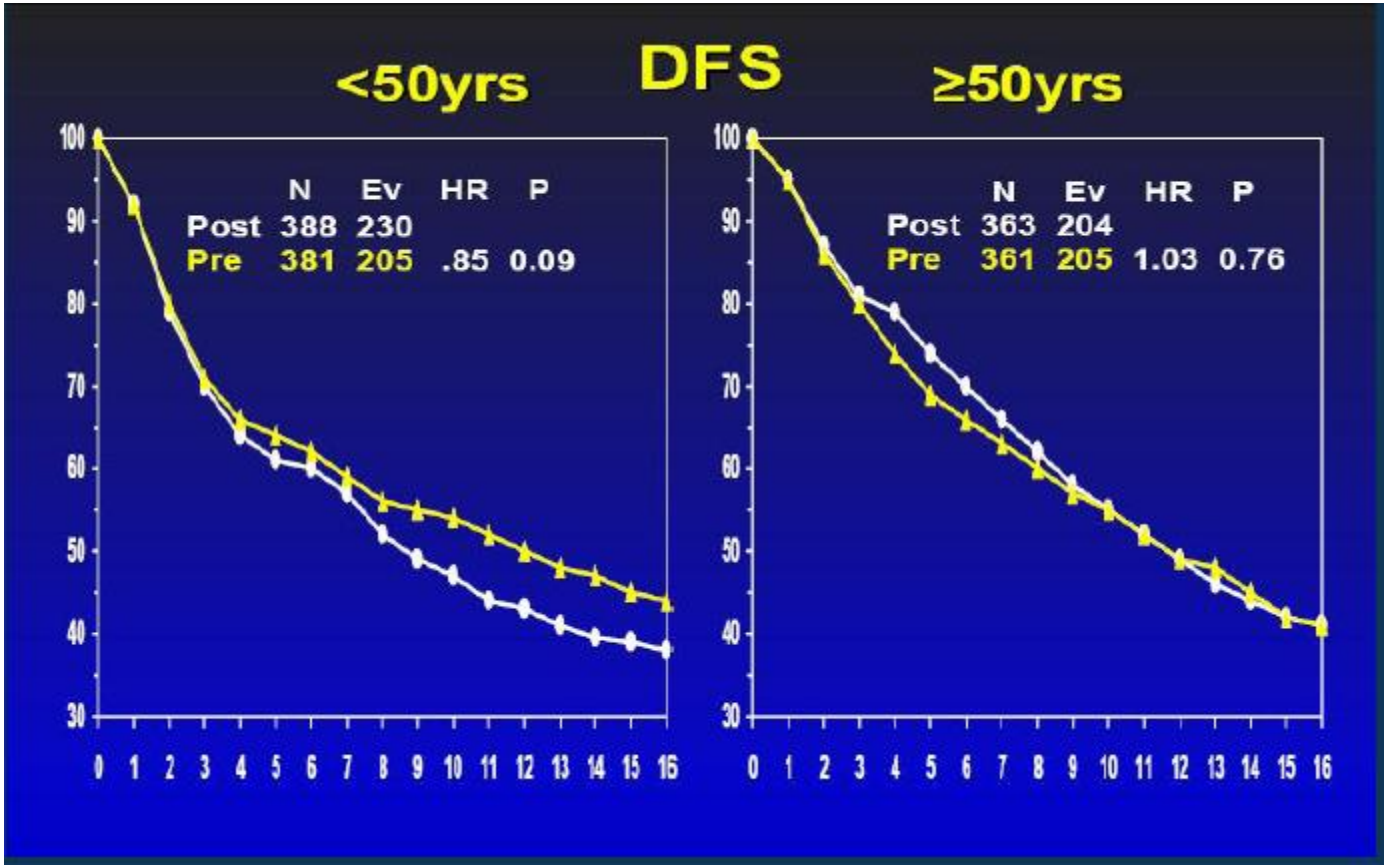




B-18, Wolmark 2008 JCO

ESTRO School

Neoadjuvant vs. adjuvant chemotherapy: DFS and age < 50 years



OS: HR=0.81, P=0.06

Trend in favor of neoadjuvant chemotherapy in DFS and OS for women less than 50y

B-18, Wolmark 2008 JCO

ESTRO School

Neoadjuvant chemotherapy
-Survival-

- Survival is as good as with adjuvant therapy
- Relation between:
  - cOR and overall survival??
  - pCR and disease free survival??
  - pCR and overall survival??
- Prognostic information??

Clinical response disease free / overall survival

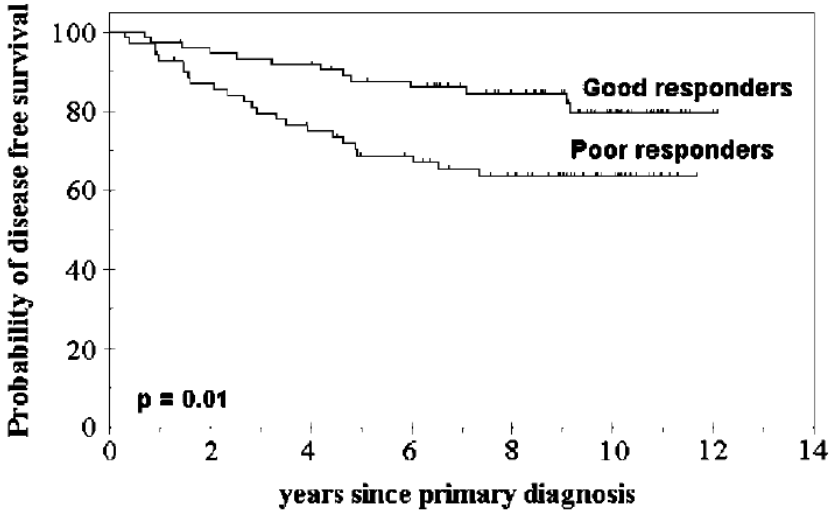
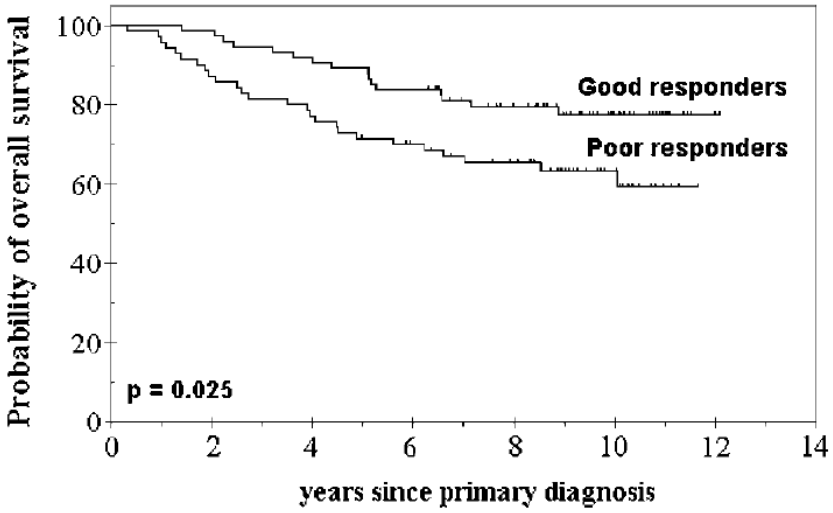


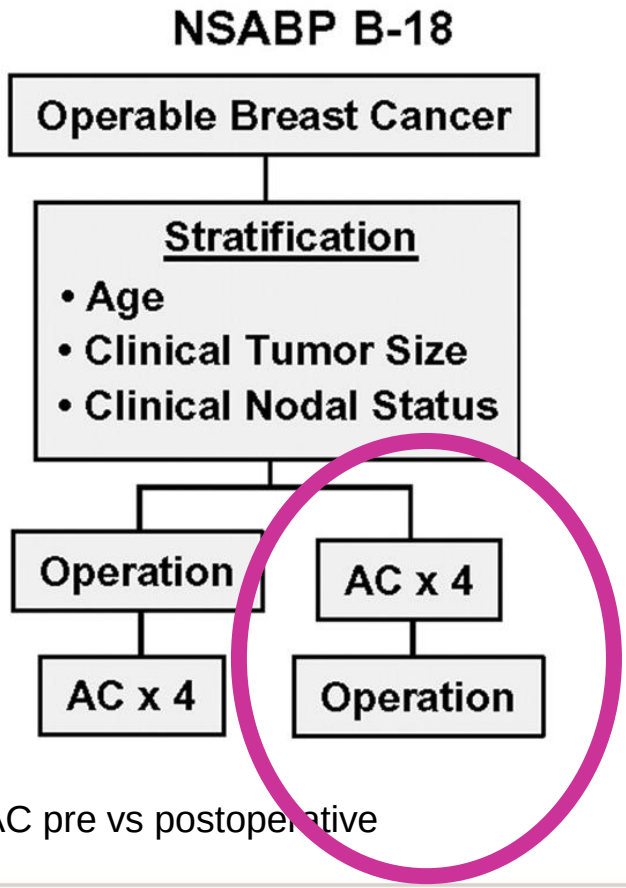
Figure 1. Disease-free survival of good and poor responders.



Cleator, 2005 Ann of Oncol

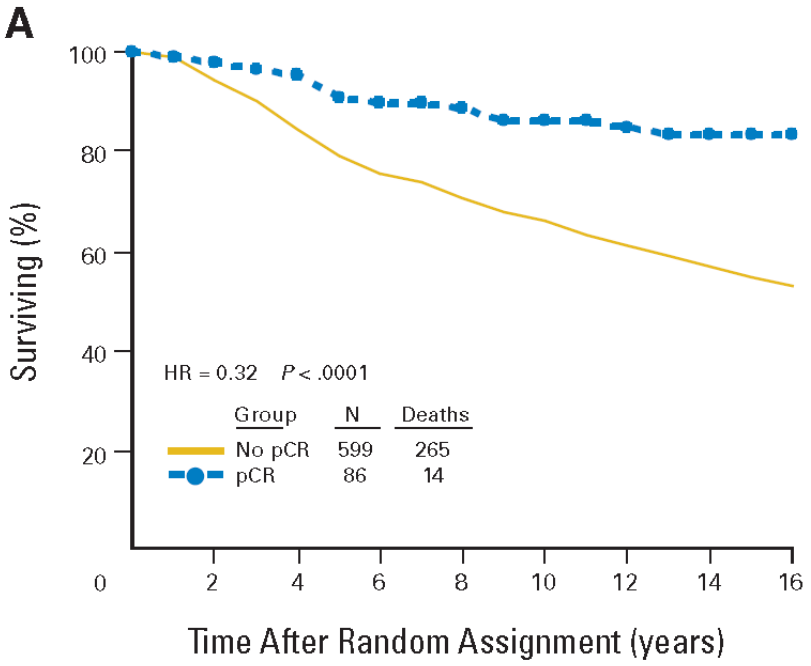
ESTRO School

pCR and disease-free / overall survival



B-18: AC pre vs postoperative

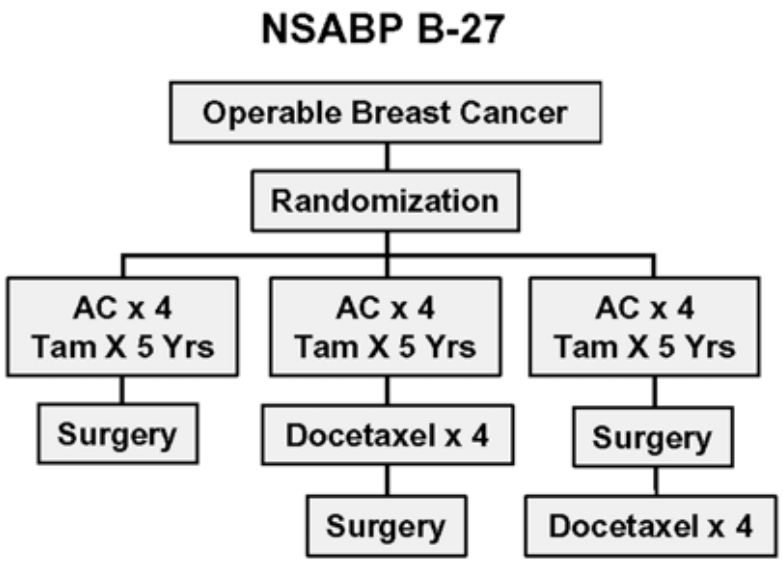
DFS HR = 0.47, P < 0.0001



Rastogi, 2008 JCO

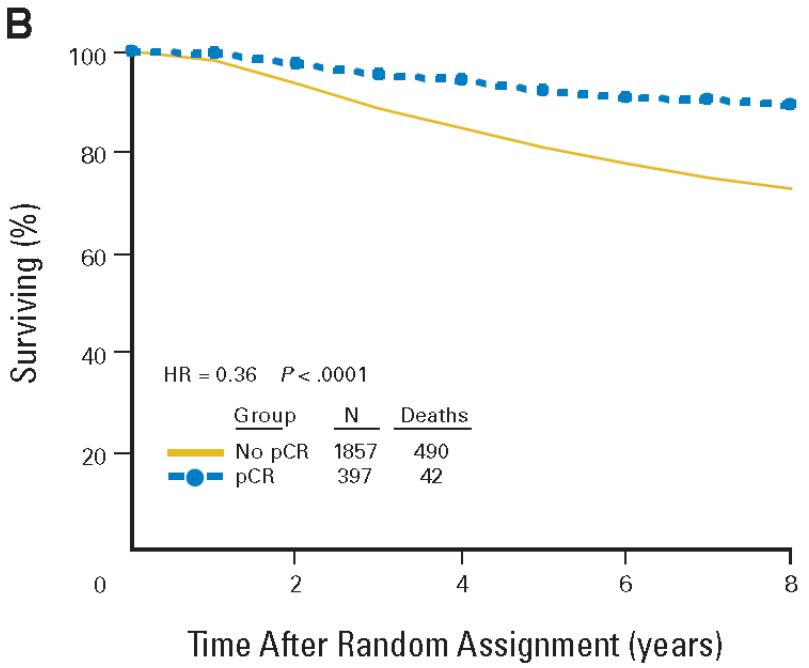
ESTRO School

pCR and disease-free / overall survival



B-27: Effect of adding T to pre-operative AC

HR = 0.49, P < 0.0001



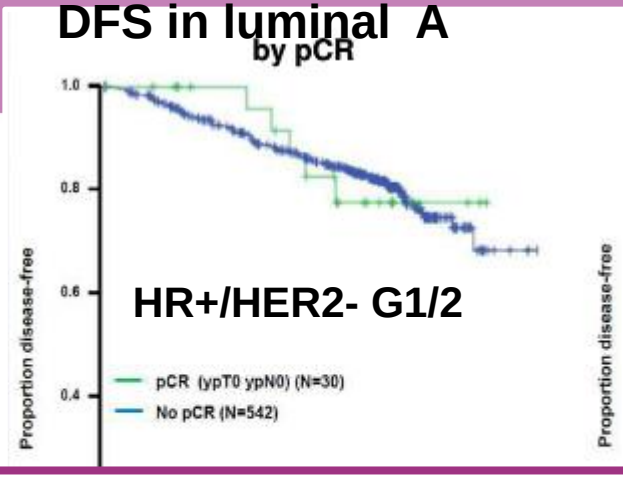
Rastogi, 2008 JCO

ESTRO School

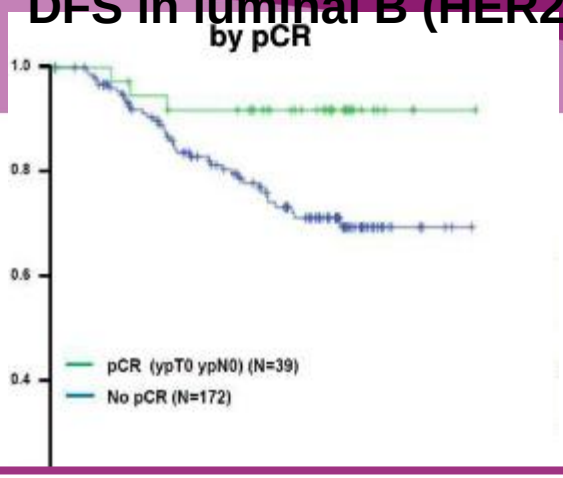
Definition phenotypes (St. Gallen definition)

Phenotype	Definition
Luminal A	HR+, HER2-, G1/2
Luminal B (HER2-)	HR+, HER2-, G3
Luminal B (HER2+)	HR+, HER2+
HER2+ (non-luminal)	HR-, HER2+
Triple-negative	HR-, HER2-

DFS in luminal A

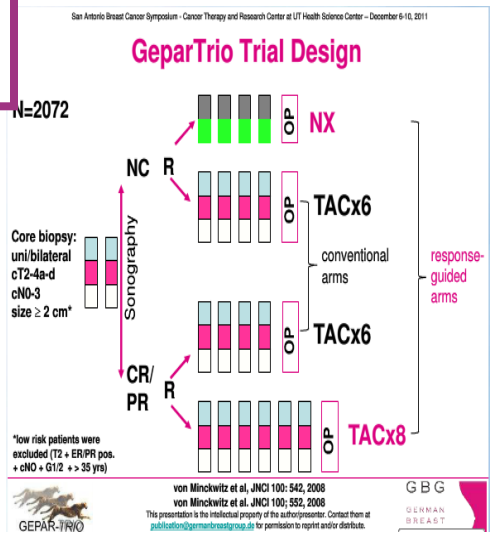


DFS in luminal B (HER2+)



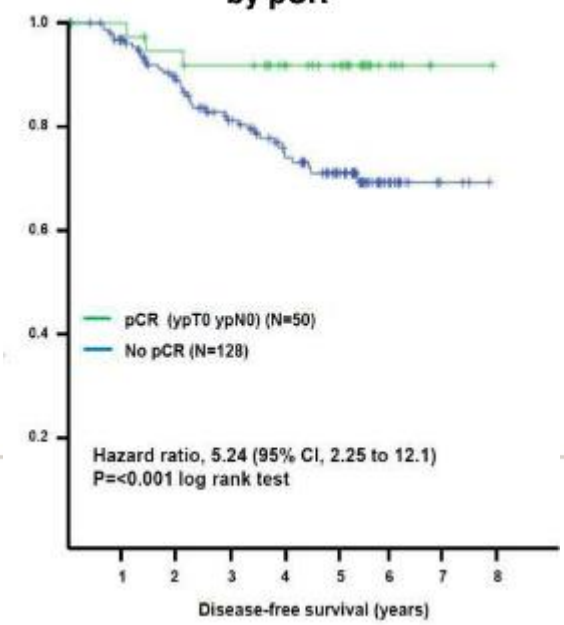
pCR related to event free survival in HER2+ and triple negative BC

Gepartrio trial design



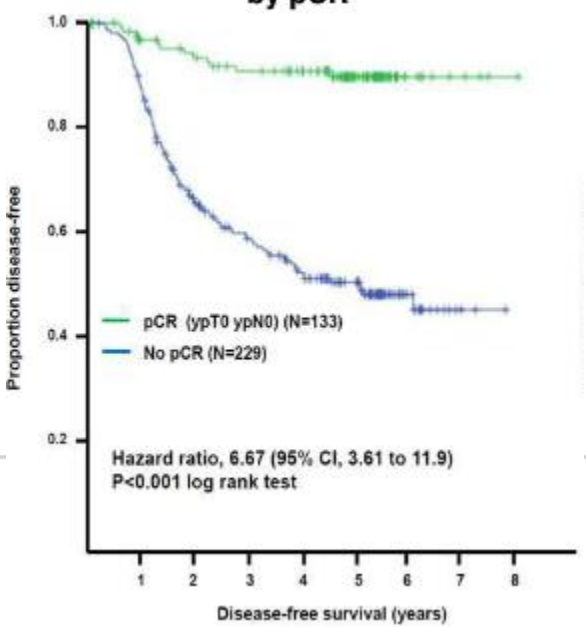
Disease-free survival (years)

DFS in HER2+ (non-luminal)



Disease-free survival (years)

DFS in TN



ESTRO School

Breast cancer subtypes and pCR

Luminal-type tumors:
This treatment effect could not be predicted by pCR as these tumors have lower pCR rates and their prognosis does not depend on pCR

pCR related to event free survival in HER2+ and triple negative BC

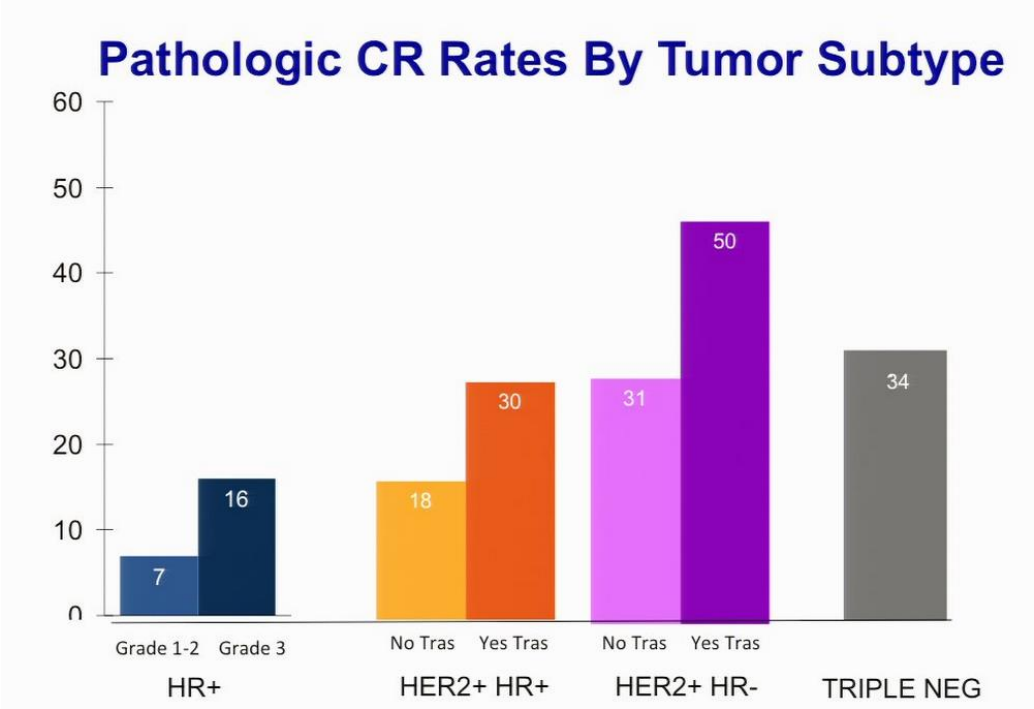
Is respons neoadjuvant chemotherapy correlated with improved outcome?

- cOR is associated with improved outcome
- pCR is associated with better DFS and OS
  - Probably not in all subgroups (luminal A?)
  - Prognostic information

Predictive markers of pCR

- There is no individual pathological or molecular marker that can reliably predict response to NAC in an individual patient

- Patients with ER-negative, high-grade tumors are more likely to respond than tumors with opposite characteristics



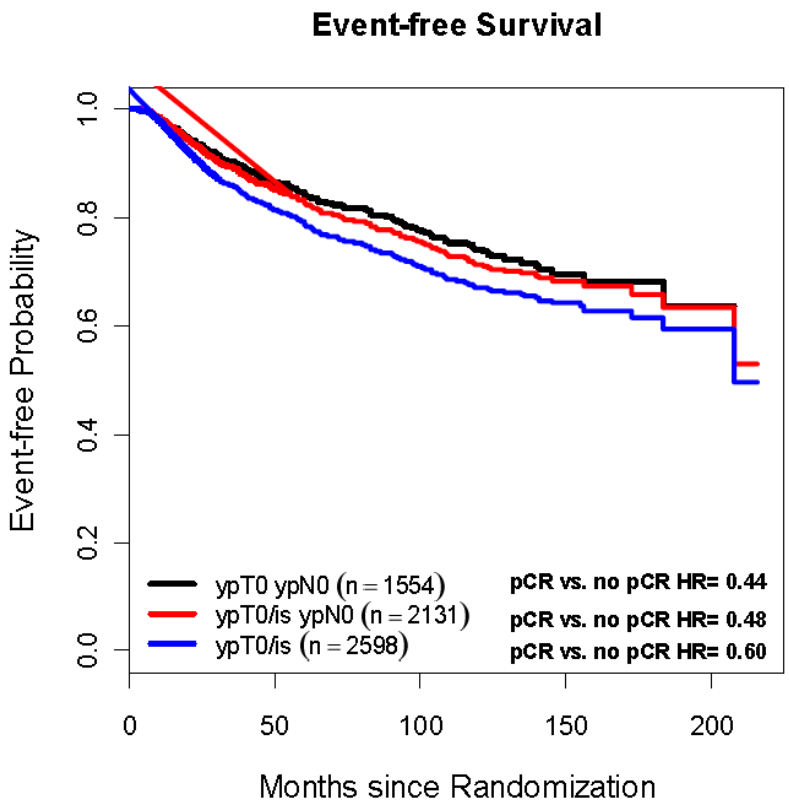
P. Cortazar, Lancet 2014

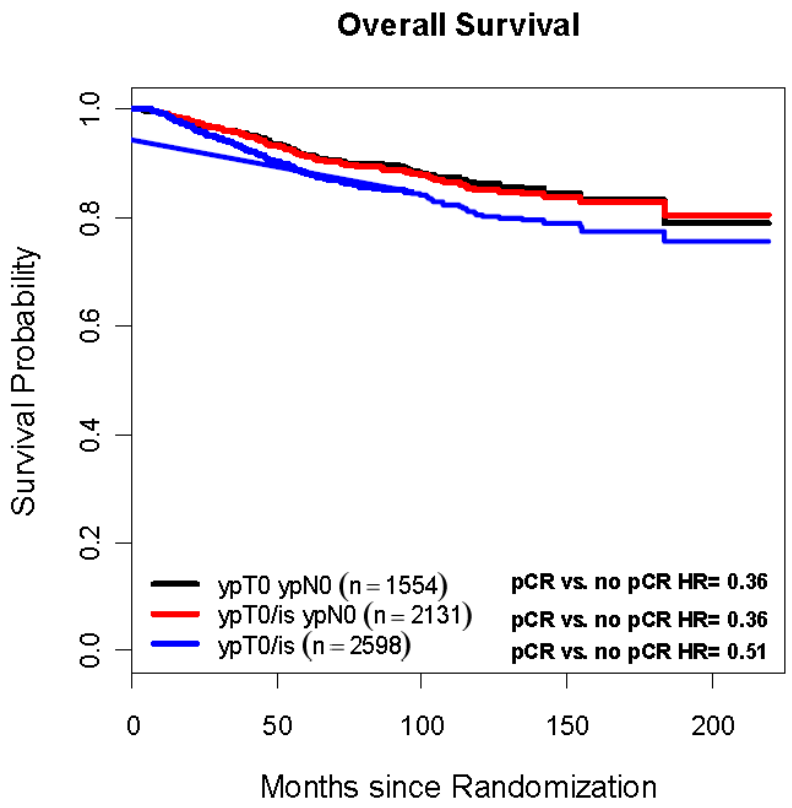
ESTRO School

Different endpoints for pCR after NAC

- ypT0 ypN0
  - Absence of invasive cancer in the breast and axillary nodes
  - **Absence of DCIS**
- ypT0/is ypN0
  - Absence of invasive cancer in the breast and axillary nodes
  - **DCIS allowed**
- ypT0/Tis
  - Absence of invasive cancer in the breast and DCIS allowed
  - **Regardless of nodal involvement**

Association of pCR definitions and Survival

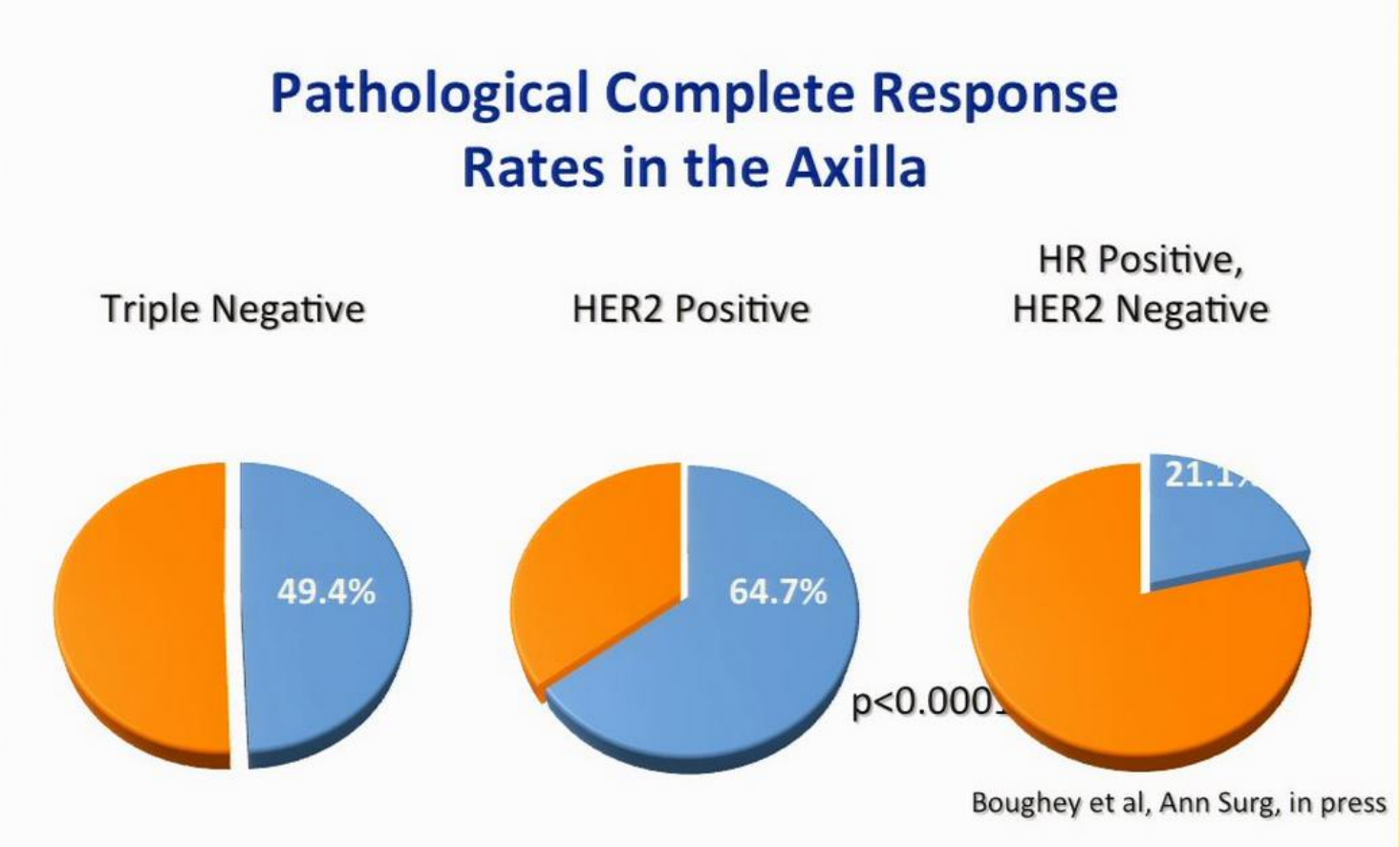




ypN in definition: better association with survival

ESTRO School

Response rates Axilla after NAC



Axillary lymph nodes and neoadjuvant therapy

• Today's strategies aim to minimize the rate of patients who undergo axillary lymph node dissection

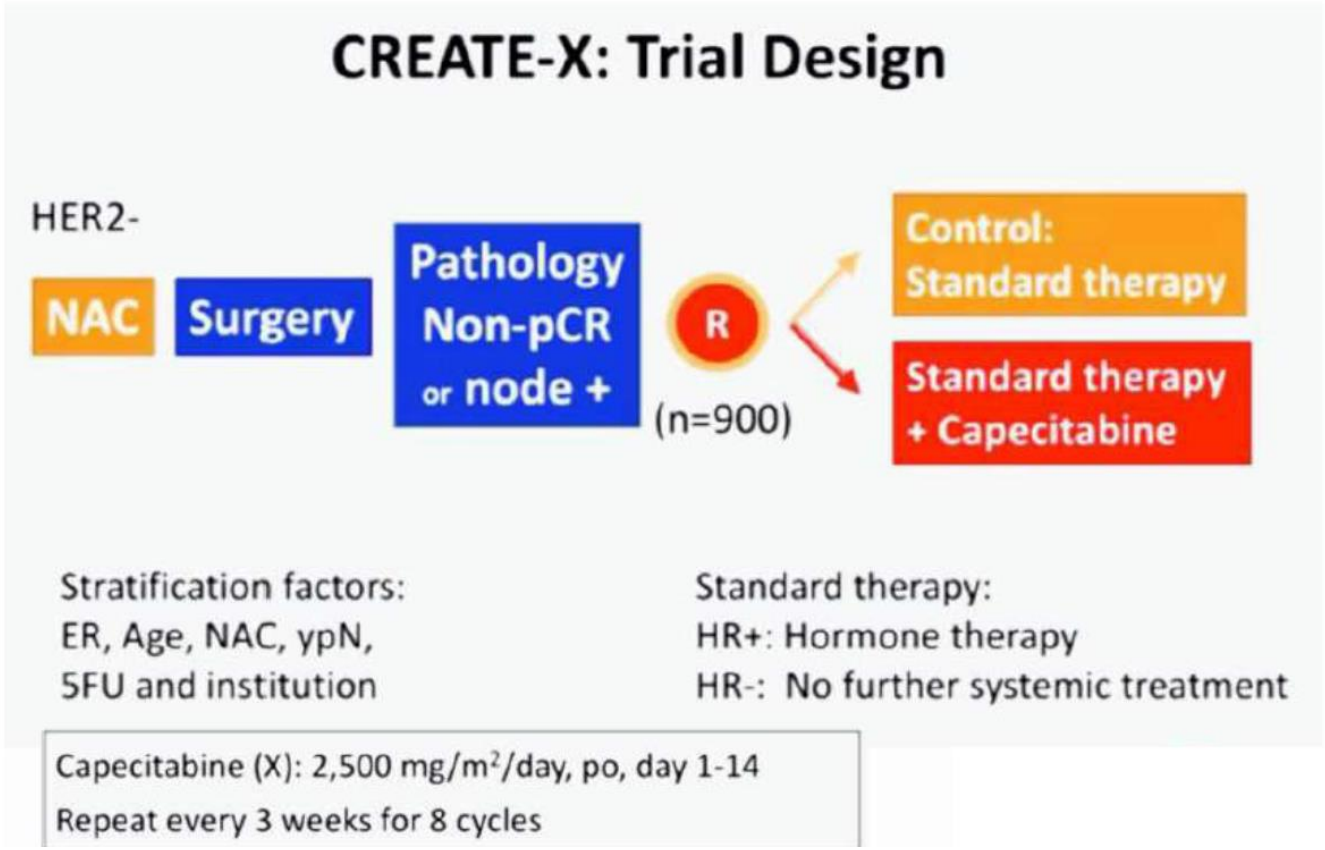
•A procedure with low false negative rates is preferred to predict the axillary status after chemotherapy

SNB: for patients with a clinically negative axilla at time of diagnosis

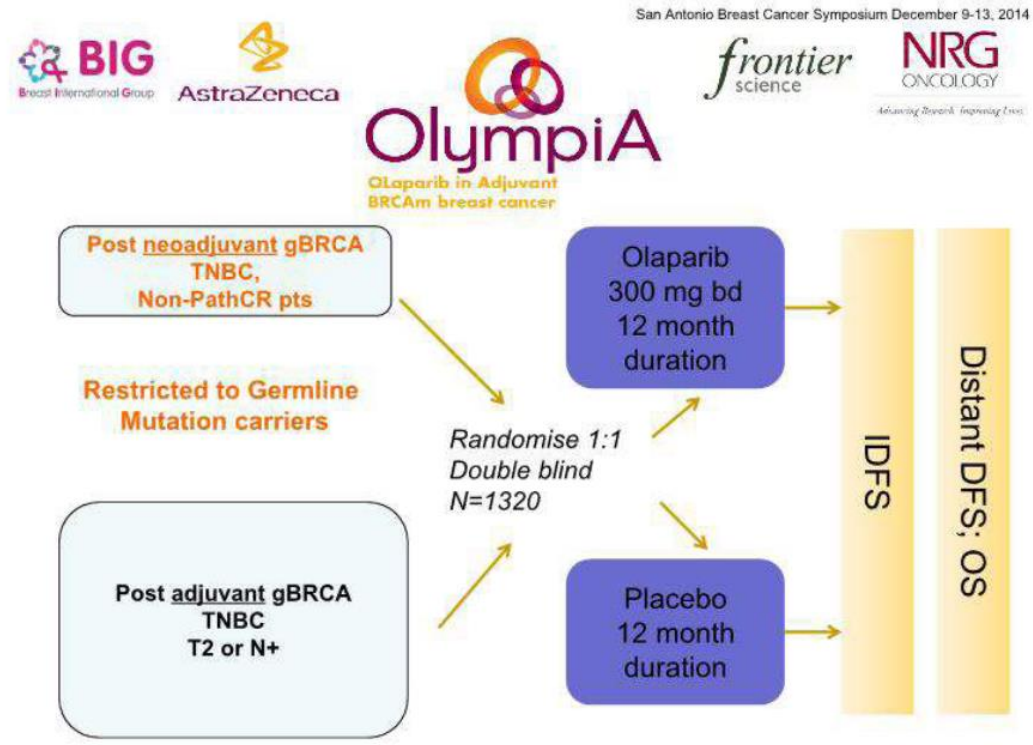
- To spare patients from further regional treatment preferred after NAC

What if no pCR after NAC

What if no pCR after neoadjuvant chemotherapy



Non pCR after NAC: PARP inhibition in gBRCA mutant patients (HER2-): Olympia study



This presentation is the intellectual property of the author/presenter. Contact them at andrew.tutt@icr.ac.uk for permission to reprint and/or distribute

Neoadjuvant systemic therapy optimal for all patients?

- NAC is optimal for all patients **who are candidates for systemic therapy**
- If indication for systemic therapy is uncertain, surgical FIRST is preferable
- Only if a multidisciplinary team is available

Conclusion neoadjuvant chemotherapy

Safe application of NAC in treatment of women with early stage breast cancer in order to down-stage surgical requirement, to evaluate chemosensitivity and to facilitate translational research*

- Survival and ipsilateral breast recurrence is comparable after neoadjuvant and adjuvant chemotherapy, NAC = safe therapy
- Prognostic information
- Assessment of in vivo response to therapy with NAC
- Excellent tool for translational research
- Accelerated approval new drugs

Future

- Allows better individualization of therapy according to mid-course treatment effect
  - Using early information treatment effect can serve to design better treatment
- Spare patients from further regional treatment who are downstaged from a positive to a negative LN status

***Vd Hage, Cochrane 2007**

Neoadjuvant chemotherapy and Radiotherapy

Neoadjuvant chemotherapy

Many new questions for radiation oncology/locoregional treatment

The risk of LRR according to pathological extent of disease after neoadjuvant chemotherapy is different than the risk in patients treated with initial surgery

Lack of pathologic stage to guide indications

- Treatment response and indications
  - Breast conservation
  - Postmastectomy radiation
  - Regional lymph node radiation
- Are new strategies for poor responders needed?

Clinical studies on locoregional treatment after NAC by L. Boersma

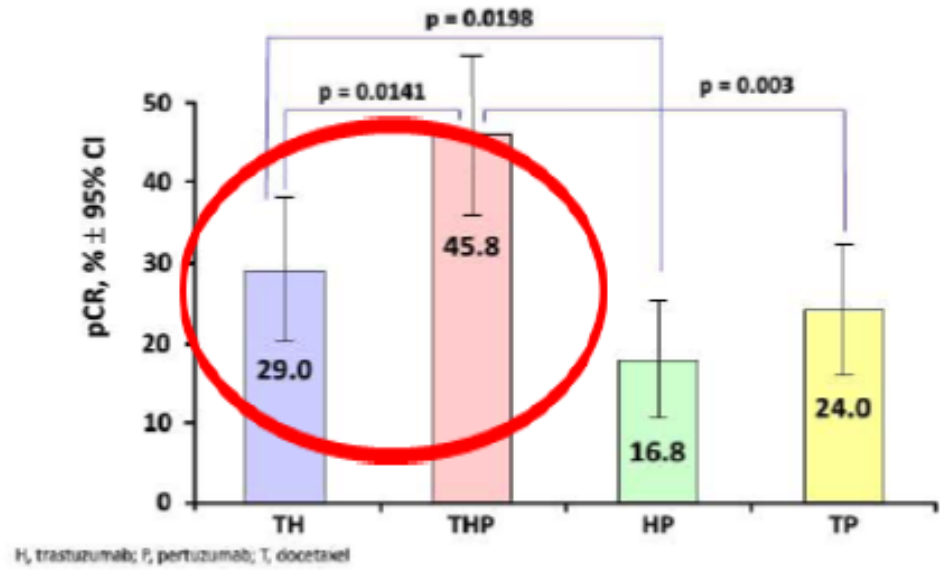
Is Neoadjuvant chemotherapy always appropriate for new drug approval or to change practice?

Example:

What is the role of pertuzumab in the treatment of HER2 positive Breast Cancer, in combination with trastuzumab and docetaxel?

Pertuzumab as neoadjuvant treatment HER2+

NeoSphere pCR rates: ITT population summary



TH=docetaxel-trastuzumab

THP=docetaxel-trastuzumab-pertuzumab

HP=trastuzumab-pertuzumab

TP=docetaxel-pertuzumab

Gianni, 2016

ESTRO School

FDA approval pertuzumab

In 2013 the FDA granted accelerated approval to pertuzumab for use in combination with docetaxel and trastuzumab for HER2+ patients.

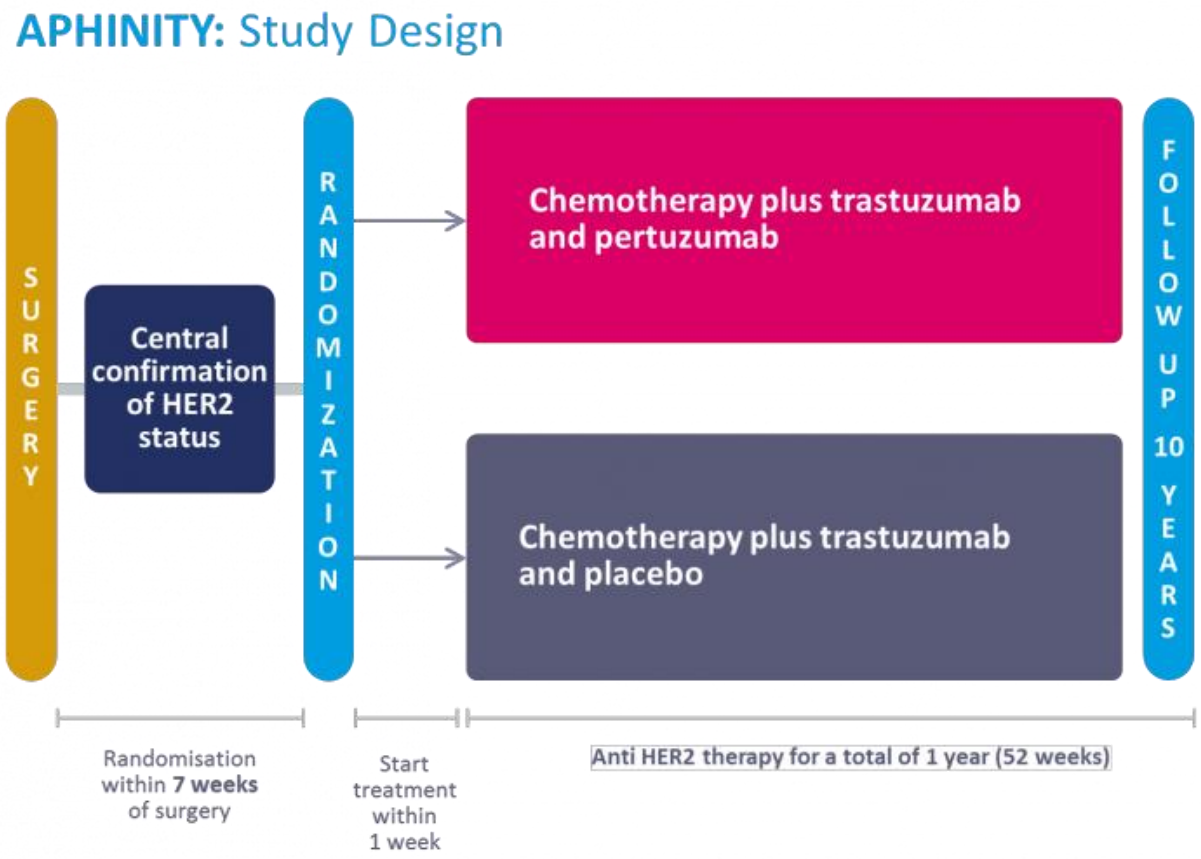
NEOSPHERE: It nearly doubled the pCR rate

They concluded

“Large improvement in pCR rate was reasonable likely to predict clinical benefit“

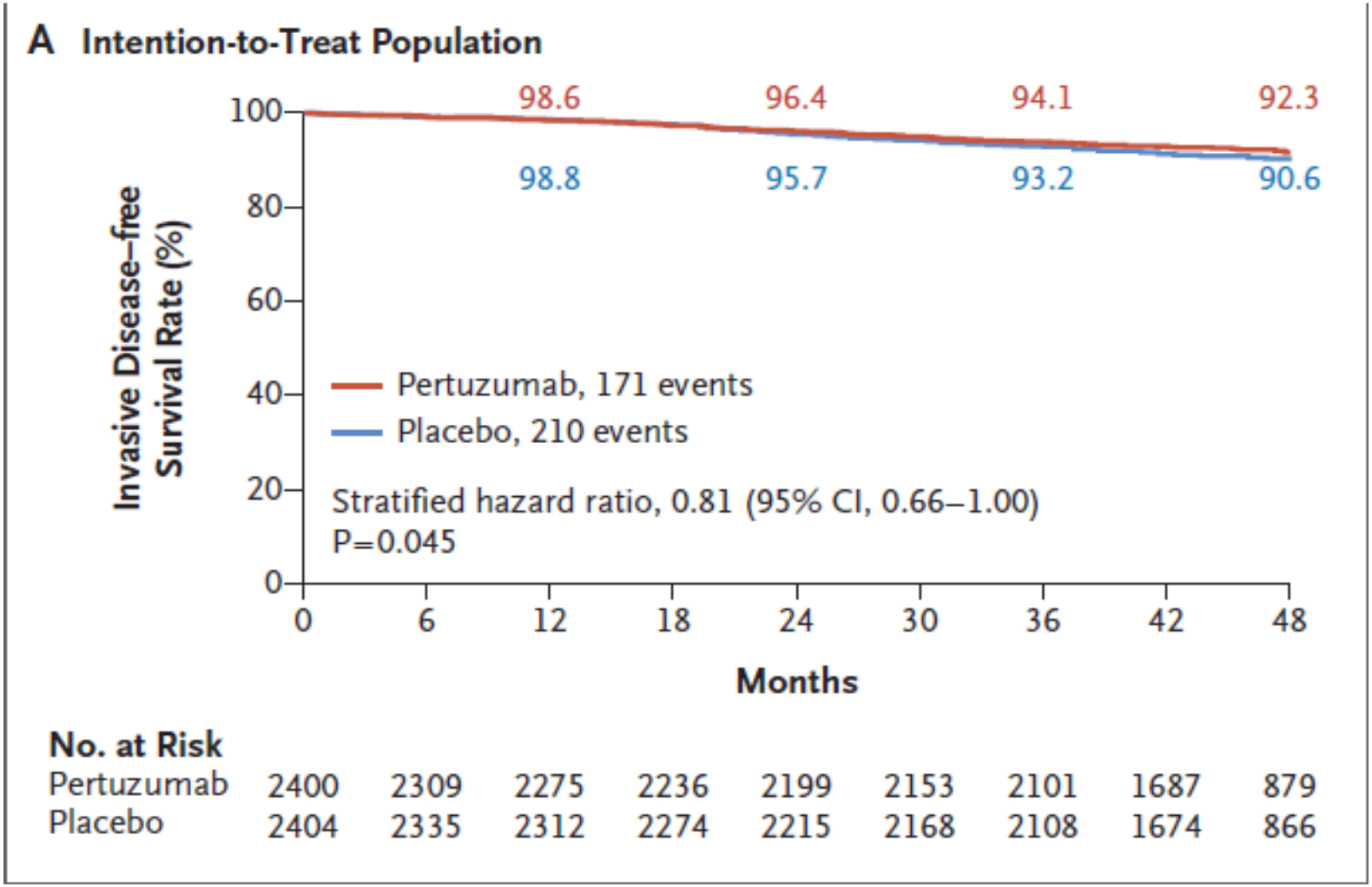
A confirmatory trial should be ongoing

Aphinity trial design



ESTRO School

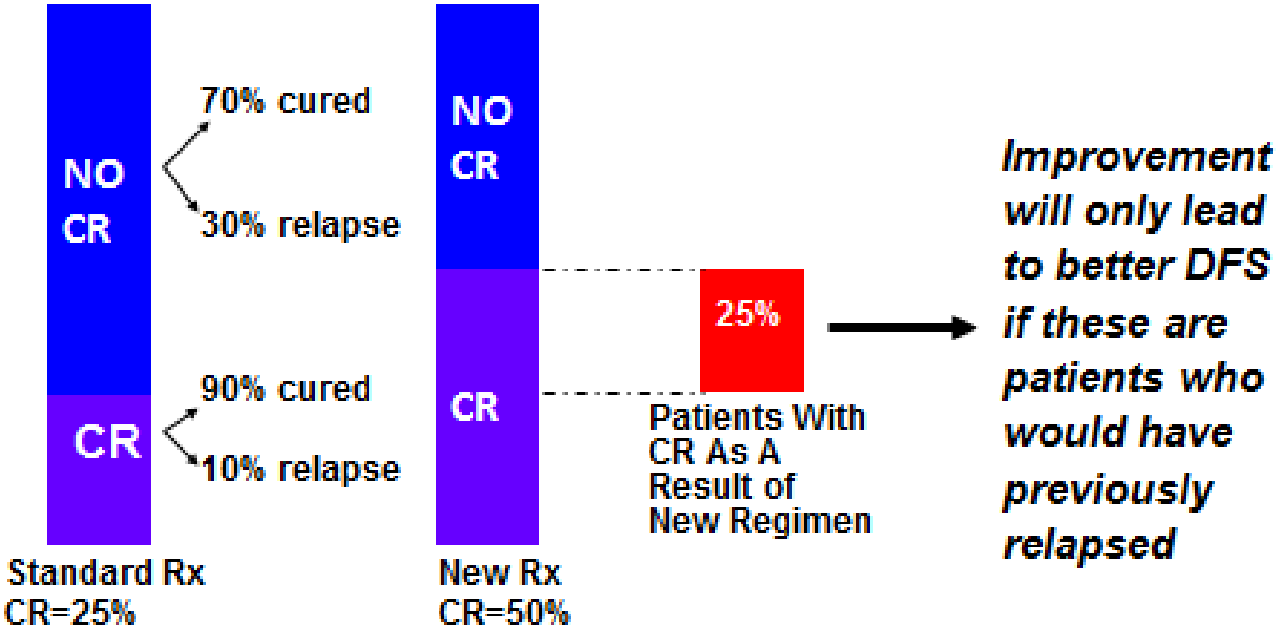
Aphinity trial



A substantial improvement in pCR may not necessarily indicate a substantial improvement in survival

Long term follow up is still required

Why Improvement in Pathologic Complete Response May Not Lead to Change in DFS



Pathologic CR is marker of better outcome, not a required step in the process

ESTRO School

Interpretation clinical neoadjuvant trials

Greater understanding of pathologic endpoints for neoadjuvant trials is necessary to design and interpret future clinical trial

Uniform staging

Neoadjuvant chemotherapy

Downstaging of disease and facilitation of less surgery

Better prognostication

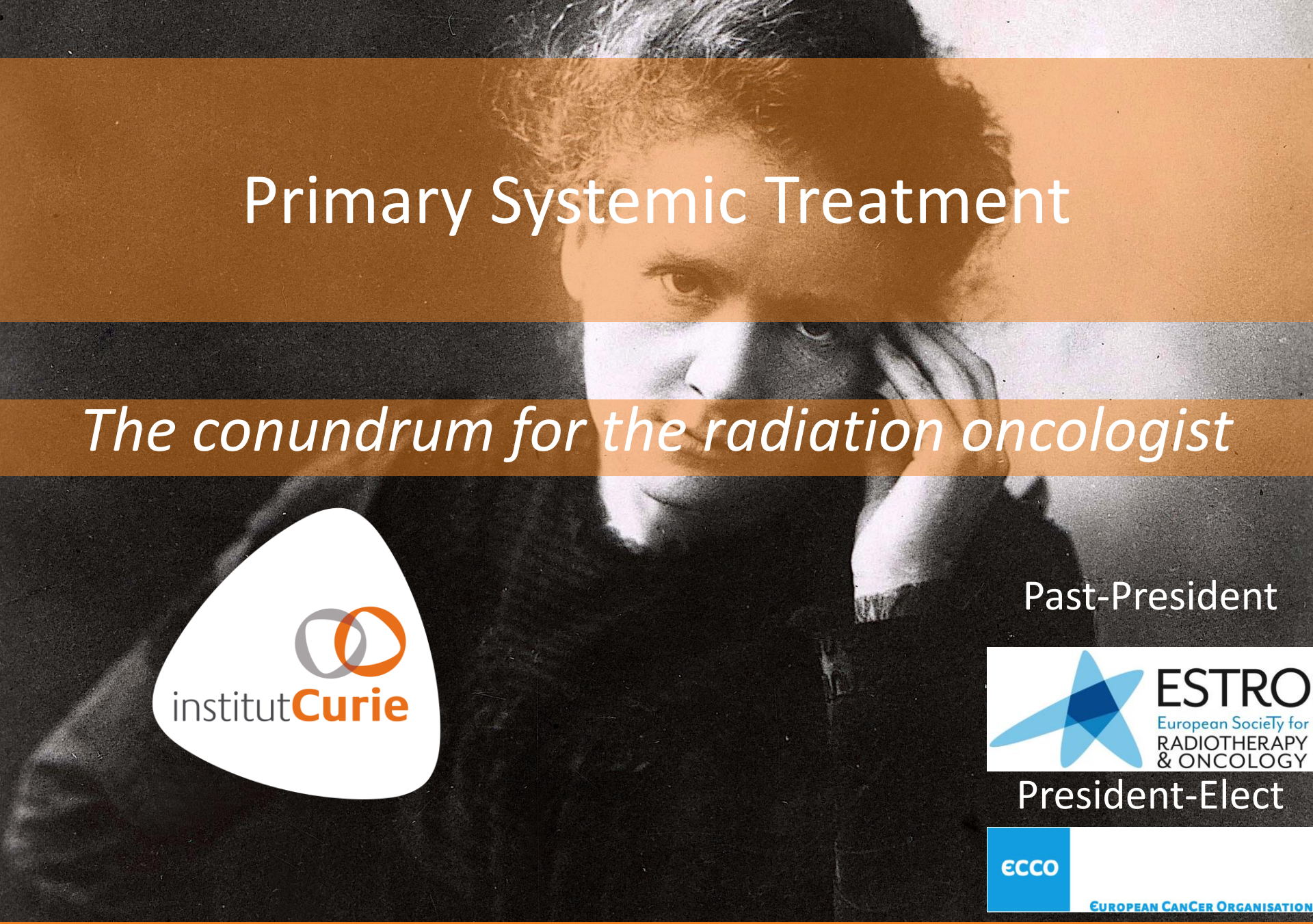
New clinical trial opportunities

Tissue-based research for translational science

Questions?

Primary Systemic Treatment

The conundrum for the radiation oncologist



institutCurie

Past-President

ESTRO
European Society for
RADIOTHERAPY
& ONCOLOGY

President-Elect

ECCO
EUROPEAN CANCER ORGANISATION

Philip Poortmans, MD, PhD

I have no conflict of interest

The conundrum of PST for the rad. oncologist

1. Introduction
    a. *Some notes about post-operative RT*
    b. *The rise of primary systemic therapy*
2. Interaction with systemic therapy
3. Current evidence
4. On going trials and future directions
5. A technical note
6. Discussion & Conclusions

Conundrum of PST: post-operative RT

Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Lancet 2011; 378: 1707–16

EBCTCG Lancet 2011; 378: 1707–1716

ESTRO School

Conundrum of PST: post-operative RT

oa
OPEN ACCESS

Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials

EBCTCG (Early Breast Cancer Trialists' Collaborative Group)*

Lancet 2014; 383: 2127–35

EBCTCG. Lancet. 2014;383:2127-35.

ESTRO School

Conundrum of PST: post-operative RT

Interpretation: *RT reduced recurrence and breast cancer mortality after BCT (N0/N+) and after mastectomy (N+).*

EBCTCG Lancet 2011; 378: 1707–1716 & 2014;383:2127–35.

ESTRO School

Conundrum of PST: post-operative RT

Interpretation: *RT reduced recurrence and breast cancer mortality after BCT (N0/N+) and after mastectomy (N+).*

Similar effects:

- Irrespective of the number of involved lymph nodes
- Whether systemic therapy was given or not
- More benefit after partial or no AD
- Less benefit if only regional RT

Most patients received comprehensive nodal RT!

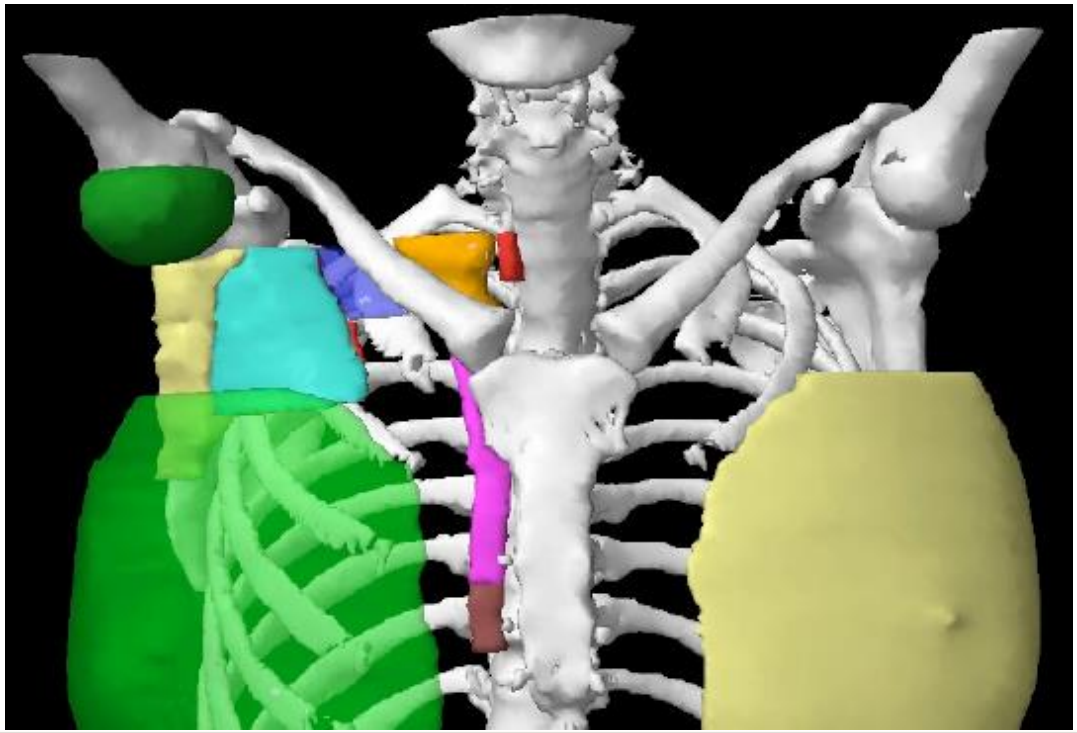
EBCTCG Lancet 2011; 378: 1707–1716 & 2014;383:2127–35.

ESTRO School

Conundrum of PST: post-operative RT

EORTC 10981-22023 "AMAROS"

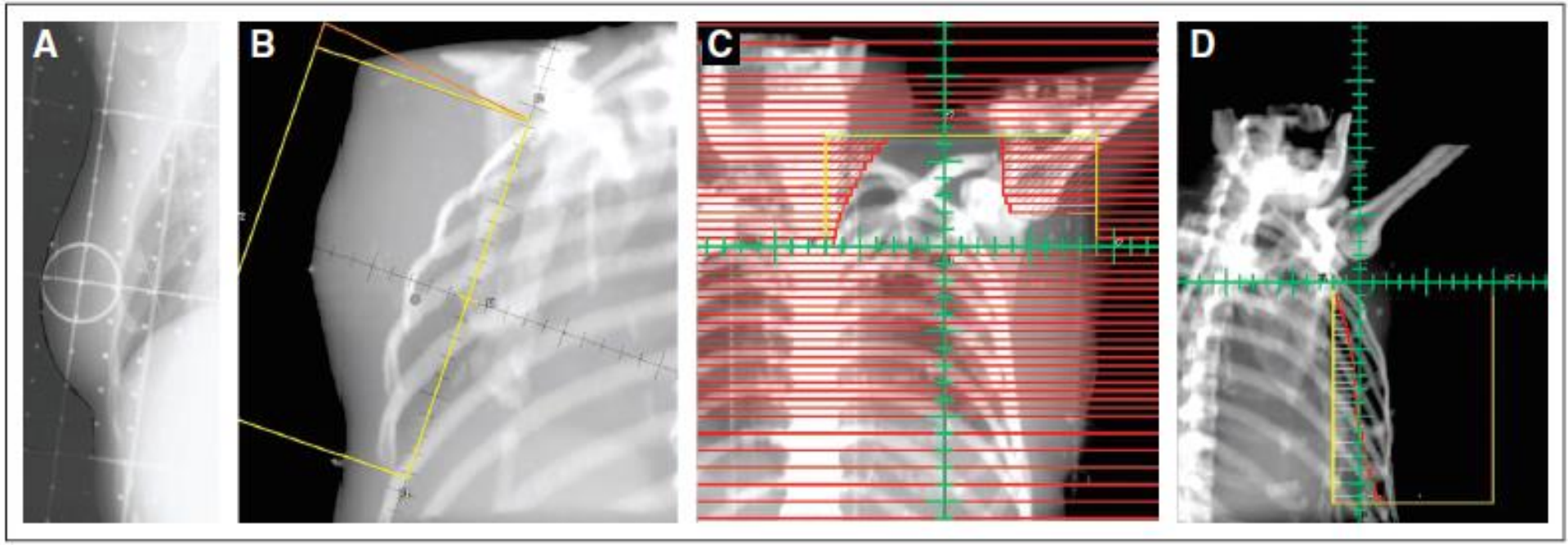
RT-fields: inappropriate (too large)!!!



ESTRO School

Conundrum of PST: post-operative RT

ACOSOG Z0011: QART: 228 replies *(= the best 29%?)*



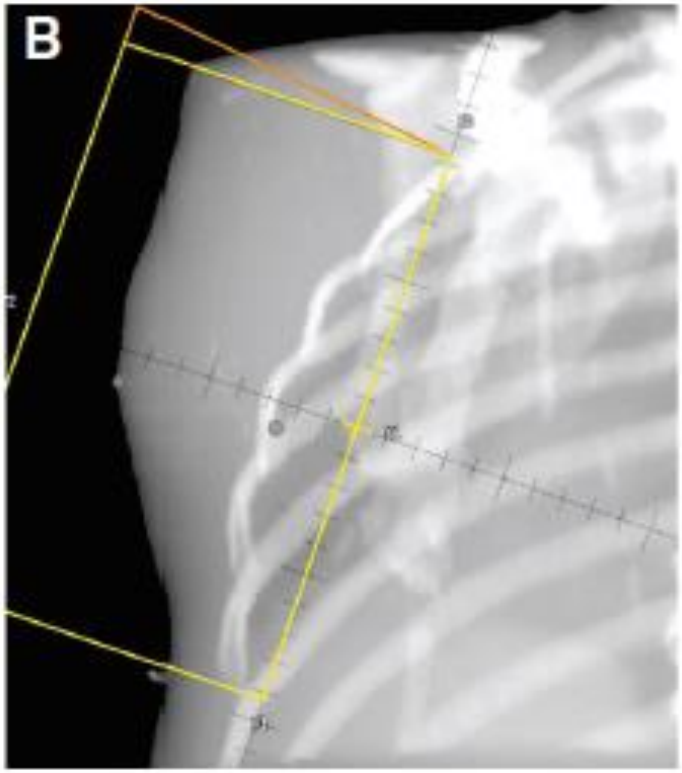
ALND:	39.4%	21.2%
SLNB:	43.7%	16.9%

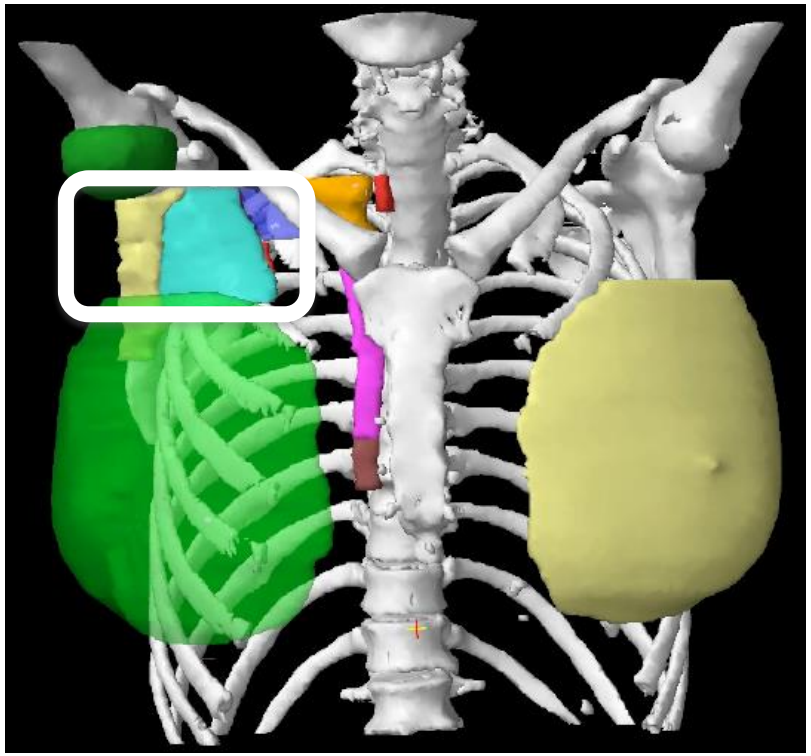
Jagsi R, et al. J Clin Oncol 2014;32:3600-6.

ESTRO School

Conundrum of PST: post-operative RT

ACOSOG Z0011: QART: 228 replies *(= the best 29%?)*





ALND: 0.56cm = part L1-2-3-Rotter

SLNB: 0.69cm = part L1-2-3-Rotter

Jagsi R, et al. J Clin Oncol 2014;32:3600-6.

ESTRO School

The conundrum of PST for the rad. oncologist

1. Introduction
    a. *Some notes about post-operative RT*
    b. *The rise of primary systemic therapy*
2. Interaction with systemic therapy
3. Current evidence
4. On going trials and future directions
5. A technical note
6. Discussion & Conclusions

Conundrum of PST: the rise of PST

Definition of *neo-* in English:

neo–

COMBINING FORM

1 New.
'neonate'

2 A new or revived form of
'neo-Georgian'

Origin
From Greek neos 'new'.

Definition of *adjuvant* in English:

adjuvant

ADJECTIVE

Medicine
(of therapy) applied after initial treatment for cancer, especially to suppress secondary tumour formation.

Origin
Late 16th century: from Latin adjuvant- 'helping towards', from the verb adjuvare, from ad- 'towards' + juvare to 'help'.

https://en.oxforddictionaries.com/definition/

ESTRO School

Conundrum of PST: the rise of PST

Definition of *neoadjuvant* in English:

neoadjuvant

ADJECTIVE

Medicine

Designating cancer treatment (usually chemotherapy) that is administered before the start of a second method of treatment (usually surgery or radiotherapy), with the aim of improving the outcome of the latter.

Origin

1980s; earliest use found in Cancer.

https://en.oxforddictionaries.com/definition/

Conundrum of PST: the rise of PST

Definition of *primary* in English:

primary

---

2 Earliest in time or order.

'the primary stage of their political education'

Conundrum of PST: the rise of PST

The rise of primary systemic therapy:

- ✓ Initially reserved for locally advanced BC
- ✓ Later to facilitate breast conservation
- ✓ Now also for all who will anyway require adjuvant chemotherapy
- ✓ Other reasons: buying time for genetic counselling; evaluation of new treatments

Conundrum of PST: the rise of PST

Limitations of primary systemic therapy:

- ✓ Delay for patients with tumours that are resistant to systemic therapy
- ✓ Lacking initial pathological information (pTpN) to tailor postoperative radiation therapy
- ✓ Radiation therapy preceding surgery poorly investigated

The conundrum of PST for the rad. oncologist

1. Introduction
2. Interaction with systemic therapy
3. Current evidence
4. On going trials and future directions
5. A technical note
6. Discussion & Conclusions

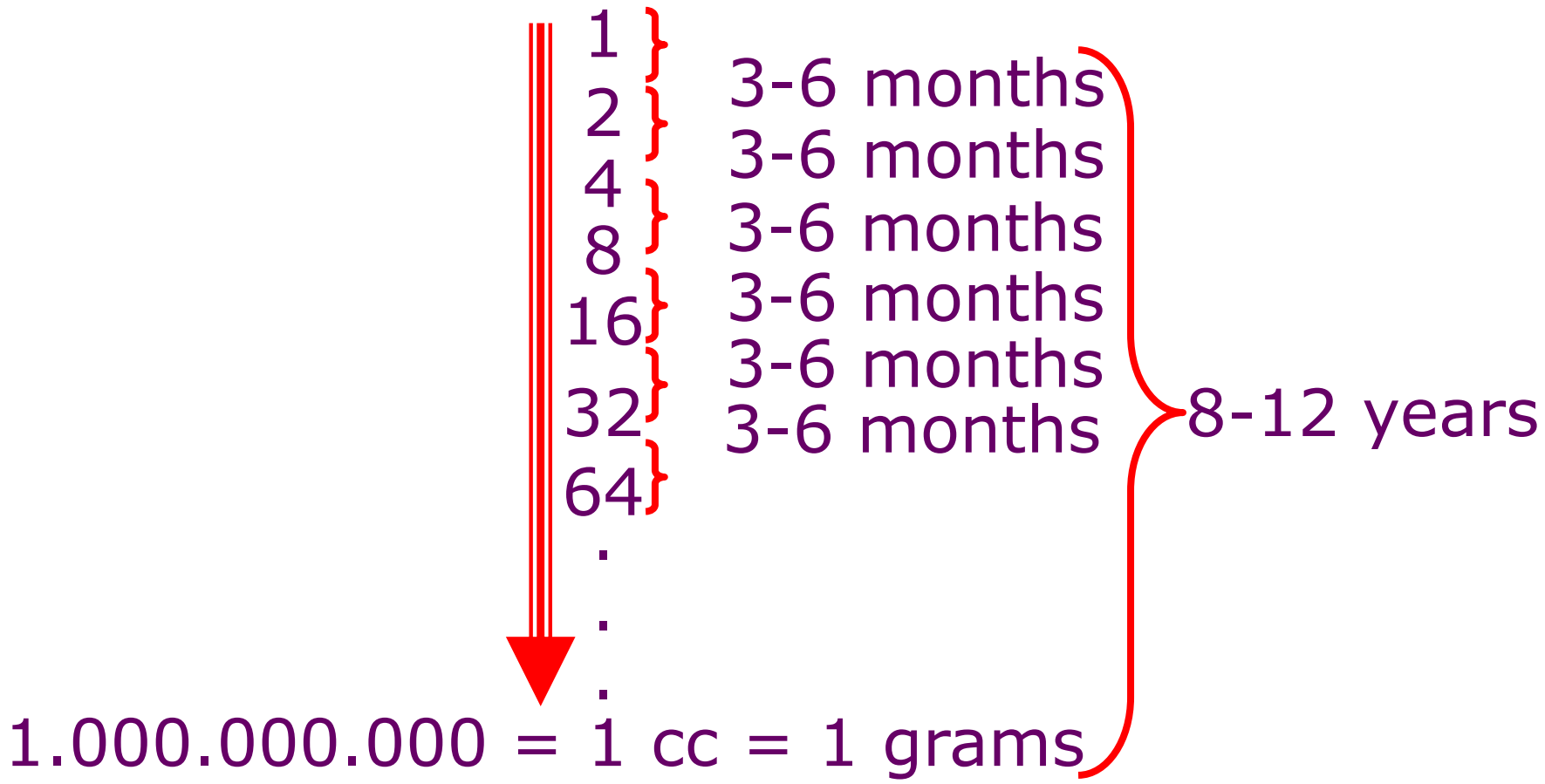
Conundrum of PST: interaction RT - ST

Conundrum of PST: interaction RT - ST

What is the size of a cancer cell

$= 0{,}01\ mm^3$

Conundrum of PST: interaction RT - ST

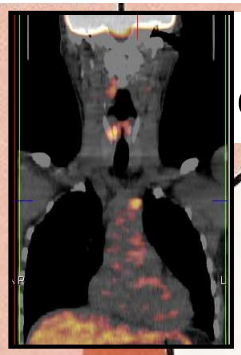


Conundrum of PST: interaction RT - ST

Duplication time

= 3 months

Detectable with special techniques



Physically detectable.

tumoren te klein om te kunnen worden waargenomen

Not detectable at all

256 cm³

16 cm³

1 cm³

tijd (jaar) 0 1 2 3 4 5 6 7 8 9 10 11 12 13

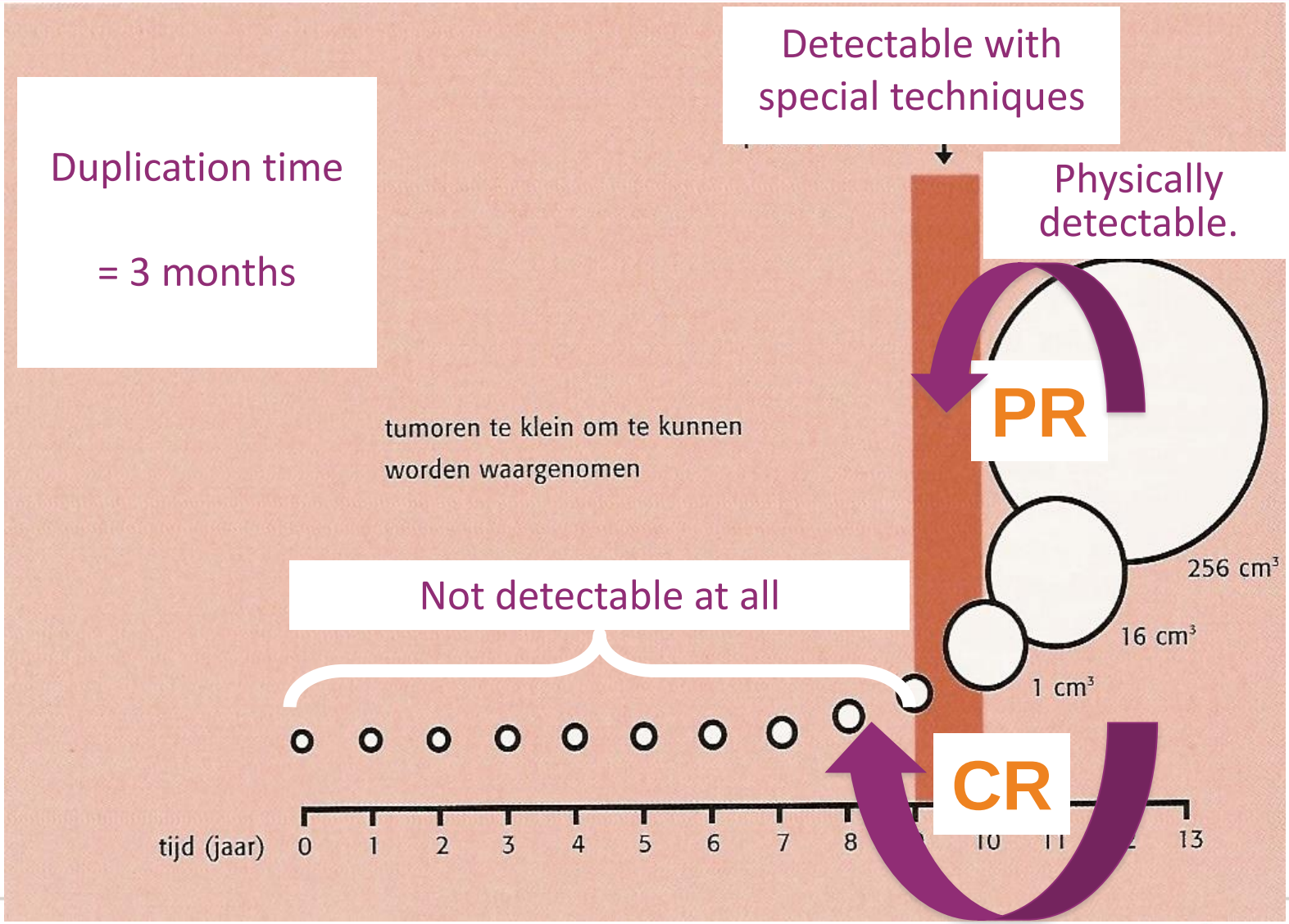
ESTRO School

Conundrum of PST: interaction RT - ST

So what is a “complete pathological remission"?

- Resection specimen = 100 grams ➔ 100.000.000.000 cells
- Do you know a pathologist who can perform a complete evaluation?
- It will rather be around 1 to 5% of the material…

Conundrum of PST: interaction RT - ST



Conundrum of PST: interaction RT - ST

Systemic treatment cures breast cancer

Contributes to cure

Conundrum of PST: interaction RT - ST

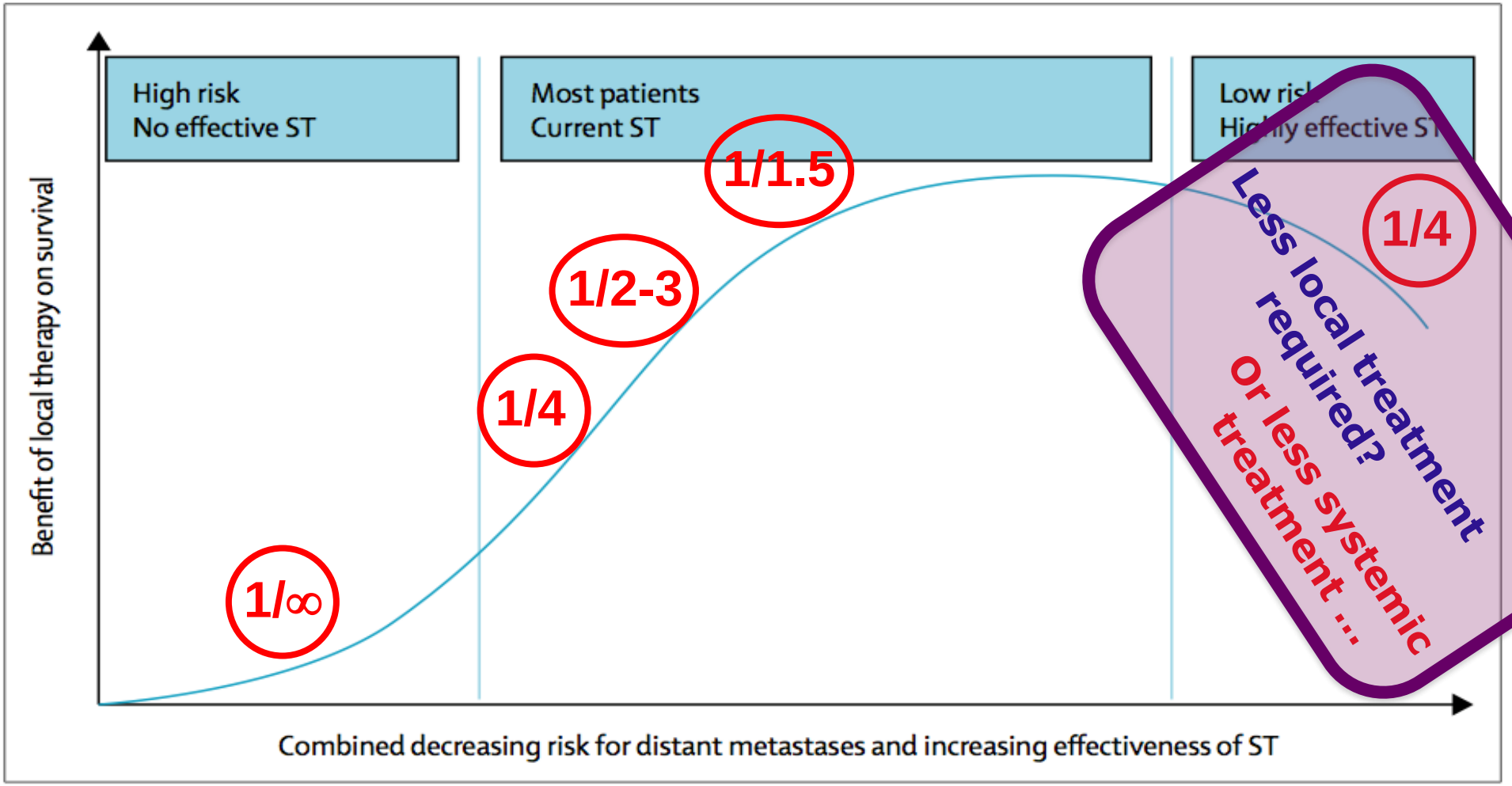


***Figure*: Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour**

Poortmans P. Lancet. 2014 Jun 21;383(9935):2104-6.

ESTRO School

Conundrum of PST: interaction RT - ST

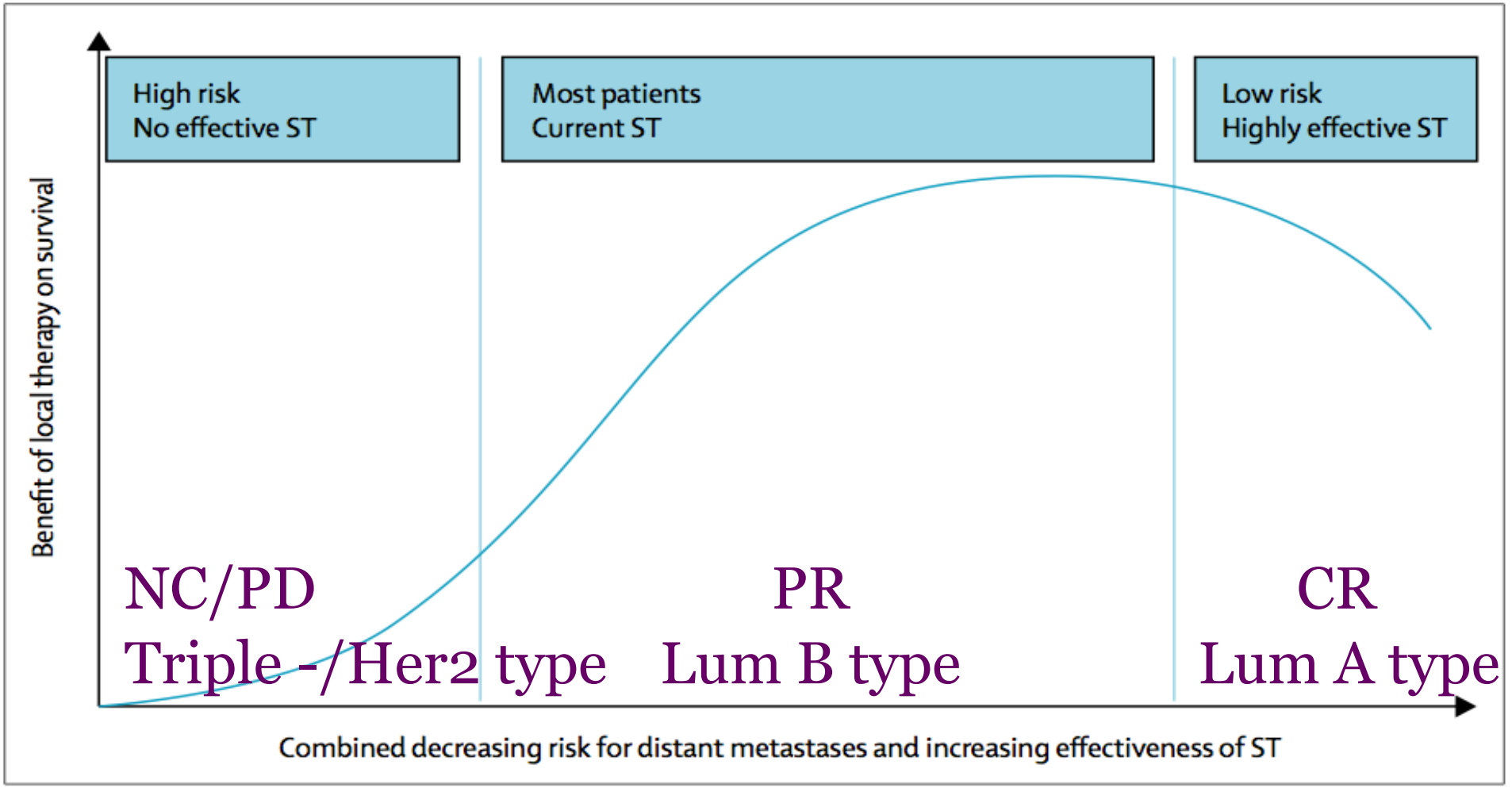


***Figure*: Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour**

Poortmans P. Lancet. 2014 Jun 21;383(9935):2104-6.

ESTRO School

Conundrum of PST: interaction RT - ST

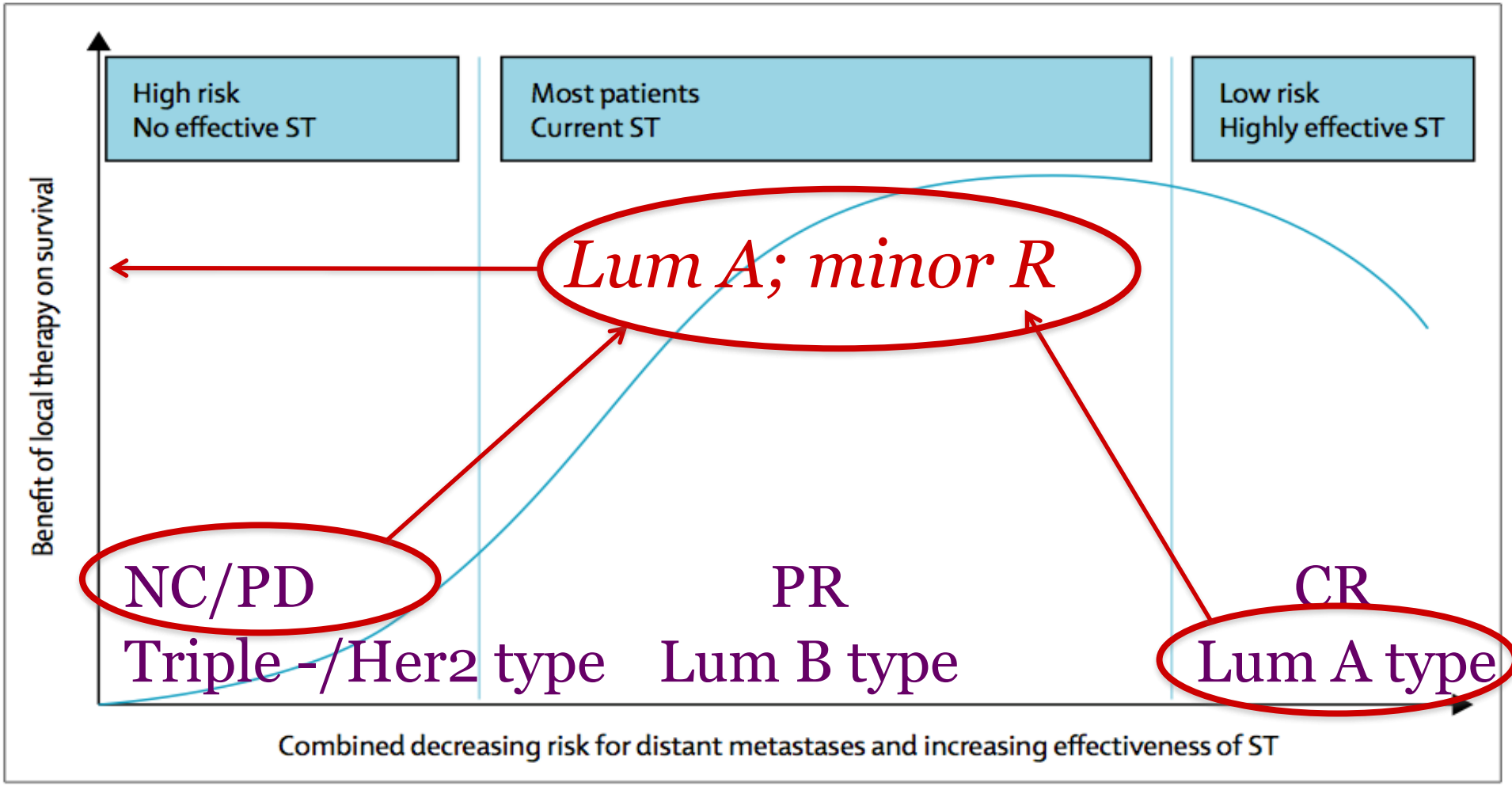


***Figure*: Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour**

Poortmans P. Lancet. 2014 Jun 21;383(9935):2104-6.

