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Welcome to the ESTRO Palliative Care and Radiotherapy Course

Brussels 2017

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Scope of the course

- Common symptoms in advanced cancer
- Pathophysiology of symptoms in advanced cancer

- Pharmacological management
- Radiotherapy in pain, brain metastases, cord compression, lung cancer, liver metastases

- Case studies

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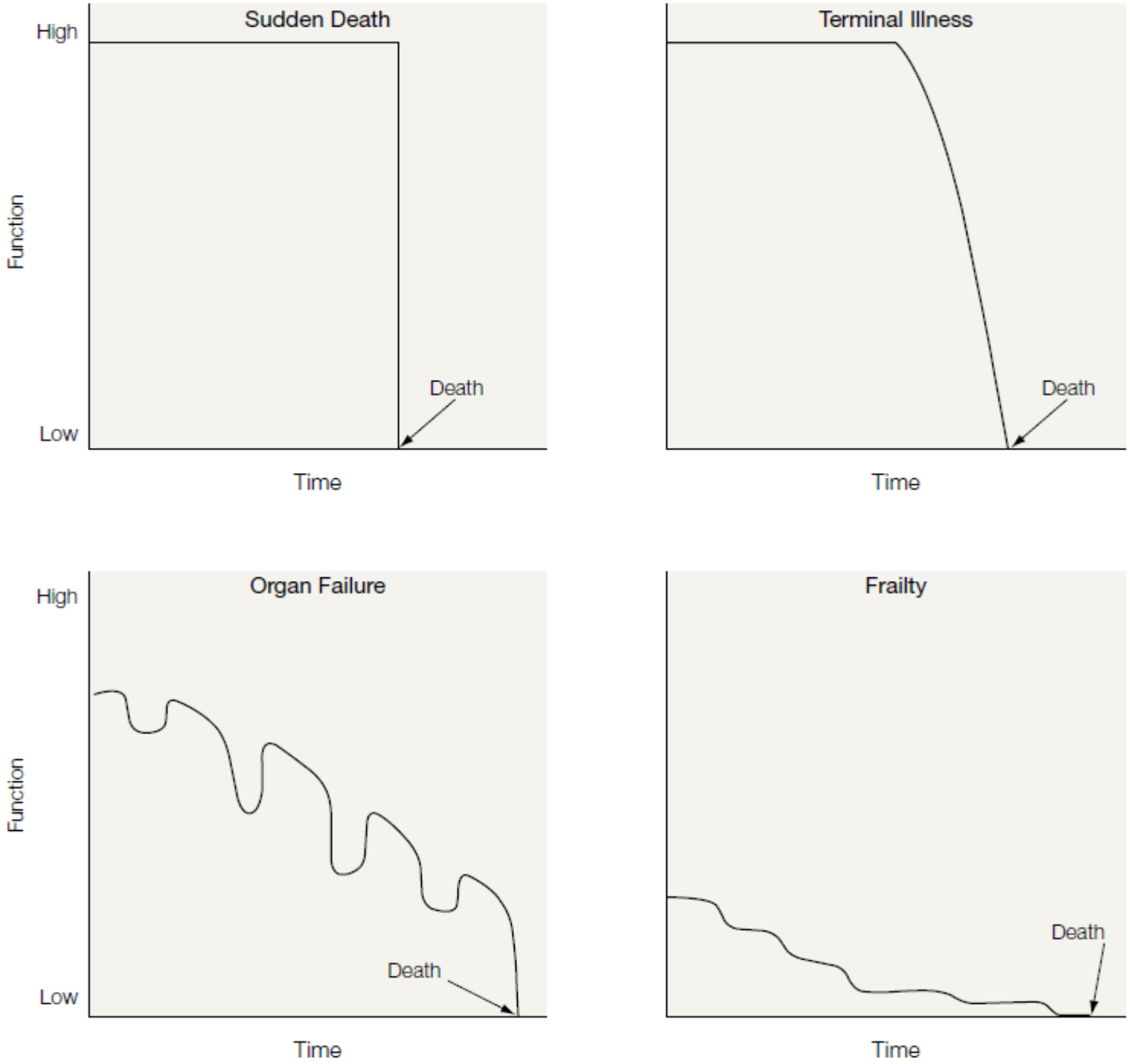
Trajectories of death



Lunney et al JAMA 2003; 289: 2387-2392

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Symptom trends in the last year of life, 1998-2010: A cohort study

Ann Intern Med. 2015 February 3; 162(3): 175–183

Adam E. Singer, MPhil[1,2], Daniella Meeker, PhD, MS[3], Joan M. Teno, MD, MS[4], Joanne Lynn, MD, MA, MS[5], June R. Lunney, PhD, RN[6], and Karl A. Lorenz, MD, MSHS[7,2,3]

		1998	2000	2002	2004	2006	2008	2010
Cancer	Moderate or severe pain	59.8 (52.3, 67.4)	60.5 (54.9, 66.0)	61.1 (57.1, 65.1)	61.7 (58.6, 64.9)	62.4 (58.7, 66.1)	63.0 (57.8, 68.2)	63.7 (56.6, 70.8)
	Any pain	62.1 (54.9, 69.3)	63.3 (58.0, 68.6)	64.6 (60.9, 68.2)	65.8 (63.0, 68.5)	66.9 (63.8, 70.0)	68.1 (63.8, 72.4)	69.3 (63.3, 75.3)
	Depression	51.6 (46.1, 57.0)	52.1 (48.0, 56.2)	52.7 (49.5, 55.8)	53.2 (50.2, 56.2)	53.8 (50.0, 57.6)	54.3 (49.3, 59.4)	54.9 (48.3, 61.6)
	Periodic confusion	39.3 (33.9, 44.6)	40.6 (36.5, 44.6)	41.9 (38.8, 44.9)	43.2 (40.5, 45.9)	44.5 (41.2, 47.8)	45.8 (41.3, 50.3)	47.2 (41.1, 53.3)
	Dyspnea	50.5 (45.1, 55.9)	51.3 (47.1, 55.5)	52.0 (48.7, 55.3)	52.7 (49.6, 55.8)	53.5 (49.9, 57.1)	54.2 (49.6, 58.8)	55.0 (49.0, 61.0)
	Incontinence	42.2 (36.6, 47.9)	42.0 (37.5, 46.5)	41.8 (38.2, 45.3)	41.5 (38.4, 44.7)	41.3 (37.9, 44.7)	41.1 (36.8, 45.3)	40.8 (35.4, 46.3)
	Severe fatigue	75.3 (69.1, 81.6)	76.3 (71.8, 80.9)	77.3 (74.2, 80.4)	78.2 (75.9, 80.5)	79.1 (76.6, 81.7)	80.0 (76.5, 83.5)	80.9 (76.1, 85.7)
	Anorexia	77.1 (72.3, 82.0)	78.2 (74.6, 81.9)	79.3 (76.5, 82.1)	80.3 (77.8, 82.8)	81.3 (78.5, 84.1)	82.3 (78.7, 85.8)	83.2 (78.8, 87.6)
	Frequent vomiting	19.9 (13.5, 26.2)	20.4 (15.3, 25.5)	21.0 (17.1, 24.9)	21.6 (18.6, 24.6)	22.2 (19.3, 25.0)	22.8 (19.2, 26.3)	23.4 (18.5, 28.4)

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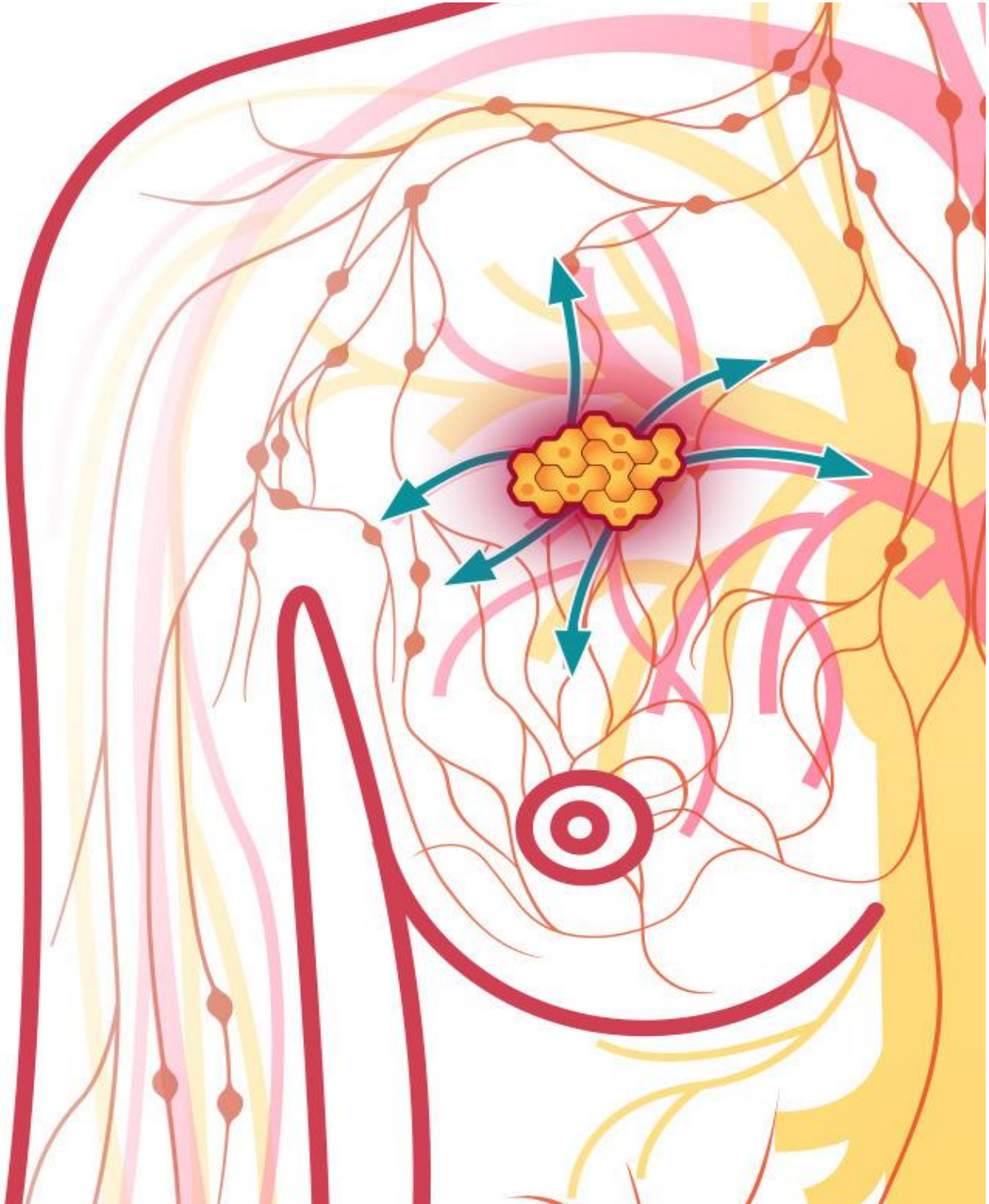

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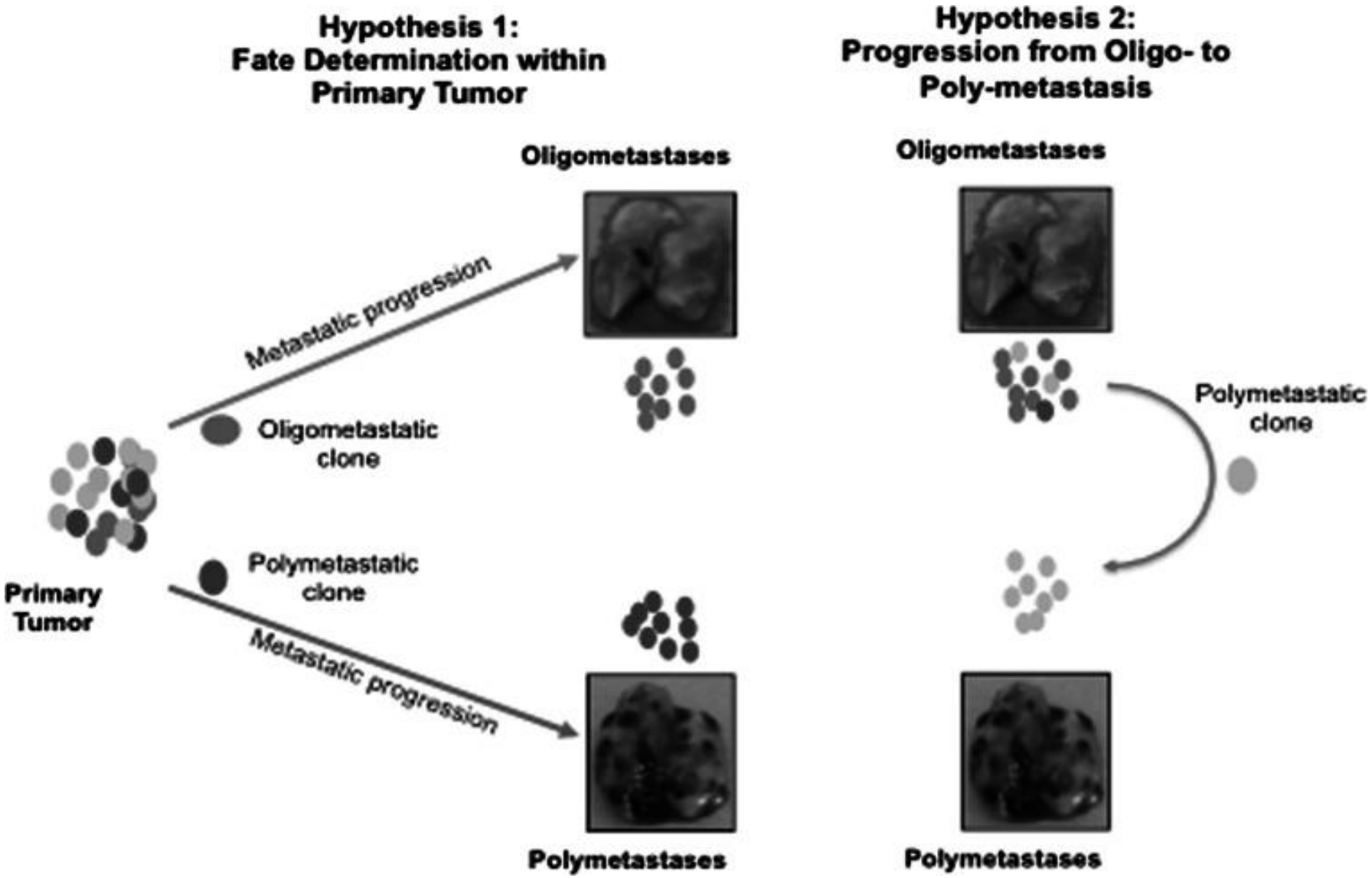

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Clin Exp Metastasis (2014) 31:735–748

Oligometastases

Oligometastatic
A malignancy that has progressed to a limited number of haematogenous metastases, defined in most studies as 1–3 or 1–5 metastatic lesions.

Synchronous oligometastasis
A clinical scenario in which oligometastatic disease is detected at the time of diagnosis of the primary tumour.[111]

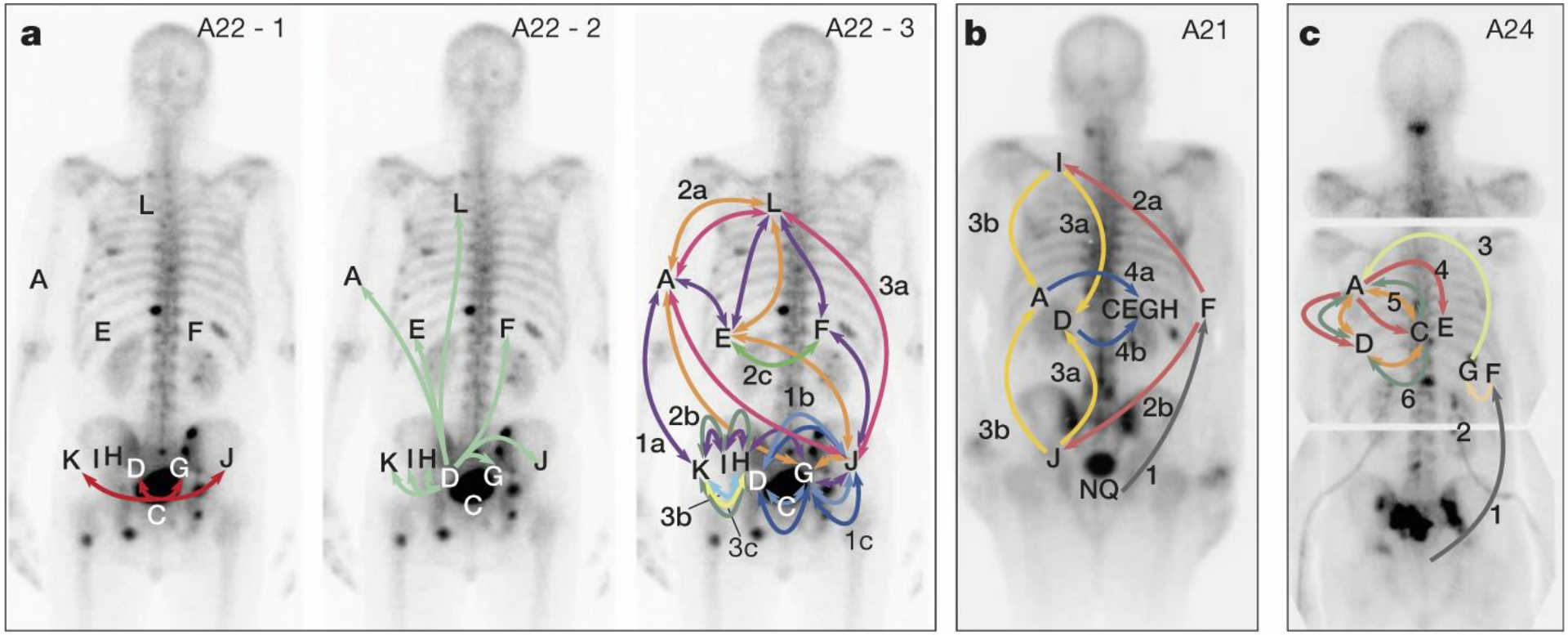
Metachronous oligometastasis
The development of oligometastatic disease after treatment of the primary tumour. The interval for classification of 'metachronous' versus 'synchronous' is not standardized.[111]

Oligorecurrence
Oligometastasis in the setting of a controlled primary tumour.[111]

Oligoprogression
Progression of a limited number of metastatic deposits, while all other metastases are controlled with systemic therapy.

Palma et al, Nature Reviews Clin Oncol 2014

Metastasis-to-metastasis seeding occurs either by a linear or by a branching pattern of spread.



A - L. humerus BM
D - Sem. vesicle
C - Prostate
E - L. adrenal

F - R. adrenal
G - Bladder
H - Pelvic LN
I - L. pelvic LN

J - R. pelvic LN
K - L. pelvic LN
L - L. media. LN

A - L. rib
C - Liver
E - Liver
G - Liver
H - Liver
D - L. adrenal
F - R. rib nod.
I - L. clavicle
J - L. iliac crest
N - GL5 EPE
Q - GL3/5

A - R. axillary LN
C - R. diaphragm
D - R. rib
E - Xiphoid
F - L. lobe liver
G - Falciform ligam.