ESTRO School

Conundrum of PST: interaction RT - ST

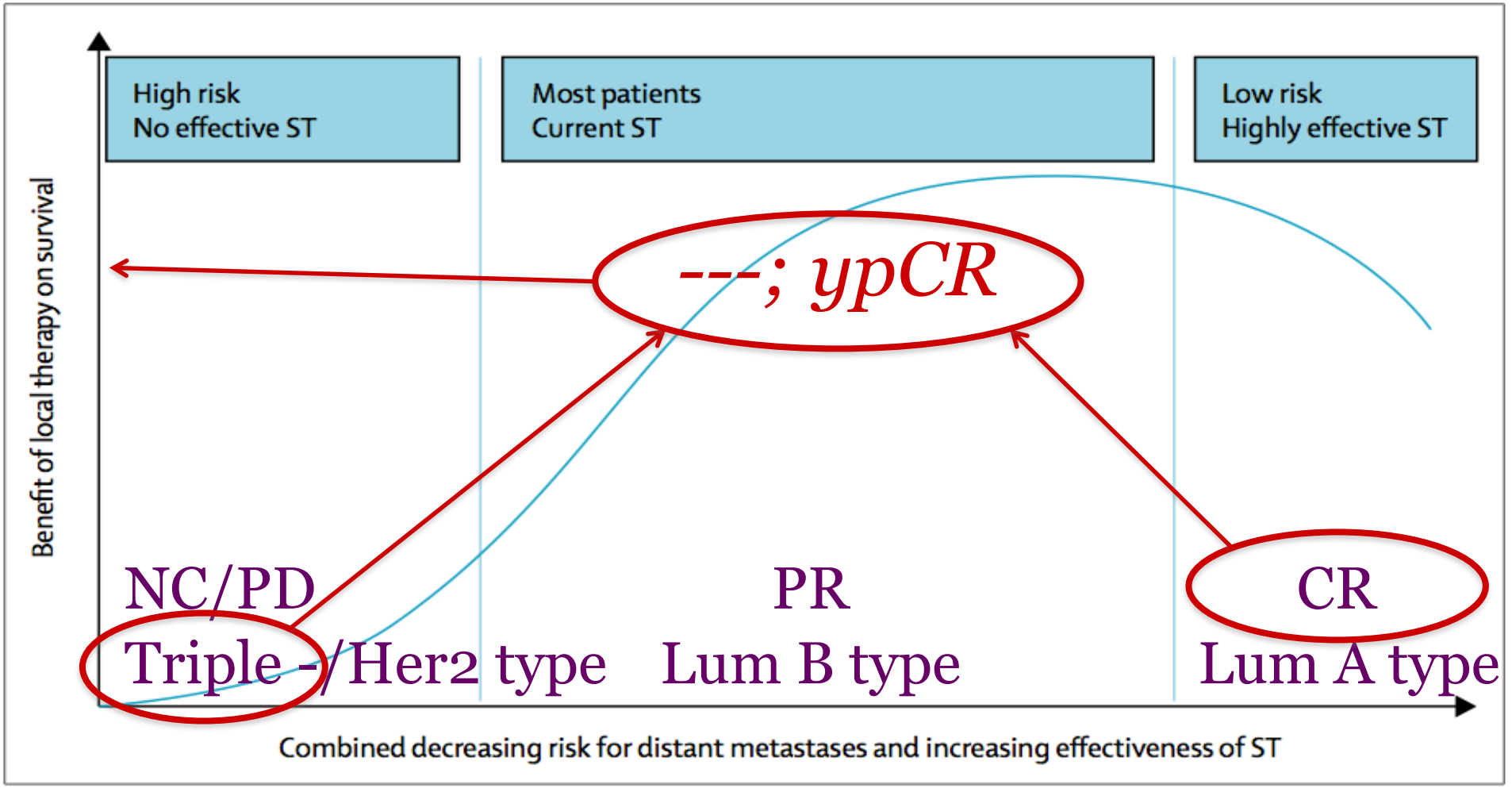


***Figure*: Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour**

Poortmans P. Lancet. 2014 Jun 21;383(9935):2104-6.

ESTRO School

Conundrum of PST: interaction RT - ST

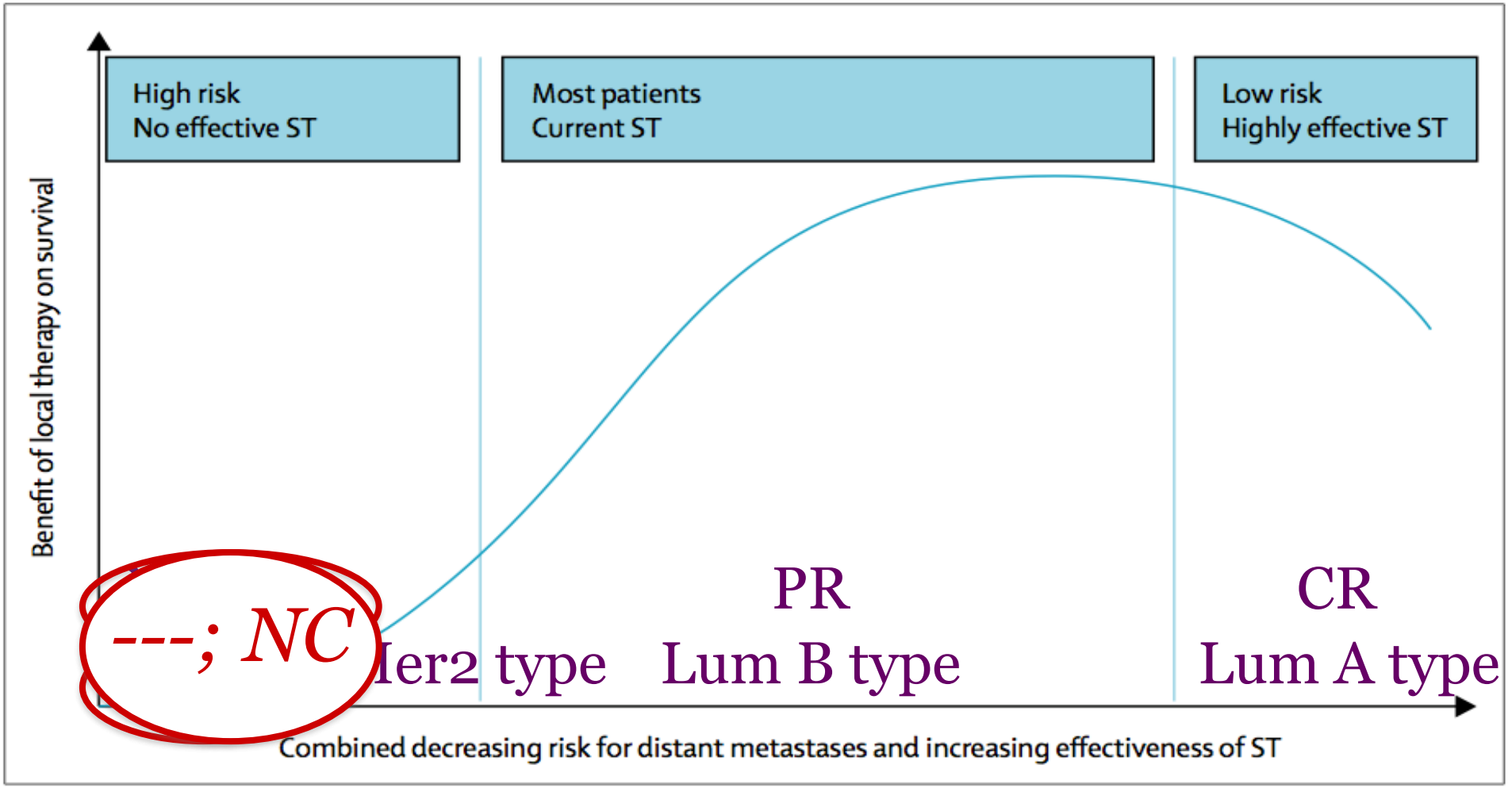


***Figure*: Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour**

Poortmans P. Lancet. 2014 Jun 21;383(9935):2104-6.

ESTRO School

The conundrum of PST for the rad. oncologist

1. Introduction
2. Interaction with systemic therapy
3. Current evidence
4. On going trials and future directions
5. A technical note
6. Discussion & Conclusions

Conundrum of PST: current evidence

Primary or adjuvant systemic therapy?

Randomized phase III trials comparing neoadjuvant with adjuvant therapy using the same chemotherapy regimen

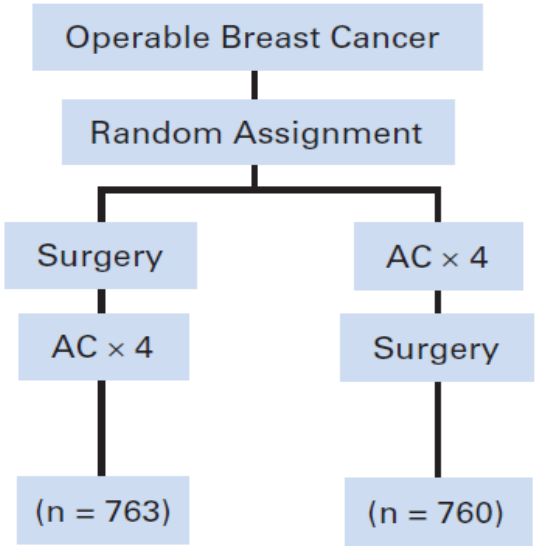
Study	*n* (stage and size)	Chemotherapy regimen	cRR (%)	pCR (%)	DFS benefit	OS benefit
Fisher et al. [3, 4], Wolmark et al. [5], NSABP B-18	1,523 (operable)	AC	80	13	No	No
Van der Hage et al. [6], EORTC 10902	698 (T1c–4bN0–1)	FEC	49	4	No	No
Gianni et al. [7, 8], ECTO	1,355	AT → CMF	78	23	No	No
Mauriac et al. [9]	272 (>3 cm)	EMV/MTV	81	NA	No	No
Scholl et al. [10], Broet et al. [11]	414 (T2–3N0–1)	FAC	85	NA	No	No
Makris et al. [12]	309 (operable)	MM(M)+Tam	84	10	No	No

Sachelarie, et al. The Oncologist 2006;11:574-589

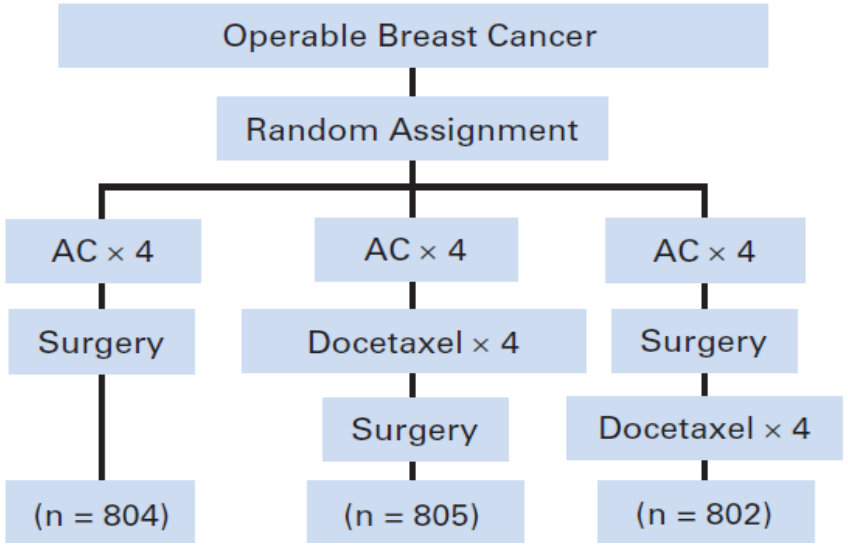
ESTRO School

Conundrum of PST: current evidence

NSABP-B18



NSABP-B27



Fisher B, et al. JCO 1997;15:2483-93 - Bear HD, et al JCO 2003;21:4165-74.

ESTRO School

Conundrum of PST: current evidence

NSABP-B18 NSABP-B27

Conclusions:

Overall:

- ✓ Equal survival when the same regimen is given before or after Sx
- ✓ Fewer mastectomies

Specific:

- ✓ Better survival for patients with a pCR after PST
- ✓ Addition of taxanes ➔
  - ✓ Increased pCR
  - ✓ No improvement in survival
  - ✓ No increased BCT rate

Fisher B, et al. JCO 1997;15:2483-93 - Bear HD, et al JCO 2003;21:4165-74.

ESTRO School

Conundrum of PST: current evidence

NSABP-B18 NSABP-B27

Conclusions:

Overall:

- ✓ Equal survival when the same regimen is given before or after Sx
- ✓ Fewer mastectomies

Specific:

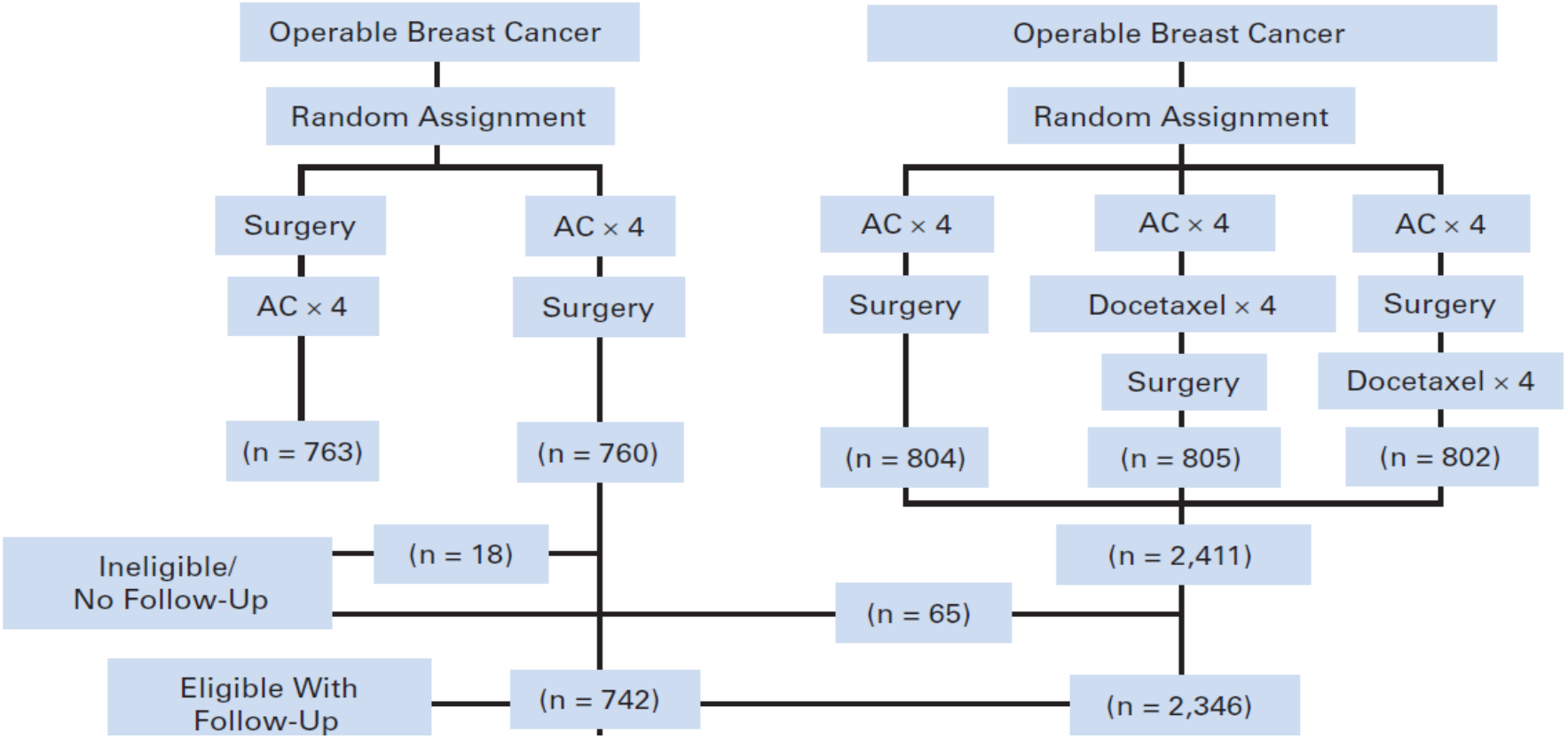
- ✓ Better survival for patients with pCR after PST
- ✓ Addition of taxanes ➔
  - ✓ Increased pCR
  - ✓ No improvement in survival
  - ✓ No increased BCT rate

Fisher B, et al. JCO 1997;15:2483-93 - Bear HD, et al JCO 2003;21:4165-74.

ESTRO School

Conundrum of PST: current evidence

Combined analysis of NSABP B18 and B27

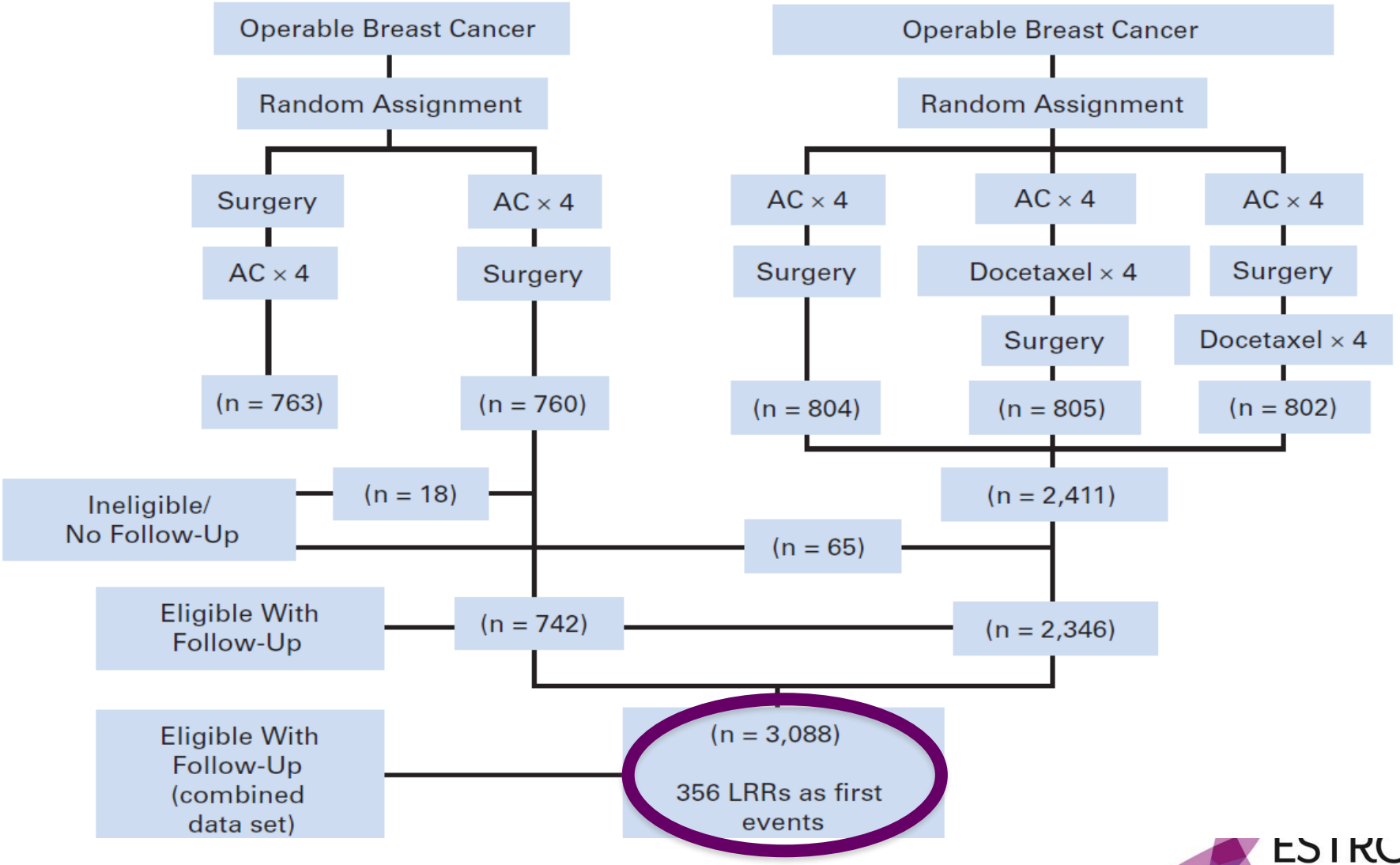


Mamounas E, et al. JCO 2012;30:3960-6.

ESTRO School

Conundrum of PST: current evidence

Combined analysis of NSABP B18 and B27



Mamounas E, et al. JCO 2012;30:3960-6.

ESTRO School

Conundrum of PST: current evidence

Combined analysis of NSABP B18 and B27

Predictors of LRR after primary chemotherapy

Conundrum of PST: current evidence

Combined analysis of NSABP B18 and B27

Predictors of LRR after primary chemotherapy

Radiation therapy in B18 and B27:

- Radiation to breast alone post-BCS
- No radiation post-mastectomy
- No regional nodal radiation

Mamounas E, et al. JCO 2012;30:3960-6.

ESTRO School

Conundrum of PST: current evidence

Combined analysis of NSABP B18 and B27

Predictors of LRR after primary chemotherapy

Follow-up 10 years:

- 335 LRR events
- 10 year cumulative incidence of LRR:
  - 12.3% (local 8.9%, regional 3.4%) for mastectomy
  - 10.3% (local 8.1%, regional 2.2%) for BCS + radiation

Conundrum of PST: current evidence

Combined analysis of NSABP B18 and B27

Predictors of LRR after primary chemotherapy

Table 3. Multivariate Analysis of Independent Predictors of 10-Year LRR According to Type of Surgery

Variable	No. of Patients	LRR Events	HR	95% CI	*P*
Patients treated with mastectomy*	1,071	131			
Clinical tumor size > 5 *v* ≤ 5 cm†			1.58	1.12 to 2.23	.0095
Clinical nodal status cN(+) *v* cN(−)†			1.53	1.08 to 2.18	.017
Nodal/breast pathologic status					< .001
ypN(−)/no breast pCR *v* ypN(−)/breast pCR†			2.21	0.77 to 6.30	
ypN(+) *v* ypN(−)/breast pCR†			4.48	1.64 to 12.21	
Patients treated with lumpectomy plus breast XRT*	1,890	189			
Age ≥ 50 *v* < 50 years†			0.71	0.53 to 0.96	.025
Clinical nodal status cN(+) *v* cN(−)†			1.70	1.26 to 2.31	< .001
Nodal/breast pathologic status					< .001
ypN(−)/no breast pCR *v* ypN(−)/breast pCR†			1.44	0.90 to 2.33	
ypN(+) *v* ypN(−)/breast pCR†			2.25	1.41 to 3.59	

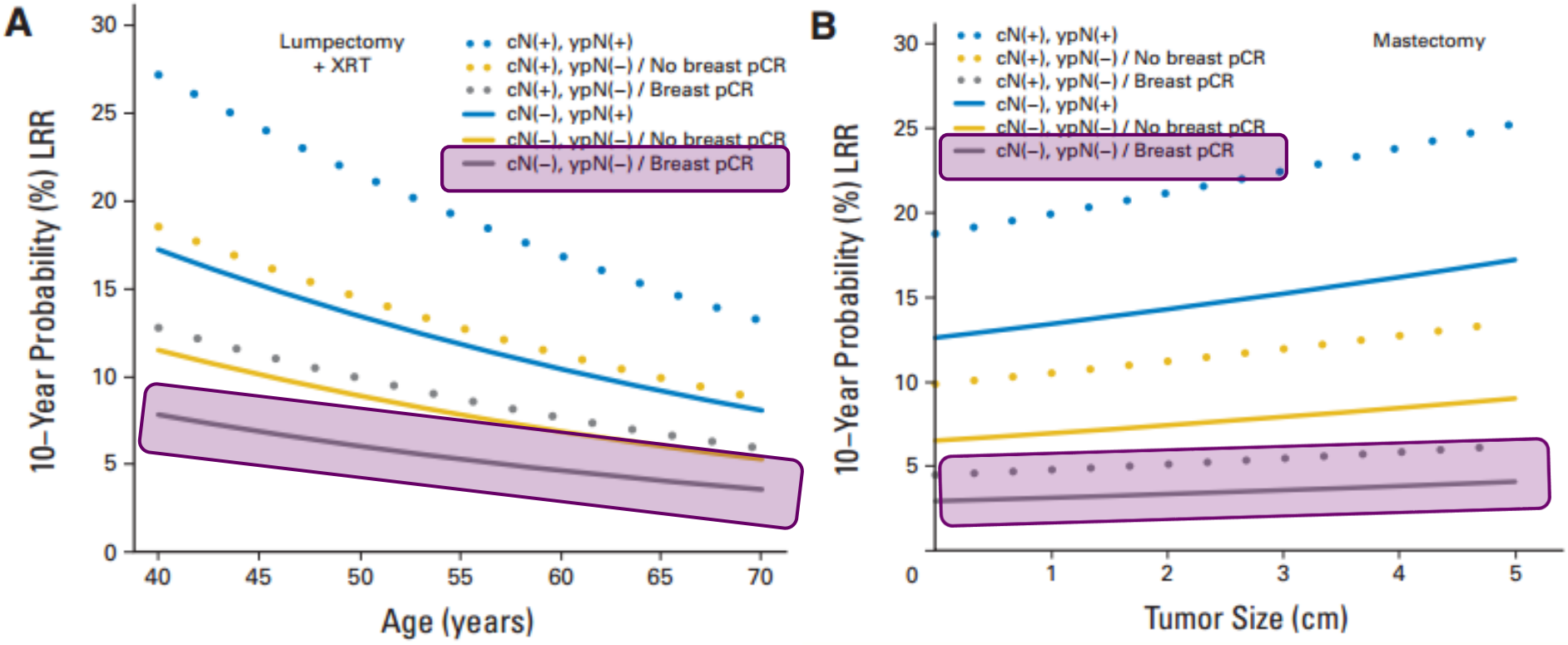
Mamounas E, et al. JCO 2012;30:3960-6.

ESTRO School

Conundrum of PST: current evidence

Combined analysis of NSABP B18 and B27

Predictors of LRR after primary chemotherapy



Mamounas E, et al. JCO 2012;30:3960-6.

ESTRO School

Conundrum of PST: current evidence

Combined analysis of NSABP B18 and B27

Predictors of LRR after primary chemotherapy

Summary:

- Predictive factors for LRR:
  - age
  - initial clinical stage prior
  - pathological response in breast and axilla
- Impact of age and clinical stage on absolute LRR rate is low if pCR in breast/axilla

Mamounas E, et al. JCO 2012;30:3960-6.

ESTRO School

Conundrum of PST: current evidence

Combined analysis of NSABP B18 and B27

Predictors of LRR after primary chemotherapy

Limitations:

- Patients with T4 and N2 disease were not eligible
- >85% patients diagnosed by FNA
- Unknown ER, PR, HER2 receptor status
- Non-contemporary systemic treatment:
  - Tamoxifen given on the basis of age (>50years) not ER
  - Chemotherapy schedules (AC*4 and AC*4-D*4)
  - No trastuzumab

Mamounas E, et al. JCO 2012;30:3960-6.

ESTRO School

Conundrum of PST: current evidence

Combined analysis of NSABP B18 and B27

Predictors of LRR after primary chemotherapy

Other limitations:

- QA of radiation therapy?
- Endpoint: DFS rather then LRR ✗

Conundrum of PST: current evidence

Retrospective analysis of 5 prospective trials at MDACC with PST & mastectomy without PMRT

Table 2. Neoadjuvant Chemotherapy Treatment Details

Protocol	Years of Study	Neoadjuvant Chemotherapy	No. of Cycles	Included Patients/Total Study Population
Advanced Primary	1974-1985	FAC	3	40/191
85-01	1985-1989	VACP	3	23/200
89-007	1989-1991	FAC	4	15/203
91-015	1991-1994	FAC or dose-escalated FAC	4	60/202
94-002	1994-1998	FAC or paclitaxel	4	60/174
Total	1974-1998			150/970

Stage distribution:

I	-	*1%*
II	-	*43%*
IIIA	-	*23%*
IIIB	-	*25%*
IV	-	*7%*

Buchholz TA, et al. JCO 2001;20:17-23.

ESTRO School

Conundrum of PST: current evidence

MDACC series: *predictive factors for LRR*

Pre-PST factors:

- ✓ Increasing clinical T stage ($p<0.0001$)
- ✓ Nodal status ($p<0.0001$)

Post-PST factors:

- ✓ Size of residual primary tumour ($p=0.0048$)
- ✓ Increasing number of involved nodes ($p<0.0001$)
- ✓ No tamoxifen ($p<0.0013$)

LRR after pCR (n = 18) = 19%:

➔ *Achievement of pCR does not preclude the need for PMRT if indicated by the initial stage of the disease*

Buchholz TA, et al. JCO 2001;20:17-23.

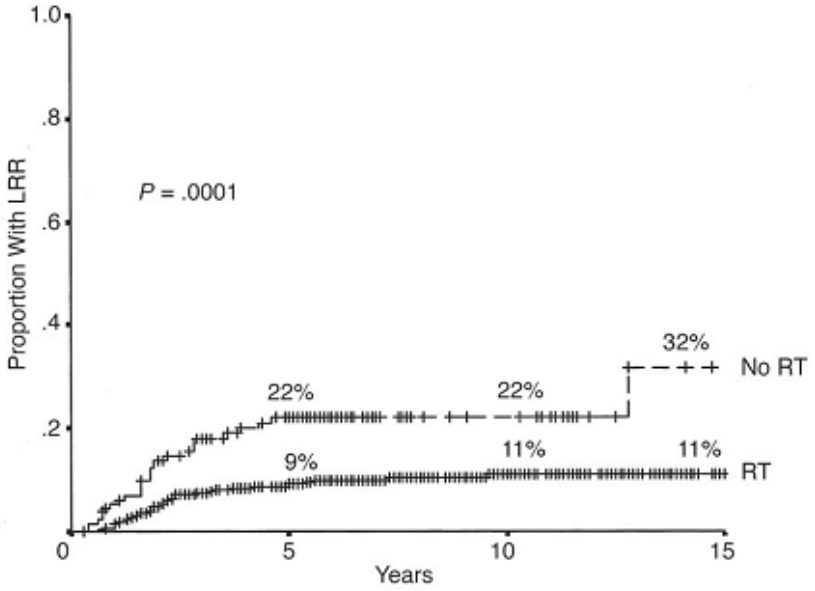
ESTRO School

Conundrum of PST: current evidence

6 studies (713 pts) PST + surgery ± RT

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Postmastectomy Radiation Improves Local-Regional Control and Survival for Selected Patients With Locally Advanced Breast Cancer Treated With Neoadjuvant Chemotherapy and Mastectomy



	No. Patients	No. Events
No RT	134	28
RT	542	50

Factor	10-year LRR Rate: No Radiation (%)	Radiation (%)	P
Clinical T-stage			
T1	0	8	.535
T2	10	7	.408
T3	22	8	.002
T4	46	15	< .0001
Clinical N-stage			
N0	23	10	.014
N1	14	9	.062
N2-3	40	12	< .0001
Pathological tumor size, cm			
0-2	13	8	.051
2.1-5.0	31	14	.002
≥ 5.1	52	13	.001
No. of positive nodes			
0	11	4	.010
1-3	13	11	.636
≥ 4	59	16	< .0001

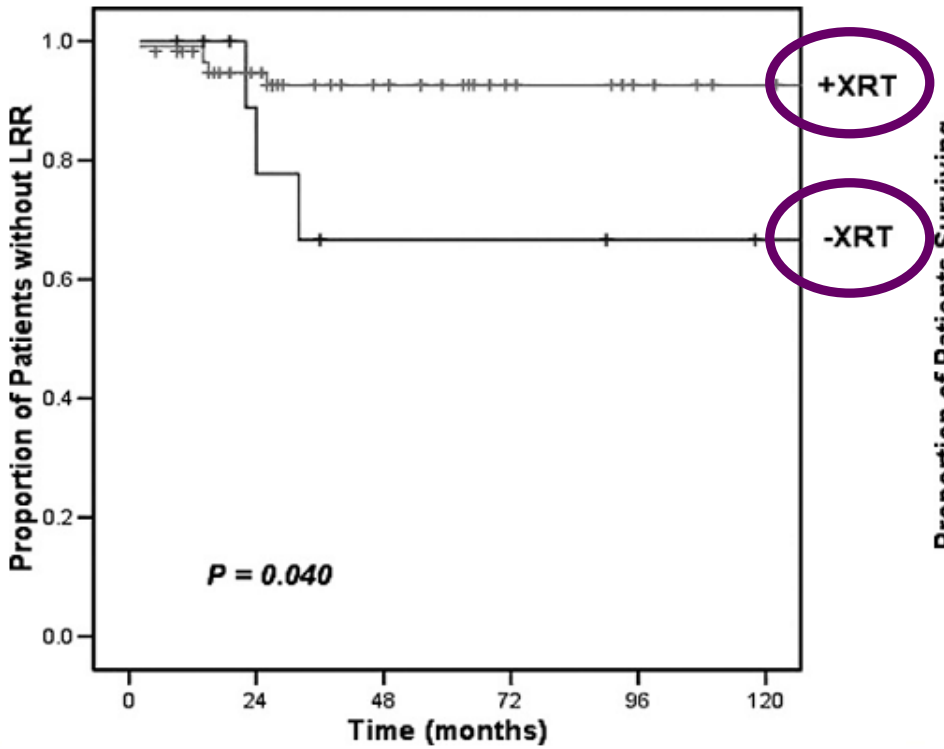
Huang EH, et al. J Clin Oncol 2004;22:4691-9

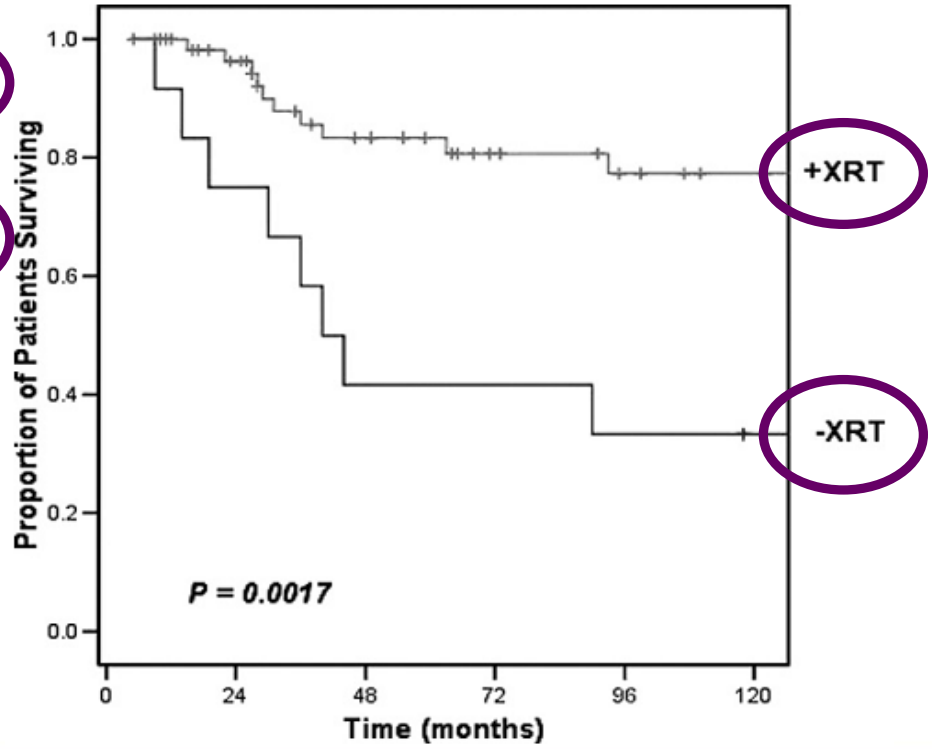
ESTRO School

Conundrum of PST: current evidence

226 pts PST ➔ pCR + surgery ± RT

POSTMASTECTOMY RADIATION IMPROVES THE OUTCOME OF PATIENTS WITH LOCALLY ADVANCED BREAST CANCER WHO ACHIEVE A PATHOLOGIC COMPLETE RESPONSE TO NEOADJUVANT CHEMOTHERAPY





McGuire SE. IJROBP 2007;68:1004-9.

ESTRO School

Conundrum of PST: current evidence

UniversitätsKlinikum Heidelberg

HIRO Heidelberger Institut für Radioonkologie
Nationales Zentrum für Strahlenforschung in der Onkologie Heidelberg
getragen von: Deutsches Krebsforschungszentrum, Universitätsklinikum Heidelberg, Heidelberger Ionenstrahl-Therapiezentrum

RadioOnkologie
Behandeln Forschen Lehren

Relationship of omission of adjuvant radiotherapy to outcomes of locoregional control and disease-free survival in patients with or without pCR after neoadjuvant chemotherapy for breast cancer: A meta-analysis on 3481 patients from the Gepar-trials.

David Krug, Bianca Lederer, Jürgen Debus, Jens Blohmer, Serban Costa, Holger Eidtmann, Claus Hanusch, Jörn Hilfrich, Jens Huober, Christian Jackisch, Sherko Kümmel, Stefan Paepke, Andreas Schneeweiss, Michael Untch, Gunter von Minckwitz, Sibylle Loibl
for the GBG and AGO-B study groups

GBG GERMAN BREAST GROUP

AGO-B BREAST STUDY GROUP

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

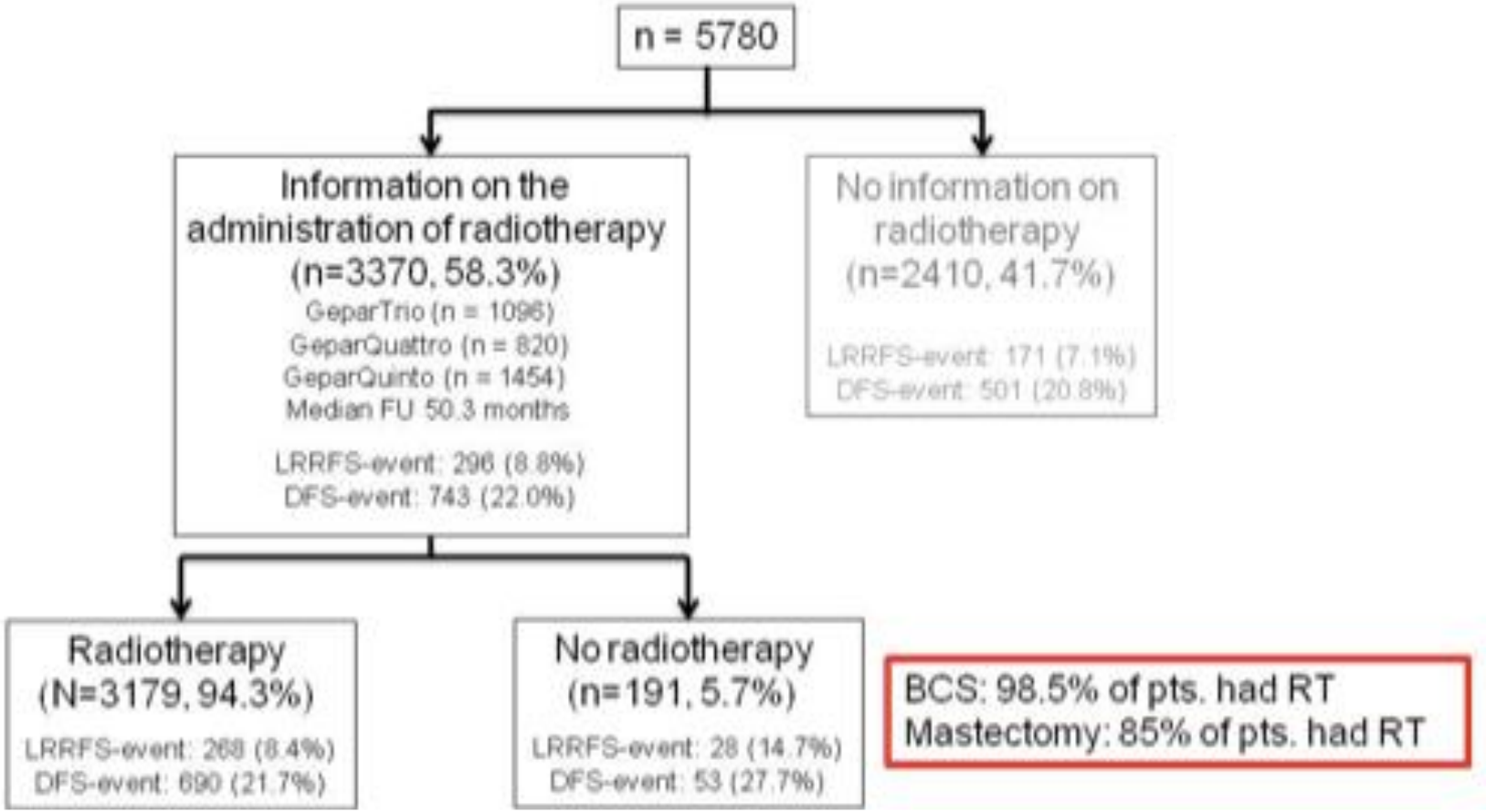
PRESENTED AT: ASCO Annual '15 Meeting

ESTRO School

Krug D, et al. JCO 2015;33:A1008

Conundrum of PST: current evidence

GBG Trials: GeparTrio, GeparQuatro, GeparQuinto



RT-indication based on initial stage: cT3/4, cN+ & on ypN+

Krug D, et al. JCO 2015;33:A1008

Conundrum of PST: current evidence

GBG Trials: GeparTrio, GeparQuatro, GeparQuinto

Overall results:

- 5yr LRFS, 90% vs 81.5%, p=0.001 for ± radiation
- 5yr DFS, 75% vs 67%, p=0.001 for ± radiation

After pCR:

- 5yr LRFS, 96% vs 87%, p=0.051 for ± radiation

No pCR:

- 5yr LRFS, 89% vs 81%, p=0.001 for ± radiation

In multivariate analysis, adjusting for baseline characteristics and pCR, RT was confirmed as an independent prognostic factor for LRFS and DFS

Krug D, et al. JCO 2015;33:A1008

ESTRO School

Conundrum of PST: current evidence

Indications for post-mastectomy RT

Factors that assist in decision making based on retrospective analyses of NSABP-B18; NSABP-B27; MDACC series; GBG Trial Meta-analysis:

- ✓ Initial stage
- ✓ Biological characteristics
- ✓ Burden of residual disease
- ✓ Response to chemotherapy

Conundrum of PST: current evidence

Is this still valid?

- Studies performed in '80^{s} & '90^{s}
- Since then practice has changed:
  - ✓ Shift towards use in earlier stage BC patients
  - ✓ Improved diagnostic tools (MRI)
  - ✓ More reliable staging tools ➔ *"Will Rogers phenomenon"*
  - ✓ More effective systemic treatments
  - ✓ Improved knowledge on patient selection *(molecular subtype)*

Conundrum of PST: current evidence

What evidence are we missing?

- Is BCT after down-staging safe?
- Indications for chest wall RT after mastectomy
- Need and extent for/of local/regional surgery?
- Indications for nodal irradiation?
- Benefit of subsequent adjuvant systemic treatment?
- Role of preoperative irradiation?

The conundrum of PST for the rad. oncologist

1. Introduction
2. Interaction with systemic therapy
3. Current evidence
4. On going trials and future directions
5. A technical note
6. Discussion & Conclusions

Conundrum of PST: trials and future directions

ACOSOG A0112012

cT1-T3 cN1 ➔ PST ➔ surgery including SLNB

If N+: Ⓡ ALND vs. RT

NCT01901094

Conundrum of PST: trials and future directions

ACTO (Russia)

cT0-T3 cN+ ➔ PST ➔ mastectomy

If N-: ® PMRT vs. observation

Conundrum of PST: trials and future directions

NSABP B51 (RTOG 1308)

cT1-T3 cN1 ➔ PST ➔ mastectomy

If ypN0: ® PMRT vs. observation

http://www.nsabp.pitt.edu/B-51.asp *https://clinicaltrials.gov/ct2/show/NCT01279304*

Conundrum of PST: trials and future directions

BOOG 2010-03 RAPChem

cT1-T2 cN1 → PST → registration project

- Group I: ypT0-2N0
  - after MRM: no radiotherapy
  - after BCT: radiation treatment of the breast with boost
- Group II: ypT0-2N1:
  - after MRM: radiation treatment of the thoracic wall
  - after BCT: radiation treatment of the breast with boost
- Group III: ypT0-2N2-3, ypT3-4N0-1, and ypT3-4N0-3:
  - after MRM: radiation treatment of the thoracic wall and supraclavicular nodes
  - after BCT: radiation treatment of the breast with boost, and supraclavicular nodes

ESTRO School

Conundrum of PST: trials and future directions

The missing link: pre-operative RT?

European Journal of Cancer 78 (2017) 116–117

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Editorial

Preoperative radiation therapy: The 'new' targeted breast cancer treatment?

Coles CE, Fourquet A, Poortmans P. Eur J Cancer

Conundrum of PST: trials and future directions

The missing link: pre-operative RT?

ELSEVIER

European Journal of Cancer

Volume 76, May 2017, Pages 45–51

Original Research

Preoperative radiotherapy in breast cancer patients: 32 years of follow-up

F.G. Riet[a], , , F. Fayard[b], R. Arriagada[a, h], M.A. Santos[c], C. Bourgier[d], M. Ferchiou[e], S. Heymann[a], S. Delaloge[f], C. Mazouni[g], A. Dunant[b], S. Rivera[a]

Riet FG, et al Eur J Cancer 2017;76:45-51.

ESTRO School

Conundrum of PST: trials and future directions

The missing link: pre-operative RT?

European Journal of Cancer 82 (2017) 184–192

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Current Perspective

Preoperative breast radiation therapy: Indications and perspectives

S.V. Lightowlers [a,*], L.J. Boersma [b], A. Fourquet [c], Y.M. Kirova [c], B.V. Offersen [d], P. Poortmans [c], A.N. Scholten [e], N. Somaiah [f], C.E. Coles [g]

Lightowers SV, et al. European Journal of Cancer 2017;82:184e192.

The conundrum of PST for the rad. oncologist

1. Introduction
2. Interaction with systemic therapy
3. Current evidence
4. On going trials and future directions
5. A technical note
6. Discussion & Conclusions

Medical Radiology Diagnostic Imaging

Seymour H. Levitt
James A. Purdy
Carlos A. Perez
Philip Poortmans
Editors

Technical Basis of Radiation Therapy
Practical Clinical Applications
Fifth Edition

This well-received book, now in its fifth edition, is unique in providing a detailed description of the technological basis of radiation therapy. Another novel feature is the collaborative writing of the chapters by North American and European authors. This considerably broadens the book's perspective and increases its applicability in daily practice throughout the world. The book is divided into two sections. The first covers basic concepts in treatment planning, including essential physics and biological principles related to time-dosefractionation, and explains the various technological approaches to radiation therapy, s as intensity-modulated radiation therapy, tomotherapy, stereota radiotherapy, and high and low dose rate brachytherapy. Iss to quality assurance, technology assessment, and cost also reviewed. The second part of the book discus tical clinical applications of the different radi in a wide range of cancer sites. All of th leaders in the field. This book will ers, students, and practitioner basic technological facto

ISSN 0942-
ISBN 978-3-64
9 783642 11157

springer.com

Levitt · Purdy · Perez
Poortmans *Eds.*

diation Therapy

5th Ed.

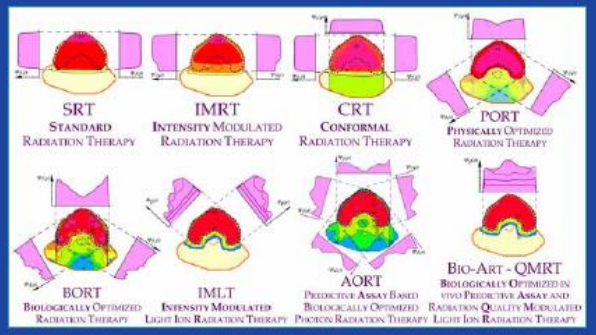
Medical Radiology
Diagnostic Imaging
A.L. Baert
M.F. Reiser
H. Hricak
M. Knauth

herapy

nical Applications

Edition

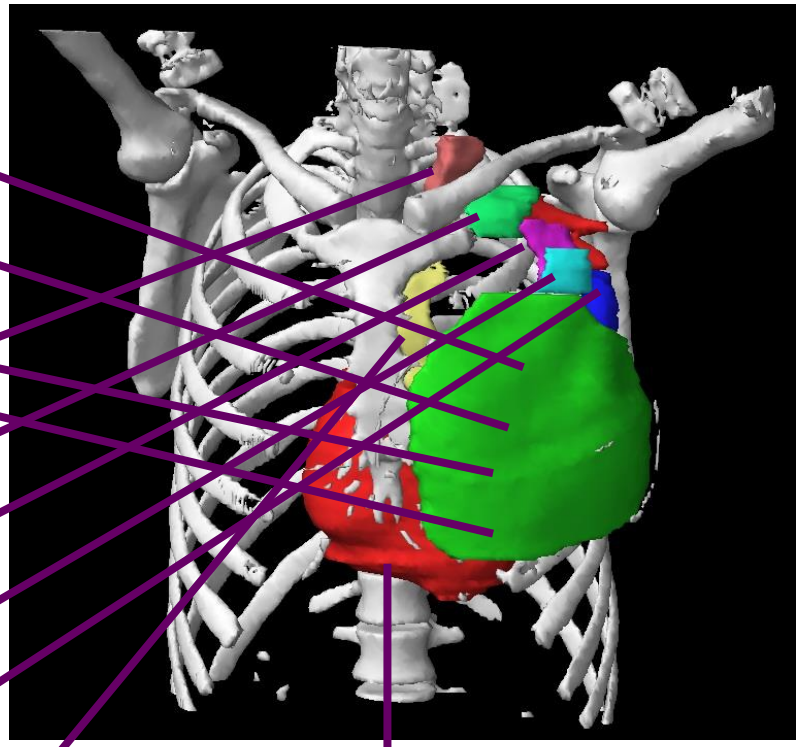
Springer



Techniques serve the goal –
not the other way around!

Conundrum of PST: a technical note

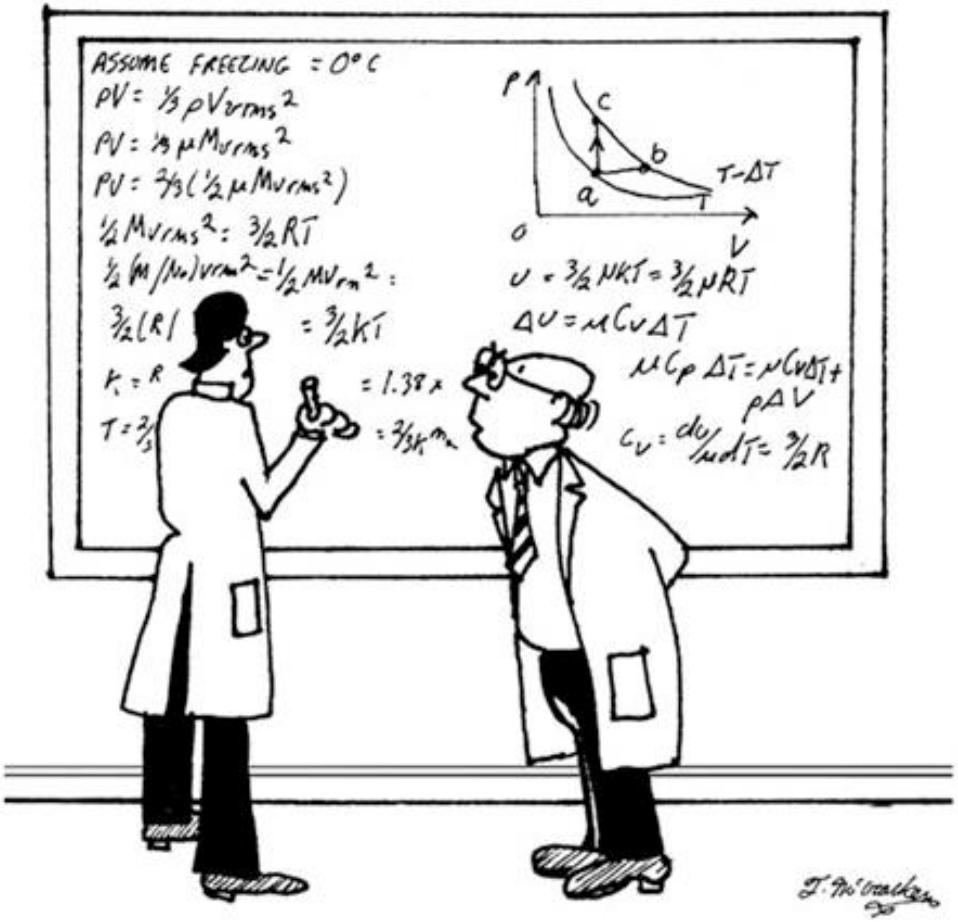
- Breast
- Boost
- PBI
- Thoracic wall
- LN supraclavicular
- LN axilla level III
- LN axilla level II
- LN axilla Rotter
- LN axilla level I
- LN internal mammary



Offersen BV, et al. Radiother Oncol 2015;114:3-10 & 2016;118:205-8.

ESTRO School

Conundrum of PST: a technical note



"WELL SURE, IF YOU WANT TO GET TECHNICAL ABOUT IT."

ESTRO School

Conundrum of PST: a technical note

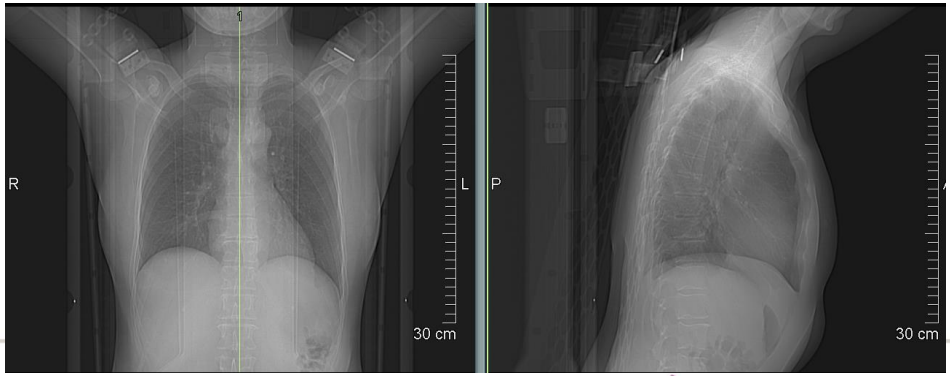
Planning-CT-scan before and after PST

March 2013: patient age 49

- Tumour central in left breast:
- Biopsy (histology): IDA G3; triple –
- FNA axillary LN: +
- FNA supraclavicular LN: +
- Conclusion after staging: cT3N3M0

Treatment: PST

- Referred for evaluation by RO
- TAC x 6



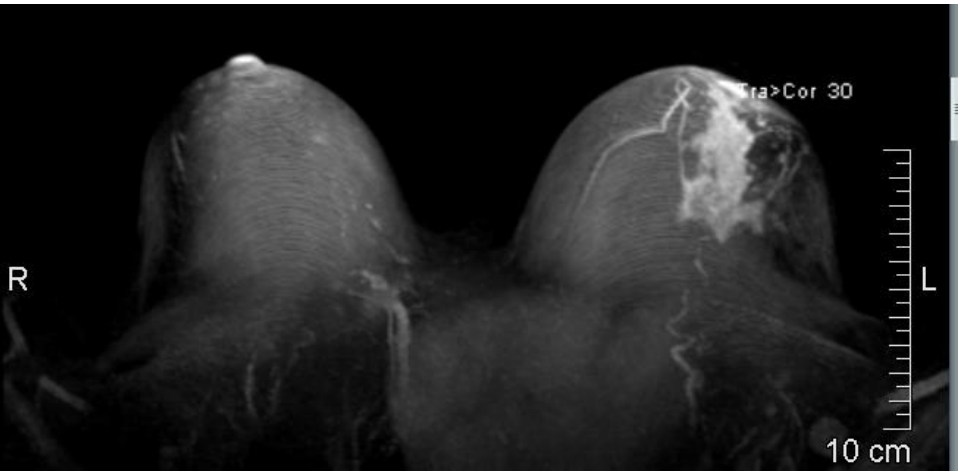
ESTRO School

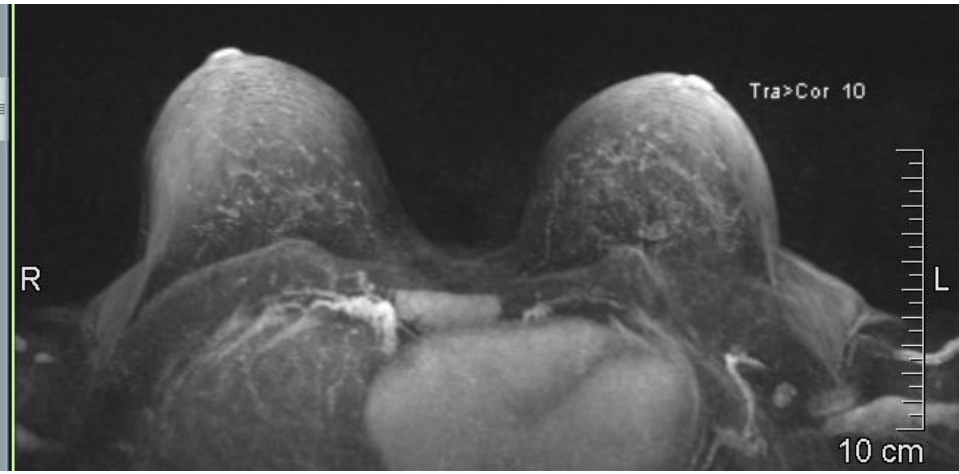
Conundrum of PST: a technical note

Planning-CT-scan before and after PST

May 2013:

- Major tumour regression on MRI





Treatment:

- Continue TAC ➔ July 2013
- MRM: ypT0ypN0
- PMRT + boost on non-removed nodes

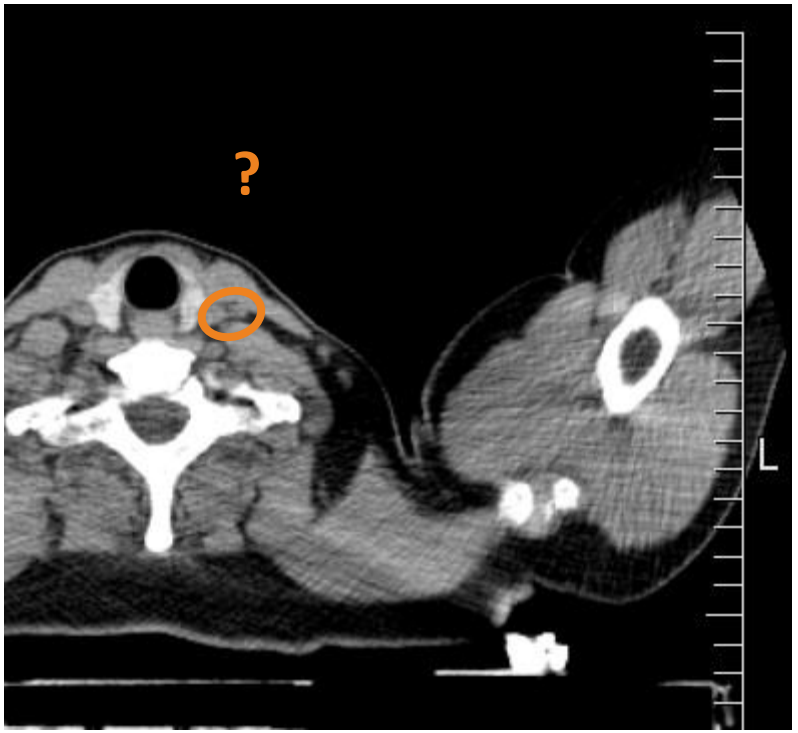
ESTRO School

Conundrum of PST: a technical note

Planning-CT-scan before and after PST

March 2013

September 2013



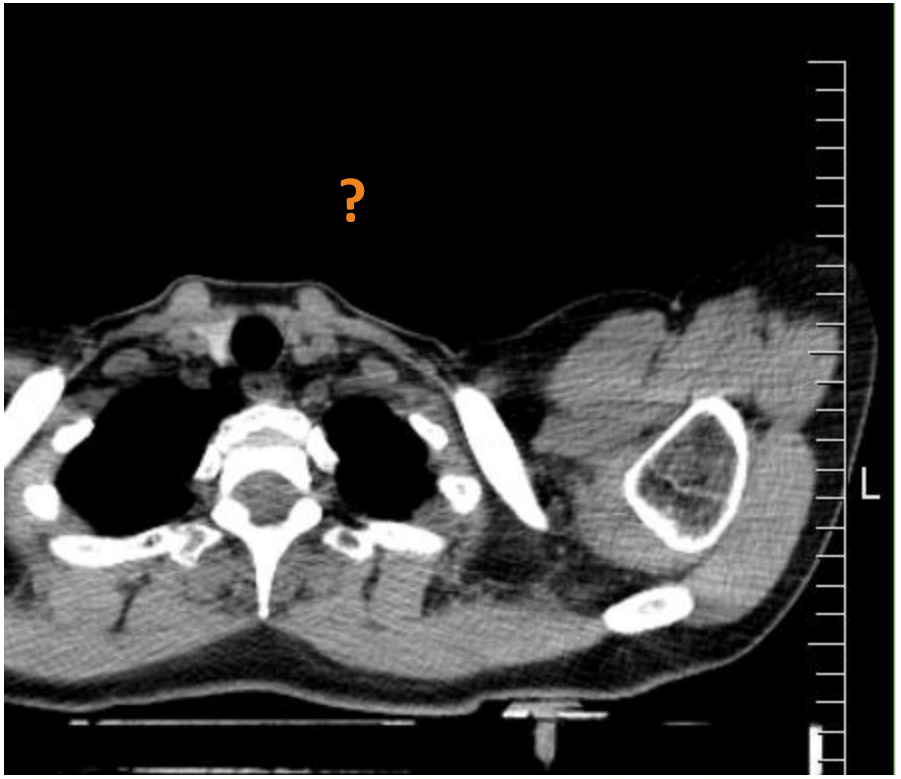
ESTRO School

Conundrum of PST: a technical note

Planning-CT-scan before and after PST

March 2013

September 2013

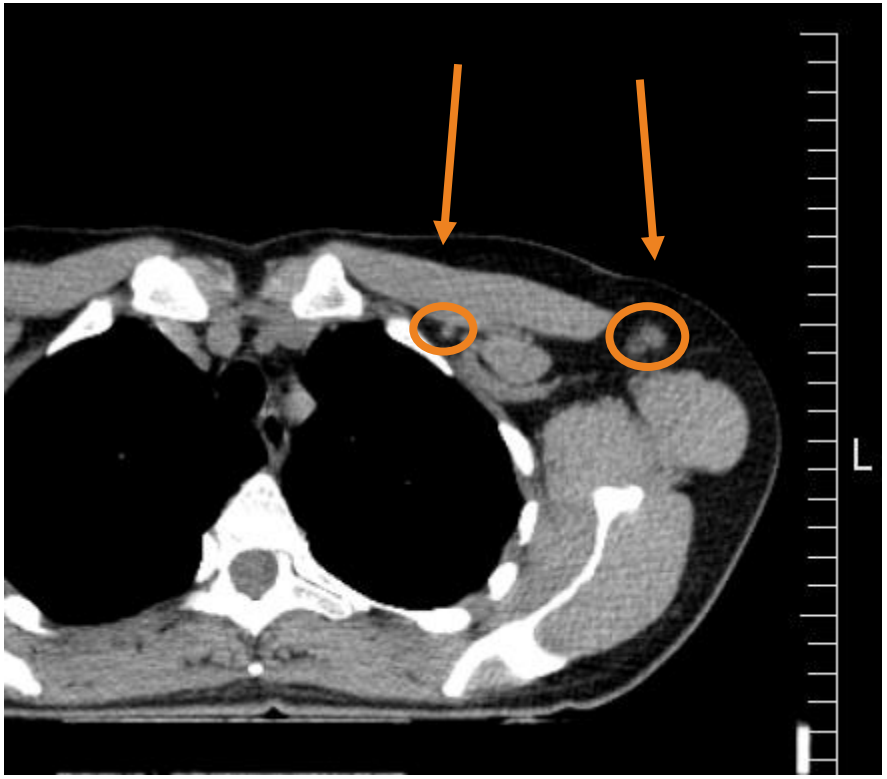


ESTRO School

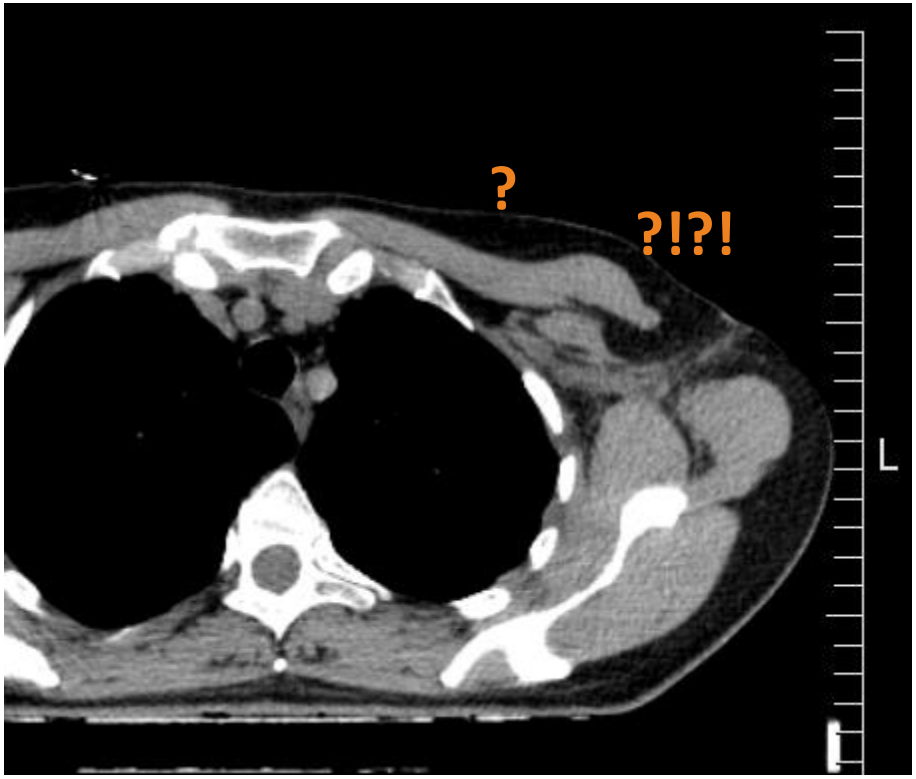
Conundrum of PST: a technical note

Planning-CT-scan before and after PST

March 2013



September 2013

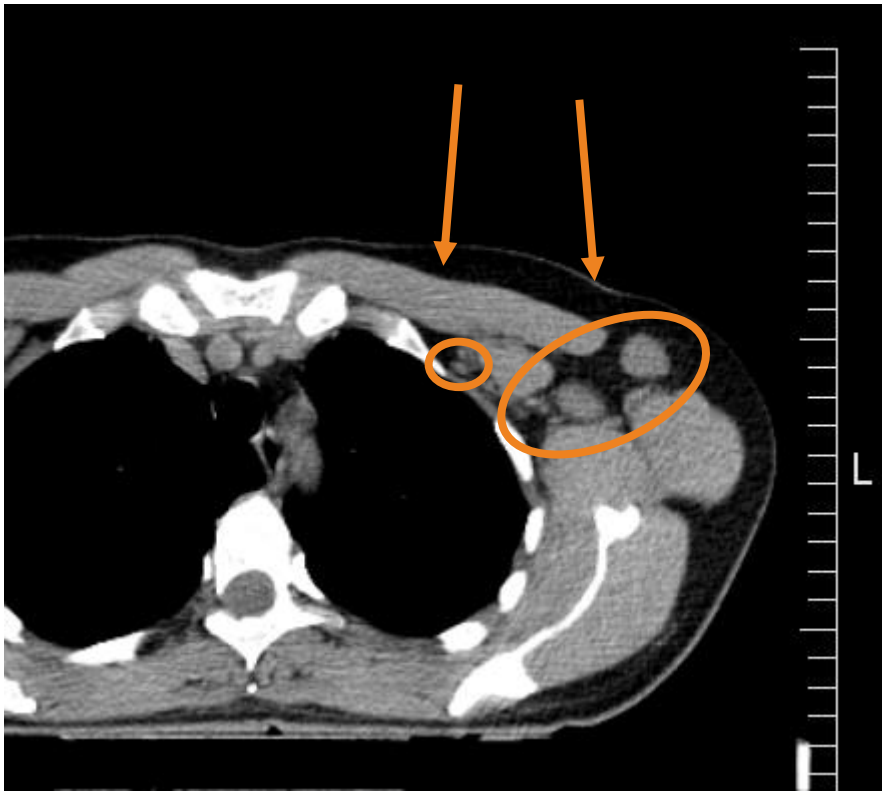


ESTRO School

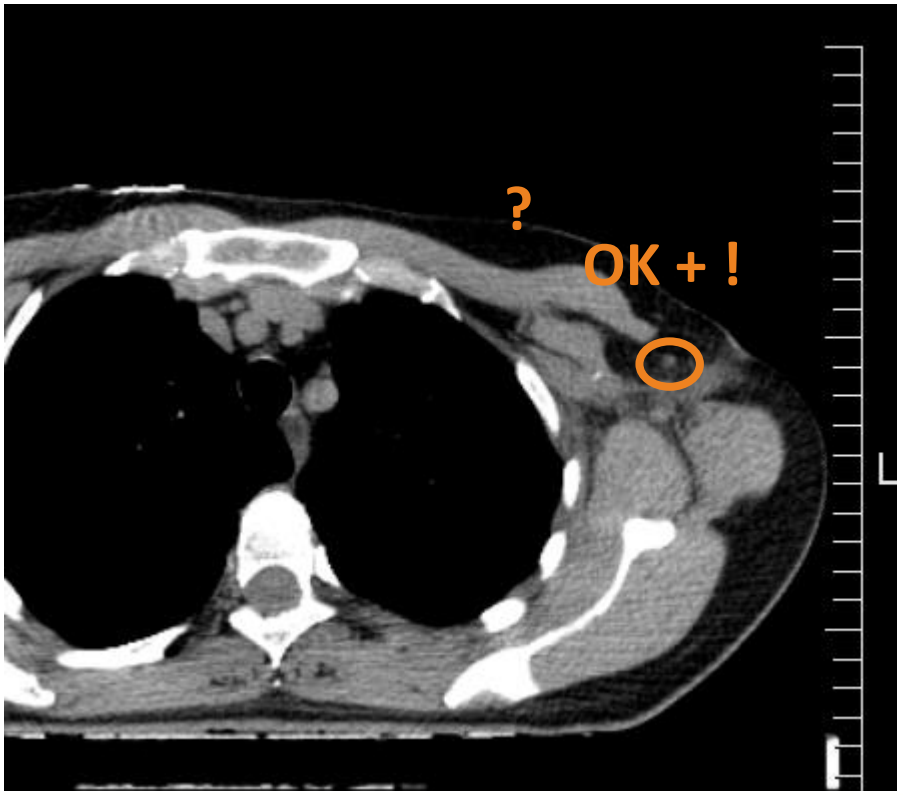
Conundrum of PST: a technical note

Planning-CT-scan before and after PST

March 2013



September 2013

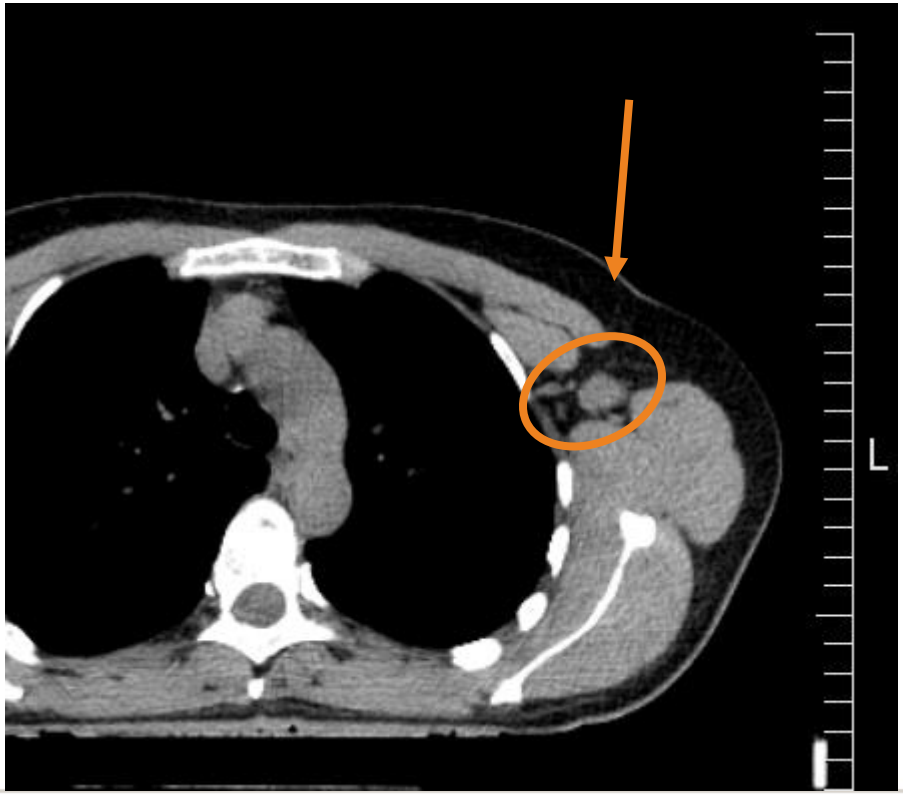


ESTRO School

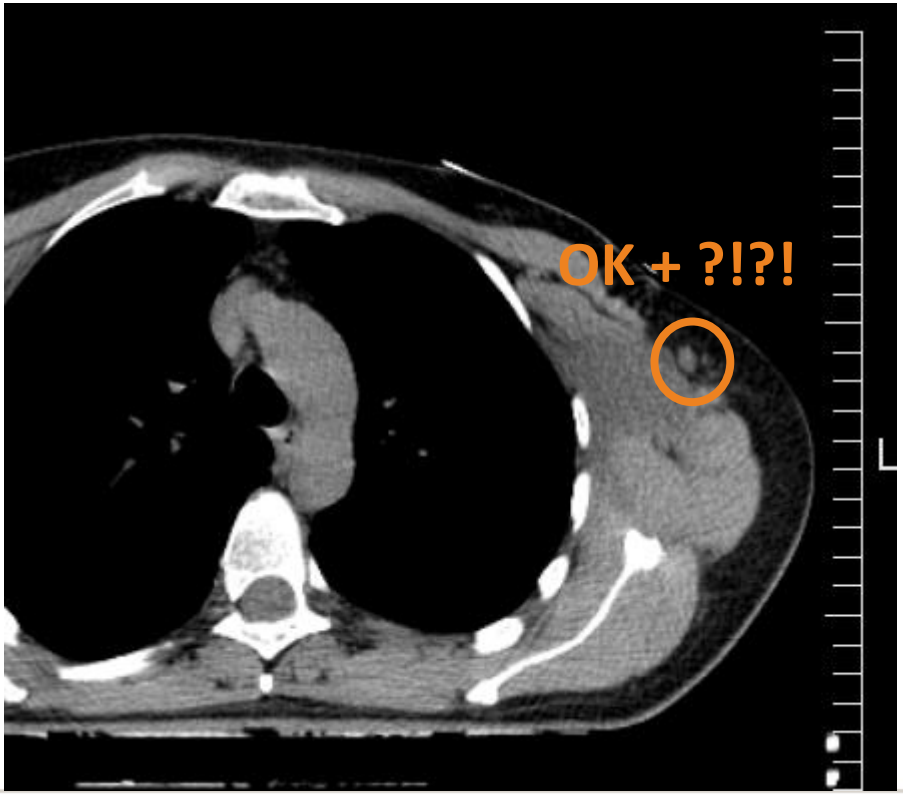
Conundrum of PST: a technical note

Planning-CT-scan before and after PST

March 2013



September 2013

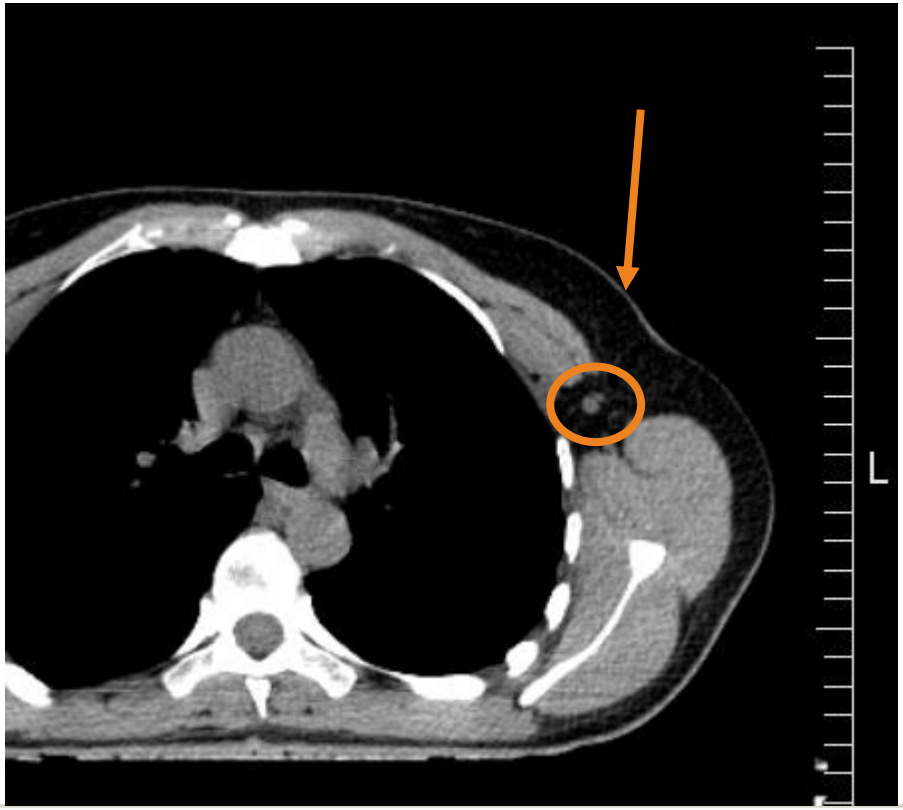


ESTRO School

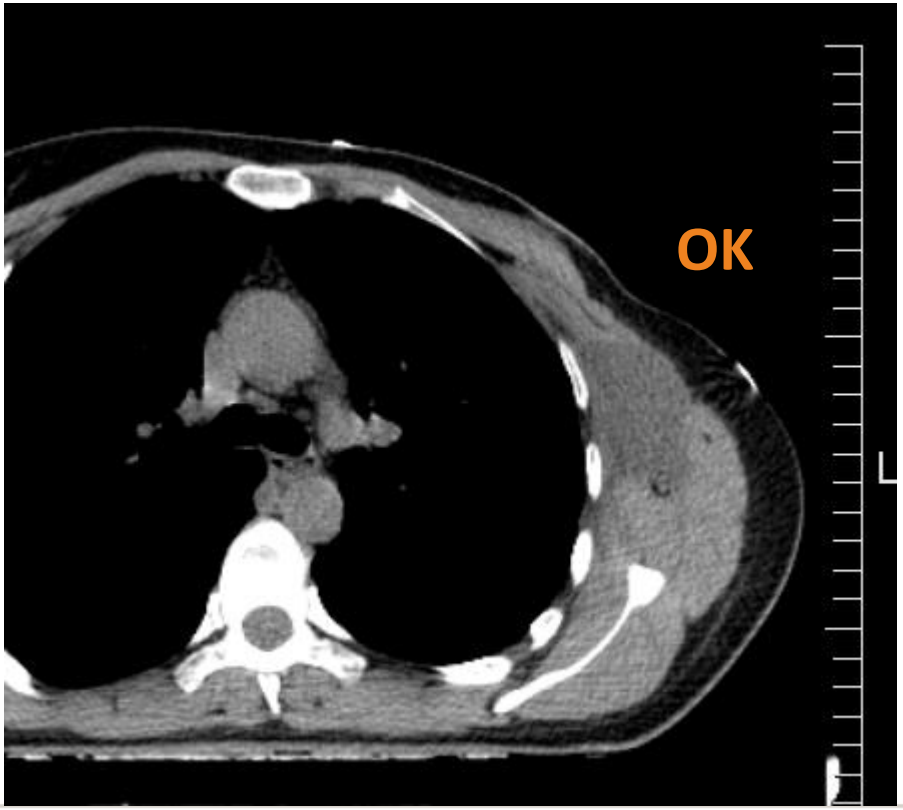
Conundrum of PST: a technical note

Planning-CT-scan before and after PST

March 2013



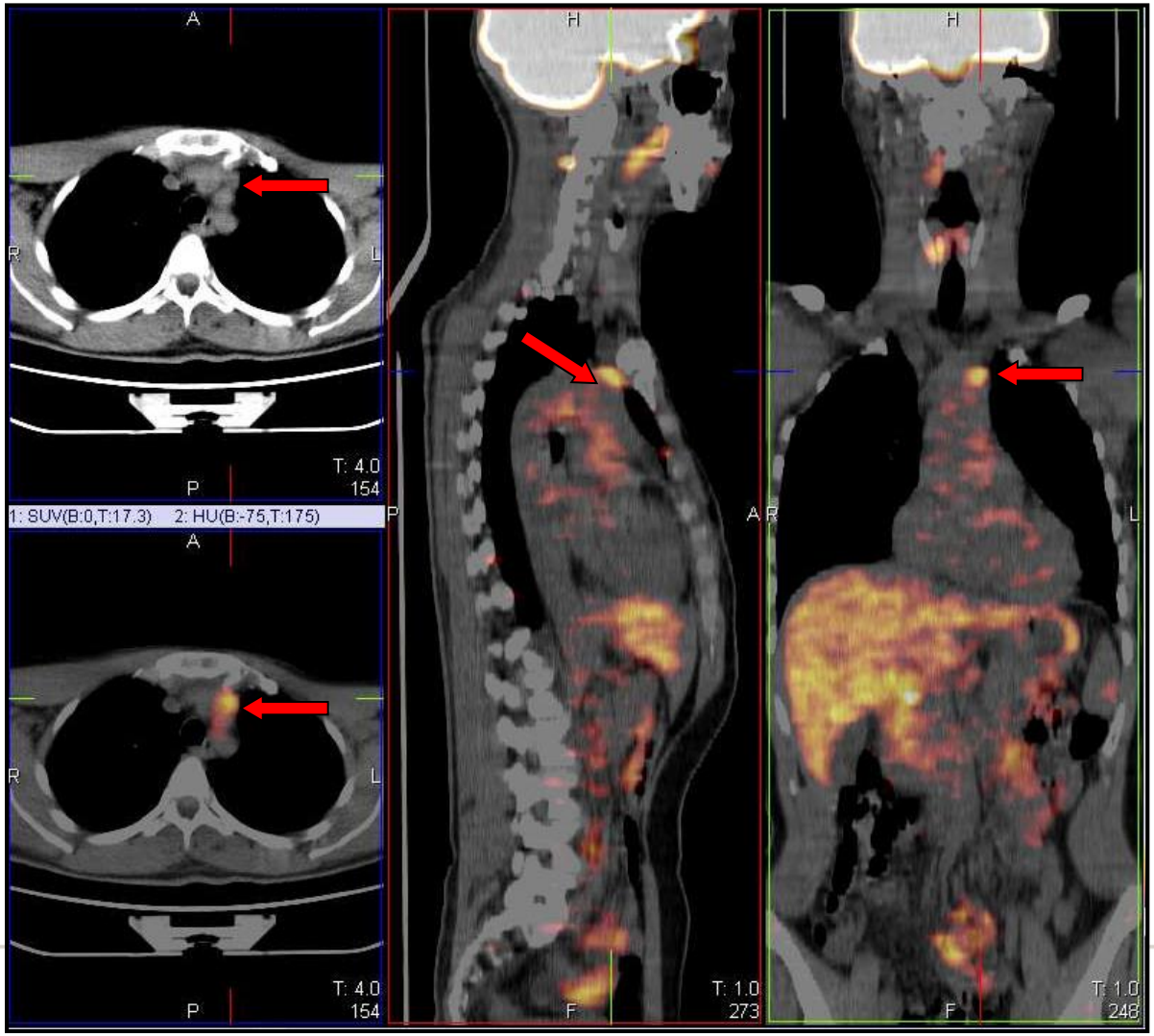
September 2013



ESTRO School

Conundrum of PST: a technical note

Or even a PET-CT?



Courtesy of MC Valli and A Fozza

ESTRO School

The conundrum of PST for the rad. oncologist

1. Introduction
2. Interaction with systemic therapy
3. Current evidence
4. On going trials and future directions
5. A technical note
6. Discussion & Conclusions

Conundrum of PST: discussion & conclusions

Better local treatment adds to the effects of systemic therapy on local recurrence and on breast cancer mortality.

EBCTCG Lancet 2005; 365: 1687-1717; EBCTCG Lancet 2005; 366: 2087–2106

ESTRO School

Conundrum of PST: discussion & conclusions

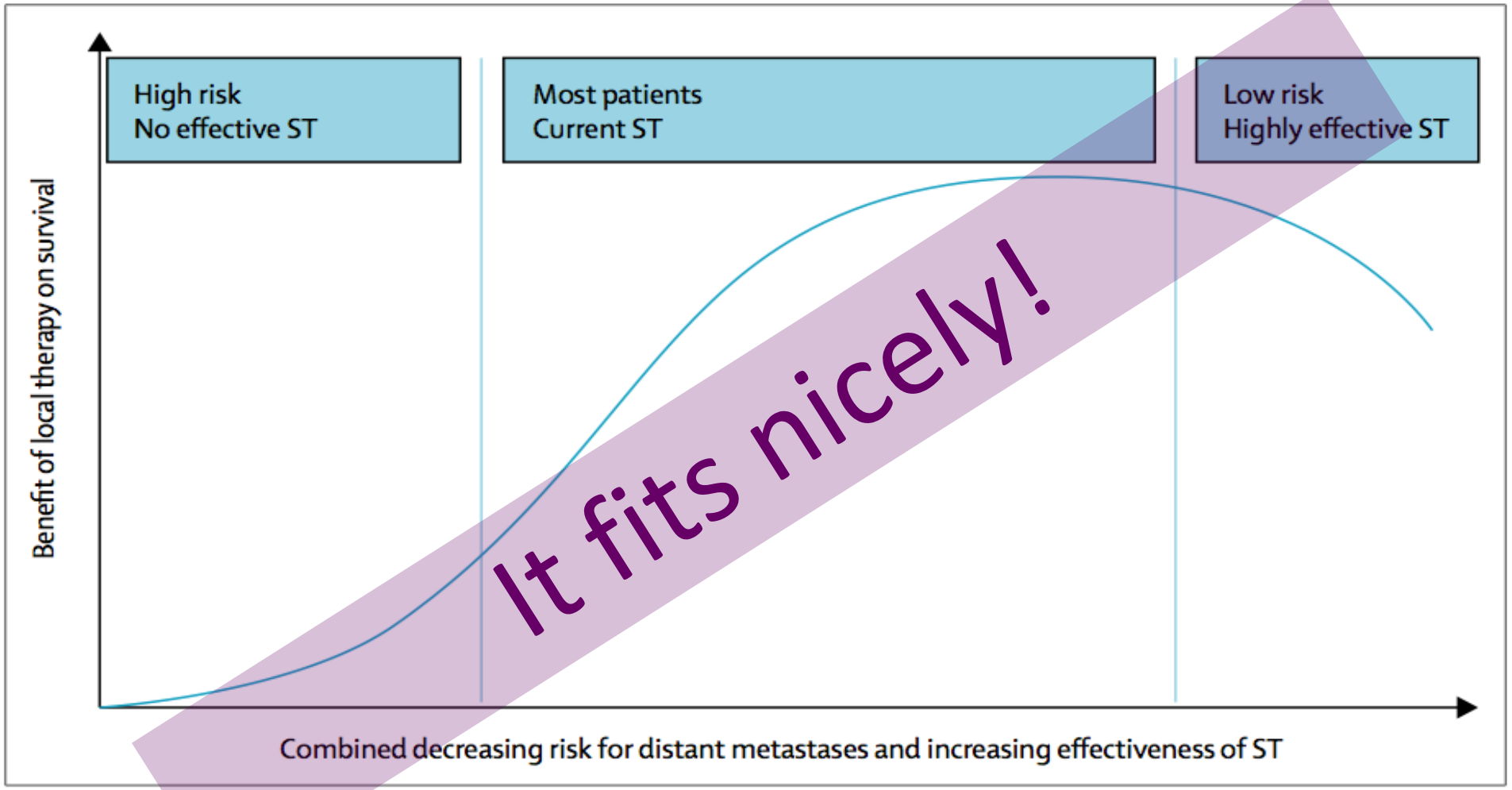


***Figure*: Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour**

Poortmans P. Lancet. 2014 Jun 21;383(9935):2104-6.