G Gundem *et al. Nature* **000**, E1-E5 (2015) doi:10.1038/nature14347

Fundamentals of pain management

- Initial assessment
- Diagnosis of the underlying cause
- Initiation of treatment
  - general
  - specific
- Review and reassessment

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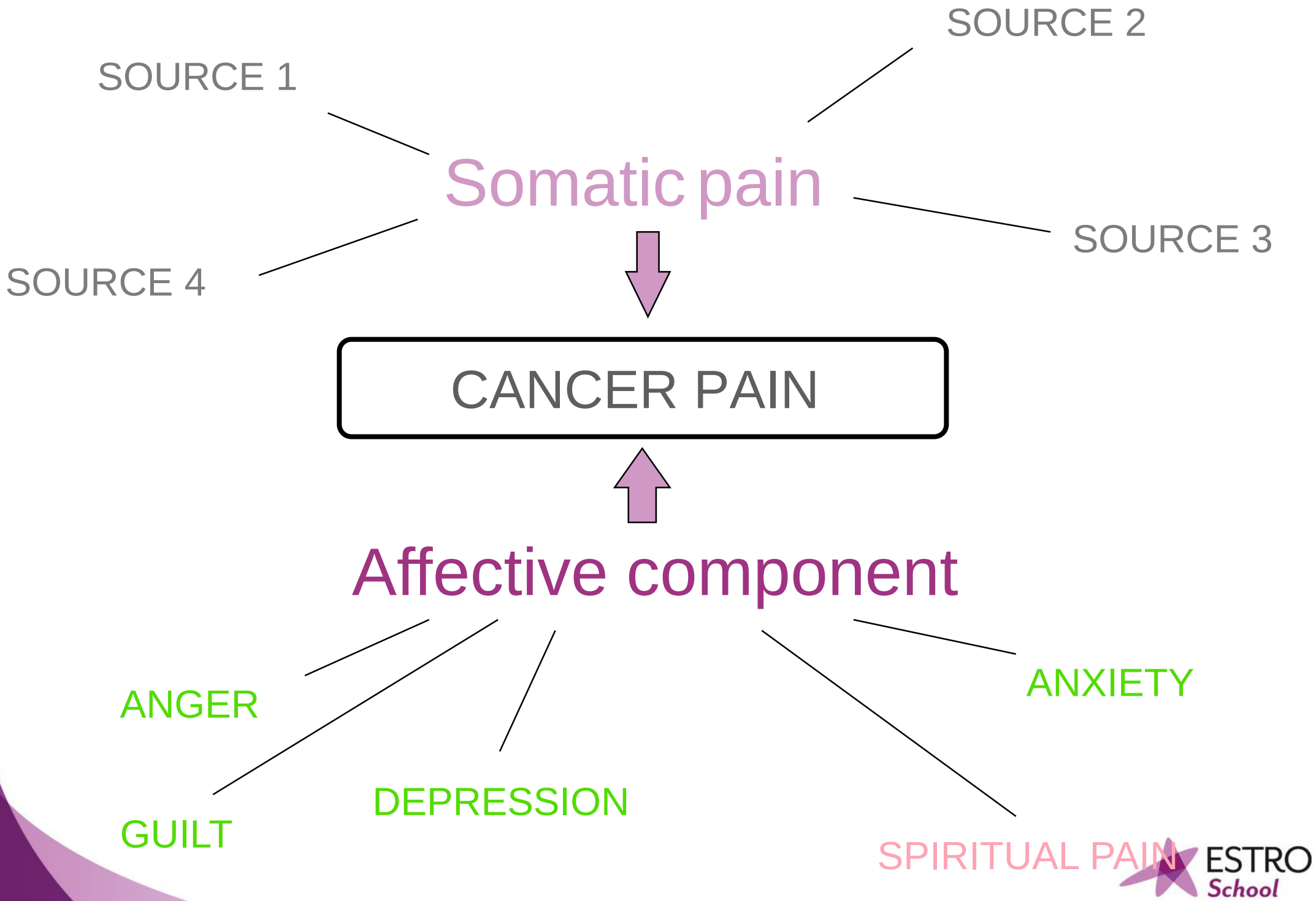
SOURCE 1
SOURCE 2
Somatic pain
SOURCE 3
SOURCE 4
CANCER PAIN
Affective component
ANGER
ANXIETY
GUILT
DEPRESSION
SPIRITUAL PAIN

Categories of cancer pain

Type	Features	Example
Somatic	Localised	Bone mets
	Persistent	Cellulitis
	Tenderness	Myositis
Visceral	Poorly localised	Hepatomegaly
	Variable	Ca Pancreas
	Assoc symptoms	PA nodes
Neuropathic	Nerve distribution	Brachial
	Shooting pain	L Sacral
	Paraesthesia	Spinal root

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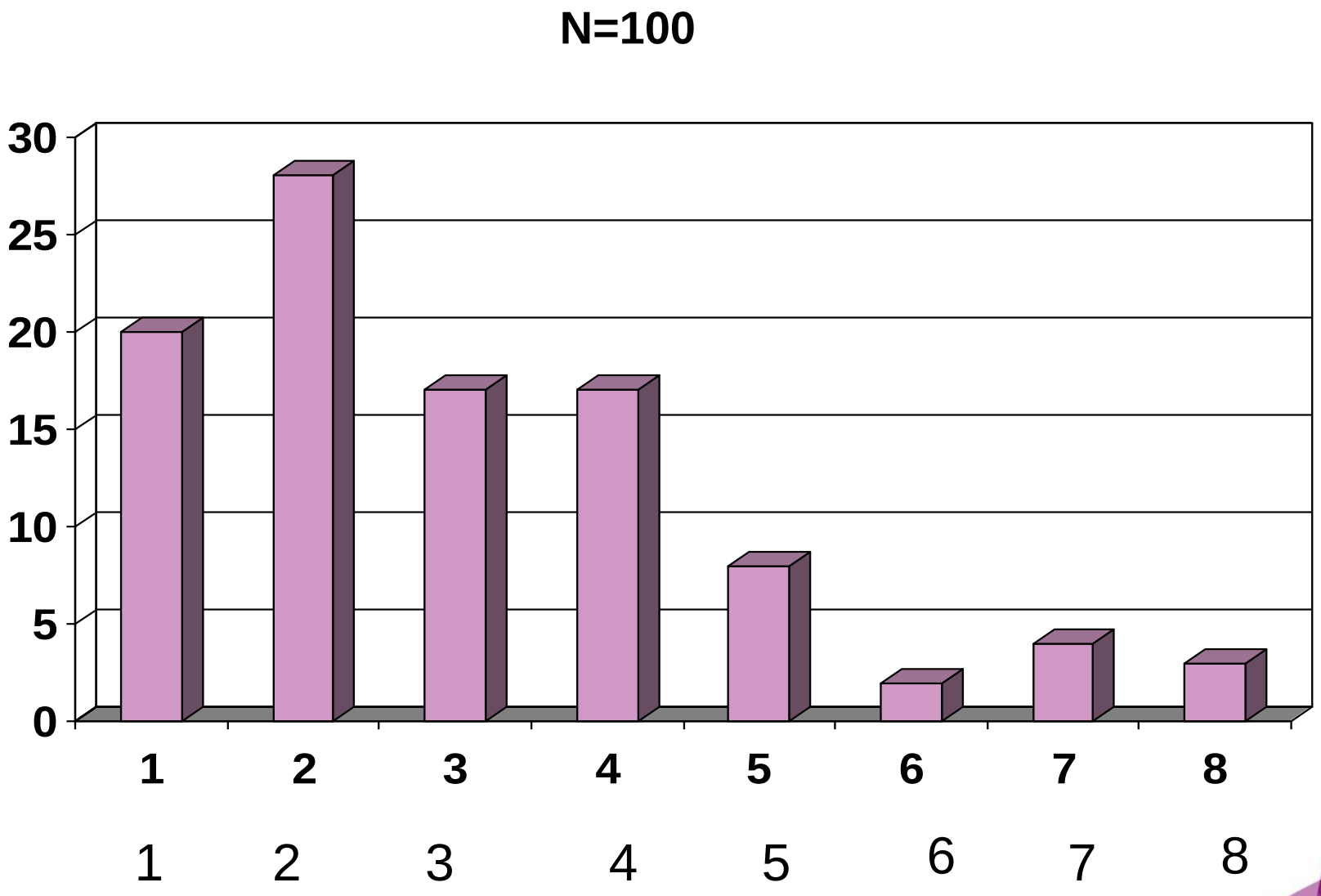
Number of individual pains in cancer patients [Twycross 1983]



Causes of pain in 100 cancer patients

[Twycross 1983]

- Cancer: 67%
- Related to treatment: 5%
- Associated pain: 6%
  [constipation, bed sores, catheters]
- Unrelated pain: 22%
  [Musculoskeletal, migraine etc]

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Palliative radiotherapy

- Bone metastases
- Brain metastases
- Spinal canal compression
- NSCLC
- Bleeding
- Fungation

Optimal palliation

- Shortest, simplest, least toxic treatment……..
  ……..*consistent with efficacy*

- *By definition……*this is a single dose…
  ……..*provided it works*

Preferred place of death

Preferences	Number of patients (n=120)
PPD	
Home	51*
Nursing home	2
Hospice	39
Oncology centre	12
Other hospital	2
Unsure	13
No answer	1
Acceptable places of death†	
Home	80
Nursing home	12
Hospice	97
Oncology centre	77
Other hospital	21
Relative's home	3
Abroad	2
No answer	1

*43% (95% CI 34% to 51%).
†Patient could choose any/all options.

BMJ Supportive & Palliative Care 2011;**1**:310–314.

Unrelated to:
Age
Sex
Cancer site
Marital status

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Preferred place of death

Unrelated to:

Age
Sex
Cancer site
Marital status

Carstairs (deprivation) quintiles			
1	27	23	0.031
2	15	22	
3	4	10	
4	3	11	
5	2	3	

Actual place of death

Actual place of death	Patient's PPD	'Acceptable' place of death for patient	'Unacceptable' place of death for patient
Home (n=20)	15	4	1 (PPD: hospice – 1)
Hospice (n=34)	17	12	3 (PPD: home – 3)
Cancer centre (n=4)	0	3	1 (PPD: hospice – 1)
Other hospital (n=13)	0	2	11 (PPD: home – 5; hospice – 3; cancer centre – 2; unsure – 1)

BMJ Supportive & Palliative Care 2011;**1**:310–314.

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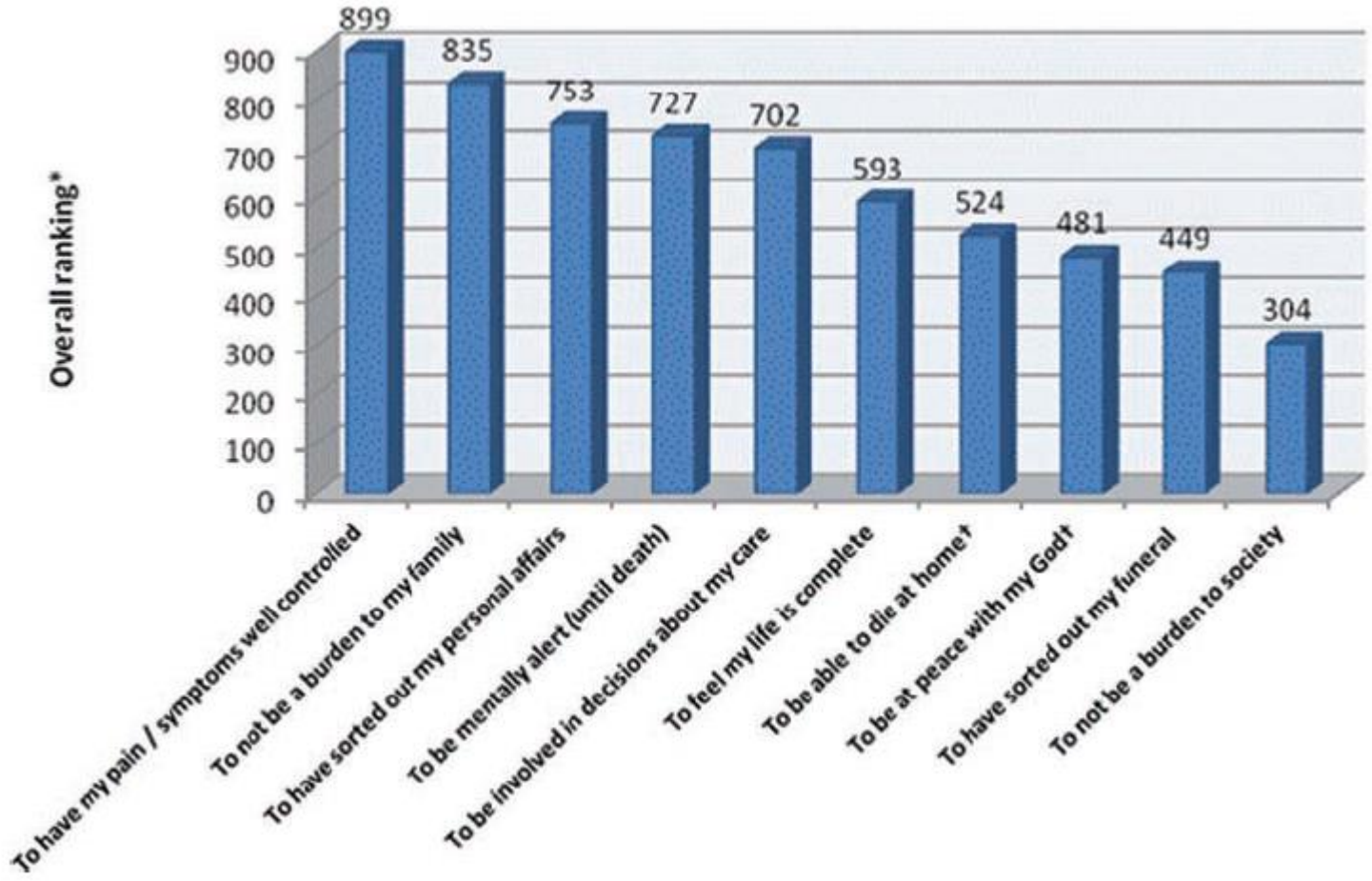
Opinions of patients with cancer on the relative importance of place of death in the context of a 'good death'

Melanie Waghorn,[1] Holly Young,[2] Andrew Davies[1]



BMJ Supportive & Palliative Care 2011;**1**:310–314.

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Opportunity Cost
How much time would you invest?

Prognosis	single#	10#	20#
3m	0.1%	13%	29%
6m	0.05%	7%	14%
12m	0.027%	3.3%	7%

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Scope of the course

- Common symptoms in advanced cancer
- Pathophysiology of symptoms in advanced cancer

- Pharmacological management
- Radiotherapy in pain, brain metastases, cord compression, lung cancer, liver metastases

- Case studies

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Principles of pharmacology in cancer pain

P J Hoskin

Mount Vernon Hospital

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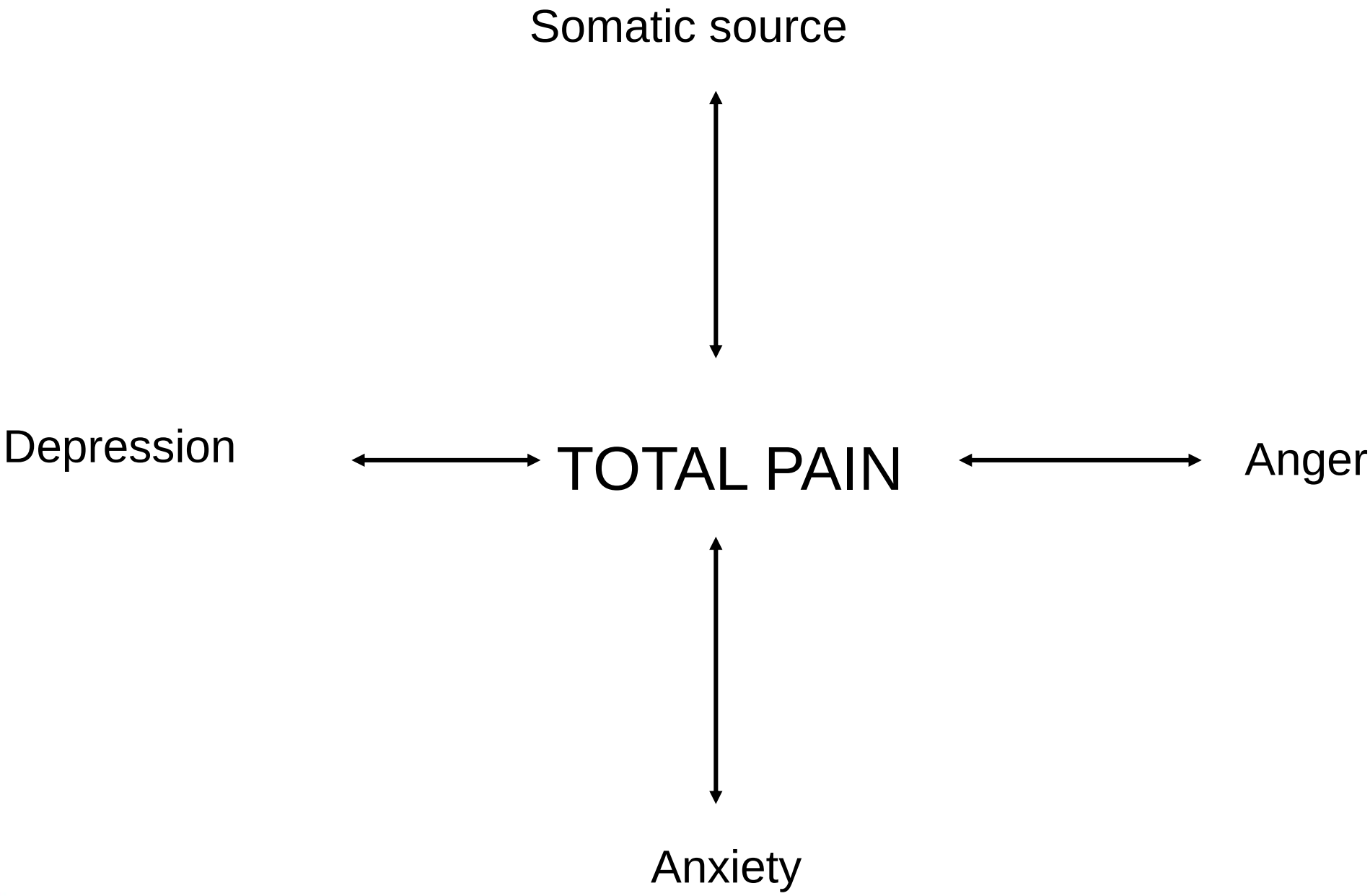
Somatic source
Depression
TOTAL PAIN
Anger
Anxiety

Hope
Reassurance
Explanation
Understanding
Rest
Sleep
Diversion

Analgesics
Anxiolytics
Antidepressants

Threshold raised

Hopelessness
Fear
Uncertainty
Anger
Anxiety
Depression
Fatigue
Insomnia
Discomfort
Isolation
Inactivity

Threshold lowered

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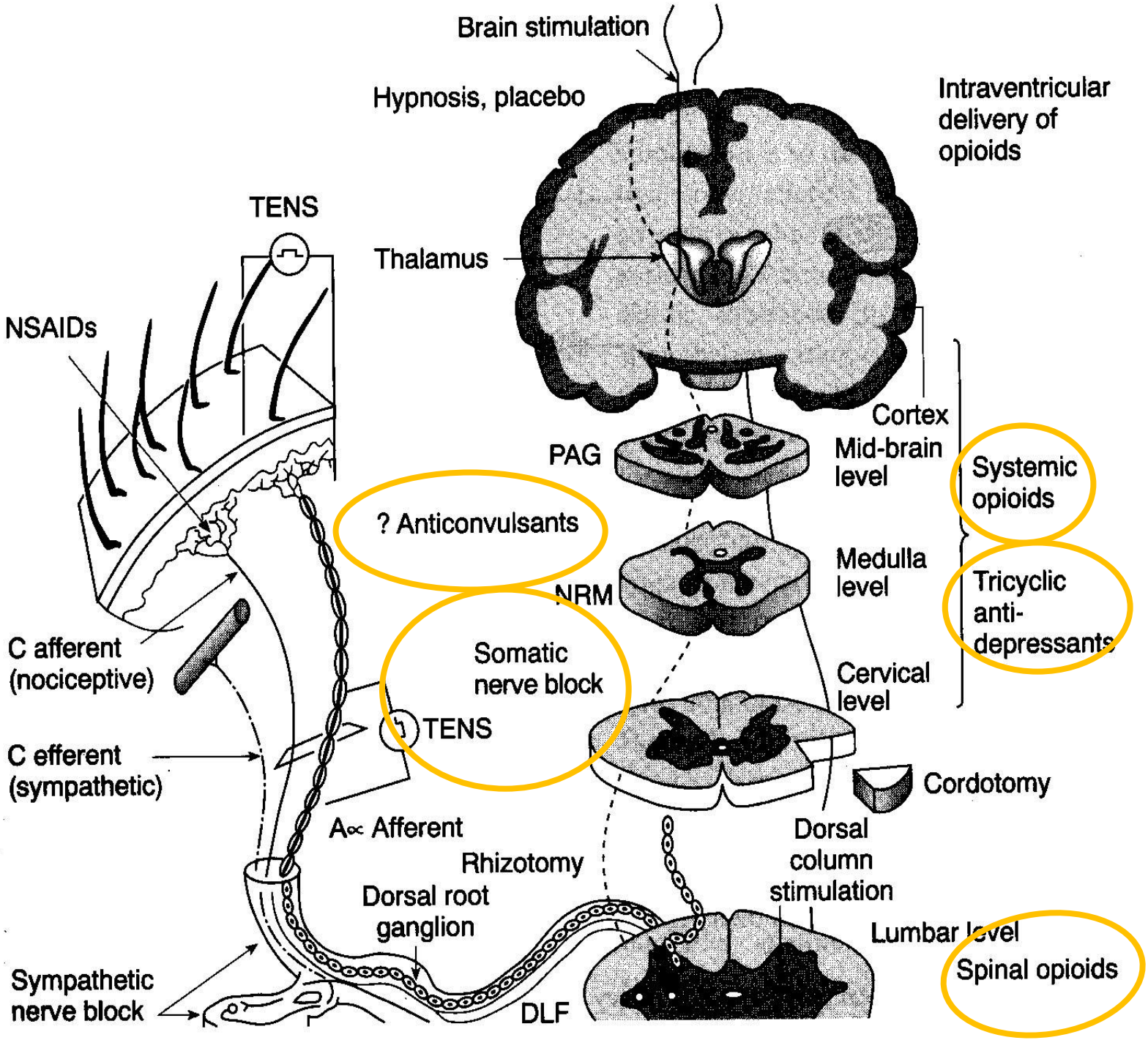
Brain stimulation
Hypnosis, placebo
Intraventricular delivery of opioids
TENS
Thalamus
NSAIDs
Cortex
PAG
Mid-brain level
Systemic opioids
? Anticonvulsants
Medulla level
NRM
Tricyclic anti-depressants
Somatic nerve block
Cervical level
C afferent (nociceptive)
TENS
C efferent (sympathetic)
Cordotomy
Aα Afferent
Rhizotomy
Dorsal column stimulation
Dorsal root ganglion
Lumbar level
Spinal opioids
Sympathetic nerve block
DLF

Fundamentals of pain management

- Initial assessment
- Diagnosis of the underlying cause
- Initiation of treatment
  - general
  - specific
- Review and reassessment

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Principles of symptom control

- Make a diagnosis
- Individualise treatment
- Keep it simple

Treatment of cancer pain
Objectives

- Pain free at night
- Pain free a rest
- Pain free on movement

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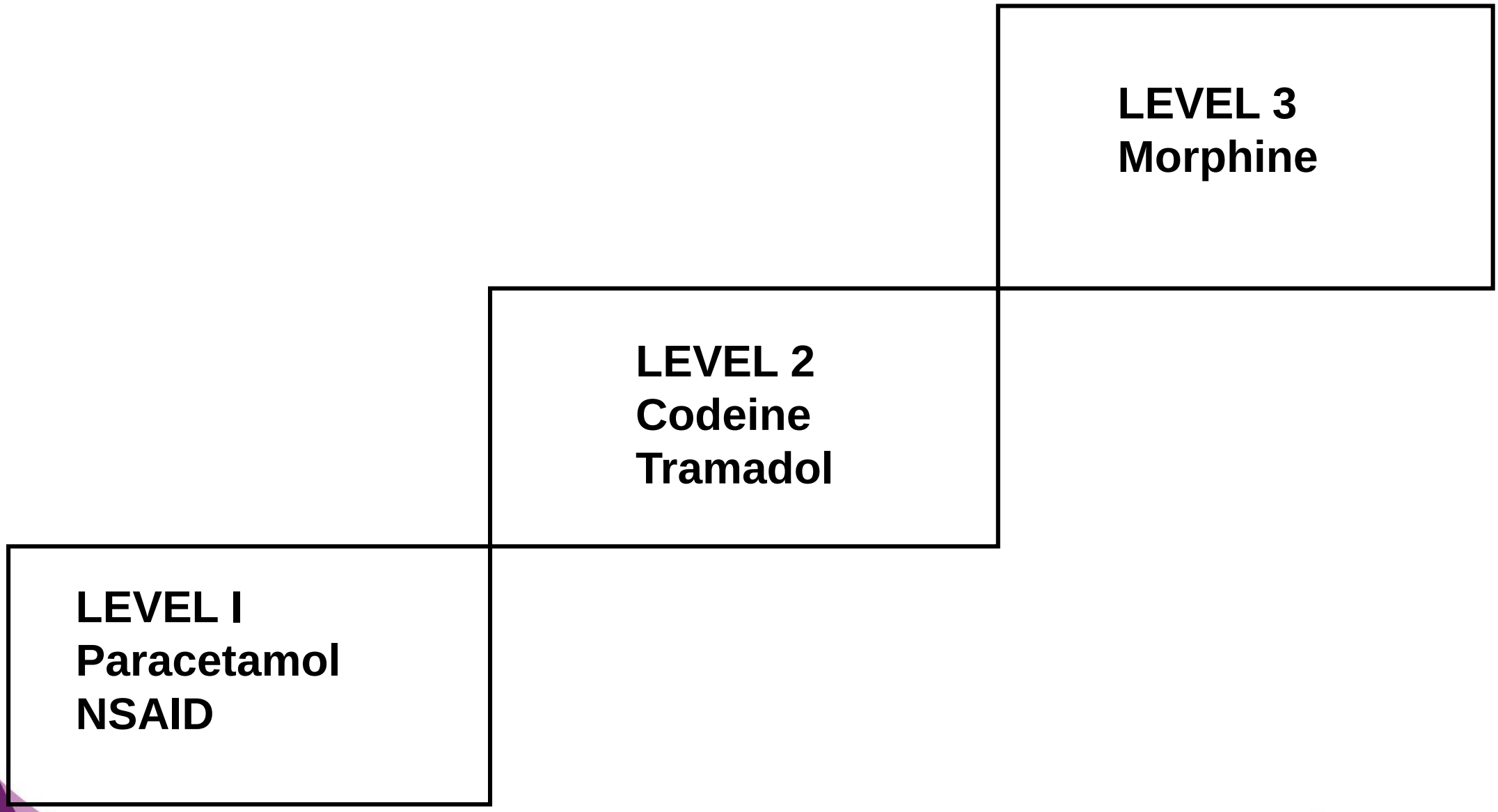
Pharmacological pain relief

- Regular medication to prevent pain
- Ready access to breakthrough medication

- Initiate with immediate release formulations or sustained release formulations and adequate breakthrough

- Monotherapy is not usually sufficient
- Monitor any changes
- Be prepared to withdraw ineffective medication

Analgesic ladder



Analgesics: the WHO ladder

- Prospective series of 129 patients

[Ventafidda et al 1987]

Pain control using ladder in 871

Step 1 alone:	11%
Step 2 alone:	24%
Step 3 alone:	26.5%
All 3 steps:	33.6%

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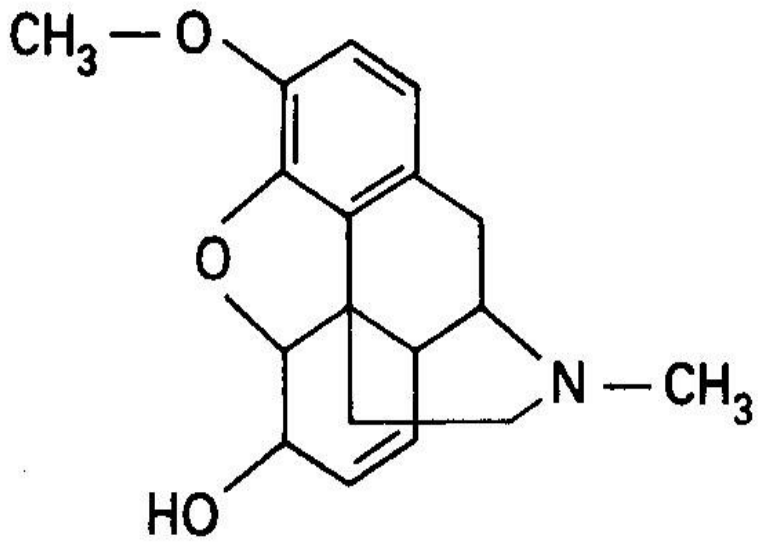
Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC

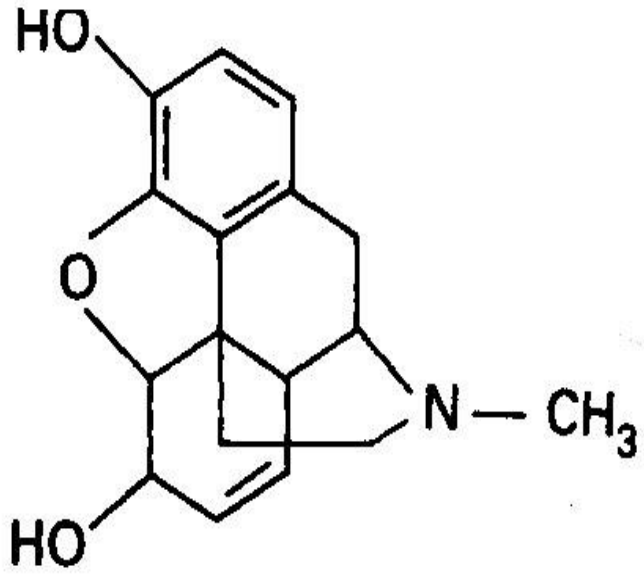
Lancet Oncol 2012; 13: e58–68

Level II analgesics

Codeine	Step II drug only: use alone or in combination with paracetamol; daily doses ≥360 mg not recommended
Tramadol	Step II drug only: use alone or in combination with paracetamol; daily doses ≥400 mg not recommended
Hydrocodone	Step II drug only: used as a substitute for codeine in some countries
Oxycodone	Step II opioid when used at low doses (eg, ≤20 mg per day) alone or in combination with paracetamol
Morphine	Step II opioid when used at low doses (eg, ≤30 mg per day)
Hydromorphone	Step II opioid when used at low doses (eg, ≤4 mg per day)



Codeine



Morphine

Tramadol

- Weak opioid agonist
- Acts on noradrenaline and 5HT uptake in spinal cord

- Single dose efficacy 150mg = 60mg codeine

- Chronic use = codeine
- Similar side -effect profile to codeine/DHC
  - ?less constipating
  - NB epileptogenic with phenothiazines

- Max dose 100mg 6hrly = morphine 10mg 4 hourly

Opioid drugs

AGONISTS

Morphine
Codeine
Oxycodone
Dihydrocodeine
Hydromorphone
Pethidine
Levorphanol
Oxymorphone
Methadone
Fentanyl
Dextropropoxyphene
Diamorphine
Tramadol
Phenazocine
Dextromoramide

PARTIAL AGONISTS

Buprenorphine

AGONIST-ANTAGONIST

Pentazocine
Butorphanol
Nalbuphine
Dezocine
Meptazinol

ANTAGONISTS

Naloxone
Naltrexone (methylnaltrexone)
Naloxegol

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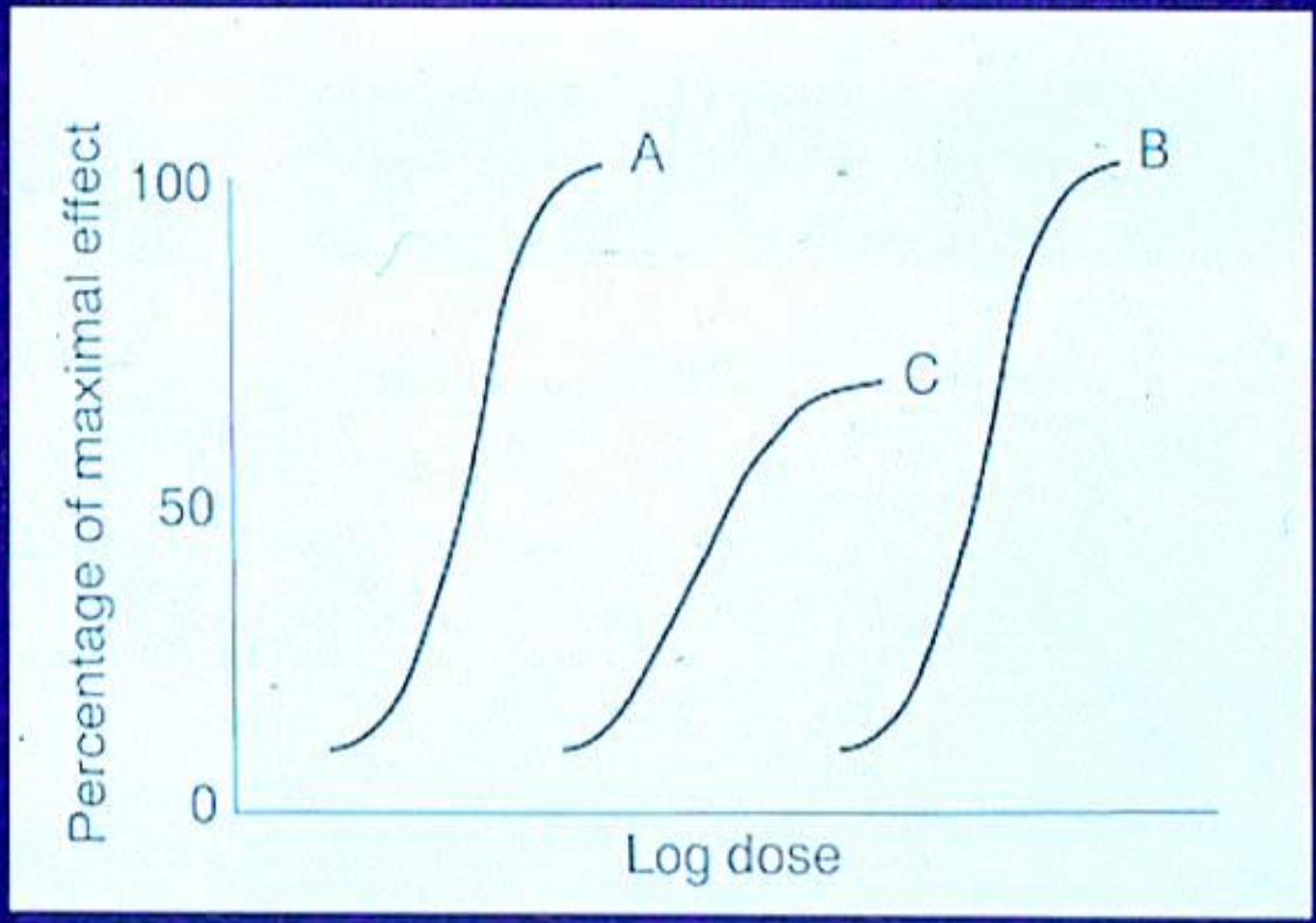
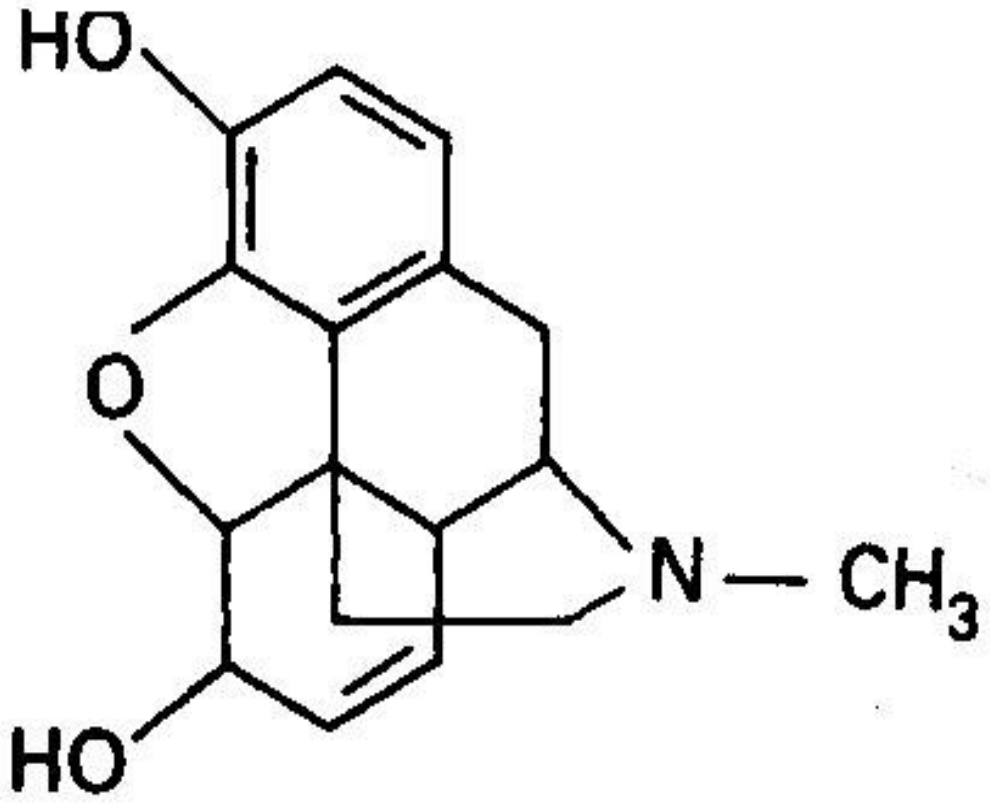
Dose response curves for pure agonists (A) and (B) and partial agonist (C)





Morphine

Opioid receptors

- μ analgesia, respiratory depression
  miosos, euphoria, reduced GI motility
- δ analgesia (in animal models)
- κ analgesia, dysphoria, miosis
  psychotomimetic effects
  respiratory depression

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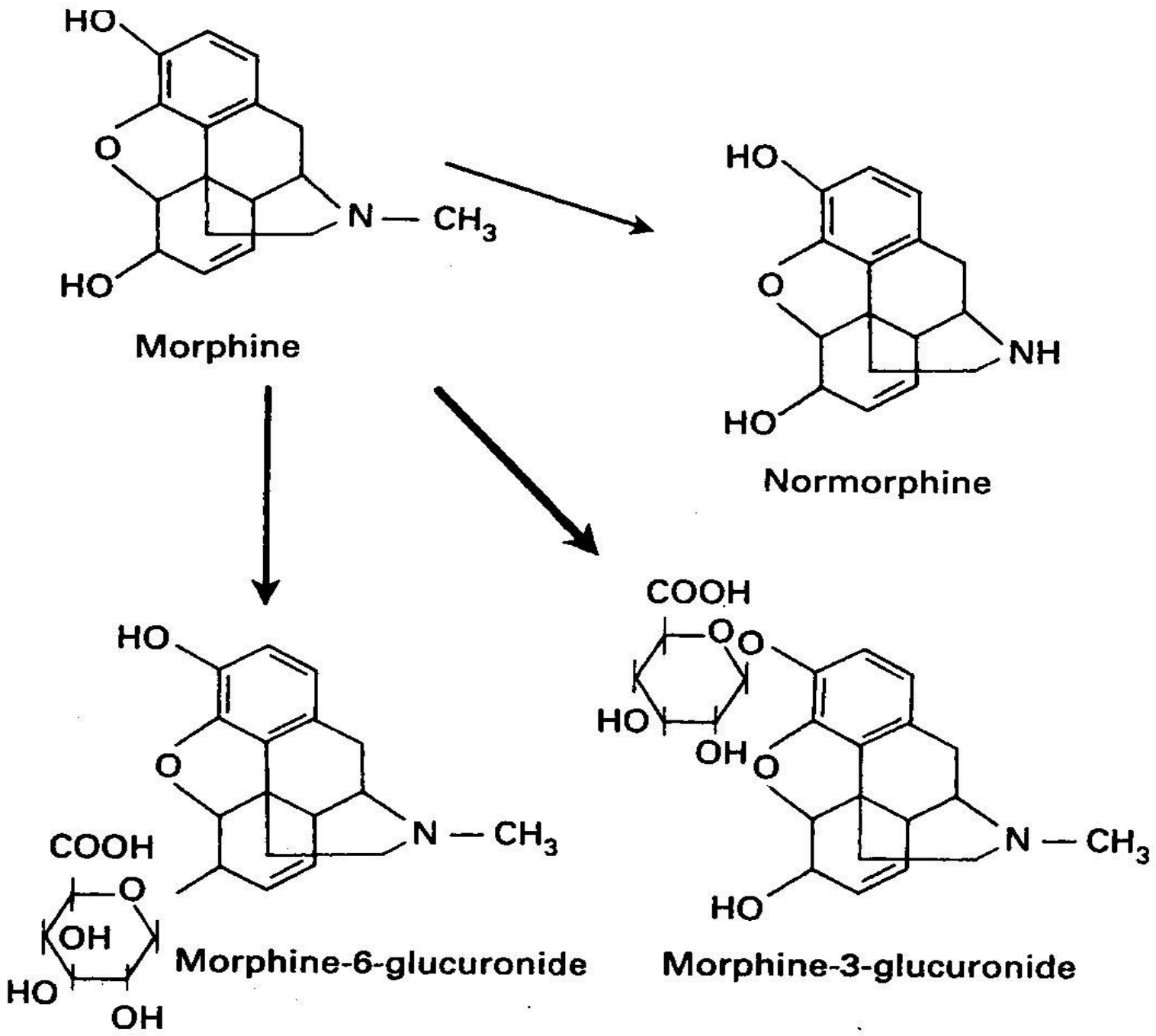
Level III analgesia

- Morphine

- Immediate release 4 hourly or controlled release 12 hourly
- If immediate release a double dose at night
- Breakthrough as required
- Laxative mandatory
- Anti-emetic access essential

Morphine pharmacokinetics

- Oral bioavailability around 30%
- Similar rectal absorption
- Plasma T½ 2 to 3 hours
- Extensive first pass metabolism
- Major metabolites are M3G and M6G
- Renal excretion of parent drug and metabolites
- Enterohepatic circulation also occurs



Morphine metabolites

- Active: M6G
  Codeine

- Inactive: M3G
  Normorphine
  M ethereal sulphate

Morphine metabolites; plasma levels

- Morphine: M3G 1: 20-30
- Morphine: M6G 1: 3-10

M6G analgesic efficacy

Relative analgesic efficacy: rat hot plate model

	Morphine	M6G
Shimomura et al 1971		
Subcutaneous	1	3.7
Intracerebral	1	45
Pasternak et al 1987		
Intraventricular	1	20

Bioavailability of M6G

Route	Ratio $AUC_{morphine} : AUC_{M6G}$
IV	1: 2.0
Oral solution	1: 10.9
Oral MST	1: 11.1
Buccal	1: 11.0

Morphine: ***Dose titration***

- Starting dose is 10mg four hourly
- Double dose if ineffective after 48 hours up to 80mg then use 50% increments
- Breakthrough dose must be

  same as 4 hourly dose

- Median 4 hourly dose requirement is 40 mg

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Controlled release morphine

- 8 hourly, 12 hourly or 24 hourly

- If switching from 4 hourly morphine start from same total 24 hour dose as immediate release morphine once dose requirements defined by titration
- No loading dose required

- Ensure breakthrough morphine also available
- Anticipate slow increase in morphine dose with time

- Median dose in advanced cancer 40-60mg 4 hourly

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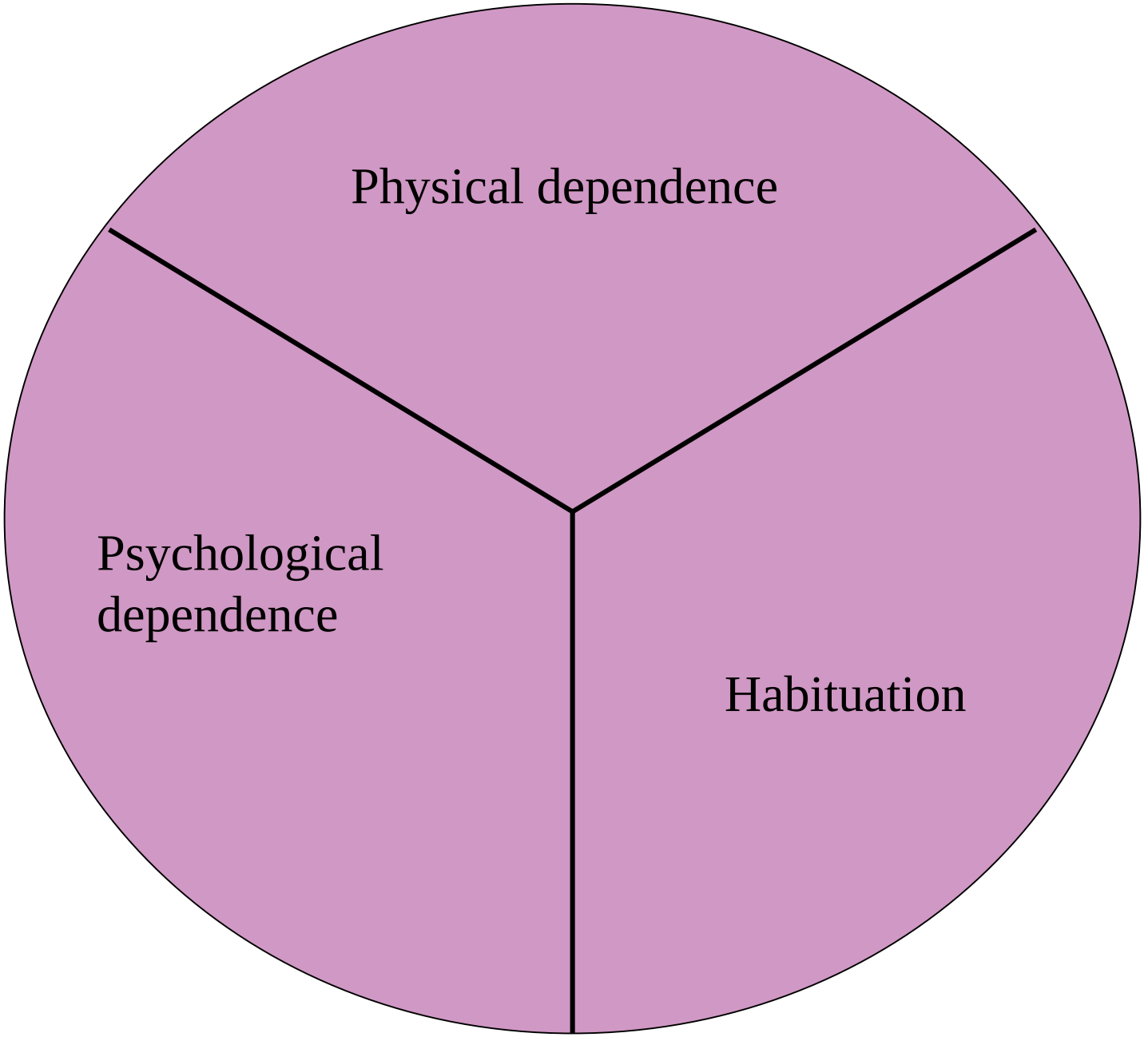
Respiratory depression

- Only seen with doses above those needed for analgesia or where accumulation occurs due to inappropriate dosing or renal failure
- Receptor tolerance develops with titration
- Pain is the ‘physiological antagonist’ of respiratory depression


Physical dependence
Psychological dependence
Habituation

Opioid pseudoaddiction

- Abnormal behaviour as a direct consequence of inadequate pain control:

Inadequate prescription of analgesia

↓

Escalation of analgesic demands

Associated behavioural change to convince others of pain severity

↓

Crisis of mistrust

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Parenteral opioids

- ***NOT*** intrinsically more potent: dose ratio 1: 2-3

- Appropriate only where drug delivery is a problem
  - intestinal obstruction
  - intractable vomiting
  - complete dysphagia
  - falling LOC
  - AP resection

- Diamorphine used only because more soluble

Transdermal fentanyl

- Fentanyl more potent than morphine;
  - equianalgesic dose 25µg/hr = 10-20mg 4 hourly
- Morphine required for breakthrough pain

- Controlled release formulation
- T½e is around 12 hours
- Absorption temperature dependent

- Side-effect profile similar to morphine
- Morphine ⟶ Fentanyl may cause withdrawal reaction in 10% …..? 24 hour overlap period required

Pain poorly responsive to opioids

- Opioid irrelevant pain
- Opioid intolerance
- True opioid resistance

Pain poorly responsive to opioids

- Opioid irrelevant pain
  - Reassess: neuropathic, non-cancer
  - Introduce adjuvant analgesics
  - Review indications for non-drug therapy
- Opioid intolerance
- True opioid resistance

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Pain poorly responsive to opioids

- Opioid irrelevant pain
- Opioid intolerance
- True opioid resistance

Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC

Lancet Oncol 2012; 13: e58–68

	Relative analgesic ratio	Strength of the recommendation for use
Oral morphine to oral oxycodone	1:1·5	Strong
Oral oxycodone to oral hydromorphone	1:4	Strong
Oral morphine to oral hydromorphone	1:5	Weak
Oral morphine to TD buprenorphine*	75:1	Weak
Oral morphine to TD fentanyl†	100:1	Strong

TD=transdermal. *Example: 60 mg oral morphine to 35 µg/h TD buprenorphine (equivalent to 0·8 mg per 24 h). †Example: 60 mg oral morphine to 25 µg/h TD fentanyl (equivalent to 0·6 mg per 24 h).