ESTRO School

Conundrum of PST: discussion & conclusions

NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Breast Cancer

Version 2.2017 — April 6, 2017

NCCN.org

NCCN Guidelines for Patients® available at www.nccn.org/patients

Continue

Version 2.2017, 04/06/17 National Comprehensive Cancer Network, Inc. 2017, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

ESTRO School

Conundrum of PST: discussion & conclusions

Printed by Philip Poortmans on 4/9/2017 5:25:33 AM. For personal use only. Not approved for distribution. Copyright © 2017 National Comprehensive Cancer Network, Inc., All Rights Reserved.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PREOPERATIVE SYSTEMIC THERAPY: ADJUVANT THERAPY

SURGICAL TREATMENT

ADJUVANT TREATMENT

Mastectomy and surgical axillary staging[l,mm] ± reconstruction.[p]
If SLNB performed prechemotherapy and negative findings, omit axillary lymph node staging.
See BINV-11

- Complete planned chemotherapy regimen course if not completed preoperatively.
- Adjuvant radiation therapy[r] post-mastectomy is based on maximal disease stage from pre-chemotherapy tumor characteristics at diagnosis and post-chemotherapy pathology results. Adjuvant radiation therapy is recommended:
  - As indicated on BINV-3
  - For cT3-4, cN2-3, stage III, residual disease >2 cm any ypN+

and

- Endocrine therapy if ER-positive and/or PR-positive[z] (category 1)
- Complete up to one year of trastuzumab therapy if HER2-positive (category 1). May be administered concurrently with radiation therapy[r] and with endocrine therapy if indicated.

Lumpectomy with surgical axillary staging.[l,mm]
If SLNB performed prechemotherapy and negative findings, omit axillary lymph node staging.
See BINV-11

- Complete planned chemotherapy regimen course if not completed preoperatively.
- Adjuvant radiation therapy[r] post-lumpectomy is based on maximal disease stage from pre-chemotherapy tumor characteristics at diagnosis and post-chemotherapy pathology results. Adjuvant radiation therapy is recommended:
  - As indicated on BINV-2
  - For cT3-4, cN2-3, stage III, residual disease >2 cm any ypN+

and

- Endocrine therapy if ER-positive and/or PR-positive[z] (category 1)
- Complete up to one year of trastuzumab therapy if HER2-positive (category 1). May be administered concurrently with radiation therapy[r] and with endocrine therapy if indicated.

See Surveillance/ Follow-up (BINV-16)

Conundrum of PST: discussion & conclusions

Decreasing role of surgery:

Global Breast Cancer Conference
GBCC 2017
April 20 (Thu) - 22 (Sat), 2017
The Shilla Jeju Hotel, Jeju Island, Korea

www.gbcc.kr

Plenary Lecture 3 : Has Axillary Clearance has Become Obsolete?			
Date & Time	Apr 21 (Fri.), 08:30-09:30	Venue	**Halla Hall**
Moderators	**Prof.Soo-Jung Lee** (Yeungnam Medical Center, Korea)		
Speakers	**Prof.Emiel Rutgers** (Netherlands Cancer Institute, Netherlands)		

- Less extensive surgery after PST ➔ none?
  - *HER2+: pCR rates >50%*
  - *TN: pCR rates >30%*

ESTRO School

Conundrum of PST: discussion & conclusions

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Over-irradiation

In general, the use of RT compensates for the decreasing extent of surgery to the breast and the axillary lymph nodes, eliminating residual tumour cells while maintaining better aesthetic and functional results. In some occasions, however, the indications for the extent of RT have to be based on limited pathological staging information. Research is ongoing to individualise RT more on the basis of biological factors including gene expression profiles. When considering age, treatment decisions should rather be based on biological instead of formal age.

Poortmans P, et al. Breast. 2017;31:295-302.

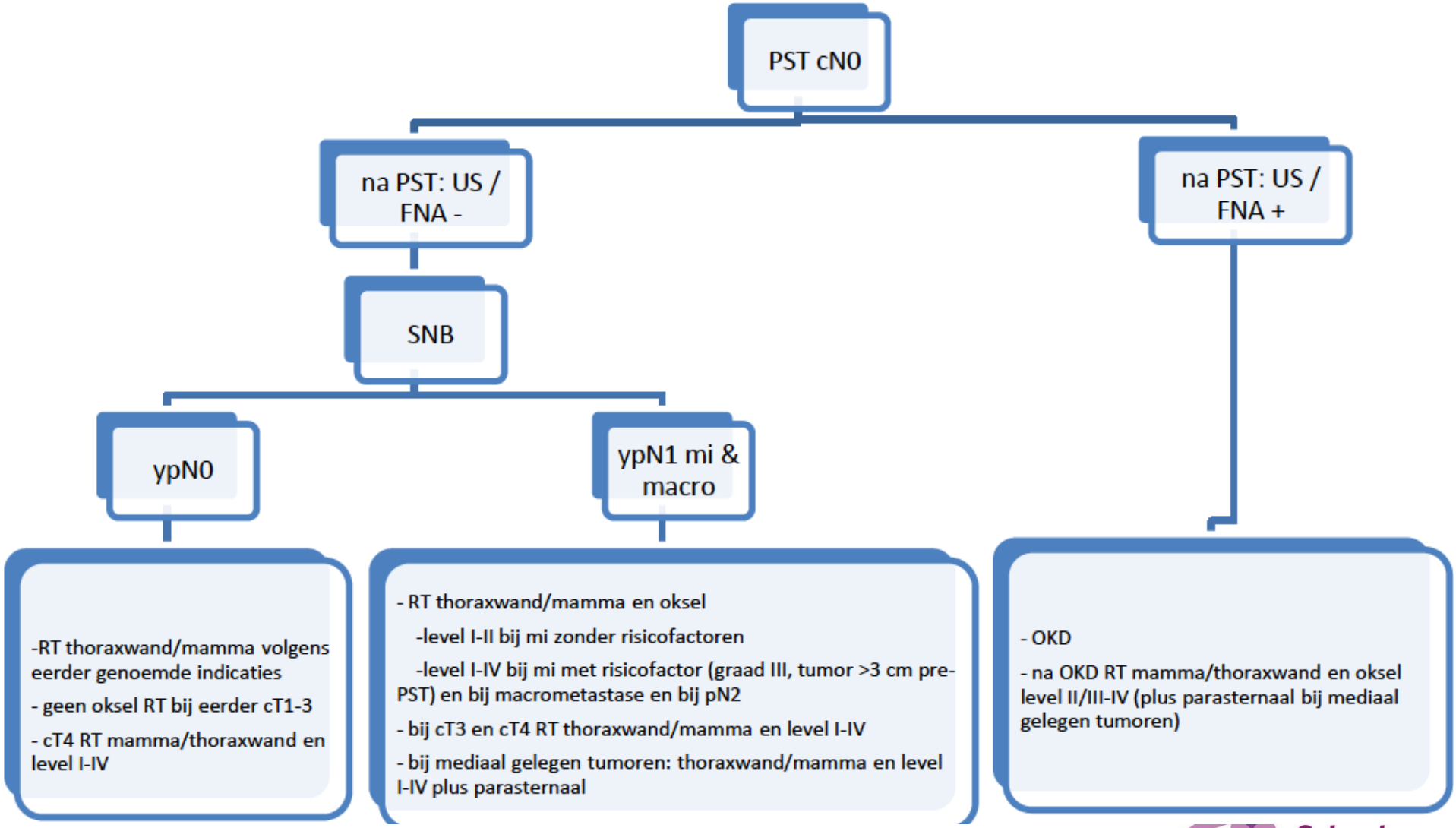
ESTRO School

Conundrum of PST: discussion & conclusions

➔ *consensus agreements*

Conundrum of PST: discussion & conclusions

3.1. PST; cN0 (US +/- FNA)

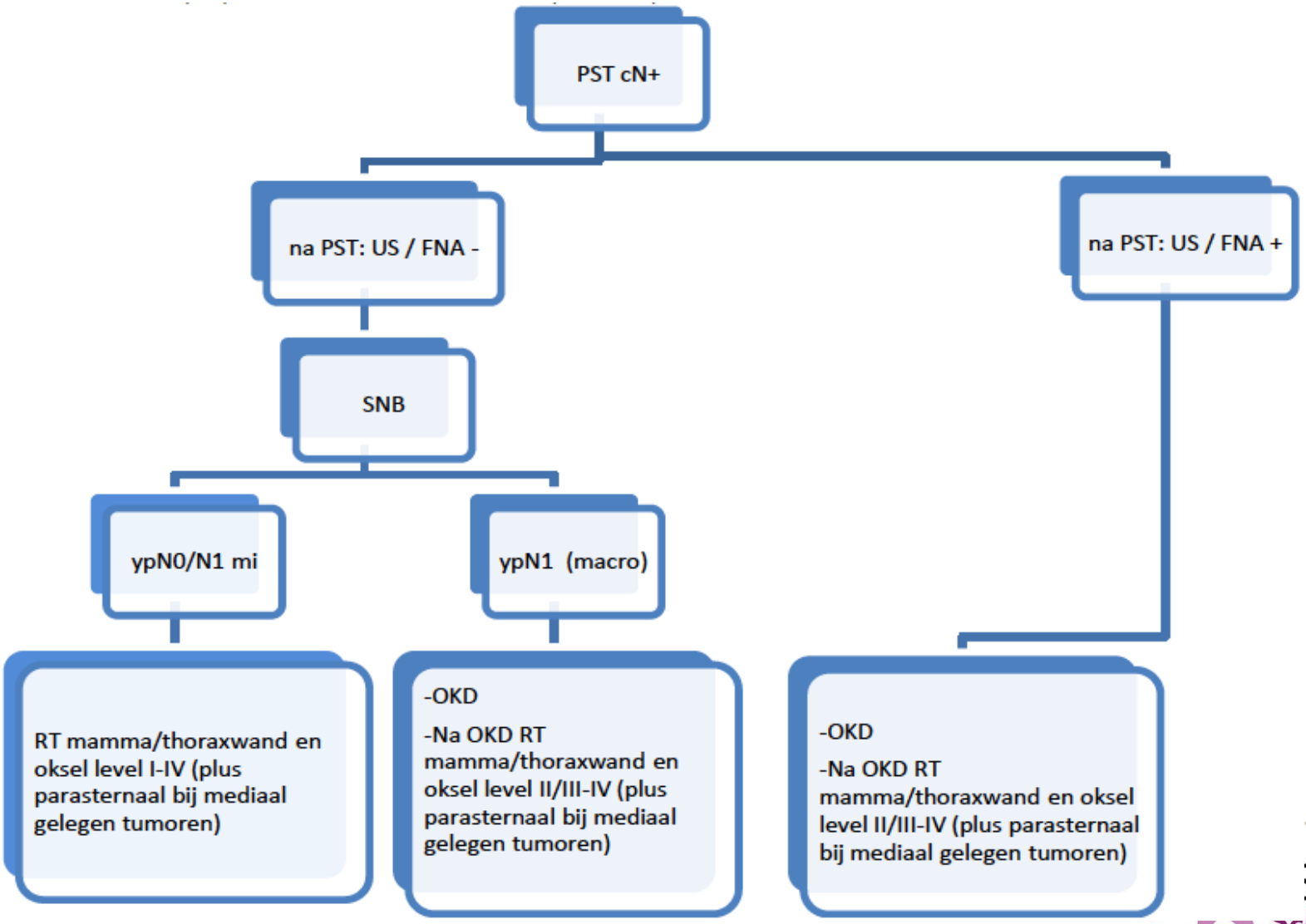


Protocol Radboud umc, March 2016.

School

Conundrum of PST: discussion & conclusions

3.2. PST; cN+(1-3) (US +/- FNA); MARI advised



Protocol Radboud umc, March 2016.

Conundrum of PST: discussion & conclusions

Tools to individualise:

- Response to PST *(= predictor of RLR risk)*
- Pre-PST stage incl histology; VI; molecular profile; …
- Age

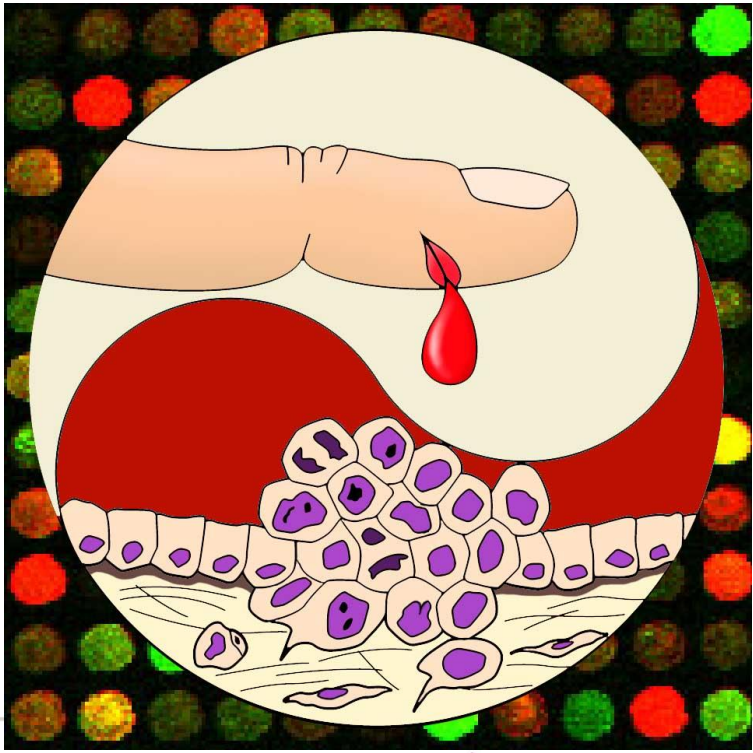
Conundrum of PST: discussion & conclusions

Wound Response Signature

In vitro Wound Model – 516 genes

Prognostic Significance in

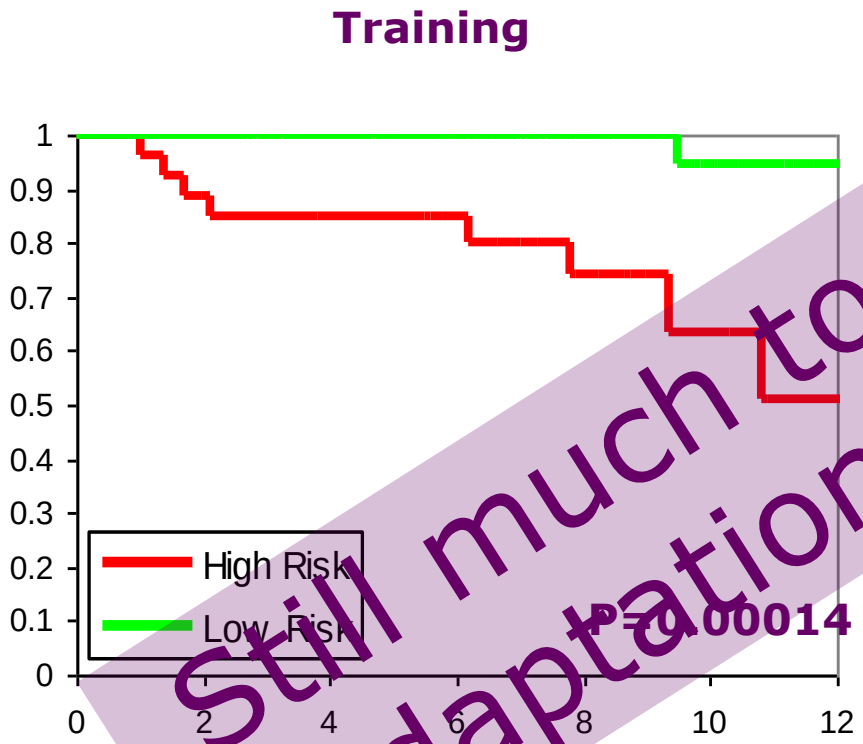
- Breast
- Lung
- Gastric cancer

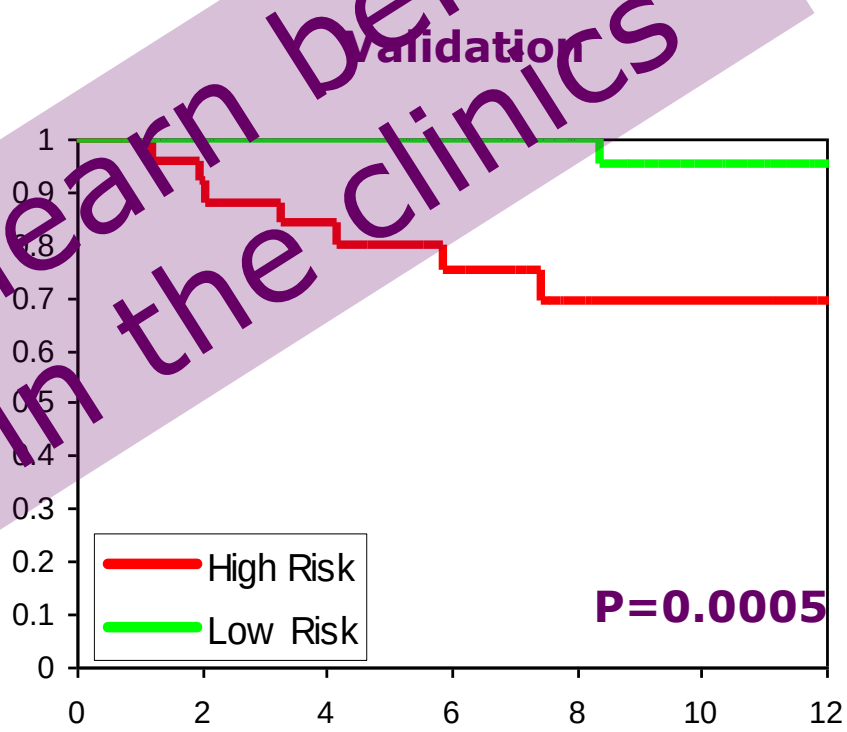


Iyer et al Science 1999 83-7; Chang et al PLoS Biology 2004 Feb 2 2 1- 9

Conundrum of PST: discussion & conclusions

Predict of Local Recurrence in Early Breast Cancer





Still much to learn before adaptation in the clinics

Nuyten DS et al, Breast Cancer Res. 2006;8(5):R62.

ESTRO School

Precision radiation medicine

Personalised/individualised/stratified approaches:

- Biological optimisation
- Technological optimisation
- Shared decision making

Conundrum of PST: discussion & conclusions

Still a lot of work to be done!

- Extent of surgery?
- Timing of radiation therapy?
- Molecular and genetic evaluation of tumour and normal tissue – also sequential? Liquid biopsies?
- Role of immune system and host response?
- Value of radiation genomics?
- Combinations with other therapies: immuno; nanoparticles; others.

Conundrum of PST: discussion & conclusions

Still a lot of work to be done!

- Predictive molecular and genetic testing of normal tissue and tumour responsiveness.
- The role of the immune system and host response.
- Test general hypotheses relating to radiation genomics and normal tissue responses.
- Large databases including radionomics
- Nanoparticles as radiosensitisers.
- Sequential/serial biopsies.
- Overall treatment time.

Conundrum of PST: discussion & conclusions

Still a lot of work to be done!

Abstract P5-16-14: NOSTRA PRELIM: A non randomised pilot study designed to assess the ability of image guided core biopsies to detect residual disease in patients with early breast cancer who have received neoadjuvant chemotherapy to inform the design of a planned trial

Francis A, et al. SABCS 2016; Cancer Res 2017;77:P5-16-14..

Conundrum of PST: discussion & conclusions

What is new tomorrow will be challenged again / and probably be obsolete the day after tomorrow.

Conundrum of PST: discussion & conclusions

- Primary systemic treatment is increasingly used
- Radiation therapy is indicated for most patients
- The role of surgery is questioned
- High-level evidence is missing
- Available evidence supports basing indications for RT on disease extent at diagnosis
- Individualisation based on tumour- and patient-related factors can be done, combined with the response to PST
- For fine-tuning we need results from on-going and future clinical trials

Conundrum of PST: discussion & conclusions

- Primary systemic treatment is increasingly used
- Radiation therapy is indicated for most patients
- The role of surgery is questioned
- High-level evidence is missing
- Available evidence supports basing indications for RT on disease extent at diagnosis
- Individualisation based on tumour- and patient-related factors can be done, combined with the response to PST
- For fine-tuning we need results from on-going and future clinical trials

Conundrum of PST: discussion & conclusions

- Primary systemic treatment is increasingly used
- Radiation therapy is indicated for most patients
- The role of surgery is questioned
- High-level evidence is missing
- Available evidence supports basing indications for RT on disease extent at diagnosis
- Individualisation based on tumour- and patient-related factors can be done, combined with the response to PST
- For fine-tuning we need results from on-going and future clinical trials

Conundrum of PST: discussion & conclusions

- Primary systemic treatment is increasingly used
- Radiation therapy is indicated for most patients
- The role of surgery is questioned
- High-level evidence is missing
- Available evidence supports basing indications for RT on disease extent at diagnosis
- Individualisation based on tumour- and patient-related factors can be done, combined with the response to PST
- For fine-tuning we need results from on-going and future clinical trials

ESTRO School

Conundrum of PST: discussion & conclusions

- Primary systemic treatment is increasingly used
- Radiation therapy is indicated for most patients
- The role of surgery is questioned
- High-level evidence is missing
- Available evidence supports basing indications for RT on disease extent at diagnosis
- Individualisation based on tumour- and patient-related factors can be done, combined with the response to PST
- For fine-tuning we need results from on-going and future clinical trials

Conundrum of PST: acknowledgements

- Meritxell Arenas
- Cynthia Aristei
- Marianne Aznar
- Harry Bartelink
- Liesbeth Boersma
- Celine Bourgier
- Charlotte Coles
- Laurence Collette
- Sarah Darby
- Marion Essers
- Alain Fourquet
- Sandra Hol
- Orit Kaidar-Person
- Youlia Kirova
- Lorenzo Livi
- Andreas Makris
- Icro Meattini
- Birgitte Offersen
- John Yarnold
- And many others!

ESTRO School

institutCurie

Clinical studies on locoregional treatments after PST:

maturing, accruing and nurturing

Liesbeth Boersma, Radiation Oncologist

MAASTRO Clinic/ University Hospital Maastricht, The Netherlands

ESTRO Teaching Course on Breast Cancer, Dublin, Sept. 10-13th 2017

Contents

- Introduction
  - Overview current open questions in LR treatment after PST
- Studies on local management
  - Restaging the breast after PST
  - Reduce local treatment
- Studies on (loco) regional management
  - Restaging the axilla after PST
  - Reduce mainly axillary treatment

Introduction

- Primary systemic treatment (PST) is being given more frequently
- Timing of systemic treatment: not relevant for outcome, *as long as treatment consists of same ingredients (?)*
- Indications for locoregional RT: based upon pathologic findings after primary surgery → how to interpret ypTNM status ?

Central question:

Can subgroups be identified in whom locoregional treatment after PST can be reduced ?

Indications for post-operative radiotherapy in case after PST: pTNM vs ypTNM

- Buchholz et al., 2002 IJRBOP:
  - NO RT indicated based on ypTNM (N = 150)
  - NO RT indicated based on pTNM (N = 1031)
  - Results: 5 yr LRR 27% vs 15%, respectively, p = 0.001
- Further analysis of the retrospective series:
  - Not only ypTNM but also cTNM stage prior to chemotherapy is important:
    - Stage III prior to PST: 20% LRR, even after excellent response !
    - pts with pCR – high LRR rate : 33% !

Indications for post-operative radiotherapy in case after PST

- *Tumor biology AND initial stage AND response to chemotherapy are probably the driving forces for a local recurrence (Mittendorf et al, 2013)*

- RT is indicated if:
  - RT was already indicated based on cTNM stage prior to chemotherapy: Stage III and higher : cT3/4 and/or cN2/3 *thus even in case of pCR !*
  - In patients with ypTNM stages T3-4 and/or N2-3.

- What about the patients with clinical stage T0-2N0-1 ?

What about patients with cT1-2N0-1 disease ?

- cT1-2N0 → ypT0-2 ypN0 after PST:
  RT after MRM probably not required (SUPREMO trial to be awaited).

- cT1-2N1 → ypT0-2 ypN0-1
  Role of RT unclear;
  - Some advocate LR- RT, since the cN1 might have been pN2 disease
  - Some advocate LR- RT, since RT in cN+ improves OS
  - Some advocate L(R) RT based on risk factors prior to chemo: vascular invasion, grade; however, no reliable scoring on biopsy..?→

→ Over- or undertreatment ?

Contents

- Introduction:
  - Overview current open questions in LR treatment after PST
- Studies on local management
  - Restaging the breast after PST
  - Reduce local treatment
- Studies on (loco) regional management
  - Restaging the axilla after PST
  - Reduce mainly axillary treatment

Restaging of the breast

Most studies agree that MRI is most reliable way for noninvasive restaging

Mini-review of Price et al (2015):

- MRI is reliable for surgical planning purposes in tumor that are:
  - Triple negative
  - Her2 positive
  - Hormone receptor negative,
  - Especially if they are of a solid imaging phenotype.

- MRI shows lower concordance with surgical pathology in:
  - Hormone receptor positive cancers
  - Lesions with non mass enhancement

Re-staging of the breast: ongoing studies

Two studies comparing biopsy findings with final pathology findings

NRG Oncology study, USA, NCT03188393:

- *Assessing the Accuracy of Tumor Biopsies After Chemotherapy to Determine if Patients Can Avoid Breast Surgery*
  - N = 175, between 2017 – 2019:
  - Stereotactic biopsy any time before BCS.

MICRA study, Netherlands, NTR 6120

- *Minimally Invasive Complete Response Assessment of the breast after primary systemic treatment*
  - N = 440, between 2016-2019.
  - 8 biopsies immediately prior to surgery; 4 at <0.5 cm distance of the marker; 4 at 1.0-1.5 cm distance of the marker.

Studies on local treatment
Omission of breast surgery after PST

- "Neoadjuvant Chemotherapy Followed by RT Alone in BC Patients"
  - Study from Brazil: NCT03213925, phase 2 study
  - If cCR on MRI: Only RT breast with boost
  - Inclusion 2017 - 2020; Number of patients not given.
  - Primary endpoint: IBTR at 5 yrs.

- NOSTRA trial UK
  - RCT for ER negative Her2 positive patients with pCR:
    - RT alone vs surgery with RT.
  - First pilot aimed at staging: breast biopsies followed by surgery (Francis et al, abstract Cancer Research 2017)

Studies on local treatment
Omission of breast surgery after PST

- Eliminating Breast Cancer Surgery in Exceptional Responders With PST
  - Study from MD Anderson NCT02945579, phase 2 study
  - If c/pCR based on image guided breast biopsy: Only RT breast < 12 weeks of end of chemotherapy
  - Inclusion 2017 – 2022, aimed to include 50 patients
  - Primary endpoint: Feasibility i.e. no IBTR < 6 months for first 6 patients; then: 5 yr IBTR

Study on local RT
Omission of RT thoracic wall

- SUPREMO study (NCT00966888) www.supremo-trial.com
- Selective Use of Postoperative RadiothErapy after MastectOmy

- Worldwide study of the NHS- UK:
  - Patients with (y)pT1-2N1 disease; (y)pT1-2N0 with G3 and / or LVI
  - Randomised between thoracic wall RT or no thoracic wall RT
  - Patients treated with PST were eligible as well
  - Target was 1600 patients; trial closed April 30th 2013, 1688 patients enrolled
  - Data are maturing…

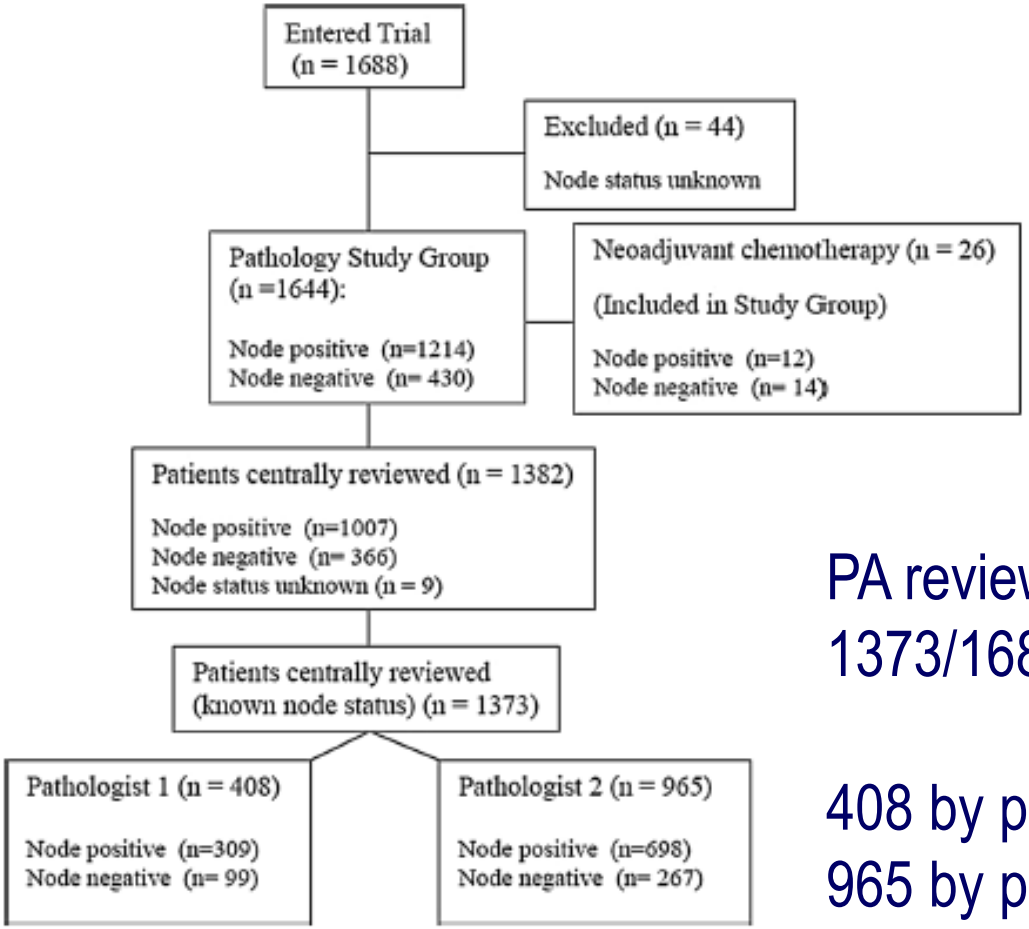
  - Major contributors: UK (75%), NL (10%)

MAASTRO CLINIC

ESTRO School

Study on local RT
Omission of RT thoracic wall

- Pathology review of the SUPREMO study was published this year….:



PA review of 1373/1688 patients:

408 by pathologist 1
965 by pathologist 2

Thomas et al, 2017

Study on local RT
Omission of RT thoracic wall

- Pathology review of SUPREMO study was published this year….:

	Node positive				Node negative			
	Grade 3		Lvi		Grade 3		Lvi	
	Reported	Reviewed	Reported	Reviewed	Reported	Reviewed	Reported	Reviewed
Number	496	326	481	162	362	219	158	35
%	40.8%	33.7%	39.6%	16.9%	87.4%	64.2%	38.2%	9.9%

- Large differences in reporting on Grade 3 and LVI, both in pN+ and in pN0 group ! Partly due to review on only 1 slide.
- 25 cases re-evaluated by two pathologists: 80% agreement; 20% disagreement grade 2/3; 8% disagreement LVI yes/no
- 19% of pN0 patients would have been ineligible

Thomas et al, 2017

Contents

- Introduction:
  - Overview current open questions in LR treatment after PST
- Studies on local management
  - Restaging the breast tumor after PST
  - Reduce local treatment
- Studies on (loco) regional management
  - Restaging the axilla after PST
  - Reduce mainly axillary treatment

Restaging the axilla

- About 40% of patients with positive axillary nodes prior to PST convert to ypN0; can't these patients benefit from less axillary treatment ?
- Studies on noninvasive restaging:

European Journal of Radiology 84 (2015) 41–47

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Review

Noninvasive nodal restaging in clinically node positive breast cancer patients after neoadjuvant systemic therapy: A systematic review

R.J. Schipper[a,b,c,*], M. Moossdorff[b,c], R.G.H. Beets-Tan[a,c], M.L. Smidt[b,c], M.B.I. Lobbes[a]

[a] Department of Radiology, Maastricht University Medical Center+, Maastricht, The Netherlands
[b] Department of Surgery, Maastricht University Medical Center+, Maastricht, The Netherlands
[c] GROW – School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands

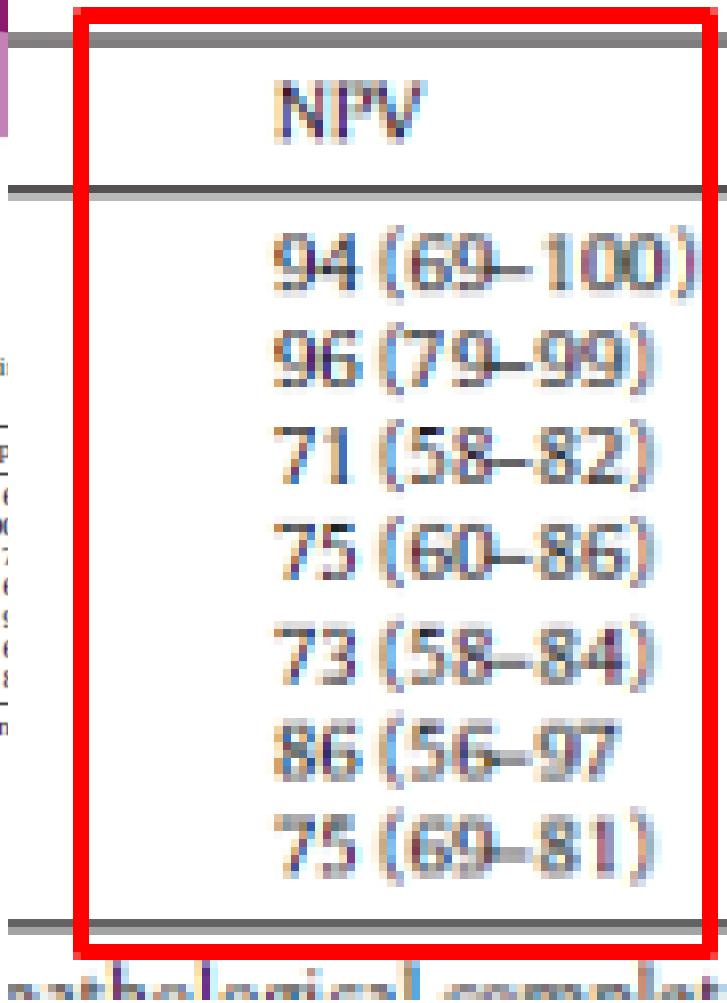
Restaging the axilla

- Noninvasive restaging:

Table 4
On overview on the diagnostic performance of each restaging technique per restaging tool for predicti
treatment.

Restaging tool	Study	Sensitivity	Sp
Clinical examination	Arimappamagan et al.	86 (42–99)	
Axillary ultrasound	Arimappamagan et al.	86 (42–99)	10
	Hieken et al.	58 (42–73)	
MRI	Hieken et al.	59 (39–76)	
FDG PET-CT	Koolen et al.	48 (28–68)	
	Hieken et al.	85 (54–97)	
Nomogram	Schipper et al.	43 (33–53)	

PPV; positive predictive value; NPV; negative predictive value. 95% confidence intervals between paren
response as reported in original publication.



Conclusion:

There is not (yet) a noninvasive restaging technique able to identify patients with pCR in the axilla after PST

Review Schipper et al 2015

Restaging the axilla

- Invasive re-staging:
  - **SN after PST – with confirmatory ALND**
    - SENTINA trial[1]; ACOSOG Z1071[2] and FNAC trial[3]
    - Prospective cohort study[4] (no ALND if ≥ 3 SN negative)
  - **Removal of clipped pathological node – with confirmatory ALND**
    - MARI[5] (Marking of the Axilla with Radioactive Iodine)
    - Clipped node i.c.w. SN [2,6]
    - RISAS study: recruiting

[1]Kuehn et al 2013; [2]Boughey et al 2013, 2016, 2017 [3]Boileau et al 2015; [4]Mamtani et al 2016; [5] Donker et al 2015; [6]Caudle et al 2016.

SN after PST in patients with cN+ disease

TABLE 2 FNR according to number of SLNs removed and type of lymphatic mapping in three prospective trials of SLNB after NC in patients with documented axillary nodal involvement at presentation

	ACOSOG Z1071[86] ($n = 756$)	SENTINA[87] ($n = 592$)	FN SNAC[88] ($n = 153$)	Across studies
FNR with single SLN	31.5 %	24.3 %	18.2 %	26.0 %
	17/54	17/70	4/22	38/146
FNR with ≥2 SLNs	12.6 %	9.6 %	4.9 %	10.8 %
	39/310	15/156	3/61	57/527
FNR with >2 SLNs	9.1 %	4.9 %	N/A	7.8 %
	20/220	5/102		25/322
FNR with dual tracer	10.8%	8.6%	5.2%	10.3%

FNR false-negative rate, *N/A* not available

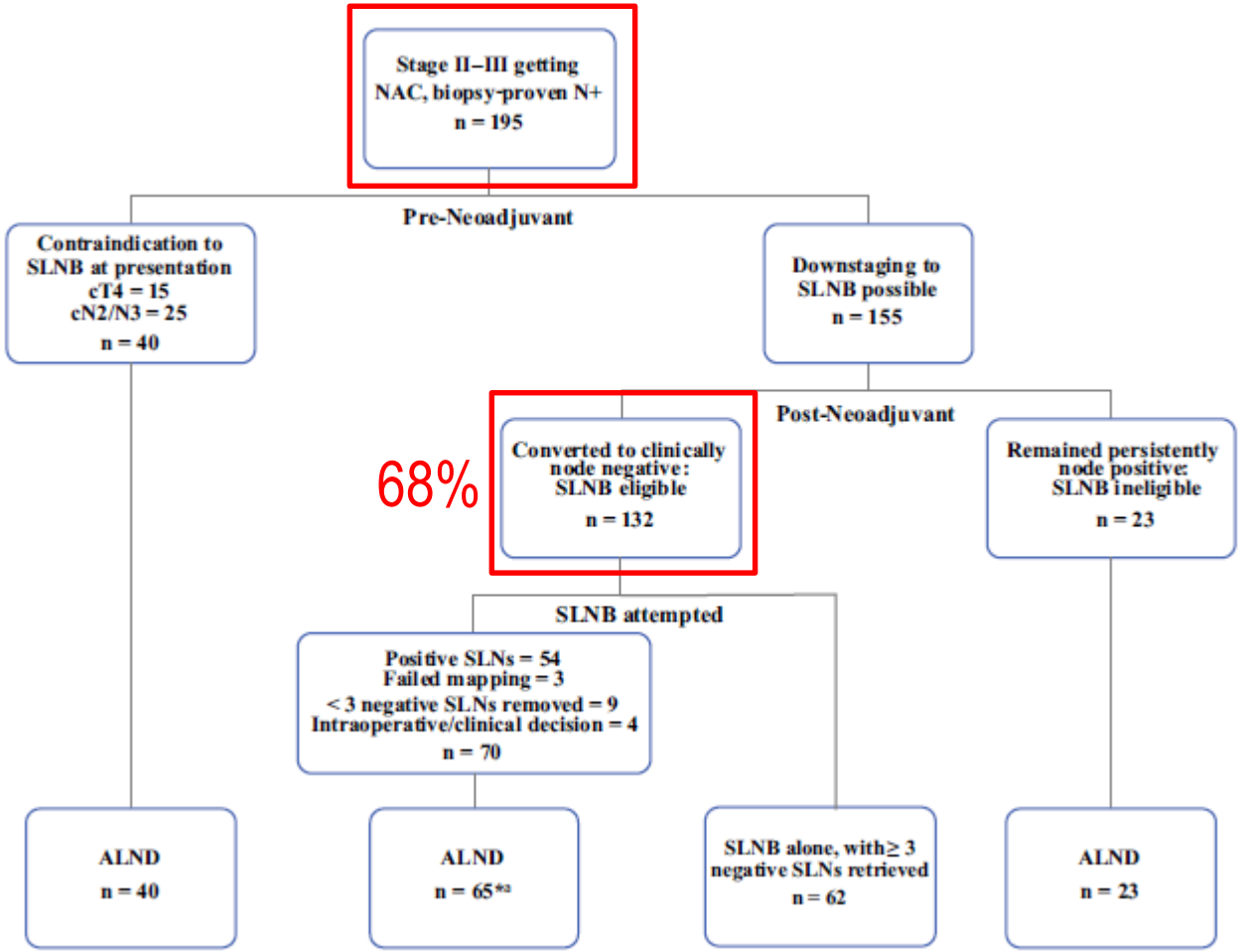
False negative rate reduced when:

Number of SNs harvested: > 2 or 3

if yN0(i+) – Isolated Tumour Cells considered as positive nodes

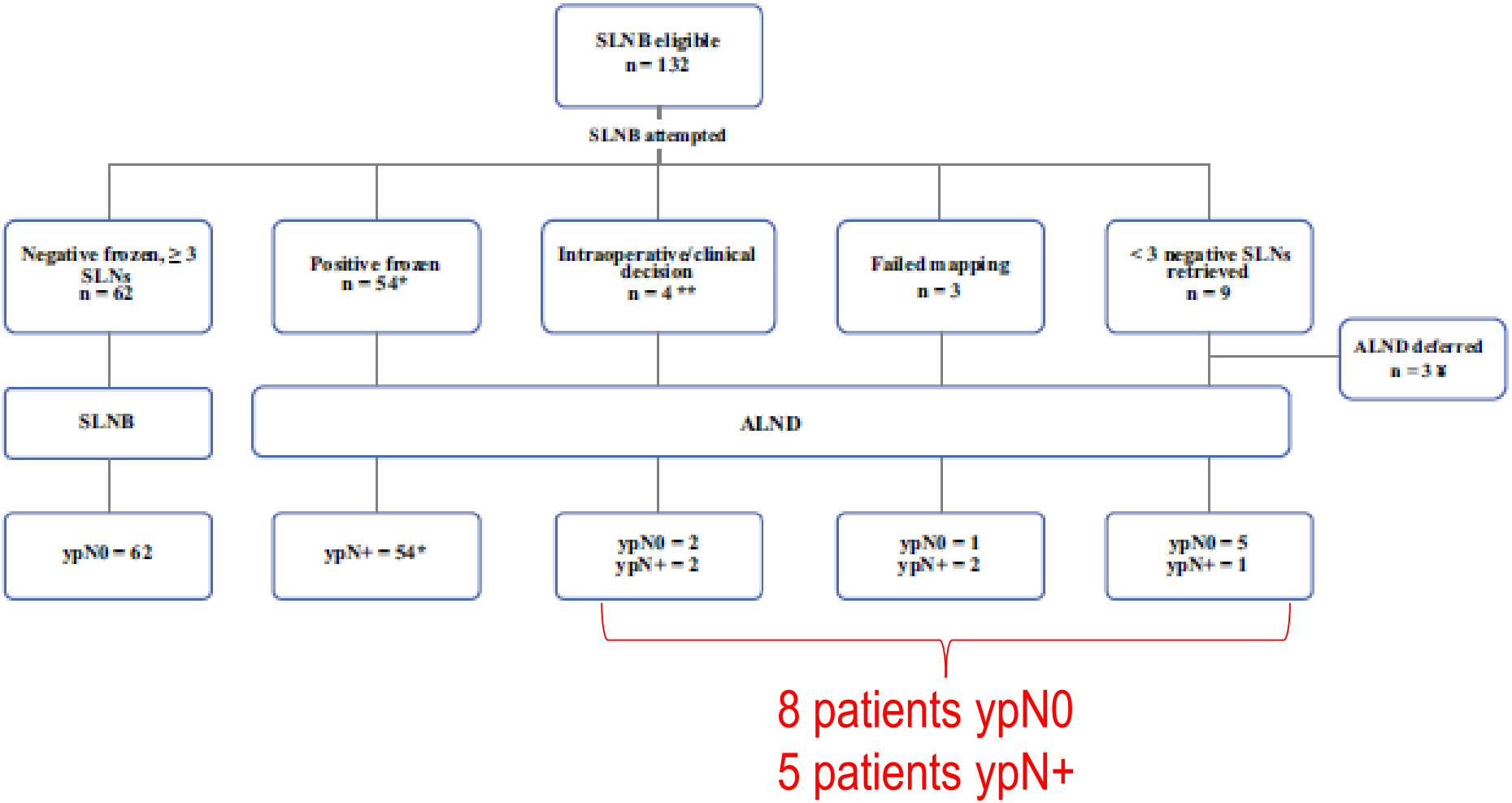
Mamounas et al, Ann Surg Oncol 2015

SN after PST in patients with cN+ disease
Prospective cohort study: inclusion 2013-2015



Mamtani et al (2016)

SN after PST in patients with cN+ disease
Prospective cohort study: inclusion 2013-2015



Mamtani et al (2016)

Removal of MARI/ clipped node +/ - SN after PST in patients with cN+ disease

- Prior to PST: clip pathological node with clip or radioactive Iodine seed
  → After PST: remove the clipped node

- Donker et al, Ann Surg 2015
- MARI procedure, i.c.w. ALND, N = 100

- Caudle et al, JCO 2016:
- Removal of clipped node + SN, i.c.w. ALND, N = 118

- Boughey et al, Ann Surg 2016:
- Removal of SN i.c.w. ALND, and analysis of clipped node in ALND, N = 141

Removal of MARI/ clipped node after PST in patients with cN+ disease

	False Negative rate	Negative Predictive Value
MARI[1]	7%	84%
Clipped node[2]	4.1%	93%
Clipped node in ALND[3]	8.4%	82%
Clipped node + SN [2]	2%	97%
SN + Clipped node in ALND[3]	6.8%	N.A.

RISAS study (NCT02800317)

Primary Radioactive Iodine Seed Localisation in the Axilla in Axillary Node Positive Breast Cancer Combined With Sentinel Node Procedure (RISAS) Following Neoadjuvant Chemotherapy

- MARI i.c.w. SN, followed by ALND in The Netherlands, recruiting:
- Primary outcome:
  - Identification rate and accuracy (sensitivity, negative predictive value (NPV) and false negative rate (FNR)) for identifying axillary pCR
- Secondary outcome:
  - Same as primary, but then for MARI and SN separately
- Number of patients:
  - 200 patients to be included from October 2016-October 2018

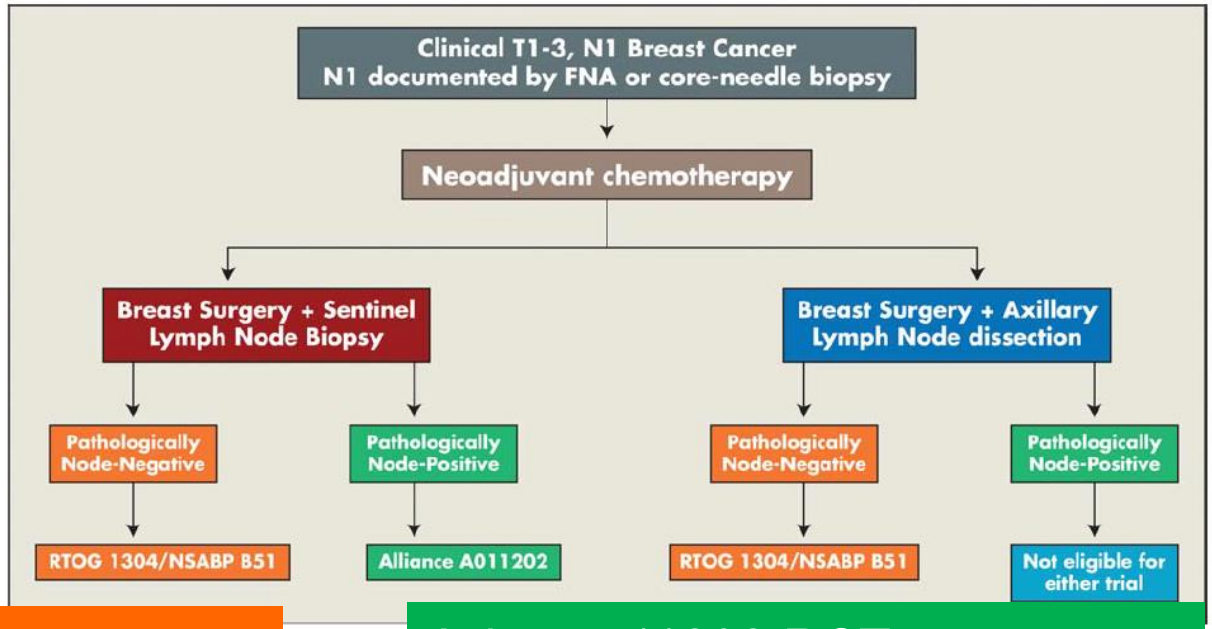
Studies on locoregional treatment after PST

- 2 RCTs currently recruiting:
  - NSABP-51 and Alliance 11201 (USA)
- 1 RCT in preparation:
  - ATNEC trial (UK)

- Several prospective cohort studies with reduced treatment:
  - Galimberti: 5 yr follow-up
  - ACOSOG Z 1071: data are maturing
  - Mamtani: data are maturing
  - RAPCHEM: data are maturing
  - Several Dutch strategies: are currently registered in Dutch Cancer Registry

NSABP 51 & Alliance 11202

(NCT01872975) & (NCT01901094)



NSABP-51 RCT:

No RT vs. locoregional RT

N: 1636 patients

Primary endpoint: 10 yr DFS

Alliance 11202 RCT:

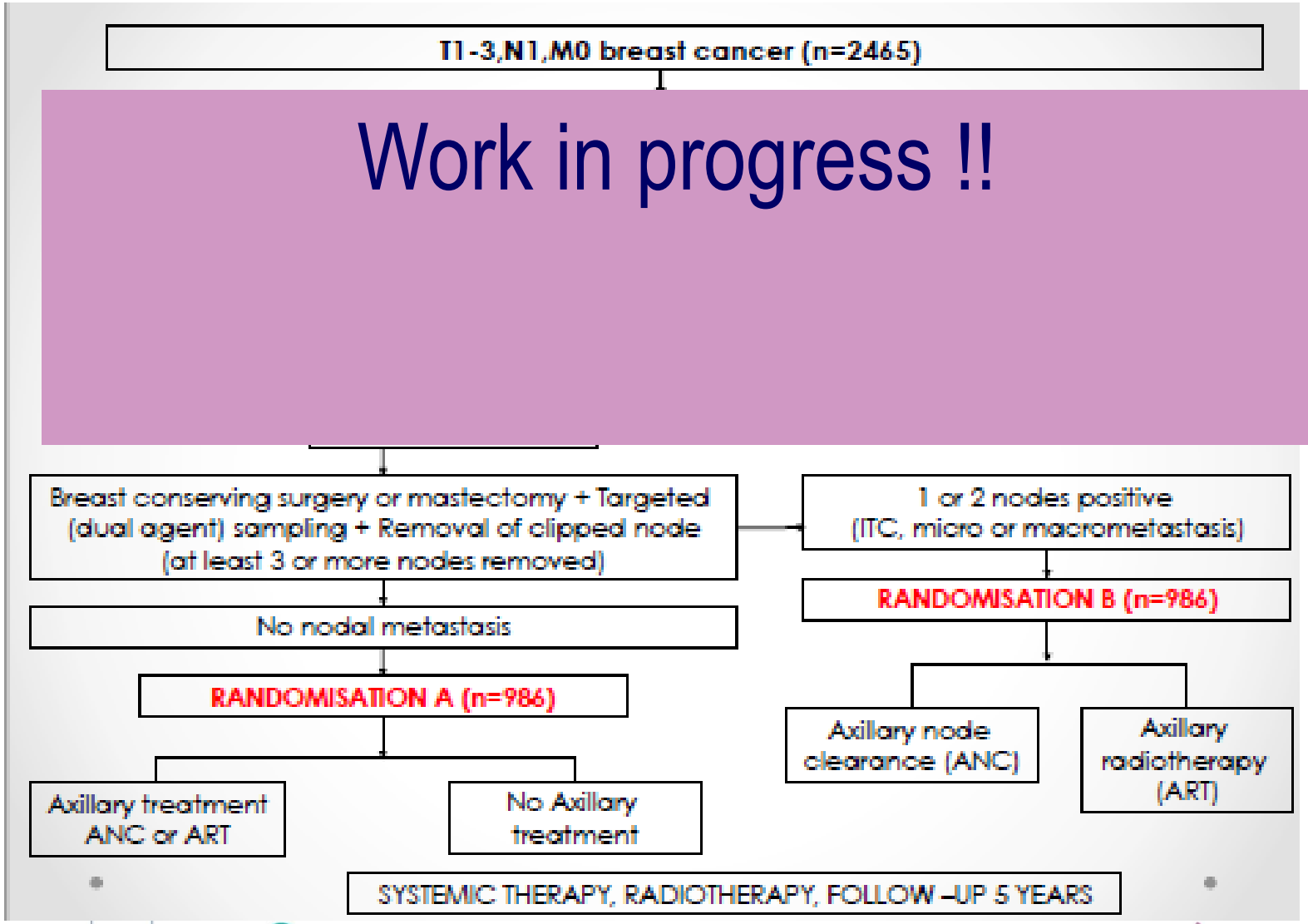
Locoregional RT vs. ALND +RT

N: 2918 patients

Primary endpoint: 5yr DFS

Bazan and White Cancer 2015

Studies on locoregional treatment
ATNEC trial – Goyal et al, NHS, UK: in preparation



point:

Slide courtesy Charlotte Coles

5 yr f-up of SN only after PST, median f-up 61 mo

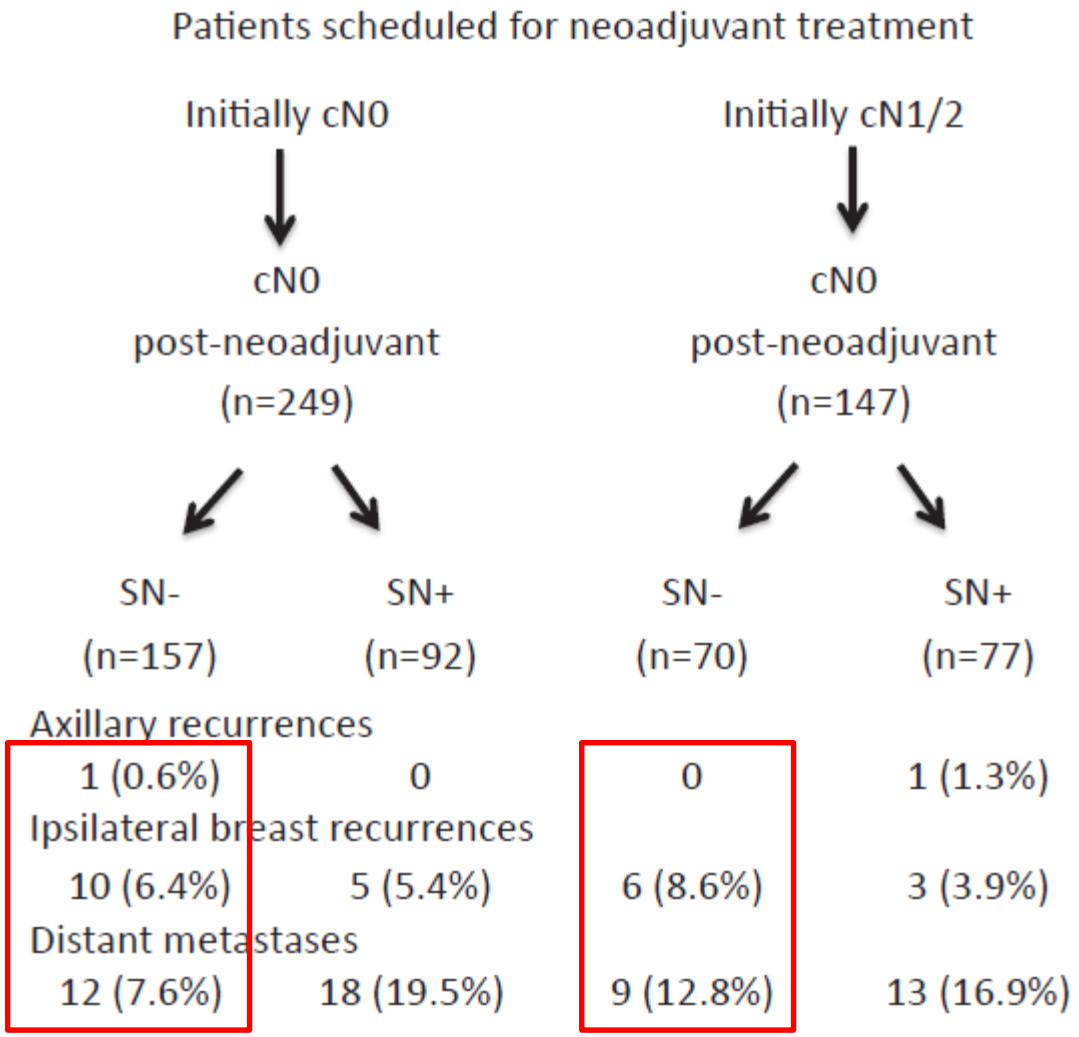


Figure 1. Study flow chart.

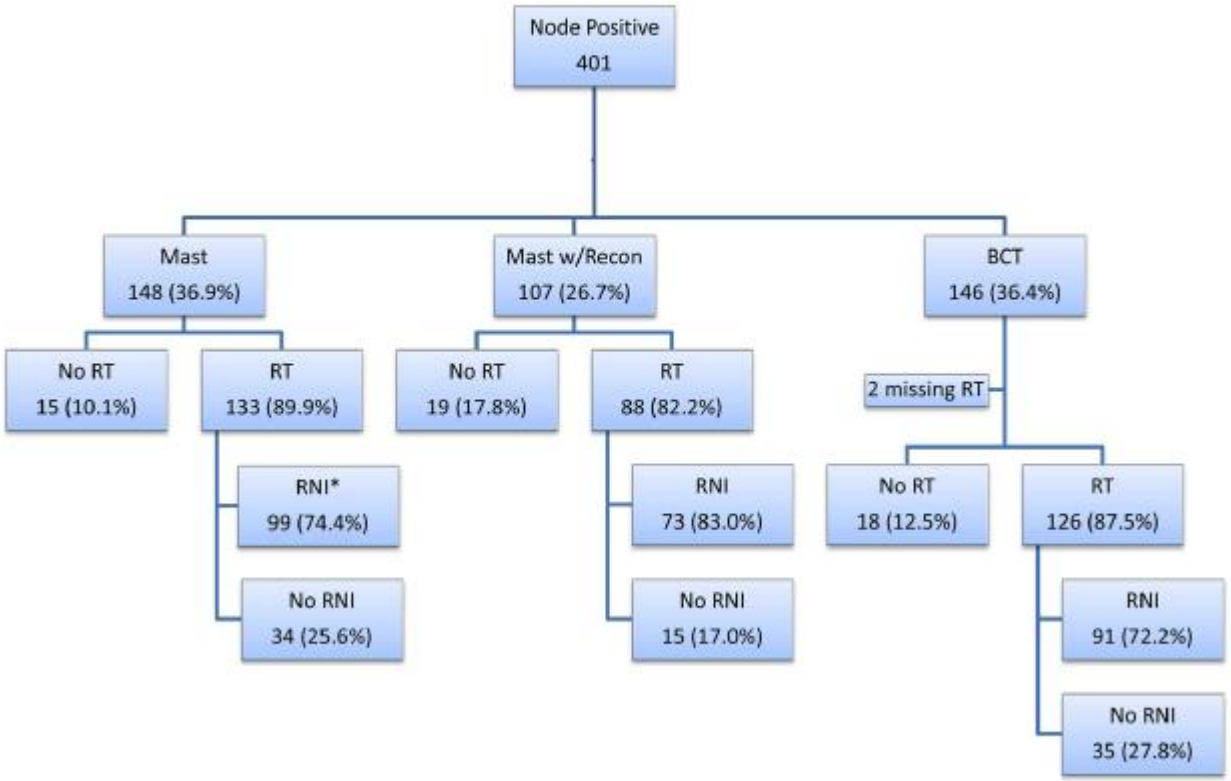
Only scarce information on applied RT .. About 75% received at least breast/ thw RT

Galimberti et al EJSO 2016

Studies on locoregional treatment after PST

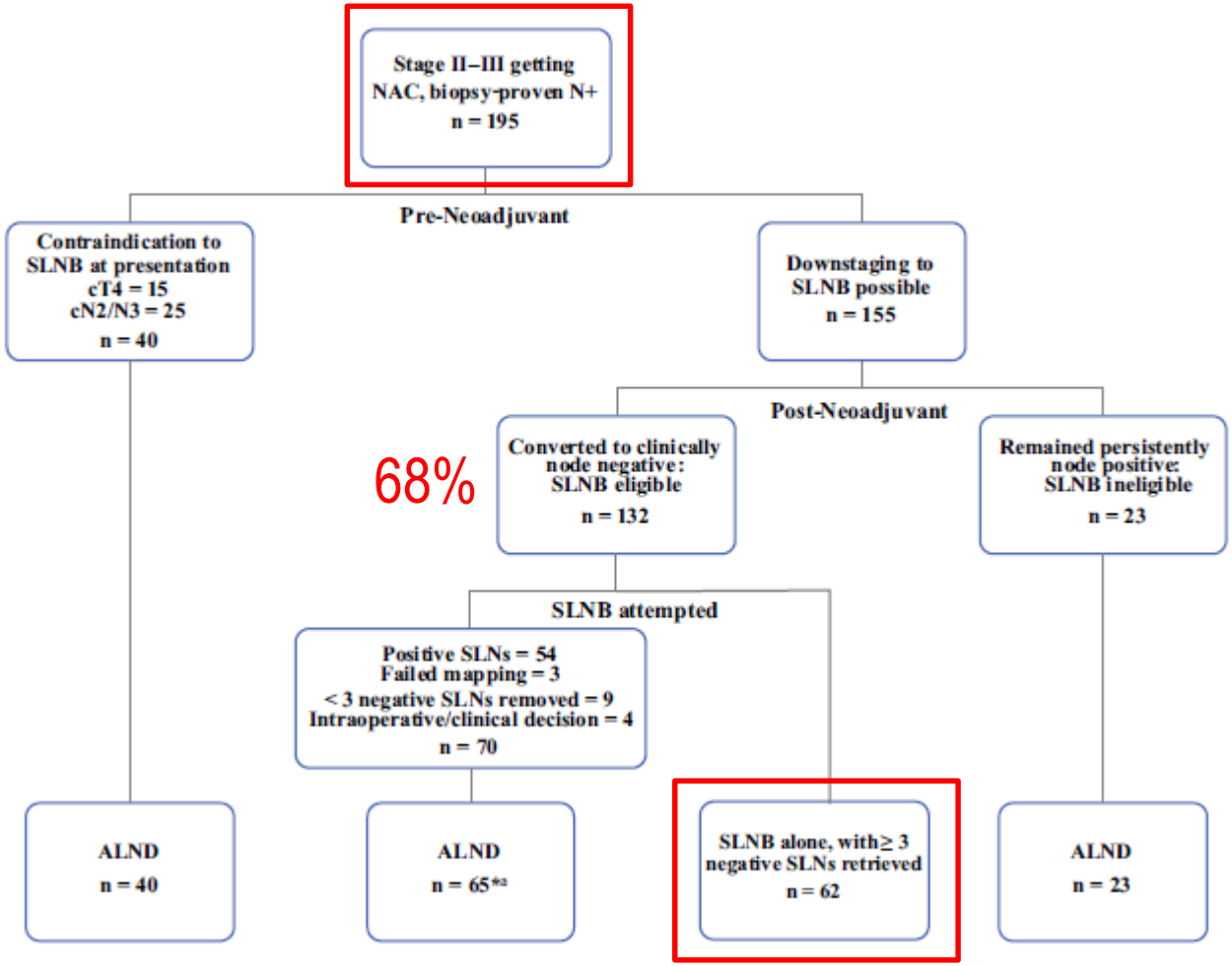
Patterns of local-regional management following neoadjuvant chemotherapy in breast cancer: Results from ACOSOG Z1071 (Alliance)

Bruce G. Haffty[1], **Linda M. McCall**[2], **Karla V. Ballman**[3], **Sarah McLaughlin**[4], **Reshma Jagsi**[5], **David W. Ollila**[6], **Kelly K. Hunt**[7], **Thomas A. Buchholz**[8], and **Judy C. Boughey**[9]



Haffty et al,2016

SN after PST in patients with cN+ disease
Prospective cohort study: inclusion 2013-2015



32% no ALND: no data yet on follow-up

Mamtani et al (2016)

RAPCHEM study (NCT01279304)
cT1-2N1 (> 3 suspicious nodes excluded), treated with PST

- Group I low risk: ypT0-2N0:
  - after MRM: no RT; after BCT: RT breast
  - If SN/MARI is negative: no RT

- Group II intermediate risk: ypT0-2N1:
  - after MRM: RT thoracic wall; after BCT: RT of breast
  - if SN/MARI micromets and no RF: add RT of the axilla level 1&2

- Group III high risk: ypT0-2N≥2:
  - RT thoracic wall/ breast **and** periclavicular nodes.
  - if SN/MARI shows metastasis, add RT of the axilla1&2 or perform ALND.

RT of the axillary and internal mammary chain nodes is optional. Each participating centre should state their treatment policy on beforehand.

RAPCHEM study (NCT01279304)
cT1-2N1 (> 3 suspicious nodes excluded), treated with PST

Inclusion 2011-2015: 860 patients.

Preliminary analysis March 2016:

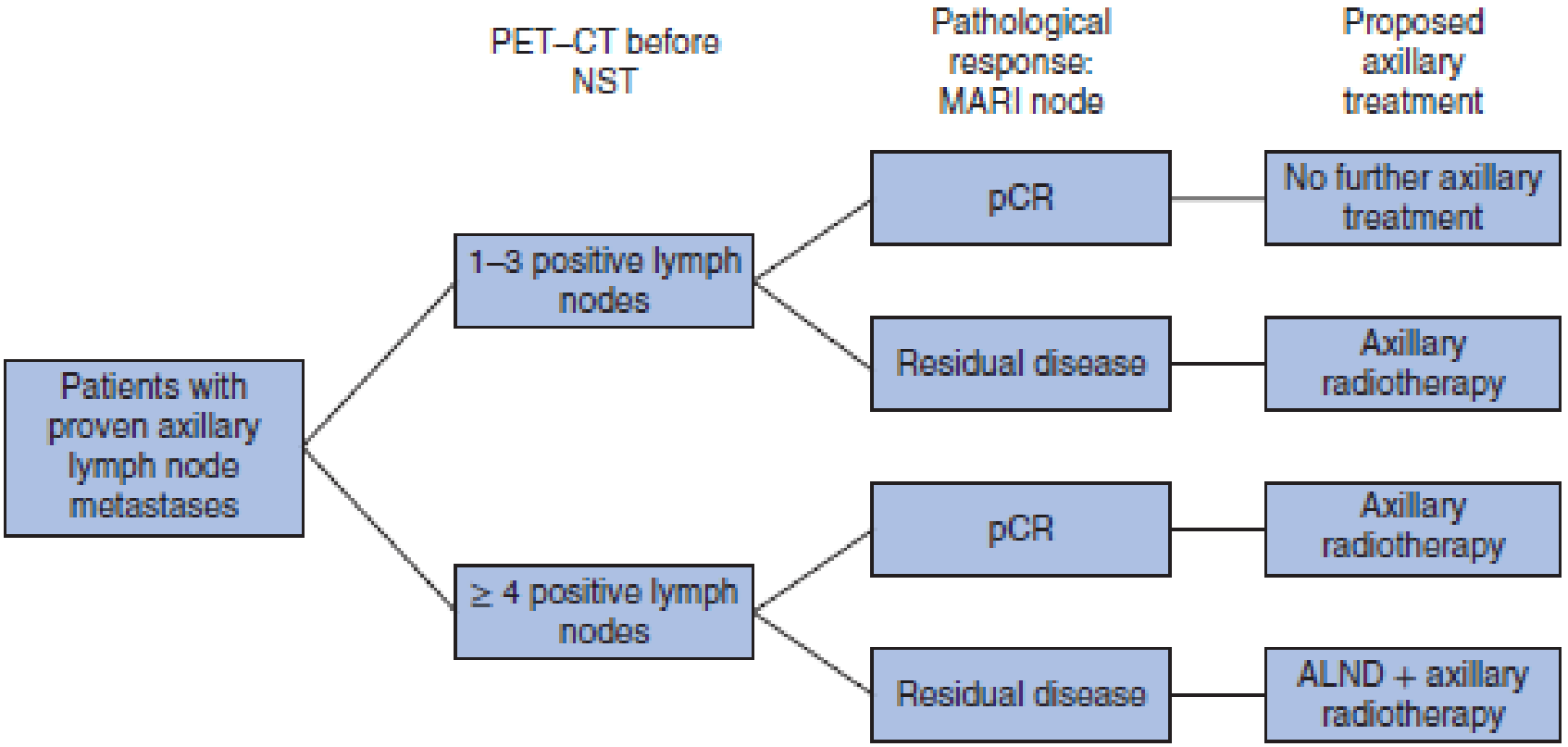
Number of patients per risk group	ALND	SN only, no ALND	Total
Group 1	209	33	242
Group 2	263	28	291
Group 3	98	21	119
Total	**570**	**82**	**652**

Actual treatment vs. protocol guideline (%)	According to protocol guideline	Less RT than protocol guideline	More RT than protocol guideline	Just different from protocol guideline
Group 1	60,3	1,2	38,4	0
Group 2	45,7	22	30,1	1,7
Group 3	42	9,2	37,8	10,9
All	**50,5**	**12**	**34,8**	**2,8**

- Data maturing to reach at least 5 year of follow-up…

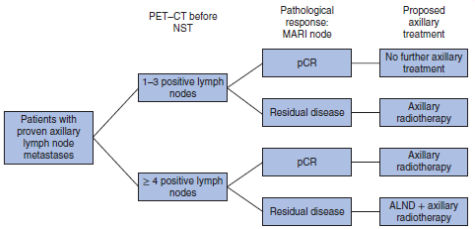
Boersma et al, poster EBCC 2016

Proposed axillary treatment after PST (Netherlands Cancer Institute)



Koolen et al, Br J Surg 2017

Proposed axillary treatment after PST (Netherlands Cancer Institute)



If applied to 93 patients undergoing PET-CT:

- 74% of patients an ALND would have been avoided
- **3%** (3 pts with false negative MARI) would have been **"undertreated"**
- **17%** (13 ART, but no additional pos. nodes; 3 x ALND in case of ≥ 4 nodes) would have been **"overtreated"**
- **= current practice !** Data to be obtained through Dutch Cancer Registry

Koolen et al, Br J Surg 2017

Take Home Messages

- Indication for locoregional RT depends on both pre-treatment characteristics and ypTNM status

- For patients with cT4 disease or cT3N+ disease and/or cN2/3: locoregional RT is currently indicated independent of response.

- For patients with cT1-2(3)N0-1 disease, lots of studies are ongoing:
  - Re-staging: SN + clipped node seems most promising: *Note: pCR*
  - Already any data available on long-term follow-up of reduced treatment !
  - Data of prospective cohort studies applying reduced treatment are maturing
  - RCTs are recruiting..

It will take at least 5 - 10 years before we have sufficient long term follow-up before we have real evidence for reduced treatment

ESTRO School

ESTRO Teaching Course on the Multidisciplinary management of Breast Cancer.
Dublin, Republic of Ireland. September 2017

Whole Breast Reconstruction

Lynda Wyld

Reader In Surgical Oncology

University of Sheffield

Consultant Oncoplastic Breast Surgeon

Doncaster and Bassetlaw Teaching Hospital

UK.

Disclosure:

- I have no conflict of interest to report

Lecture plan

- Indications for mastectomy and reconstruction
- Oncological considerations
- Classification and Techniques
- Surgical and patient outcomes

Indications for Mastectomy and Reconstruction

What are the current Indications for Mastectomy?

- **Absolute**
- Patient choice
- Inflammatory cancer
- Failed conservation surgery

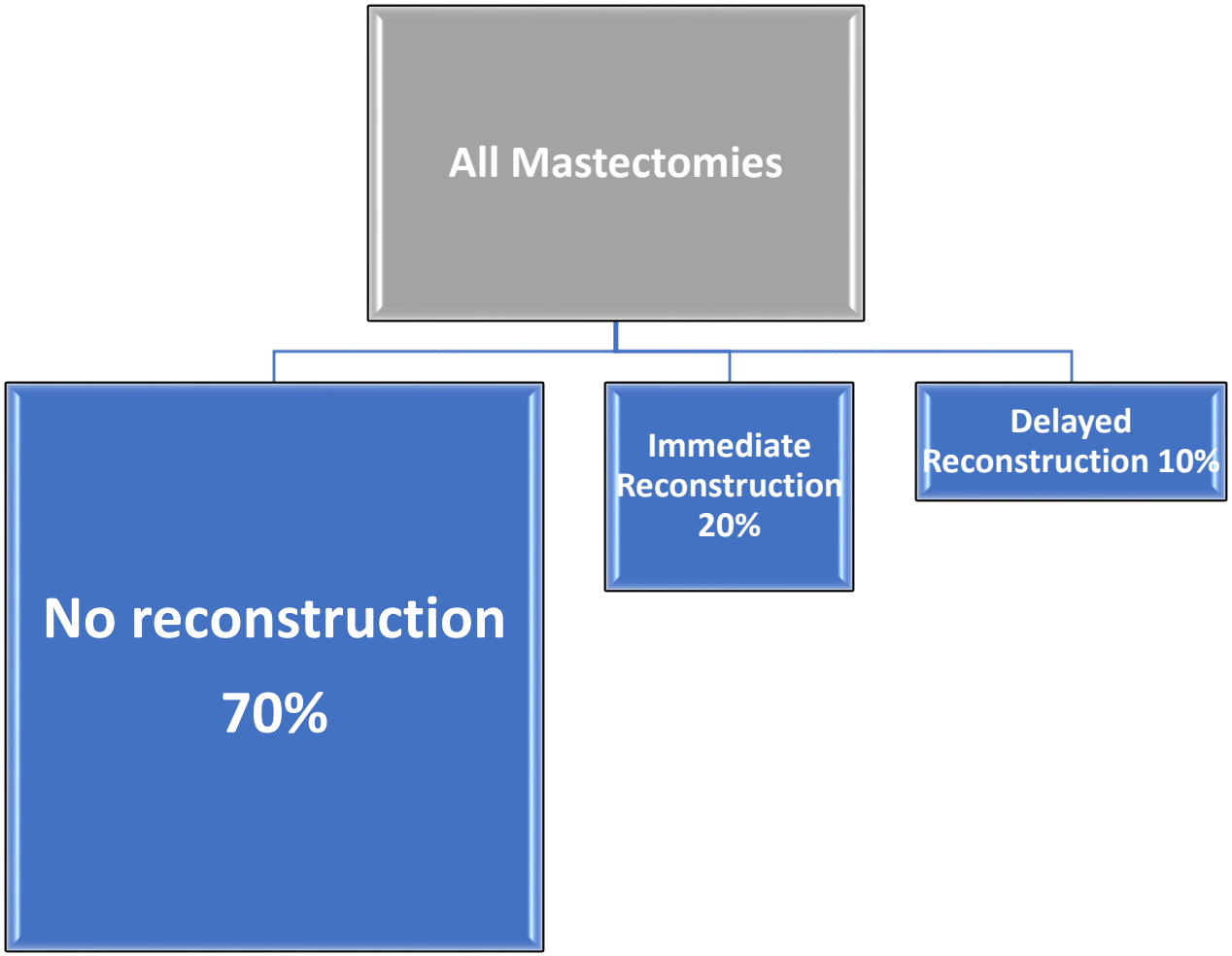
- Multicentric carcinoma or DCIS spanning >1 quadrant or separated by more than 4cm…..*may be safe with oncoplastic techniques if oligocentric*
- Previous radiotherapy….*some exclusions may be safe*
- Size of tumour? Upper limit…..*neoadjuvant therapy may help*

- **Relative**
- BRCA gene carrier…..*but debate about survival advantage for some sub groups*

- Large size of tumour relative to breast size….*but neoadjuvant therapy and oncoplastics may address this*.

- Multifocal breast cancer……but may be safe with oncoplastic techniques

UK Practice (National Audit 2011)



Temporal and regional UK variation

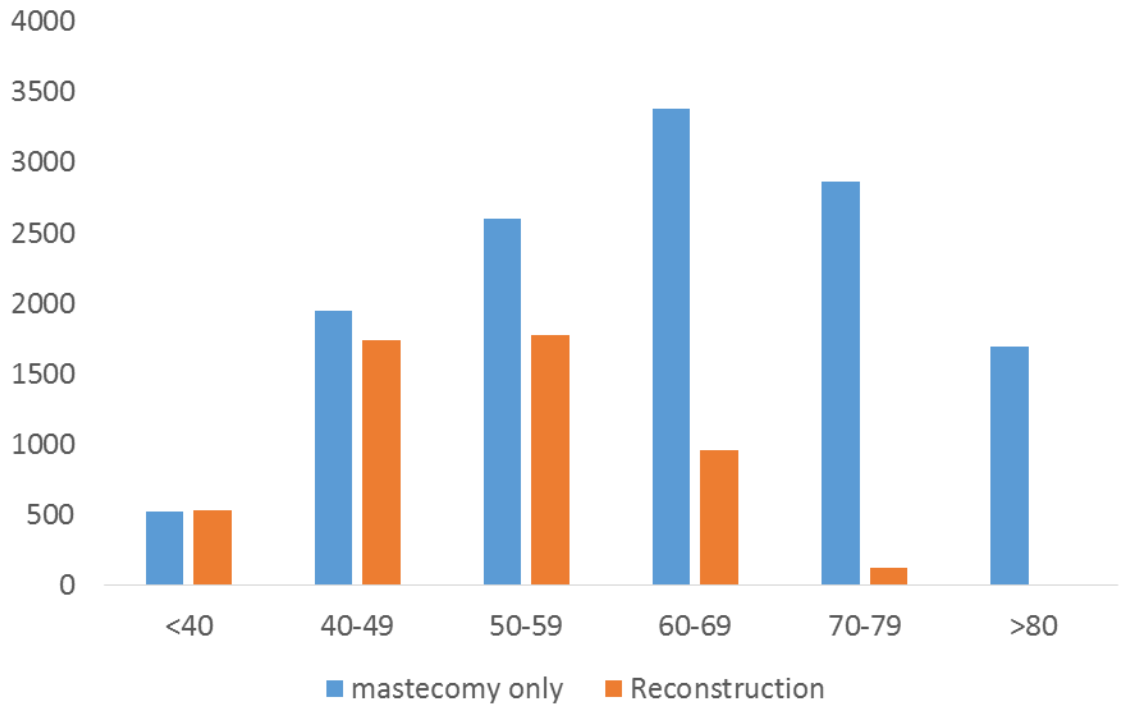
(Jeevan et al, BJS 2016)

- Delayed reconstruction rate has risen from 2 to 10 % between 2000 and 2015
- Immediate has risen from 7 to 20% over the same time period
- BUT huge regional variation between 15 and 37% across the UK

Impact of Deprivation on Reconstruction Rates

- Hazard ratios show clear inverse link between immediate reconstruction and index of multiple deprivation with the most deprived only having 56% the chance of reconstruction compared to the most deprived. (Jeevan et al, 2016)
- May reflect later stage of diagnosis, other health issues (higher rates of smoking, obesity, diabetes in deprived cohorts) and lack of patient interest.

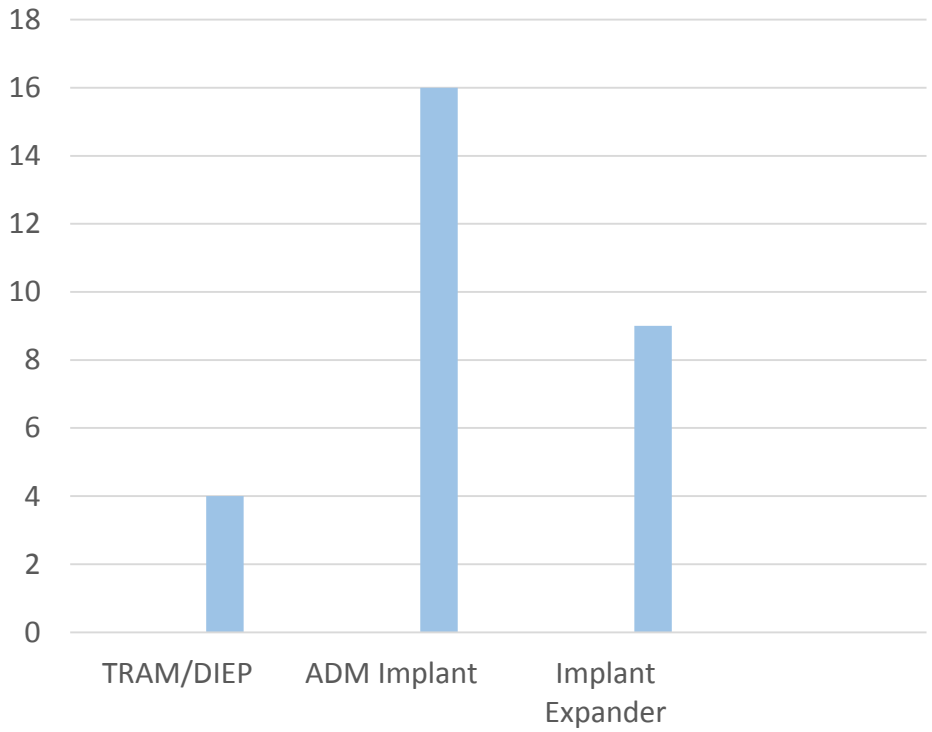
Reconstruction Rates by Age Group



Rates of reconstruction by age group (UK Nat. Mast. Audit 2010)

Reconstruction methods in older women (UK Age Gap Cohort Study)

31/924 (3.4%) women having mastectomy

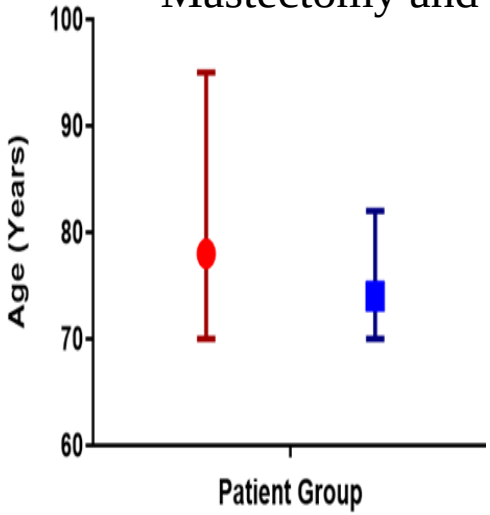


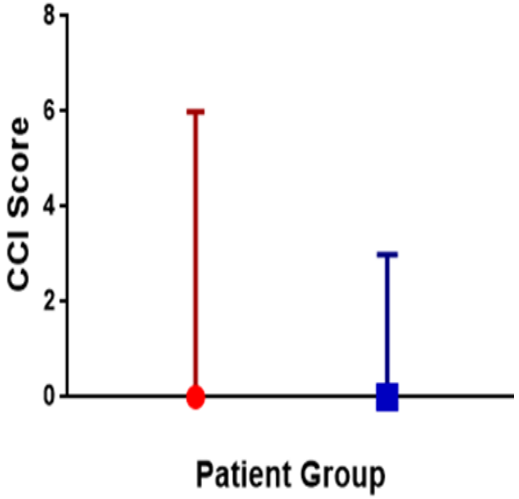
- 17 local complications:
  - 7 seromas,
  - 2 haematomas,
  - 5 infections and
  - 3 flap necrosis
- no systemic complications.

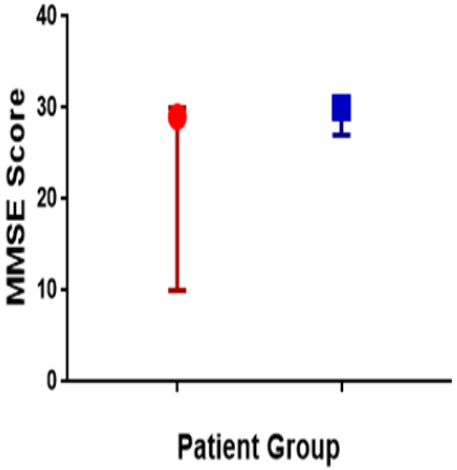
Over 70 reconstruction fitness variation

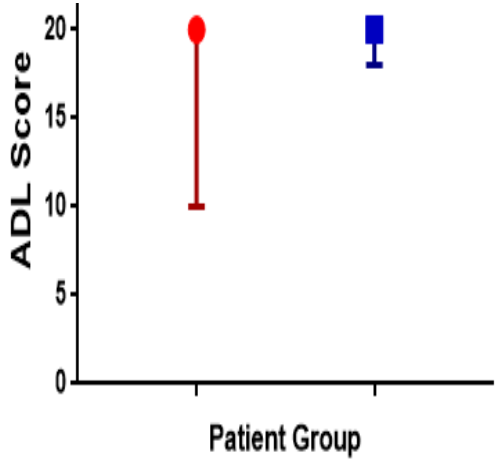
Mastectomy only

Mastectomy and reconstruction







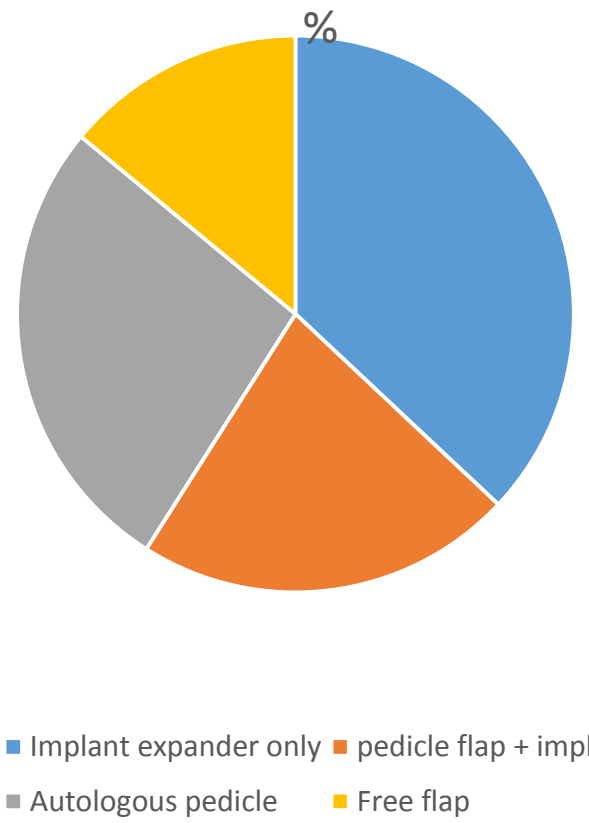


Oncological Considerations

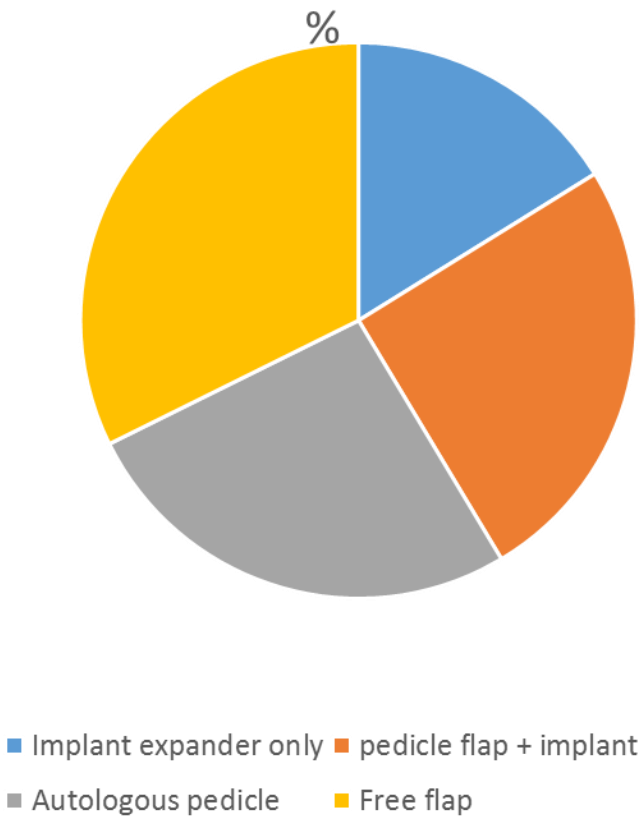
Primary or Delayed Reconstruction

- **Primary**
  - Increased options for skin preservation and therefore better objective cosmesis
  - Reduced psychological trauma from disfigurement
  - May delay chemotherapy or radiotherapy if complications
  - Radiotherapy may spoil result. Indications may broaden after the recent EBCTCG data
- **Delayed**
  - Minimal risk of delays in other adjuvant therapies from complications
  - Irradiated tissue may be excised when reconstructing and healthy tissue used to recreate breast
  - Limited skin preservation options
  - Loss of the infra mammary fold
  - Period without a breast-may never have reconstruction or face long delays as no longer urgent

Type of Reconstruction



Immediate

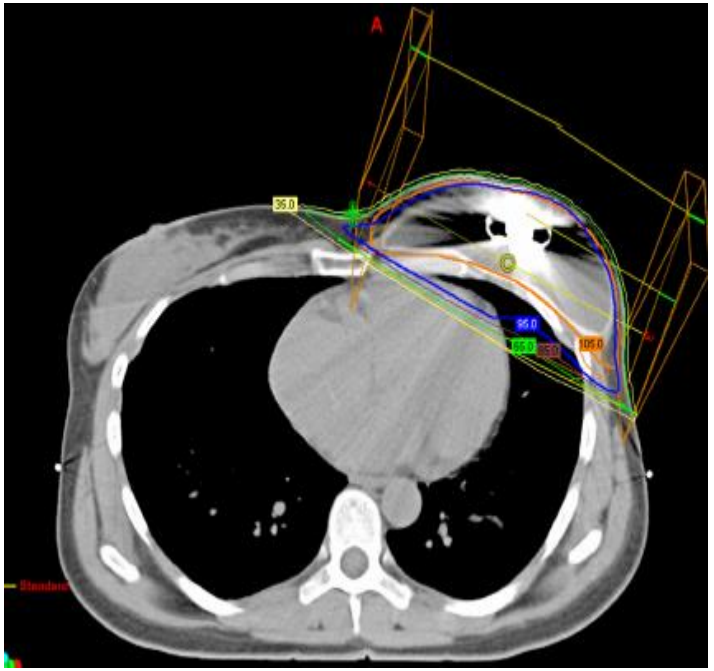


Delayed

- NMBRA 2010

When will radiotherapy be needed?