Pain poorly responsive to opioids

- Opioid irrelevant pain
- Opioid intolerance
- True opioid resistance

Opioid resistance: ‘wind up’

- ***Allodynia:*** altered sensitivity of central neurones with relatively minor pain being perceived as severe pain

- NMDA (N-methyl-D-aspartate receptors mediate allodynia

- NMDA receptor antagonists eg methadone or ketamine may be of value in resetting opoioid tolerance: hence work best ***with*** morphine

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Ketamine

- Indicated in allodynia and hyperalgesia

- Use needs careful supervision:
  - continue opioids but titrate dose down
  - haloperidol or benzodiazepine may be indicated for psychotomimetic effects
  - benzodiazepine will increase bioavailability by inhibition of liver metabolism

Incident pain

- Short acting strong opioid:
  - Dextromoramide
  - Fentanyl 'lollipop'

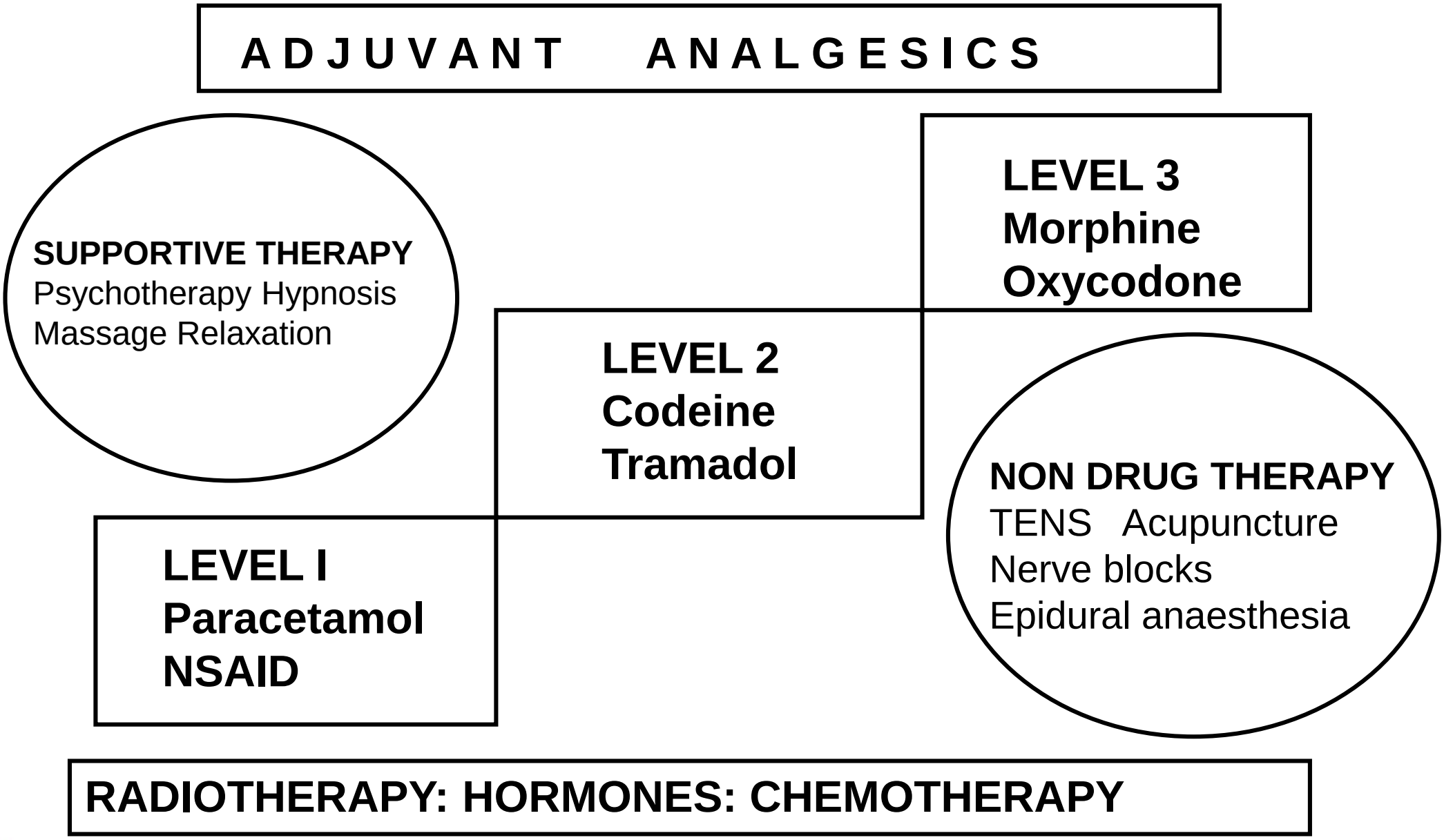
Adjuvant analgesics

- Modify underlying pain process
- Consider at all stages of analgesic ladder

Adjuvant analgesics

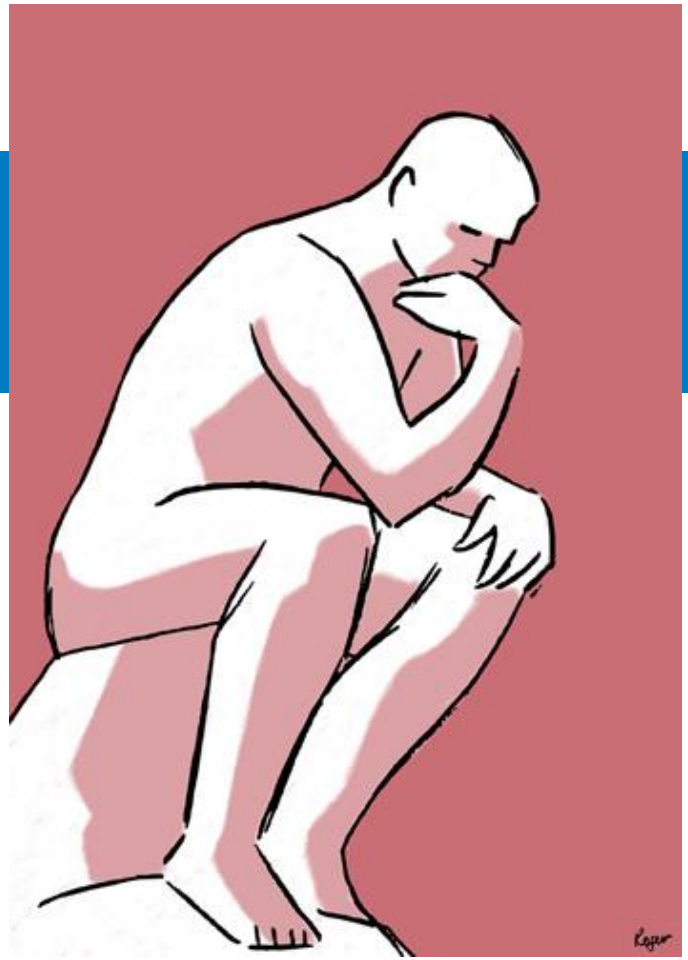
- NSAIDs
- Steroids
- Anxiolytics
- Antidepressants
- Neuroleptics
- Anticonvulsants
- Muscle relaxants
- Bisphosphonates

Analgesic ladder



Leiden University
Medical Center

Evaluation of pain and other symptoms



Signal, screen, monitor, diagnose

Yvette van der Linden

Centre of Expertise Palliative Care

& Dept. of Radiotherapy

Why should we evaluate? When… ? How… ?

Why…….

- to list all complaints
- to accomplish proactive care
- to check what your doing!
- to integrate a proactive attitude

-> apply method of palliative reasoning

" the sooner any symptom load is diminished, the sooner improvement (stabilizing) QoL, and, if treatment not effective, switch to another"

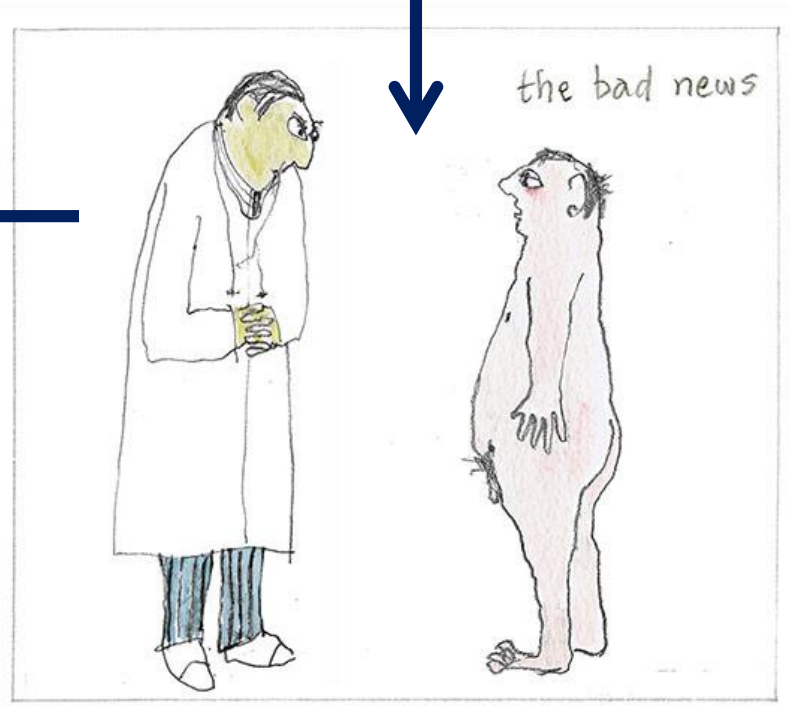
When…….

- as soon as you expect any treatment effect
  - Pain medication -> 24 hrs
  - RT for bone mets -> 4 weeks

How…….

- simply by asking? Yes, but…….


I've been so
forgetful
lately.
I've been so
forgetful
lately.


the bad news


KARLSSON

Use the right measurement tools

1. Signalling
2. Monitoring
3. Screening
4. Diagnostic

Use the right measurement tools

1. Signalling

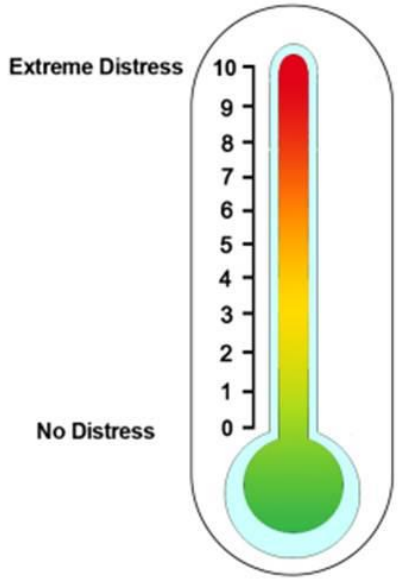
- *What's bothering the patient?*
- *What is the intensity of the symptom?*

Example

- yes / no

The Distress Thermometer

First please circle the number (0-10) that best describes how much distress you have been experiencing in the past week including today.



Second, please indicate if any of the following has been a problem for you in the past week including today. Be sure to check YES or NO for each.

YES	NO	Practical Problems
☐	☐	Child Care
☐	☐	Housing
☐	☐	Insurance/financial
☐	☐	Transportation
☐	☐	Work/school
		Family Problems
☐	☐	Dealing with children
☐	☐	Dealing with partner
☐	☐	Dealing with close
☐	☐	Friend/relative
		Emotional Problems
☐	☐	Depression
☐	☐	Fears
☐	☐	Nervousness
☐	☐	Sadness
☐	☐	Worry
☐	☐	Loss of interest in usual activities
☐	☐	**Spiritual/religious concerns**

YES	NO	Physical Problems
☐	☐	Appearance
☐	☐	Bathing/dressing
☐	☐	Breathing
☐	☐	Changes in urination
☐	☐	Constipation
☐	☐	Diarrhoea
☐	☐	Eating
☐	☐	Fatigue
☐	☐	Feeling Swollen
☐	☐	Fevers
☐	☐	Getting around
☐	☐	Indigestion
☐	☐	Memory/concentration
☐	☐	Mouth sores
☐	☐	Nausea
☐	☐	Nose dry/congested
☐	☐	Pain
☐	☐	Sexual
☐	☐	Skin dry itchy
☐	☐	Sleep
☐	☐	Tingling in hands/feet

Other problems

_____

_____

_____

Use the right measurement tools

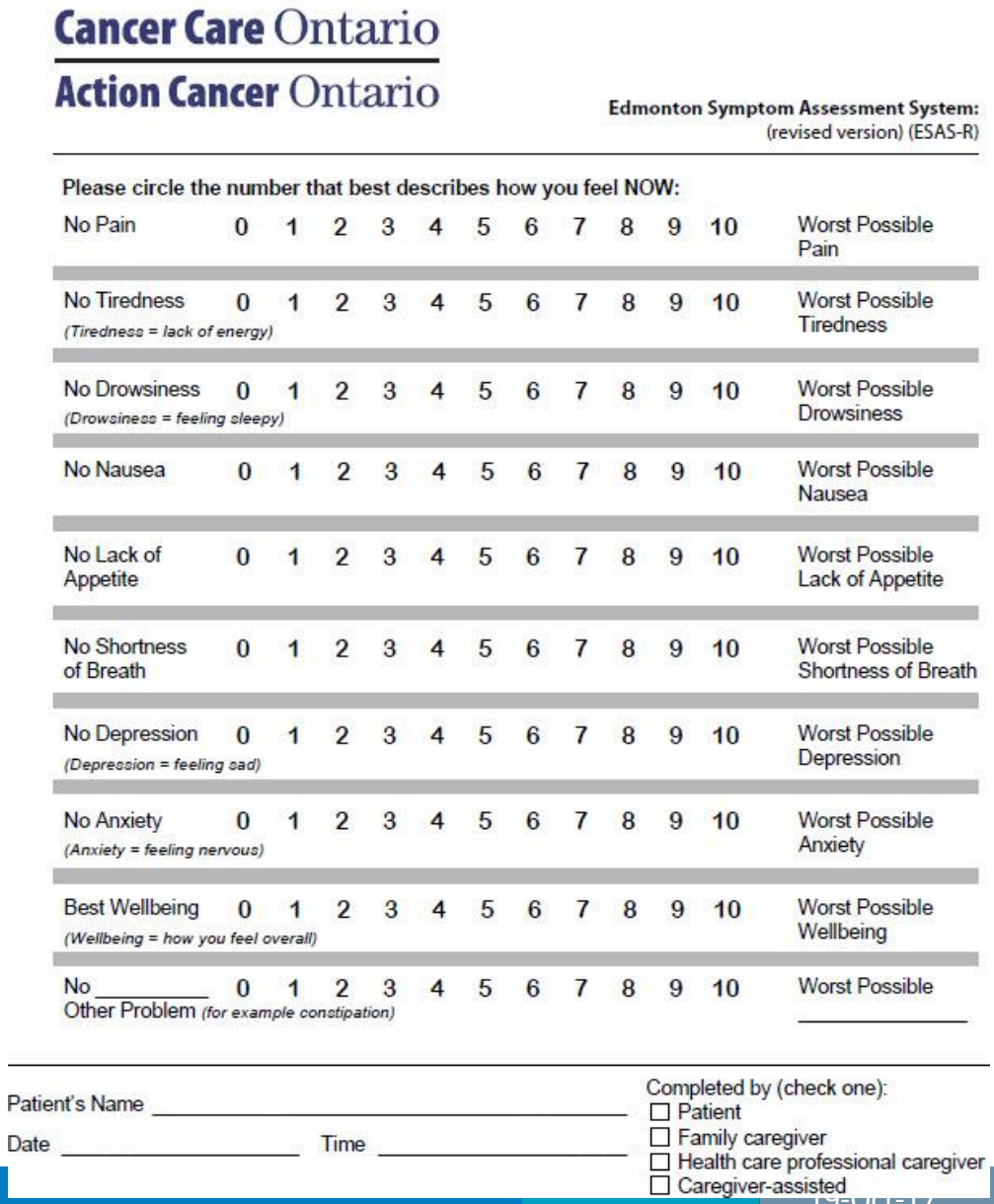
1. Signalling

2. Monitoring

- *What is the variation in time?*
- *What is the effect of treatment?*

Example

- ESAS -> NRS



Cancer Care Ontario
Action Cancer Ontario

Edmonton Symptom Assessment System:
(revised version) (ESAS-R)

Please circle the number that best describes how you feel NOW:

No Pain	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Pain
No Tiredness *(Tiredness = lack of energy)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Tiredness
No Drowsiness *(Drowsiness = feeling sleepy)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Drowsiness
No Nausea	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Nausea
No Lack of Appetite	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Lack of Appetite
No Shortness of Breath	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Shortness of Breath
No Depression *(Depression = feeling sad)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Depression
No Anxiety *(Anxiety = feeling nervous)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Anxiety
Best Wellbeing *(Wellbeing = how you feel overall)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Wellbeing
No _____ Other Problem *(for example constipation)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible _____

Patient's Name _____

Date _____ Time _____

Completed by (check one):
☐ Patient
☐ Family caregiver
☐ Health care professional caregiver
☐ Caregiver-assisted

Use the right measurement tools

1. Signalling
2. Monitoring

3. Screening

- Standardized measurement

using a specific tool, that indicates the presence of a diagnosis (e.g. delirium, depression)

Example

Hospital Anxiety and Depression Score (HADS)

This questionnaire helps your physician to know how you are feeling. Read every sentence. Place an "X" on the answer that best describes how you have been feeling during the LAST WEEK. You do not have to think too much to answer. In this questionnaire, spontaneous answers are more important

A	**I feel tense or 'wound up':**	
	Most of the time	3
	A lot of the time	2
	From time to time (occ.)	1
	Not at all	0
D	**I still enjoy the things I used to enjoy:**	
	Definitely as much	0
	Not quite as much	1
	Only a little	2
	Hardly at all	3
A	**I get a sort of frightened feeling as if something awful is about to happen:**	
	Very definitely and quite badly	3
	Yes, but not too badly	2
	A little, but it doesn't worry me	1
	Not at all	0
D	**I can laugh and see the funny side of things:**	
	As much as I always could	0
	Not quite so much now	1
	Definitely not so much now	2
	Not at all	3
A	**Worrying thoughts go through my mind:**	
	A great deal of the time	3
	A lot of the time	2
	From time to time, but not often	1
	Only occasionally	0
D	**I feel cheerful:**	
	Not at all	3
	Not often	2
	Sometimes	1
	Most of the time	0
A	**I can sit at ease and feel relaxed:**	
	Definitely	0
	Usually	1
	Not often	2
	Not at all	3

D	**I feel as if I am slowed down:**	
	Nearly all the time	3
	Very often	2
	Sometimes	1
	Not at all	0
A	**I get a sort of frightened feeling like "butterflies" in the stomach:**	
	Not at all	0
	Occasionally	1
	Quite often	2
	Very often	3
D	**I have lost interest in my appearance:**	
	Definitely	3
	I don't take as much care as I should	2
	I may not take quite as much care	1
	I take just as much care	0
A	**I feel restless as I have to be on the move:**	
	Very much indeed	3
	Quite a lot	2
	Not very much	1
	Not at all	0
D	**I look forward with enjoyment to things:**	
	As much as I ever did	0
	Rather less than I used to	1
	Definitely less than I used to	2
	Hardly at all	3
A	**I get sudden feelings of panic:**	
	Very often indeed	3
	Quite often	2
	Not very often	1
	Not at all	0
D	**I can enjoy a good book or radio/TV program:**	
	Often	0
	Sometimes	1
	Not often	2
	Very seldom	3

Zigmond, AS; Snaith, RP (1983).