- Difficult to predict before surgery.
- T3 and T4 cancers usually attract a recommendation for post-operative chest wall radiotherapy.
- High grade PLUS nodal disease may be offered radiotherapy
- Close margin posteriorly or anteriorly: careful review of imaging as may be VERY tricky to go back afterwards



Radiotherapy

- Problems
  - High rate of capsule formation with implants:
    - 5% normal,
    - 40% after RT
  - Skin viability risk
  - Wound healing
  - Loss of elasticity
  - Fat necrosis
  - Fibrosis
  - Implant extrusion

Rates of Capsule Formation after RT and Breast Reconstruction

- Rate is broadly 3 fold higher when rates of capsule formation are compared between those who do or do not have RT

- Highly significant in all studies

Implant removal/replacement after RT

- 29% rate of removal or replacement at 7 years after mastectomy and RT
- Cause:
  - Infection 40%
  - Implant extrusion, shift, leak or rupture 10%
  - Patient request 3%
  - Multifactorial 48%

Involve the MDT *BEFORE* Immediate Reconstruction

- Options to aid prediction:

1. SLNB before mastectomy to aid in planning of both implant and flap based reconstructions (if using an axillary pedicle for a flap)

2. Grade and immunophenotype on core: Her-2/TNP/grade 3

3. Imaging review re posterior clearance and proximity to skin and nipple

4. ? Role for an oncoplastic MDT (some low level evidence this enhanced the rate of immediate breast reconstruction, El Gammal et al, 2017)

Summary of Studies of rates of Capsule Formation with ADM

Author	Number breast ops	Study type	Surgery type	Length FU/ months	Rate of Capsule formation
Spear 2008	58	Prospective series	Immed. expander	26	1.7%
Maxwell 2009	78	Retrospective series	Mixed, including revisions	12	1% baker 2
Salzberg 2011	455	Retrospective series	Immed. implant	29	0.4%
Vardanian 2011	208	Retrospective cohort	Immed. Expander/ADM	NS	3.8%
	129	Retrospective cohort	Immed. expander	NS	19%

Acellular Dermal Matrix and Post Operative Radiotherapy

Valdatta et al, 2014, Meta-analysis shows that RT plus ADM is associated with a higher rate of complications (RR~3 fold)

Complications of autologous reconstruction +/- radiotherapy

Schaverian et al, Journal Plastic reconstructive and aesthetic surgery, 2013

Showed that overall rate of complications is similar with autologous reconstruction (comparing RT or not) BUT higher rates of revision surgery and fat necrosis if RT is given after reconstruction

Immediate Delayed Technique and RT

(Ayoub et al, Annals Surgical Oncology, 2017)

Large series of cases (384) with skin sparing mastectomy and tissue expander placement.

13% of women lost their TE prior to definitive reconstruction

80% of definitive reconstructions were autologous

Other Technical Issues due to preop RT

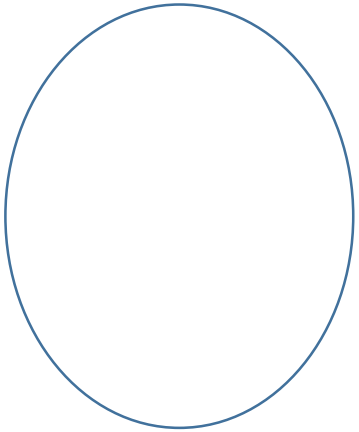
- May have had RT to chest wall, internal mammary chain, axilla.
- May have had axillary clearance
- Pedicles may be unreliable for anastomosis of flap
- May have had more aggressive cancer
- Quality of the skin:
  - Radiation fibrosis
  - Thin, poorly vascularised flaps
- Muscle denervation and irradiation of pectoralis may compromise submuscular pocket

Neoadjuvant RT

- A logical extension of the above

- USA SEER database analysis of 2500 cases shows potentially enhanced rates of second cancer and excellent rates of disease control, so appears to be at least as oncologically sound as post surgery RT (Poleszczuk et al, Breast Cancer Research, 2017)

- *Baltodano et al.*
- *Plast Reconstr Surg Glob*
- *Open 2017;5:e1108;*



Oncological Safety of Skin Sparing Mastectomy

- Skin sparing mastectomy has generally got good rates of local control in most large series, comparable to rates for mastectomy.

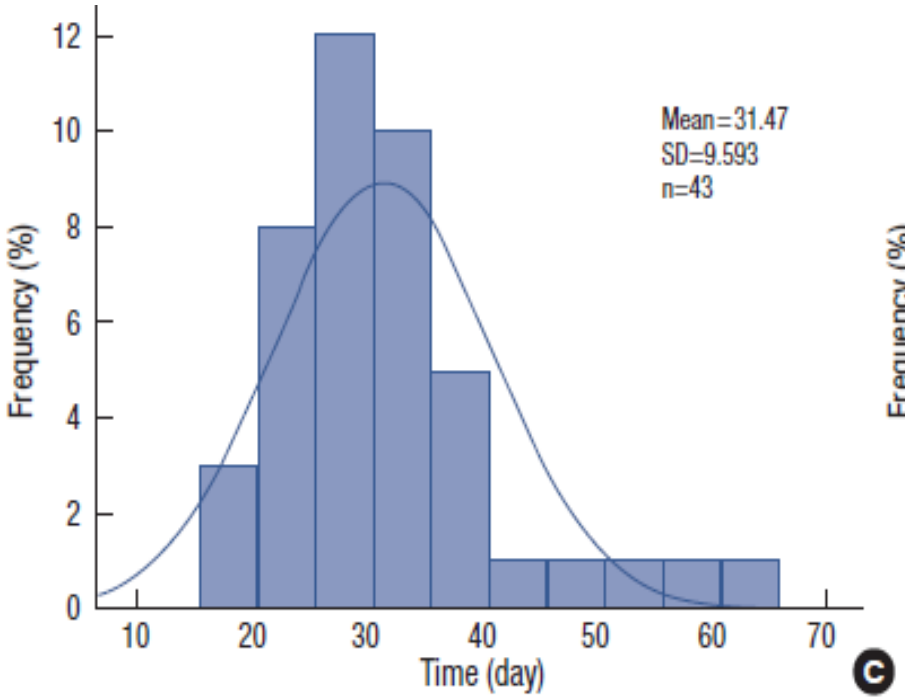
Author	No .SSM vs Mx	LRR SSM
Newman 1998	372	6.2%
Carlson 2003	539	5.5%
Lanitis 2010	825 vs 2518	5.7 vs 4.0 %
Sheikh 2011	177 vs 249	1.1 vs 0.8%

Chemotherapy Delay

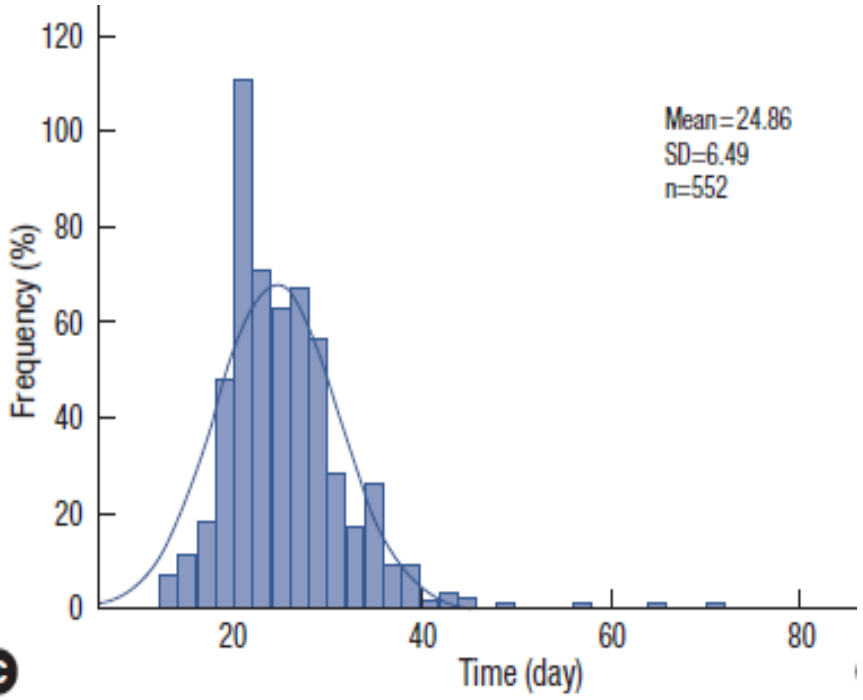
- Chemotherapy, if needed, may be delayed slightly by immediate reconstruction.
- No large studies
- Meta-analysis suggests time increases between 13 and 36% between surgery and chemotherapy.
- No data on the oncological significance of this

- Consideration of neoadjuvant chemo if complex surgery planned and chemo known to be needed

Delayed Chemotherapy with Immediate Reconstruction?



Immediate reconstruction



No Immediate reconstruction

Lee et al, 2011, EJBC

Primary Systemic Therapy

- Indicated in cases where locally advanced
- But, in cases where chemo is inevitable, up front use may avoid risk of delays
- May allow time for gene testing, especially in younger women in whom risk of a gene is higher and may wish to chose mastectomy (unilateral or bilateral) if positive.

The Nipple: to Spare or not to Spare

- **In a non-ptotic breast**
- Disease proximity: greater than 2-2.5 cm
- Nipple shave to confirm

In a ptotic breast

Wise pattern skin reduction not compatible with nipple preservation unless by free nipple graft.

Bucket handle techniques may be used but risk of nipple loss

- Increased risk if multicentric disease, (4% if unifocal versus 34% if multicentric 4 quadrantic disease. If 1cm, 8% risk versus 20% if more than 5cm

Reconstruction Techniques

Patient variability!

General fitness,

Shape, ptosis & size of breast,

Spare tissue availability,

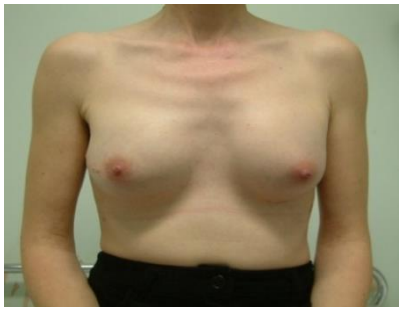
Attitudes to silicone implants,

Personal choice,

Personal activities/employment,

Time off work,

Abdominal/breast scars



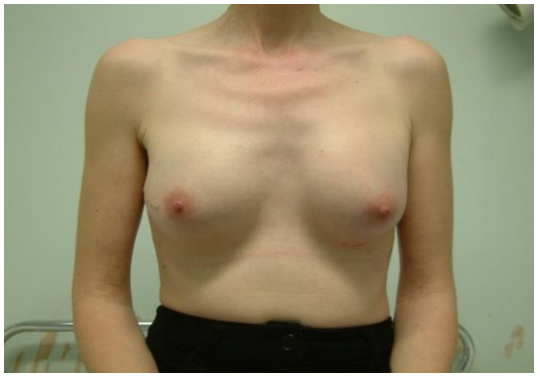
Skin Envelope Planning

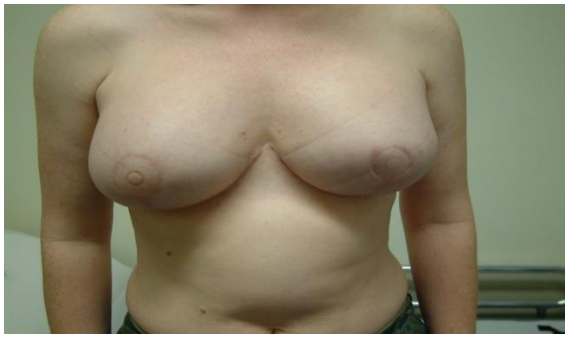
Blood supply: scars, previous reduction or augmentation, radiotherapy, flap length.

Ptosis.

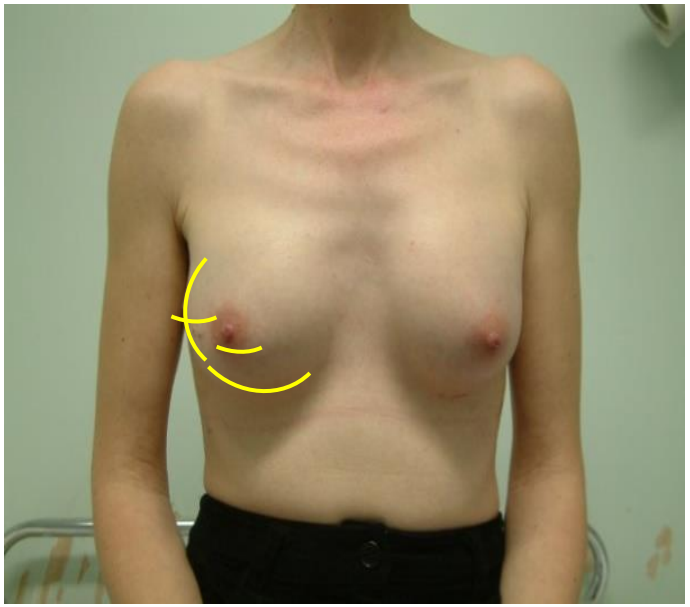
Cleavage scars

Tumour position relative to overlying skin and nipple



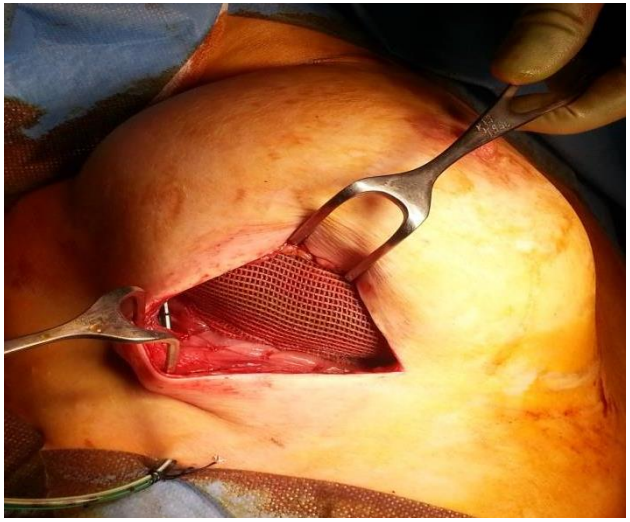


Dealing with Ptosis: None



- No skin envelope tightening needed.
- Skin incision can be placed anywhere for optimal cosmesis
- Acellular Dermal Matrix may not be needed as fully submuscular pocket may be adequate but caution is thin skin coverage

Dealing with Ptosis: Minor



- No skin envelope tightening needed.
- May correct simply by use of a slightly larger volume reconstruction
- ADM valuable to give a fuller breast volume, better shape, better inframammary fold definition than a submuscular pocket

Superior Periareolar Mastopexy

- Suitable for minor adjustment of ptosis to elevate nipple height.
- 1 third areolar circumference.
- Can extend laterally to gain further lift and better access.
- Again ADM ideal as not usually enough ptosis for a wise pattern/dermal sling technique.
- De-epithelialise the crescent and use for a double layer closure

Dealing with Ptosis: Severe

- Reduction Pattern techniques.
- Wise Pattern
- Lends itself beautifully to dermal sling (fully or ADM supplemented).
- Wise pattern is higher risk if directly over ADM so careful selection needed or retain a paddle of de-epithelialised skin at the T junction.

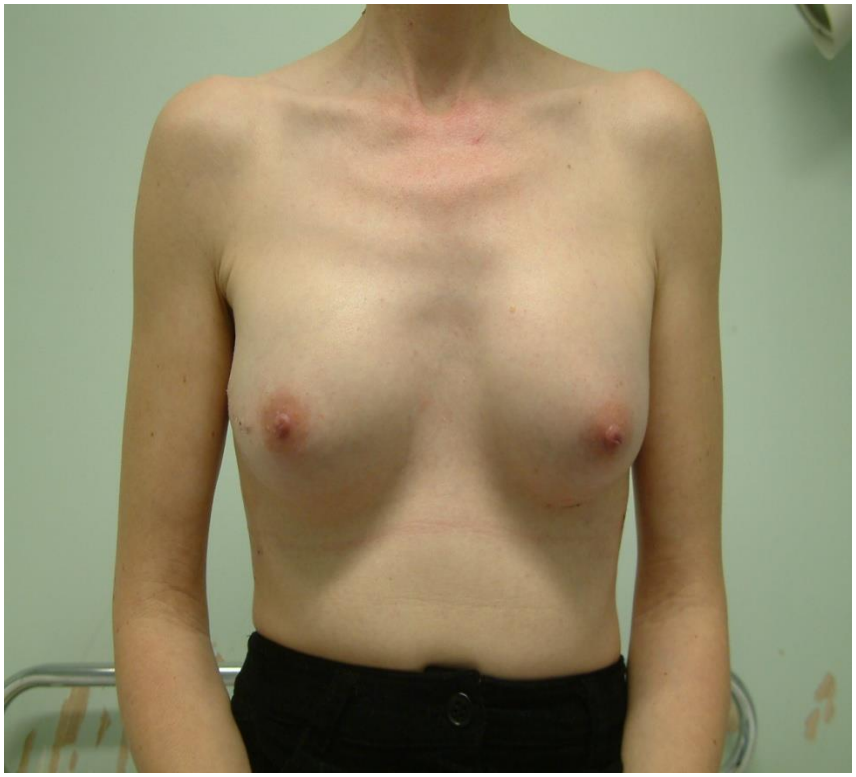
Wise Pattern Problems

- Full thickness skin flap necrosis of T junction and vertical limb 12% of 75 breasts
- Partial thickness in 14%
- Implant loss in 4.7%
- All had dermal sling, so implant covered but major risk if using wise pattern with ADM
- (Santanelli, 2013)

- Risk factors (multivariate analysis):
  - Smoking: OR 16
  - Prosthesis weight over 470 gm OR 7
  - Obesity (BMI) trend towards significance

Technical considerations in women with little subcutaneous fat

- Implant based reconstructions should always place the implant in the sub pectoral plane to avoid a cleavage ridge.
- Great care when dissecting flaps
- Care with ADMs.



Breast Mound Recreation

Implant Based

- Fully submuscular expander/implant
- Implant augmented latissimus dorsi.
- Dermal Sling and Implant
- Acellular Dermal Matrix and Implant

Autologous

- Autologous Latissimus Dorsi
- TRAM/DIEP Flap
- SGAP/IGAP (Superior/Inferior Gluteal Artery Perforator)
- Transverse Upper Gracillis (TUG) Flap
- Perforator flaps: LICAP, TDAP, AICAP
- Lipomodelling

Implant/Expander

- Who is suitable
  - Women with small, minimally or non-ptotic breasts, (B/C cup).
  - Women who prefer simpler, shorter procedure, or who have health problems which contra-indicate a long procedure.
  - Acceptance of risks of implants

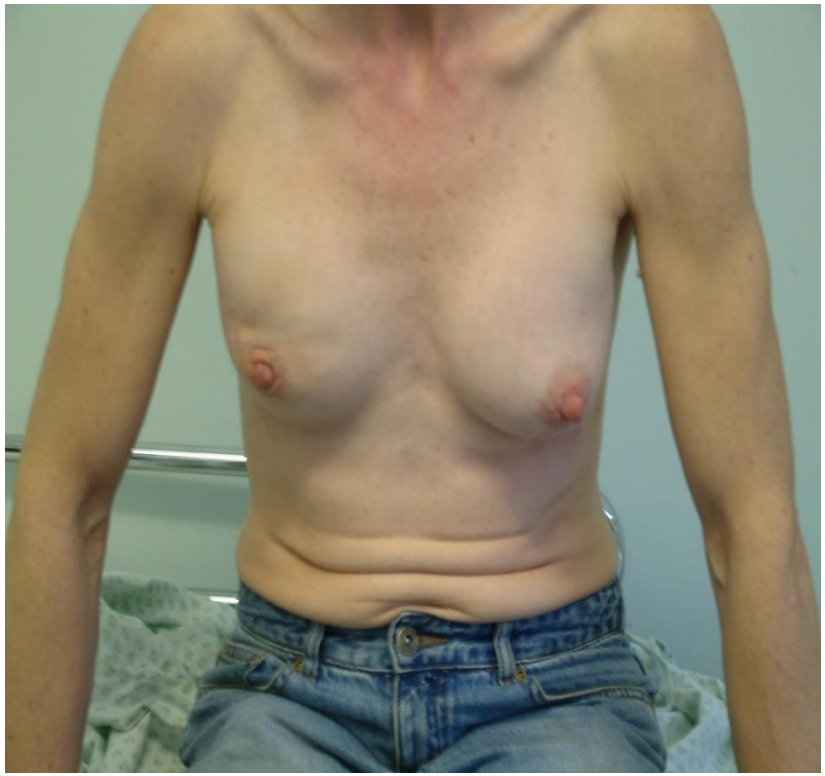
- **New issue with BI-ALCL**

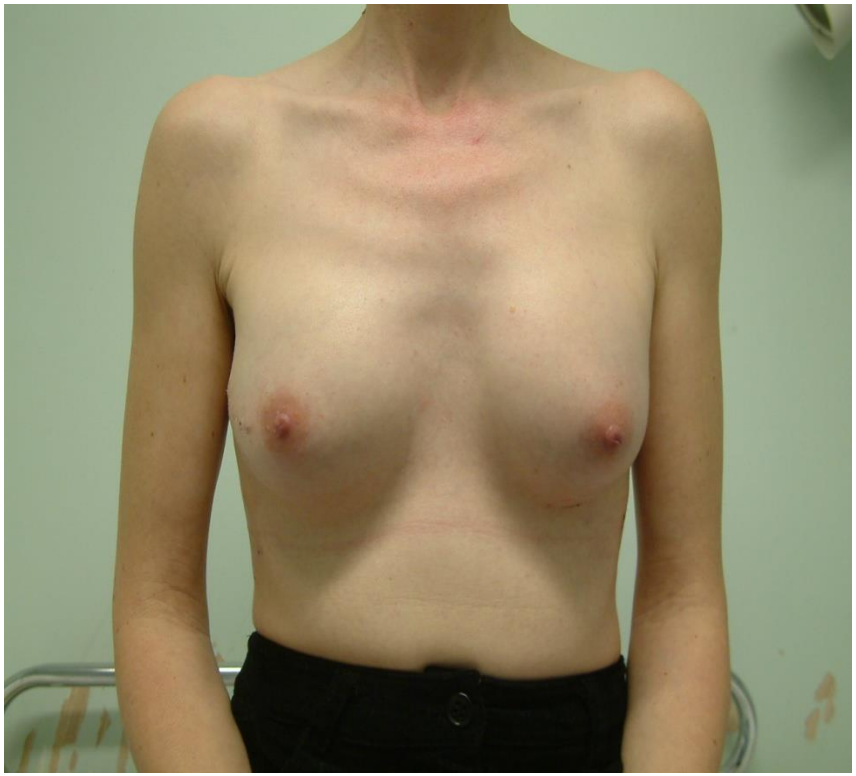
- Contra-indications
  - Radiotherapy
  - Large ptotic breasts
  - High expectations for symmetry, unless bilateral procedure

Implant Position

- Sub-mammary or sub-pectoral are standard for augmentation.
- Post-mastectomy, subcutaneous seems logical, especially with a skin sparing technique, BUT high risk of implant loss, wrinkling, infection…..
- Partial or fully sub-muscular is therefore preferred.
- 1 or 2 stage options

Reconstruction with submuscular expander implant:





Acellular Dermal Matrix, ADM

- Gives a more ptotic shape and greater breast volume than submuscular
- May not need to expand
- Derived from porcine, bovine, human dermis or pericardium
- Slightly higher infection rate (retrospective)
- Expensive!

Dermal Sling + Implant and Goldilocks

- Only suitable for women with ptosis to a degree that could have a wise pattern reduction and want a lift and size reduction.

- De-epithelialise the inferior skin and use of endogenous dermal to support and provide a pocket for an implant or to ‘scrunch up’ to create the breast mound!

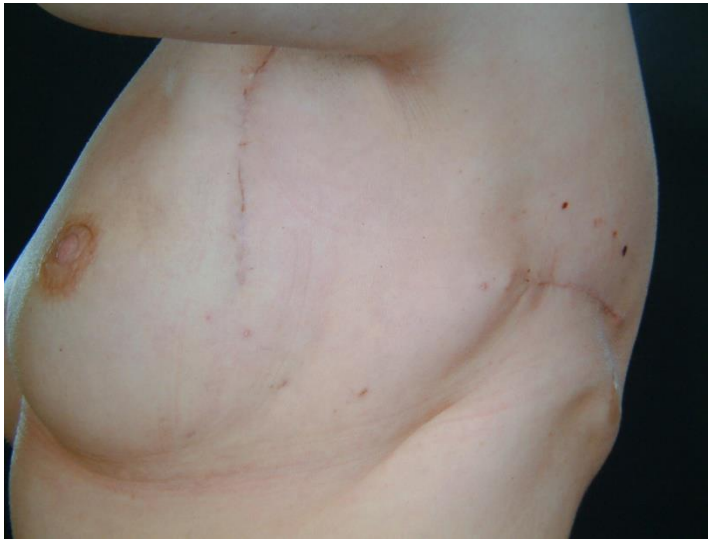
Latissimus Dorsi

- Flat sheet of muscle.
- Blood and nerve supple from axilla
- Can be moved as muscle only, muscle and fat and skin, or muscle and skin.
- Minimal physical limitation afterwards.

Latissimus Dorsi Flap

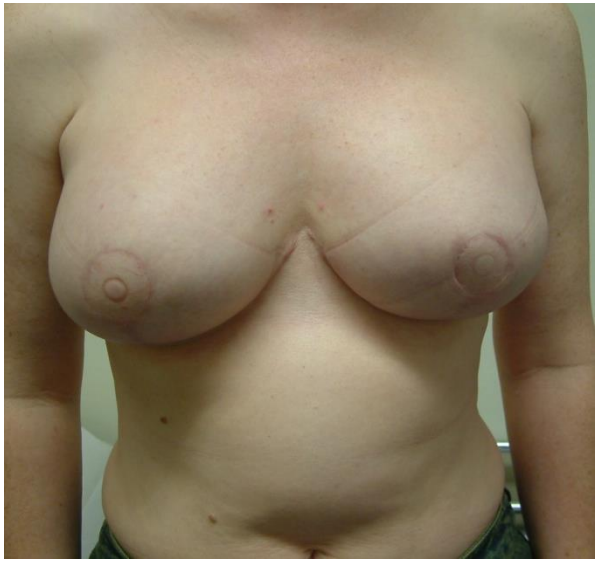
- Who is suitable
  - Most sizes and shapes can be achieved.
  - Not all suitable for autologous
  - Ptosis and D+ cup can be achieved.
- Contra-indications
  - Long term back pain
  - Physical job or hobby
  - Previous axillary surgery with evidence of pedicle damage
  - **Axillary RT**

Latissimus Dorsi-variations

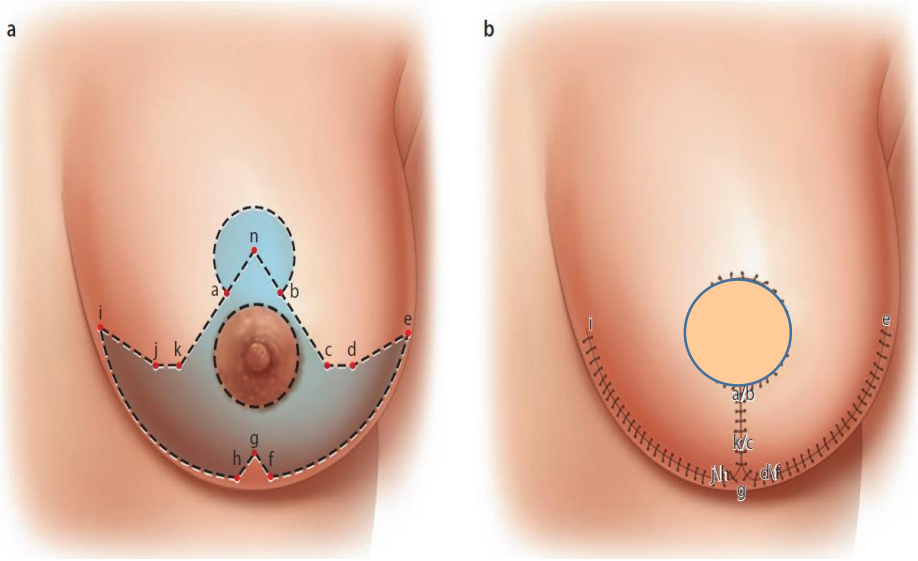


- Primary Subcutaneous mastectomy with nipple preservation.
- Nipple shave to ensure no residual disease
- Lateral scar gives good access and cosmesis.

Latissimus Dorsi-variations



- Bilateral Wise pattern mastectomy



Latissimus Dorsi-Limitations

Can achieve some ptosis but within limits

Can get good DD cup size but not much more

Back morbidity: long scar, back pain, prolonged seroma.

Latissimus dorsi limitations

DIEP Flap

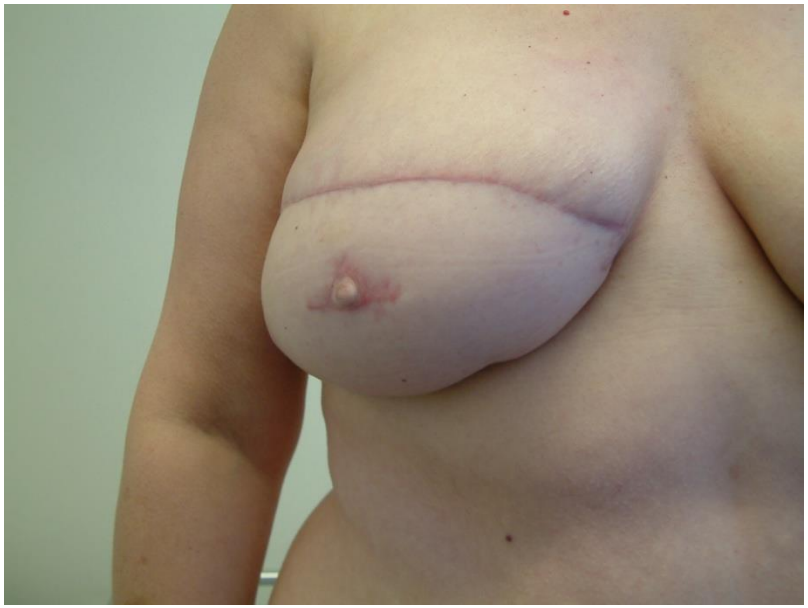
Who is suitable.

- Need to have enough of a ‘tummy’ for a tummy tuck.
- Not too much. BMI 30-35 maximum.
- Need to be well motivated.
- Fit

Contraindications

- Very obese (BMI >35), smokers, diabetics, hypertensives.
- Previous surgery to abdomen compromising pedicle and flap size
- Chest wall radiotherapy may compromise the pedicle if needs to be plumbed into the internal mammary.
- Axillary RT or poor quality surgery may compromise the pedicle if to be plumbed into the thoracodorsal vessels

TRAM or DIEP Flap



Lipomodelling in the Mastectomy Setting

- Pre delayed reconstruction to thicken a poor quality/irradiated flap.
- To enhance projection/volume of an autologous reconstruction
- To thicken or smooth a thin or irregular skin flap
- To build an entire breast!!
- (photos coutesy of R Bonomi)

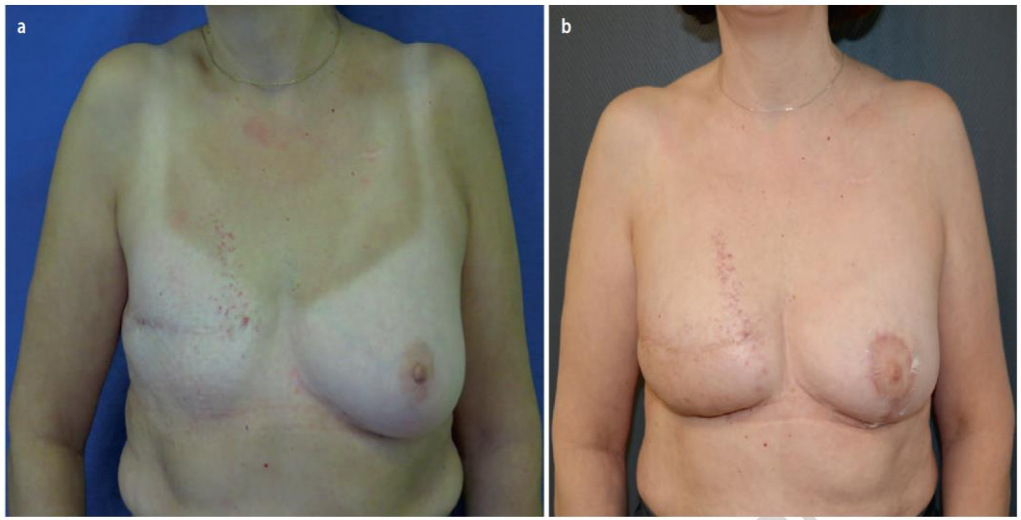


Fig. 20.4 **a** Patient awaiting right breast reconstruction exclusively with lipomodelling. **b** Patient following right breast reconstruction exclusively with lipomodelling (four sessions of lipomodelling required, with a total of 756 cc of purified fat injected) and left mastopexy reduction for symmetrisation

Maintain/Restore Symmetry

'What do you think of your breasts as they are now/what would they ideally be like?'

Late asymmetry may require ongoing correctional procedures such as lipomodelling to thicken flaps, nipple height adjustment, volume adjustment.

Risk Factors for nipple necrosis

Large US series of 500 cases, (Coldwell et al 2013)

- Nipple necrosis 4.4 percent

- Risk Factors for nipple or skin necrosis:

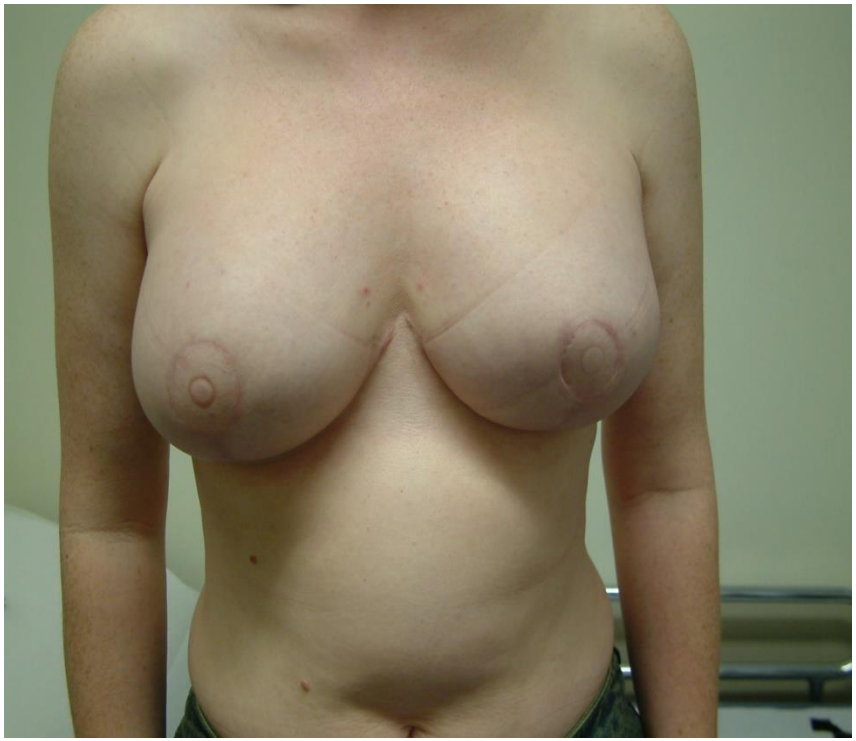
- Smoking (OR, 3.3)
- Periareolar incisions (OR, 3.63)
- Increasing body mass index (OR, 1.154)
- Preoperative irradiation (OR, 4.86).

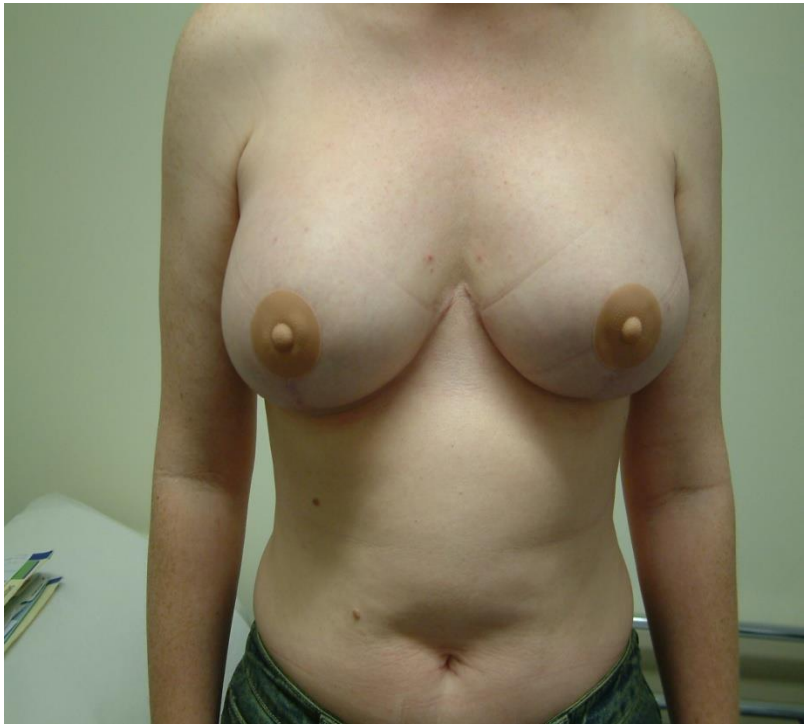
- Inframammary fold incision decreased complications (OR, 0.018)

Nipple Reconstruction: Prosthetic

- May be ‘off the shelf’ or bespoke.
- Bespoke are made by taking a cast of the patient’s own nipple and making a silicone rubber prosthesis which is then coloured to match.

Stick-on Nipples





Nipple reconstruction techniques

- Skate flap
- Star flap
- CV flap
- Trefoil flap
- Nipple sharing
- Free nipple graft

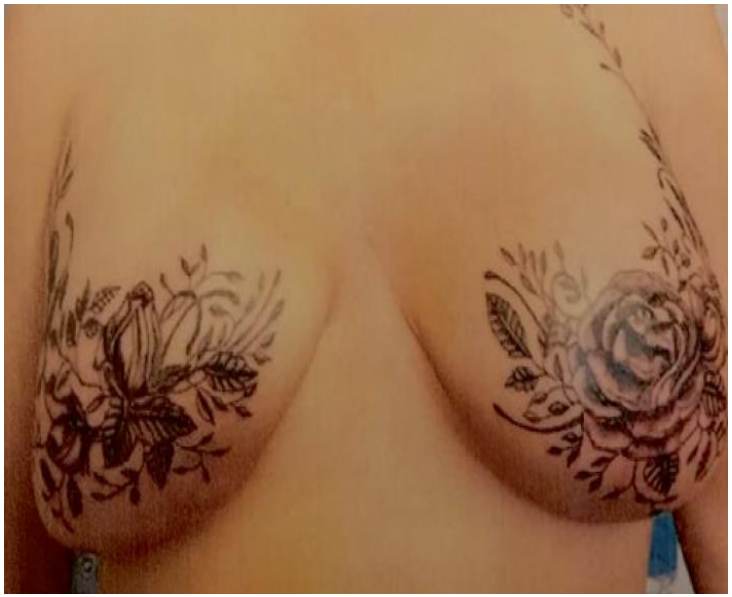
- Skin grafting for areolar reconstruction
- Tattooing for areolar reconstruction

Nipples: Trefoil flap and tattoo

Nipple Reconstruction with Wise Pattern

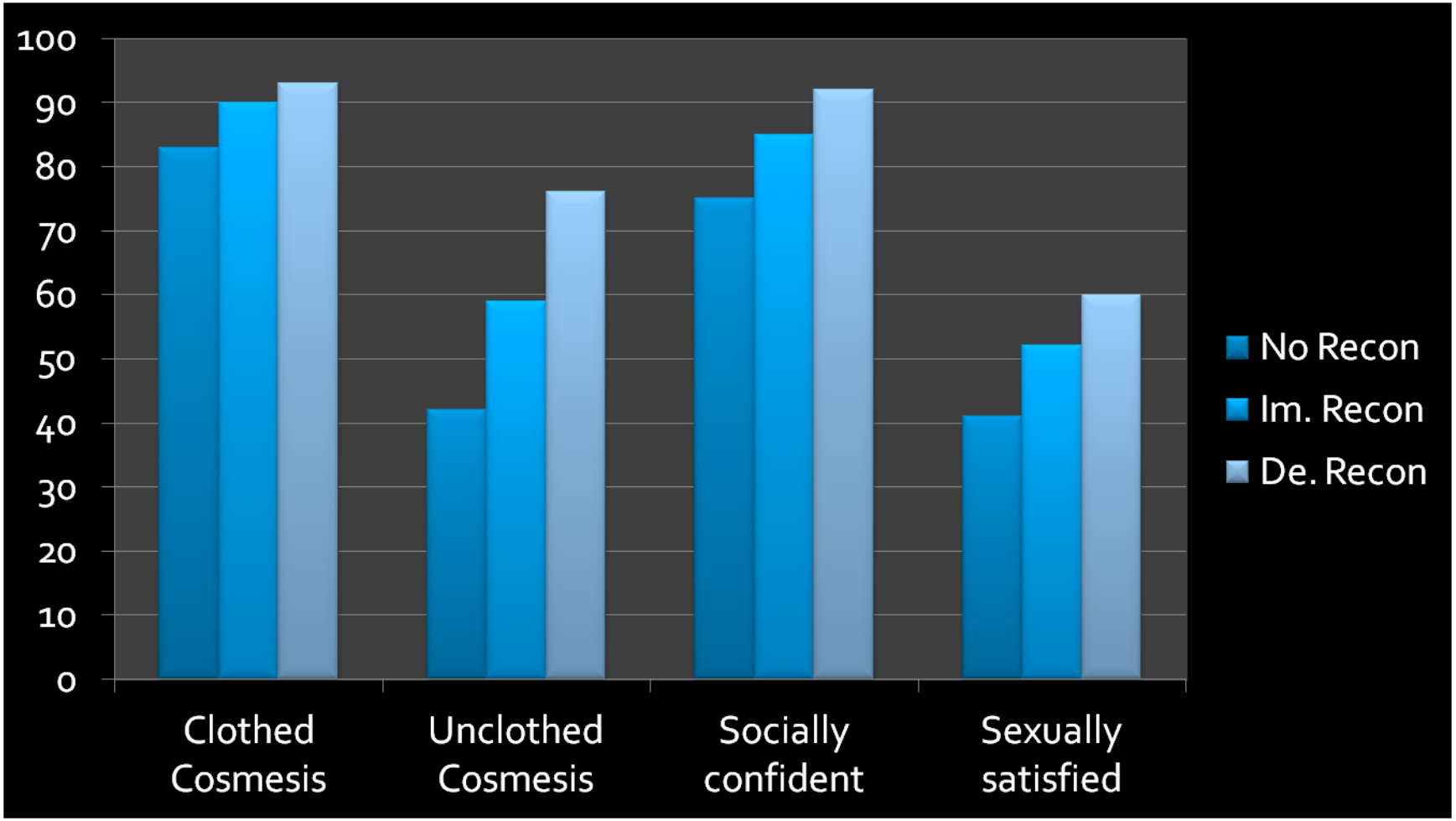
- Double S type flap at the wise pattern apex in the areolar folded to make a new nipple.
- Free nipple graft
- Standard nipple reconstruction and areolar tattoo

Tattoos



Patient satisfaction and outcomes

Patient Satisfaction (NMBRA 2011)



Summary

Treatment needs to be tailored to the individual.

Complex planning and decision making

Manage expectations: Reconstructions are NEVER perfect

Radiation therapy prior to or after breast reconstruction?

Birgitte Vrou Offersen,

Clinical oncologist

Aarhus University Hospital, Denmark

1980-ies

Pivotal trials

BCT as an alternative for MRM

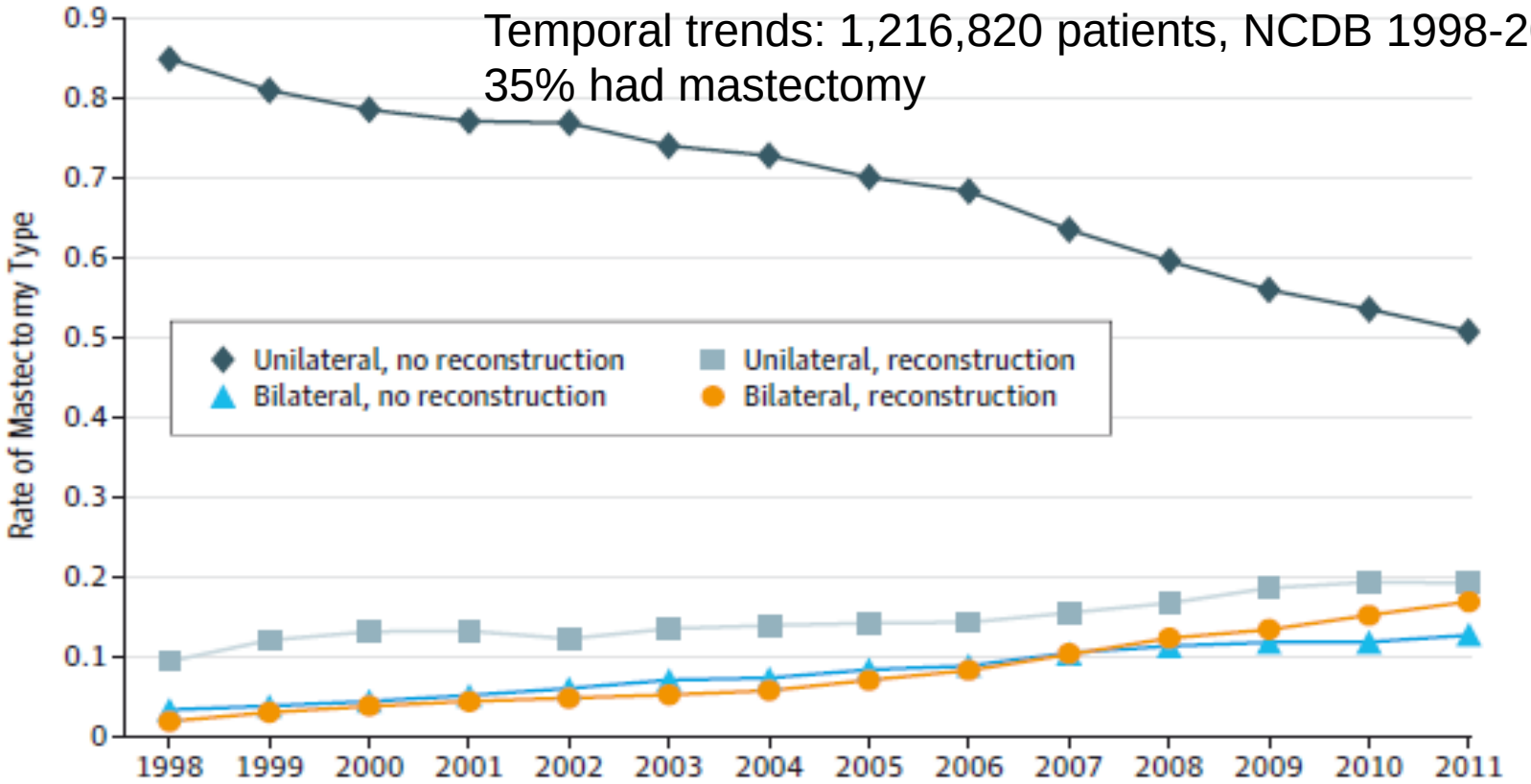
1990-ies

The NIH Consensus Conference defined

“BCT as the standard of excellence in early breast cancer care”

USA-Low risk/BCS eligible

Temporal trends: 1,216,820 patients, NCDB 1998-2011
35% had mastectomy



Younger women were more likely to undergo mastectomy irrespective of tumor size

Steeper **increases** in mastectomy rates for women with **N0**, **smaller tumors, DCIS**

Breast **reconstruction increased** from 11.6% to **36.4%**

Bilateral mastectomy for <u>unilateral</u> disease increased from 1.9% to **11.2%**

Reconstruction for bilateral mastectomy **increased** from 36.9% to **57.2%**

Kummerow, JAMA Surg 2015

School

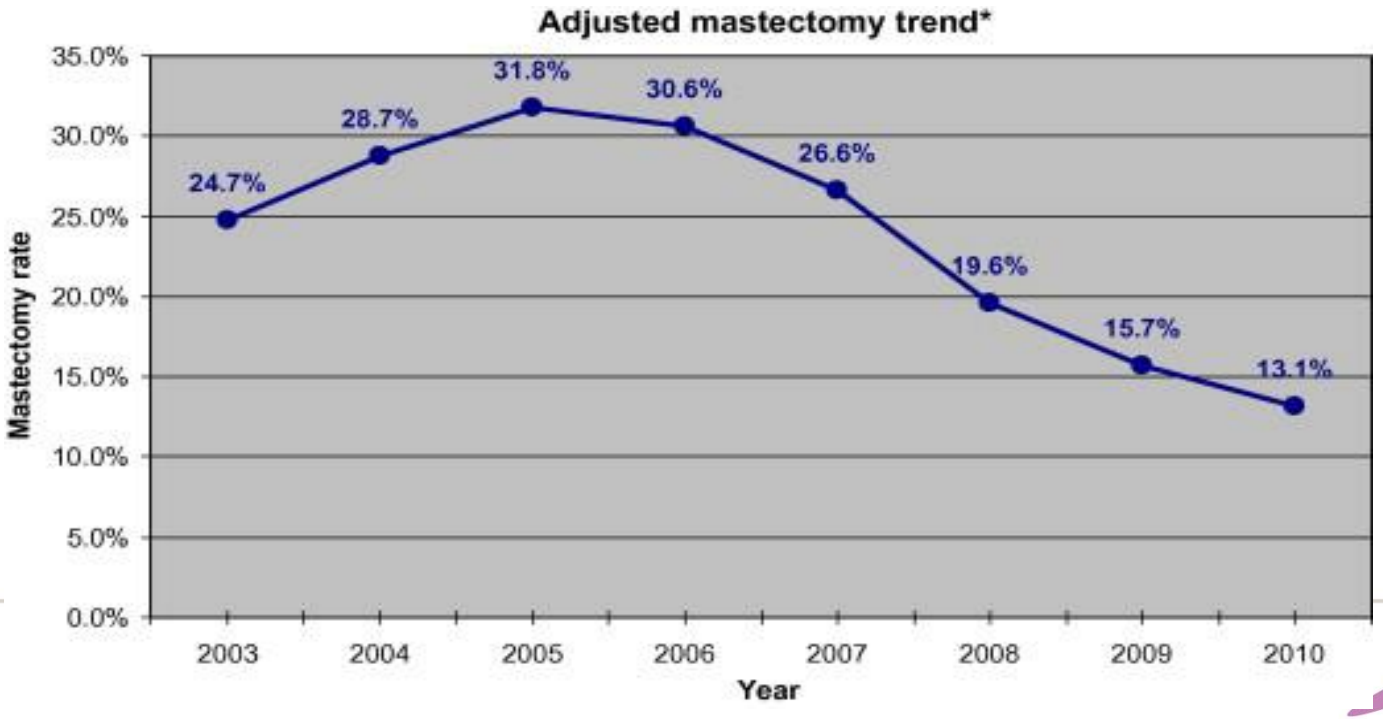
Europe– Low risk/BCS eligible

EUSOMA (2003-2010):

A total of **15,369 pts**

27 % mastectomies

Statistically significant **decrease** in mastectomy rates from 2005 to 2010, a progressive **reduction** of **4.24%/year**.



Garcia-Etienne, Eur J Cancer 2012

ESTRO School

Immediate Reconstruction of the Radiated Breast: Recent Trends Contrary to Traditional Standards

Shailesh Agarwal, MD[1], Kelley M. Kidwell, PhD[2], Aaron Farberg, MD[1], Jeffrey H. Kozlow, MD, MS[1], Kevin C. Chung, MD, MS[1], and Adeyiza O. Momoh, MD[1]

SEER 2000-2010:

- The **immediate breast reconstruction** rate among pts **requiring RT increased** from **13.6** to **25.1 %**
- **IR with implant-only increased** from **27** to **52 %** (p<0.001) with a decrease in **IR tissue-only** from **56 to 32 %** (p<0.001).

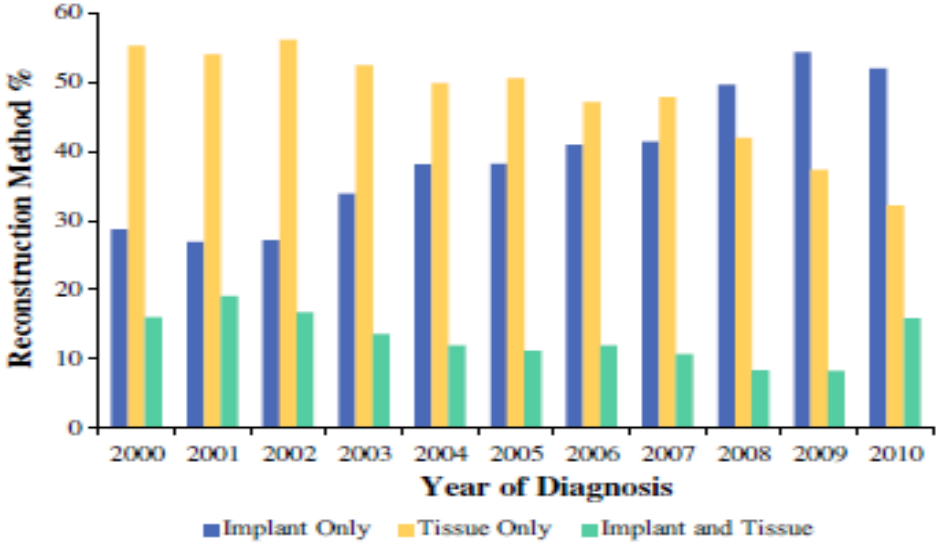


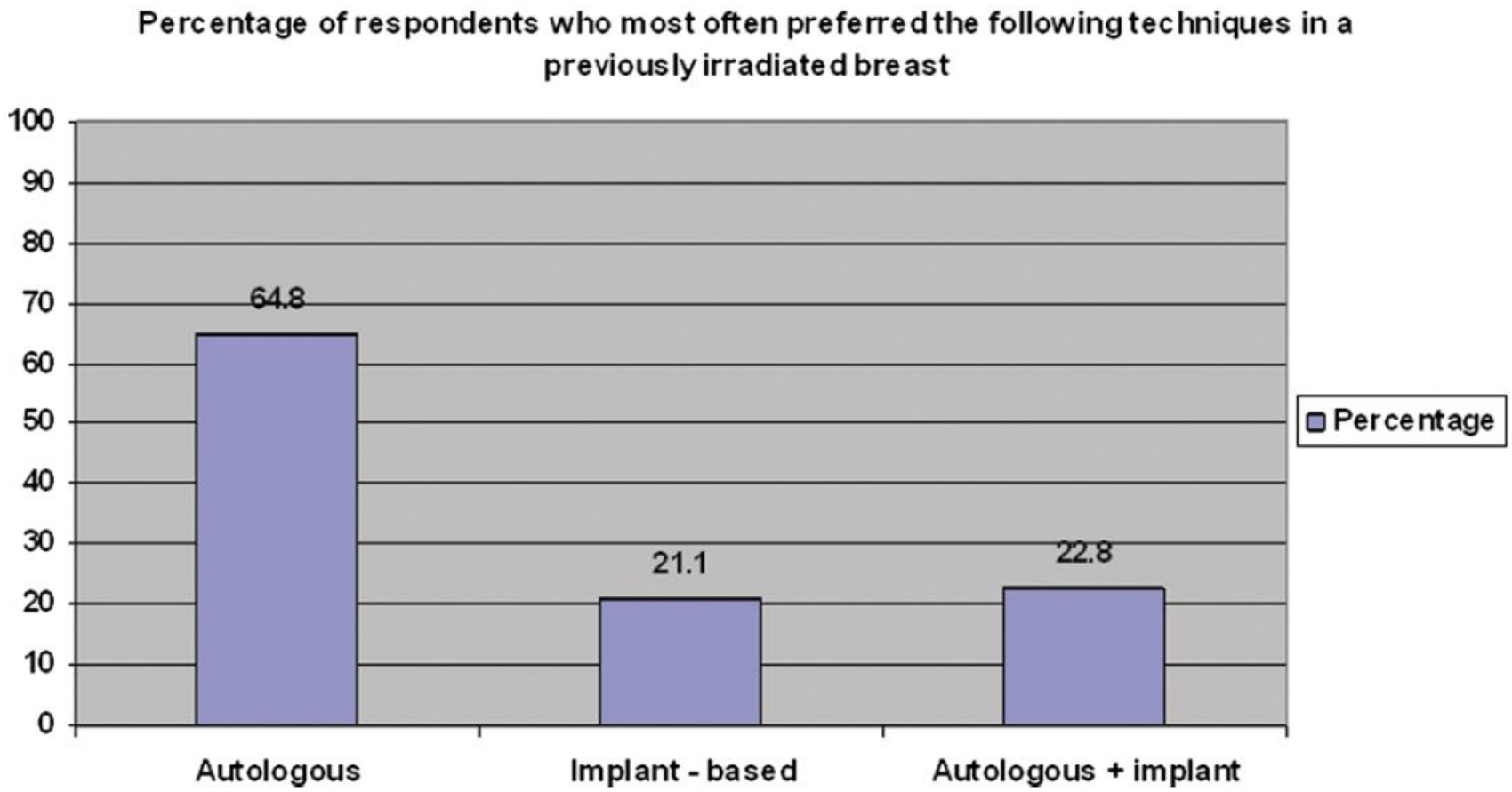
FIG. 2 Reconstruction rates by method in radiated patients from 2000 to 2010

Agarwal Ann Surg Oncol 2015

ESTRO School

So, there is a trend towards more immediate implant-based reconstruction in pts who need RT in the USA

Survey of Practice Pattern among US Plastic Surgeons N=358 who perform breast reconstruction routinely



- 81 % respondents do not perform immediate recon if RT is indicated
- 60 % agree with preop SLN before immediate reconstruction

Gurunluoglu *Ann Pl Surg*, 2013

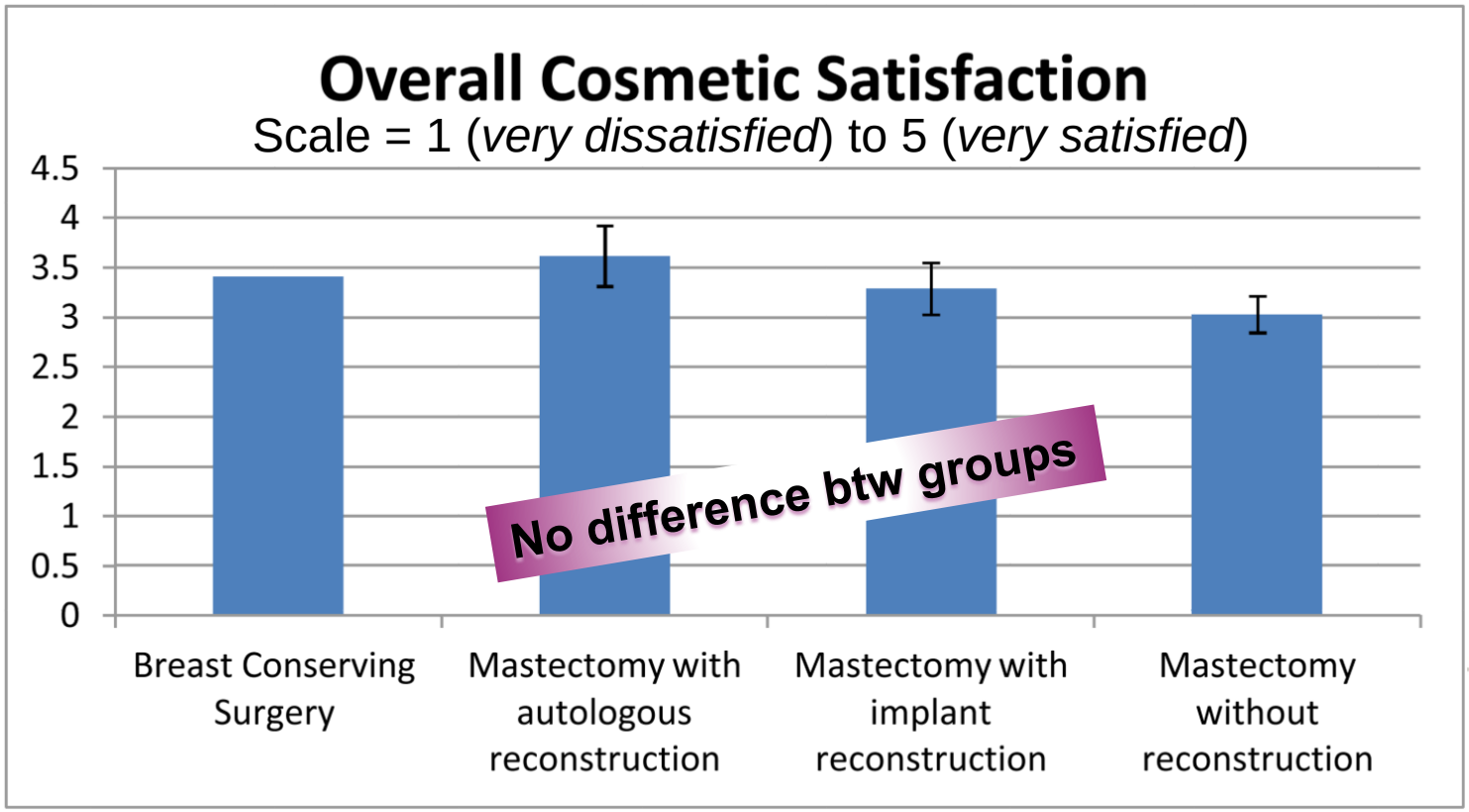
ESTRO School

Patient-Reported Quality of Life and Satisfaction with Cosmetic Outcomes After Breast Conservation and Mastectomy with and without Reconstruction: Results of a Survey of Breast Cancer Survivors

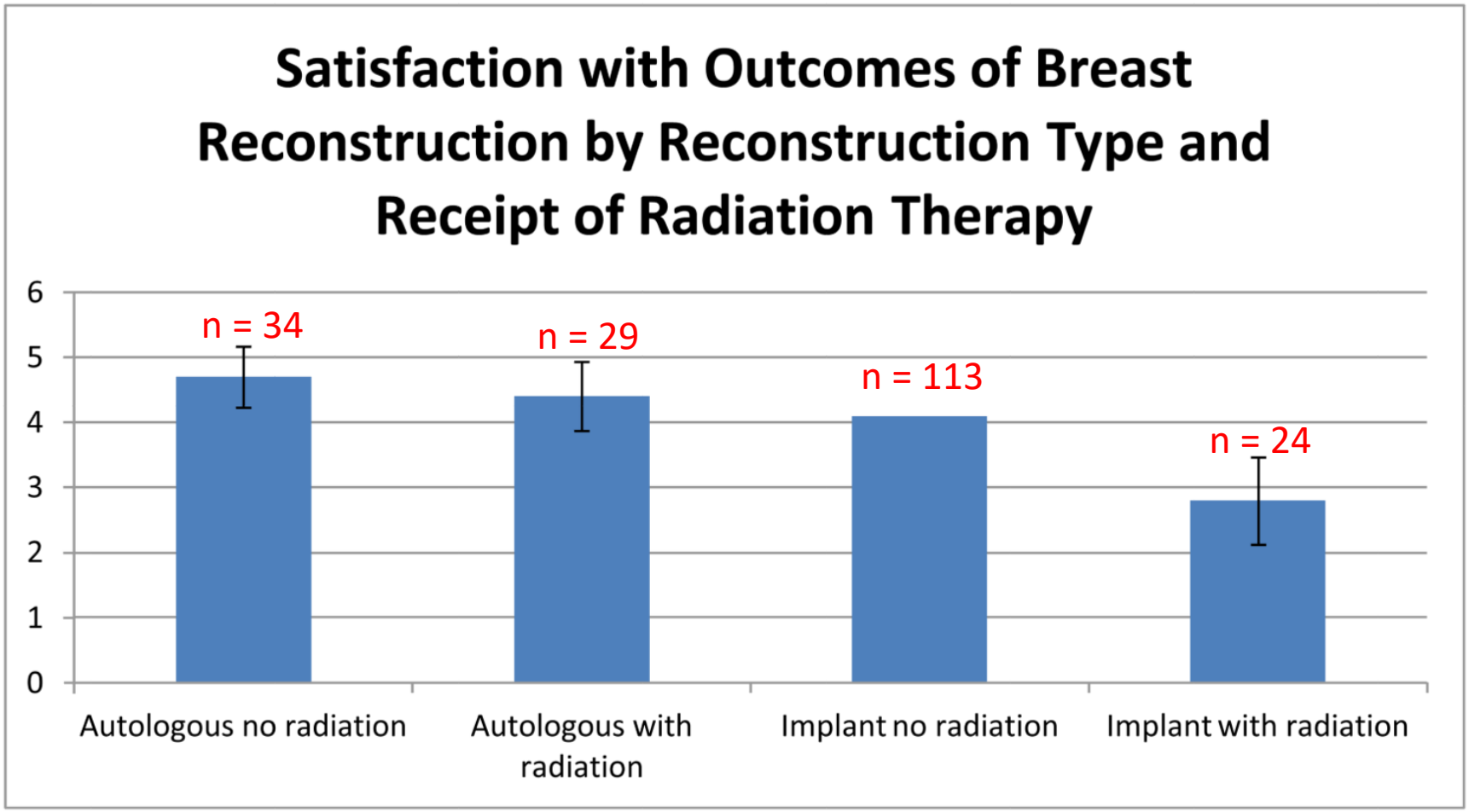
Ann Surg 2015

Reshma Jagsi[1], **Yun Li**[2], **Monica Morrow**[3], **Nancy Janz**[2], **Amy Alderman**[4], **John Graff**[5], **Ann Hamilton**[6], **Steven Katz**[1,2], and **Sarah Hawley**[1,2,7]

1450 patients treated 2005-2007 (SEER database)
All had responded QoL questionnaire 9 mths and 4 yr post BC surgery



ESTRO School



P<0.001

No information on timing of RT in relation to reconstruction

(Survey-based, not prospective)

ESTRO School

Why is immediate reconstruction in pts who need RT increasing?

Patients	Surgeons
Cosmetic satisfaction was similar for BCS and mastectomy w reconstruction (Jegasi, 2015)	Less technically demanding operations (Momoh, 2014; Agarwal 2015)
Younger pts don't want "ptotic breasts" (Agarwal, 2015; Seth 2015)	Shorter operative times (Momoh, 2014; Agarwal 2015)
Younger pts – less "donor" sites (Momoh, 2014; Agarwal 2015; Seth 2015)	Avoidance of donor sites (Momoh, 2014; Agarwal 2015)
Immediate reconstruction has physiological and QoL implications (Eldar, 2005)	Potential for shorter recovery (Momoh, 2014; Agarwal 2015)
Insurance (US) covers both breasts-> oncoplastic surgery	Better reimbursement for implant reconstruction (Agarwal 2015; Seth 2015)
Immediate implant reconstruction & RT: Satisfaction 90%, Would choose the same method of reconstruction 94% (Corderio, 2014)	Despite higher rates of capsular contracture, aesthetic results were good to excellent (McCarthy, 2005; Corderio, 2014)

Courtesy Orit Kaidar-Person, Israel

Patients	Surgeons
Cosmetic satisfaction was similar for BCS and mastectomy w reconstruction (Jegasi, 2015)	Less technically demanding operations (Momoh, 2014; Agarwal 2015)
Younger pts don't want "ptotic breasts" (Agarwal, 2015; Seth 2015)	Shorter operative times (Momoh, 2014; Agarwal 2015)
Younger pts – less "donor" sites	Avoidance of donor sites
Immediate reconstruction has physiological and QoL implications (Eldar, 2005)	Potential for shorter recovery (Momoh, 2014; Agarwal 2015)
Insurance (US) covers both breasts-> oncoplastic surgery	Better reimbursement for
Immediate implant reconstruction & RT: Satisfaction 90%, Would choose the same method of reconstruction 94% (Corderio, 2014)	Despite higher rates of capsular contracture, aesthetic results were good to excellent (McCarthy, 2005; Corderio, 2014)

Confused ? It depends on WHO and <u>WHEN</u> you ask

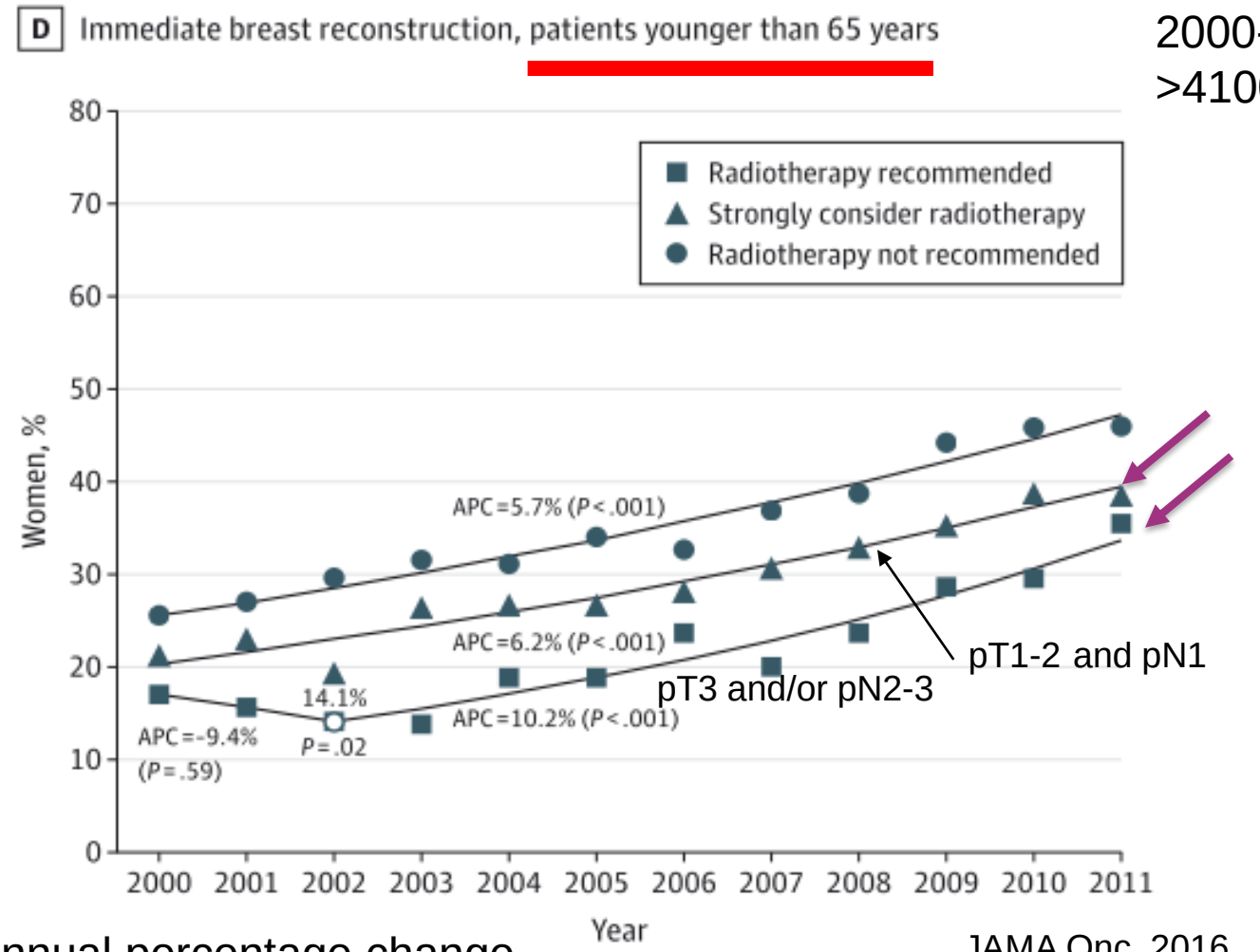
Is this also true for Europe?

Courtesy Orit Kaidar-Person, Israel

Temporal Trends in Post-Mastectomy Radiation Therapy and Breast Reconstruction

Lane L. Frasier, MD[1], Sara Holden, MD[1], Timothy Holden, MD MS[2], Jessica R. Schumacher, PhD[1], Glen Leverson, PhD[1], Bethany Anderson, MD[3], Caprice C. Greenberg, MD MPH[1,4], and Heather B. Neuman, MD MPH[1,4]

SEER database, 2000-2011, >41000 patients



APC, annual percentage change

JAMA Onc, 2016

ESTRO School

Timing of post-mastectomy RT and breast reconstruction

A Systematic Review of Morbidity Associated with Autologous Breast Reconstruction Before and After Exposure to Radiation Therapy- Are Current Practices Ideal?

Brian P. Kelley, MD[1], **Raouf Ahmed, BSc Hons**[2], **Kelley M. Kidwell, PhD**[3], **Jeffrey H. Kozlow, MD MS**[4], **Kevin C. Chung, MD MS**[5], and **Adeyiza O. Momoh, MD**[6]

A Systematic Review of Complications of Implant-Based Breast Reconstruction with Pre-Reconstruction and Post-Reconstruction Radiation Therapy

Adeyiza O. Momoh, MD[1], **Raouf Ahmed, BSc Hons**[2], **Brian P. Kelley, MD**[3], **Oluseyi Aliu, MD**[3], **Kelley M. Kidwell, PhD**[4], **Jeffrey H. Kozlow, MD**[5], and **Kevin C. Chung, MD MS**[6]

Momoh & Kelly, Ann Surg Onc 2014

ESTRO School

Timing of post-mastectomy RT and breast reconstruction

A Systematic Review of Morbidity Associated with Autologous Breast Reconstruction Before and After Exposure to Radiation Therapy- Are Current Practices Ideal?

897 papers — 20 relevant information — 6 pre-recon RT; 9 post-recon RT; 5 both pt

A Systematic Review of Compli… …it-Based Breast Reconstruction with Pre… …and Post-

1006 papers — …rmation — 14 pre-recon RT; 23 post-recon RT

Did someone say selection bias??

Momoh & Kelly, Ann Surg Onc 2014

ESTRO School

Timing of RT and reconstruction *TE/implant*

Systematic review:

26 studies included out of 1006 published 1992-2012 :

- 3 studies analyzed for **Pre**-reconstruction RT
- 12 studies analyzed for **Post**-reconstruction RT
- 11 on both **Pre** and **Post**

Among these 26 studies

- 23 Retrospective
- 3 -> “prospective cohorts” of **Post**-reconstruction RT

Mean age 48 years (range, 44-54)

Median # of pts in the studies 55 (range, 13-159)

Median follow up 34.5 months (range, 15-96)

Momoh, Ann Surg Onc 2014

Timing of RT and reconstruction *TE/implant*

Complication	RT -> Reconstruction Pooled rate (95% CI)	Reconstruction-> RT Pooled rate (95% CI)
Mild Capsular contracture	30% (0-77)	37% (20-55)
Severe Capsular contracture	25% (0-45)	32% (20-46)
Major complications	18% (5-36)	31% (17-46)
Minor complications	49% (25-72)	39% (24-55)
Failure	19% (10-29)	20% (15-25)
Successful implant reconstruction	83% (68-94)	80% (68-90)

Momoh, Ann Surg Onc 2014

School

Timing of RT and reconstruction *TE/implant*

Complication	RT -> Reconstruction Pooled rate (95% CI)	Reconstruction-> RT Pooled rate (95% CI)
Mild Capsular contracture	30% (0-77)	37% (20-55)
Severe Capsular contracture	25% (0-45)	32% (20-46)
Major complications	18% (5-36)	31% (17-46)
Minor complications	49% (25-72)	39% (24-55)
Failure	19% (10-29)	20% (15-25)
Successful implant reconstruction	83% (68-94)	80% (68-90)

Unacceptable

Momoh, Ann Surg Onc 2014

School

Timing of RT and reconstruction *TE/implant*

Caution:

Pre-reconstruction RT was in most cases pts who were treated initially with BCT
Post-reconstruction RT was delivered after placement of TE or implant

Very difficult to get hold on timing:

- Immediate (RT to chest wall before implant)
- Immediate (RT to implant)
- RT to chest wall and delayed TE/implant
- RT to deflated TE
- RT to inflated TE

Conclusions—Review of the current literature suggests similar overall success and failure rates with pre-reconstruction and post-reconstruction radiation therapy exposure. Failure rates in both groups of patients are clinically significant when considering implant reconstruction in the setting of radiation.

- So this is not something you just start to do next Monday……..

Momoh, Ann Surg Onc 2014

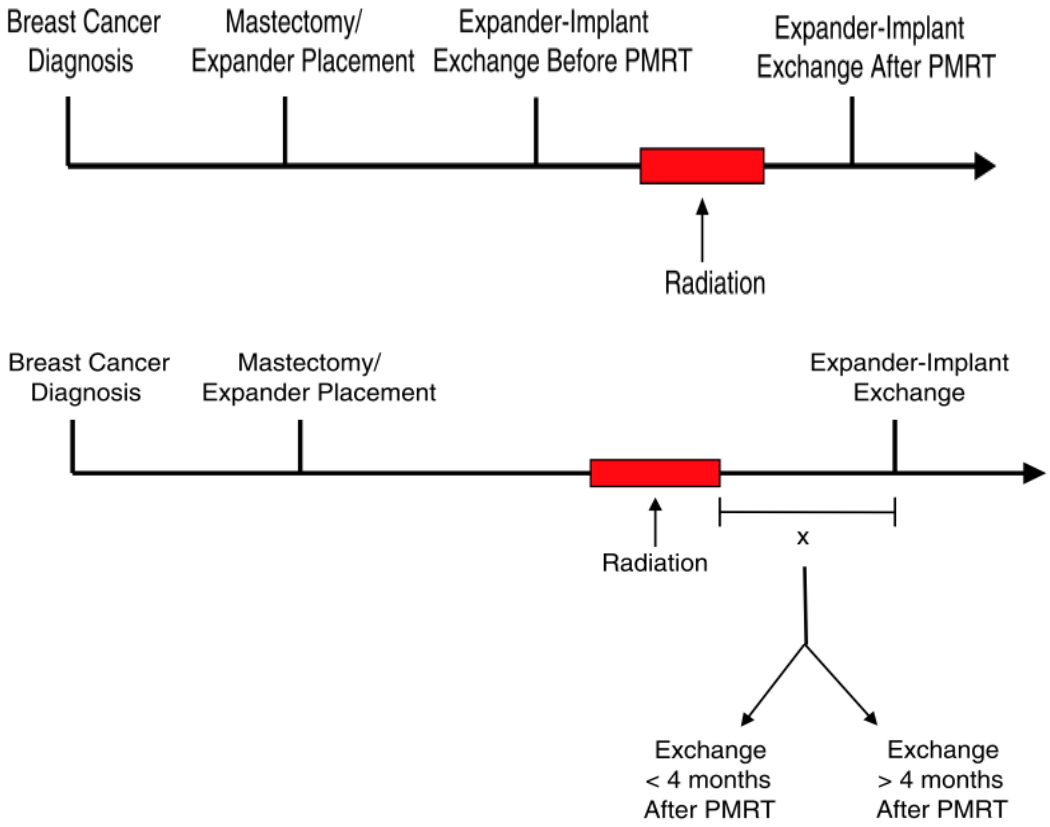
ESTRO School

Timing of RT and reconstruction *TE/implant*

MSKCC

- Mastectomy and TE placement
- Expansion starting 10-14 days postop
- Expansion during chemotherapy
- Exchange for permanent implant 4 weeks after chemotherapy
- Radiation 4 weeks after exchange

Yale University Hospital



"Our findings suggest that <u>neither</u> the sequencing nor timing of expander-implant exchange in the setting of PMRT affects overall complication or reconstruction failure rate" (Lentz, Yale, 2013)

Timing of RT and reconstruction *TE/implant*

Moreover…

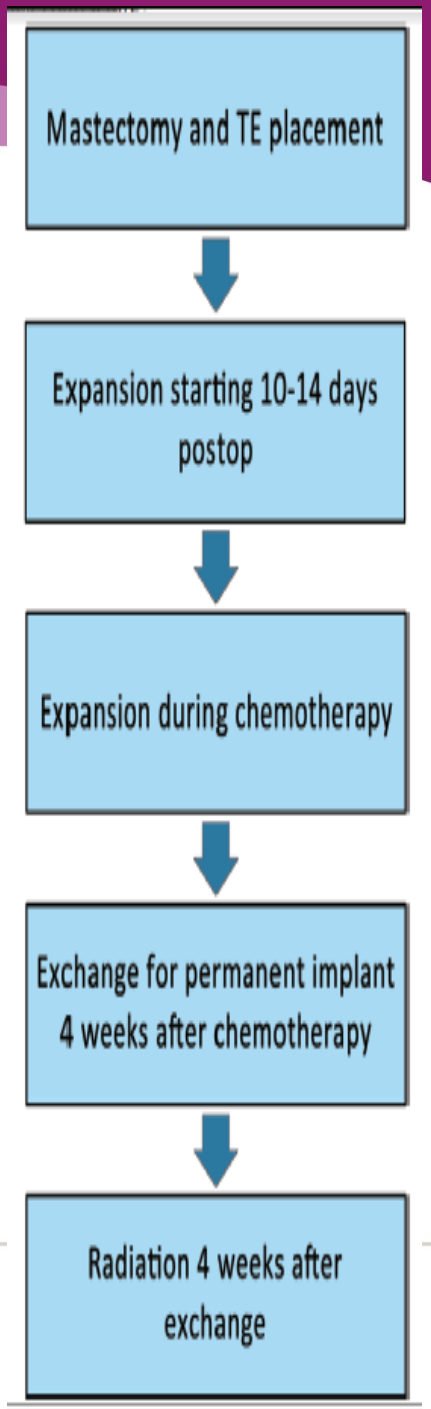
Oncologic outcome was not reported in the systematic review **nor** in some of the studies…

MSKCC – 7 yrs f/u – OS - 93%, LC-100%

Momoh, Ann Surg Onc 2014

More things to think about…

MSKCC	3 surgeons, n=151 Median F/U 86m	Single surgeon, n=319 Mean F/U 56.8m
Implant removal	**13.3%**	**9.1%**
Replacement	**17.1%**	**12.7%**



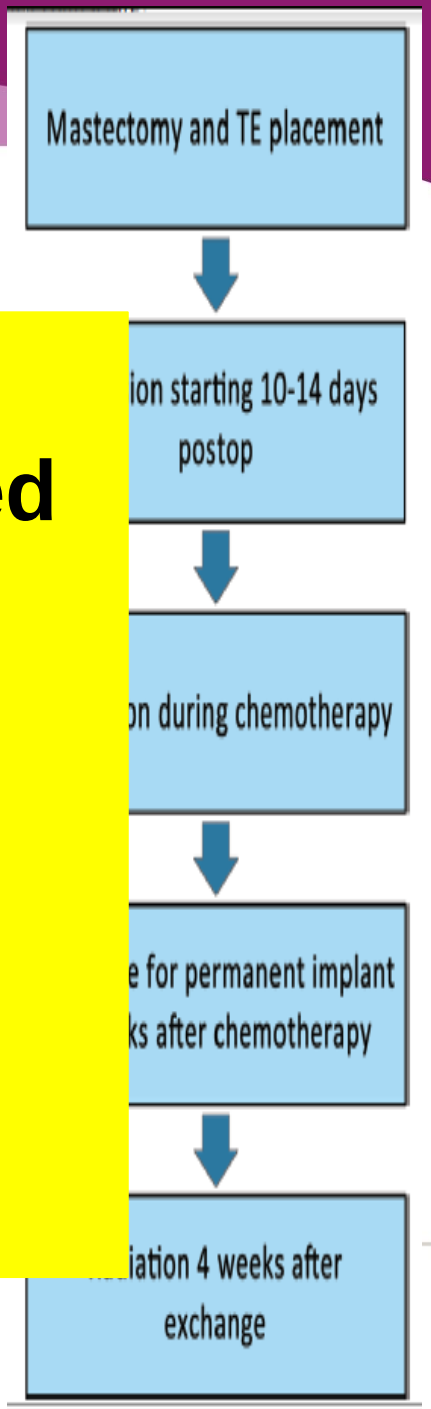
MSKCC, 2012 and 2014 publications

More things to think about…

Significant heterogeneity was noted between studies for multiple complications

(Momoh, Ann Surg Onc 2014)

Surgical potential confounders:
type flap, TE, silicone, saline, fully muscle covered, subcutaneous implant, nipple sparing…



MSKCC, 2012 and 2014 publications

Timing of RT and reconstruction ***TE/implant***

Gets even **MORE** confusing…

RT doses were not uniformly reported

Use of bolus

Use of Boost

Momoh, Ann Surg Onc 2014

Total dose 50 Gy (range 45–60), including boost, 1.8-2 Gy per fx, 4–6-MV photons and wedges, without any bolus (Tallet et al, 2003)

Total dose 50 -50.4 Gy, 1.8-2 Gy per fx, no boost, daily bolus 0.5-1 cm, IMRT after 2002 (Ho, 2012 & 2014)

Current Practice Patterns
Radiation Oncologists

Pre-RT deflation:

- 75 % do not routinely deflate TE pre-RT
- 11.5 % routinely deflate TE pre-RT

Bolus over TE:

- 52% use all the time
- 37% never use
- 11% use sometimes

Can't blame only the surgeons…

Boost in TE:

- 23% boost all
- 43% boost some
- 34% don't boost

Chen, Rad Onc, 2013

ESTRO School

Timing of post-mastectomy RT and breast reconstruction

A Systematic Review of Morbidity Associated with Autologous Breast Reconstruction Before and After Exposure to Radiation Therapy- Are Current Practices Ideal?