Use the right measurement tools

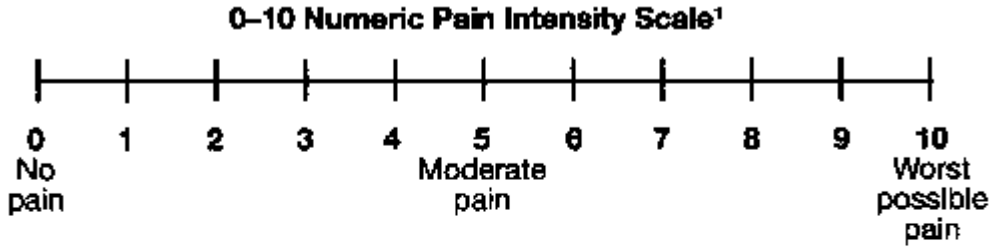
1. Signalling
2. Monitoring
3. Screening

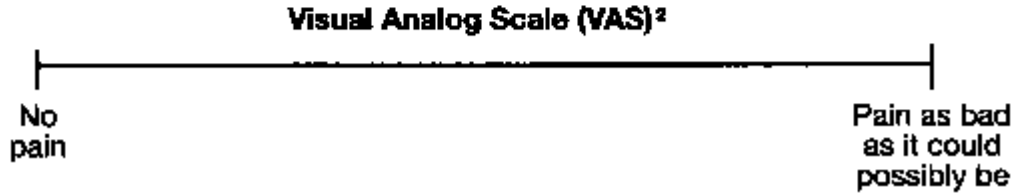
4. Diagnostic
- Using objective criteria to diagnose (e.g. depression using DSM V)

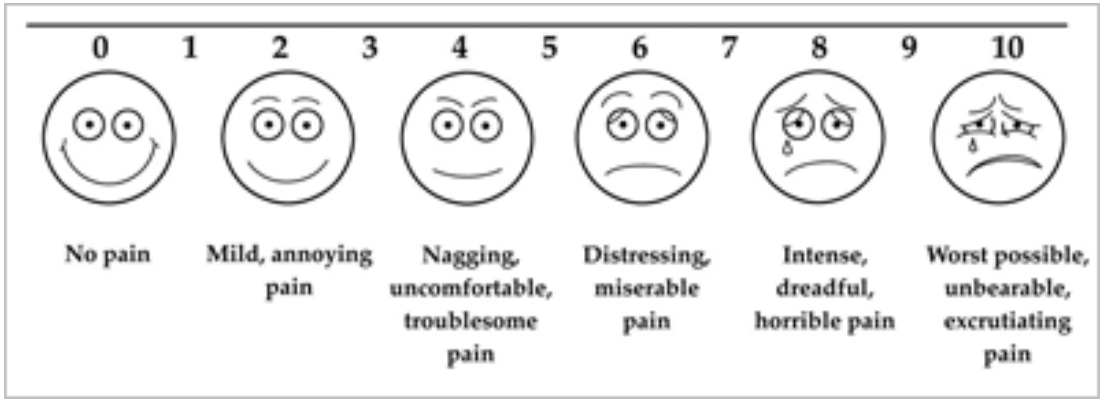
Tools for pain

Unidimensional

- NRS
  - Cut off 4-5
  - ≥ 2 points reduction
- VAS







Multidimensional

- Brief Pain Inventory
  - NRS
    - Last three days
  - 7 QoL questions
  - Pain medication intake

(Cleeland and Ryan, 1994)

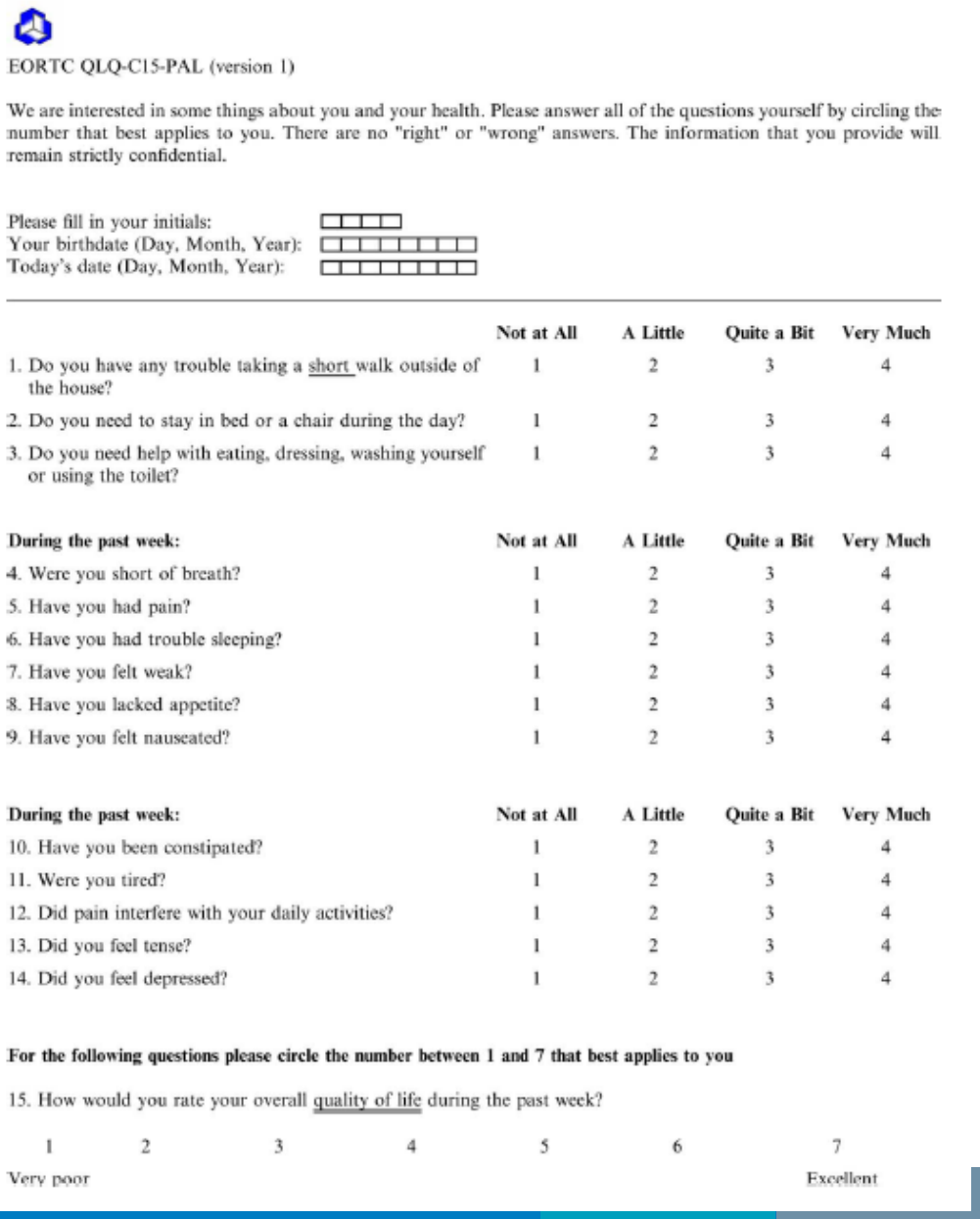
Tools to assess changes in QoL

EORTC QLQ

- C-30
- C-15 PAL

And additional specific lists

- BM 22 -> bone mets
- BN 20 -> brain mets



EORTC QLQ-C15-PAL (version 1)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ☐☐☐☐
Your birthdate (Day, Month, Year): ☐☐☐☐☐☐☐☐
Today's date (Day, Month, Year): ☐☐☐☐☐☐☐☐

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
2. Do you need to stay in bed or a chair during the day?	1	2	3	4
3. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
4. Were you short of breath?	1	2	3	4
5. Have you had pain?	1	2	3	4
6. Have you had trouble sleeping?	1	2	3	4
7. Have you felt weak?	1	2	3	4
8. Have you lacked appetite?	1	2	3	4
9. Have you felt nauseated?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
10. Have you been constipated?	1	2	3	4
11. Were you tired?	1	2	3	4
12. Did pain interfere with your daily activities?	1	2	3	4
13. Did you feel tense?	1	2	3	4
14. Did you feel depressed?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

15. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC BM22 questionnaire -> focus of patients

Rank	QOL Issue	Freq.	%
1	Long-term (chronic) pain	124	41
2	Worry about becoming dependent on others	124	41
3	Difficulty carrying out usual daily tasks	121	40
4	Worry about loss of mobility compromising independence	112	37
5	Difficulty in carrying out meaningful activity	102	34
6	Able to perform self-care	96	32
6	Able to perform role functioning	96	32
8	Worry about disease progression, deterioration in condition and future complications	95	31
9	Financial burden due to the illness	80	26
10	Lack of energy	71	23

EORTC BM22 questionnaire -> focus of doctors

Rank	QOL Issue	Freq	%
1	Able to perform self-care	66	61
2	Short-term (acute) pain relief	64	59
3	Long-term (or chronic) pain	61	57
4	Uncontrolled, unmanageable pain not relieved by pain killers	62	57
5	Pain at night preventing sleep	56	52
6	Limited movement due to pain	49	45
7	Pain at rest	46	43
8	Hope for sustained pain relief	45	41
8	Able to perform role functioning	44	41
10	Difficulty carrying out usual daily tasks	43	40

15 pain

7 other

For use combined with PAL-15

EORTC QLQ – BM22

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the **past week**. Please answer by circling the number that best applies to you.

During the past week have you had pain in any of the following parts of your body?	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
1. in your back?	1	2	3	4
2. in your leg(s) or hip(s)?	1	2	3	4
3. in your arm(s) or shoulder(s)?	1	2	3	4
4. in your chest or rib(s)?	1	2	3	4
5. in your buttock(s)?	1	2	3	4
During the past week:				
6. Have you had constant pain?	1	2	3	4
7. Have you had intermittent pain?	1	2	3	4
8. Have you had pain not relieved by pain medications?	1	2	3	4
9. Have you had pain while lying down?	1	2	3	4
10. Have you had pain while sitting?	1	2	3	4
11. Have you had pain when trying to stand up?	1	2	3	4
12. Have you had pain while walking?	1	2	3	4
13. Have you had pain with activities such as bending or climbing stairs?	1	2	3	4
14. Have you had pain with strenuous activity (e.g. exercise, lifting)?	1	2	3	4
15. Has pain interfered with your sleeping at night?	1	2	3	4
16. Have you had to modify your daily activities because of your illness?	1	2	3	4
17. Have you felt isolated from those close to you (e.g. family, friends)?	1	2	3	4
18. Have you worried about loss of mobility because of your illness?	1	2	3	4
19. Have you worried about becoming dependent on others because of your illness?	1	2	3	4
20. Have you worried about your health in the future?	1	2	3	4
21. Have you felt hopeful your pain will get better?	1	2	3	4
22. Have you felt positive about your health?	1	2	3	4

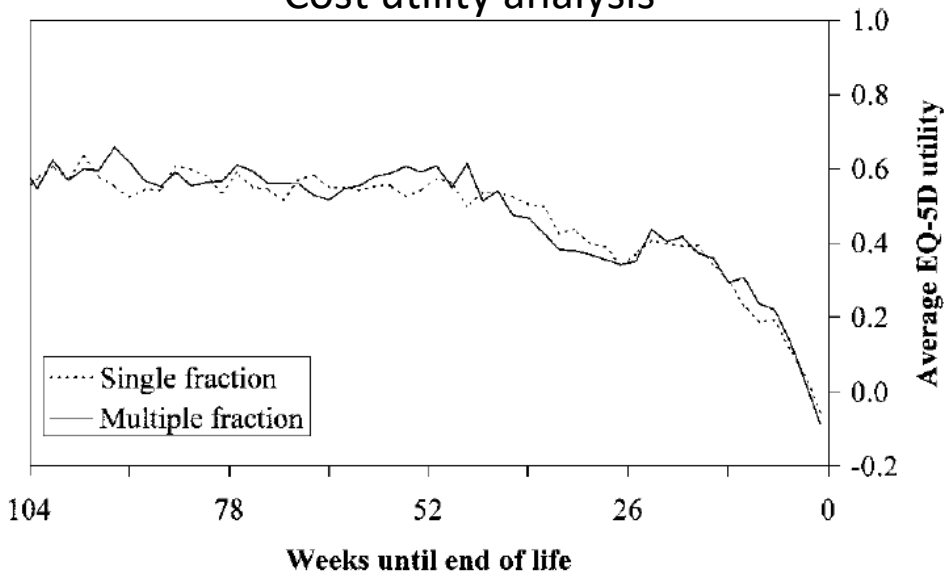
EuroQol group questionnaire

EQ-5D

- Standardized measure of health status
- Applicable to wide range of diseases
- Economic evaluations

E.g. Dutch Bone Metastasis Study

- Cost utility analysis



By placing a tick in one box in each group, please indicate which statements best describe your health today.

Mobility
- I have no problems in walking about ☑
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care
- I have no problems with self-care ☑
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

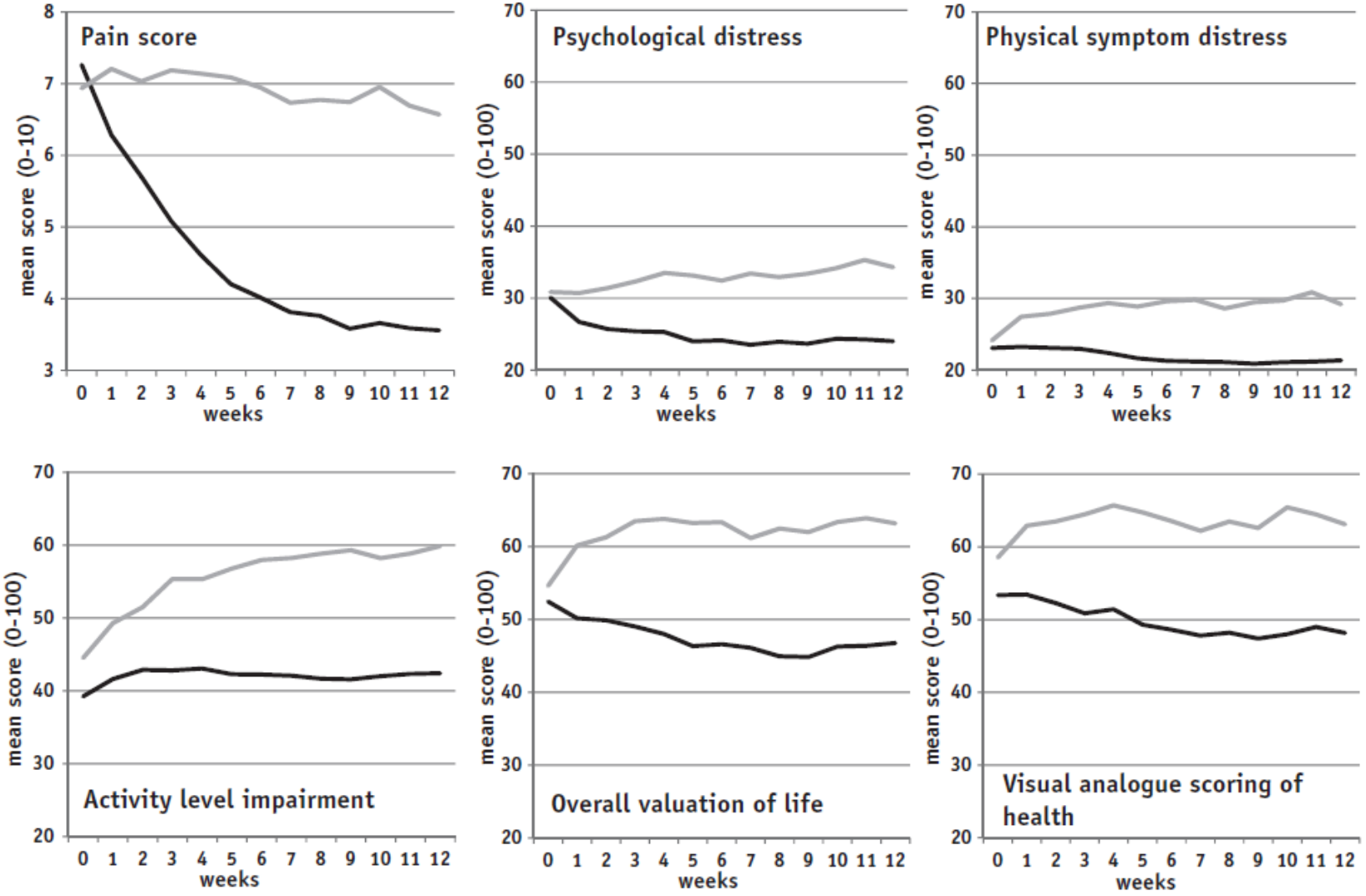
Usual Activities *(e.g. work, study, housework, family or leisure activities)* ☐
- I have no problems with performing my usual activities
- I have some problems with performing my usual activities ☑
- I am unable to perform my usual activities ☐

Pain/Discomfort
- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☑

Anxiety/Depression
- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☑
- I am extremely anxious or depressed ☐