Brian P. Kelley, MD[1], **Raouf Ahmed, BSc Hons**[2], **Kelley M. Kidwell, PhD**[3], **Jeffrey H. Kozlow, MD MS**[4], **Kevin C. Chung, MD MS**[5], and **Adeyiza O. Momoh, MD**[6]

A Systematic Review of Complications of Implant-Based Breast Reconstruction with Pre-Reconstruction and Post-Reconstruction Radiation Therapy

Adeyiza O. Momoh, MD[1], **Raouf Ahmed, BSc Hons**[2], **Brian P. Kelley, MD**[3], **Oluseyi Aliu, MD**[3], **Kelley M. Kidwell, PhD**[4], **Jeffrey H. Kozlow, MD**[5], and **Kevin C. Chung, MD MS**[6]

Momoh & Kelly, Ann Surg Onc 2014

ESTRO School

Timing of RT and reconstruction ***FLAP***

Complication	RT before Flap reconstruction Pooled rate (95% CI)	RT after Flap reconstruction Pooled rate (95% CI)
Wound healing	**10% (0.04-0.77)**	**14% (0-0.38)**
Fat necrosis	**10% (0.06-0.14)**	**13% (0.07-0.2)**
Infection	**4% (0.02-0.06)**	**6% (0.03-0.1)**
Hematoma	**2% (0.01-0.04)**	**1% (0.01-0.04)**
Seroma	**4% (0.02-0.05)**	**4% (0-0.12)**
Flap fibrosis	**-**	**27% (0.12-0.45)**
Flap loss	**1% (0-0.02)**	**4% (0-0.04)**
Partial flap necrosis	**6% (0.03-0.11)**	**-**
Vascular thrombosis (reoperation)	**4%(0.03-0.06)**	**-**

Similar rates of complications and success for pre- and post-reconstruction RT

Immediate autologous reconstruction should be considered as a valuable option even when PMRT is indicated (up to **4%** flap loss)

Kelley, Ann Surg Onc 2014

School

Timing of RT and reconstruction

Reconstruction - RT

The differences between overall **complications** and **outcomes** with **flap-based** surgery before/after RT are more subtle compared to **TE/implant**

BUT

Immediate TE/implant has become the more popular technique

Kelley, Ann Surg Onc 2014

Timing of RT and reconstruction

Again…

not much about Oncological Outcomes (not much data, seems okay, but…)

different RT doses, bolus, boost…

different surgical techniques!

Kelley, Ann Surg Onc 2014

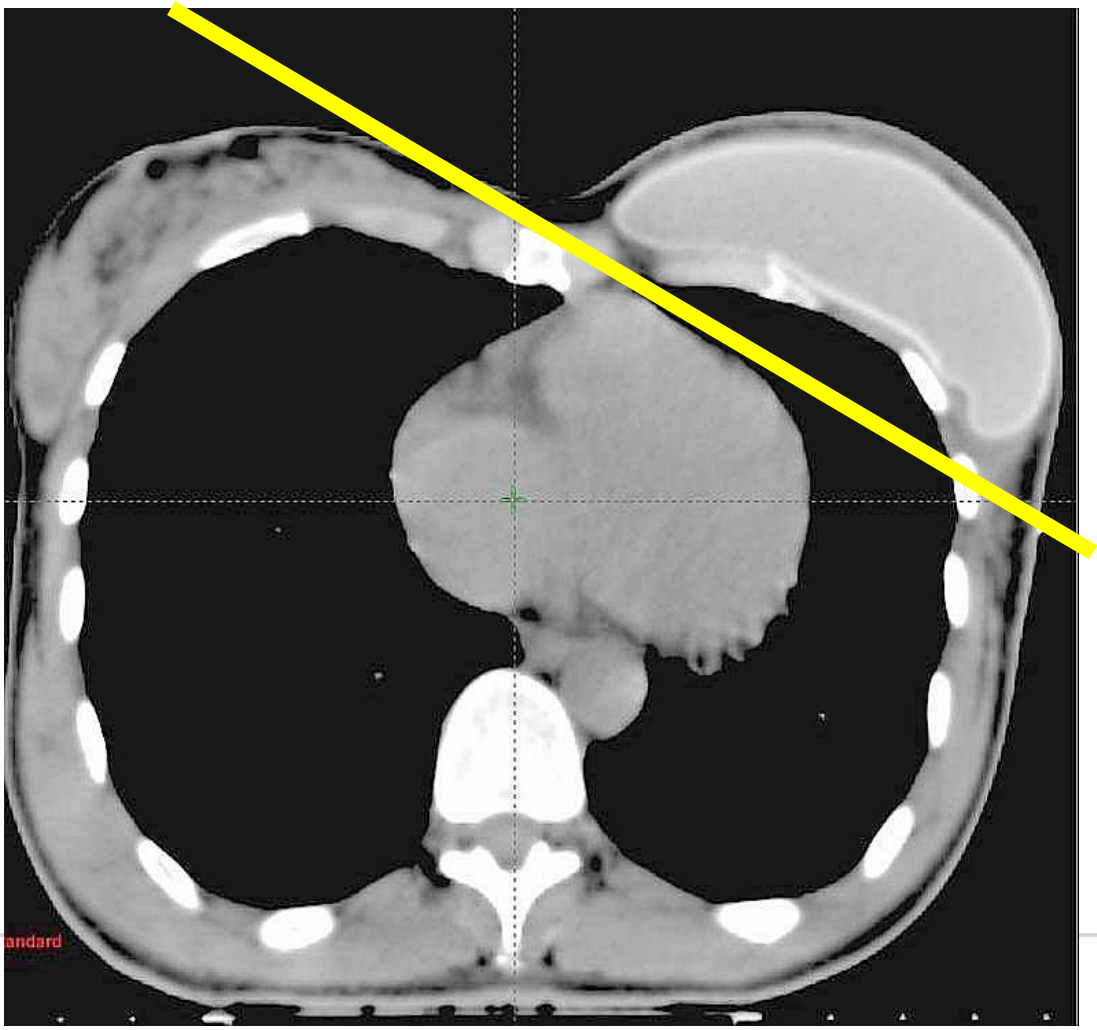
Safety after immediate reconstruction?

Delays in treatment due to immediate reconstruction

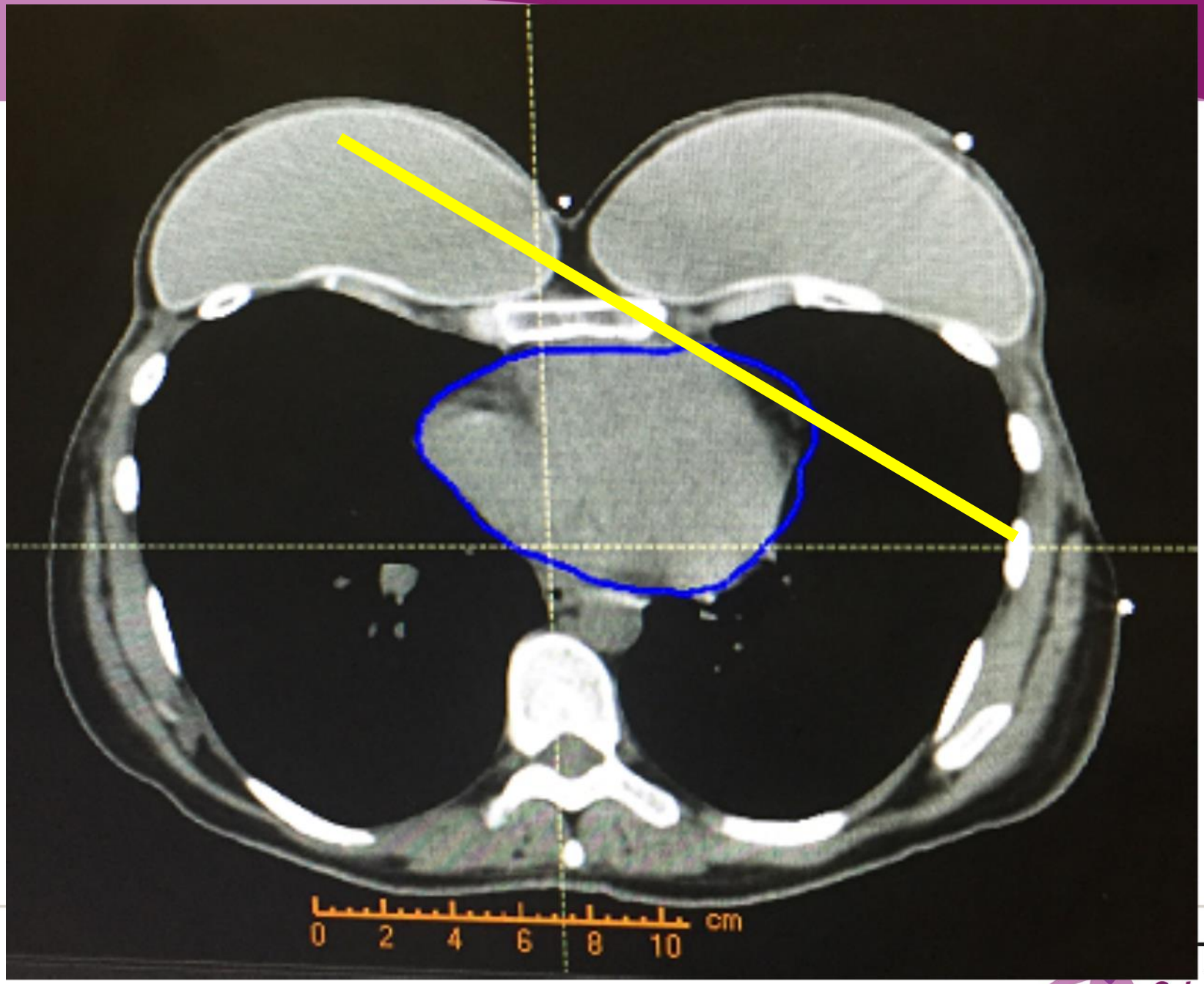
Impact of a reconstructed breast on adequate CW and IMN radiation delivery

Normal tissue dose (lung, heart, liver, stomach)

PMRT after reconstruction: *Chest wall shape*



Courtesy Poortmans, 2014



Kaidar-Person O et al, 2017

Radiation Delivery

THE IMPACT OF IMMEDIATE BREAST RECONSTRUCTION ON THE TECHNICAL DELIVERY OF POSTMASTECTOMY RADIOTHERAPY

Table 3. Frequency of treatment planning scores by deductions

Score	Mastectomy + reconstruction + RT $N = 112$ (%)	Mastectomy + RT $N = 106$ (%)
−2.5 Point deduction	8 (7)	0
−2.0 Point deduction	12 (11)	1 (1)
−1.5 Point deduction	15 (13)	0
−1.0 Point deduction	23 (21)	6 (6)
−0.5 Point deduction	6 (5)	10 (9)
No deductions (4/4)	48 (43)	89 (84)

Scored 4 categories: 1. CW and 2. IMN Coverage, 3. Lung Avoidance 4. Heart Avoidance

Scores for each category: 0, 0.5, 1. Best score = 4/4

Motwani, IJROBP, 2006

Radiation Delivery

THE IMPACT OF IMMEDIATE BREAST RECONSTRUCTION ON THE TECHNICAL DELIVERY OF POSTMASTECTOMY RADIOTHERAPY

Table 4. Assessment of postmastectomy radiotherapy plans

	Optimal without reconstruction (%)	Optimal after reconstruction (%)	*p*-value
Objective			
Chest wall coverage	100	78	<0.0001
Treatment of IMC	93	45	<0.0001
Minimization of lung irradiation	97	83	0.0015
Avoidance of heart and epicardial vessels	92	85	0.1435
Side			
Left (all objectives)	94	51	<0.0001
Right (all objectives)	92	41	<0.0001

Motwani, IJROBP, 2006

What is the largest study?

Ann Surg Oncol
DOI 10.1245/s10434-017-5956-6

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

A 10-Year Experience with Mastectomy and Tissue Expander Placement to Facilitate Subsequent Radiation and Reconstruction

Zeina Ayoub, MD[1], Eric A. Strom, MD[1], Valentina Ovalle, MD[2], George H. Perkins, MD[1], Wendy A. Woodward, MD, PhD[1], Welela Tereffe, MD, MPH[1], Benjamin D. Smith, MD[1], Simona F. Shaitelman, MD[1], Michael C. Stauder, MD[1], Karen E. Hoffman, MD[1], Sarah M. DeSnyder, MD[3], Patrick B. Garvey, MD[4], Mark W. Clemens, MD[4], Carlos H. Barcenas, MD, MSc[5], Henry M. Kuerer, MD, PhD[3], and Steven Kronowitz, MD[6]

MD Anderson, single institution, retrospective study on all pts operated since 2002-13
Strategy: DELAYED-IMMEDIATE RECONSTRUCTION

Published online Aug 1st, 2017

ESTRO School

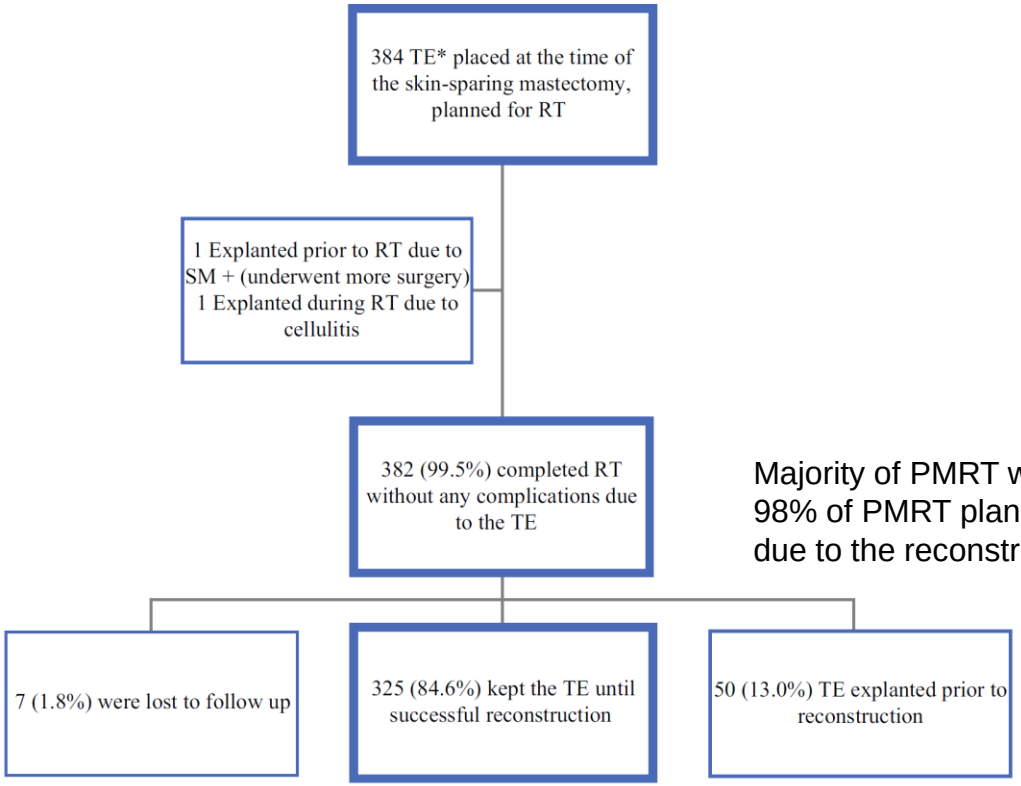


FIG. 2 Delayed-immediate reconstruction approach outcomes

Majority of PMRT was loco-reg RT incl IMN
98% of PMRT planning was without compromises due to the reconstruction

384 patients
95% stage II-III breast cancer
Median FU 5.6 yr (range 1.3-13.4)
5 yr locoreg control 99.0%
5 yr DFS 86.1%
5 yr OS 92.4%

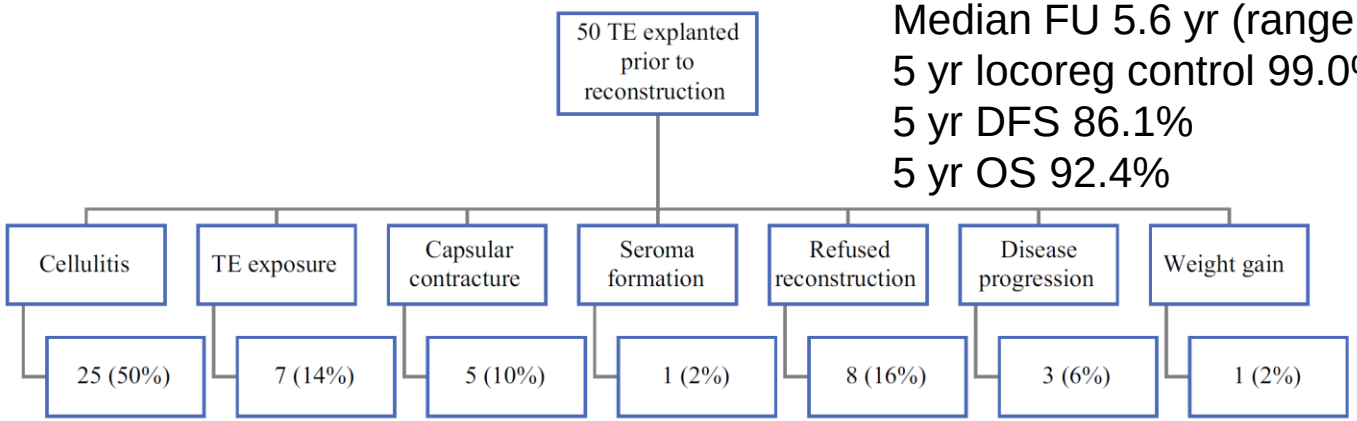


FIG. 3 Reasons for tissue expander explantation after PMRT

ESTRO School

DISCUSSION

SSM with immediate reconstruction is an incredibly attractive surgical approach, because it results in patients never experiencing the absence of a breast mound and provides a natural-looking reconstruction by directly using the native breast skin. Several studies have shown

complications.[1–3,14–19] Despite these concerns, preservation of the skin is desirable for patients for several reasons. First, it maintains a breast mound throughout the 6–12 months of adjuvant therapy. Second, it preserves the chest "footprint" of the native breast, which facilitates subsequent reconstruction; and finally, it permits multiple options, such as implant-only reconstruction and autologous reconstruction without a skin paddle.

Still so many questions with regards to RT

Boost? Where to boost?

Bolus material/thickness/schedule/where

Effect of Metallic port in TE on RT delivery

(Damast 2006)

Fractionation

Target definition

Constraints

We are facing risk of severe selection bias and unmeasured confounding factors

So, what to do?

A randomised trial is needed!

According to current publications, we are entering a new era: frequency of immediate reconstructions will increase

Pro trial:

- **Max control on who does what how to whom when**
- **Techniques (surgical/RT) well described and no surprise**
- **Only way to ensure optimal follow up**

ESTRO School

A randomised trial is needed!

According to current publications, we are entering a new era: frequency of immediate reconstructions will increase

Pro trial:

- **Max control on who does what how to whom when**
- **Techniques (surgical/RT) well described and no surprise**
- **Only way to ensure optimal follow up**

ESTRO School

The DBCG RT Recon Trial

Aim:

investigate risk of complications following breast reconstruction in early breast cancer patients operated with mastectomy for high risk breast cancer with indication for post-mastectomy radiation therapy (PMRT)

Hypothesis:

the risk of complications is not increased by performing delayed-immediate reconstruction compared with delayed reconstruction in relation to the timing of PMRT

R → **delayed-immediate reconstruction (before PMRT)**

R → **delayed reconstruction (after PMRT)**

If you are interested, contact Birgitte Offersen: birgoffe@rm.dk or bvo@oncology.au.dk

The DBCG RT Recon Trial

Primary endpoint

Any complication deeming *invasive* intervention necessary :

- Infection
- Haematoma
- Seroma
- Loss of implant
- Necrosis

The DBCG RT Recon Trial

STUDY POPULATION

Inclusion criteria

Invasive breast cancer

Indication for unilateral mastectomy and deemed fit to undergo unilateral breast reconstruction

PMRT indicated according to guidelines

Exclusion criteria

Pregnant or lactating

Conditions indicating that the patient cannot go through breast reconstruction, PMRT or follow up, or a condition where the treating specialist thinks the patient should not participate in the trial

Not being able to participate due to language problems

The DBCG RT Recon Trial

Treatment arm A
Delayed-immediate reconstruction

- Initial surgery
  - Skin sparing/nipple sparing mastectomy and axillary surgery
  - silicone gel implant and mesh
- **PMRT**
- Final reconstruction 6 months later
  - Autologous
    - Flaps
    - Fat transfer
  - Implant-based
    - +/- ADM
    - Flap + implant
    - Fat transfer

Treatment arm B
Delayed reconstruction

- Initial surgery
  - total mastectomy and axillary surgery
- **PMRT**
- Final reconstruction 6 months later
  - Autologous
    - Flaps
    - Fat transfer
  - Implant-based
    - +/- ADM (?)
    - Flap + implant
    - Fat transfer

ESTRO School

DBCG workshop to reach national consensus on target delineation and treatment planning September 18th, 2017 and then the protocol will be finished

We will start end of 2017 or primo 2018

”Target delineation group” so far was L Boersma (NL), I Mjaaland (N), C Coles (UK), P Poortmans (F) and BV Offersen (DK)

Late Side-effects of Radiation Therapy

Sarah Darby
Nuffield Department of Population Health
University of Oxford
United Kingdom

Plan of talk

- Identifying the late side-effects of radiotherapy
- Deriving dose-response relationships for late-effects
- Estimating absolute risks of late effects

Using information from randomized trials to identify late side-effects

- Randomized trials of breast cancer treatments are usually conducted in order to study breast cancer recurrence and mortality.

- They provide valid information on other endpoints as well.

Effect of Radiotherapy on Non-breast-cancer Mortality and on Incidence of Second Cancers before any Recurrence of Breast Cancer

(40,781 women in 75 trials of radiotherapy versus no radiotherapy)

	Number of events			Rate ratio (95% CI)	P value
	RT	No RT	Excess with RT		
Death without breast cancer recurrence					
Heart disease	705	548	143	1.30 (1.15—1.46)	<0.0001
Non-breast cancer	475	375	67	1.19 (1.03—1.37)	0.02
Other specified causes	638	629	6	1.01 (0.90—1.14)	0.83
Second cancer incidence without prior breast cancer recurrence					
Leukaemia	43	23	17	1.71 (1.05—2.79)	0.03
Lung, years 0-9	71	60	5	1.08 (0.76—1.53)	0.66
Lung, years 10+	94	40	47	2.10 (1.48—2.98)	<0.0001
Oesophagus	23	10	13	2.42 (1.19—4.92)	0.01
Contralateral breast	881	673	130	1.20 (1.08—1.33)	0.0006

Taylor et al on behalf of EBCTCG, JCO 2017; 35:1641

These randomised trials show conclusively that breast cancer radiotherapy as given in these trials can cause heart disease contralateral breast cancer, lung cancer, oesophagus cancer and leukaemia

By itself this information is interesting

…. ***but of little practical value***

Limitations of Randomized Trials for Studying Late Effects of Breast Cancer Radiotherapy

- Old fashioned radiotherapy techniques and little detailed information on regimens, so accurate doses to organs at risk cannot be calculated
- Incidence information not usually available for heart disease (and only sometimes for second cancer)
- Women at increased risk of heart disease or lung cancer tend not to be included in trials

Plan of talk

- Identifying the late side-effects of radiotherapy
- Deriving dose-response relationships for late-effects
- Estimating absolute risks of late effects

Example of heart disease

To produce a clinically useful dose-response relationship we need:

- **Large studies of women in the general population**
  - patients who have comorbidities or complicated problems are not usually entered into trials
- **Long follow-up**
- **Data on non-fatal as well as fatal events**
- **Sufficient detail on RT to calculate cardiac doses**
- **Information on pre-existing risk factors for heart disease**

Question

Do we get the right answer if we compare irradiated and unirradiated women using observational (ie non-randomised) data from cancer registries?

Comparison of Randomised and Observational Data

- Data sources:
  - Randomised: EBCTCG
  - Observational: SEER Cancer Registries

- Treatment comparison:
  - Radiotherapy versus not in women after BCS, or after mastectomy in pN+ disease

McGale et al, JCO 2016; 34:3356

EBCTCG and SEER
Radiotherapy versus not

EBCTCG:
42,080 in 78 trials of radiotherapy vs no radiotherapy

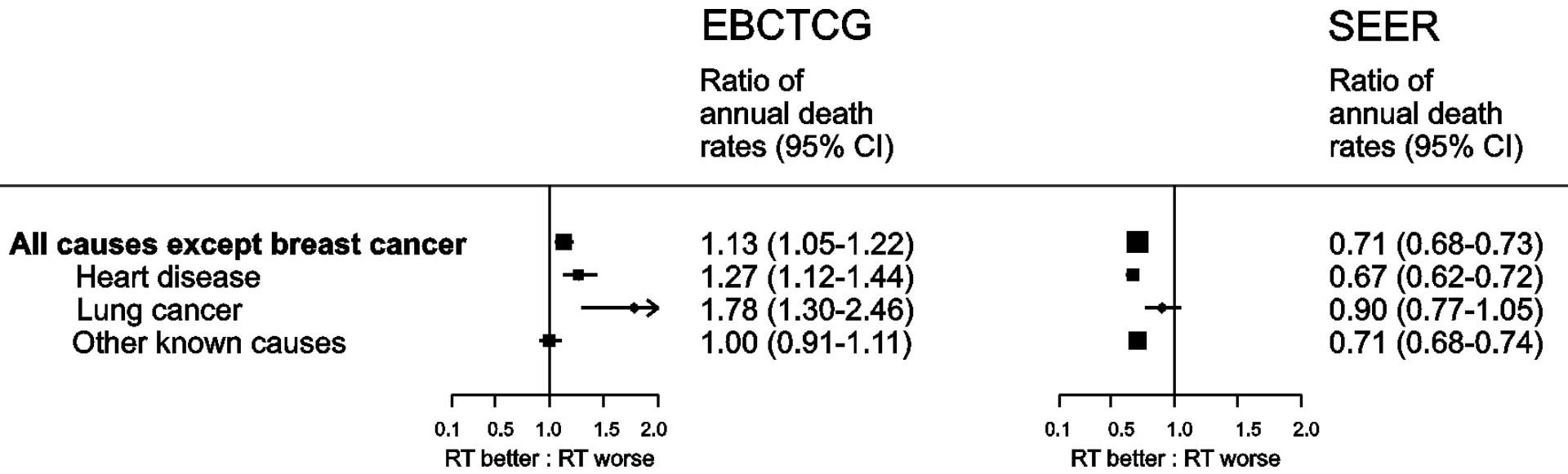
SEER:
329,235 women given BCS or pN+ and mastectomy

McGale et al, JCO 2016; 34:3356

EBCTCG and SEER 1990-2008

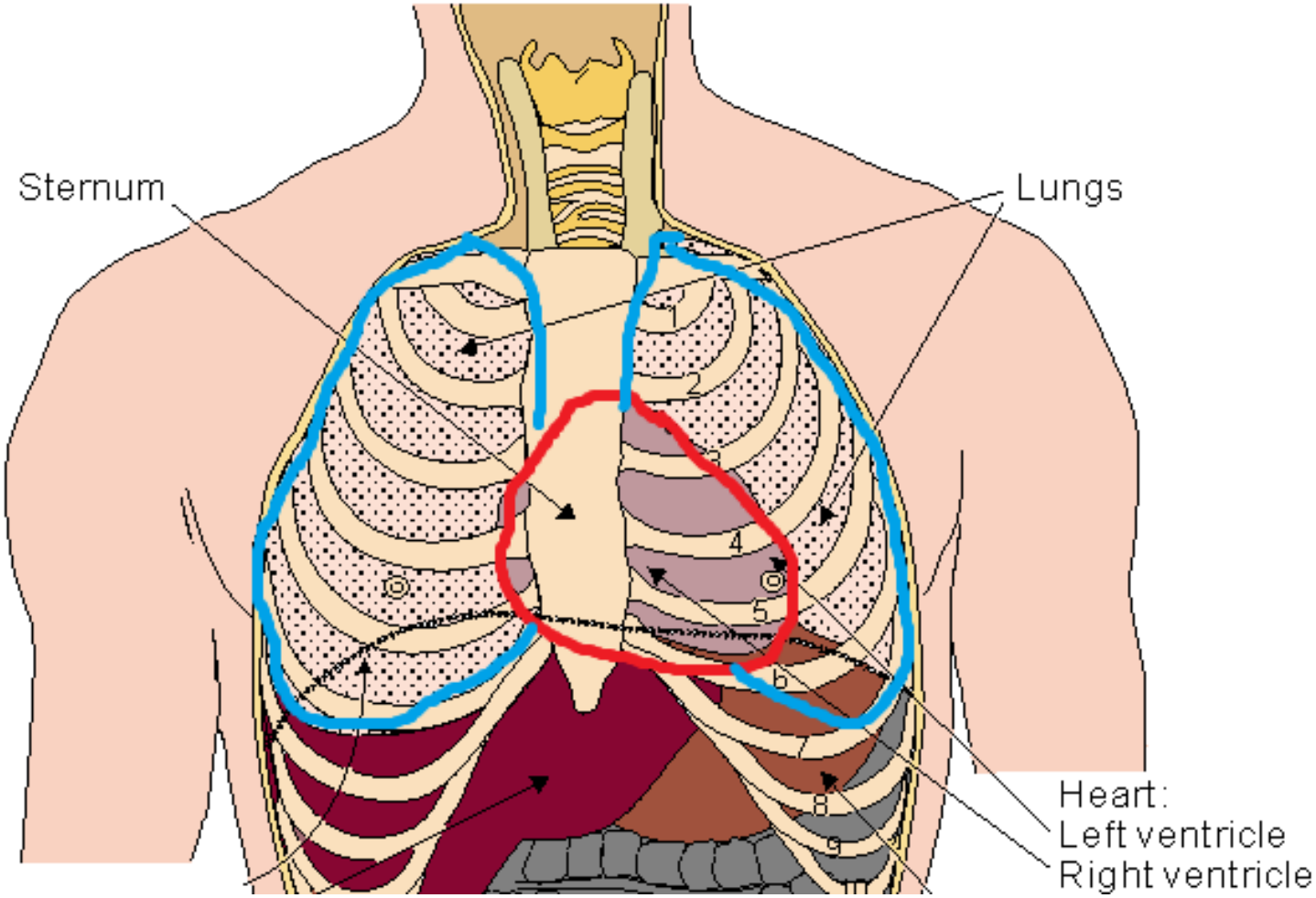
Non-breast-cancer mortality

RT vs no RT



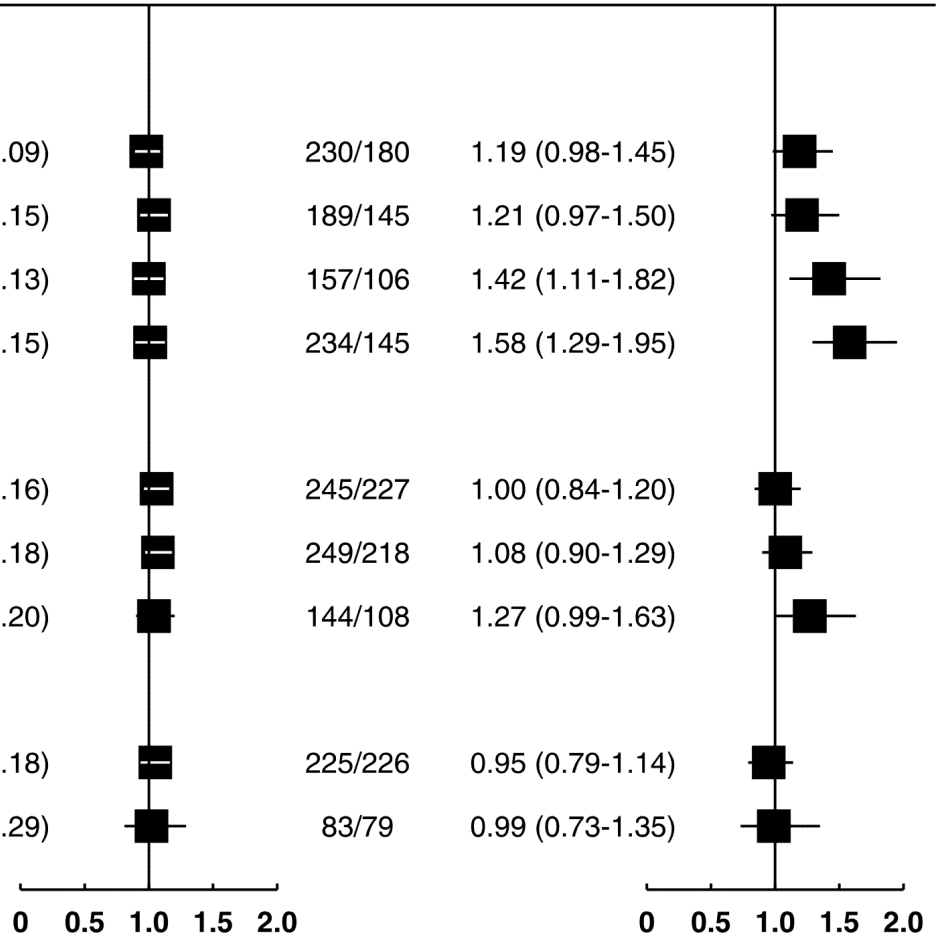
SEER data stratified by: age, follow-up year, stage, year, ethnicity, tumour size, no of nodes, grade, ER status, quadrant, axillary surgery

McGale et al, JCO 2016; 34:3355


Sternum
Lungs
Heart:
Left ventricle
Right ventricle

SEER data: Left versus right-sided breast cancer: subsequent cardiac mortality ratios by radiotherapy status

Years from breast cancer diagnosis to cardiac death	No radiotherapy		Radiotherapy	
	Cardiac deaths left/right	Cardiac mortality ratio left versus right & 95% CI	Cardiac deaths left/right	Cardiac mortality ratio left versus right & 95% CI
Diagnosed 1973-1982				
< 5 years	717/679	0.98 (0.89-1.09)	230/180	1.19 (0.98-1.45)
5 - 9	673/614	1.04 (0.93-1.15)	189/145	1.21 (0.97-1.50)
10 - 14	469/441	1.00 (0.87-1.13)	157/106	1.42 (1.11-1.82)
15+	515/480	1.01 (0.89-1.15)	234/145	1.58 (1.29-1.95)
Diagnosed 1983-1992				
< 5 years	880/785	1.06 (0.96-1.16)	245/227	1.00 (0.84-1.20)
5 - 9	815/729	1.07 (0.97-1.18)	249/218	1.08 (0.90-1.29)
10+	390/361	1.04 (0.90-1.20)	144/108	1.27 (0.99-1.63)
Diagnosed 1993-2001				
< 5 years	567/508	1.05 (0.93-1.18)	225/226	0.95 (0.79-1.14)
5 - 9	144/136	1.02 (0.81-1.29)	83/79	0.99 (0.73-1.35)



Darby et al, Lancet Oncol 2005; 6:557

To produce a clinically useful dose-response relationship we need:

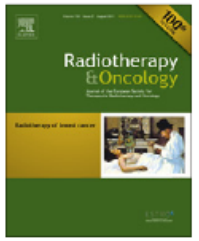
- ✓ **Large studies of women in the general population**
  - patients who have comorbidities or complicated problems are not usually entered into trials
- ✓ **Long follow-up**
- **Data on non-fatal as well as fatal events**
- **Sufficient detail to calculate cardiac doses**
- **Information on pre-existing risk factors, eg prior heart disease**

Radiotherapy and Oncology 100 (2011) 167–175

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Cardiac morbidity

Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden

Paul McGale [a], Sarah C. Darby [a,*], Per Hall [b], Jan Adolfsson [c], Nils-Olof Bengtsson [d], Anna M. Bennet [b], Tommy Fornander [e], Bruna Gigante [f], Maj-Britt Jensen [g], Richard Peto [a], Kazem Rahimi [h], Carolyn W. Taylor [a], Marianne Ewertz [i]

[a] *Clinical Trial Service Unit, University of Oxford, UK;* [b] *Department of Medical Epidemiology and Biostatistics, Karolinska Institute;* [c] *Department of Clinical Sciences, Karolinska University Hospital, Stockholm, Sweden;* [d] *Department of Oncology, University Hospital, Umeå, Sweden;* [e] *Radiumhemmet, Karolinska University Hospital* [f] *Deparment of Cardiology, Karolinska University Hospital, and Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden;* [g] *Danish Breast Cancer Group Secretariat, Copenhagen University Hospital, Denmark;* [h] *Cardiology Department, John Radcliffe Hospital, Oxford, UK;* [i] *Department of Oncology, Odense University Hospital, University of Southern Denmark, Odense, Denmark*

Cohort study

Left-sided versus right-sided breast cancer: heart disease incidence ratios in women given adjuvant radiotherapy for breast cancer

Disease category	Radiotherapy: Number of events left/right n=17,912/16,913	Incidence ratio, left vs. right (95% CI)	P
Ischaemic heart disease	**878/712**	**1.18 (1.07-1.30)**	**0.001**
Hypertensive heart disease	209/182	1.11 (0.91-1.35)	0.32
Pulmonary embolism	165/148	1.08 (0.86-1.35)	0.51
Pericarditis	**60/36**	**1.61 (1.06-2.43)**	**0.03**
Valvular heart disease	**94/60**	**1.54 (1.11-2.13)**	**0.009**
Other rheumatic heart disease	2/2	0.82 (0.11-5.90)	0.84
Acute endocarditis	8/7	1.07 (0.39-2.97)	0.89
Myocardial disease	37/37	0.99 (0.63-1.57)	0.97
Conduction disorders & arrythmias	445/453	0.94 (0.82-1.07)	0.35
Cardiac arrest	36/27	1.28 (0.78-2.12)	0.33
Heart failure	**310/315**	**0.95 (0.81-1.11)**	**0.51**
Other & ill defined heart disease	31/37	0.78 (0.48-1.26)	0.30
All heart disease	**2275/2016**	**1.08 (1.02-1.15)**	**0.01**

Analyses based on first diagnosis of any type of heart disease after diagnosis of breast cancer. (results similar considering any diagnosis rather than just first):

McGale et al, Rad Onc 2011

To produce a clinically useful dose-response relationship we need:

- ✓ **Large studies of women in the general population**
  - patients who have comorbidities or complicated problems are not usually entered into trials
- ✓ **Long follow-up**
- ✓ **Data on non-fatal as well as fatal events**
- **Sufficient detail to calculate cardiac doses**
- **Information on pre-existing risk factors, eg prior heart disease**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 14, 2013 VOL. 368 NO. 11

Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

Sarah C. Darby, Ph.D., Marianne Ewertz, D.M.Sc., Paul McGale, Ph.D., Anna M. Bennet, Ph.D., Ulla Blom-Goldman, M.D., Dorthe Brønnum, R.N., Candace Correa, M.D., David Cutter, F.R.C.R., Giovanna Gagliardi, Ph.D., Bruna Gigante, Ph.D., Maj-Britt Jensen, M.Sc., Andrew Nisbet, Ph.D., Richard Peto, F.R.S., Kazem Rahimi, D.M., Carolyn Taylor, D.Phil., and Per Hall, Ph.D.

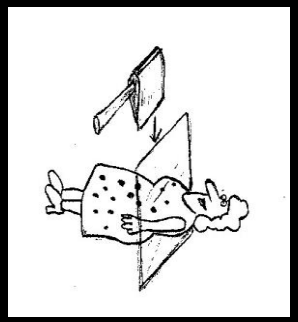
Case-control study

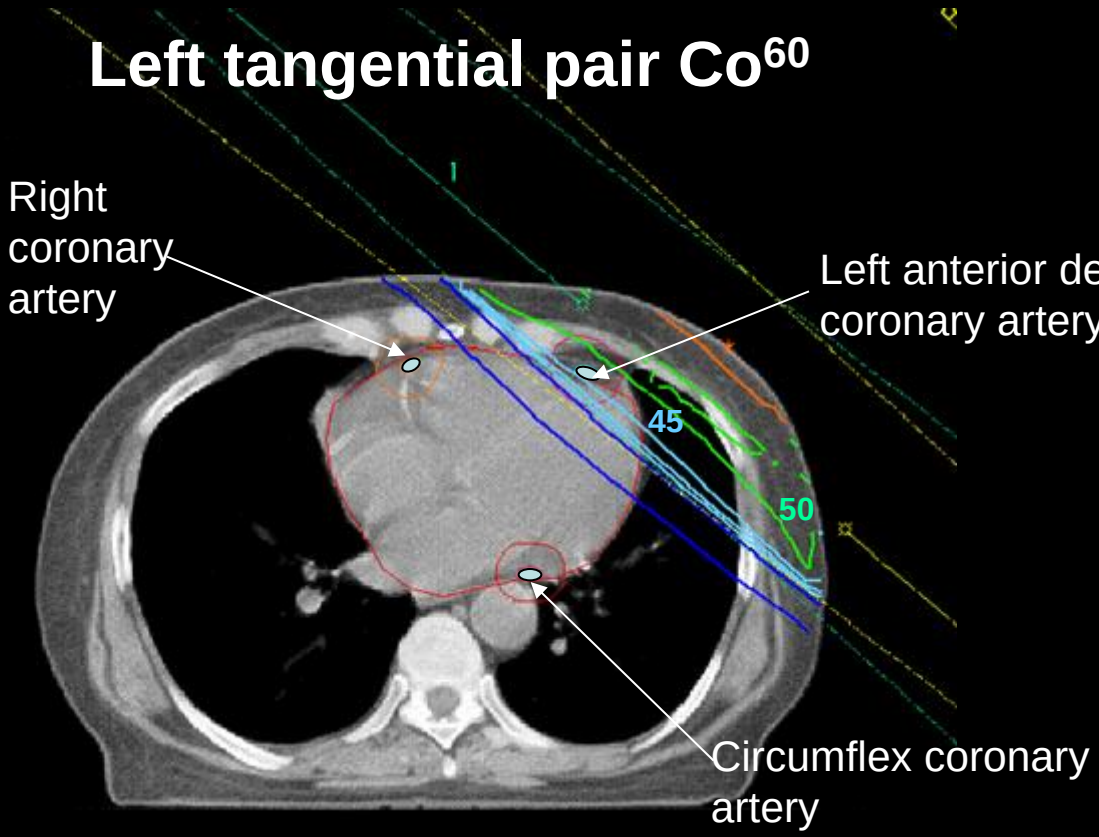
Population-based case-control study of major coronary events (MCEs)

- Population: Women irradiated for breast cancer identified from population-based cancer registries (Denmark: 1977-2006, Stockholm: 1958-2002)
- 963 Major Coronary Events (MCEs) before breast cancer recurrence identified from nationwide disease registers
- 1205 controls also irradiated for breast cancer but without recurrence identified from nationwide disease registers (matched for country, age, calendar period & time since cancer diagnosis)
- Information from oncology records obtained by research nurses (tumor characteristics, medical history, including prior heart disease)
- Individual radiotherapy treatment information obtained by research nurses

NEJM 2013; 368:987-98

Left tangential pair Co^{60}

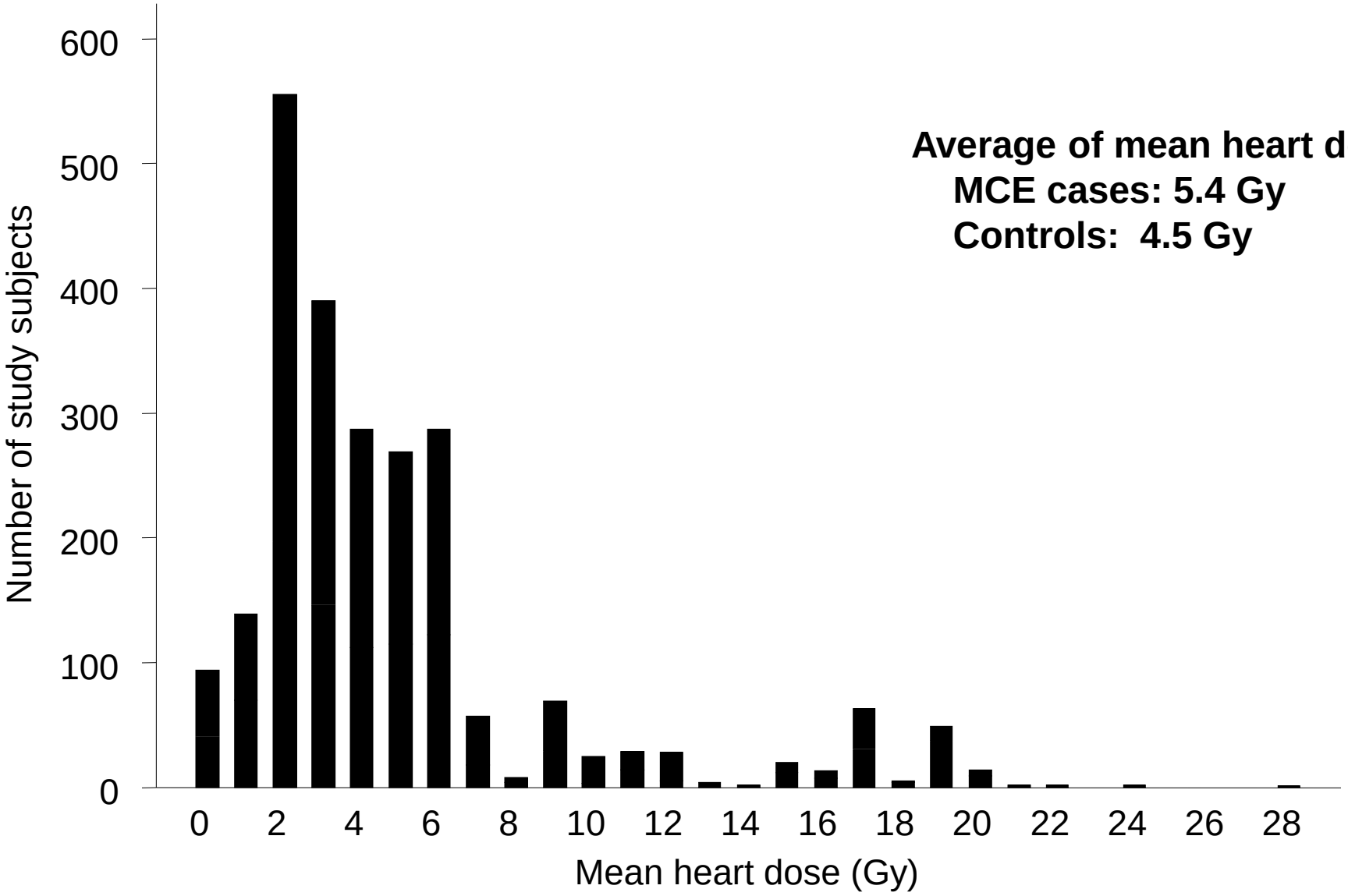




- Detailed dose-plan for each woman reconstructed on modern planning system
- 97 x 2 different regimens reconstructed using CT-scan for patient with typical anatomy
- Physical dose to whole heart estimated from dose-volume histogram
- Mean heart dose in study subjects: 4.9 Gy

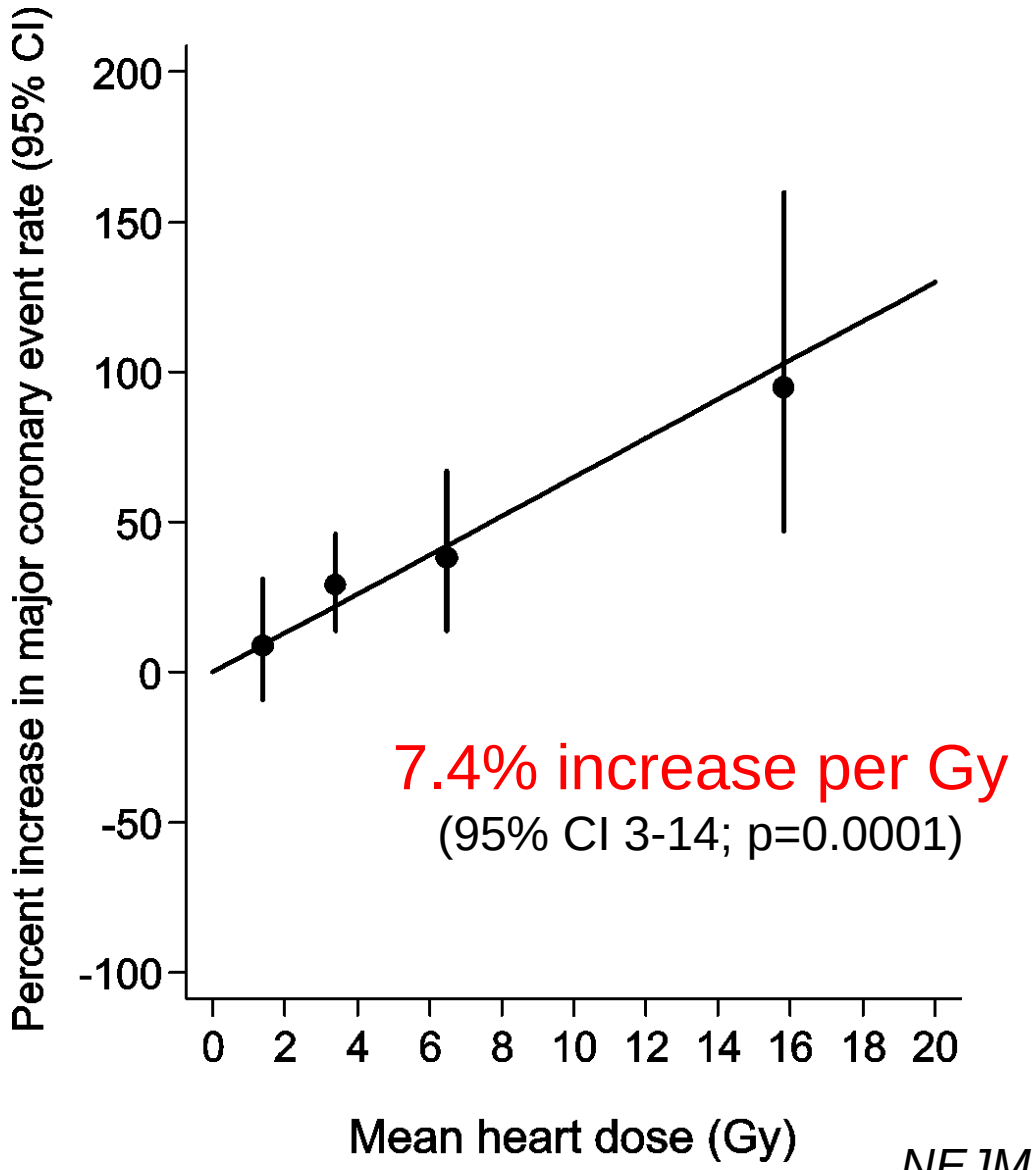
Taylor *et al,* Rad Onc 2011

Distribution of mean heart doses in case-control study of MCEs after breast cancer RT



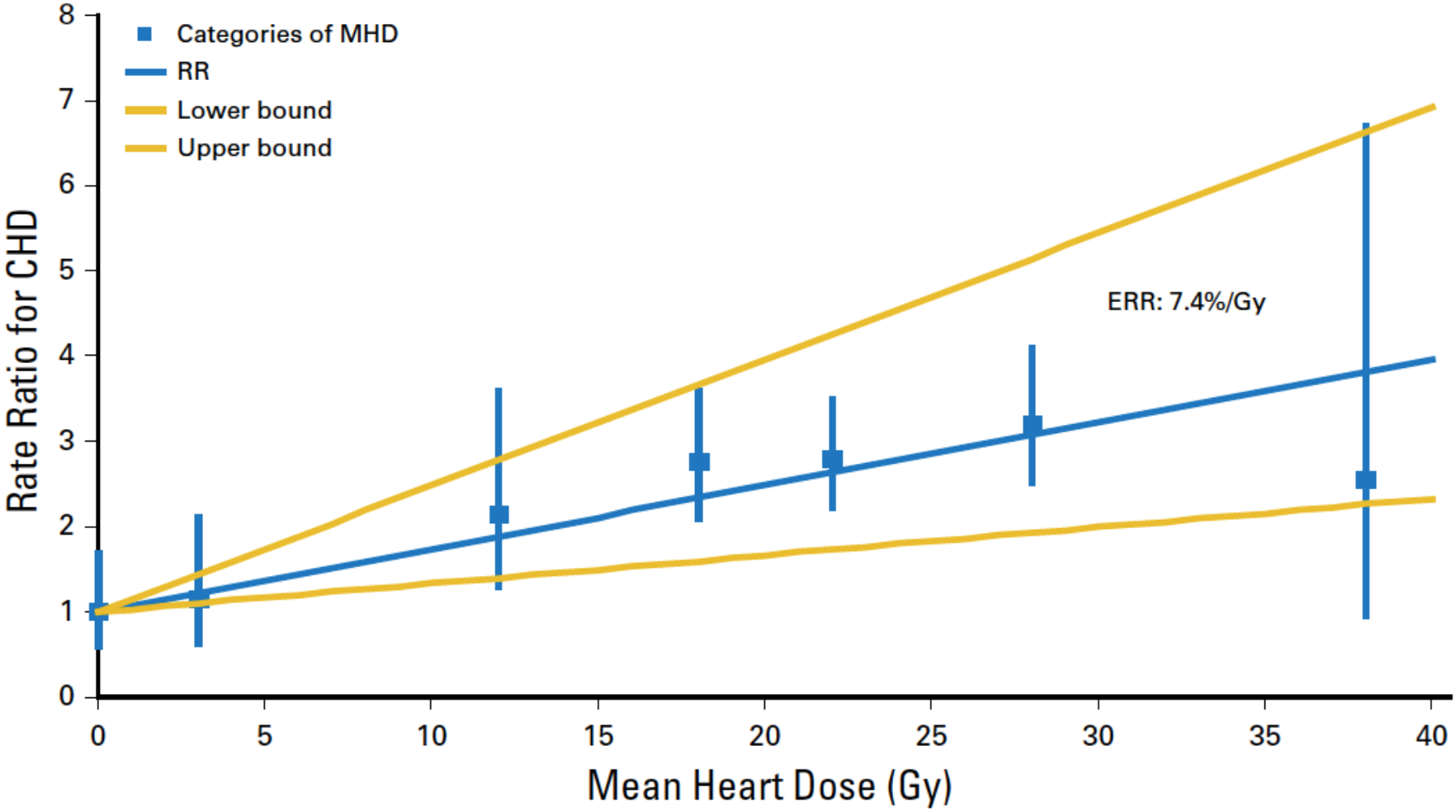
NEJM 2013; 368:987-98

Radiation Associated Cardiac Events (RACE)
Dose-response Relationship for Major Coronary Events



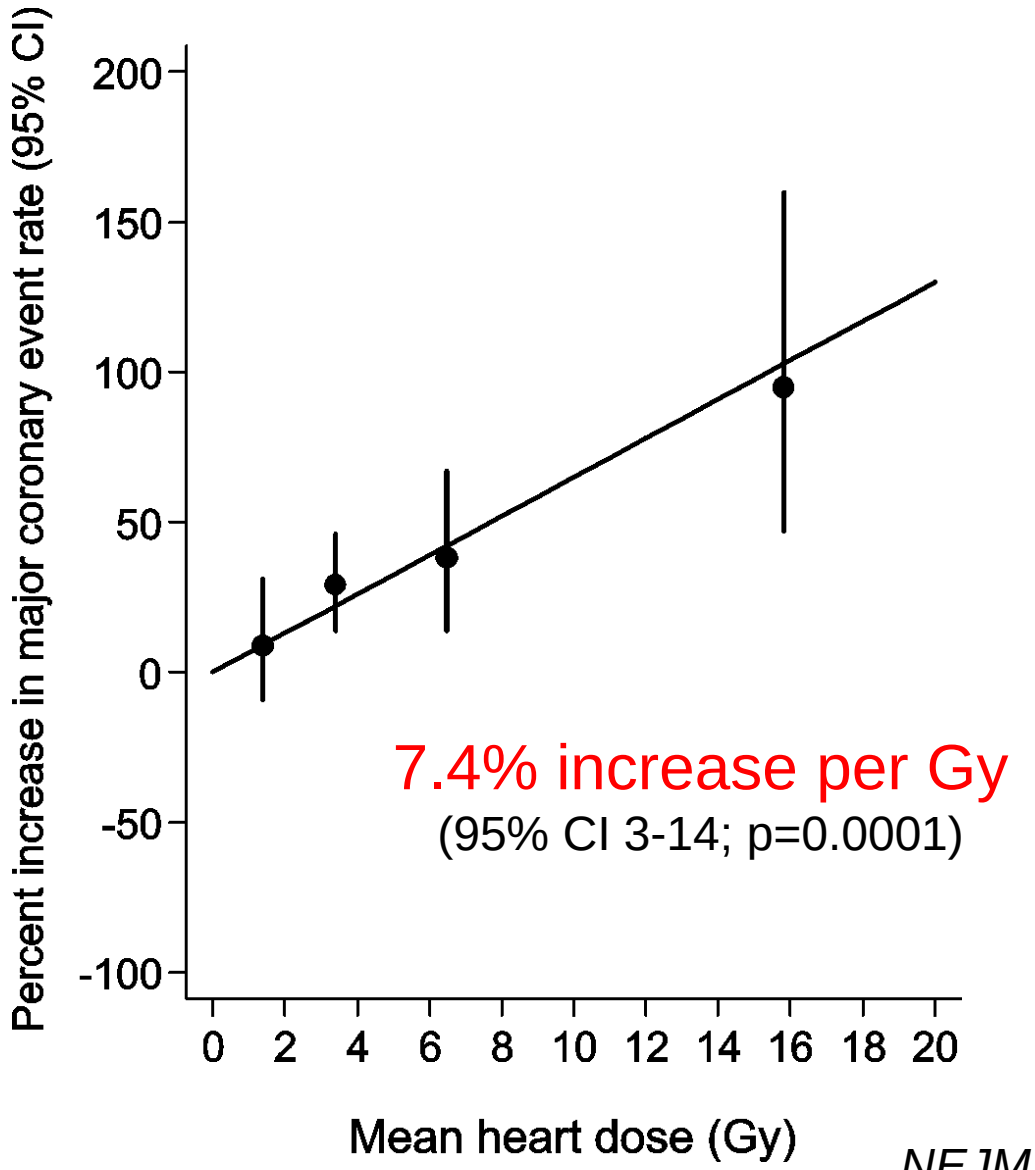
NEJM 2013; 368:987-98

Dose-response Relationship for Coronary Heart Disease in Dutch Hodgkin Lymphoma Survivors



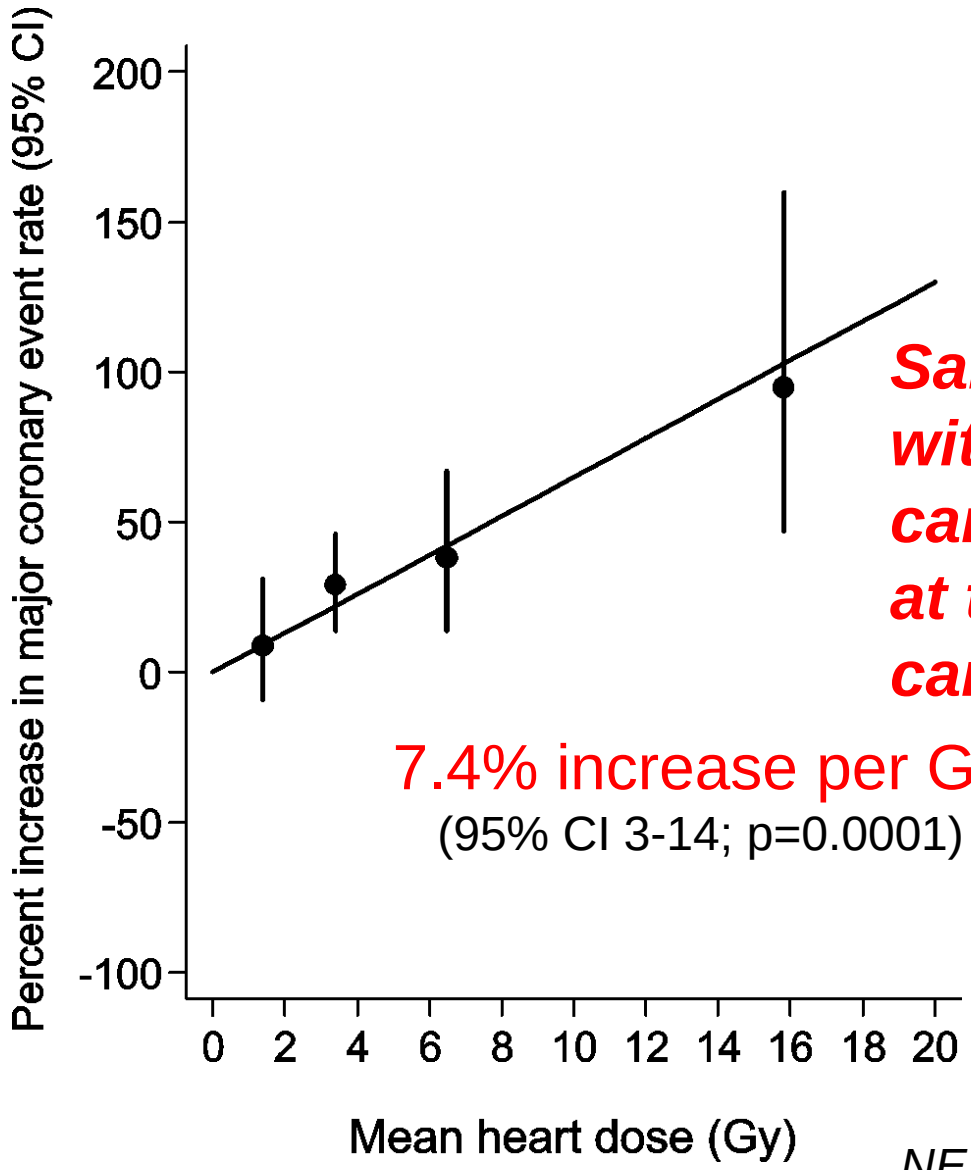
Nimwegen et al, J Clin Oncol 2015;34:235

Radiation Associated Cardiac Events (RACE)
Dose-response Relationship for Major Coronary Events



NEJM 2013; 368:987-98

Radiation Associated Cardiac Events (RACE)
Dose-response Relationship for Major Coronary Events



Same slope for women with and without cardiac risk factors at time of breast cancer diagnosis

7.4% increase per Gy

(95% CI 3-14; p=0.0001)

NEJM 2013; 368:987-98

Plan of talk

- Identifying the late side-effects of radiotherapy
- Deriving dose-response relationships for late-effects
- Estimating absolute risks of late effects

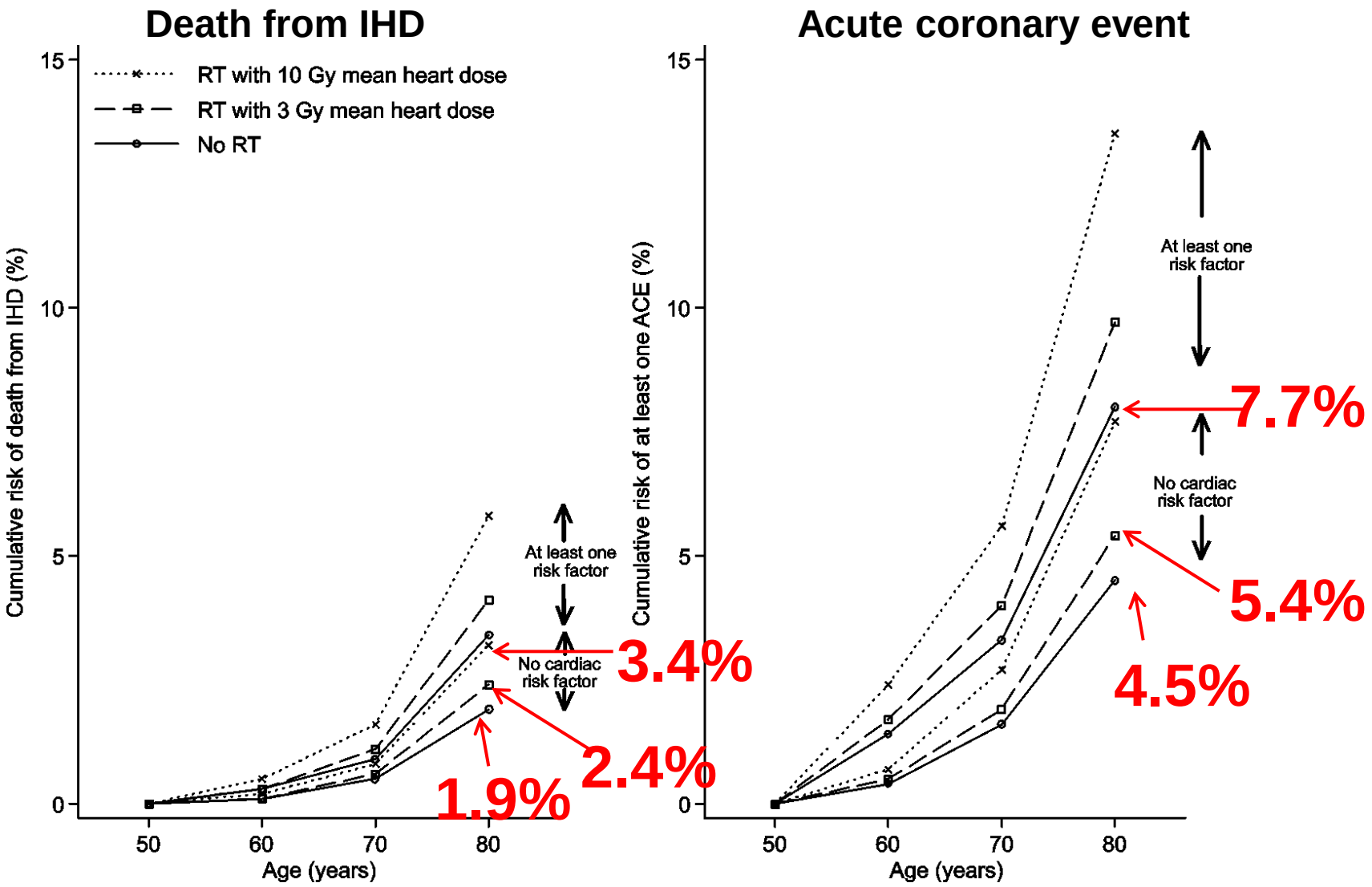
- The dose-response relationship from the case-control study estimates risk in terms of the **percentage** increase per Gy
- It can be combined with **recent population-based rates** of:
  - death from ischaemic heart disease

or

  - incidence of acute coronary events
- to provide estimates of the **absolute** risks

Radiation Associated Cardiac Events (RACE)

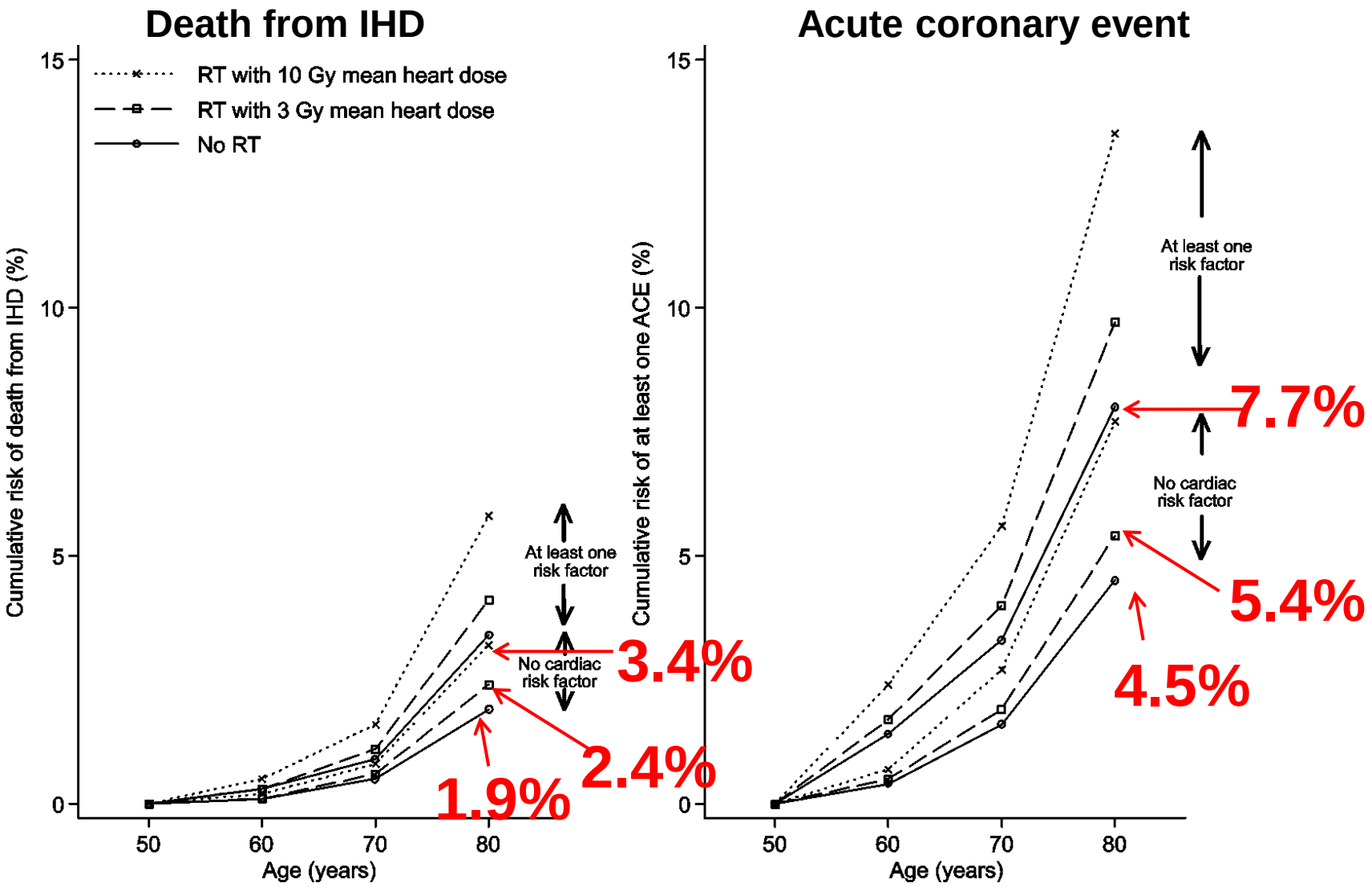
Illustrative calculations for a woman aged 50 at RT



NEJM 2013; 368:987-98

Radiation Associated Cardiac Events (RACE)

Illustrative calculations for a woman aged 50 at RT



Need to take other causes of death into account

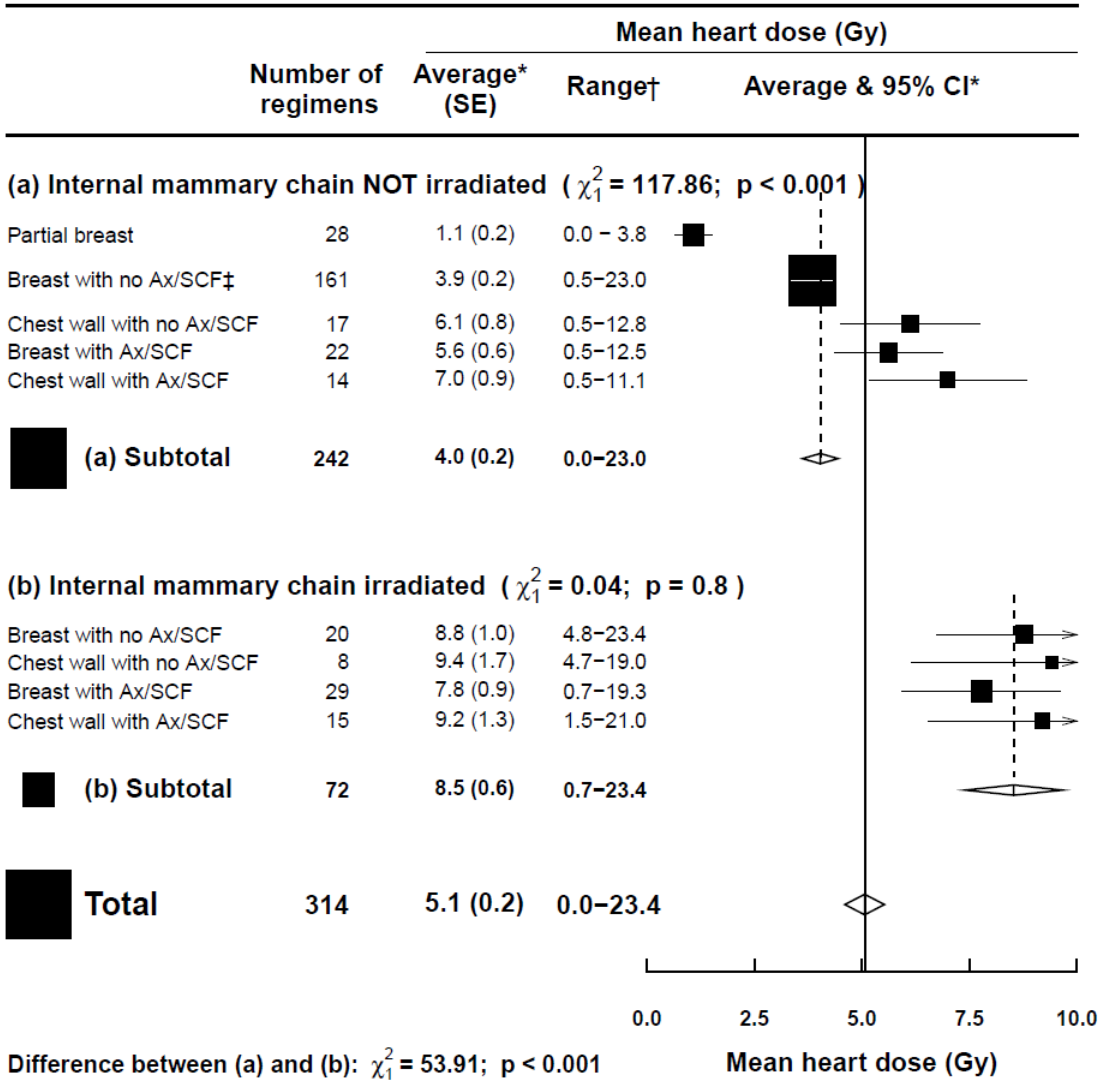
NEJM 2013; 368:987-98

Current Issues in Radiation-related Heart Disease

- Effect of radiation in patients receiving cardiotoxic chemotherapy (eg anthracyclines)
- Are some parts of the heart more sensitive than others?
- Increased cardiac risk with increasing use of IMC RT?

Systematic review of published estimates of cardiac doses from left breast radiotherapy: 2003-2013

(398 regimens in 149 studies)



Taylor et al. Int J Radiat Oncol Biol Phys 2015

Dose-response Relationships for Other Important Late Side-effects

- Lung cancer – approach similar to heart disease with smoking as main risk factor

- Contralateral breast cancer – contralateral breast hard to contour on CT scans so different approach to dose estimation needed, eg using thermolunimescent dosimeters in tissue equivalent phantoms (eg Stovall et al, IJROBP, 2008; 72:1021)

Overall conclusion

- To make the best choice for each patient, careful evaluation of both the absolute benefits and of the absolute risks of radiotherapy is needed.
- For many patients this will provide reassurance that the benefits of radiotherapy outweigh the risks
- It will also enables the remaining patients to be identified, so that alternative treatment options can be considered.

The end

Contemporary techniques

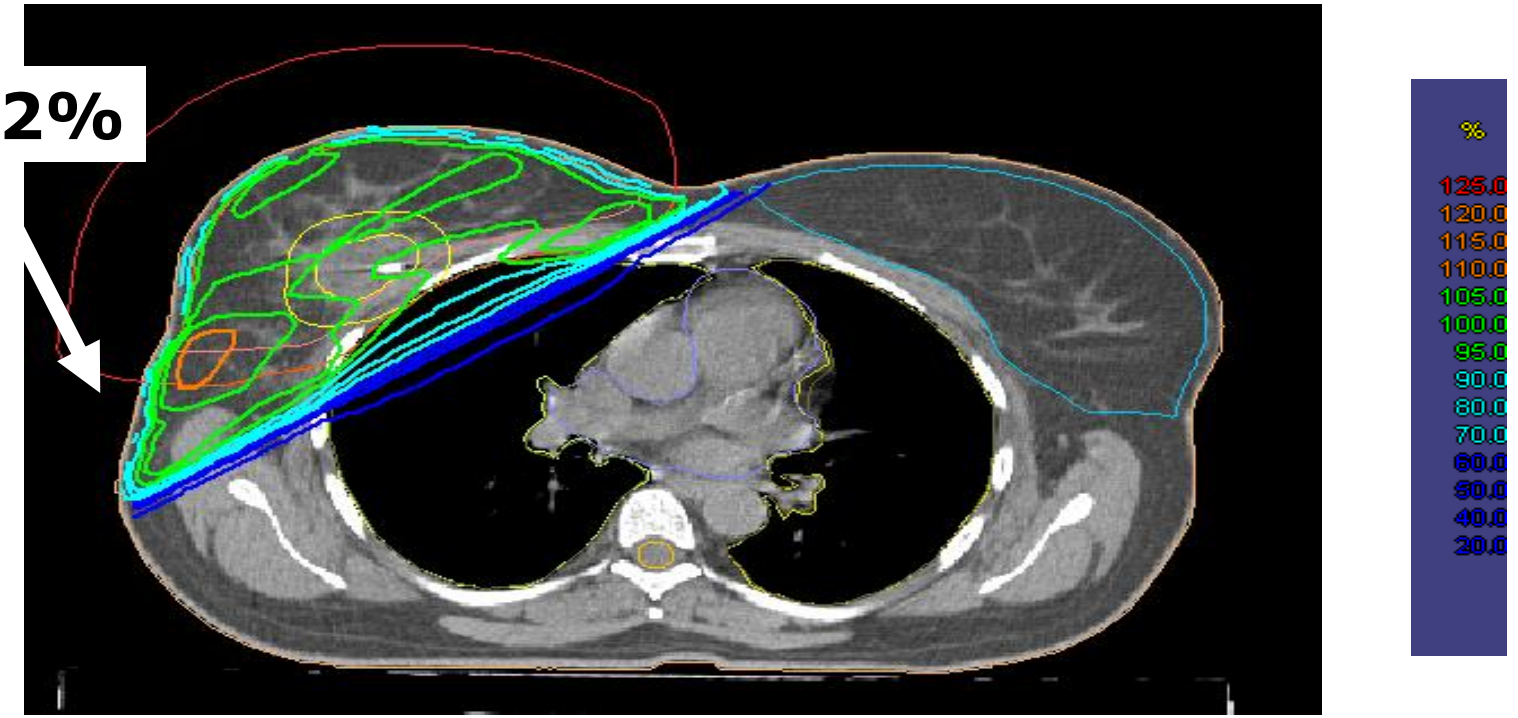
Marianne Aznar

marianne.aznar@manchester.ac.uk

ESTRO School

PROFOUND HYPOFRACTIONATION

What hypofractionation means for treatment planning:



➔ Under- and especially overdosage are more relevant for late effects with hypofractionation

Yarnold et al., Breast 19, 176-79, 2010

ESTRO School

FAST-forward planning constraints : 5.2 Gy x5
5.4 Gy x5

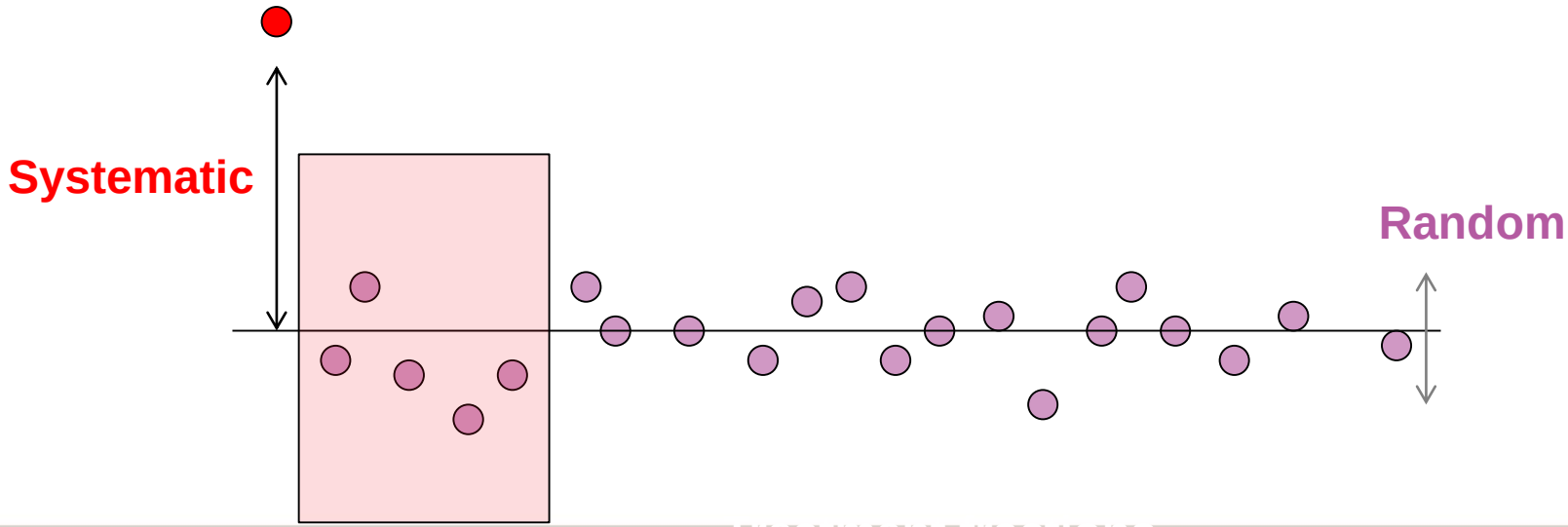
PTV V95%>95%

Upper dose limit : <5% of the volume should receive ≥105%
<2% of the volume should receive ≥107%
global max <110% of the prescribed dose

More field-in-field / IMRT / VMAT

Random vs systematic uncertainties

$$M = 2.5\,\Sigma_{tot} + 1.64\,(\sigma_{tot} - \sigma_p)$$



Random vs systematic uncertainties: what does it mean ?

When the fraction number is reduced, execution ("random") errors may have a systematic component

They won't "cancel out"

But in breast cancer, we don't want to increase the PTV margins !

So how do we minimize execution errors?

More advanced IGRT: daily, 3D

REDUCING DOSE TO OARS: DEEP INSPIRATION

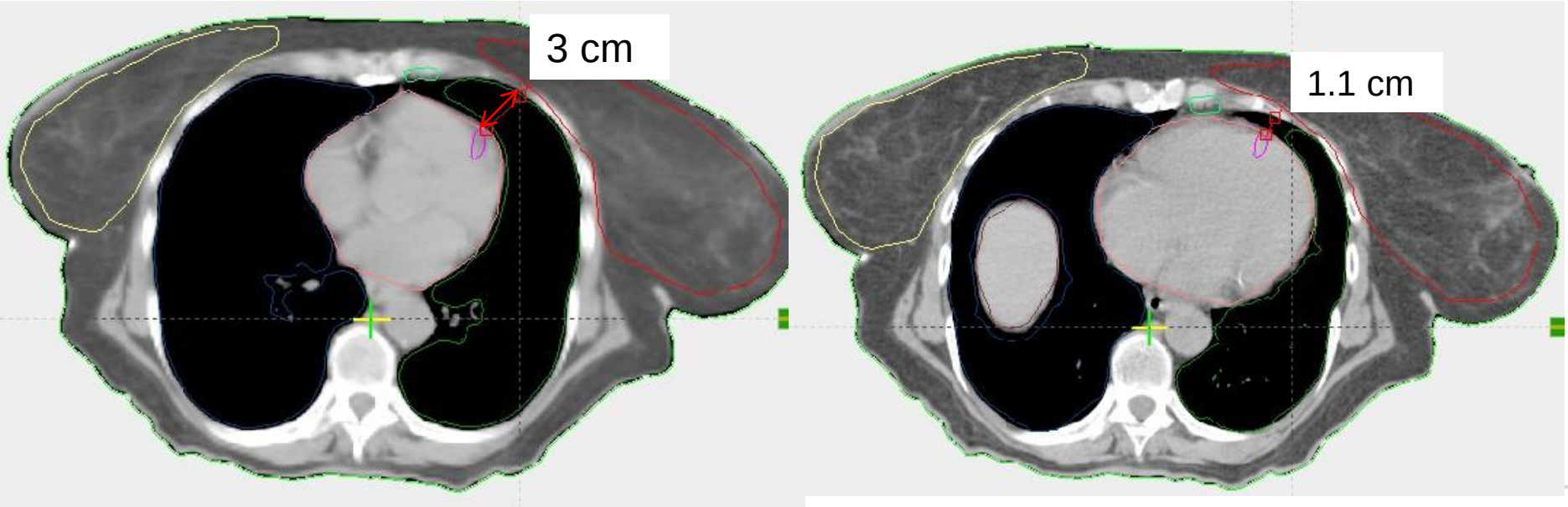
Aim of breathing management in breast treatments

Not to reduce motion

Increase spatial separation between target and risk organs

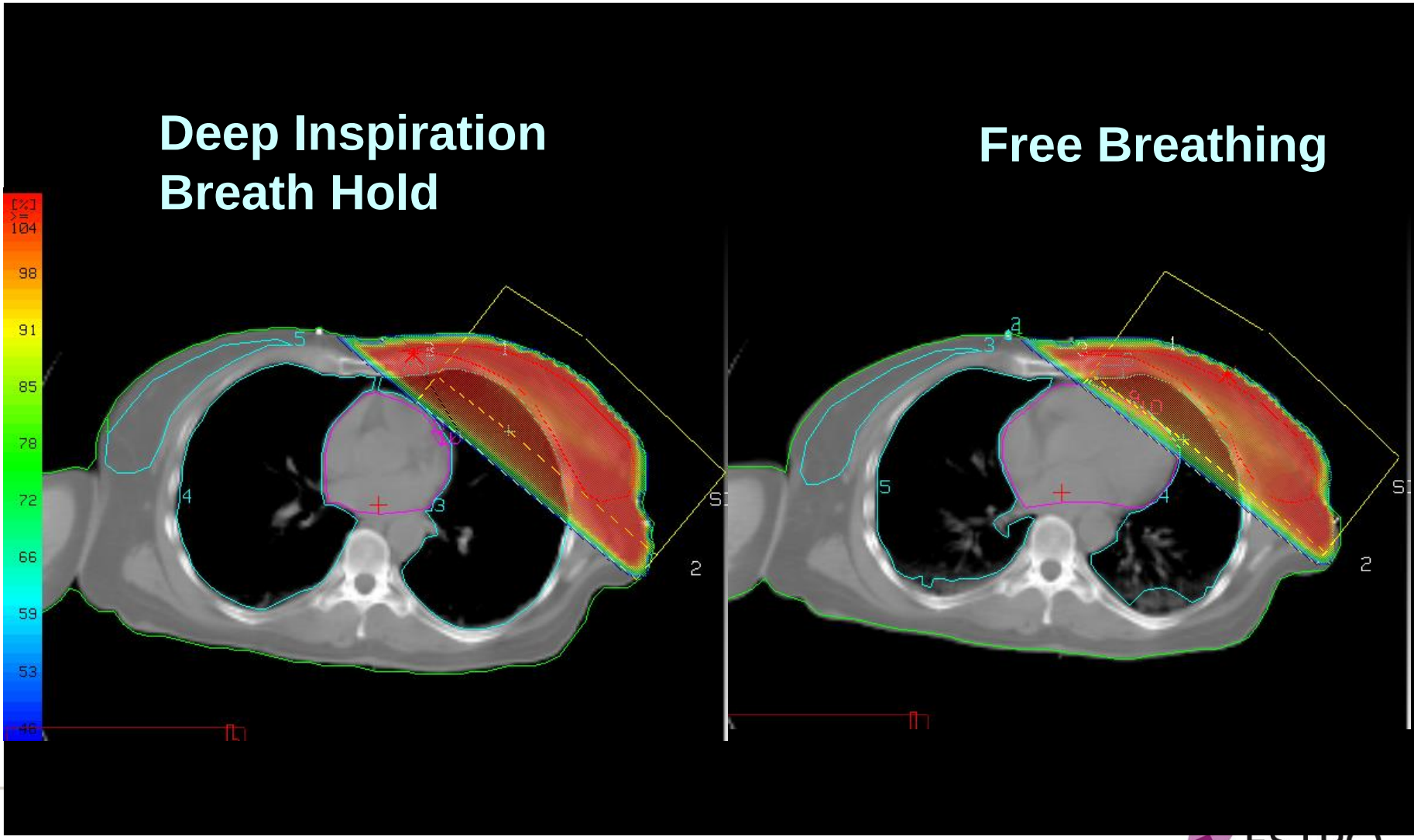
Deep Inspiration

Free breathing



ESTRO School

Dose comparison – free breathing/inspiration



How much can you gain?
Systematic reviews of the effect of DIBH

Target	Heart (mean dose)	Ipsilateral lung (mean dose)
Breast / CW	- 2.5 Gy	- 1 Gy
Breast/CW + axilla/SCF		-2 Gy
Breast/CW + axilla/SCF+ IMC	- 5 Gy	- 3 Gy

Sources: Taylor et al, IJROBP 2015
Aznar et al (in preparation)

ESTRO School

Most commonly used systems (non-exhaustive)

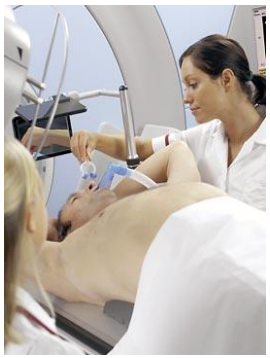
Based on an external signal (e.g. marker, surface)

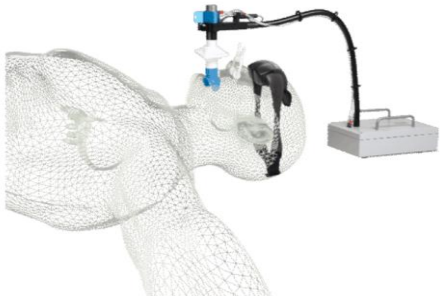
RPM/Gating

VisionRT

Based on expiratory volume

ABC





SpiroDynR'x

The simpler, the better?