Responding patients have improved Quality of Life

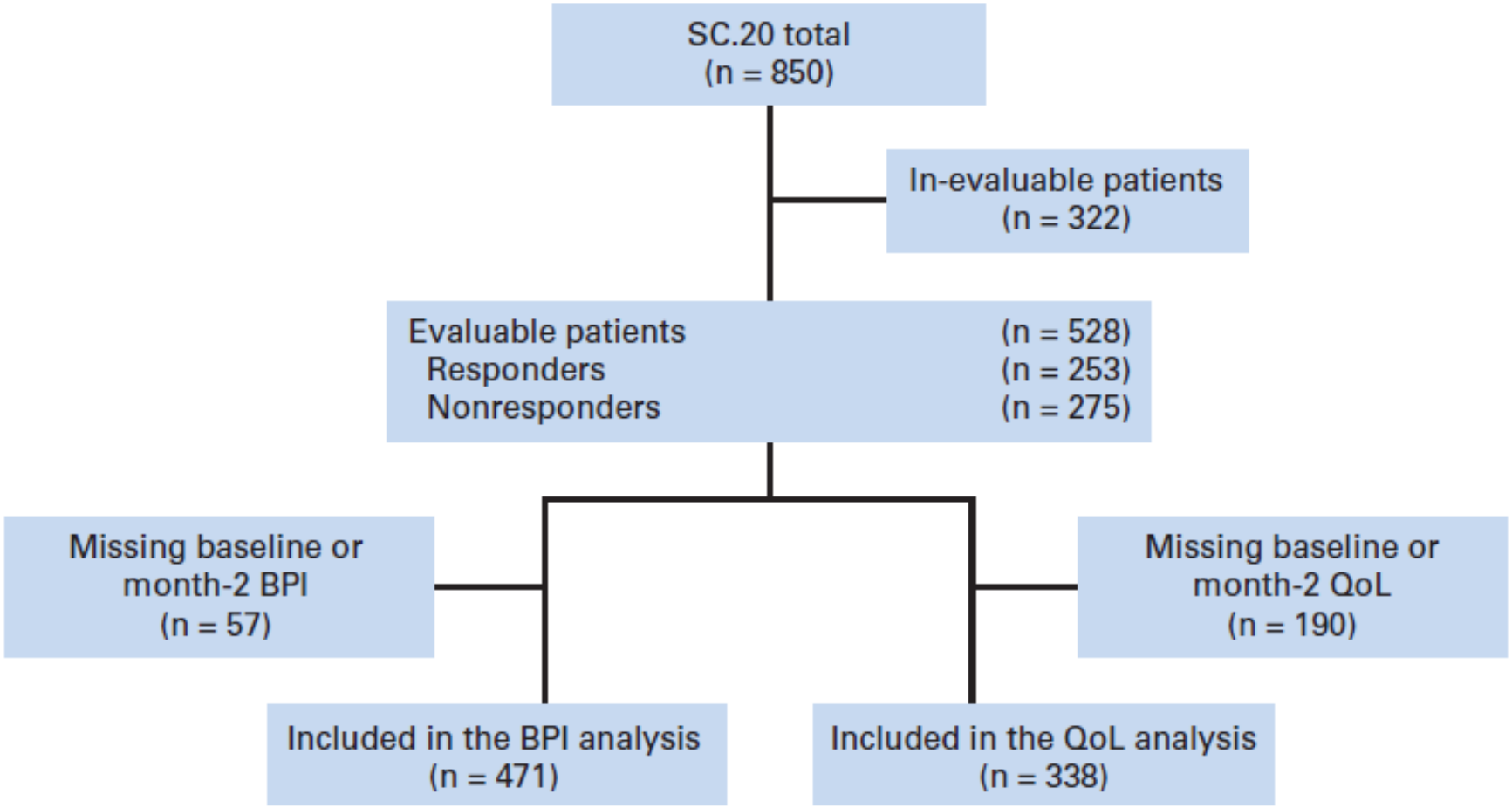
N= 1157



Westhoff et al. IJROBP 2015

Not just pain → effect on quality of life

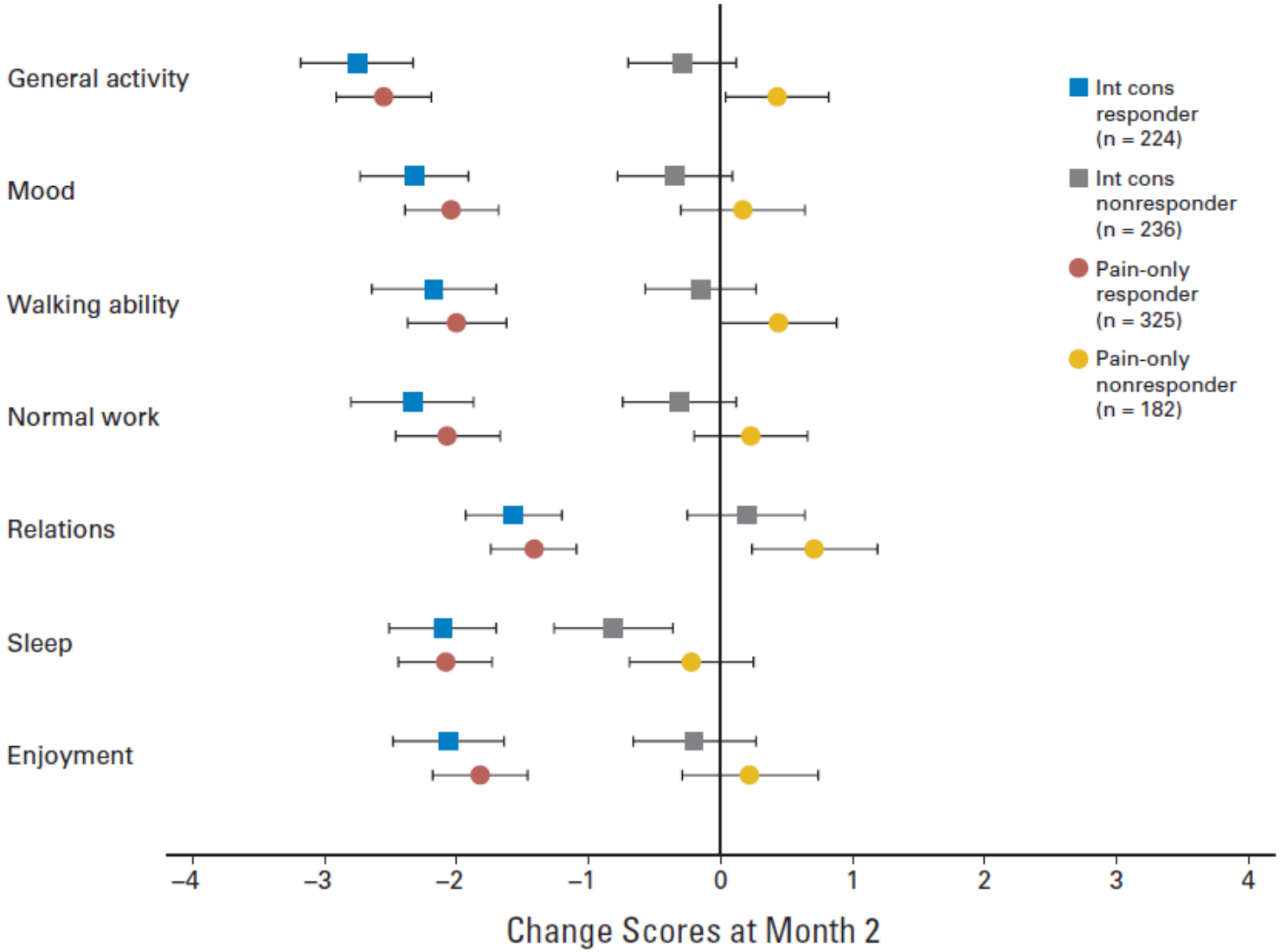
Best research evidence



Chow et al. JCO 2014

Re-responders have better QoL → BPI

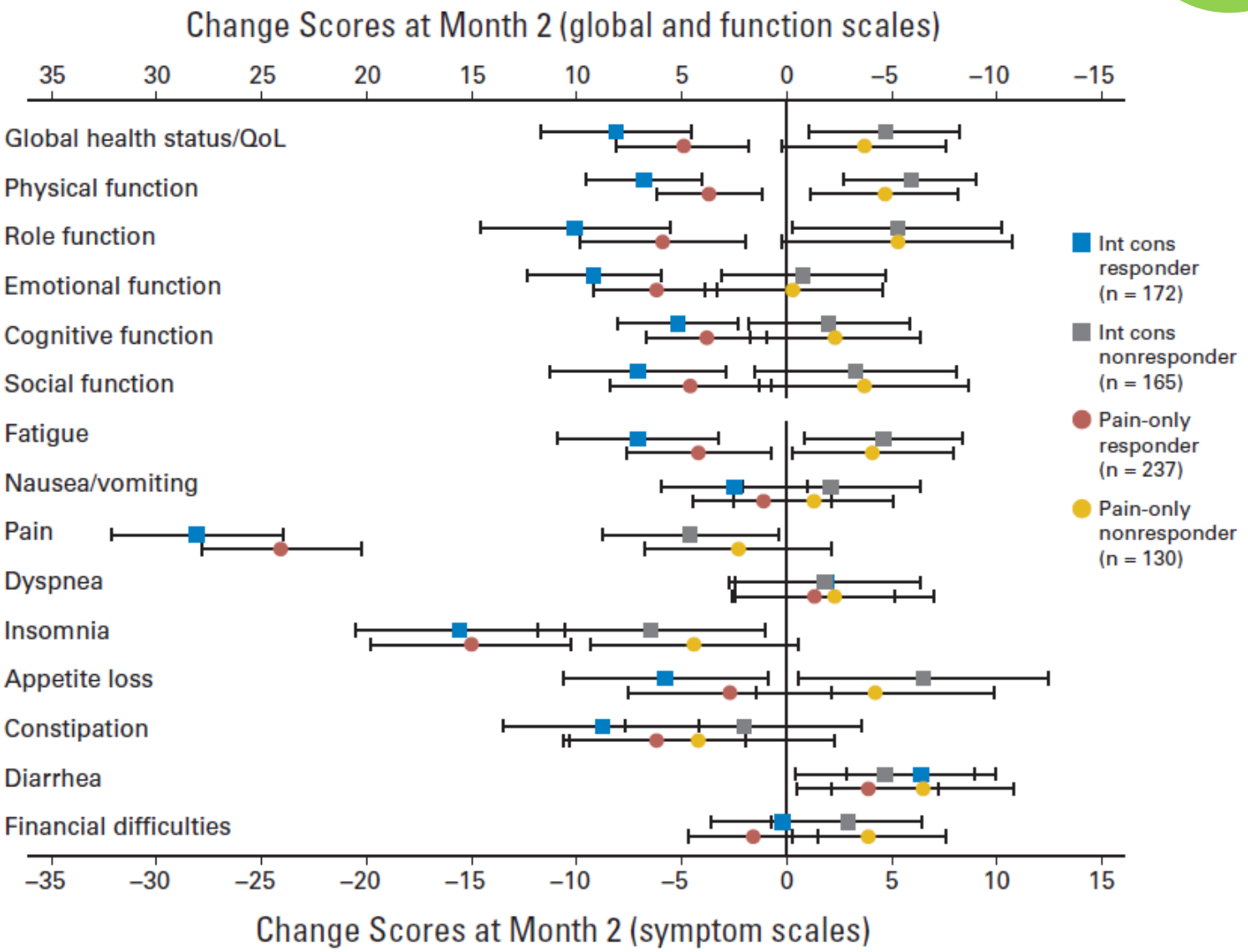
Best research evidence



Chow et al. JCO 2014

Re-responders have better QoL → EORTC-C30

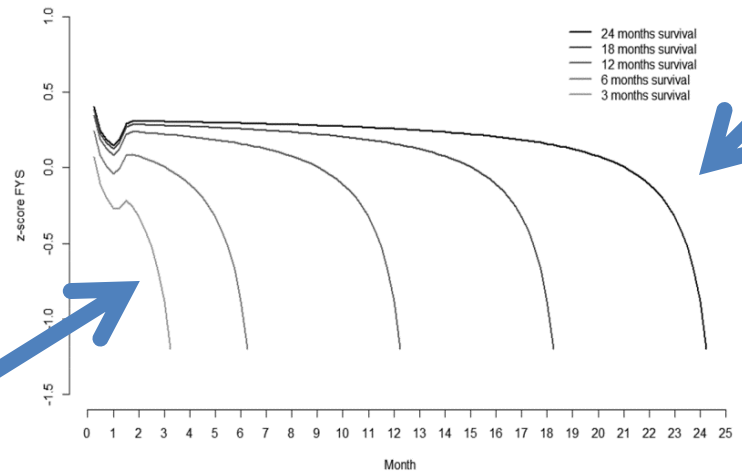
Best research evidence



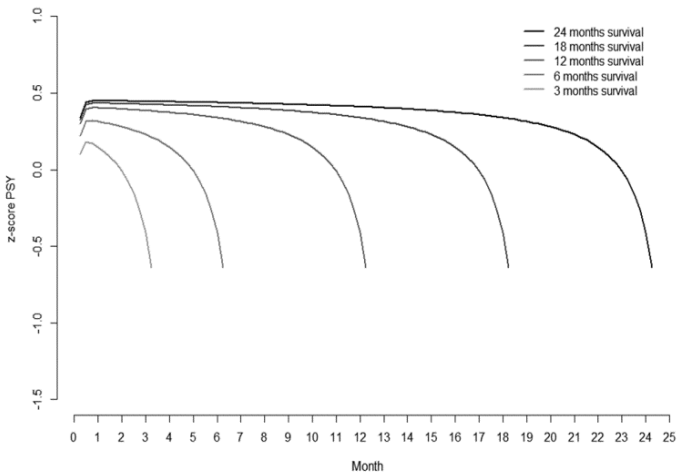
Chow et al. JCO 2014

Quality of life declines towards death

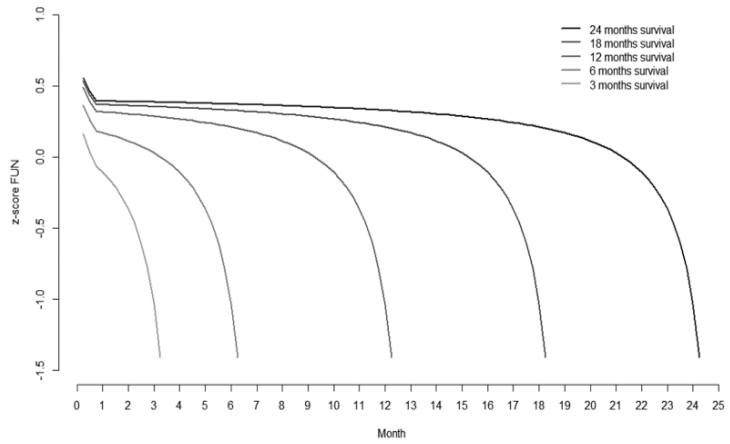
A. PHYSICAL DOMAIN



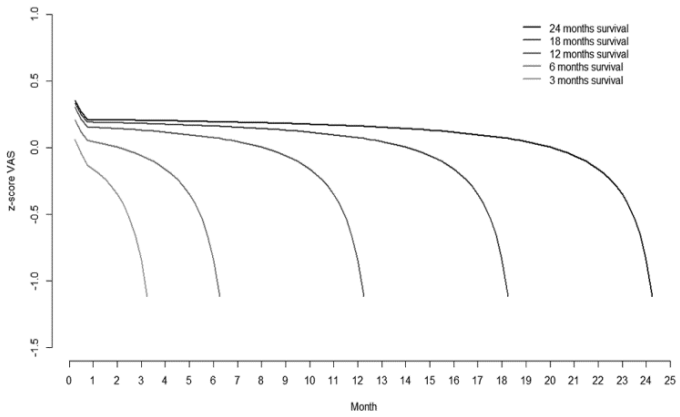
B. PSYCHOSOCIAL DOMAIN



C. FUNCTIONAL DOMAIN



D. VAS-gh



Westhoff et al, IJROBP 2016

Assessment and Evaluation of symptoms helps understanding needs, treatment outcome

International guidelines help us to apply EBM

CLINICAL INVESTIGATION

UPDATE OF THE INTERNATIONAL CONSENSUS ON PALLIATIVE RADIOTHERAPY ENDPOINTS FOR FUTURE CLINICAL TRIALS IN BONE METASTASES

Edward Chow, M.B.B.S.,* Peter Hoskin, M.D.,† Gunita Mitera, Ph.D.(C),* Liang Zeng, B.Sc.(C),* Stephen Lutz, M.D.,‡ Daniel Roos, M.D.,§ Carol Hahn, M.D.,‖ Yvette van der Linden, M.D.,¶ William Hartsell, M.D.,# and Eshwar Kumar, M.B.B.S. ** on behalf of the International Bone Metastases Consensus Working Party

ASTRO GUIDELINE

PALLIATIVE RADIOTHERAPY FOR BONE METASTASES: AN ASTRO EVIDENCE-BASED GUIDELINE

Stephen Lutz, M.D.,* Lawrence Berk, M.D., Ph.D.,† Eric Chang, M.D.,‡ Edward Chow, M.B.B.S.,§ Carol Hahn, M.D.,¶ Peter Hoskin, M.D.,‖ David Howell, M.D.,# Andre Konski, M.D.,** Lisa Kachnic, M.D.,†† Simon Lo, M.B., Ch.B.,‡‡ Arjun Sahgal, M.D.,§§ Larry Silverman, M.D.,¶¶ Charles von Gunten, M.D., Ph.D., F.A.C.P.,‖‖ Ehud Mendel, M.D., F.A.C.S.,## Andrew Vassil, M.D.,*** Deborah Watkins Bruner, R.N., Ph.D.,††† and William Hartsell, M.D.‡‡‡

International Bone Metastases Consensus Working Group

Complete Response	Pain reduction by two scores or more to zero and OMED* stable or reduced
Partial Response	Pain reduction by two scores or more and OMED stable or reduced
	Stable pain and OMED reduction by 25% or more
Non responders	
Progressive Disease	Pain increase by two scores or more and OMED stable or increased
	No change in pain and OMED increased by 25% or more (or start of morphine use after baseline)
Stable Disease	Stable pain and stable OMED
Undetermined Response	Other cases

*OMED= oral morphine equivalent dose

Topics

use of pain scales (VAS, NRS), use of a booklet, BPI

Guidance -> bone consensus working group, example pain with without pain medication

Pain= QoL improvement -> outcome retreatment, Paulien

Verschil screening/monitoring instruments (dia verschil aanduiden) en verschillende instrumenten (LAST / ESAS / USD 4D / DOS) and, EORTC QLQ for research

BM22, PAL 15, painpainpain

how to integrate into daily practice? Eg. ehealth

Pain and other symptoms

Johan Menten

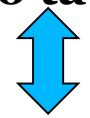
Radiation Oncology & Palliative Care

University Hospital Gasthuisberg

Leuven (Belgium)

Pain and other symptoms

Experts consider how to tackle overtreatment in US Healthcare



Palliative treatment➔ palliative care➔ terminal care

"It's clear that not just one thing needs to be changed to fix the problem.

We have to have a culture change in medicine that will include

-changing payment schemes,

-how medical journals report studies,

-how patients receive their information,

-how professional guidelines are devised,

-and how we perceive good care.

BMJ 2012;344:e3144

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer

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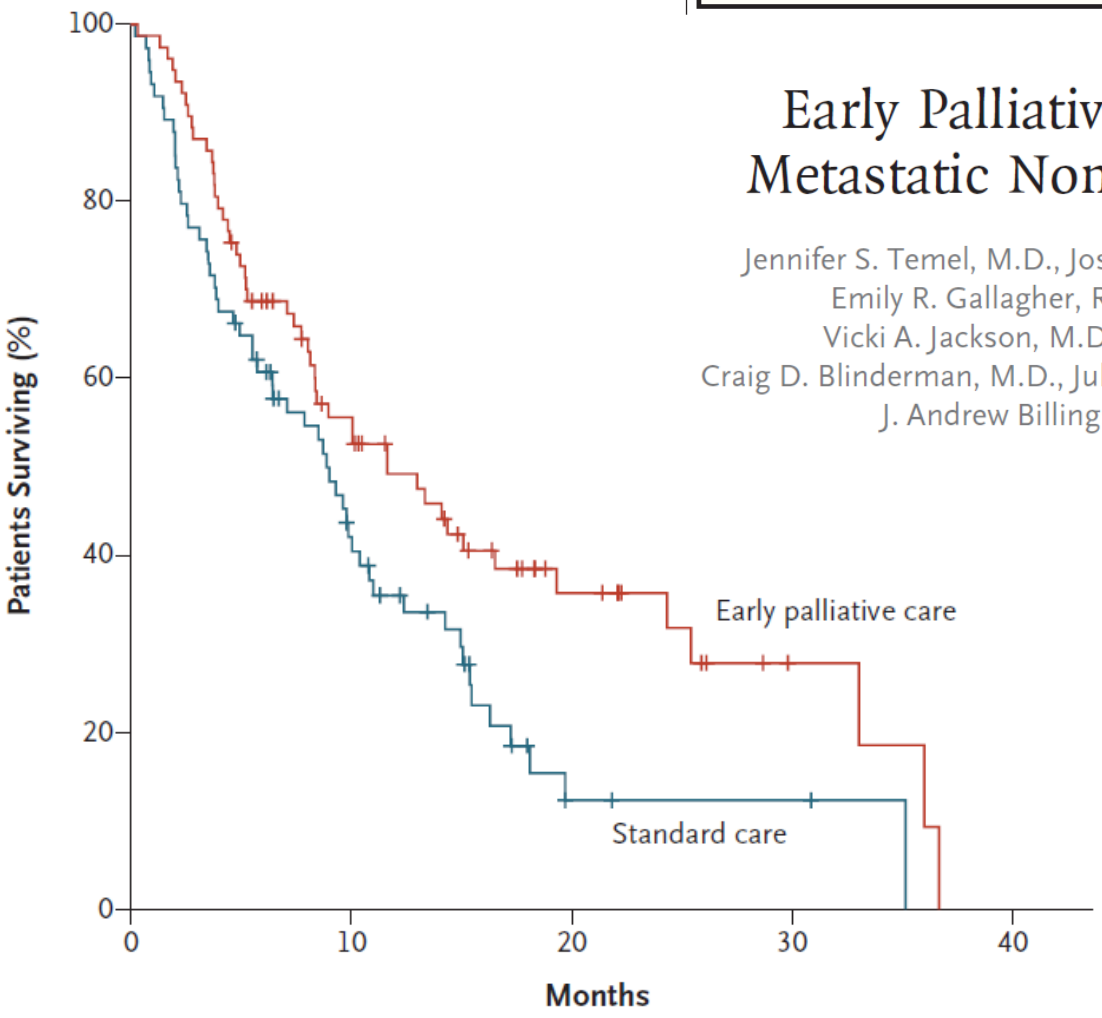

Figure 3. Kaplan–Meier Estimates of Survival According to Study Group.

n engl j med 2010; 363;8

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Pain and other symptoms

Early palliative intervention for patients with advanced cancer.

Otsuka M, Koyama A, Matsuoka H, Niki M, Makimura C, Sakamoto R, Sakai K, Fukuoka M.

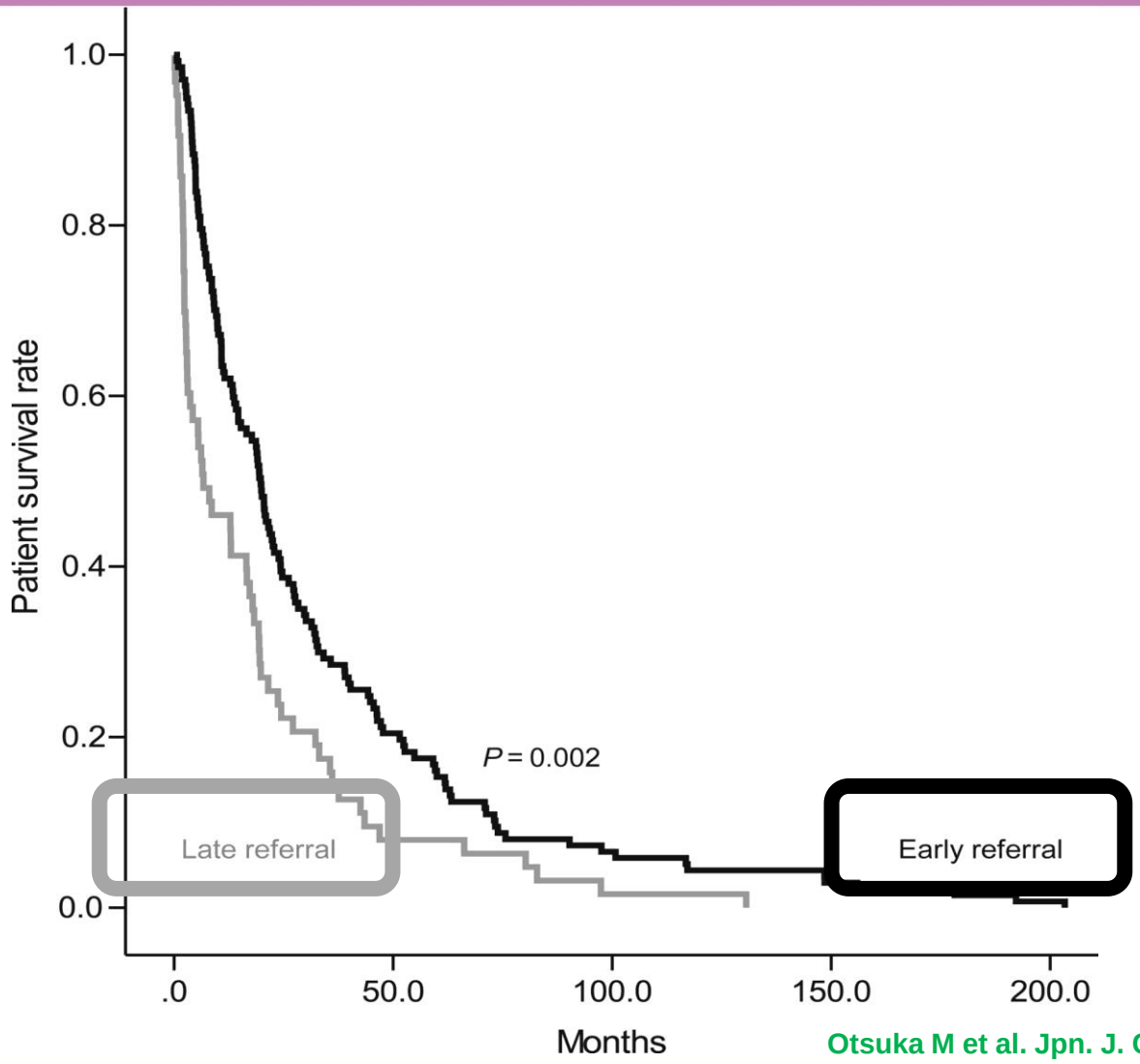
Department of Palliative Care, Sakai Hospital, Kinki University Faculty of Medicine, Japan. mtsuka@sakai.med.kindai.ac.jp

201 advanced cancer patients
treated over a period of 4 years were divided into two groups:

- Patients with pal care for <7 days (late referral group, n = 64)
- Patients with pal care for ≥7 days (early referral group, n = 137).

Jpn J Clin Oncol. 2013 Aug;43(8):788-94

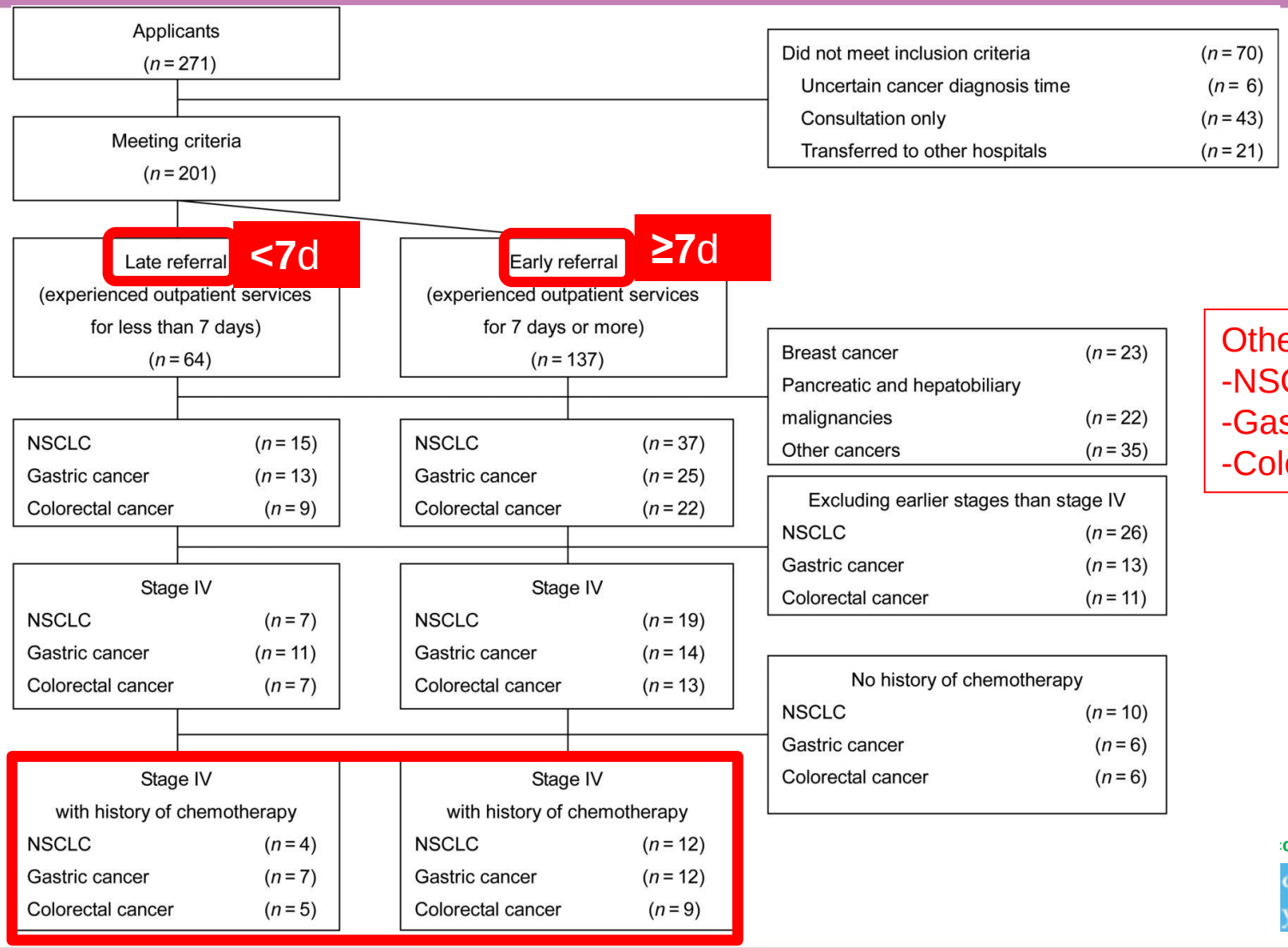
Kaplan–Meier estimates of survival according to study groups.



Otsuka M et al. Jpn. J. Clin. Oncol. 2013;43:788-794

Japanese Journal of Clinical Oncology

Flow diagram of the study protocol.



Other than
-NSCLC
-Gastric ca
-Colorectal ca

ol. 2013;43:788-794

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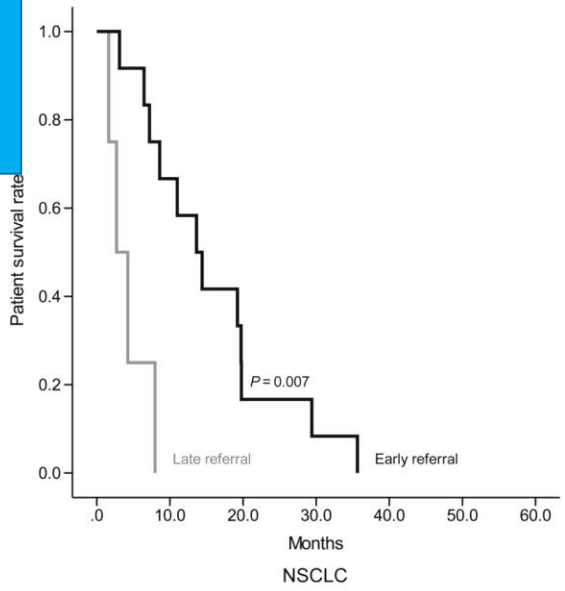
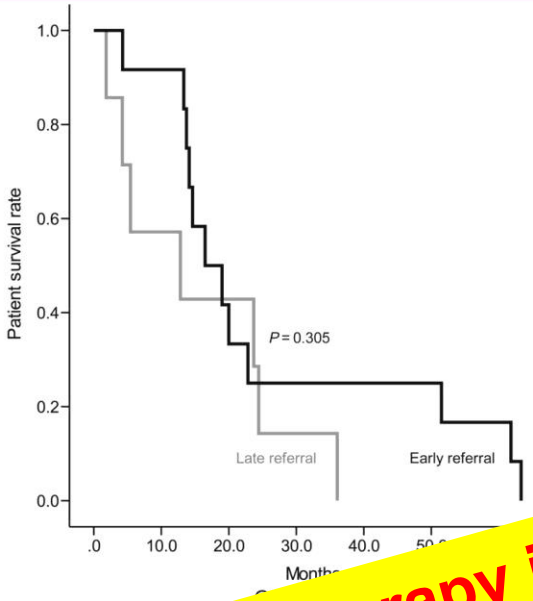
Kaplan–Meier estimates of survival in the two study groups.

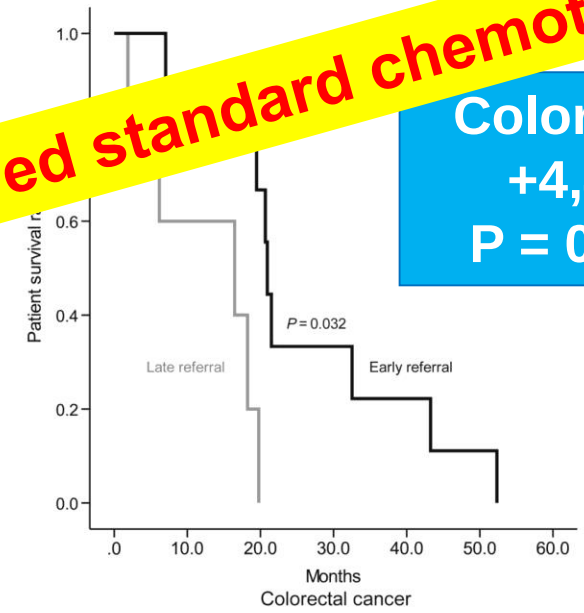
NSCL
+10,5m
P = 0,01





Gastric
+5,1m
P = 0,31

all patients received standard chemotherapy in both groups



Colorectal
+4,4m
P = 0,039

Otsuka M et al. Jpn. J. Clin. Oncol. 2013;43:788-794

Japanese Journal of Clinical Oncology

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Wiley Online Library

Cochrane Library

Trusted evidence.
Informed decisions.
Better health.

Home > Evidence Based Medicine > Evidence-Based Health Care > The Cochrane Library > Abstract

All trials were of good methodological quality with no risk of bias

Intervention Review

Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung canc

Non-Small Cell Lung Cancer Collaborative Group

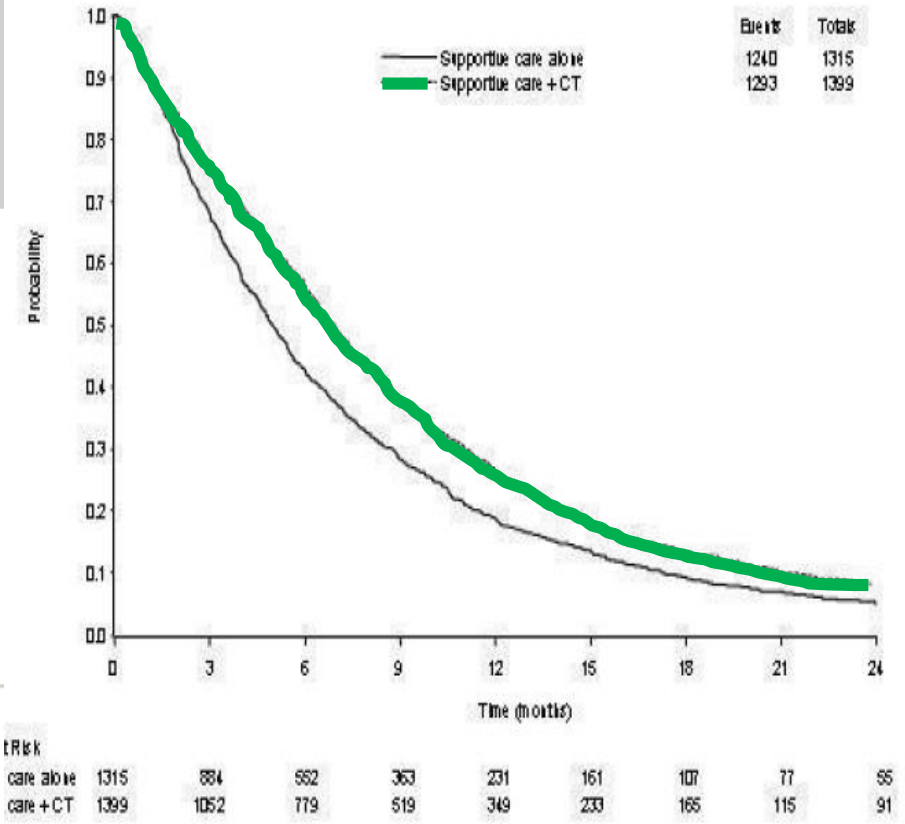
Editorial Group: Cochrane Lung Cancer Group

Published Online: 12 MAY 2010

Browse by Topic

-This meta-analysis of chemo in the supportive care setting demonstrates that chemo improves OS in all patients with advanced NSCLC.

-Patients who are fit enough and wish to receive it should be offered chemotherapy.



More & better treatment…?

Palliative Care patients are patients with:

life-limiting chronic diseases *especially in the far-advanced stages*

such as
- -cancer,
- -heart, liver, renal, repiratory failure,
- - neurodegenerative disorders
- -…frailty and aged persons

Terminal care is the final care for a good death

after long term **palliative care** for a good life

Palliative care : when does that start?

-Advance care planning (~ communication skills)

-Integrate palliative care earlier in the disease trajectory

-2006: The gold standard framework,

-Palliative prognostic index

Too many times:
-Patients are waiting for the doctor to start a palliative initiative…
&
-Physicians are waiting for questions of the patient…

The **7 Key messages – or core tasks** (or quality standards),

7 C's, according to GSF:

C1 –Communication: ask for symptom control/wishes/needs in every contact!!!

C2 –Coordination: who can be contacted for questions/problems?

C3 -Control of symptoms: evaluate treatment effect

C4 -Continuity (incl. 'out of hours' (≠ *voice mail*))

C5 -Continued learning: stay at the "state of the art"

C6 -Carer support: for your team and for yourself

C7 -Care in the dying phase: for patient (+family + carers+ bereavement)

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Total pain…?

Causes for suffering *(that need palliative care)* include:

-Disease/therapy-mediated **physical** symptoms

PAIN, DYSPNEA & FATIGUE

-**Psychological** symptoms ➔**feeling of uselessness**

(depression, anxiety,.....)

-More difficult to quantify and to treat are:

- the **existential or spiritual** dimensions of suffering

(*loss of a sense of purpose in living).*

- progressive loss of function
- dramatic changes in **social** status and roles within family, in occupational domains ...

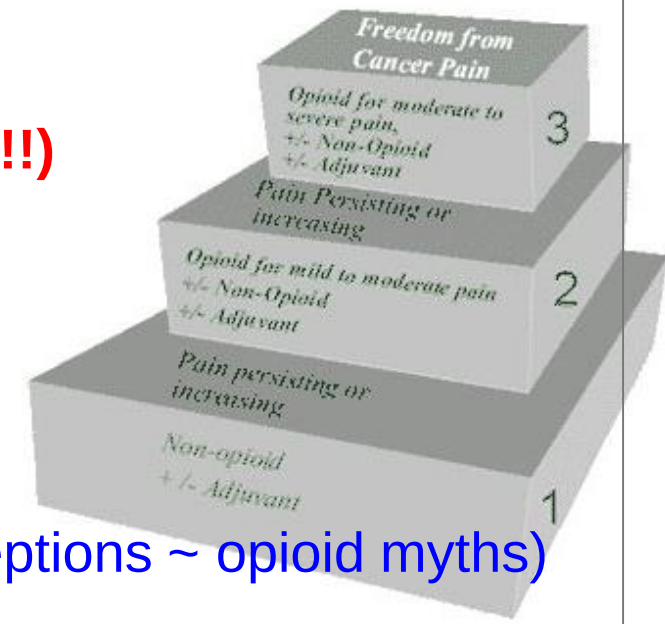
➔ **overwhelming sense of despair.**

Pain in oncology

	Prevalence of pain
Curative therapy	**± 30%**
Palliative therapy	**± 50-60%**
Palliative care	**± 80-90%**

More & better treatment…?

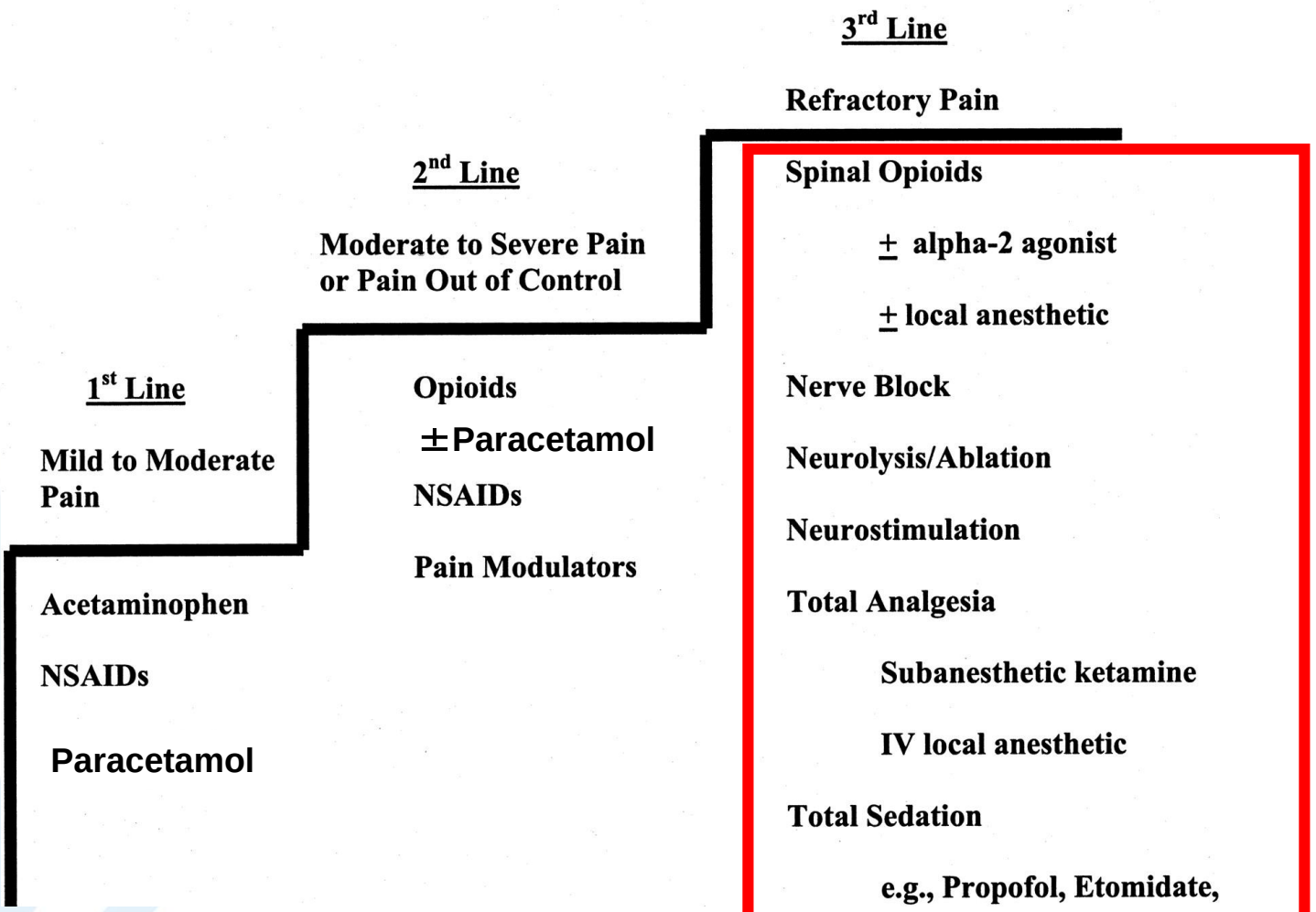
A relatively easy-to-follow generic approach to cancer pain management, the **WHO 3-step ladder**,
has been validated as being useful
for most patients with cancer-related pain (**1985!!!)**



But….a subset of patients still remains:

-withholded from this guideline
  -lack of knowledge
  -undertreatment (due to opioid misconceptions ~ opioid myths)
  -lack of availability of opioids
-not leading to the possible effective pain relief

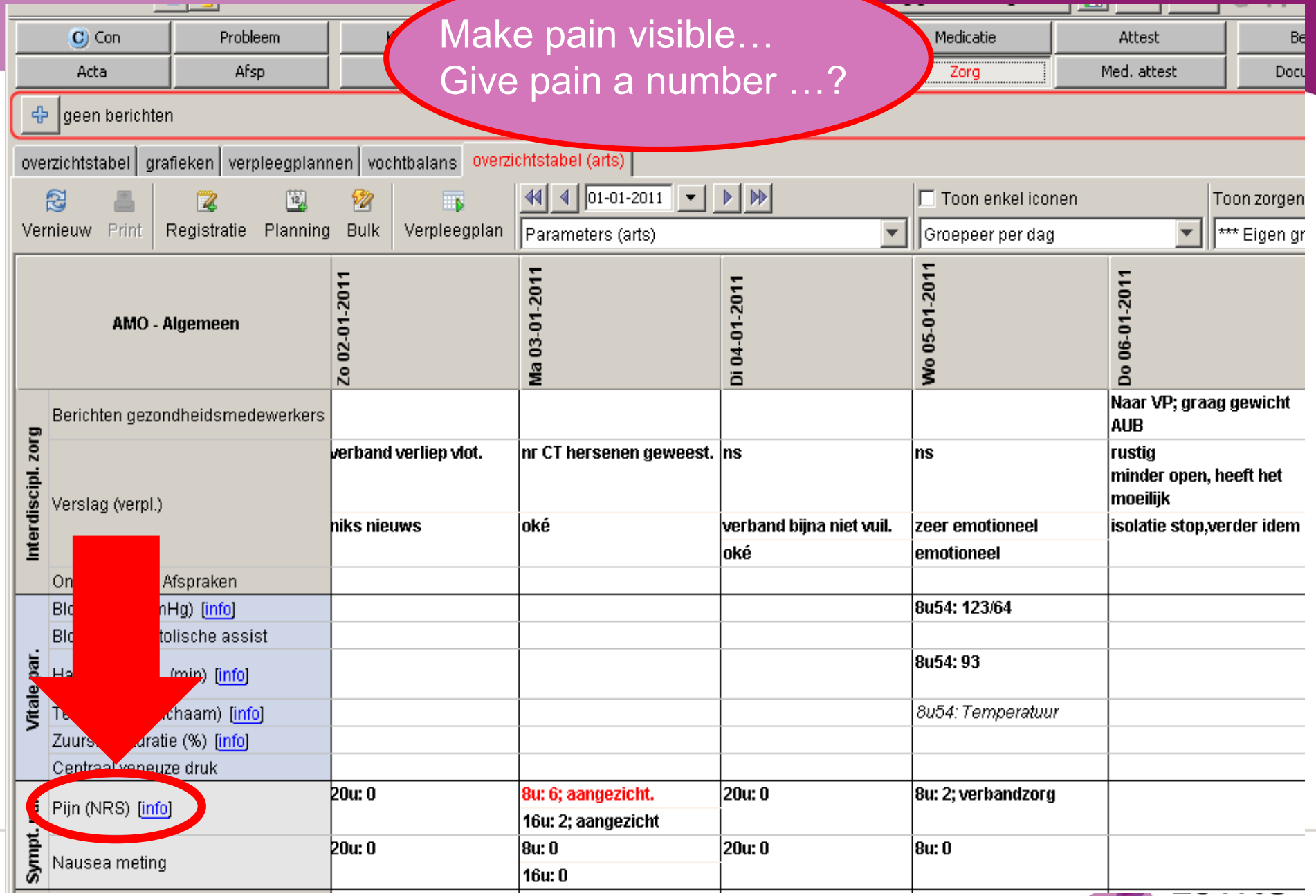
Modification of the WHO stepladder approach to pain control.