Radiotherapy and Oncology 108 (2013) 242–247

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Phase III randomised trial

The UK HeartSpare Study: Randomised evaluation of voluntary deep-inspiratory breath-hold in women undergoing breast radiotherapy

Frederick R. Bartlett[a,*], Ruth M. Colgan[b], Karen Carr[a], Ellen M. Donovan[b], Helen A. McNair[a], Imogen Locke[a], Philip M. Evans[b,c], Joanne S. Haviland[d], John R. Yarnold[a,e], Anna M. Kirby[a]

[a] Department of Academic Radiotherapy, Royal Marsden NHS Foundation Trust; [b] Joint Department of Physics, Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Sutton; [c] Centre for Vision, Speech and Signal Processing, Faculty of Engineering and Physical Sciences, University of Surrey, Guildford; [d] Clinical Trials and Statistics Unit (ICR-CTSU); and [e] Division of Radiotherapy and Imaging, Institute of Cancer Research, Sutton, UK

Voluntary breath hold preferred over "forced"

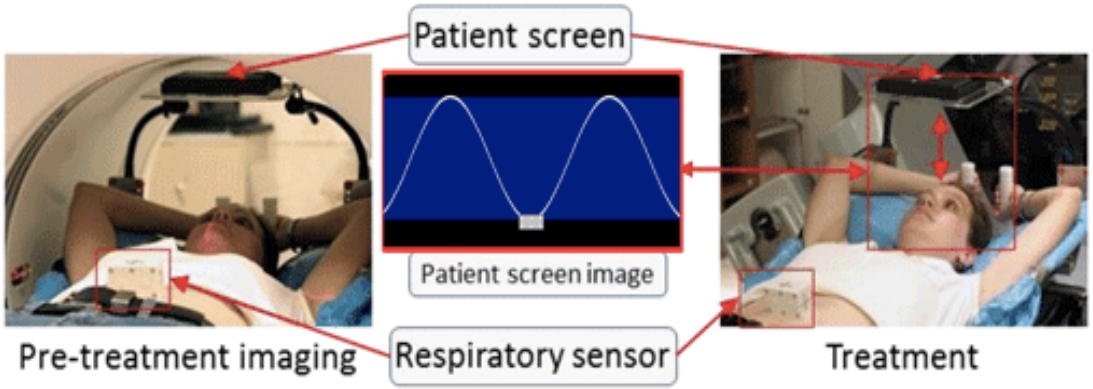


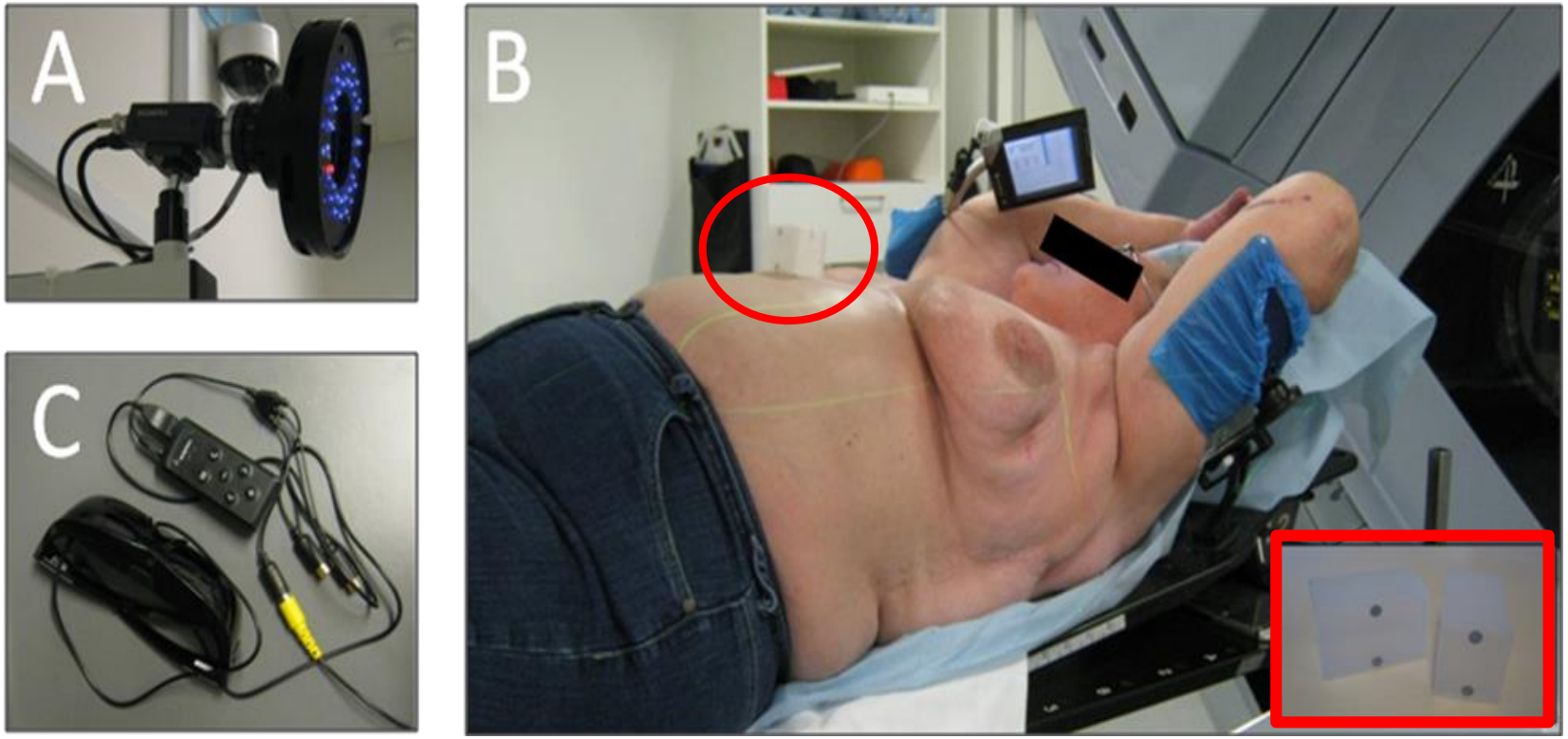
Figure 1. AV biofeedback system. Display screen and marker block on the abdomen shown. The visual display (centre) as seen by the subject (sans arrows) of the AV biofeedback system shows the guiding wave (white curve) and a marker position (marker block) in real time. The AV biofeedback system is compatible for both imaging (left) and treatment (right) environments.

Paul Keall
Sydney

School

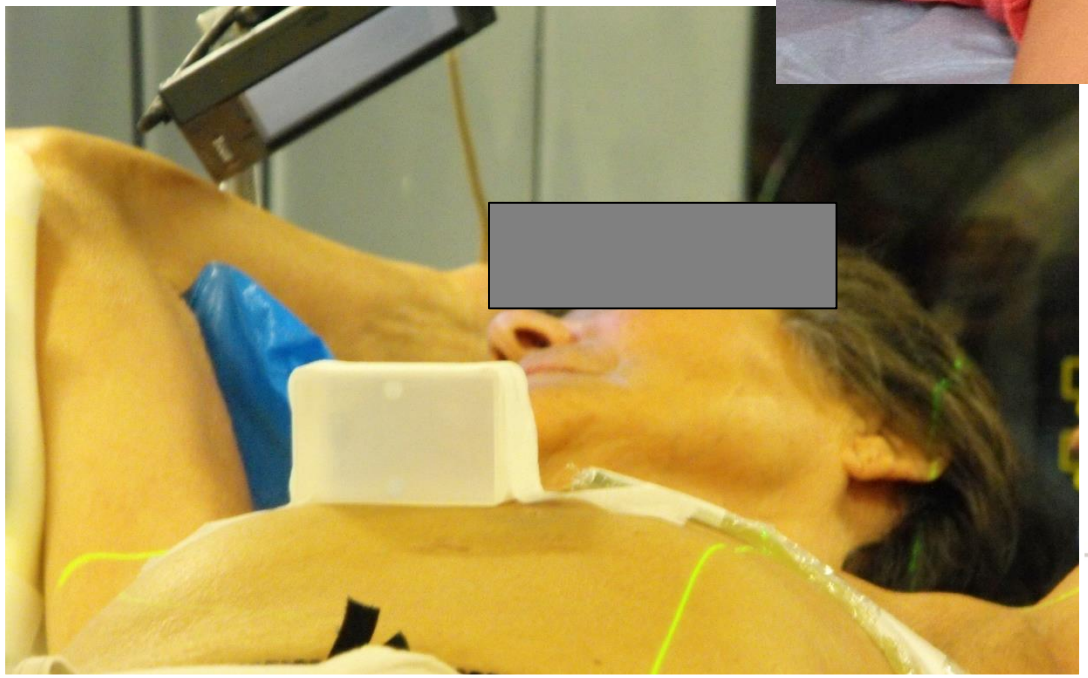
Deep inspiration breath hold with visual coaching

Courtesy of Sidsel Damkjær, Copenhagen

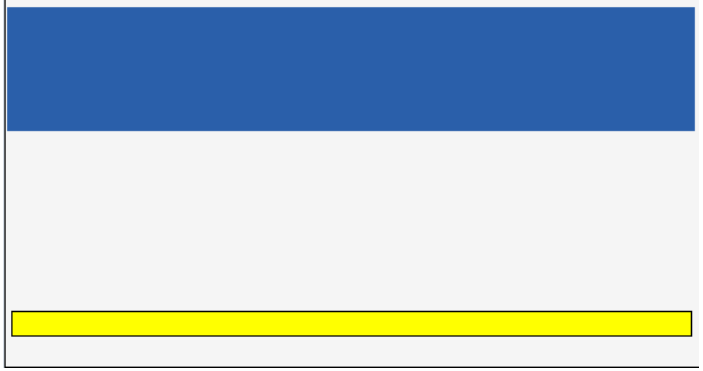


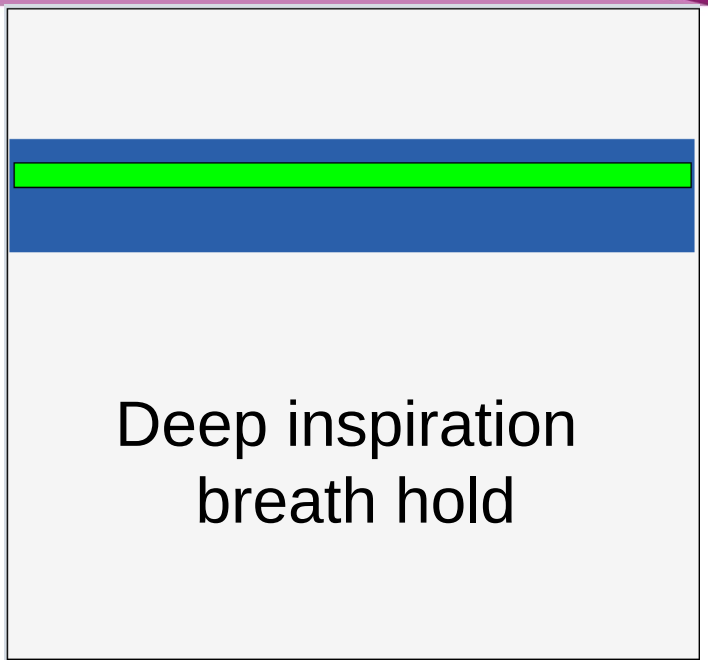
At Rigshospitalet: RPM system from Varian + third part screens/goggles

Alternatives: ABC system from Elekta, VisionRT, C-RAD sentinel…

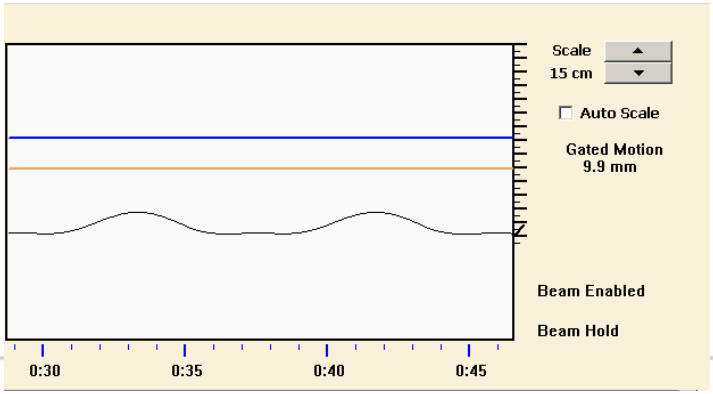


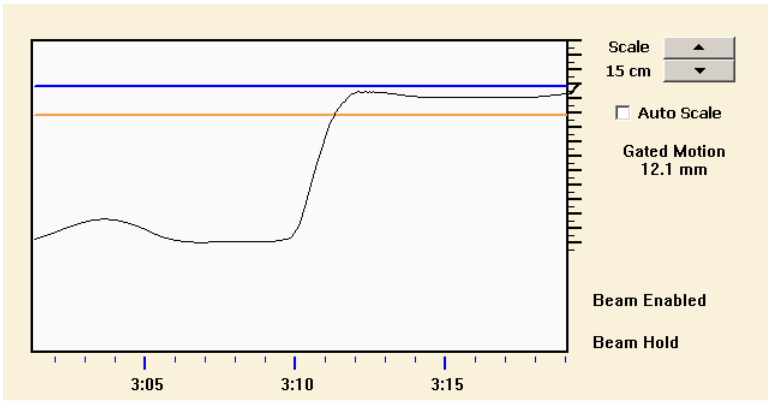
Free breathing





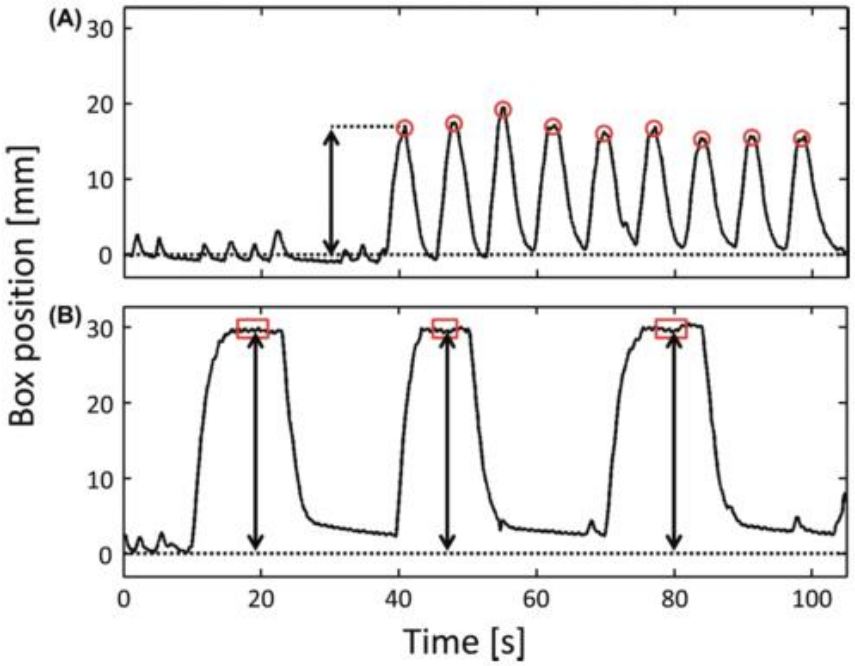
Deep inspiration
breath hold





ESTRO School

Reproducibility of deep inspiration level



Damkjaer
Acta Oncol 2013

	Audio-coached EIG mean (range)	Visually guided DIBH mean (range)
Mean inspiration level [mm]	16.6 (5–35)	20.5 (5–34)
Mean standard deviation [mm]	1.66 (0.5–3.5)	0.38 (0.2–0.6)

No equipment ? No excuse !!

The ”no equipment” solution:

- short hyperventilation followed by breath hold
- Monitoring is visual (draw the light field on the patient, observed through control room monitors)
- Video article: ***Bartlett et al J Vis Exp 2014***

ESTRO School

Treatment at deep inspiration

PROs

Simple technology

Sparing of OARs without dose bath

Applicable to other patient groups

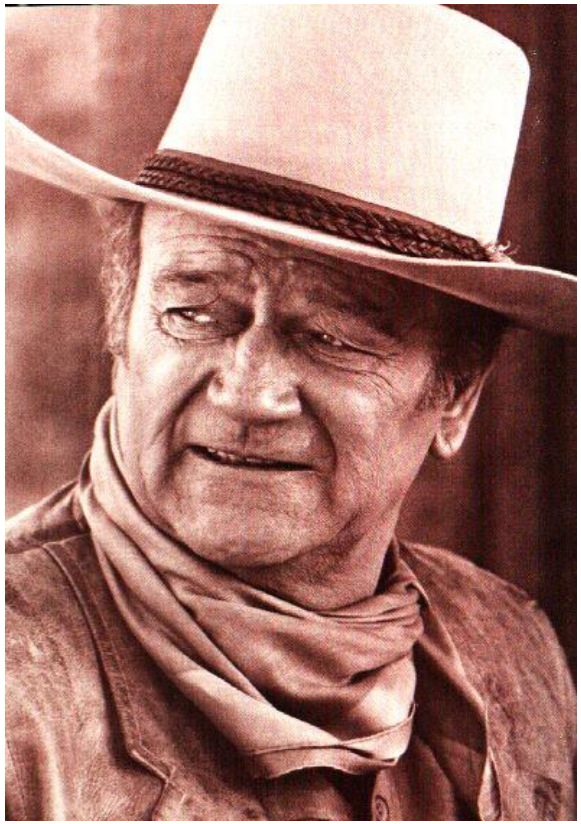
CONs

Increased workload (coaching)

May increase treatment time

Patient cooperation?

Compliance?



Lung cancer

Breast cancer

Courtesy of M Guckenberger

Take home message for DIBH

Just do it !

Start with node-positive left-sided patients
consider expanding to: node-positive right sided
Or selected node negative left-sided
Or left-sided with boost…

Once you're over the learning curve, the time investment decreases drastically

Expand to other patient groups!

ESTRO School

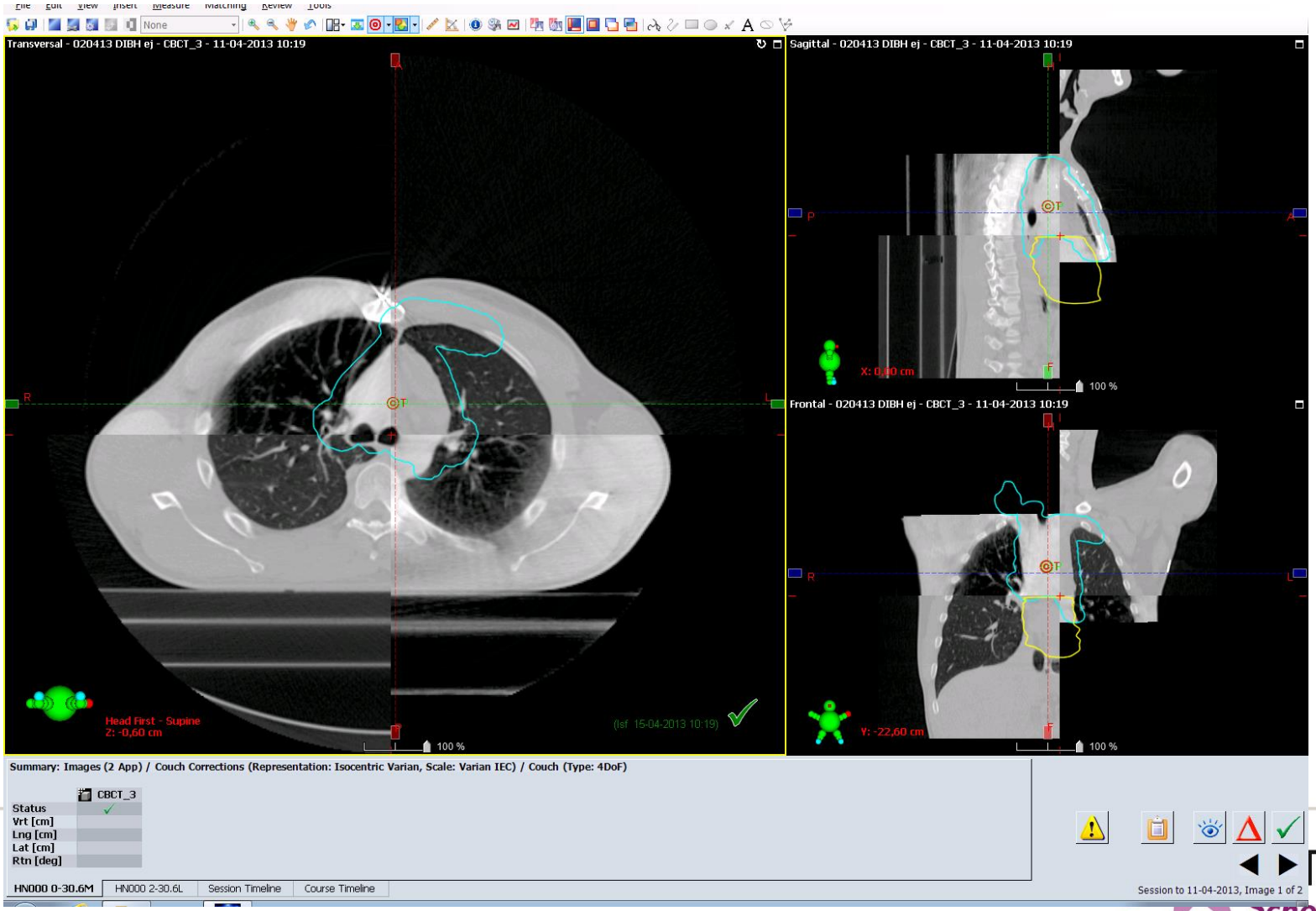
IGRT

POSITION VERIFICATION IN DIBH

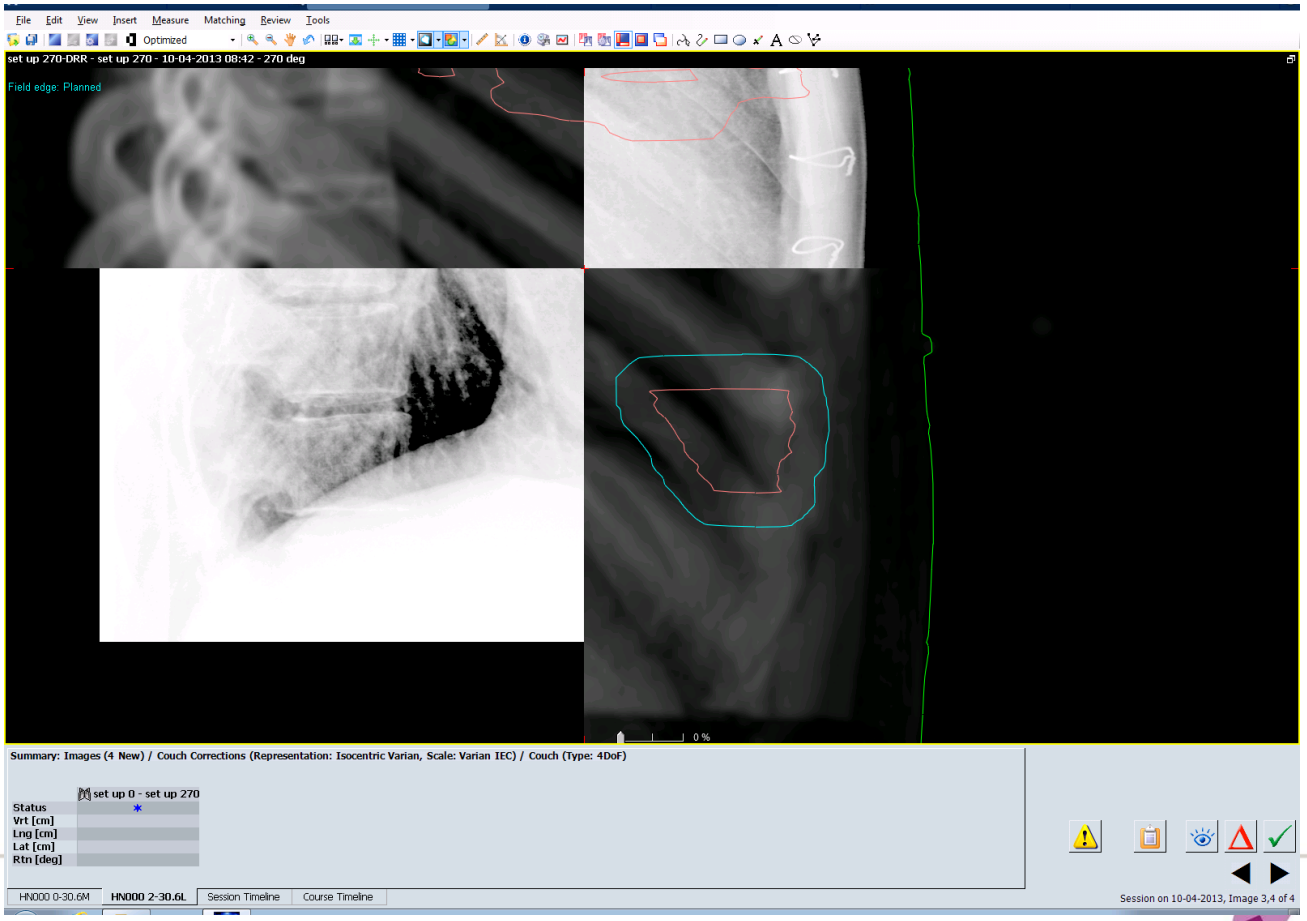
ESTRO School

NB: lymphoma patient

Can check heart position and lung inflation



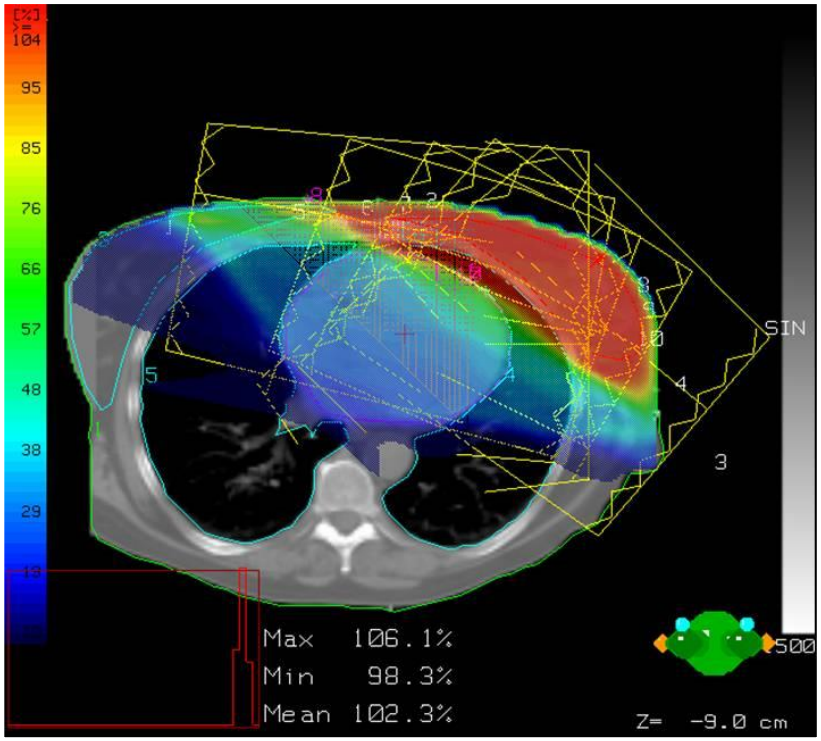
Daily 2D images: fuse on spine, check sternum

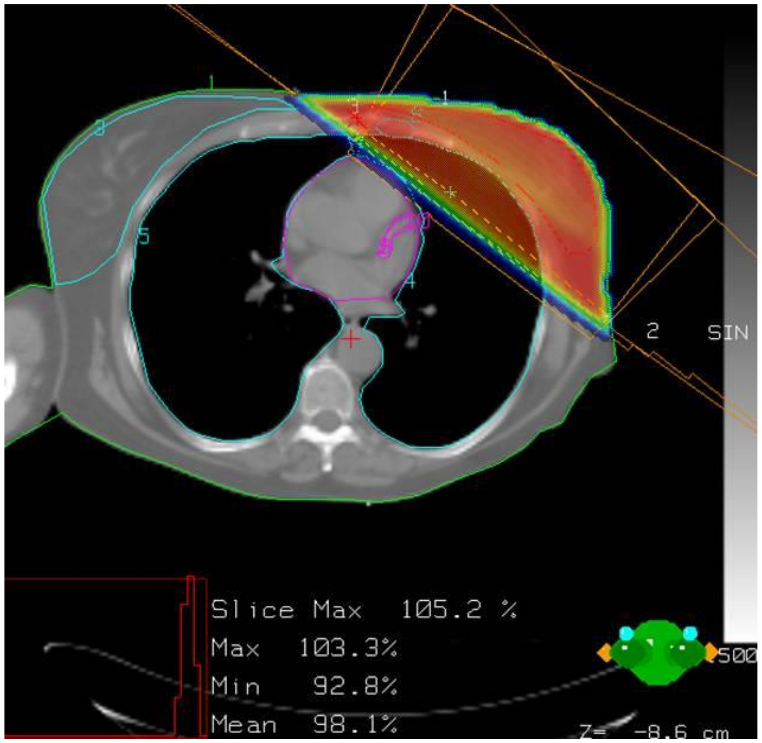


ESTRO School

COMBINING THE TWO ?

IMRT or deep inspiration treatment?





- 20-30 breast patients with IMRT or RapidArc /year
- Since 2003, > 1500 patients treated with respiratory management

ESTRO School

Combining DIBH and VMAT

At Rigshospitalet:

For IGRT: 2 very short DIBHs (one per image)
For each 3D field: one DIBH
For each arc: 1 to 2 DIBHs

Total: worst case scenario 8-10 breath holds of 10 to 20 sec (patient catches her breath between fields)

Treatment time slot of 10-15 min

When do you gain from adding IMRT/VMAT to DIBH?

Only if the mean heart dose (in 3D DIBH) > approx 3Gy

Osman et al R&O 2014

Take Home message

IMRT/VMAT will reduce the mean heart dose if it is high to start with… but difficult to get below approx 3 Gy (dose bath)

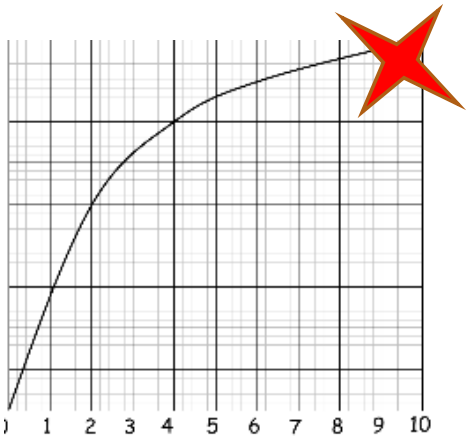
Combine with DIBH for best results

Combination might require special license / QA

ESTRO School

Breast cancer :

Optimised treatment planning to minimise side effects: from easy and not expensive to highly sophisticated techniques



Youlia M. Kirova

institutCurie

To reduce the cardiac toxicity reducing the doses to heart and coronaries

FRANÇOIS BACLESSE, M.D.
1896-1967

Five-Year Results in 431 Breast Cancers Treated Solely by Roentgen Rays *

FRANCOIS BACLESSE, M.D.
From the Fondation Curie, Paris, France

Annals of Surgery
January 1965

TABLE 1. *Results in Cancer of the Breast Treated Solely by Roentgen Rays. Columbia Clinical Classification*

Clinical Stage	Treated	Surviving 5 Years	(%)	Clinically "Cured"* 5 Years	(%)	Living with Local Recurrence or Distant Metastases After 5 Years
Stage A	50	27	54	27	54	0
Stage B	86	58	67	53	61	5
Stage C	95	39	41	32	34.7	7
Stage D	200	27	13	21	10	6
Total	431	151	35	133	30.8	18

* Without clinical or radiographic evidence of persisting local or regional cancer, or distant metastasis.

1936 : François **Baclesse** (Institut Curie) jette les bases du traitement conservateur du cancer du sein

Lateral Isocentrique RT: To avoid lung and heart irradiation

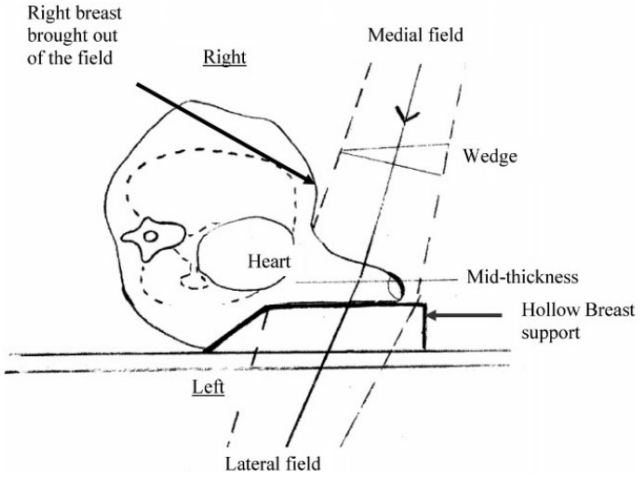


Figure 1. Schematic presentation of the isocentric lateral decubitus (ILD) technique for radiotherapy of the left breast.

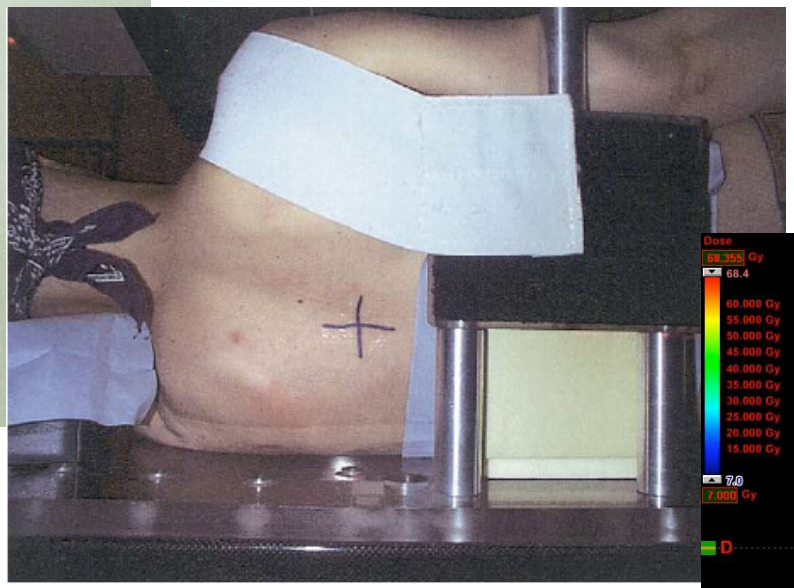
786 *The British Journal of Radiology, October 2006*

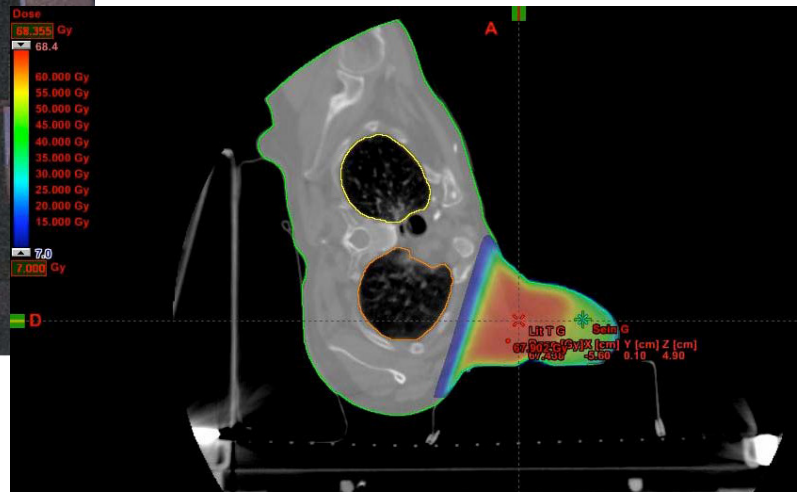
- *Fourquet et al. Radiother Oncol, 1991*
- *Campana et al. Int J Radiation Oncology Biol Phys, 2005*
- *Bollet et al. Br J Radiol, 2006*
- *Kirova et al . Int J Radiation Oncology Biol Phys, 2008*
- *Capezzali et al, GI J Br Can Res, 2013*
- *Kirova et al, Radiother Oncol, 2014*
- *Bronsart et al, Radiother Oncol 2017*

Lateral Isocentrique RT: To avoid lung and heart irradiation

Figure 1: Lateral decubitus position during the CT scan for the treatment planning.

Lateral Isocentrique RT: To avoid lung and heart irradiation





Lateral Isocentrique RT: To avoid lung and heart irradiation

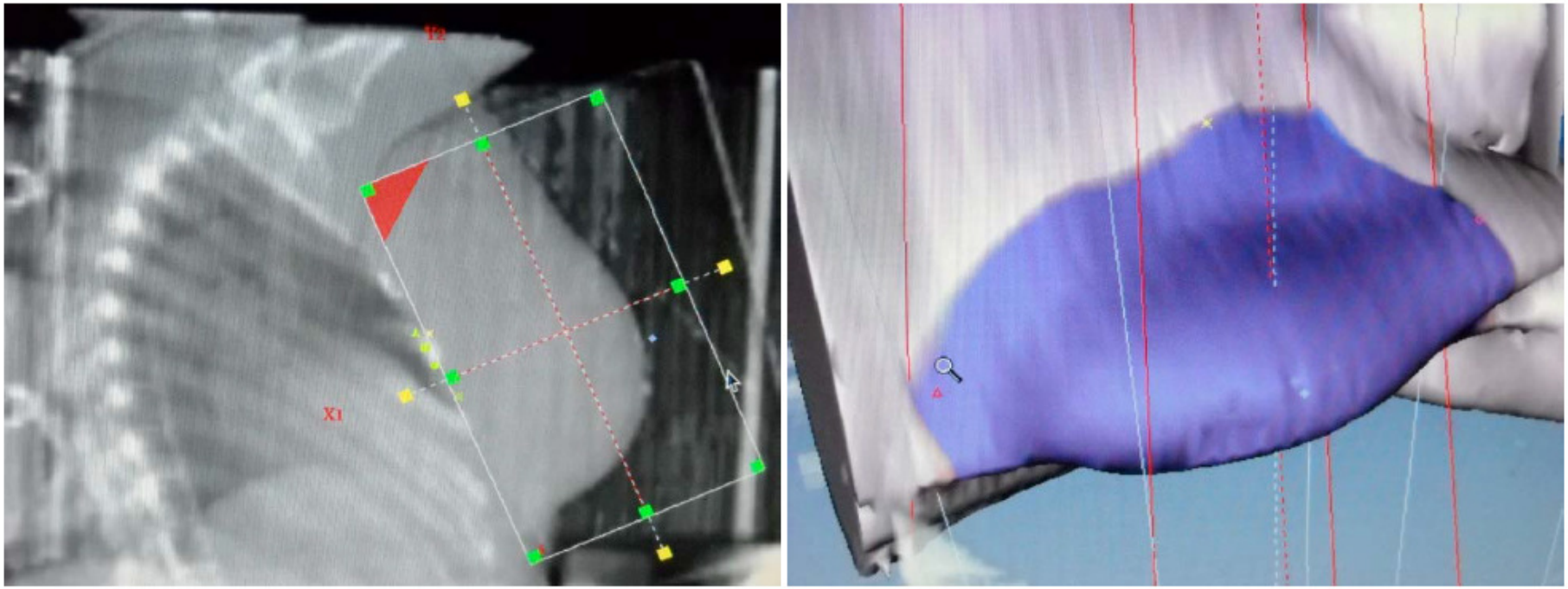


Figure 2: Virtual simulation of the left breast in lateral position.

Lateral Isocentrique RT: To avoid lung and heart irradiation

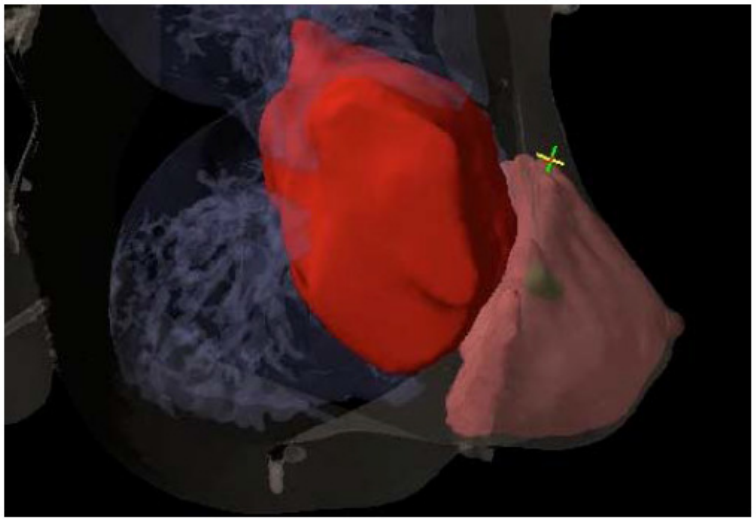
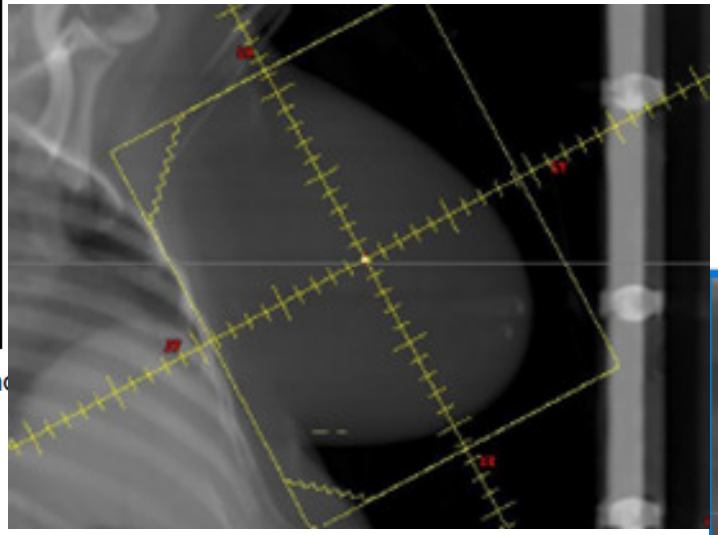
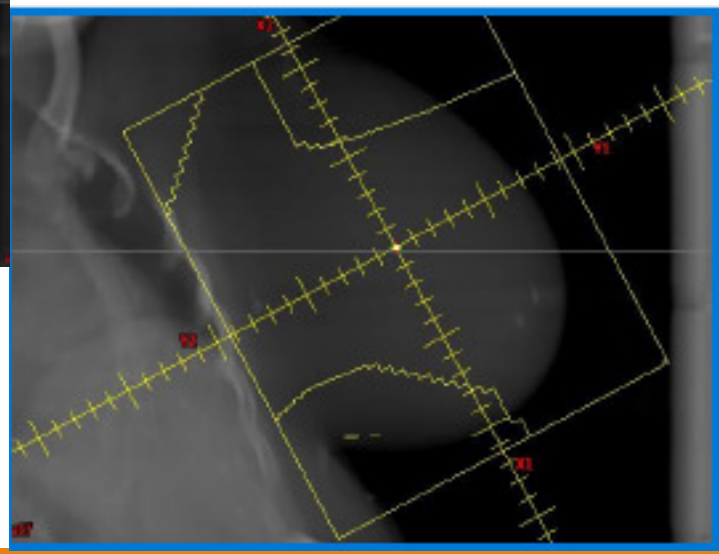


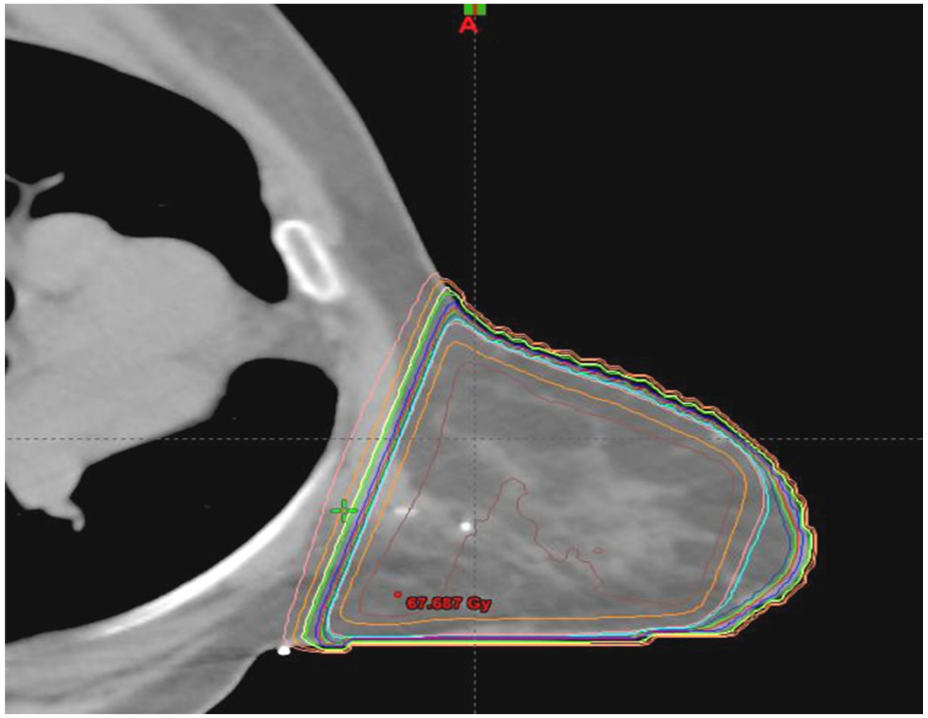
Figure 3: 3D reconstruction of the target volumes (breast and boost) and OAR (lung and heart).

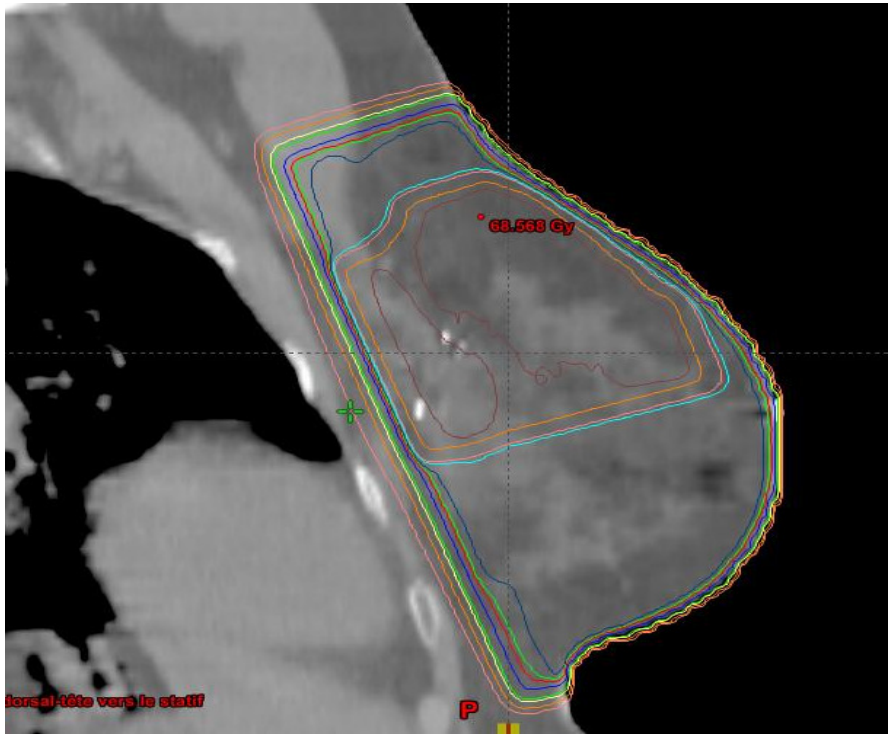




Dose distribution: Breast 50 Gy + boost 16 Gy

Fourquet, Breast Cancer Management 2012





66 Gy
62.7 Gy
53.5 Gy

50 Gy
47.5 Gy
25 Gy

Lateral Isocentrique RT: To avoid lung and heart irradiation

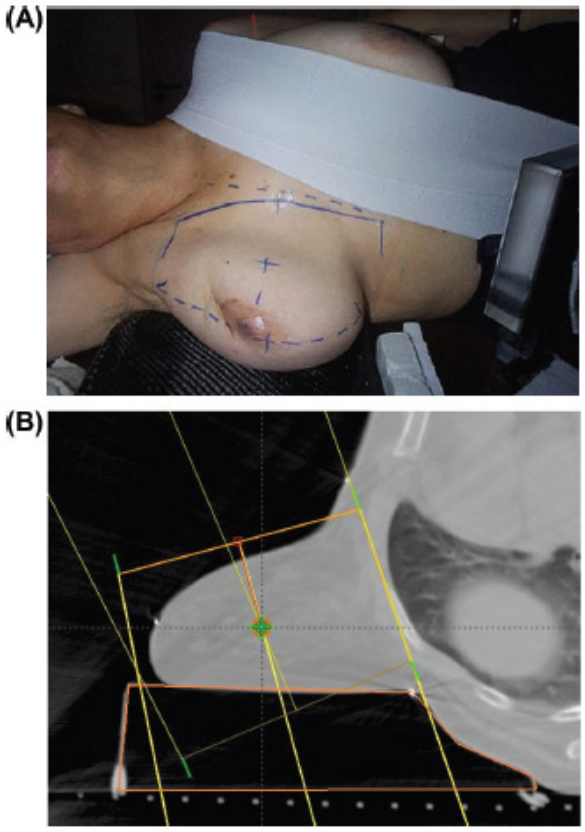


Fig. 1. (A) Patient position and immobilization device. (B) The breast lies on the flat part of the breast board. The edge of the angled side is marked by a metallic wire which is visible on CT scan and DRR (arrow).

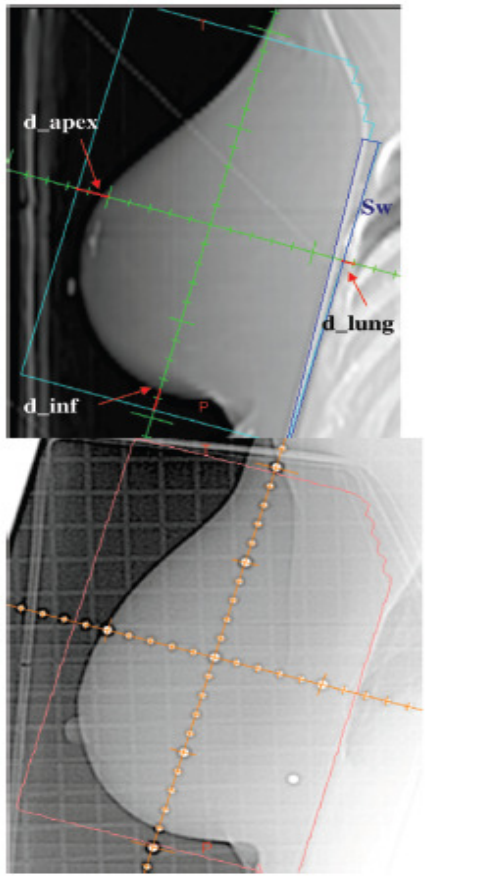


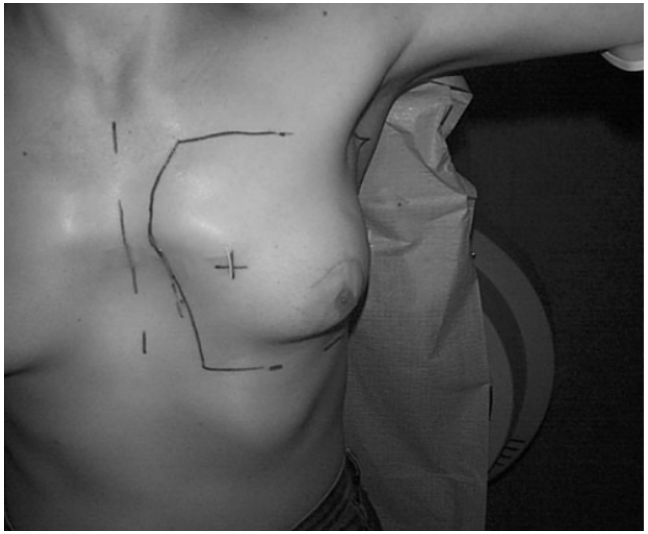
Fig. 3. Digitally reconstructed radiographs (DRRs) are produced and registered weekly, during treatment, to the portal images. Parameters measurements to assess patient set-up errors between the DRR (left) and the weekly portal image (right).

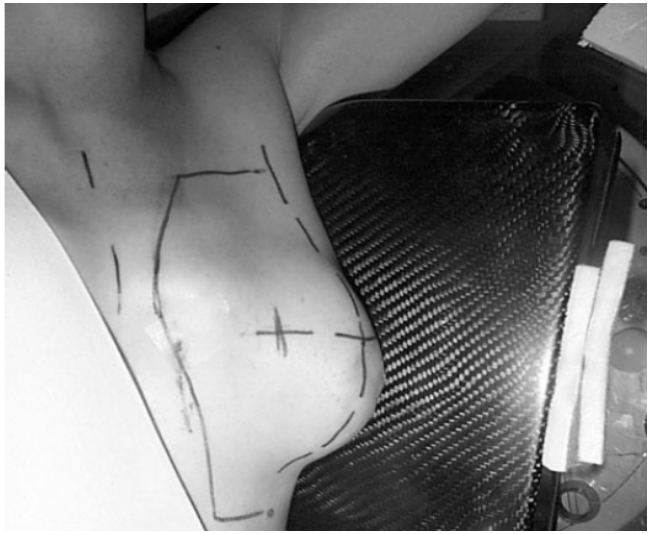
Doses to OAR,

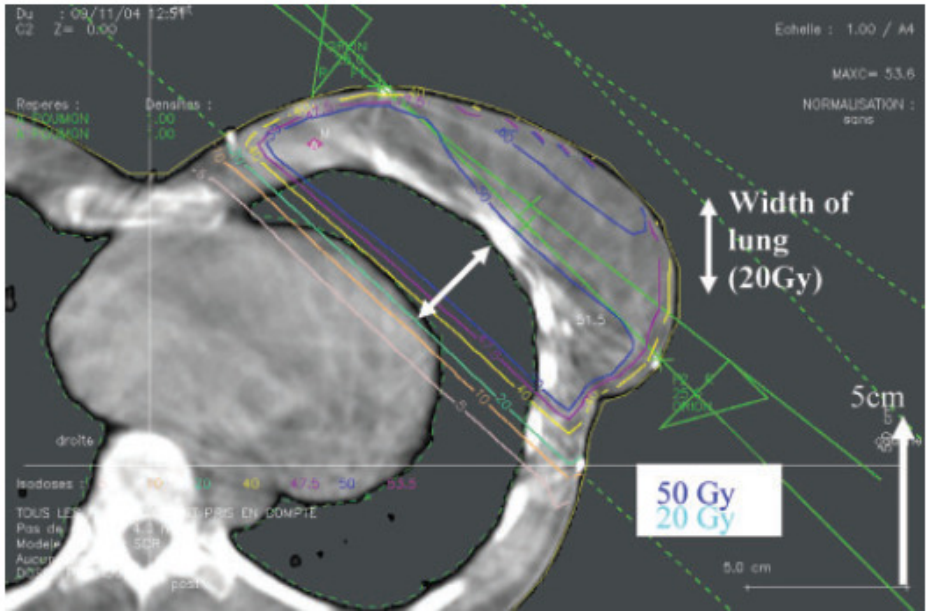
Bronsart et al, Radiother Oncol 2017

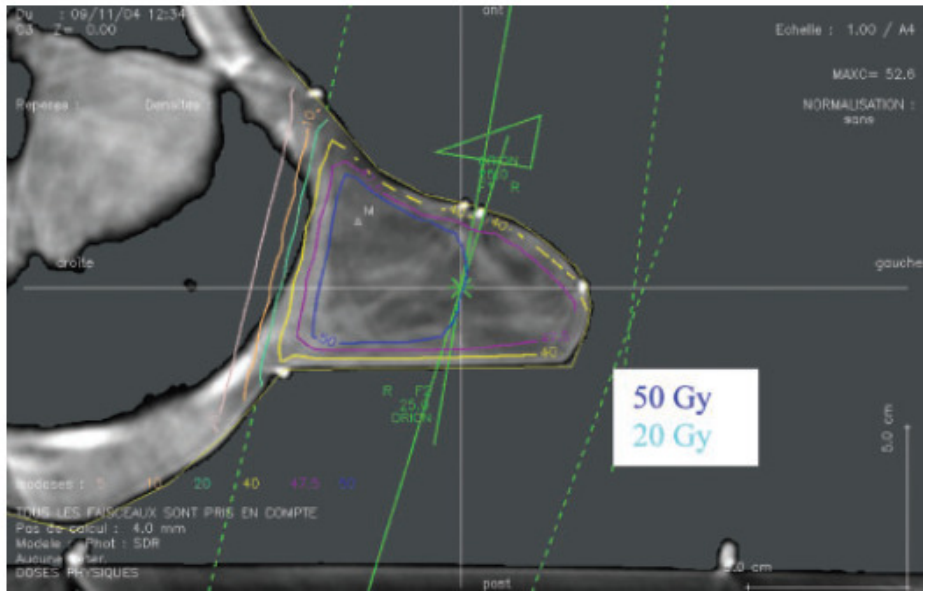
Table 2
Dosimetric results.

Treatment regimen	Mean dose			
	28.5 Gy/5 fr	41.6 Gy/13 fr	40 Gy/15 fr	50 Gy + 16 Gy
Right Breast				
Ipsilateral lung	0.53	1	1.71	1.04
Contralateral lung	0	0.003	0.01	0.05
Heart	0.25	0.37	0.31	0.52
Left Breast				
Ipsilateral lung	0.45	0.94	1.55	2.43
Contralateral lung	0	0.05	0.12	0.13
Heart	0.5	0.9	0.92	1.53






Width of lung (20Gy)
5cm
50 Gy
20 Gy
5.0 cm


50 Gy
20 Gy

Protons to reduce the long term toxicities

…not so simple because the cardiac toxicity is multifactorial

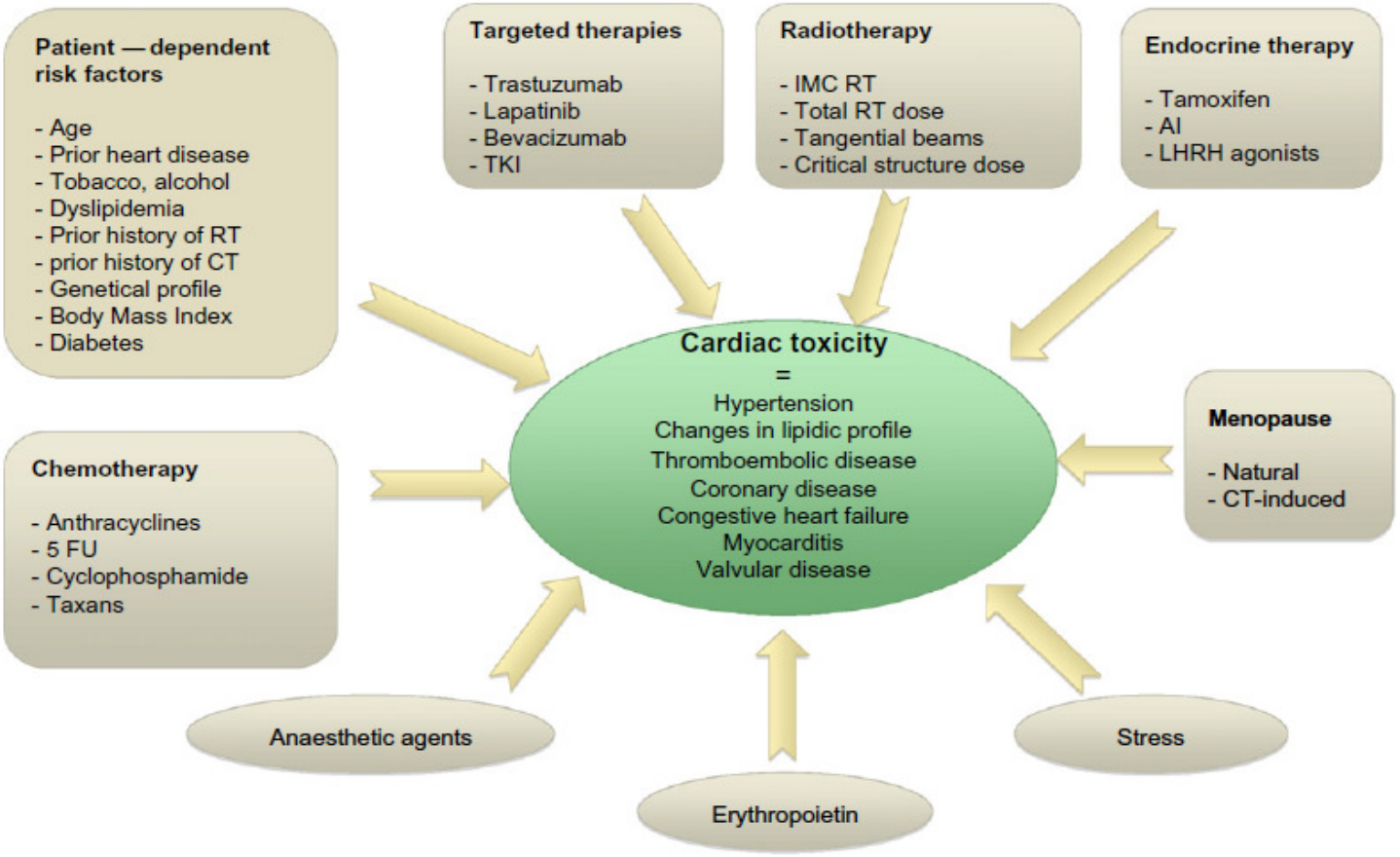
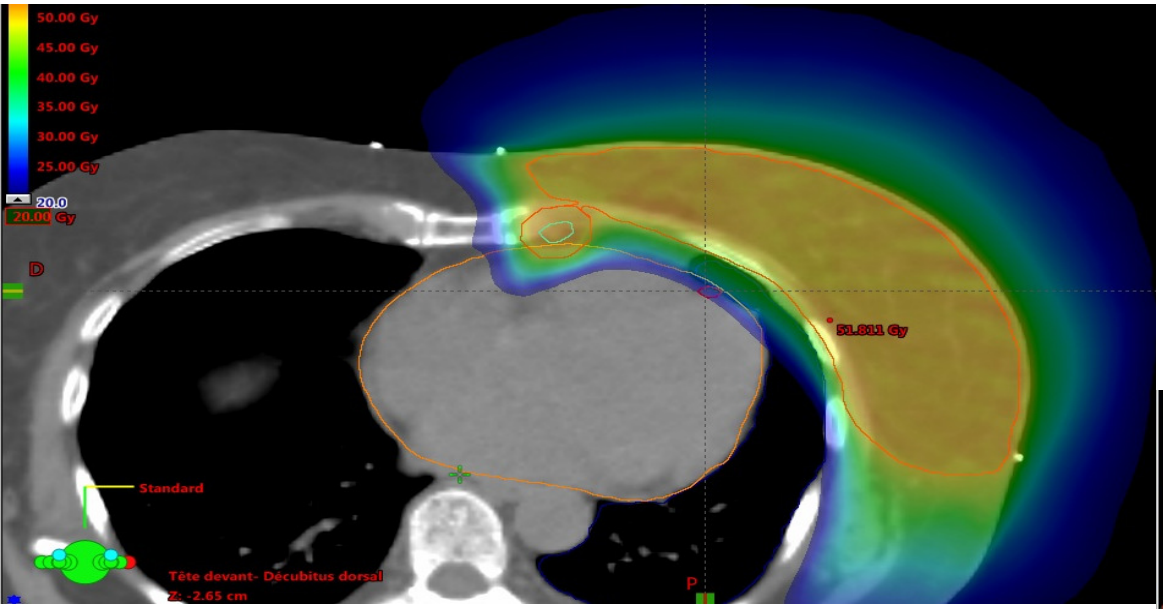


Fig. 1. List of factors that may potentially lead to cardiac hazard in breast cancer patients.

Please cite this article in press as: Chargari C et al. Cardiac toxicity in breast cancer patients: From a fractional point of view to a global assessment. *Cancer Treat Rev* (2010), doi:10.1016/j.ctrv.2010.08.007

institutCurie
Ensemble, prenons le cancer de vitesse

Dosimetric work: best photons vs protons



Photons using IMRT by Tomotherapy

-Homogeneous dose distribution

-Optimal couverage but higher dose to heart, corronaries and lung

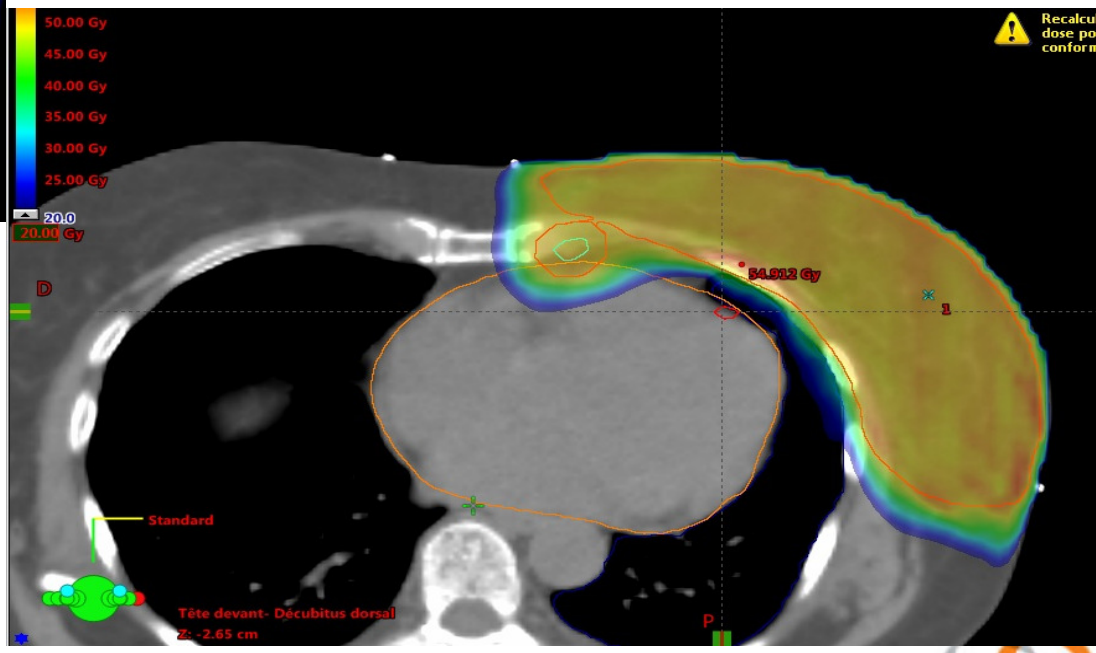
-Low but increased dose to contralateral breast

Protons using 2 fields →

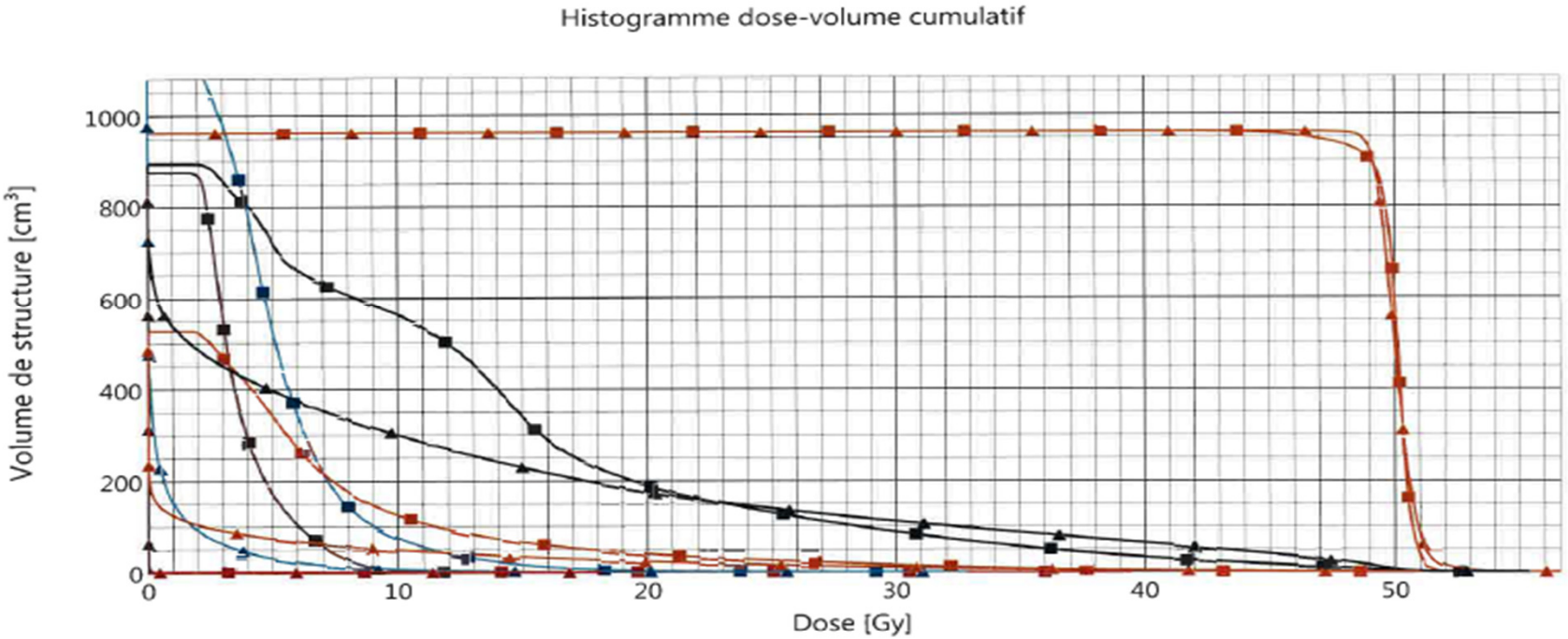
-Homogeneous dose distribution

-Optimal couverage and lower dose to heart and corronaries

-No dose delivered to contralateral breast (young high risk patients+++)



Dosimetric work



HDV	Structure	État de la structure	Recouvrement [%/%]	Volume	Dose min.	Dose max.	Dose moyenne	Dose modale	Dose médiane	Écart type
	PTV Sein G	Approuvée	100.0 / 100.0	962.8 cm³	40.9 Gy	52.7 Gy	50.0 Gy	50.2 Gy	50.1 Gy	0.8 Gy
	POUMON D	Approuvée	100.0 / 100.1	1173.4 cm³	1.1 Gy	32.8 Gy	5.3 Gy	4.1 Gy	4.7 Gy	2.9 Gy
	POUMON G	Approuvée	100.0 / 100.1	894.3 cm³	1.8 Gy	52.7 Gy	14.6 Gy	4.9 Gy	13.2 Gy	10.4 Gy
	SEIN D	Approuvée	100.0 / 100.0	875.9 cm³	1.5 Gy	14.1 Gy	3.9 Gy	2.7 Gy	3.3 Gy	1.6 Gy
→	COEUR	Approuvée	100.0 / 100.0	527.2 cm³	1.7 Gy	51.1 Gy	8.5 Gy	5.2 Gy	6.1 Gy	7.2 Gy
	CORONAIRE G	Approuvée	100.0 / 104.4	1.1 cm³	5.5 Gy	39.5 Gy	22.1 Gy	7.3 Gy	25.7 Gy	11.9 Gy
	PTV Sein G	Approuvée	100.0 / 100.0	962.8 cm³	37.8 Gy	56.6 Gy	50.1 Gy	50.0 Gy	50.0 Gy	0.7 Gy
	POUMON D	Approuvée	100.0 / 100.1	1173.4 cm³	0.0 Gy	32.9 Gy	0.5 Gy	0.0 Gy	0.0 Gy	1.6 Gy
	POUMON G	Approuvée	100.0 / 100.1	894.3 cm³	0.0 Gy	55.3 Gy	10.2 Gy	0.0 Gy	3.2 Gy	14.0 Gy
	SEIN D	Approuvée	100.0 / 100.0	875.9 cm³	0.0 Gy	0.4 Gy	0.0 Gy	0.0 Gy	0.0 Gy	0.0 Gy
→	COEUR	Approuvée	100.0 / 100.0	527.2 cm³	0.0 Gy	51.0 Gy	2.8 Gy	0.0 Gy	0.0 Gy	7.3 Gy
	CORONAIRE G	Approuvée	100.0 / 104.4	1.1 cm³	0.0 Gy	18.2 Gy	4.4 Gy	0.0 Gy	3.8 Gy	4.0 Gy

Thank you for your attention

« Dans la vie,
rien n'est à craindre,
tout est à comprendre. »

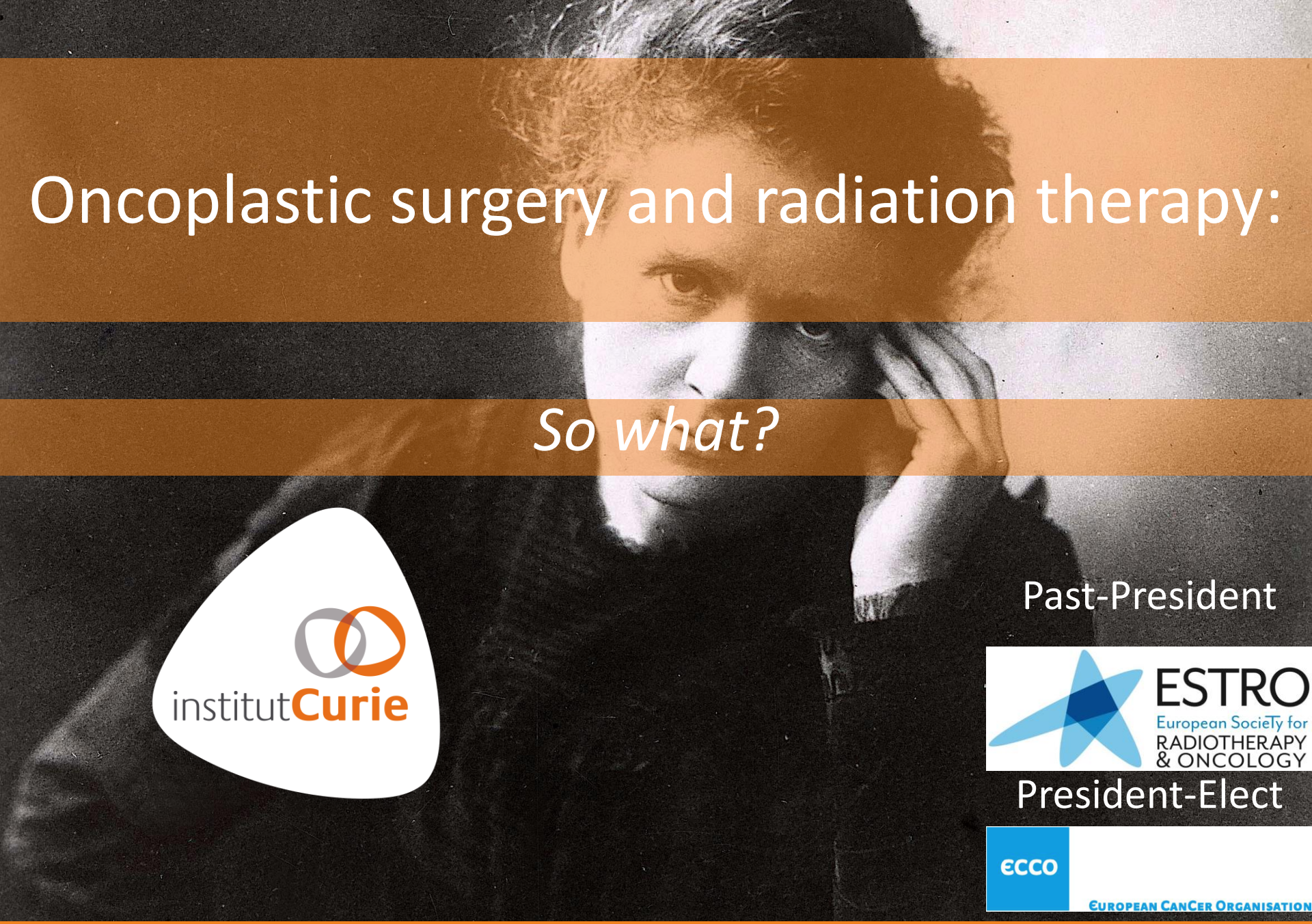
Marie Curie

carfree.fr

youlia.kirova@curie.fr

Oncoplastic surgery and radiation therapy:

So what?



institutCurie

Past-President

ESTRO
European Society for
RADIOTHERAPY
& ONCOLOGY

President-Elect

ECCO
EUROPEAN CANCER ORGANISATION

I have no conflict of interest.

Oncoplastic surgery and radiation therapy

1. Background
2. CTV boost/APBI delineation
3. Outcome
4. RT considerations
5. Examples
6. Conclusions

Oncoplastic surgery: background

Who should not undergo breast conservation?

Risk factors:

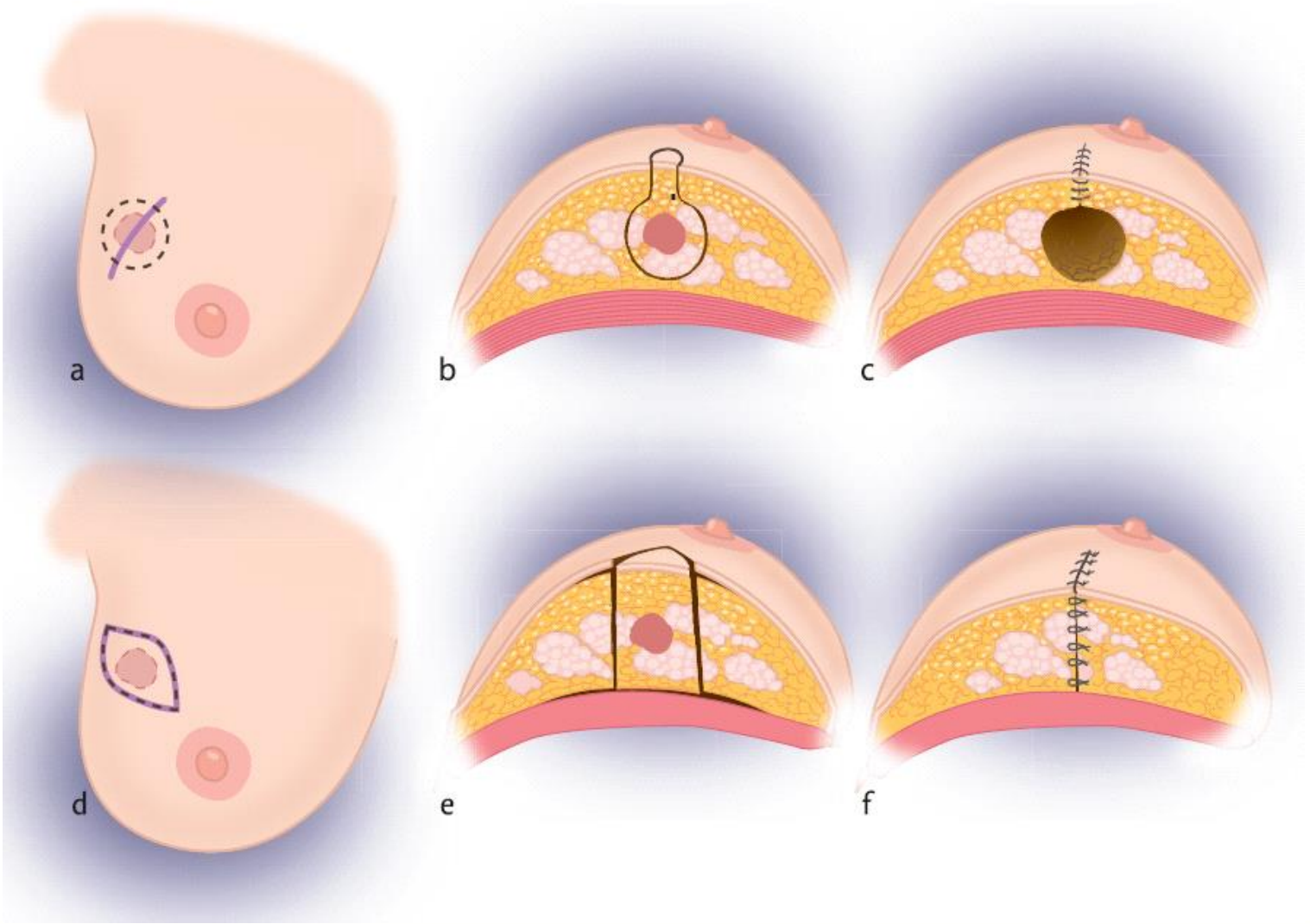
- > focally incomplete margins: x2
- < 35 years: x 2 *(yes, but: see later)*
- no radiotherapy: x 3-6

In larger cancers ➔ PST to be considered.
Oncoplastic procedures to be available.

Finally: remains an individual decision

Nijenhuis MV, Rutgers EJ. Breast. 2013;22 Suppl 2:S110-4.

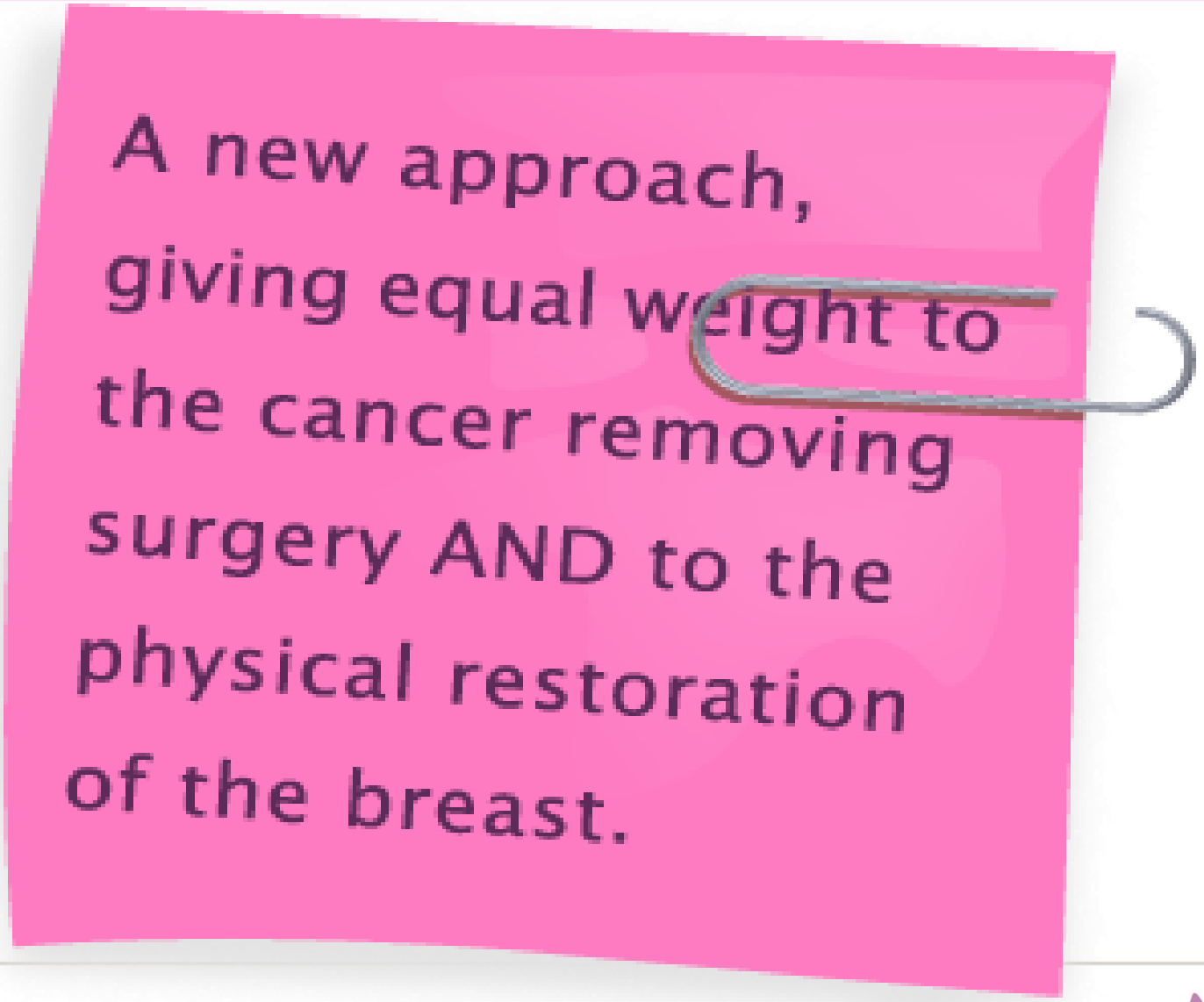
Oncoplastic surgery: background



Menke et al, NTVG 2007

ESTRO School

Oncoplastic surgery: background



http://www.drjayharness.com

ESTRO School

Oncoplastic surgery and radiation therapy

1. Background

2. CTV boost/APBI delineation

3. Outcome

4. RT considerations

5. Examples

6. Conclusions

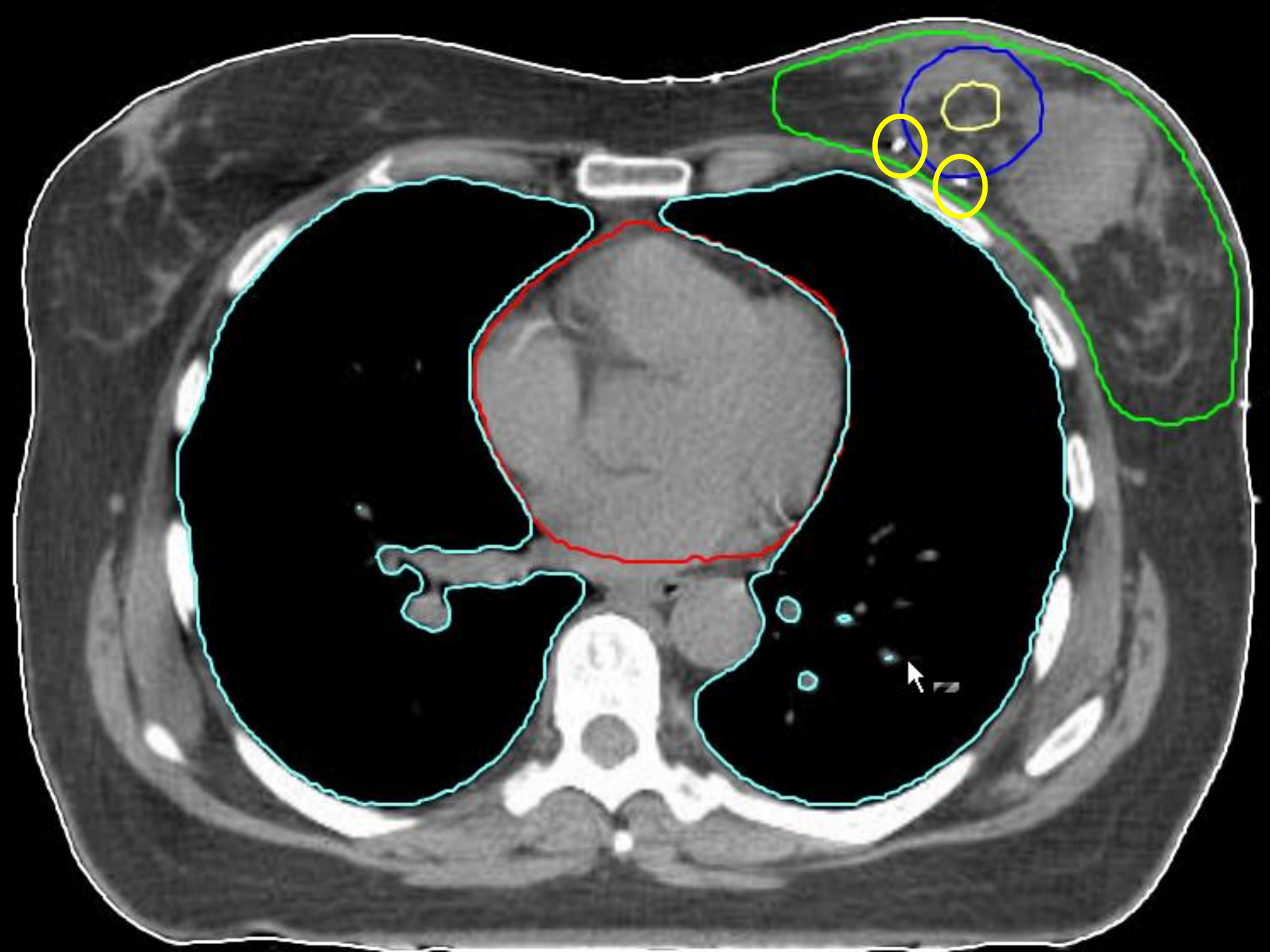
Oncoplastic surgery: CTV boost/APBI delineation

Target volume delineation of primary tumour bed:

- by dedicated RTO's
- no clips
- no seroma

van Mourik AM et al. Radiother Oncol. 2010;94:286-91.

ESTRO School



Oncoplastic surgery: CTV boost/APBI delineation

Oncoplastic surgery and radiation therapy

1. Background
2. CTV boost/APBI delineation
3. Outcome
4. RT considerations
5. Examples
6. Conclusions

Oncoplastic surgery & RT: outcome

RT & oncoplastic surgery: localisation of the tumour bed

N = 25 patients (26 tumours) incl 11 with ≥ 4 clips

Results:

≥ 4 clips: - 8 (73%) tumour bed beyond original quadrant

- 3 (27%) CTV = 2-3 separated regions

Conclusion:

➔Tumour bed can be more extensive and relocated

➔Clips after resection and before oncoplastic reconstruction

Pezner RD et al. Am J Clin Oncol 2013;36:535-9.

ESTRO School

Oncoplastic surgery & RT: outcome

Table 2 Outcomes of breast-conserving reconstruction according to the type of technique used.

	Volume replacement	Volume displacement
Total number of studies	7[a]	11[b]
Total number of patients	189	433
Median follow-up (months)	24–53	21–54
Local recurrence (%)	0–5	0–7
Cosmetic failure (%)	0–9	0–18

[a]References: 19,23,32,41–44. [b]References: 2,14,25,32,33,45–50.

Rainsbury RM. Nat Clin Pract Oncol 2007;4:657–664

ESTRO School

Oncoplastic surgery & RT: outcome

Influence of SIB, hypofractionation and oncoplastic surgery on cosmetic outcome in breast cancer

J. Lansu, A. Voogd, S. Hol, P. Poortmans, M. Essers

Breast conserving therapy changes in Tilburg region:

2005: Sequential → simultaneous boost

2009: Conventional → hypofractionation

2010: Conventional → oncoplastic surgery

Lansu JT, et al. Eur J Surg Oncol. 2015;41:1411-6.

Oncoplastic surgery & RT: outcome

Conventional fractionation and sequential boost (58 patients)

- Breast: 25 x 2 Gy
- Boost: 8 x 2 Gy
- TOTAL: 66 Gy

Conventional fractionation and SIB (42 patients)

- Breast: 28 x 1,81 Gy
- Boost: 28 x 0,49 Gy
- TOTAL: 64,40 Gy

Hypofractionation and SIB (24 patients)

- Breast: 21 x 2,17 Gy
- Boost: 21 x 0,49 Gy
- TOTAL: 55,86 Gy

Lansu JT, et al. Eur J Surg Oncol. 2015;41:1411-6.

Oncoplastic surgery & RT: outcome

Oncoplastic surgery

- Remodeling the breast by mobilizing tissue in addition to resection of the tumor
- Volume replacement or *displacement*
- Equal weight to cancer removing surgery and physical restoration of the breast
  - *Classic tumorectomy (91 patients)*
  - *Oncoplastic surgery (33 patients)*

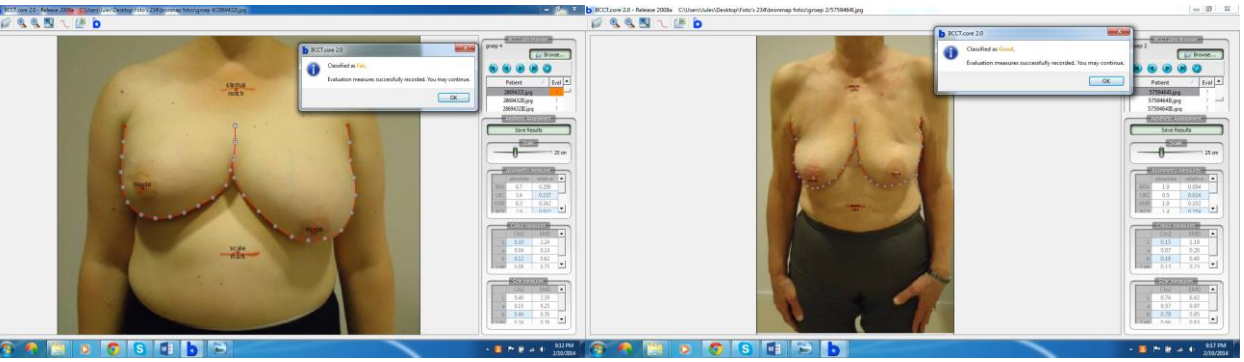
Lansu JT, et al. Eur J Surg Oncol. 2015;41:1411-6.

Oncoplastic surgery & RT: outcome

instituut Verbeeten

Materials and methods (1)

- Digital pictures one year after BCS
- *BCCT. Core*
  - *Breast Cancer Conservation Treatment. cosmetic results*
  - *Software tool developed in Porto*
    - *Asymmetry, colour differences, scar visibility*
  - *Higher score → worse cosmetic outcome*



http://medicalresearch.inescporto.pt/breastresearch/index.php/BCCT.core

ESTRO School

Oncoplastic surgery & RT: outcome

Materials and methods (2)

- Cosmetic self evaluation Young Boost Trial
  - *size*
  - *shape*
  - *skin colour*
  - *massiveness of breast*
  - *nipple position*
  - *general appearance*
  - *overall satisfaction*
  - *visibility of surgical scar*

Oncoplastic surgery & RT: outcome

Materials and methods (3)

- EORTC-QLQ-C 30
  - *5 functional scales: physical, functioning, cognitive, emotional, social*
  - *3 symptom scales: fatigue, pain, nausea*
  - *global health status*
- EORTC-QLQ-BR23:
  - *23 supplementary QOL questions for breast cancer patients to be used with QLQ C30 (functioning and symptoms)*

Lansu JT, et al. Eur J Surg Oncol. 2015;41:1411-6.

Oncoplastic surgery & RT: outcome

Results sequential vs simultaneous boost

Score (SD)	**CR arm (n=58)**	**SIB arm (n=27)**	**P value**
BCCT.core score	1.7 (0.7)	1.9 (0.6)	0.376
YBT	23.3 (14.3)	27.6 (21.1)	0.292
C30Funct. scale	89.7 (11.8)	87.1 (18.7)	0.94
C30Symptom scale	10.6 (8.1)	16.5 (12.9)	0.025
C30QOL	84.1 (16.0)	82.0 (17.4)	0.632
BR23Funct.scale	71.6 (11.2)	82.9 (13.0)	0.001
BR23Symptom scale	11.9 (11.3)	13.7 (9.3)	0.471

The patients in this comparison had conventional surgery

Lansu JT, et al. Eur J Surg Oncol. 2015;41:1411-6.

Results conventional vs hypofractionation

Score (SD)	**Conventional fractioning (n=15)**	**Hypofractionation (n=18)**	**P value**
BCCT.core score	2.45 (0.52)	2.25 (0.62)	0.4
YBT	26.94 (15.03)	29.2 (18.5)	0.71
C30Functioning scale	75.90 (22.57)	86.91 (22.18)	0.19
C30Symptom scale	17.31 (10.22)	17.97 (12.85)	0.88
C30QOL	63.45 (35.77	75.00 (22.24)	0.29
BR23Functioningscale	70.19 (16.30)	84.72 (16.91)	0.02
BR23Symptom scale	20.51 (12.35)	17.06 (13.30)	0.46

The patients in this comparison had oncoplastic surgery

Lansu JT, et al. Eur J Surg Oncol. 2015;41:1411-6.

Oncoplastic surgery & RT: outcome

Results traditional vs oncoplastic surgery

Score (SD)	**Traditional surgery (n=27)**	**Oncoplastic surgery (n=18)**	**P value**
BCCT.core score	1.83 (0.76)	2.40 (0.52)	0.01
YBT	28.11 (20.55)	26.48 (15.48)	0.8
C30Functioning scale	87.44 (18.20)	77.78 (22.48)	0.19
C30Symptom scale	16.25 (12.59)	16.67 (10.39)	0.92
C30QOL	82.08 (16.94)	62.5 (37.18)	0.05
BR23Functioning scale	82.14 (13.19)	71.18 (16.62)	0.04
BR23Symptom scale	13.42 (9.71)	18.85 (11.28)	0.15

Lansu JT, et al. Eur J Surg Oncol. 2015;41:1411-6.

Oncoplastic surgery & RT: outcome

Conclusions:

Cosmetic outcome:

- Hypofractionation ≥ conventional fractionation
- Conventional surgery > oncoplastic surgery

Quality of life:

- Hypofractionation > conventional fractionation
- Conventional surgery > oncoplastic surgery

Lansu JT, et al. Eur J Surg Oncol. 2015;41:1411-6.

Oncoplastic surgery & RT: outcome

Conclusions:

Further research:

- To be validated in other patient series
- Similar approach to be used in new prospective studies

Oncoplastic surgery and radiation therapy

1. Background
2. CTV boost/APBI delineation
3. Outcome
4. RT considerations
5. Examples
6. Conclusions

Oncoplastic surgery & RT: RT considerations

We did improve BCT rates!

Boost only when needed!

Update 2016: 1.8% LRR at 9 years !!!

Poortmans P, et al. Breast. 2017;31:295-302.

ESTRO School

Oncoplastic surgery & RT: RT considerations

APBI: who might be the candidate

- ✓ Participants of clinical trial
- ✓ Low risk patients (ASTRO) if:
  - ✓ The burden (5→3→1 week)
  - ner recurrence risk
  - xperienced team
  - require adjuvant systemic treatment (also with WBI)

→ oncoplastic surgery = complicating factor!

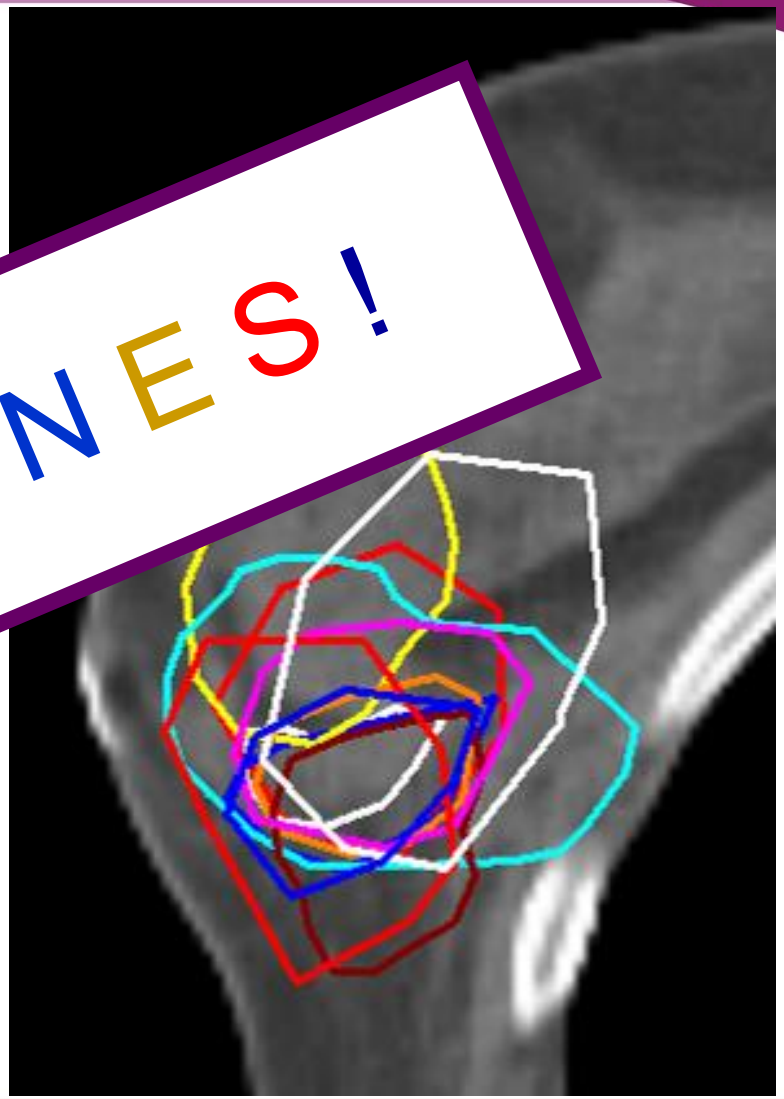
ESTRO School

Oncoplastic surgery & RT: RT considerations

Target volume delineation of primary tumour bed:

- by dedica
- m
- no

GUIDELINES!

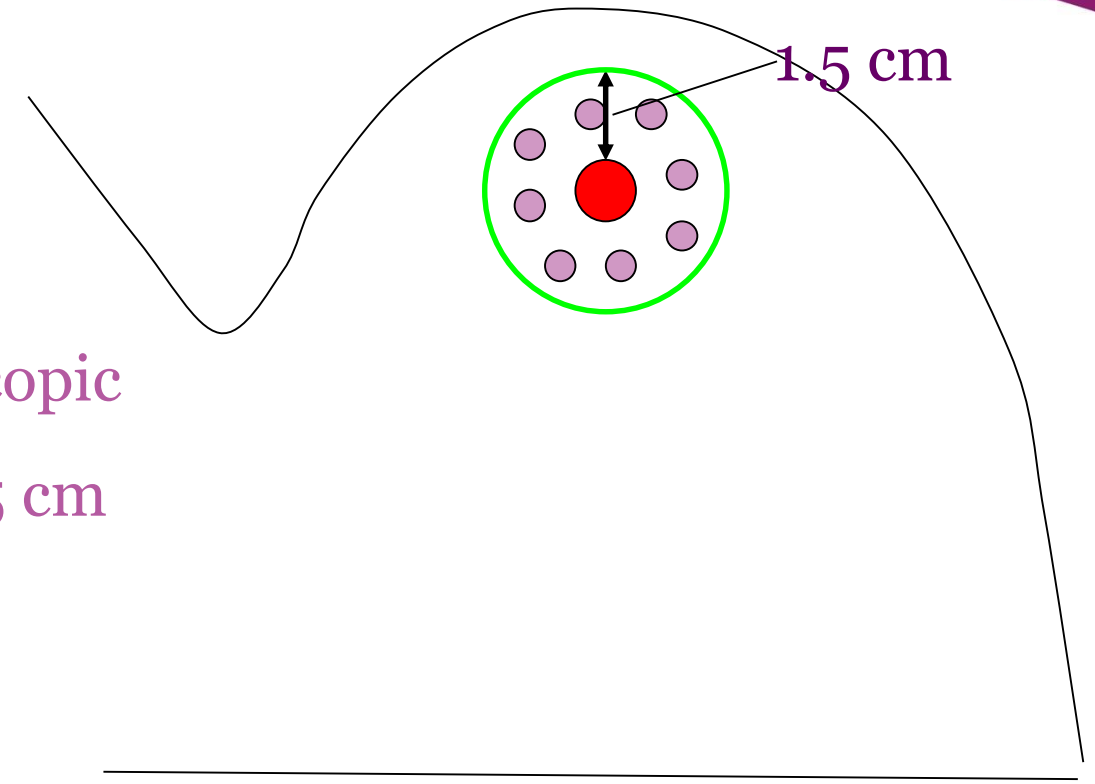


van Mourik AM et al. Radiother Oncol. 2010;94:286-91.

ESTRO School

Oncoplastic surgery & RT: RT considerations

- Tumor
- Micr. extension
- Region with microscopic extension, within 1.5 cm of primary tumor

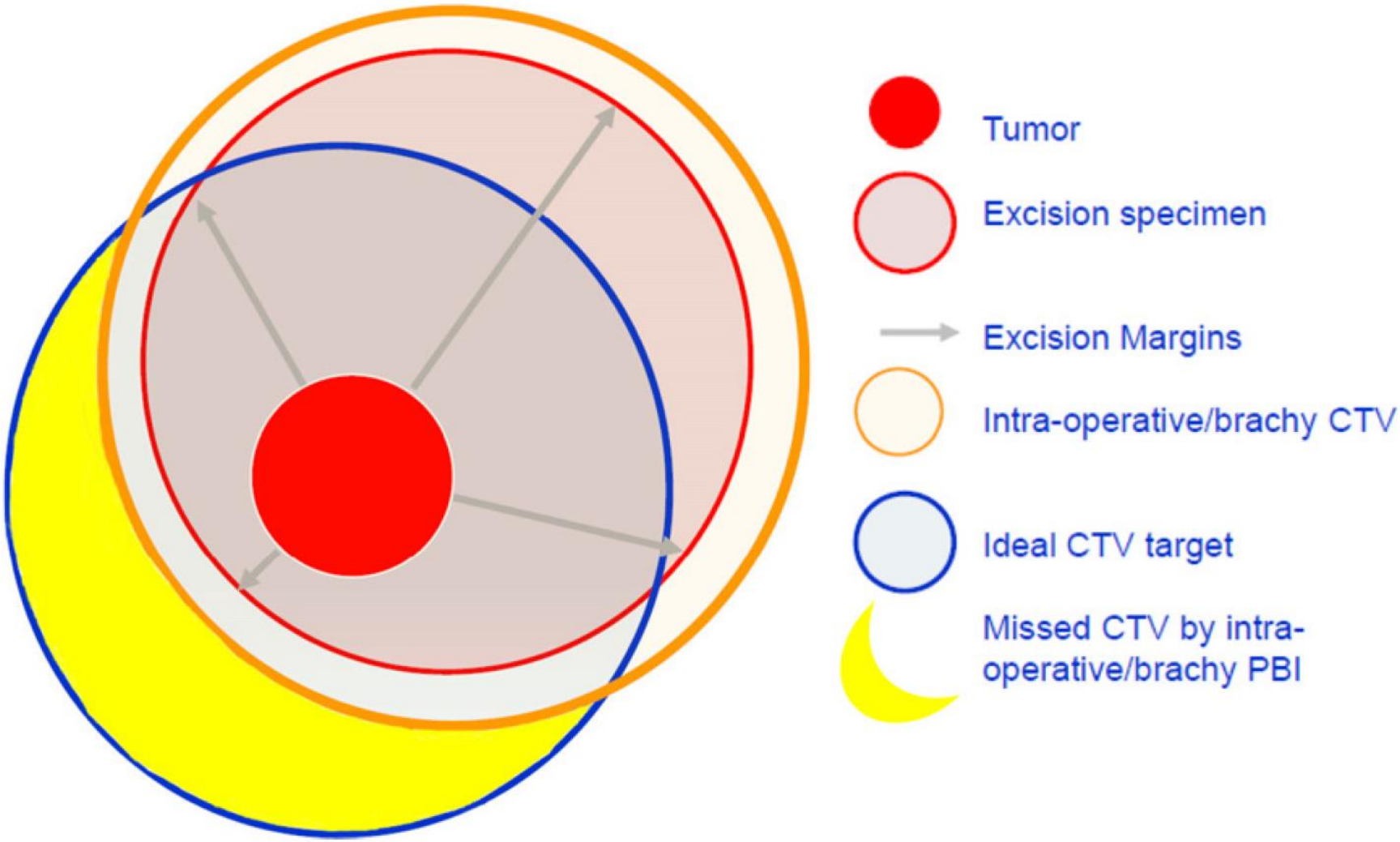


- ✓ Radio-opaque wire (scar & palpable area) to guide.
- ✓ Pre-operative localisation of tumour (phys ex, imaging).
- ✓ Features visible on the planning CT: clips, surgical effects, …

Boersma L et al. Radiother Oncol. 2012;103:178-82.

ESTRO School

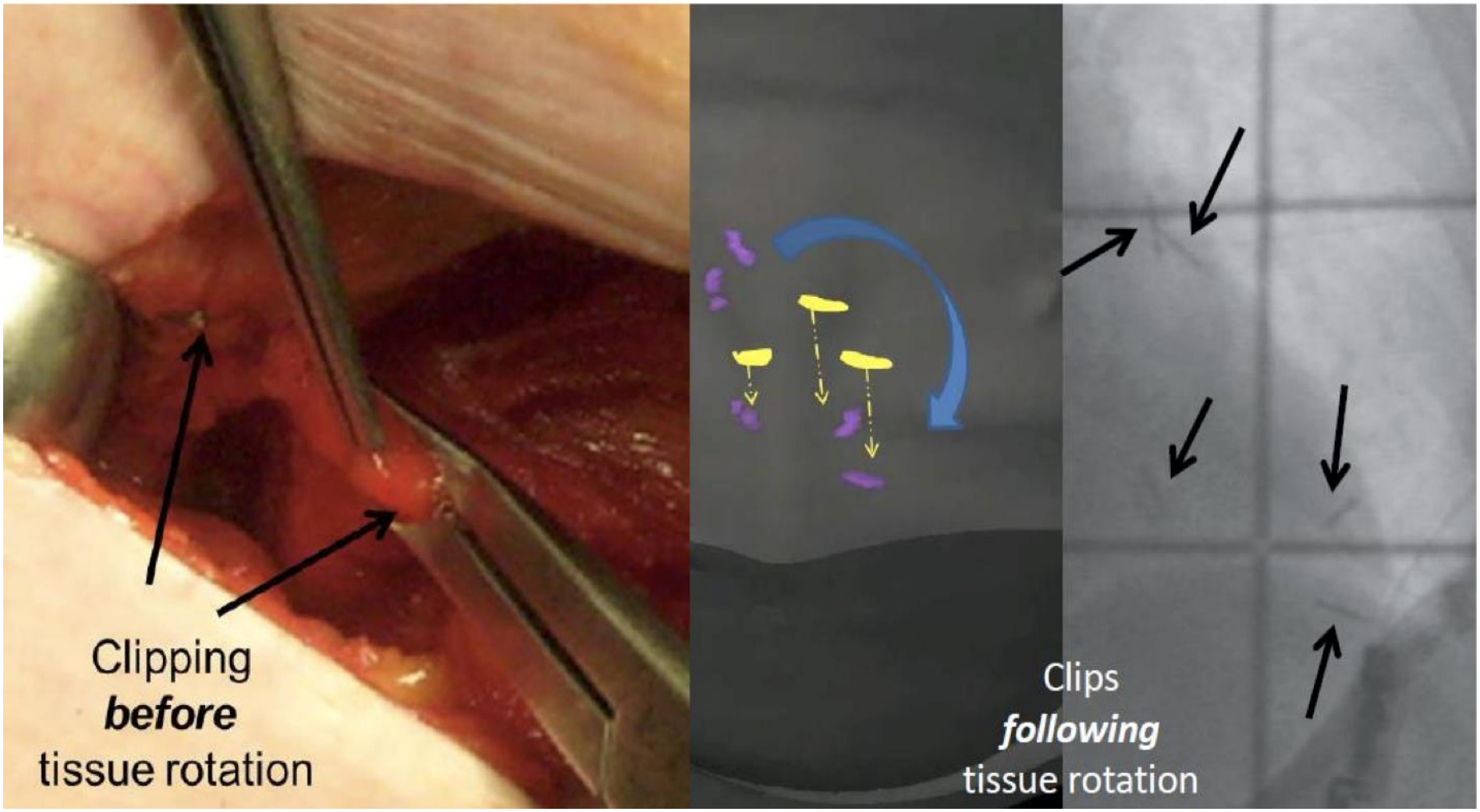
Oncoplastic surgery & RT: RT considerations



Bartelink H, et al. Radiother Oncol. 2012;104:139-42.

ESTRO School

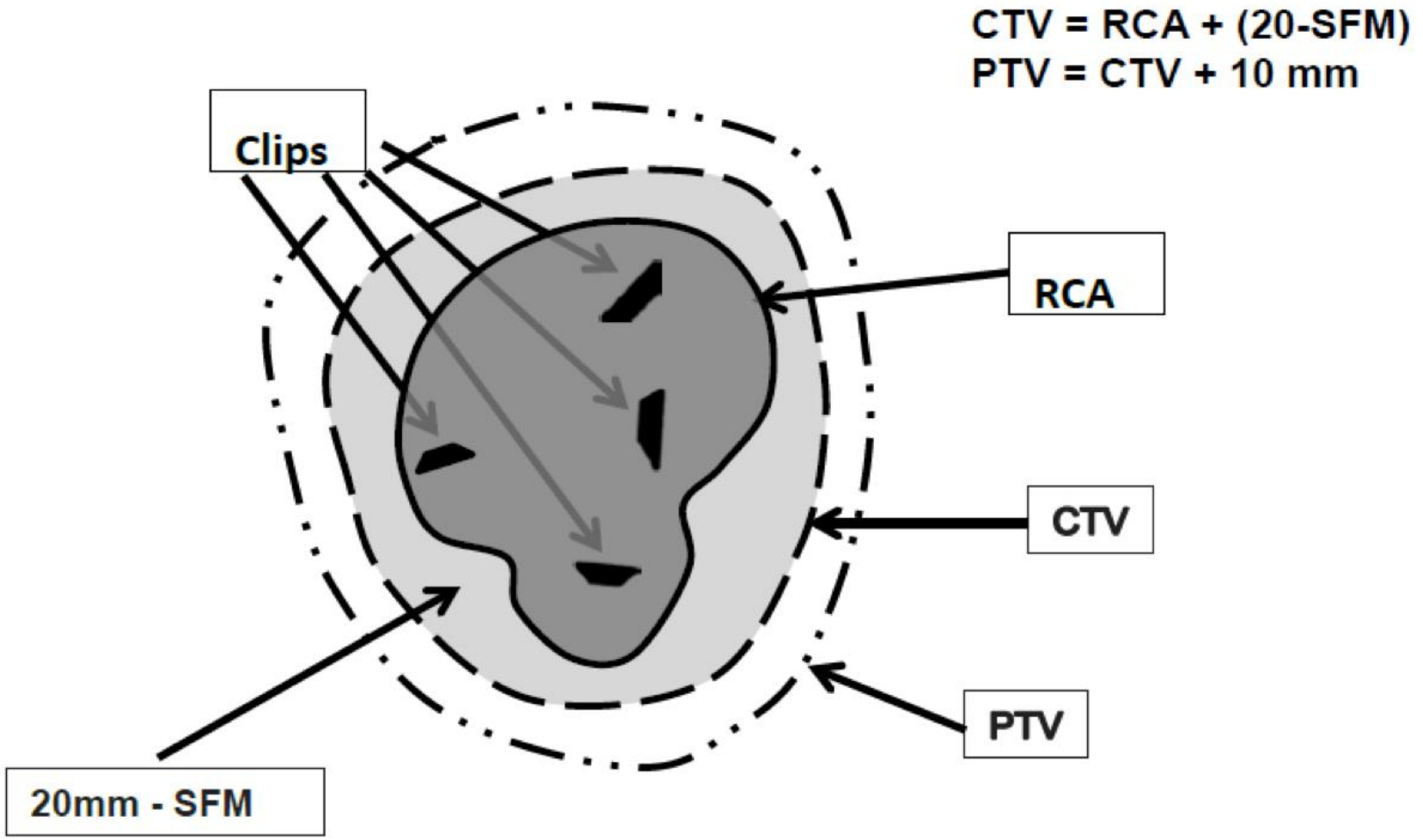
Oncoplastic surgery & RT: RT considerations



Strnad V, et al, Radiother Oncol. 2015;115:342-8.
Major T, et al, Radiother Oncol. 2016;118:199-204.

ESTRO School

Oncoplastic surgery & RT: RT considerations



RCA: relevant clipped area SFM: Smallest surgical Free Margin

Strnad V, et al, Radiother Oncol. 2015;115:342-8.
Major T, et al, Radiother Oncol. 2016;118:199-204.

ESTRO School

Oncoplastic surgery and radiation therapy

1. Background
2. CTV boost/APBI delineation
3. Outcome
4. RT considerations
5. Examples
6. Conclusions

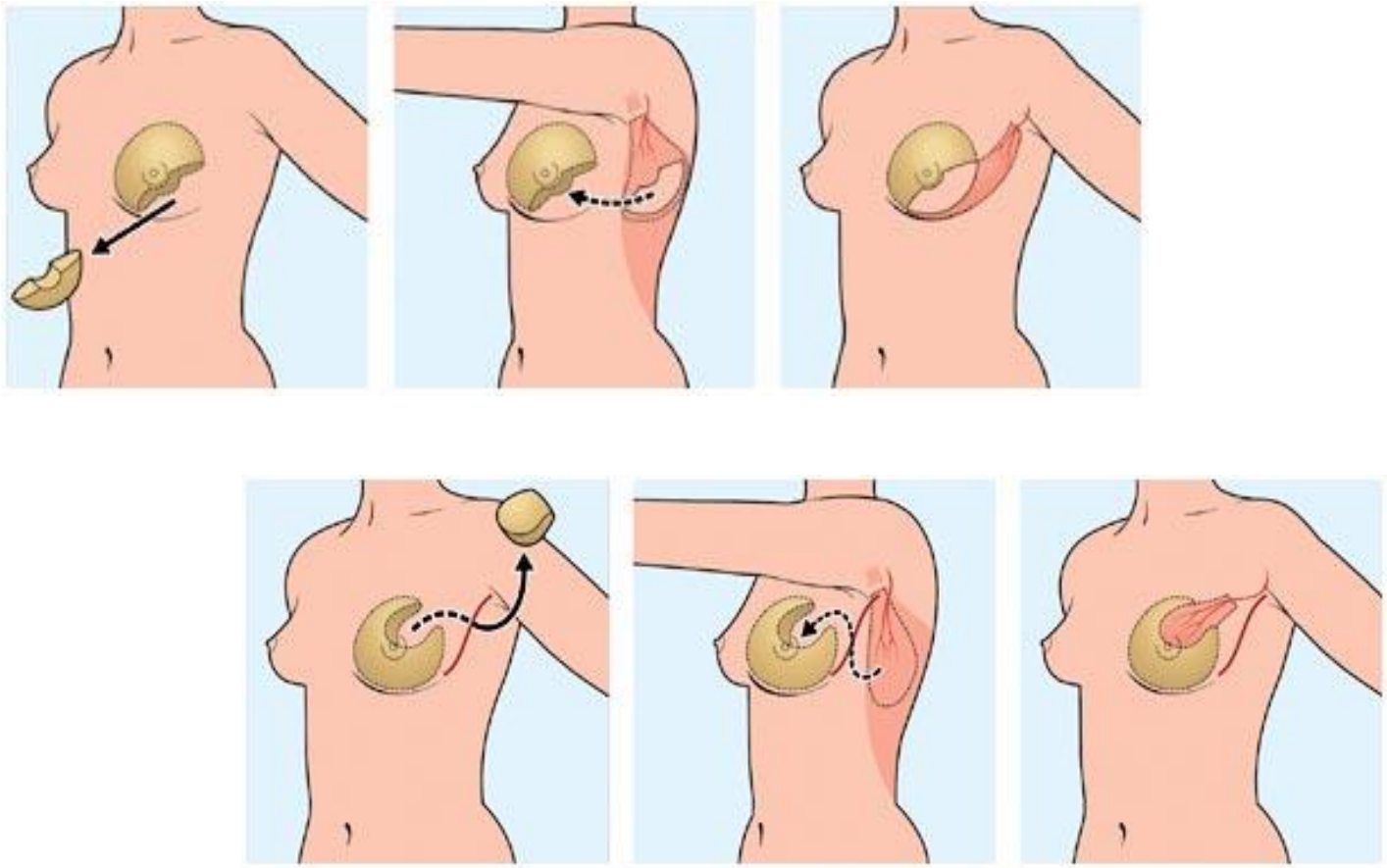
Oncoplastic surgery & RT: examples

Oncoplastic techniques

- Volume replacement
- Volume displacement

Oncoplastic surgery & RT: examples

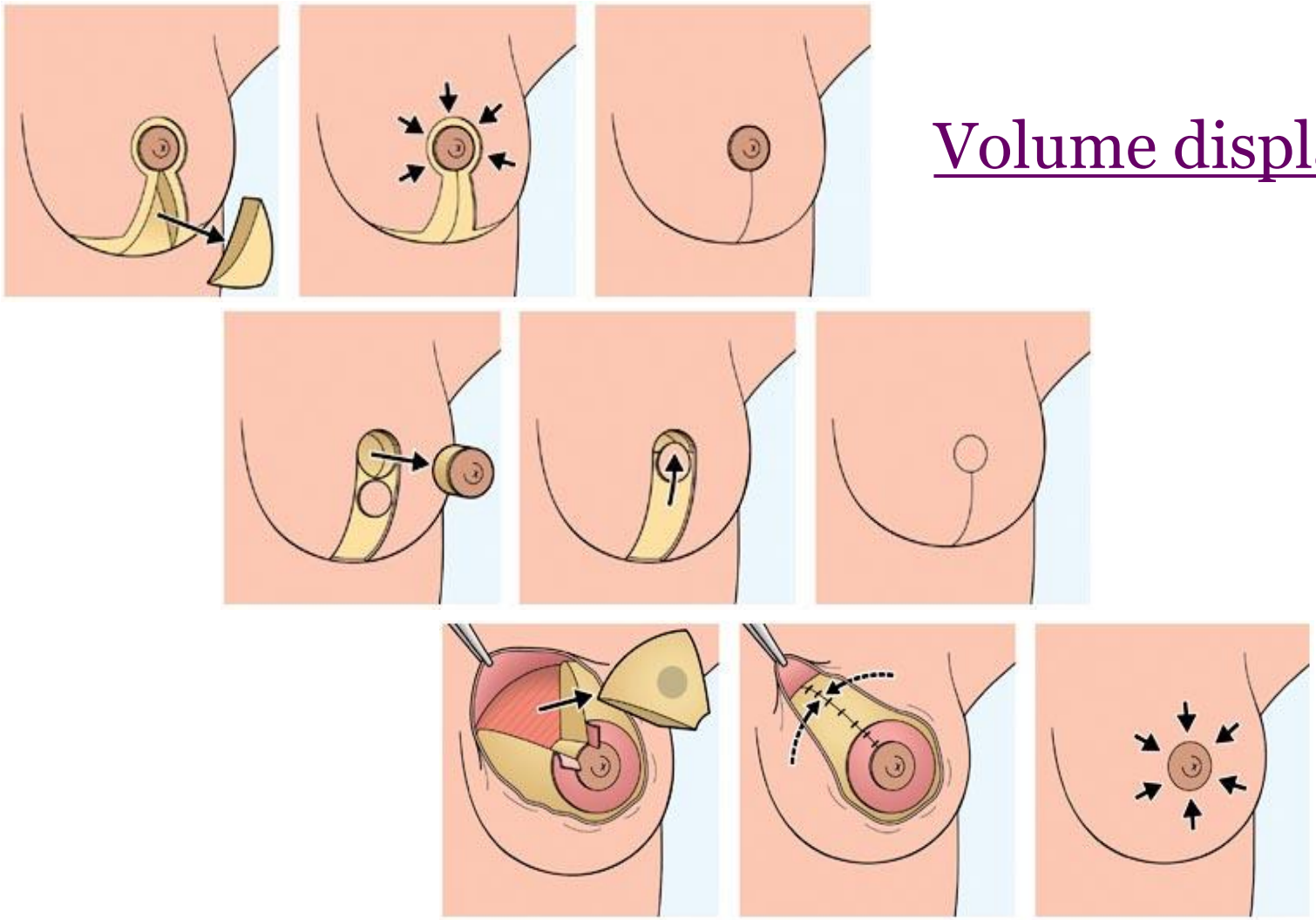
Volume replacement



Rainsbury RM. Nat Clin Pract Oncol 2007;4:657–664

ESTRO School

Oncoplastic surgery & RT: examples



Volume displacement

Rainsbury RM. Nat Clin Pract Oncol 2007;4:657–664

ESTRO School

Oncoplastic surgery & RT: examples

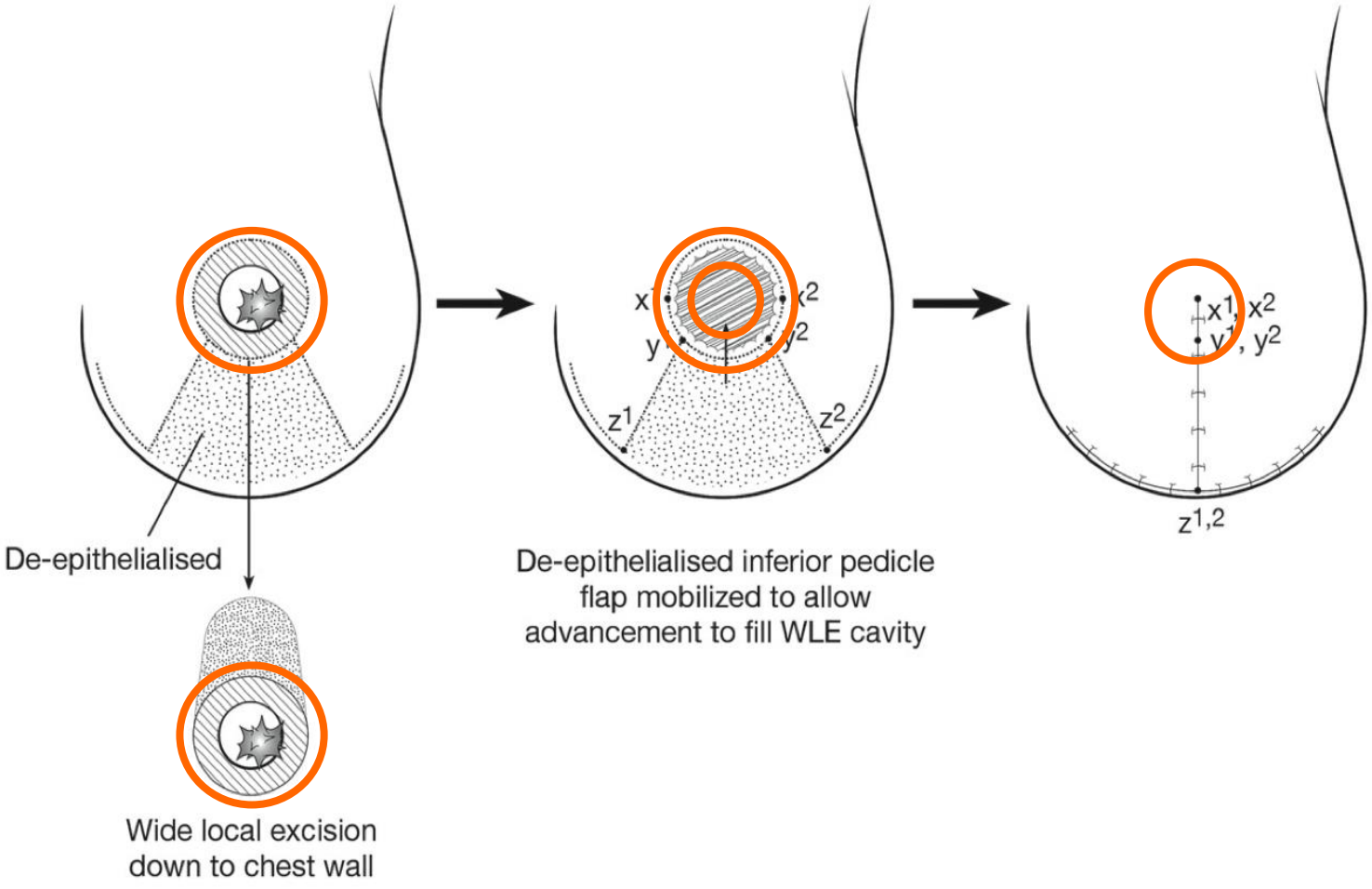


Figure 2. Inferior pedicle based advancement flap.

Iwuchukwu OC et al. Surgical Oncology 2012;21:133-41

ESTRO School

Oncoplastic surgery & RT: examples

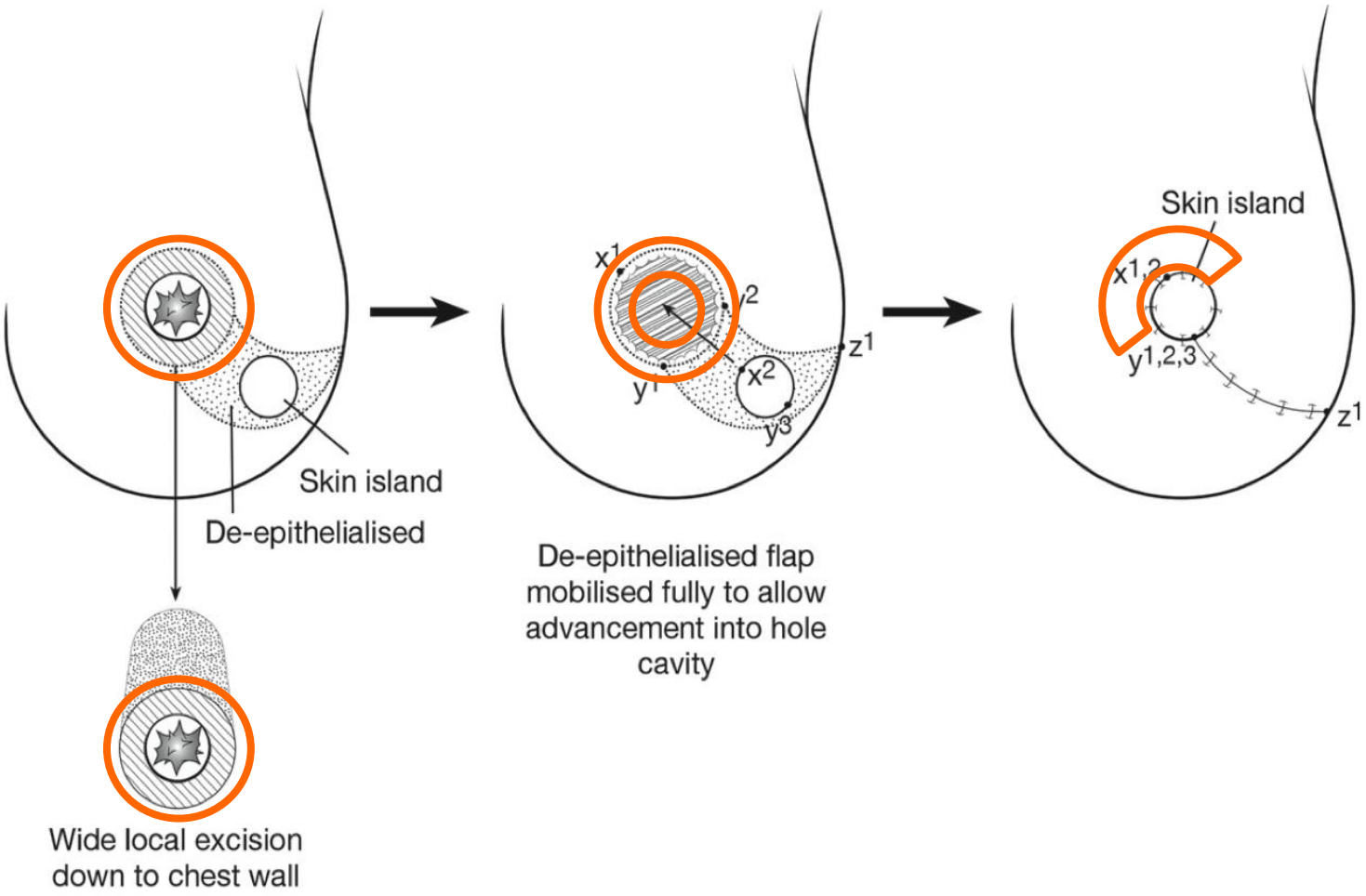


Figure 3. Grissoti flap.

Iwuchukwu OC et al. Surgical Oncology 2012;21:133-41

ESTRO School

Oncoplastic surgery & RT: examples

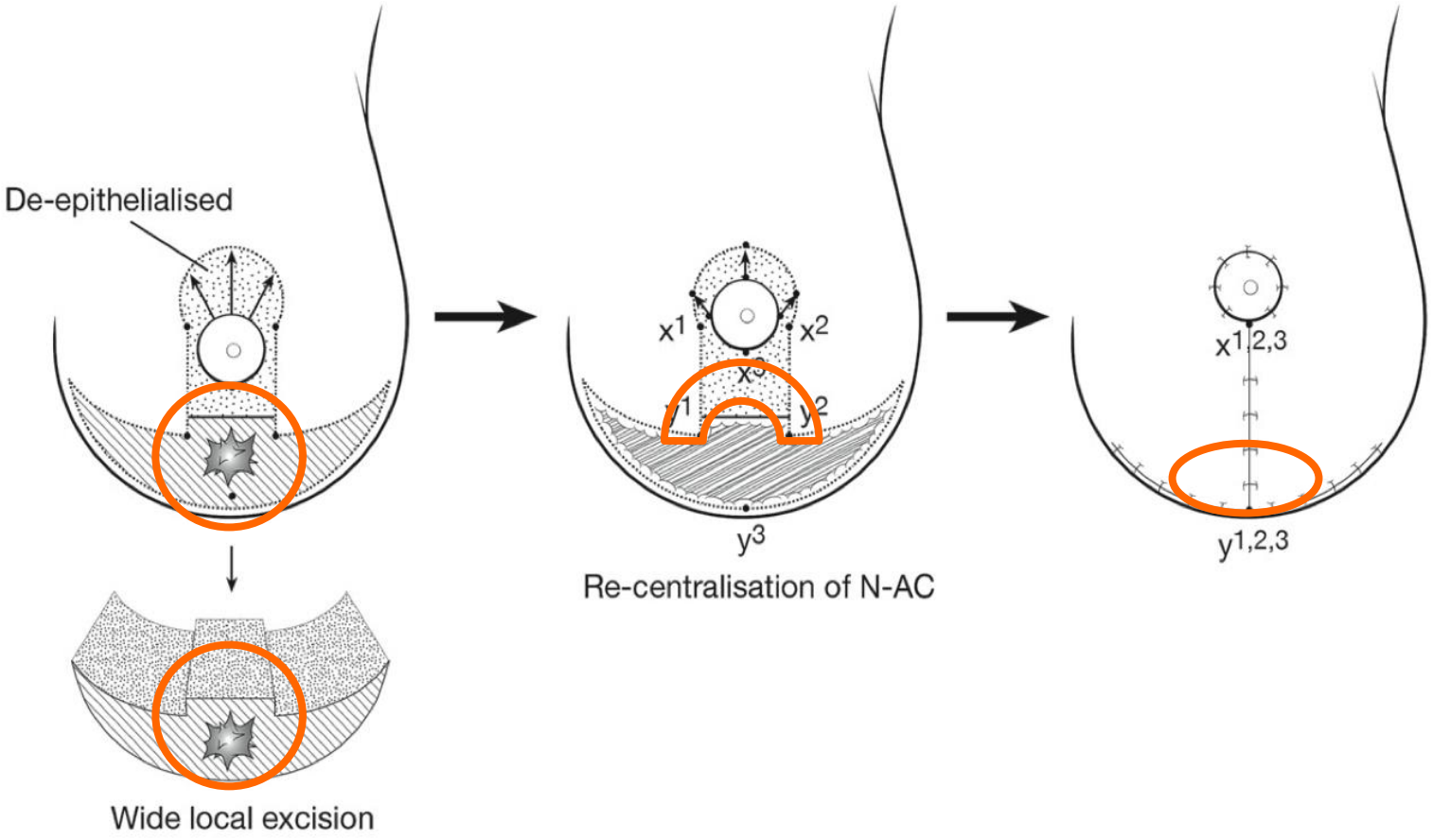


Figure 4. Superior pedicle (Wise pattern).

Iwuchukwu OC et al. Surgical Oncology 2012;21:133-41

ESTRO School

Oncoplastic surgery & RT: examples

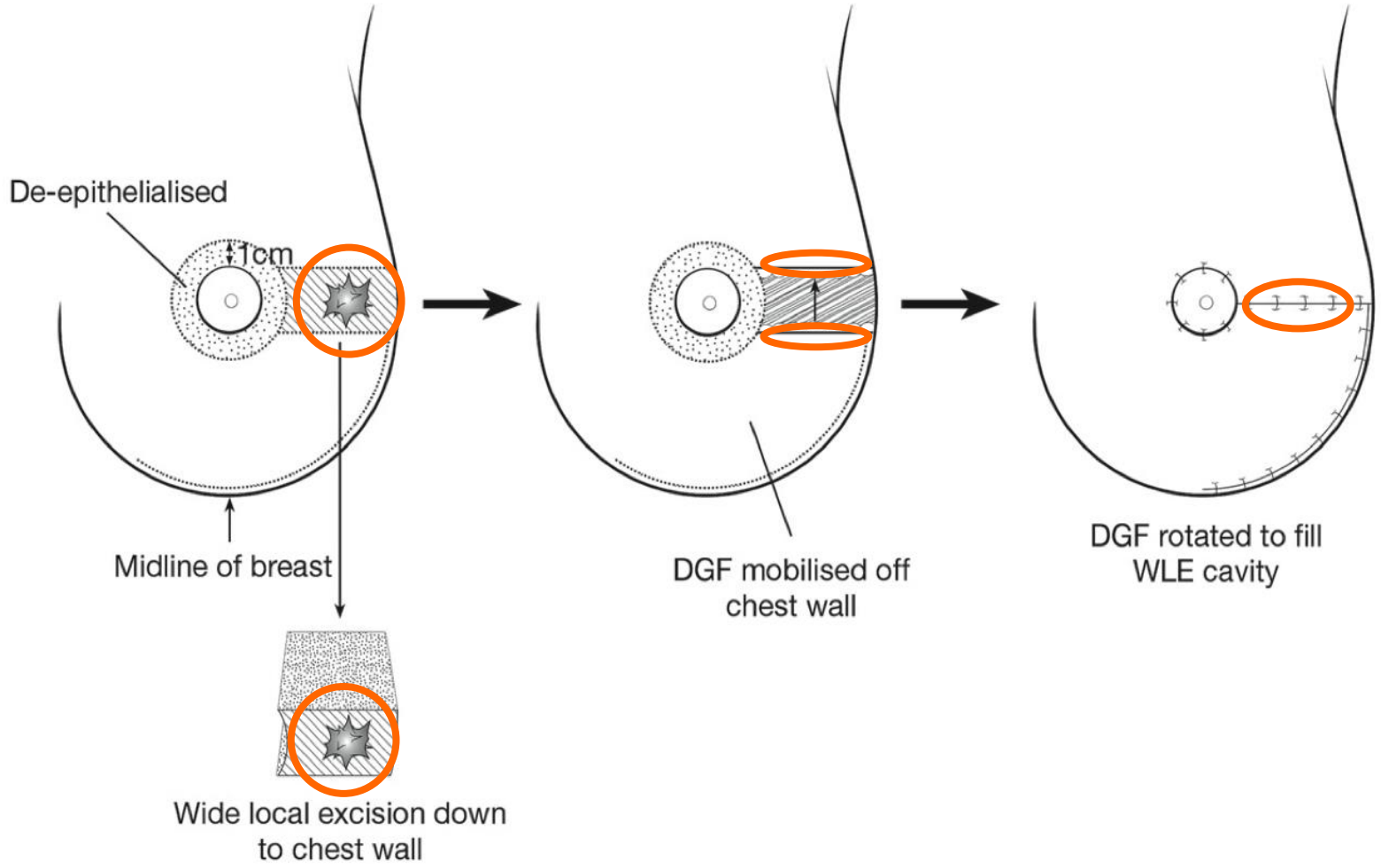


Figure 5. Matrix rotation flap.

Iwuchukwu OC et al. Surgical Oncology 2012;21:133-41

ESTRO School

Oncoplastic surgery & RT: examples

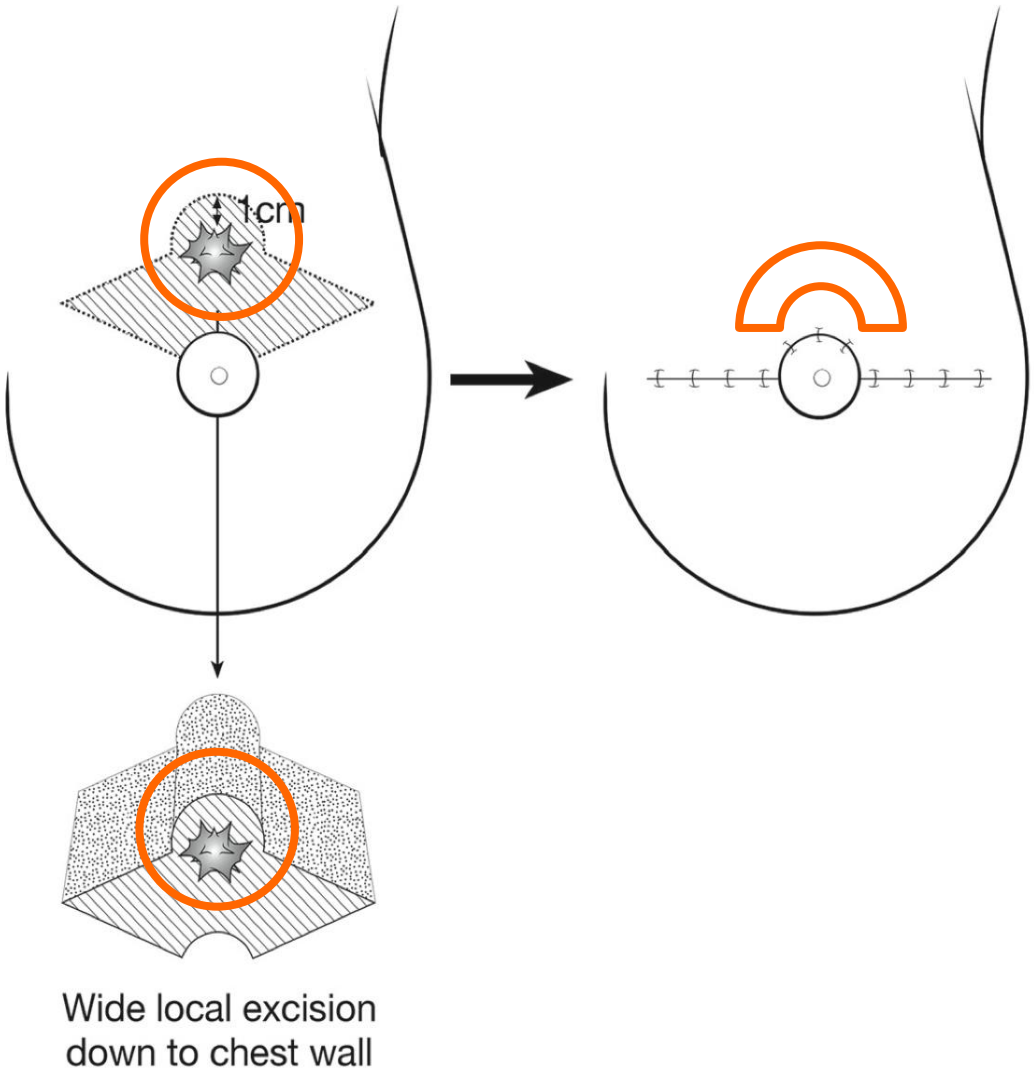


Figure 6. Batwing design.

Iwuchukwu OC et al. Surgical Oncology 2012;21:133-41

ESTRO School

Oncoplastic surgery & RT: examples

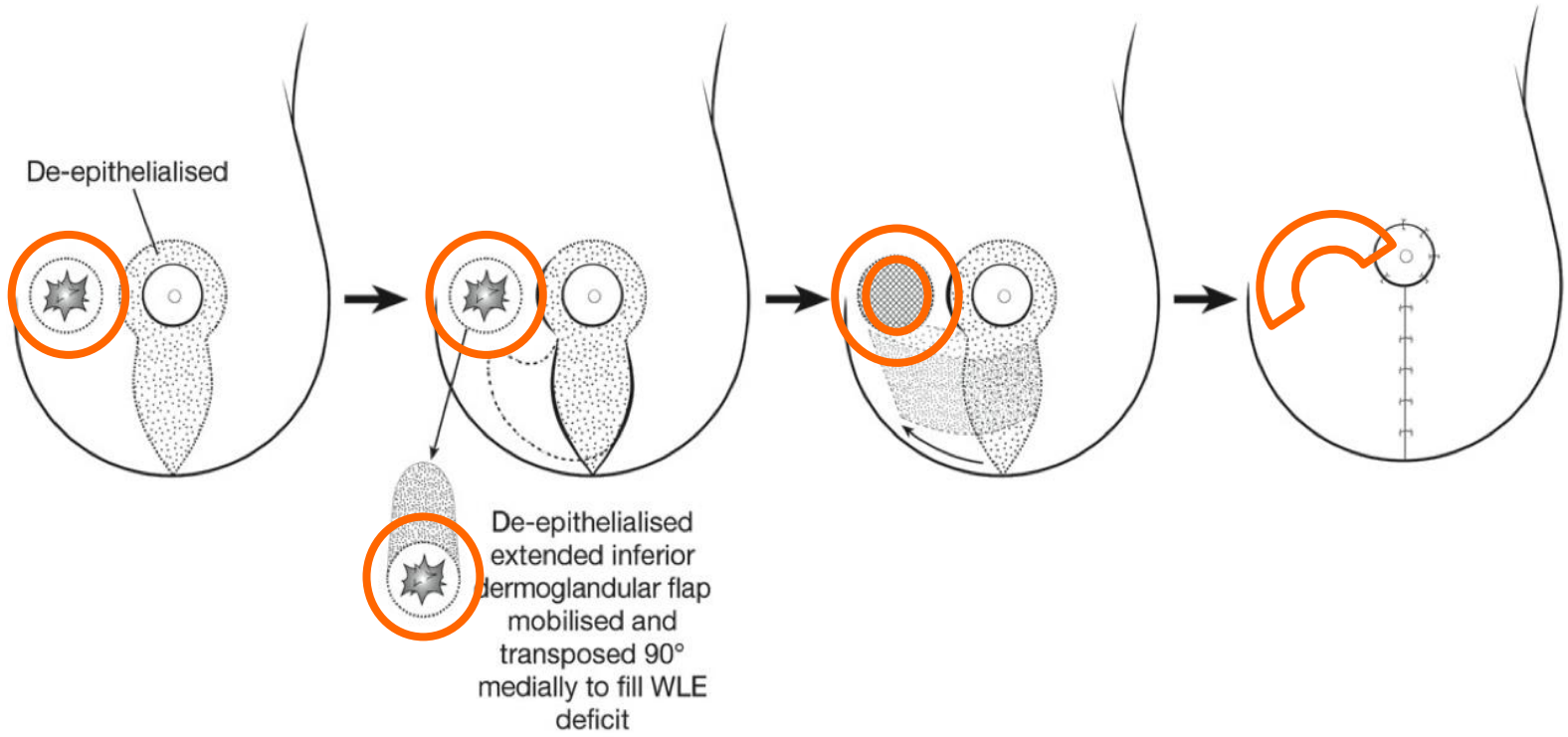
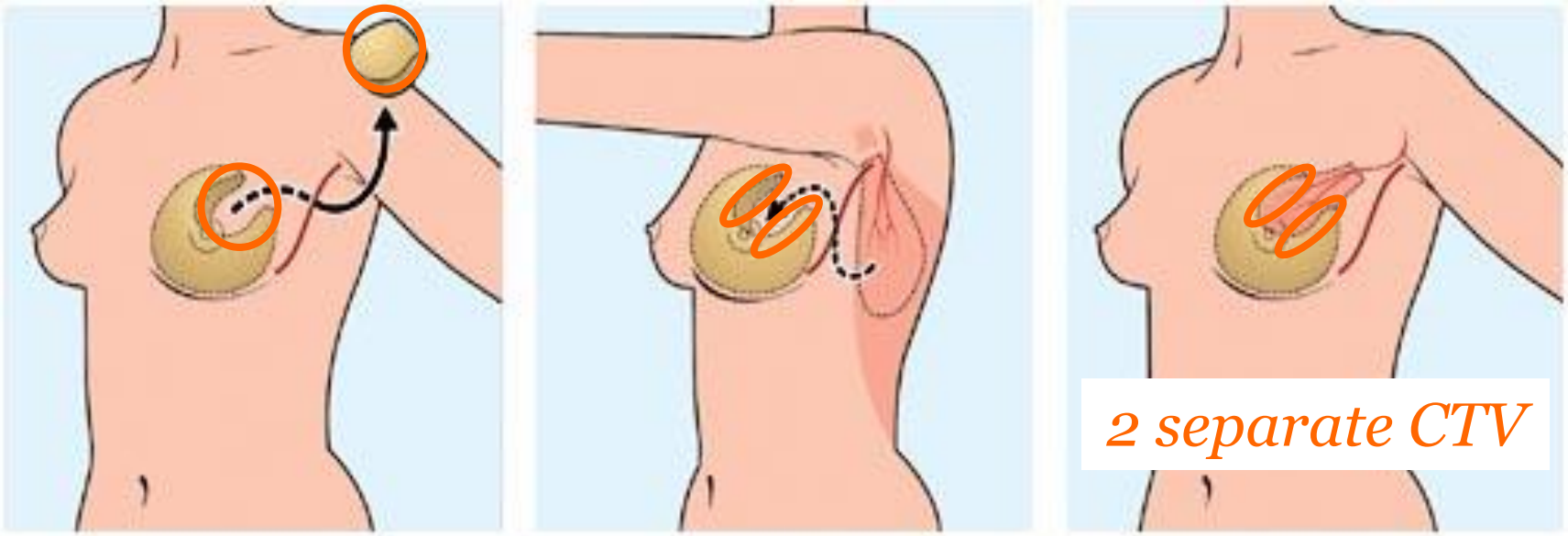


Figure 7. Extended superior pedicle with transposition of the inferior dermo-glandular flap (This can be used for both medial and lateral tumours).

Iwuchukwu OC et al. Surgical Oncology 2012;21:133-41

ESTRO School

Oncoplastic surgery & RT: examples



Rainsbury RM. Nat Clin Pract Oncol 2007;4:657–664

ESTRO School

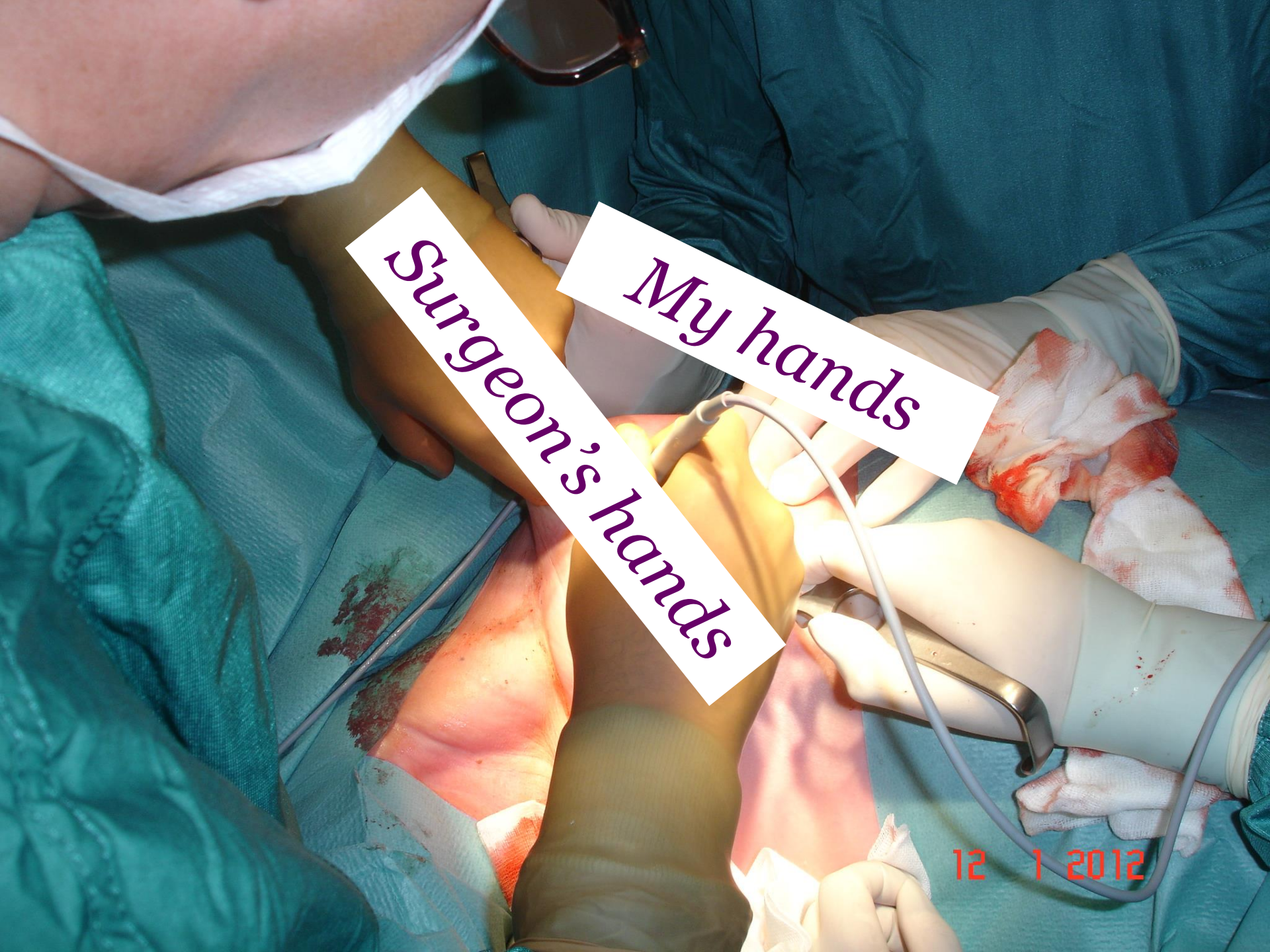
Oncoplastic surgery and radiation therapy

1. Background
2. CTV boost/APBI delineation
3. Outcome
4. RT considerations
5. Examples

6.Conclusions

Oncoplastic surgery & RT: conclusions

- TV delineation = challenge +++
- TV delineation + oncoplastic surgery = (challenge)^2
- Close collaboration surgeons and RO = essential before, during and after surgery
- Discuss use of oncoplastic surgery: tool but not goal!


My hands
Surgeon's hands
12 1 2012

Acknowledgements *(alphabetical)*

- Harry Bartelink
- Liesbeth Boersma
- Birgitte Offersen
- Vratislav Strnad & the GEC-ESTRO team
- Jules Lansu, Marion Essers & Sandra Hol
- George van der Schelling, Ernest Luiten and Margrethe Schlooz, surgeons
- Jack Venselaar and the BVI brachy team
- And many others!

ESTRO School

institutCurie

Late side-effects of systemic therapy

B.Vriens
Medical oncologist
Catharina Hospital Eindhoven
The Netherlands
ESTRO Breast Cancer 2017

ESTRO School

Why study late side effects of systemic therapy

Survival of patients treated for breast cancer

One woman out of 8 is affected with breast cancer during her life.

Breast cancer is often diagnosed at an early stage.

The number of different medical treatments is increasing.

The results of treatments are overall good and overall survival increases

Several millions women in the world are breast cancer survivors * and their number increases dramatically

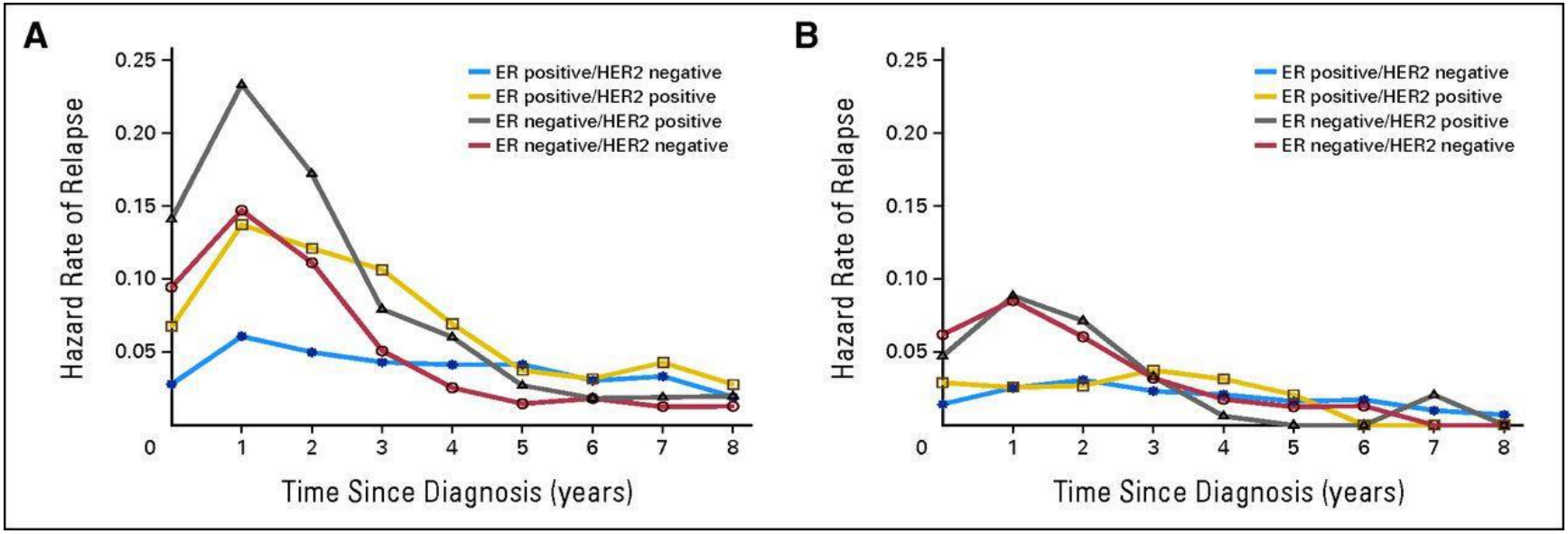
Long term complications, even rare, are becoming a public health issue

*Rowland 2000

Hazard rate of relapse according to tumor subtype and year of diagnosis (breast)

1986 to 1992

2004 to 2008

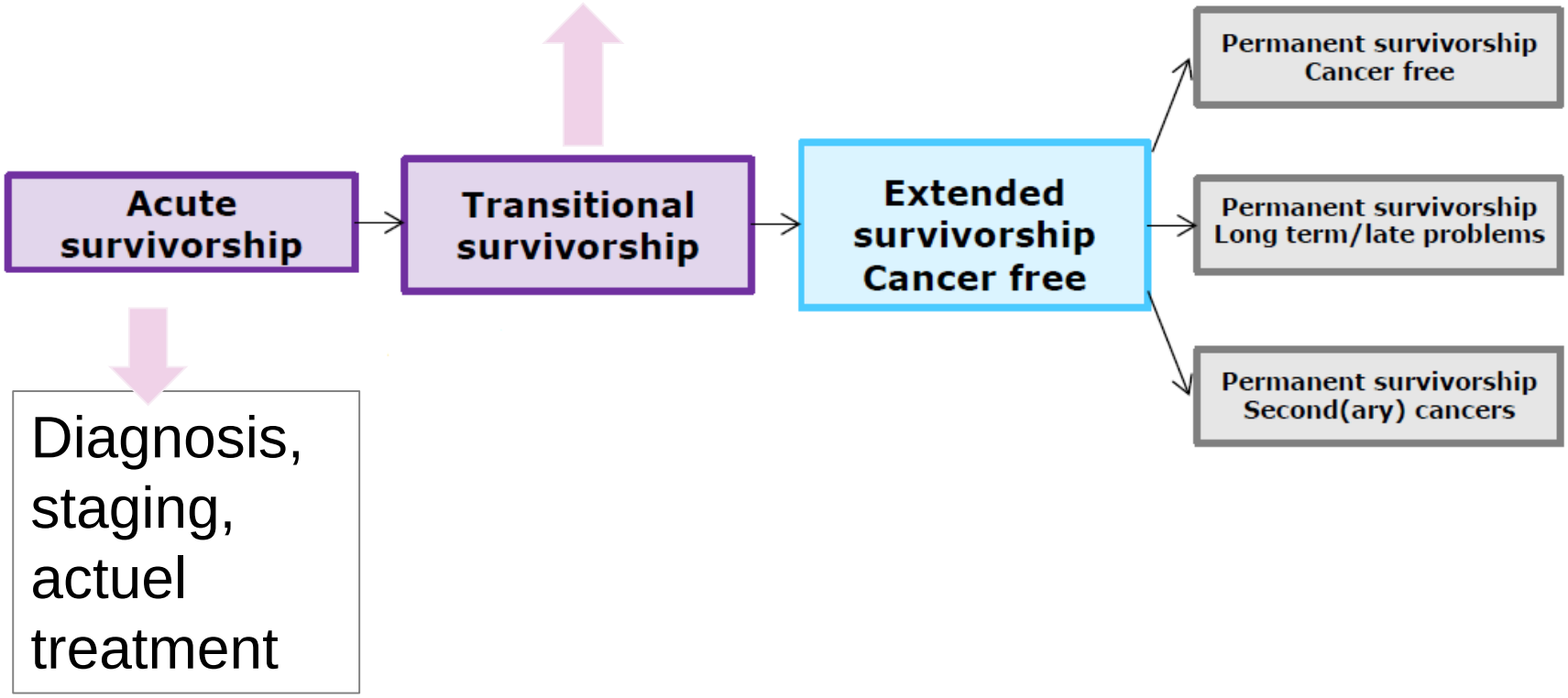


Cossetti R J et al. JCO
J Clin Oncol 2015:33(1):65-73

ESTRO School

Cancersurvivorship is described in several "seasons”

Transition from active treatment to careful observation and the emotional, social, and medical adaptations that occur



Gosain R, et al Cancer J 2013

ESTRO School

Survival of patients treated with breast cancer

More drugs are used simultaneously, sequentially and/or longer duration increasing the risk of side effects

- Increased knowledge of biology BC
- Increased treatment options

The medical oncologist is well aware of short term side effects but not of long term side effects. Long term complications are not sufficient studied in clinical trials.

There is a lack of definition and standardization of methods to study late complications

Side effects endocrine therapy

Side effects can negatively affect quality of life and have been shown to lead to treatment discontinuation.

Short and longterm side effects tamoxifen

Most commonly reported symptoms

Menopausal symptoms

- hot flushes/night sweats
- gynecologic complications/vaginal dryness
- Depression

Range from mild to severe, at times significantly affecting quality of life.

Rare but serious toxicities

- increased risks of endometrial cancer and thromboembolism (VTE).

Short and long term side effects aromatase inhibitor

Most commonly reported symptoms

Menopausal symptoms

- Musculoskeletal symptoms (AIMSS)
  - Arthralgias *incidence is 40%, 15-20% reason for treatment discontinuation*
  - Myalgias, tendonitis, and carpal tunnel syndrome
- Vaginal dryness and decreased libido
- Hot flushes

Osteoporosis *BMD -6 à 7% after 5 year compared to tamoxifen (+1 à 2%)*

Hot flushes

Neuroendocrine mechanisms underlying development of hot flushes remain poorly defined

- estrogen withdrawal at the time of menopause appears to play a role.

Advice

Lifestyle changes

- avoiding triggers
- keeping the core body temperature cool

Extensive research has been conducted to identify nonhormonal medications or nonpharmacologic options for symptom management

Type of Treatment	Treatment Options with Data that Suggest Efficacy
Antidepressant (SSRI/SNRI)	Citalopram 10–20 mg daily
	Desvenlafaxine 100–150 mg daily
	Paroxetine 10 mg daily
	Venlafaxine 37.5–75 mg daily
Anticonvulsant	Gabapentin 900 mg daily
	Pregabalin 75–150 mg daily
Antihypertensive	Clonidine *(possible efficacy)*
Complementary and alternative therapy	Relaxation training *(possible efficacy)*
	Hypnosis *(possible efficacy)*

N. Lynn Henry, ASCO 2014

ESTRO School

Ahrtralgias

- Musculoskeletal symptoms: treatment-limiting
- A number of studies have identified musculoskeletal toxicity as the most frequent cause for treatment discontinuation.
- Standard analgesics are often ineffective
- Research is being conducted to identify effective management options

Antidepressant (SSRI/SNRI)

Hormonal agent

Complementary and alternative therapy

Duloxetine 60 mg *(awaiting phase III results)*

Testosterone *(awaiting phase III results)*

Acupuncture

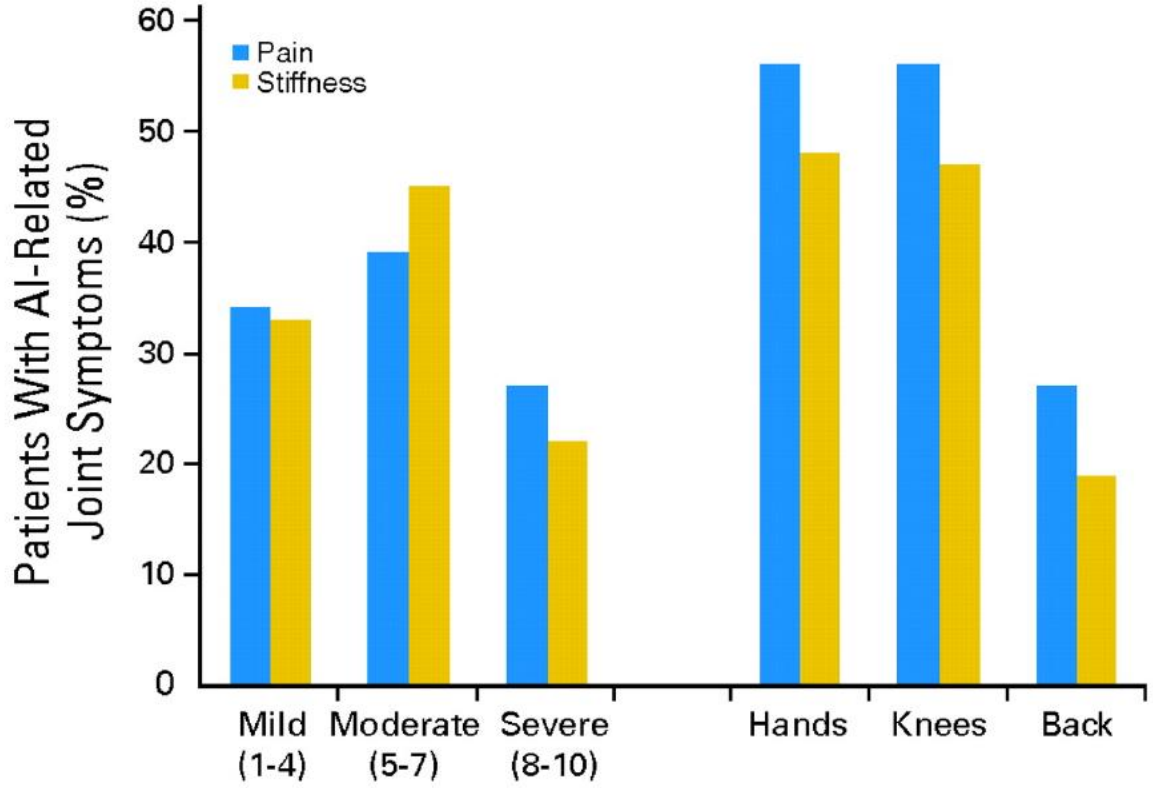
Exercise (HOPE study)

Glucosamine/chondroitin *(phase II)*

Omega 3 fatty acid *(awaiting phase III results)*

Vitamin D 30,000 IU *(prevention)*

AI related joint symptoms

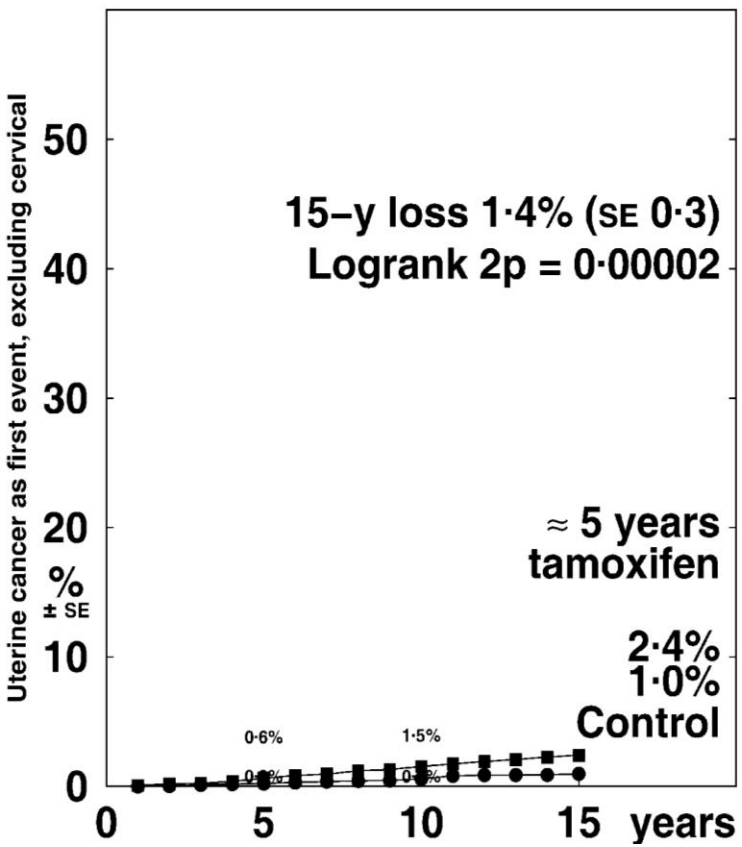


Crew, K. D. et al. J Clin Oncol; 25:3877-3883 2007

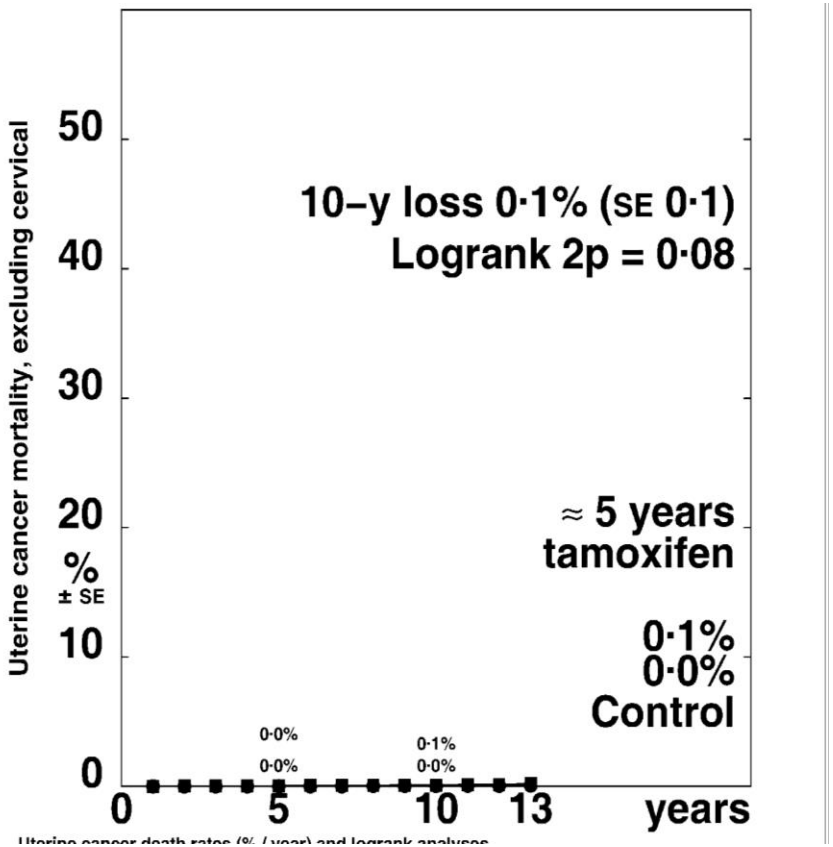
Tamoxifen (5y)vs no Tamoxifen

ER+: Effects on uterine (excluding cervix) cancer

INCIDENCE



DEATH



NB: Strongly age-related with greater absolute risk at older age

Tamoxifen increased uterine cancer incidence
(excluding cervix cancer, **RR 2·40 [0·32], p=0·00002**)

ESTRO School

Tamoxifen (5y) vs no Tamoxifen

Endometrial cancer

Relative risk: 2.40 ($p<0.00002$)

Thrombo-embolic disease/Vascular mortality

Little net effect on overall vascular mortality

Relative risk trombo-embolic disease: 2.50 (p: 0.07)

Overall, the absolute risk of death for both endometrial cancer and vascular complications is 0.2% in ten years (ECCTCG 2005)

EBCTCG, Lancet 2005
EBCTCG, Lancet 2011

TAM 5 years vs TAM 10 years

Thrombo-embolic disease RR: 1.87 (p:0.01)

Endometrial cancer RR: 1.74 (p: 0.0002)

- Incidence of endometrial cancer 3.1% in the tamoxifen arm vs. 1.6% (placebo).
- Endometrial cancer–related mortality was 0.4% in the tamoxifen arm vs. 0.2% in the placebo arm.

When compared to no TAM, the RR of 10 year TAM is between 4 and 5

Davies et al, Lancet 2013

Tamoxifen vs aromatase inhibitors

Differences	OR (AI vs TAM)	Absolute risk ( ) difference	NNH
Cardio vasc disease Hyper cholesterol	1.26 (1.10-1.43) 2.36 (2.15-2.60)	4,2 vs 3,4% (0.8%)	132
Thrombosis	0.55(0.46-0.64)	1,6 vs 2,8% (1.2%)	79
Bone fractures	1.47(1.34-1.61)	7,5 vs 5,2% (2.3%)	46
Endometrial cancer	0.34(0.22-0.53)	0,1 vs 0,5% (0.4%)	258

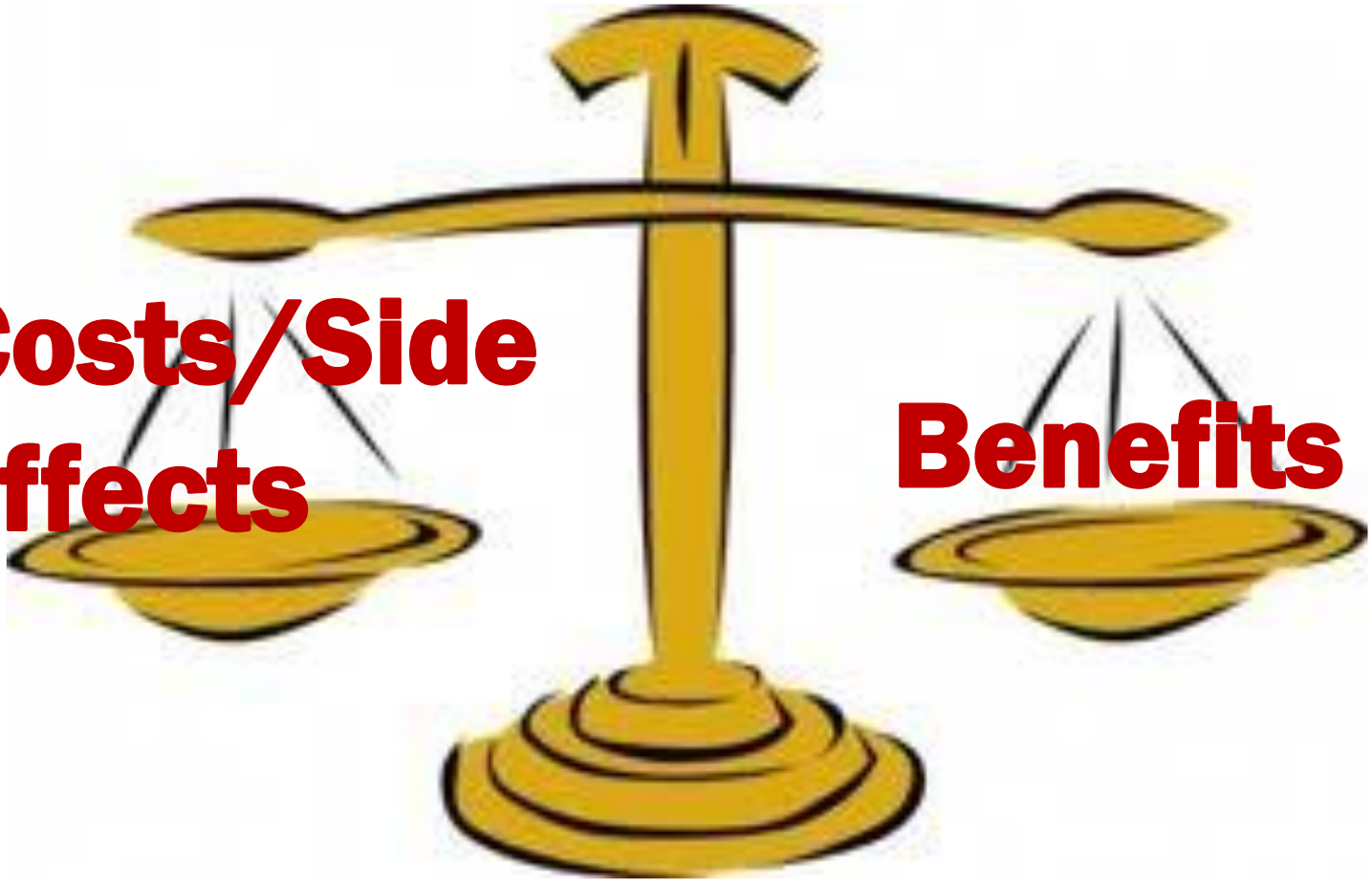
NNH: number needed to harm

Amir et al, JNCI 2011

Side effects chemotherapy

Side effects can negatively affect quality of life and have been shown to lead to treatment discontinuation.

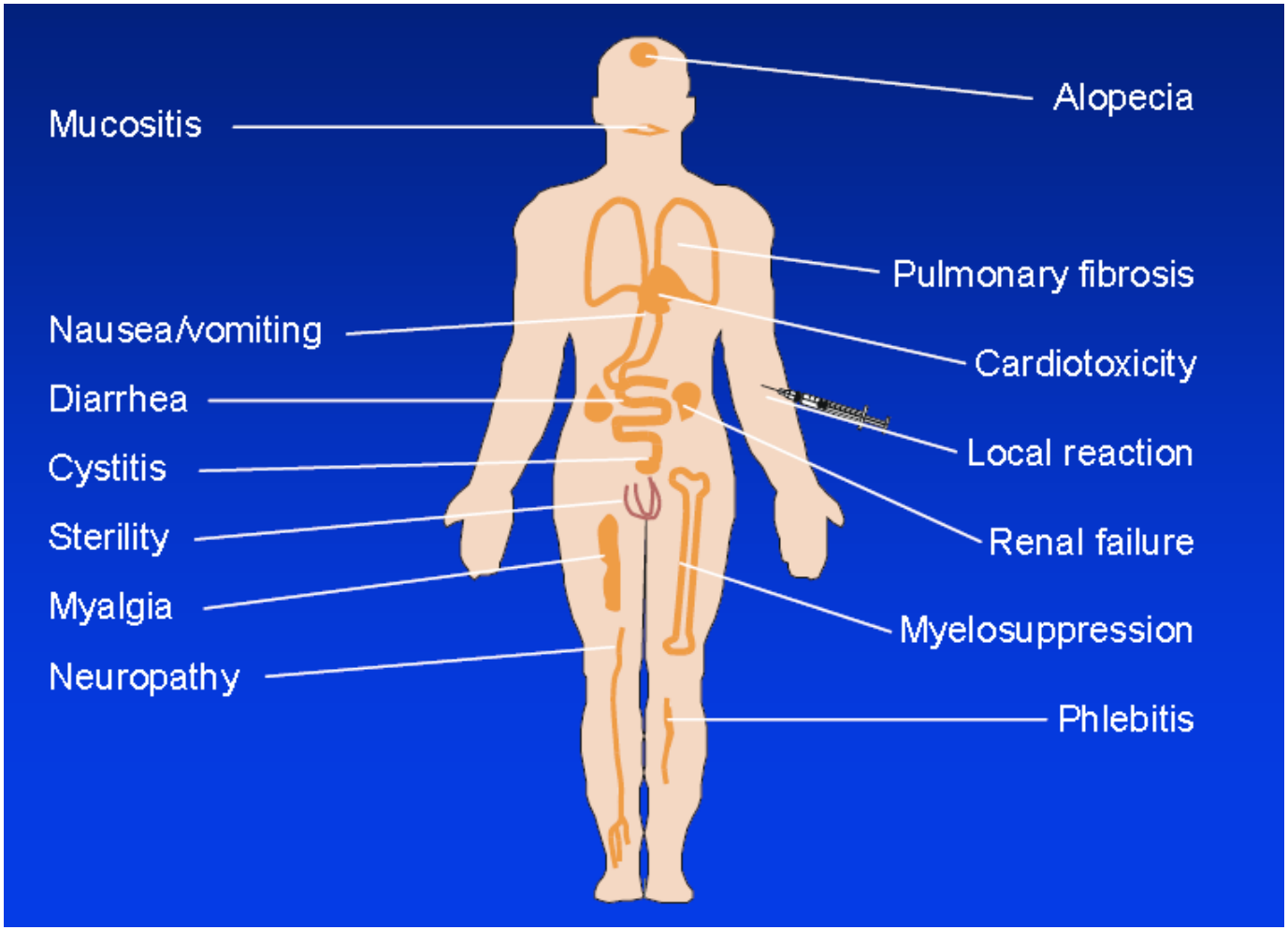
Side effects chemotherapy



Discuss with your patient!

ESTRO School

Systemic therapy and early toxicity



ESTRO School

Myelosuppression

Most agents nadir d7-14, recovery d21-28

Management febrile neutropenia

Febrile neutropenia (FN) is defined as an oral temperature >38.5° C or two consecutive readings of >38.0° C for 2 h and an absolute neutrophil count <0.5 × 10^9/l, or expected to fall below 0.5 × 10^9/l.

Sepsis work up

Antibiotics

PM G-CSF profylaxis

Mucositis

Whole GI tract from mouth to rectum is susceptible

Mild mouth complaints to severe bloody diarrhea

Breakdown of the mucosal barrier is portal of entry for the infectious agents

Treatment

- Keep mouth clean wit saline or other mouthwashes
- Topical or systemic anesthetics
- Antibiotics
- Parenteral nutrition

Pulmonary toxicity – Interstitial pneumonitis

Complaints:

- Pneumonitis/fibrosis, acute pleuritic pain, hypersensitivity
- Pulmonary edema, dyspnea, dry cough, fatigue, fever

- Appears gradually over several weeks
- Differential diagnosis: Infection, pulmonary embolus, cardiogenic edema, lower ejection fraction, progressive tumor

- Pathology: endothelial cell swelling, necrosis of pneumocytes, generalized fibrosis in end-stage

- Treatment: supportive care, steroids

Cardiovascular toxicity - chemotherapy

- Myocardial ischemia and infarction very rarely
- Cardiomyopathy (and pericarditis)
  - Symptoms: non-specific; tachycardia, dyspnea, cardiomegaly, peripheral and pulmonary edema
  - Anthracyclines and high dose chemotherapy may produce fatal cardiomyopathy
  - Acute drop in ejection fraction (hrs-wks), pericardial effusion, chronic heart failure
  - Occurs 30 days – 1 year after treatment
  - No specific therapy; supportive care
    - Diuretics, digitalis, ACE-inhibitors, b-blockers
  - Further use of anthracyclines is contra-indicated

ESTRO School

Cardiovascular toxicity – trastuzumab

- Trastuzumab is associated with cardiomyopathy
- Assesment of LVEF is indicated
- Data combination trastuzumab and radiotherapy
  - NCCTG N9831 trial: No increased cardiotoxicity with concurrent treatment
  - Late effects are not known (FU 3.7 years)
  - Concurrent trastuzumab with radiotherapy (with modern techniques, cardiac sparing) may be continued

Perez, JCO 2011

Long termside effects of – chemotherapy

Chronic fatigue

Ovarian failure

- Vasomotor symptoms
- Bone loss
- Sexual problems

Cardiovascular disease

Cognitive function

Secondary malignancies

Fatigue

‘a distressing, persistend, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion that is not proportional to recent activity and interferes with usual functioning”

Incidence during treatment 70 – 100%

Chronic fatigue

Incidence 0 - 60%*

Possible mechanisms: Hormonal dysfunction, dysregulation cytokines, dysruption biorhythm

Predictors: depression, pain,poor sleep, menopausal symptoms#

More studies are needed to evaluate the burden of this side effect

*Broeckel (1998), Bower(2000), Servaes(2002), Cella(2001)
#Lawrence 2004

Ovarian failure

Depends on drugs, total cumulative dose and age of the patient.

Younger women (less than 40 years) are likely to have transient amenorrhea

Chemotherapy induced ovarian failure leads to a rapid decrease in estradiol levels.

Many patients will be prematurely postmenopausal with vasomotor symptoms, osteoporosis, increase in cholesterol levels and cardiovascular disease, genito urinary symptoms

Patients who resume menstruations will experience a decreased fertility

Sexual problems

Incidence of chemotherapy induced amenorrhea

Table 3. Incidence of chemotherapy induced amenorrhea by regimen reported in breast cancer clinical trials.

References	Regimen	% patients developing amenorrhea
Bines *et al.* (52)	CMF ×6	20-75
Bines *et al.* (52)	AC ×4	34
Bines *et al.* (52)	MF ×6	9
Venturini *et al.* (53) Levine *et al.* (54)	CEF ×6	50-60
Martin *et al.* (55)	FAC ×6	51
Martin *et al.* (55)	TAC ×6	61
Fornier *et al.* (50)	AC ×4 → T ×4	15*
Ganz *et al.* (56)	AC ×4 → T ×4	70
Ganz *et al.* (56)	AT ×4	38
Ganz *et al.* (56)	TAC ×4	58

*only ≤40 years patients; amenorrhea ≥12 months. CMF, cyclophosphamide/methotrexate/fluorouracil; AC, doxorubicin/cyclophosphamide; MF, methotrexate/fluorouracil; CEF, cyclophosphamide/epirubicin/fluorouracil; FAC, fluorouracil/cyclophosphamide/doxorubicin; TAC, docetaxel/doxorubicin/cyclophosphamide; T, docetaxel; AT, doxorubicin/docetaxel.

Lambertini, J. Thoracic disaese 2013

Cardiovascular disease

Congestive heart failure first year

Dose dependent

Less than 1% up to 300 mg/m² doxorubicine/adriamycine

26% over 500mg/m²

Swain 2003

Table 1 Cardiac Toxicity With Select Anti-HER2 Regimens in Adjuvant and Neoadjuvant Settings

	Trial	Grade 3–4/ Symptomatic Congestive Heart Failure	Decline in Left Ventricular Ejection Fraction (LVEF)
Adjuvant	**BCIRG 006[11]**		
	AC → T	0.7%	11.2%
	AC → TH	2.0%	18.6%
	TCH	0.4%	9.4%
	NSABP B-31[12]		
	AC → P	0.3%	NR
	AC → P + H	3.3%	NR
	Cochrane review[7]		
	Nontrastuzumab-containing	0.4%	5.6%
	Trastuzumab-containing	2.5%	11.2%
Neoadjuvant	**ACOSOG Z1041[29]**		
	FEC-75 → P + H	0	17.0%
	P + H → FEC-75 + H	0.7%	27.0%
	NeoALTTO[30]		
	P + L → FEC	0.6%	NR
	P + H → FEC	1.3%	NR
	P + L+ H → FEC	2.6%	NR
	NeoSphere[35]		
	T + H → FEC	0	1.0%
	T + H + Per → FEC	0	2.0%
	Per + H + T → FEC	1.0%	0
	T + Per → FEC	0	1.0%
	TRYPHAENA[36]		
	FEC + H + Per → T + H + Per	0	5.6%
	FEC → T + H + Per	2.7%	4.0%
	TCH + Per	0	2.6%

AC = doxorubicin, cyclophosphamide; ACOSOG = American College of Surgeons Oncology Group; BCIRG = Breast Cancer International Research Group; FEC = fluorouracil, epirubicin, cyclophosphamide; FEC-75 = fluorouracil, epirubicin, cyclophosphamide, with epirubicin given at an attenuated dose of 75 mg/m^2; H = trastuzumab; L = lapatinib; NCCTG = North Central Cancer Treatment Group; NR: not reported; NSABP = National Surgical Adjuvant Breast and Bowel Project; P = paclitaxel; Per = pertuzumab; T = docetaxel; TCH = docetaxel, carboplatin, trastuzumab.

Brown-Glabermann et al, Oncology 2014

ESTRO School

Cardiovascular disease

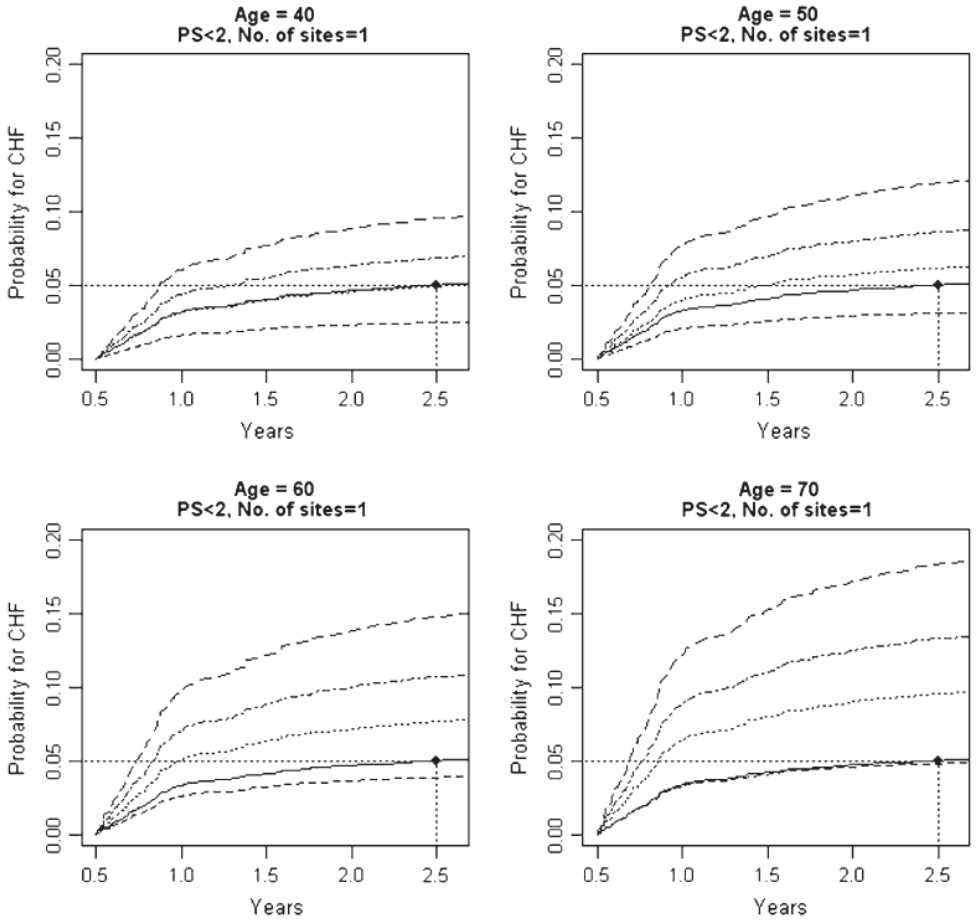
Late onset cardiovascular disease (years or decades)

- congestive heart failure, ventricular dysfunction, arrhytmia
- dose dependent
- Reduction in left ventricular mass, diastolic dysfunction

These cardiovascular conditions have often to be treated on the long term

Risk factors for cardiotoxicity

-Increased cumulative dose
-Age
-Predisposition cardiac disease
-Meidastinal irradiation
-Hormonal therapy
-Risk factors cardiovasc. disease



Risk of developing congestive heart failure over 2.5 years after epirubicin treatment

Ryberg M et al, JNCI 2008

ESTRO School

Cognitive function

Post chemotherapy but also post endocrine therapy

Impairment of verbal, visual memory, of attention, vigilance and processing speed

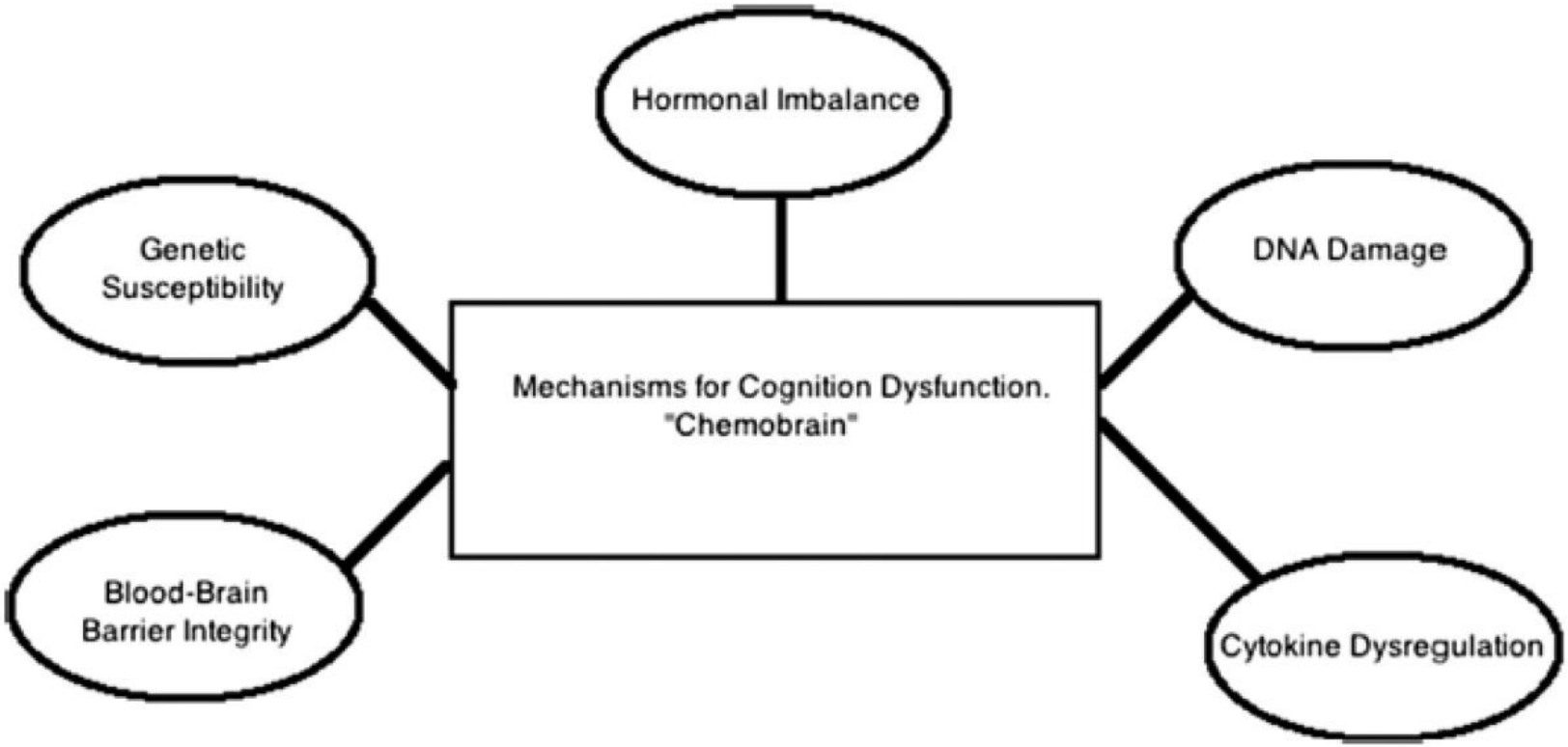
A lot of studies are ongoing

Self reported cognitive changes, 2y after ctx	CTC n=34	FEC n=36	CMF n=39	No chemo n=34
Concentration	38%	31%	31%	6%
Memory	32%	28%	21%	3%

Ahles, JCO 2012
Van Dam et al, J Natl Cancer 1998
Schagen et al, Cancer 2011

ESTRO School

Mechanisms for Cogitive dysfunction

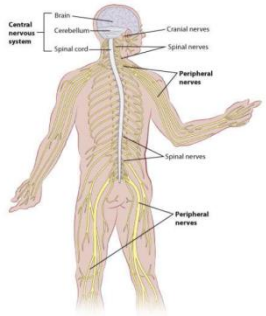


Gosain R et al, Cancer J 2013

ESTRO School

Chemo-induced peripheral neuropathy: symptoms

- Pain (which may be there all the time or come and go, like shooting or stabbing pain)
- Burning • Tingling (“pins and needles” feeling) or electric/shock-like pain
- Loss of feeling (which can be numbness or just less ability to sense pressure, touch, heat, or cold)
- Trouble using your fingers to pick up or hold things; dropping things
- Balance problems
- Trouble with tripping or stumbling while walking
- Being more sensitive to cold or heat
- Being more sensitive to touch or pressure
- Shrinking muscles
- Muscle weakness
- Trouble swallowing
- Constipation
- Trouble passing urine
- Blood pressure changes
- Decreased or no reflexes



ESTRO School

Chemo-induced peripheral neuropathy

Peripheral neuropathy can remain for years , only partially reversible (Taxanes, Oxaliplatin)

Chronic pain syndrom in 33% of the patients after chemotherapy but also endocrine therapy

Symptomatic treatment

Mostly given to relieve the pain

- Antidepressant medicines, often in smaller doses than are used to treat depression
- Anti-seizure medicines, which are used to help many types of nerve pain
- Opioids or narcotics, for when pain is severe

Pachman et al, JCO 2012

Secondary leukemias

Praga:

8 year absolute risk: 0.55%(0.33-0.78%)

* « standard » regimen : 0.37%
* High doses: 4.97% (2.06-7.87%)

Wolff Risk of marrow neoplasms

* HR surgery and chemo: 6.8 (1.3-36.1)

  surgery,chemo and RT: 7.6 (1.6-35.8)
* Risk at 10 years twice the risk at 5 years
* Risk per 1000 person.year: 0.5

Praga et al, JCO 2005, Wolff et al, JCO 2015

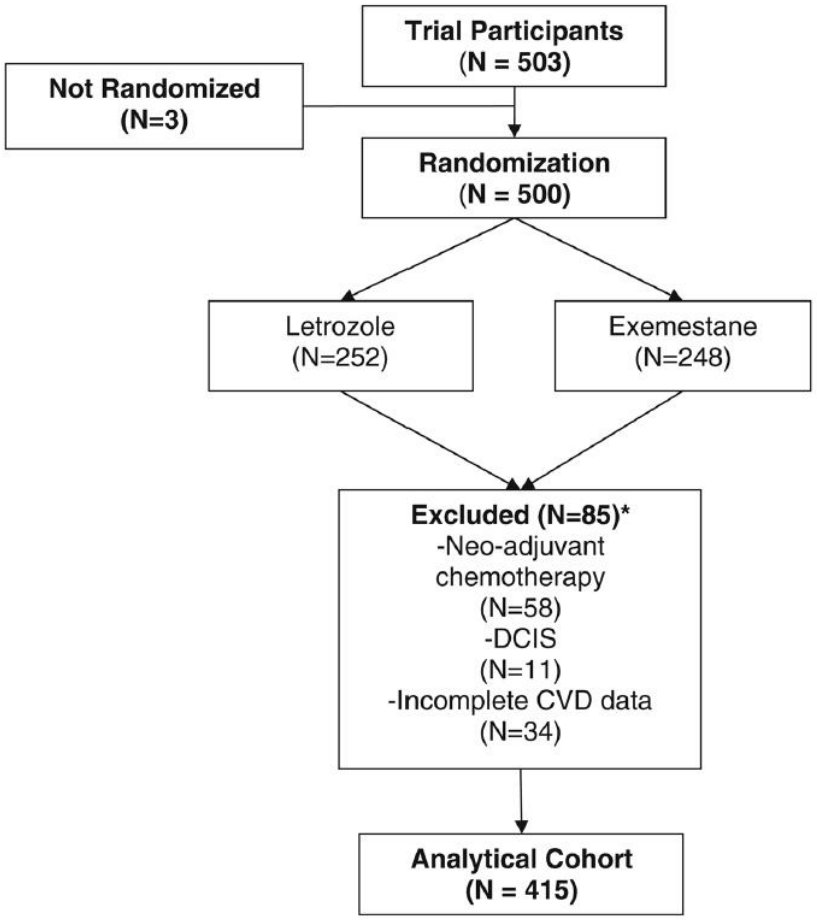
RISK-BENEFIT RATIO

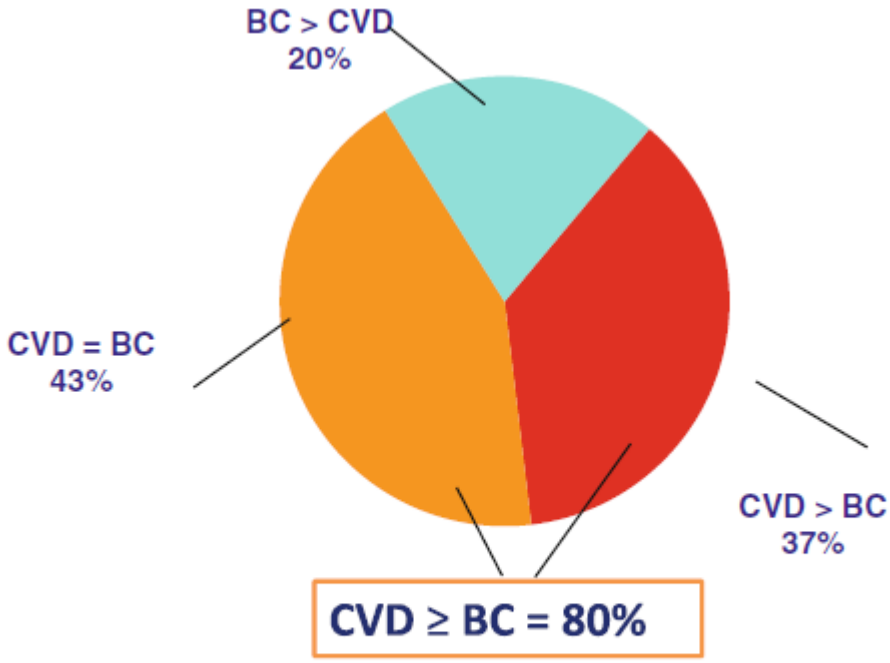
Example of cardiovascular disease

Comparison of the 10 year breast cancer recurrence rate according to Adjuvant!on line and the 10 year cardiovascular disease risk according to the Framingham risk score

415 pts receiving AI as an adjuvant treatment

Bardia et al, Breast Cancer Res Treatment 2011





CVD = 10-Year Cardiovascular Disease Predicted Risk

BC = 10-Year Breast Cancer Recurrence Predicted Risk

Fig. 3 Relative distribution of the predicted breast cancer recurrence risk (*BC*) and cardiovascular disease (*CVD*) risk among the study participants. CVD = 10-year CVD predicted risk. BC = 10-year breast cancer recurrence predicted risk

Bardia et al, Breast Cancer Research and Treatment 2011

ESTRO School

Clinical case 1

Postmenopausal 60 y of age patient , average health condition, with a tumor of 1cm, SBR1, ER positive, no axillary node

Risk of cancer death at 10 years : 1%

Absolute benefit with endocrine therapy: 0,3%

But

TAM 5y: Thrombo-embolic disease: RR: 2.5

Endometrial carcinoma: RR: 2.5

AI : Absolute increase of CV disease: 0.8%

Absolute increase of bone fractures: 2.3%

Risk of arthromyalgia , vasomotor symptoms, weight gain..

Clinical Case 2

Premenopausal 35 y of age patient, average clinical condition, with a tumor of 1.5 cm, SBR 1, ER positive, no axillary node

Risk of cancer death at 10 years: 3%

Benefit with endocrine therapy:1%, with chemo:1%, with both 1.2%

But

If TAM: RR of thromboembolic disease : 2.5

Small increase of endometrial carcinoma

Effects on « quality of life », weight control, sexual problems..

If chemotherapy: risk of bone marrow neoplasms of 0.3 to 0.5 % (much more if high dose chemotherapy), low risk of CV complications, chronic fatigue syndrom, ovarian suppression

Social and financial consequences of overtreatment

Overtreatment have psychological and social consequences: no or late return to work, less efficiency …

Overtreatment side effect have to be treated.

Overtreatment costs a lot to the patient and to society

Conclusion or…. what next ?

Current breast cancer treatment more effective

The clinician must balance efficacy of the drug and long term side effects,to evaluate the risk/benefit ratio on the long term

The clinician must discuss this with the patient

Shared decision making

The clinician must be aware of the late side effects and be able to deliver post treatment survivorship care

Questions?

Acknowledgement

J. Bonneterre, Centre Oscar Lambret- Université de Lille

Multidisciplinary Course on Breast Cancer

Dublin 10.-13.9.2017

Personalized or Individualized Medicine ?

T. Kuehn

Klinikum Esslingen , Germany

Individualized ?

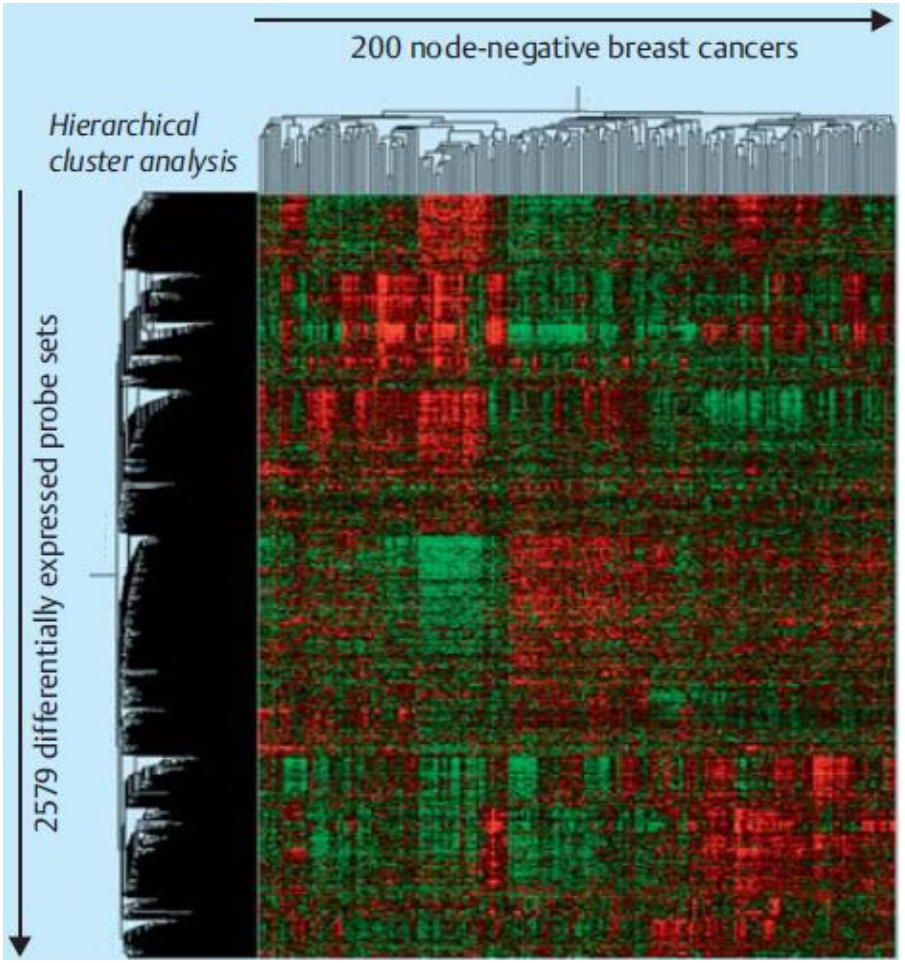
Personalized ?

ESTRO School

One fits all – 100 years

Different patients

Different tumors



Challenges to individualise treatment strategies

- Current existing tools
- Future Tools

Differences in Patients / Tumor / Treatment

- Patient
  - Age, comorbidities
  - Expectations and whishes
- Tumor
  - Prognosis
  - Responsiveness to treatment
- Treatment
  - Side effects

Significance of Guidelines

Guidelines are Important !!
Use them Wisely !!

Subtype-specific General Systemic Strategies

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2017.1

	AGO
If chemotherapy is indicated due to tumor biology, consider systemic treatment before surgery (neoadjuvant)	++
HR+/HER2- and "low risk":	
➢ Endocrine therapy without chemotherapy	++
HR+/HER2- and "high risk"	
➢ Conventionally dosed AT-based chemotherapy	++
➢ Dose dense & escalated in case of high tumor burden	+
➢ Followed by endocrine therapy	++
HER2+	
➢ Trastuzumab (plus Pertuzumab neoadjuvant) plus	++
· Sequential A/T-based regimen with concurrent T + H	++
· Anthracycline-free, carboplatinum-containing regimen	+
· Anthracycline-free, taxane regimen for low tumor burden	+
· Dose dense & escalated in case of high tumor burden	+
TNBC	
➢ Conventionally dosed AT-based chemotherapy	++
➢ Dose dense & escalated	+
➢ Neoadjuvant platinum containing chemotherapy	+

www.ago-online.de

Further Information

References

FORSCHEN
LEHREN
HEILEN

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2017.1

Breast Conservation: Surgical Technical Aspects

	Oxford / AGO LoE	GR	
➢ **Non-palpable lesion**			
➢ Wire guided localisation	2b	B	++
➢ Radionuclide guided localisation	2b	B	+/-
➢ Specimen radiography or ultrasound	2b	B	++
➢ **Tumor-free margins required** (also in unfavorable biology „no cells on ink“ are enough)	2a	A	++
➢ **Immediate intraoperative re-excision for close margins (specimen radiography and/or intra-operative pathology)**	1c	B	++
➢ **Re-excision required for involved margins (paraffin section)**	3b	C	+
➢ **Therapeutic stereotactic excision alone**	4	D	- -
➢ **Ultrasound guided surgery to prevent re-excision**	1a	A	+/-
➢ **Intraop. margin evaluation with margin probe**	1b	A	+/-

www.ago-online.de

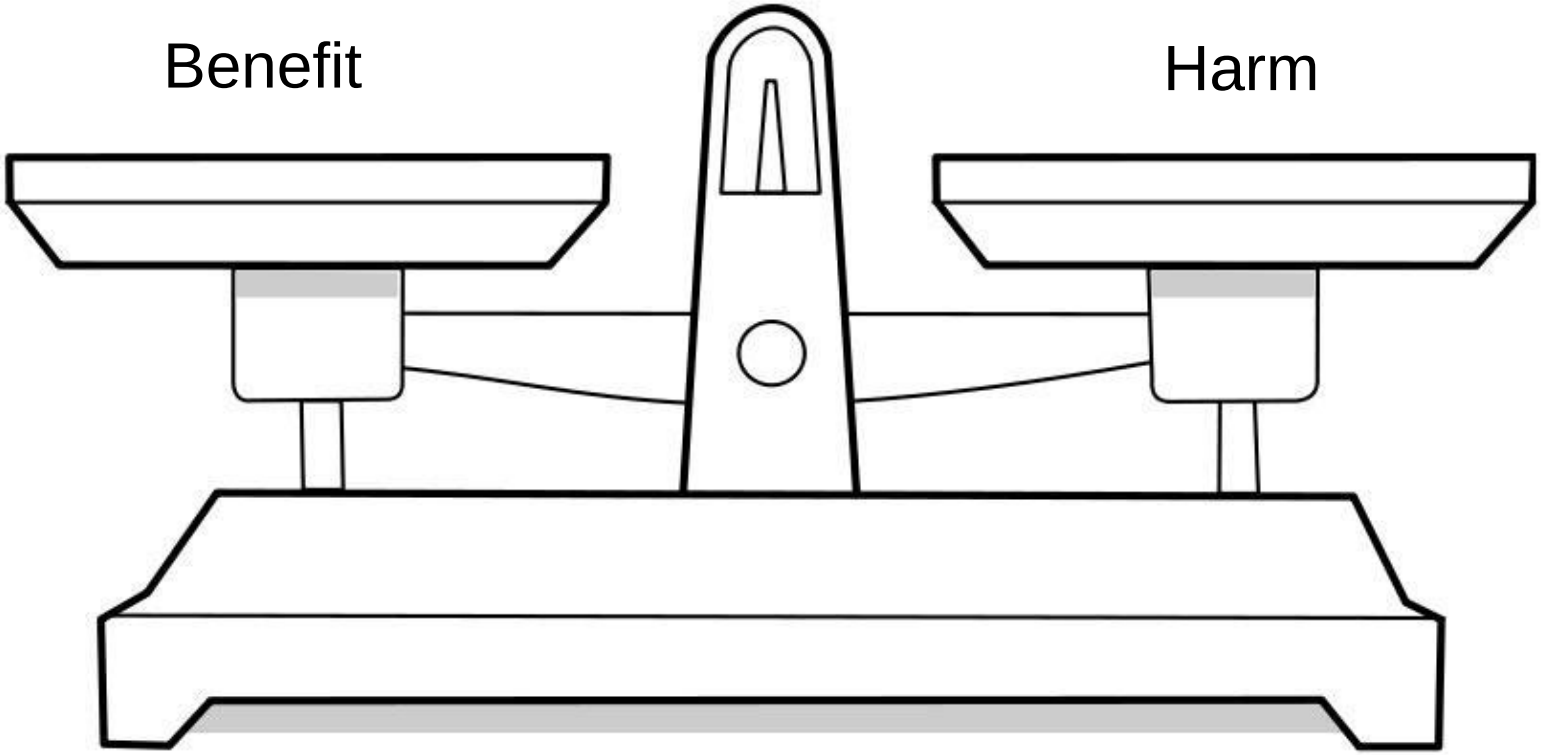
Further Information

References

FORSCHEN
LEHREN
HEILEN

Is a statistical significant benefit for a cohort always clinically significant for a single patient ?

Therapeutic Index – Individual Patients



Definition

A *Prognostic Factor is any parameter available at the time of interest e.g. primary diagnosis that correlates with disease-free or overall survival, in the absence of any therapy and, as a result, is able to correlate with the natural history of the disease.**

Marker of Recurrence and defines the aggressiveness of the disease

Need for Treatment

Definition

A *Predictive Factor* is any parameter associated with response to a given therapy.

Estimated Effect of Treatment

Low absolute risk implies low absolut benefit even from an effective treatment

High absolute risk implies higher absolut benefit from a less effective treatment

©AGO e.V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2017.1

DCIS Radiotherapy

	Oxford / AGO LoE / GR		
Radiotherapy after:			
➢ Breast conserving surgery (BCS)	1a	A	+*
➢ Mastectomy	2b	B	- -
Modality:			
➢ Partial breast radiotherapy (PBI)	3a	D	--
➢ Hypofractionated radiotherapy regimens	2b	D	-/+**
➢ Radiotherapy boost on the tumor bed	2b	D	--
➢ Women younger than 45-50 years	2b	C	+/-

* Side effects and disadvantages of radiotherapy must be balanced against risk reduction. Omitting radiotherapy implies elevated risk for local recurrence without effect for overall survival even in the subset of „good risk" patients. There remains a lack of level-1 evidence supporting the omission of adjuvant radiotherapy in selected low-risk cases: < 2.5 cm, low and intermediate nuclear grade, mammographically detected

** Analysis in ongoing trials

www.ago-online.de

Further Information

References

FORSCHEN
LEHREN
HEILEN

Results Low risk RCT

	Remarks	F-up (yr)	BCS	BCS + RT	
EORTC 10853		15	31%	18%	NNT:7.7
NSABP 17		17	35%	20%	NNT:6.6
SweDCIS		20	32%	20%	NNT:8.3
UK/NAZ	+/ - Tamoxifen	12	17%	2.6%	NNT:6.9
RTOG9804	Low risk: Grade 1-2, tumorsize < 2.5 cm, margin > 3 mm	7	6.7%	0.9% NNT: 17.2	

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2017.1

Prognostic Factors I in Early Breast Cancer

Factor	LoE_{Ox2001}	GR	AGO
➢ Tumor size	1a	A	++
➢ Nodal status	1a	A	++
➢ Distant metastases	1a	B	++
➢ Histological tumor type (colloid, mucinous, tubular etc.)	2b	B	++
➢ Grade(Elston & Ellis)	2a	B	++
➢ Age	2a	B	++
➢ Peritumoral lymphatic vessel and vascular invasion (L1 V1)	2b	B	+
➢ pCR after NACT* in (HR+/G3, HER2+, TN)	1a	A	++
➢ Obesity (BMI >30 kg/m²)	1b	B	+

* NACT = Neoadjuvant Chemotherapy

www.ago-online.de

Further Information

References

FORSCHEN
LEHREN
HEILEN

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2017.1

Prognostic Factors II in Early Breast Cancer

Factor	LoE_{Ox2001}	GR	AGO
➢ ER / PgR	2a	B	+
➢ HER2 (IHC, FISH)	2b	B	+
➢ ER / PgR / HER2/ Ki-67 as surrogate markers for molecular subtypes	2b	B	+
➢ uPA / PAI (Femtelle® ELISA)§ in N0	1a	A	+
➢ Proliferation markers			
➢➢ Ki-67 before, during or after treatment	2b	B	+

§ Validated clinical data only available for this assay

www.ago-online.de

Further Information

References

FORSCHEN
LEHREN
HEILEN

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2017.1

Reproducibility

- ER/PR: concordance central vs local is high (97%; Plan B, SABCS 2014)
- Grading: concordance central vs local is 68 % (PlanB, JCO 2016)
- HER2: frequency of false-positive test results 6 % (ASCO /CAP JCO 2013)
- Impact of routine pathologic review in N0 BC: 20% changes : grading 40%, LVI 26%, N 15%, margin 12% (JCO 2012)
- pN0 from MIRROR study: pN0 was upstaged in 22%, in central pathology review (Ann Oncol 2012)
- Inter- and intraobserver variability in measurement of ki-67 is high (J Nat. Cancer Institute 2011)

Consider Plausibilty

66 year old Patient, good health

2.2 cm tumor

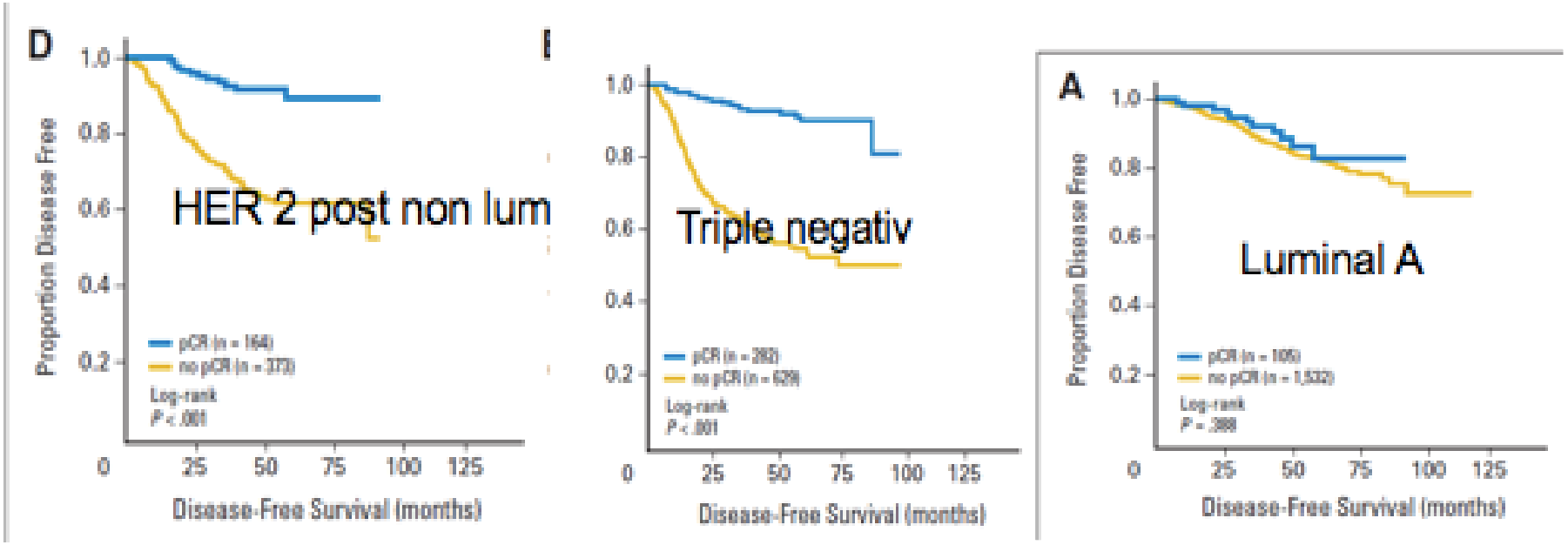
ER pos PR pos, HER 2 neg

G3

KI 67: 10 %

Responsiveness of intrinsic subtypes

Prognosis information of pCR by Subtype (N=4193)



Low responsiveness implies benefit even in higher risk patients

ER as predictive factor for Tamoxifen effect

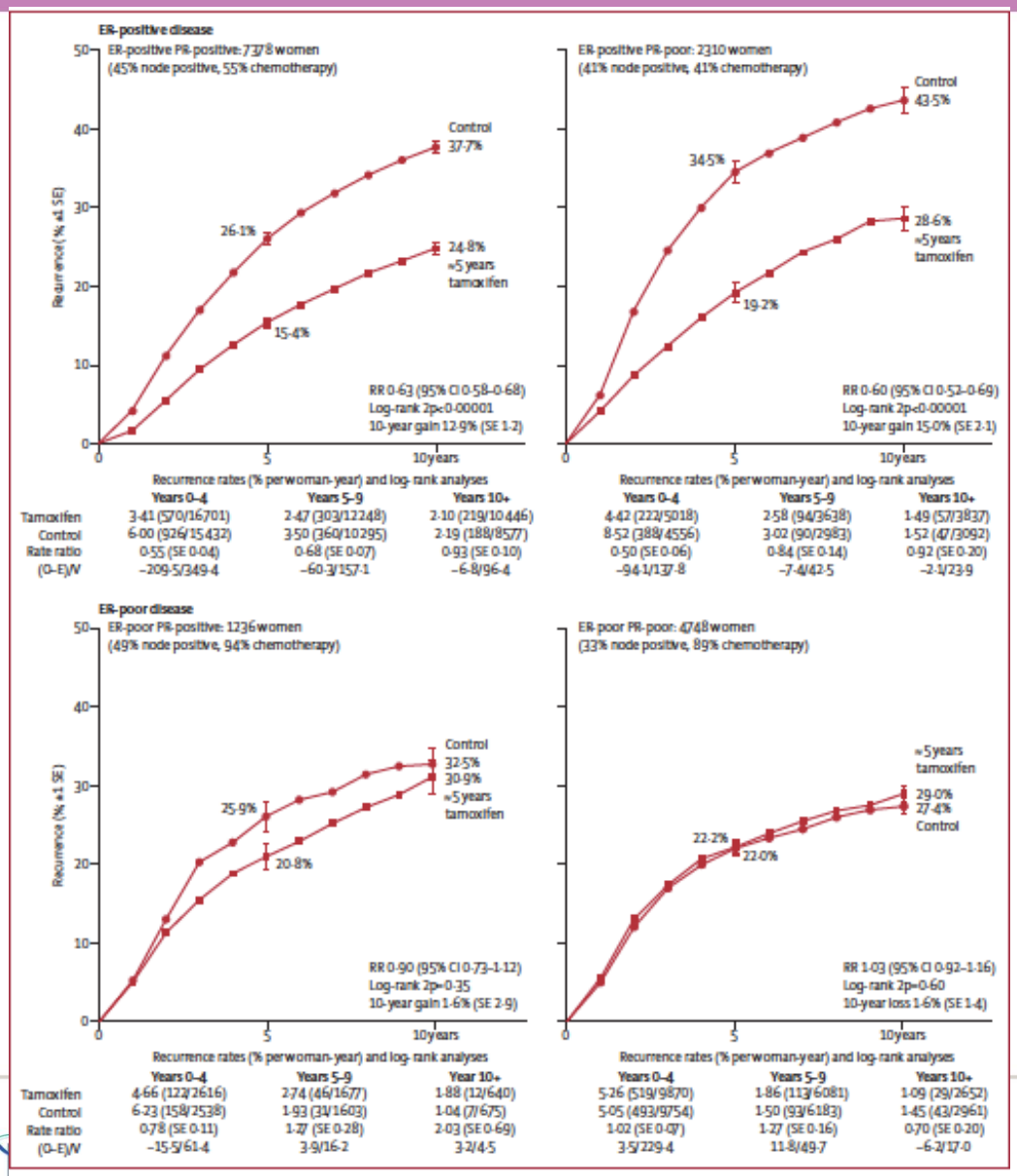


Figure 1: Relevance of measured ER and PR status to the effects of about 5 years of tamoxifen on the 10-year probability of recurrence
Outcome by allocated treatment in trials of about 5 years of adjuvant tamoxifen. Event rate ratio (RR) is from summed log-rank statistics for all time periods. Gain (and its SE) is absolute difference between ends of graphs. ER=oestrogen receptor. PR=progesterone receptor. O–E=observed minus expected, with variance V.

ESTRO School

Predictive Factors with a defined Target

ER, PR

HER 2

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2017.1

Neoadjuvant Systemic Chemotherapy Response Prediction I

Factor	CTS	LoE_{Ox2001}	GR	AGO
➢ Young age	B	1a	A	+
➢ cT1 / cT2 tumors o. N0 o. G3	B	1a	A	++
➢ Negative ER and PgR status	B	1a	A	++
➢ Triple negative breast cancer (TNBC)	B	1a	A	++
➢ Positive HER2 status	B	1a	A	++
➢ Non-lobular tumor type	B	1a	A	+
➢ Early clinical response	B	1b	A	+

www.ago-online.de

Further Information

References

FORSCHEN
LEHREN
HEILEN

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2017.1

Neoadjuvant Systemic Chemotherapy Response Prediction II

Factor	LoE_{2009}	CTS	GR	AGO
➢ Multigene signature	III	C	B	+/-
➢ (Mammaprint, Endopredict Oncotyp Dx,PAM50 Prosigna[$])				
➢ Ki-67	I	B	A	+
➢ Tumor infiltrating lymphocytes*	I	B	B	+
➢ *PIK3CA* mutation	I	B	B	+/-
➢ gBRCA in TNBC	II	B	B	+

[$] validated clinical data only available for this assay

*defined as dense lymphocytic infiltration of inner peritumoral stroma outside of the invasion front (lymphocytes make up >50% of stroma area)

www.ago-online.de

Further Information

References

FORSCHEN
LEHREN
HEILEN

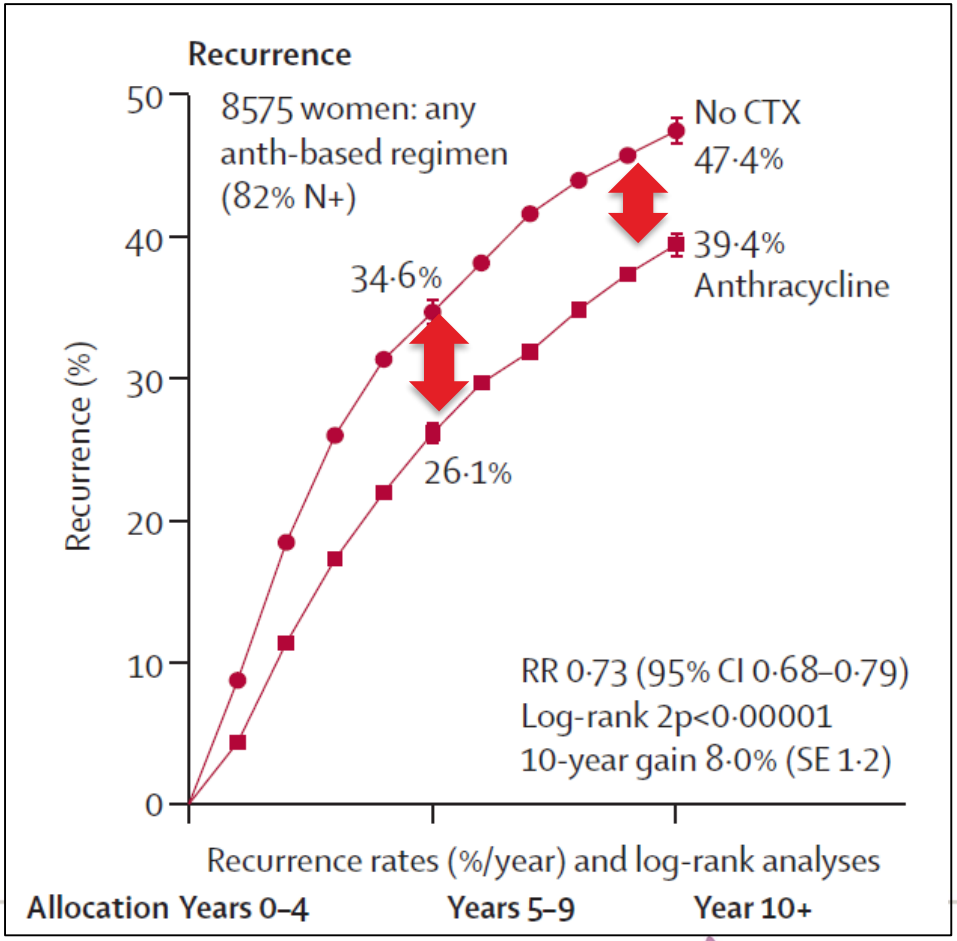
Effect of Chemotherapy

10-years recurrence rate reduced by about 10% with adjuvant chemotherapy

Benefit of adjuvant Chemotherapy is in the first 5 years

- 53.6 % will not recur without CHT

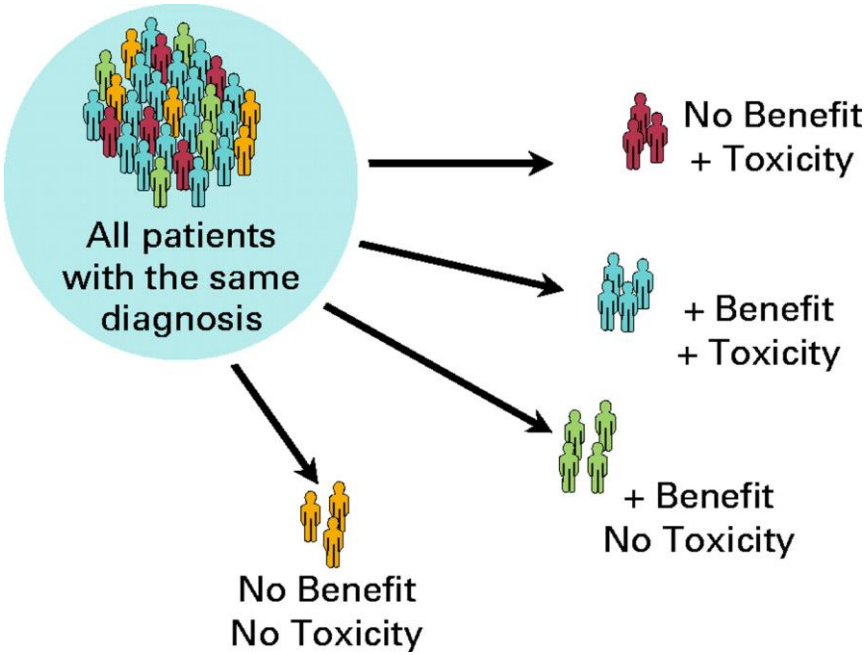
- 39.4 % will recur even after CHT



MAASTRO CLINIC

ESTRO School

The majority of breast cancer patients do not benefit from adjuvant chemotherapy

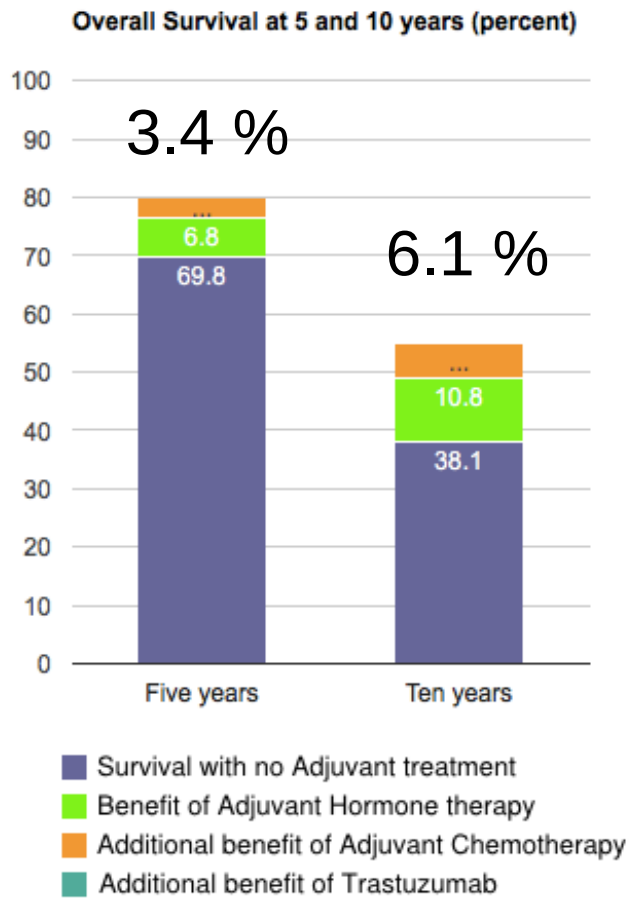


EBCTCG Lancet 2012;379:432-44. Walgren RA et al. J Clin Oncol 2005

Absolute Gain from Chemotherapy - PREDICT

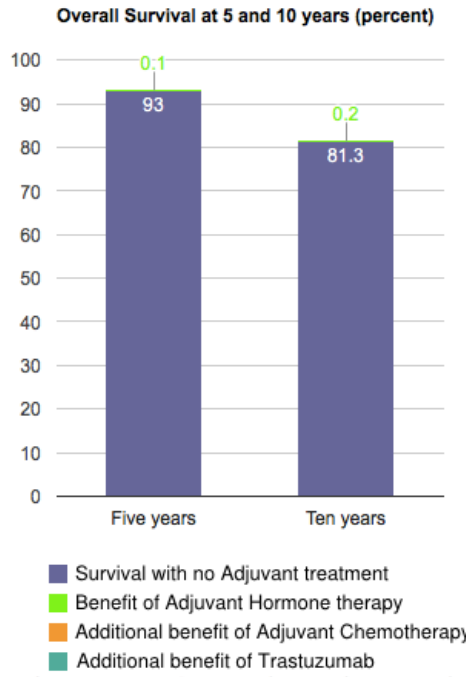
Age at diagnosis:	69		
Mode of detection:	○ Screen-detected	◉ Symptomatic	○ Unknown
Tumour size in mm:	20		
Tumour Grade:	○ 1	○ 2	◉ 3
Number of positive nodes:	3		☐ Micromet
ER status:	◉ Positive	○ Negative	
HER2 status:	○ Positive	◉ Negative	○ Unknown
KI67 status:	◉ Positive	○ Negative	○ Unknown
Gen chemo regimen:	○ No chemo	◉ Second	○ Third

Predict Surviva | Clear All Fields | Print Results

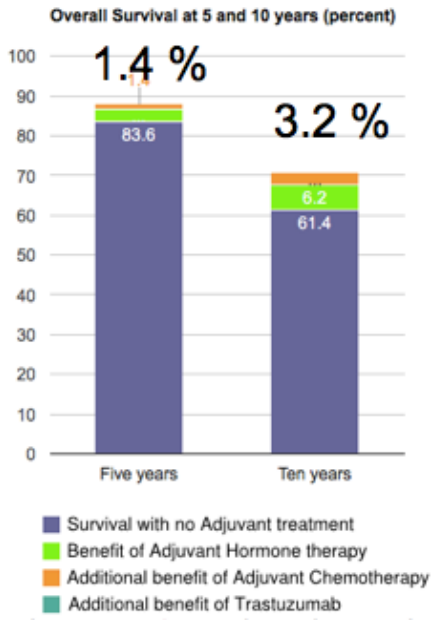


Gain of CHT according to PREDICT

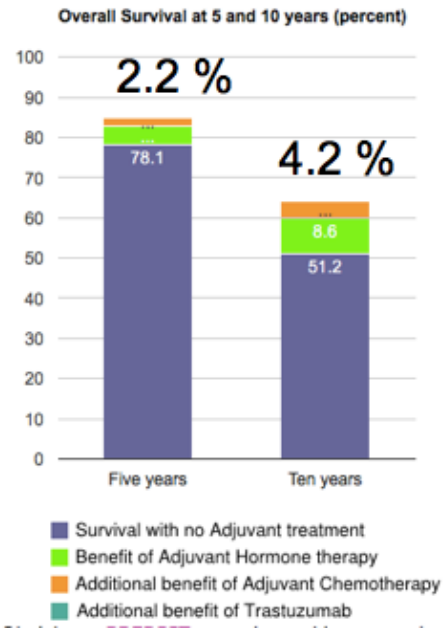
59 yrs, 20 mm, G3, ER pos, HER 2 neg, KI 67 pos



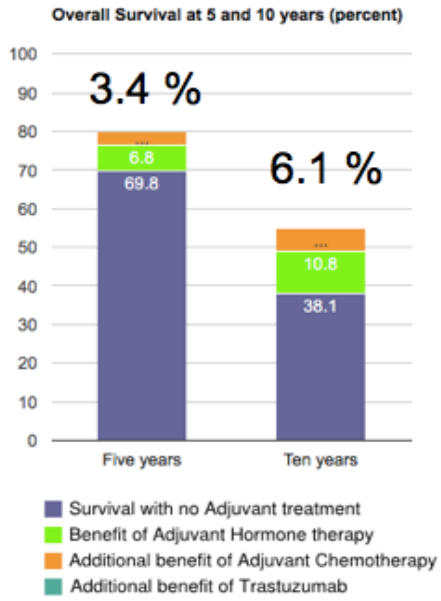
0 LN pos



1 LN pos



3 LN pos



Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Clinical Strategy and Programmes Division

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

Comprehensive Geriatric Assessment

A Summary

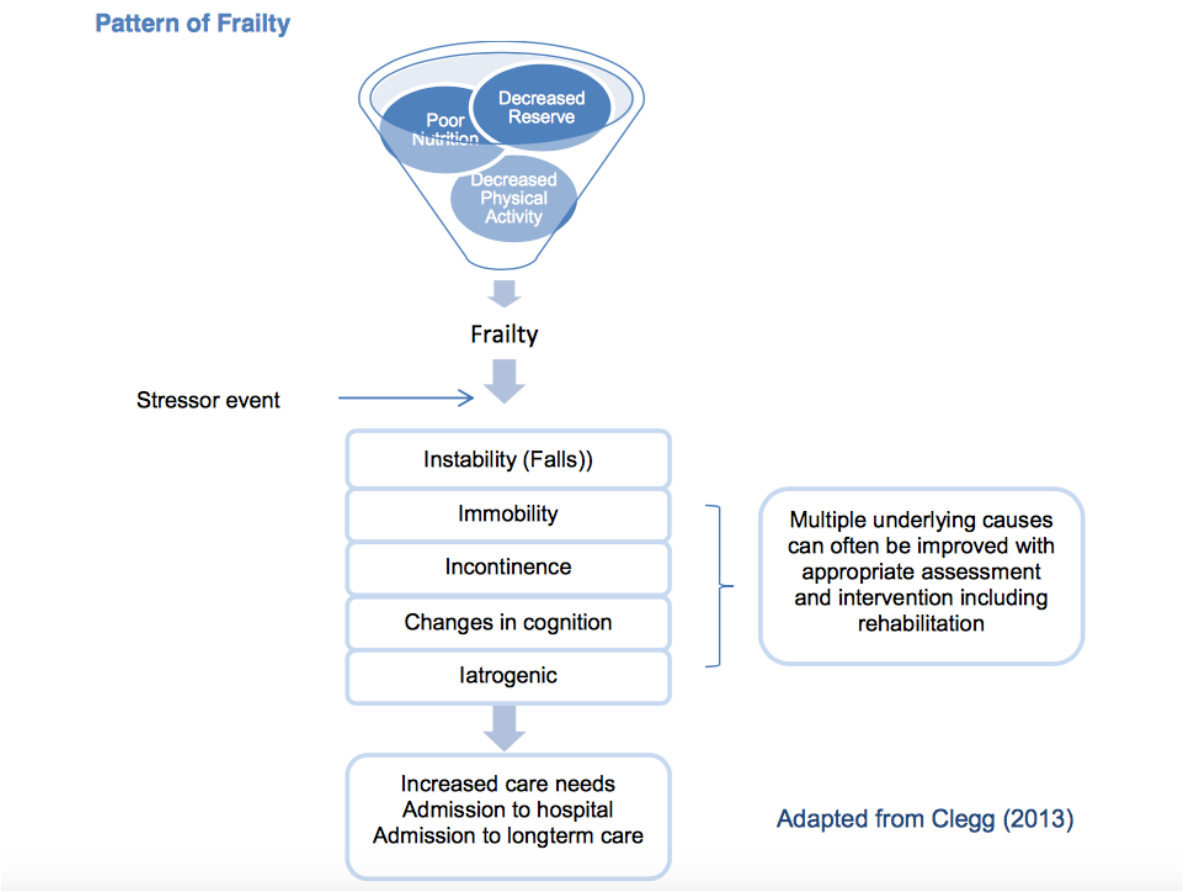
OLDER PEOPLE

Adapted from Specialist Geriatric Team Guidance on Comprehensive Geriatric Assessment
National Clinical Programme for Older People
(2016)

MAASTRO CLINIC

ESTRO School

Comprehensive Geriatric Assessment



AGO
ARBEITSGEMEINSCHAFT GYNÄKOLOGISCHE ONKOLOGIE E.V.
MAMMA
© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2017.1

Predictive Factors – Endocrine Therapy

Factor	LoE_{Ox2001}	GR	AGO
➢ **Endocrine therapy**			
➢ ER/PgR status	1a	A	++
➢ IHC staining intensity (ER/PgR)	1a	A	+
➢ **Tamoxifen**			
➢ CYP2D6 polymorphism	2b	D	-
➢ **Ovarian ablation**			
➢ Menopausal status	1c	A	++
➢ **Aromatase inhibitors vs. Tamoxifen**			
➢ Menopausal status	1c	A	++
➢ ER/PgR/HER2 as single markers	1c	A	-
➢ Lobular subtype	2b	B	+
➢ Ki-67 high (published cutoffs > 11% and >14%)	2b	B	+/-
➢ Obesity (BMI >30 kg/m²)	2b	B	+/-

www.ago-online.de

Further Information

References

FORSCHEN
LEHREN
HEILEN

Future Tools to assess prognosis and treatment effectiveness

Gene expression profiles

Gene mutations

- PIK3CA
- BRCA

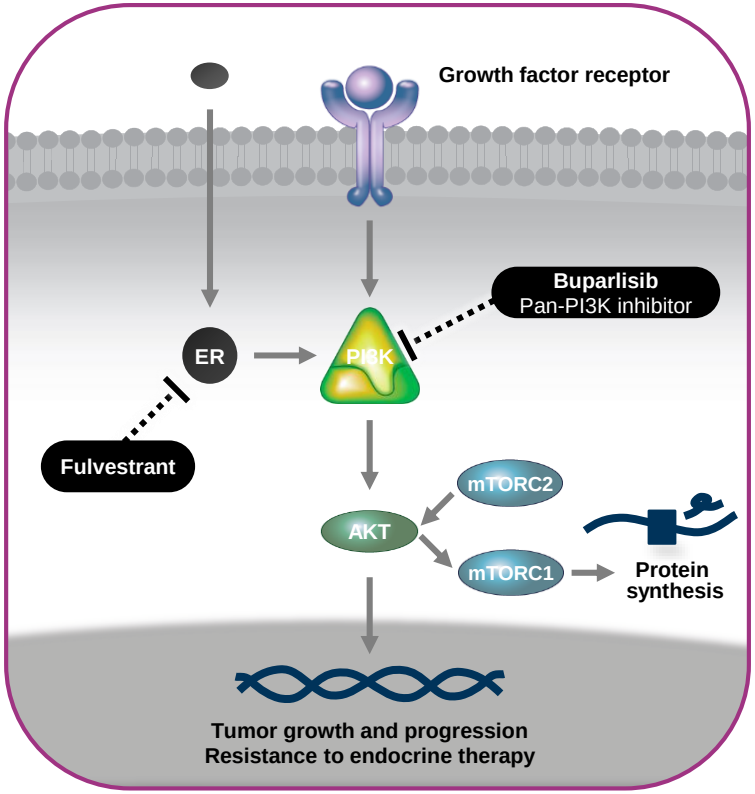
Tumor cells from Bone Marrow (Genetic profiles)

Liquid Biopsy

- CTC (circulating isolated tumorcells)
- cT DANN (circulating tumor DANN)

The PI3K Pathway is Activated in Breast Cancer

- PI3K/mTOR pathway activation is a hallmark of HR+/HER2– breast cancer cells that have developed resistance to endocrine therapy[1,2]
- The ER pathway is upregulated in tumors from patients treated with PI3K inhibitors[1]
- Dual blockade of the PI3K/mTOR and ER pathways may therefore restore sensitivity to endocrine therapy[1,3,4]

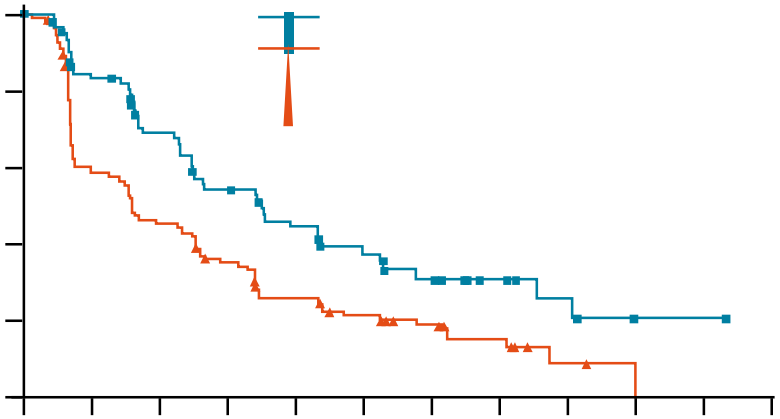


ER, estrogen receptor; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor-positive; mTOR, mammalian target of rapamycin; mTORC, mammalian target of rapamycin complex; PI3K, phosphatidylinositol 3-kinase.

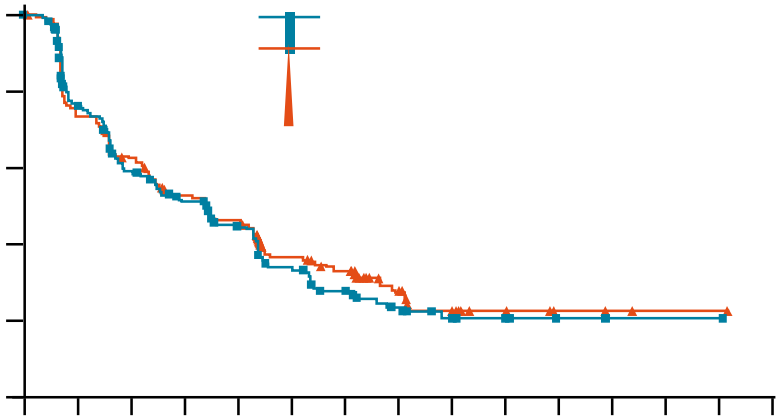
1. Bosch A, *et al. Sci Transl Med.* 2015;7:283ra51; 2. Miller TW, *et al. Cancer Discov.* 2011;1:338–351; 3. Fox EM, e*t al. Front Oncol*. 2012;2:145; 4. Yardley D, *et al. Adv Ther.* 2013;30:870–884.

Buparlisib and Fulvestrant Produced a Clinically Meaningful PFS Improvement in Patients With ctDNA *PIK3CA* Mutations

ctDNA *PIK3CA* Mutant n=200	Buparlisib + Fulvestrant n=87	Placebo + Fulvestrant n=113
Median PFS, months (95% CI)	7.0 (5.0–10.0)	3.2 (2.0–5.1)
HR (95% CI)	0.56 (0.39–0.80)	
One-sided nominal *P* value	<0.001	



ctDNA *PIK3CA* Non-mutant n=387	Buparlisib + Fulvestrant n=199	Placebo + Fulvestrant n=188
Median PFS, months (95% CI)	6.8 (4.7–8.5)	6.8 (4.7–8.6)
HR (95% CI)	1.05 (0.82–1.34)	
One-sided nominal *P* value	0.642	



CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; PFS, progression-free survival.

Prognostic Factors III in Early Breast Cancer

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2017.1

Faktor	LoE_{2009}	CTS	AGO
➢ Disseminated tumor cells (DTC, in bone marrow)	I	B	+/-
➢ Circulating tumor cells (CTC, in blood, Cell Search®) $	I	A	+/-
➢ CTC before NACT (regarding OS, DDFS, LRFI)	I[a]	B	+/-
➢ Therapy decisions based on CTC phenotypes	III	C	-
➢ Multigene assays			
➢ EndoPredoct®, Prosigna® (N0-1, HR+, Her2 -)	I	B	+*
➢ 70 gene signature (MammaPrint®) (N0-1)	I	A	+*
➢ Oncotype DX® (N0-1, HR+ HER2-, 5 Jahre)	I	A	+*
➢ IHC4 (central pathology published algorithm) #	I	B	+/-

www.ago-online.de

Further Information

References

FORSCHEN
LEHREN
HEILEN

* Should only be used in selected patients if all other criteria are inconclusive for therapeutic decision making

$ Validated clinical data only available for this assay

Cuzick et al., J Clin Oncol 29: 4273-4278, 2011

Commercially Available Molecular Tests

© AGO e. V.
in der DGGG e.V.
sowie
in der DKG e.V.

Guidelines Breast
Version 2017.1

www.ago-online.de

Further Information

References

FORSCHEN
LEHREN
HEILEN

	70 gene signature (MammaPrint®) $	21 gene Recurrence score (Oncotype DX®) $	8 gene signature (Endopredict®) $	PAM 50 (Prosigna®) $
Prognosis after 5 yrs (late recurrences)	not separately shown	no	yes	yes
Predictive impact (chemotherapy benefit)	poorly validated	yes *	not shown	not shown
Prospective-retrospective evidence (% of recruited patients)	Multicenter validation	NSABP B-14 **(14%)** NSABP B-20 **(28%)** ECOG 9127 SWOG 8814 **(40%)** ATAC **(30%)**	ABCSG 6 **(19%)** ABCSG 8 **(36%)** GEICAM-9906 **(45%)** ATAC **(10%)**	MA.12 **(59%)** MA.5 **(66%)** ABCSG 8 **(44%)** ATAC **(16%)**
Prospective evidence (5-year DFS, OS)	MINDACT (N0, N1)	$TAILOR_X$ (N0, low-risk, RS<11) PlanB (N0, high-risk/N+)	-	-

$ Validated clinical data only available for this assay
*** Trial performed bevore HER2 testing, HER2 positive patients may have been included**

ESTRO

Multidisciplinary Course on Breast Cancer

Dublin 10.-13.9.2017

Personalized or Individualized Medicine ?

T. Kuehn

Klinikum Esslingen , Germany

MAASTRO CLINIC

ESTRO School

Towards Improved Decision Aids for Adjuvant Treatments in Early Breast Cancer

Sarah Darby
Nuffield Department of Population Health
University of Oxford
United Kingdom

CANCER RESEARCH UK

UNIVERSITY OF OXFORD

predict

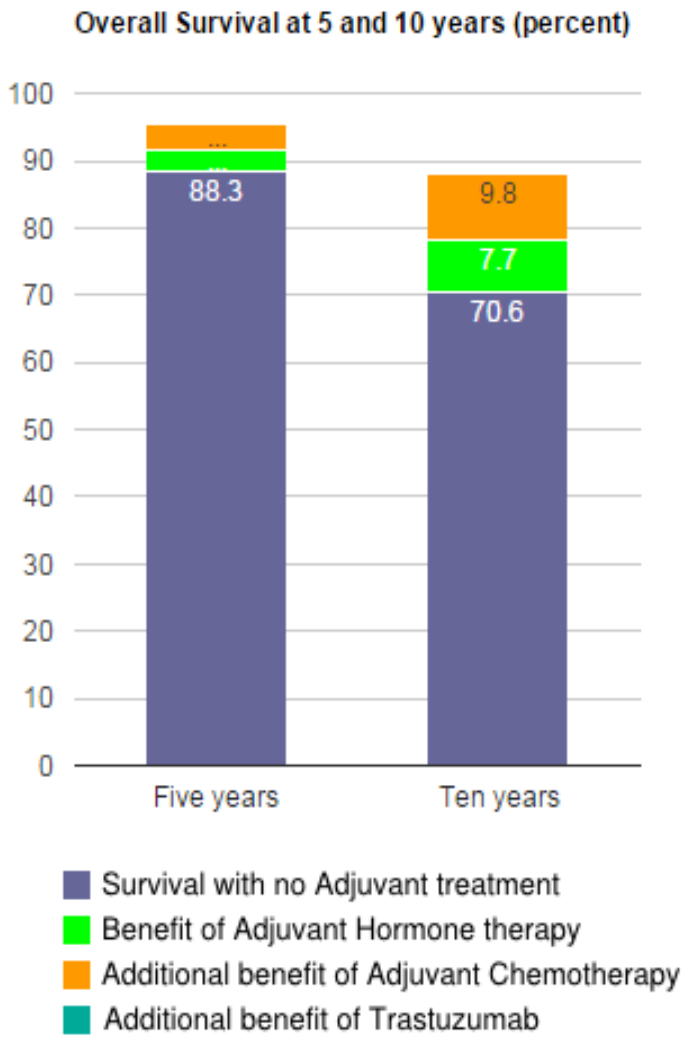
Google™ Custom Search Search

PREDICT Tool: Breast Cancer Survival; Input

Age at diagnosis:	45		
Mode of detection:	(•) Screen-detected	( ) Symptomatic	( ) Unknown
Tumour size in mm:	25 (blank if unknown)		
Tumour Grade:	( ) 1 ( ) 2 (•) 3	( ) Unknown	
Number of positive nodes:	1 (blank if unknown)		
ER status:	(•) Positive	( ) Negative	
HER2 status:	( ) Positive	(•) Negative	( ) Unknown
KI67 status:	( ) Positive	( ) Negative	(•) Unknown
Gen chemo regimen:	( ) No chemo	( ) Second	(•) Third

Predict Survival | Clear All Fields | Print Results

Contact



PREDICT Tool: Breast Cancer Survival; Results

Five year survival

88 out of 100 women are alive at 5 years with no adjuvant therapy after surgery
An extra 3 out of 100 women treated are alive because of hormone therapy
An extra 7 out of 100 women treated are alive because of hormone therapy & chemotherapy

Ten year survival

71 out of 100 women are alive at 10 years with no adjuvant therapy after surgery
An extra 8 out of 100 women treated are alive because of hormone therapy
An extra 17 out of 100 women treated are alive because of hormone therapy & chemotherapy

To view the numbers in bars hover pointer over each bar-segment
(Or tap segment if using a mobile device)

Some Potential Improvements to Existing Decision Aids

- Benefits of radiotherapy as well as systemic therapy
- Risks of late side-effects from radiotherapy & chemotherapy
- Estimates up to 20 years after initial diagnosis
- Estimates for patients diagnosed today based on large numbers of patients
- Take into account higher mortality in smokers or with pre-existing risk factors for heart disease

Problem

- The women randomised in the trials of radiotherapy versus no radiotherapy were diagnosed many years ago.

- Outcomes in breast cancer have improved since then

What happens if we try to estimate treatment effects on modern data, eg from cancer registries?

Comparison of Randomised and Observational Data

- Data sources:
  - Randomised: EBCTCG
  - Observational: SEER Cancer Registries

- Treatment comparison:
  - Radiotherapy versus not in N+ women after mastectomy

McGale et al, JCO 2016; 34:3356

EBCTCG and SEER
Radiotherapy versus not

EBCTCG:

~3000 women, N+ disease in 14 trials of radiotherapy after mastectomy

SEER:

~33,000 women with radiotherapy after mastectomy

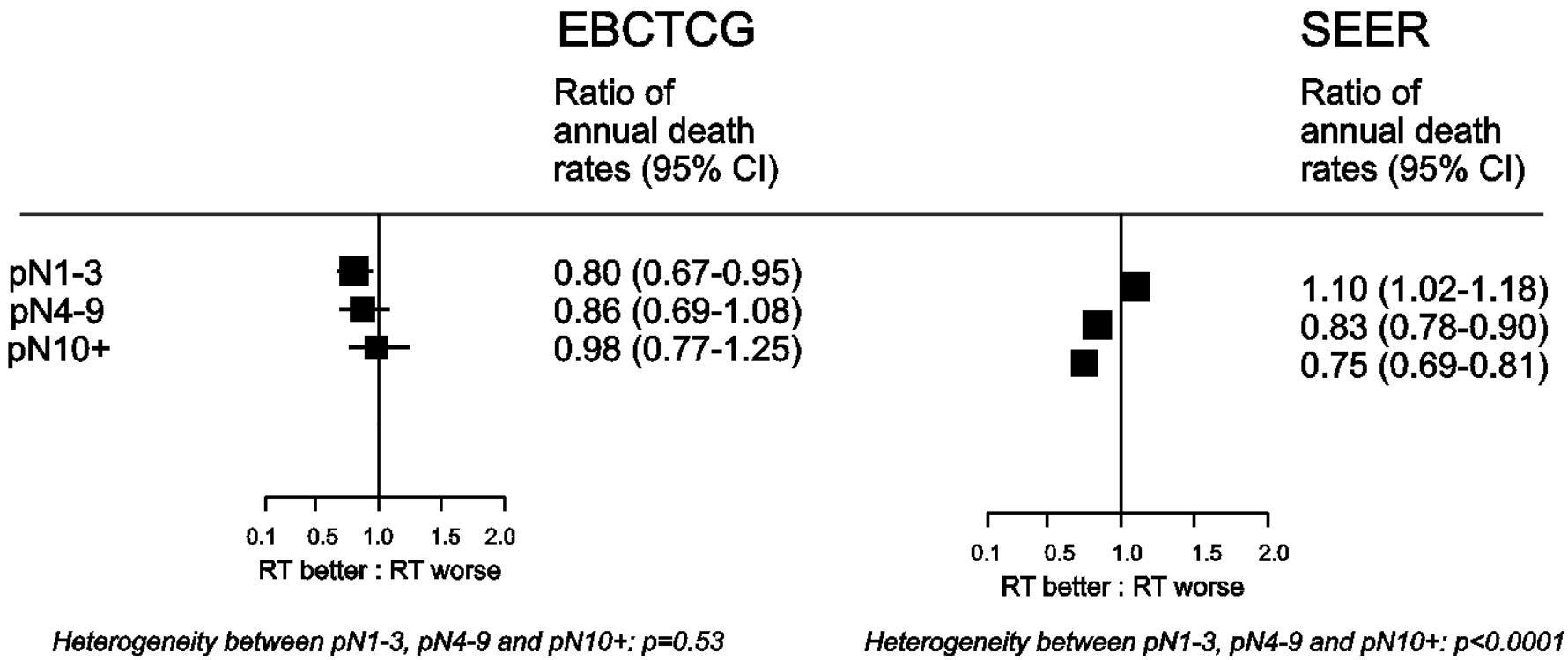
~56,000 pN+ women with mastectomy but no radiotherapy

McGale et al, JCO 2016; 34:3356

EBCTCG and SEER 1990-2008

Breast cancer mortality

RT vs No RT in pN+ given mastectomy



SEER data stratified by: age, follow-up year, stage, year, ethnicity, tumour size, no of nodes, grade, ER status, quadrant, axillary surgery

McGale et al, JCO 2016; 34:3355

Have to be ***smart!***

Need two **components** of information

plus a **trick**

How to be Smart

Today, several treatment combinations commonly used in early breast cancer (together with surgery)

Component 1:

- For each treatment combination, need mortality rates for recently diagnosed breast cancer patients for patients who received those treatments

- Then can estimate cumulative risk for patients receiving each group of treatment combinations

High Quality Data on All Women Diagnosed with Breast Cancer in England, 1997-2016

- Academic partnership set up between Oxford University and the Public Health England to review/improve data held within National Cancer Registration System (NCRAS)
- Information from all relevant sources now being brought into NCRAS: Hospital Episode Statistics (HES), Cancer Waiting Times (CWT), Radiotherapy Dataset (RTDS), Digital Imaging Dataset (DID), the Systemic Anti-Cancer Therapy (SACT) data, National Health Service Breast Screening Programme (NHSBSP) audit.
- Mortality information (including cause) already held in NCRAS

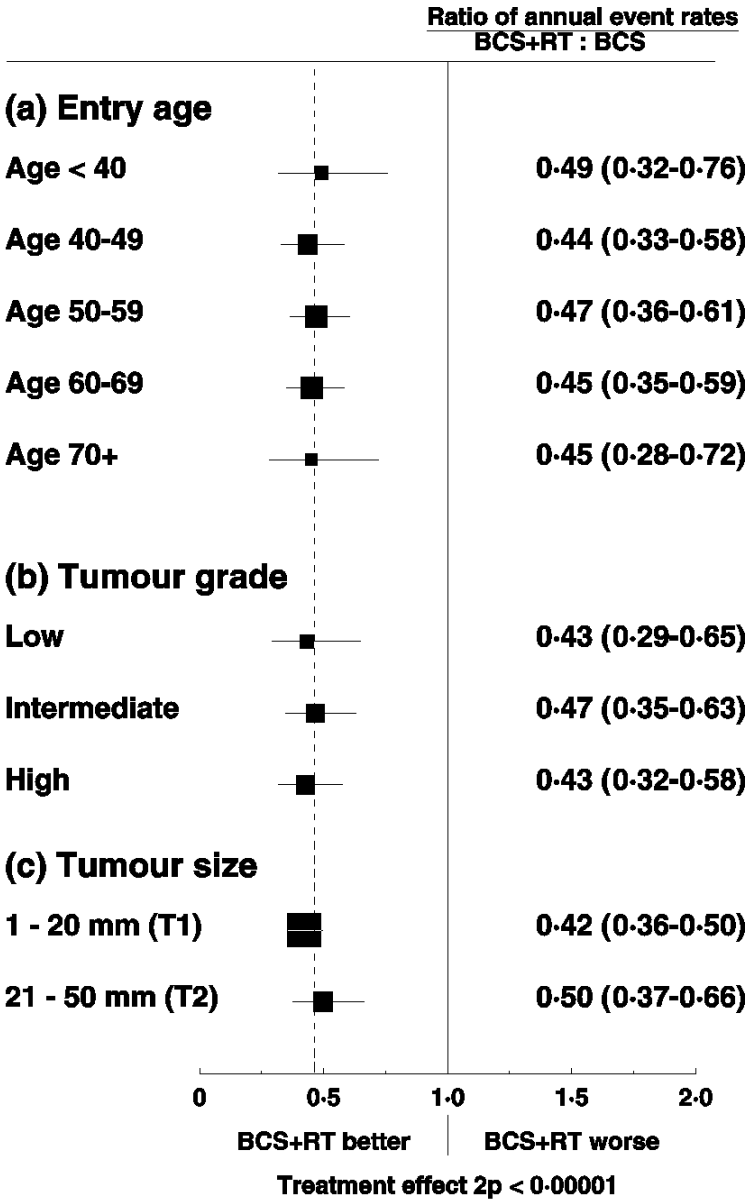
High Quality Data on All Women Diagnosed with Breast Cancer in England, 1997-2016

- Provisional data on over 500,000 women received in Oxford
- Variables: age at diagnosis, ethnicity, fitness index, deprivation score, screen detected, BCS/mast, excision margin, laterality, tumour size, tumour grade, nodal status, ER, PR, Her2, RT, systemic treatments
- Use this data to estimate **Component 1:** for each combination of treatments in common use, mortality rates for recently diagnosed breast cancer patients for patients receiving those treatments

How to be Smart - continued

- For each combination of treatments in common use, need **Component 2:**
- ie, the proportional effect of that treatment on mortality from breast cancer, heart disease and lung cancer
- Obtain these proportional effects from the randomised trials

EBCTCG: Effect of RT after BCS on recurrence and breast cancer mortality in pN0 women



In the randomised trials, the proportional benefit of RT after BCS similar across categories of age, tumour grade and tumour size, etc.

Proportional effects of individual treatments also stable against different background treatments and across calendar year

NB certain exceptions: hormonal therapy in ER+ vs ER-, RT after Mast in pN0 vs pN+

EBCTCG, Lancet, 2011; 378:1707

Now for the *Trick*

For each combination of treatments:

- Divide mortality rates for those receiving all the treatments by the rate ratios from the trials for each individual treatment in turn.
- Hence estimate mortality rates in the absence of each treatment in patients judged suitable for it
- Then estimate cumulative risk for patients without that treatment.

Some examples

- Numbers are preliminary
- For illustration only and so not included in this version