Fine P G Anesth Analg 2005;100:183-188

ANESTHESIA & ANALGESIA

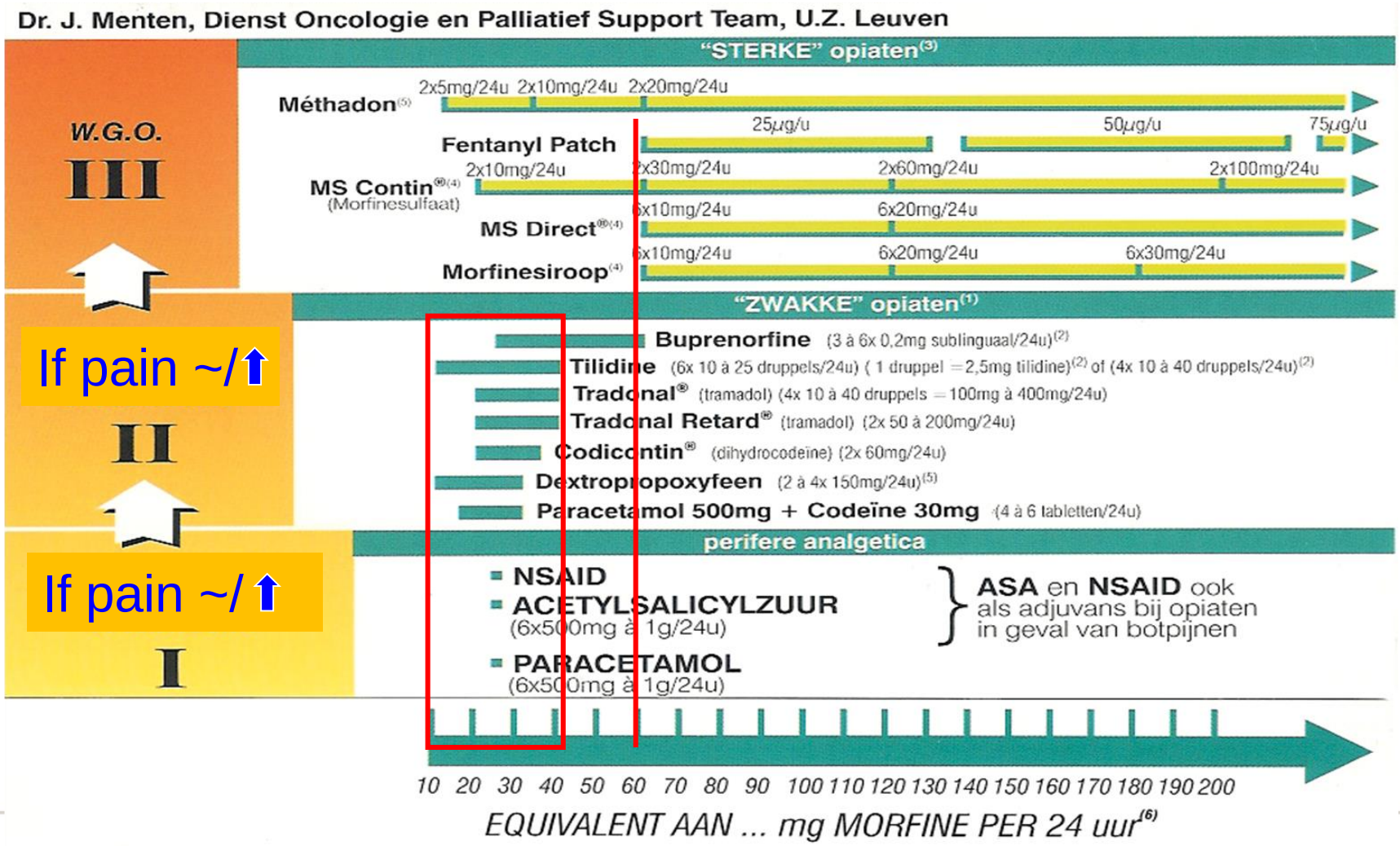
Make pain visible…
Give pain a number …?



AMO - Algemeen		Zo 02-01-2011	Ma 03-01-2011	Di 04-01-2011	Wo 05-01-2011	Do 06-01-2011
Interdiscipl. zorg	Berichten gezondheidsmedewerkers					Naar VP; graag gewicht AUB
	Verslag (verpl.)	verband verliep vlot. niks nieuws	nr CT hersenen geweest. oké	ns verband bijna niet vuil. oké	ns zeer emotioneel emotioneel	rustig minder open, heeft het moeilijk isolatie stop,verder idem
	On… Afspraken					
Vitale par.	Bl… nHg) [info]				8u54: 123/64	
	Bl… tolische assist					
	Ha… (min) [info]				8u54: 93	
	Te… chaam) [info]				*8u54: Temperatuur*	
	Zuurs… uratie (%) [info]					
	Centraal veneuze druk					
Sympt. …	Pijn (NRS) [info]	20u: 0	8u: 6; aangezicht. 16u: 2; aangezicht	20u: 0	8u: 2; verbandzorg	
	Nausea meting	20u: 0	8u: 0 16u: 0	20u: 0	8u: 0	

School

Chronic cancer pain: analgesic around the clock



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Morphine dose after step II :

1 – Maintenance dose

fi. short acting morphine (4h) 6 x 10 mg

slow release morphine (12h) 2 x 30 mg

2 - Bolus : NRS score <5 : bolus = 1/12 daily dose

NRS-score >5 : bolus = 1/6 daily dose

3 – Laxativs ALWAYS + if needed anti-emetics

Morphine equivalence:

1 - 10 mg morphine parenteral ~ (20) - 30 mg po.

2 - 90-100 mg morphine po./24h ~ 25 µg/h fentanyl patch

3 - 1 mg morphine IV ~ IM ~ SC

Strong opioids: uptitration

Moderate pain (NRS 3-6: maintenance dose +25%

Severe pain (NRS > 6) : maintenance dose +50%

=> adapt also the bolus dose for break through pain!!

➔If only short acting morphine available : increase the evening dose with 50%

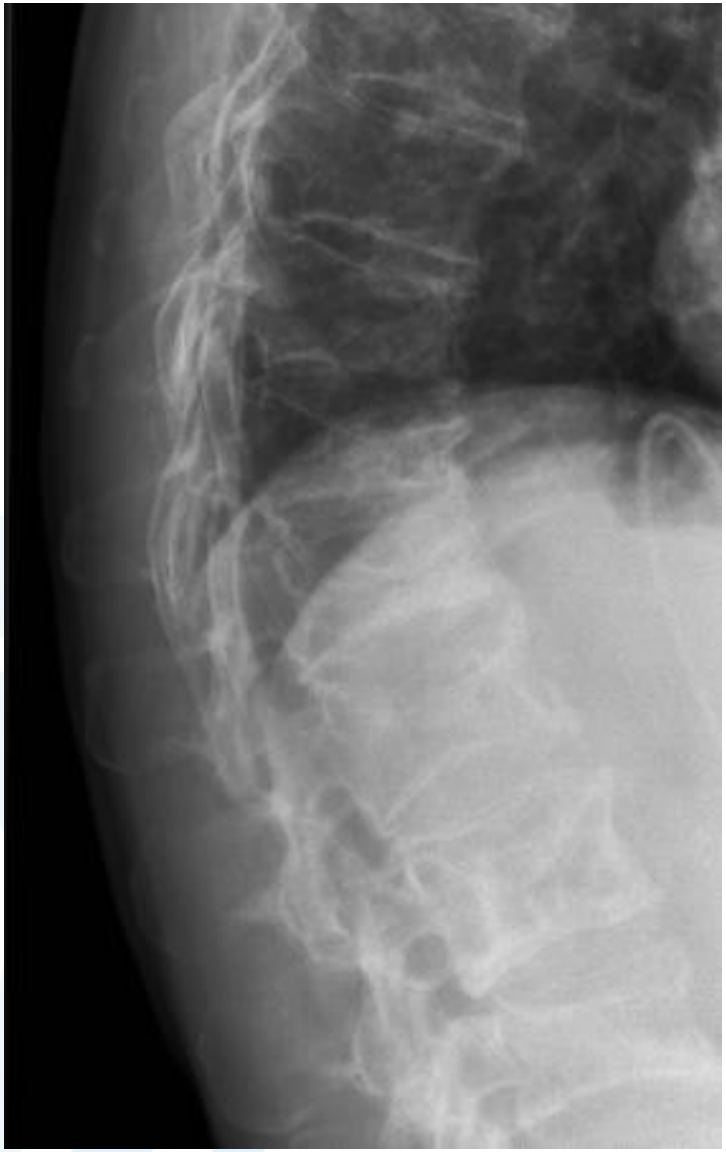
Analgesic equivalents in WHO step 3

1 Lagere dosissen noodzakelijk bij de geriatrische, frêle patiënt

maintenance (long acting opioids)		Startdosis[1] na max. dos. WHO-trap 2[2] of bij ernstige pijn (NRS ≥ 4/10)	uptitration →		
Oraal	MS Contin®- Morphine Teva® (morfinesulfaat) 10 - 30 - 60 - 100 mg	2 x 30	2 x 60	2 x 120	2 x 180
Oraal	Palladone® SR (hydromorfone) 4 - 8 - 16 - 24 mg	2 x 4	2 x 8	2 x 16	2 x 24
Oraal	Oxycontin® (oxycodone) 5 - 10 - 20 - 40 - 80 mg	2 x 15	2 x 30	2 x 60	2 x 90
Transdermaal	Durogesic® (fentanyl) 12 - 25 - 50 - 75 - 100 µg/u	(12) - 25	37	75	100
Transdermaal	Transtec® (buprenorfine) 35 - 52,5 - 70 µg/u	17,5	35	70	105
SC	Morfine HCl SC/24u (morfinehydrochloride) 10 - 40 mg[3]	20	40	80	120
bolus dose (short acting opioids : frequency as needed)					
Doorbraakpijn bij NRS ≥ 4/10	Morfineoplossing[4] - MS Direct® 10 mg- Oramorph[5] (PO) (morfinesulfaat)	10	20	40	60
Doorbraakpijn bij NRS ≥ 4/10	Oxynorm® Instant (PO) (oxycodone) 5 - 10 - 20 mg	5	10	20	30
Doorbraakpijn bij NRS ≥ 4/10	Palladone® IR (PO) (hydromorfone) 1,3 - 2,6 mg	1,3	2,6	2 x 2,6	3 x 2,6
Doorbraakpijn bij NRS ≥ 4/10	Temgesic® (SL) (buprenorfine) 0,2 mg	0,2	0,4	0,8	1,2
Doorbraakpijn bij NRS ≥ 4/10	Morfine HCl (SC of IV) (morfinehydrochloride) 10 - 40 mg[3]	5	5 - 10	10 - 15	20
Doorbraakpijn bij NRS ≥ 4/10	Oxynorm® (SC of IV) (oxycodone) 10 mg/ml of 50 mg/ml	5	5 - 10	10 - 15	20
Doorbraakpijn bij NRS ≥ 4/10	Palladone® (SC of IV) (hydromorfone) 2 - 10 - 20 mg/ml	1	1 - 2	2 - 3	4

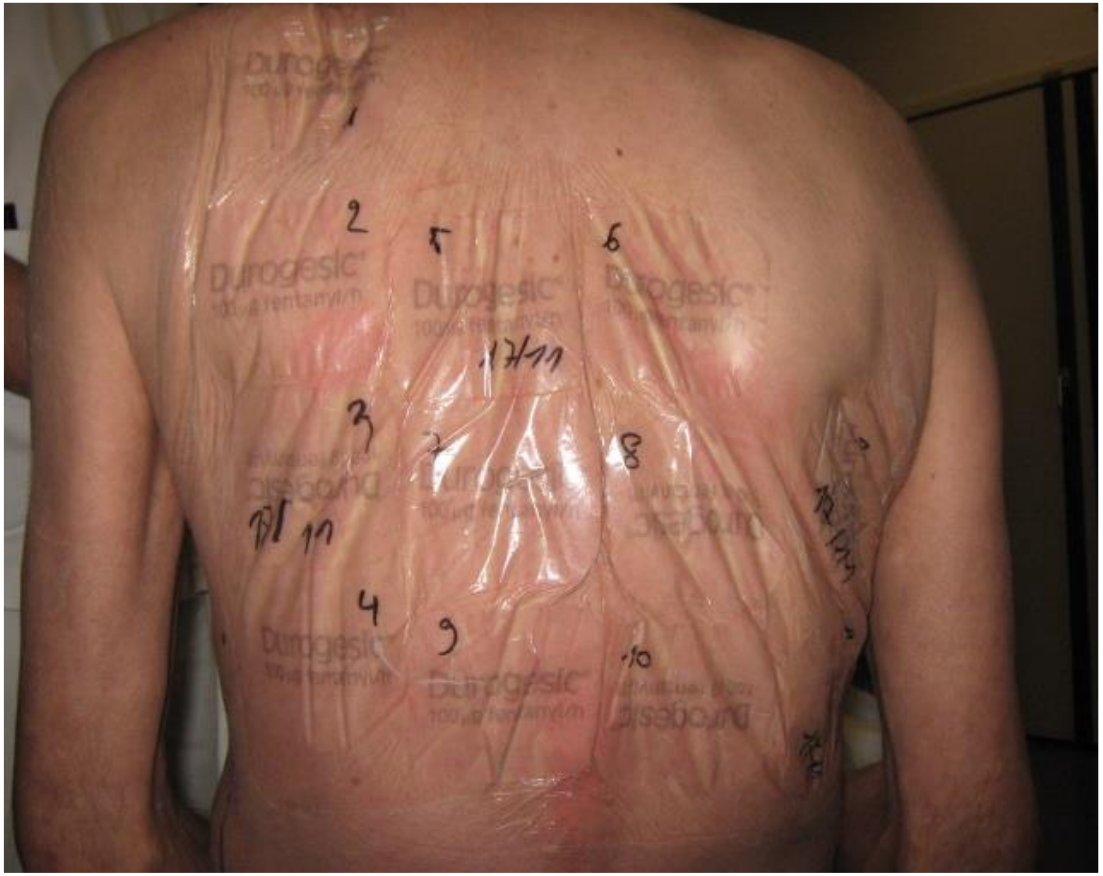
2 Maximum dosis trap 2 = bv. 400 mg Contramal® = 40 mg morfine PO
3 Ampullen van 10, 20 en 30 mg in de thuiszorg
4 Morfineoplossing: morfinehydrochloride in water (niet in UZ Leuven-formularium)
5 Oramorph® verkrijgbaar in druppels 20 ml/flesje PO (1 ml = 16 dr = 20 mg), in oplossing PO (100 ml, 2 mg/ml), in vials PO van 5 ml met 10 of 30 mg/5 ml

Morbus Kahler in …every single bone…!!



60 mg/day

1200 µg fentanyl /h
= 12 patches of 100mg!!!



Strong opioids: break down is the other way around as the up-titration

Never stop high doses of strong opioids if used for at least 3 weeks, nut down titration

(patch (25µg/h ~ 100 mg M po/d !!!)

=> Withdrawal symptoms !!

-diarrea, abdominal colics

-arythmia

-swetting, tachypnoe, delirium

-"as if I started to die"

Strong opioid intoxication

Somnolence

Myoclonus

Pin point pupils

Constipation

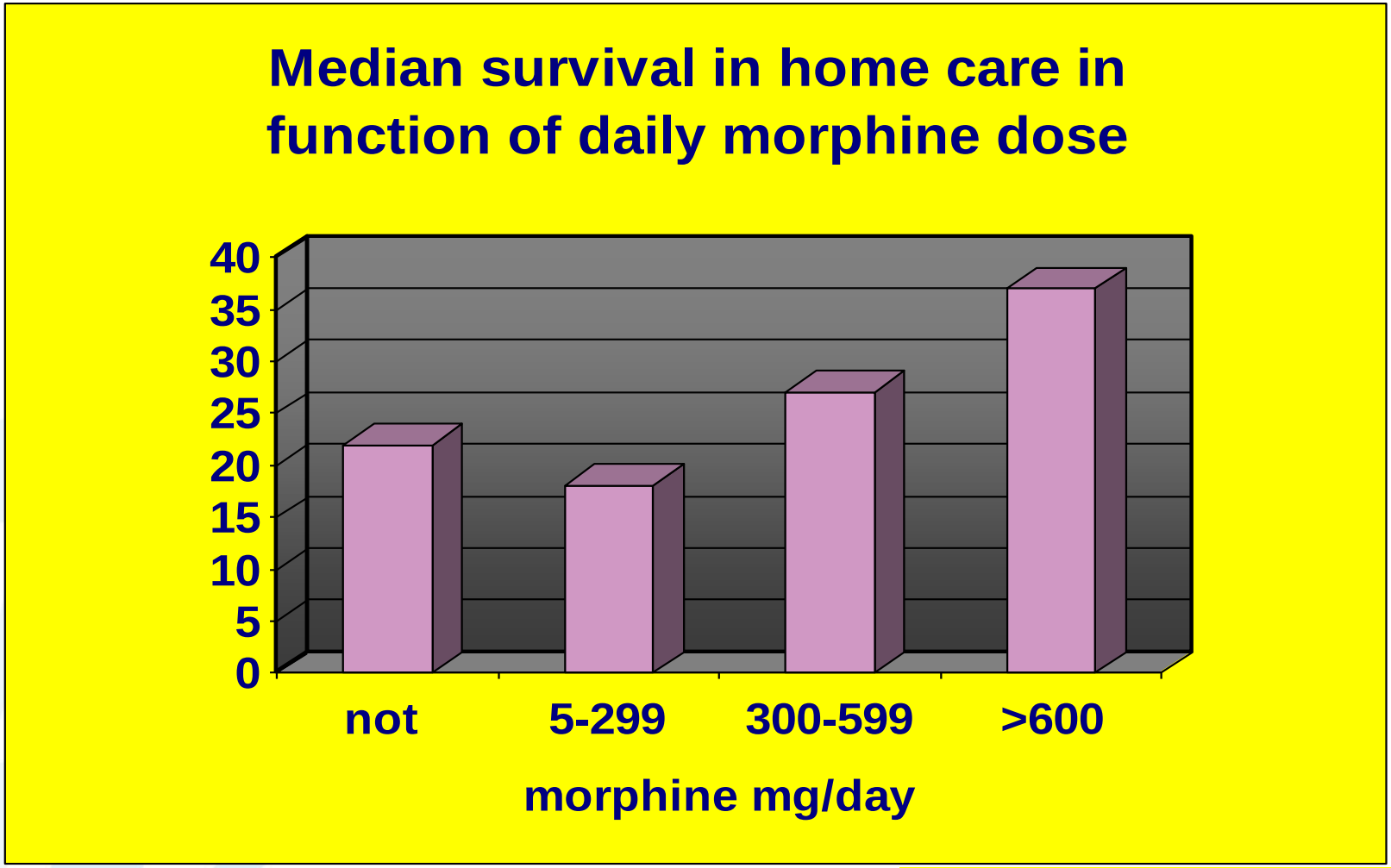
Deterioration of general condition

R/Naloxone 0,4mg/ml

➔ 0,1 ml/SC or IV every 2 min till the symptoms disappear

Transfer to intensive care unit for 24h: why ?

Opioids & life expectancy?

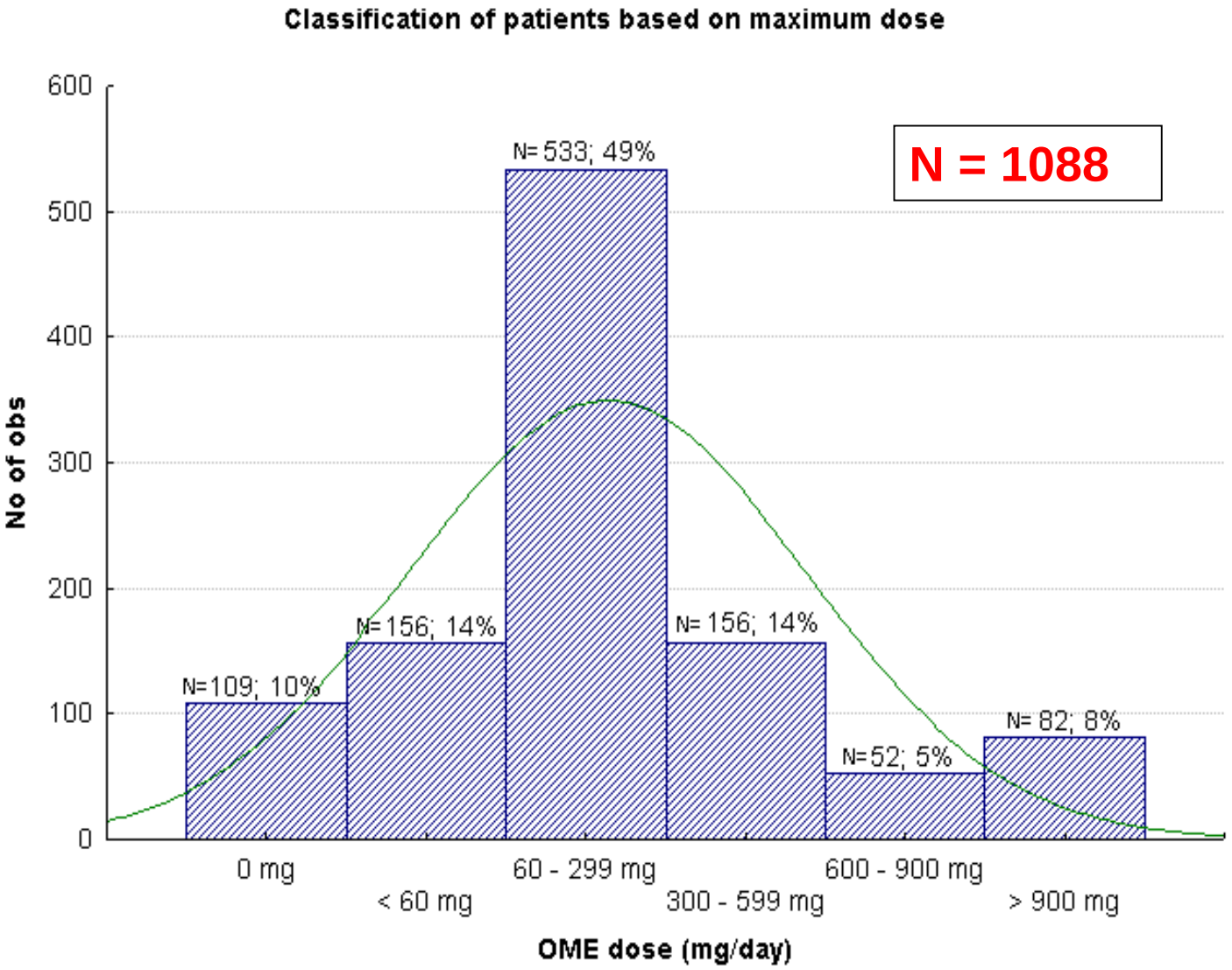


Bercovitch et al. Cancer 2004; 101 (6):1473-7

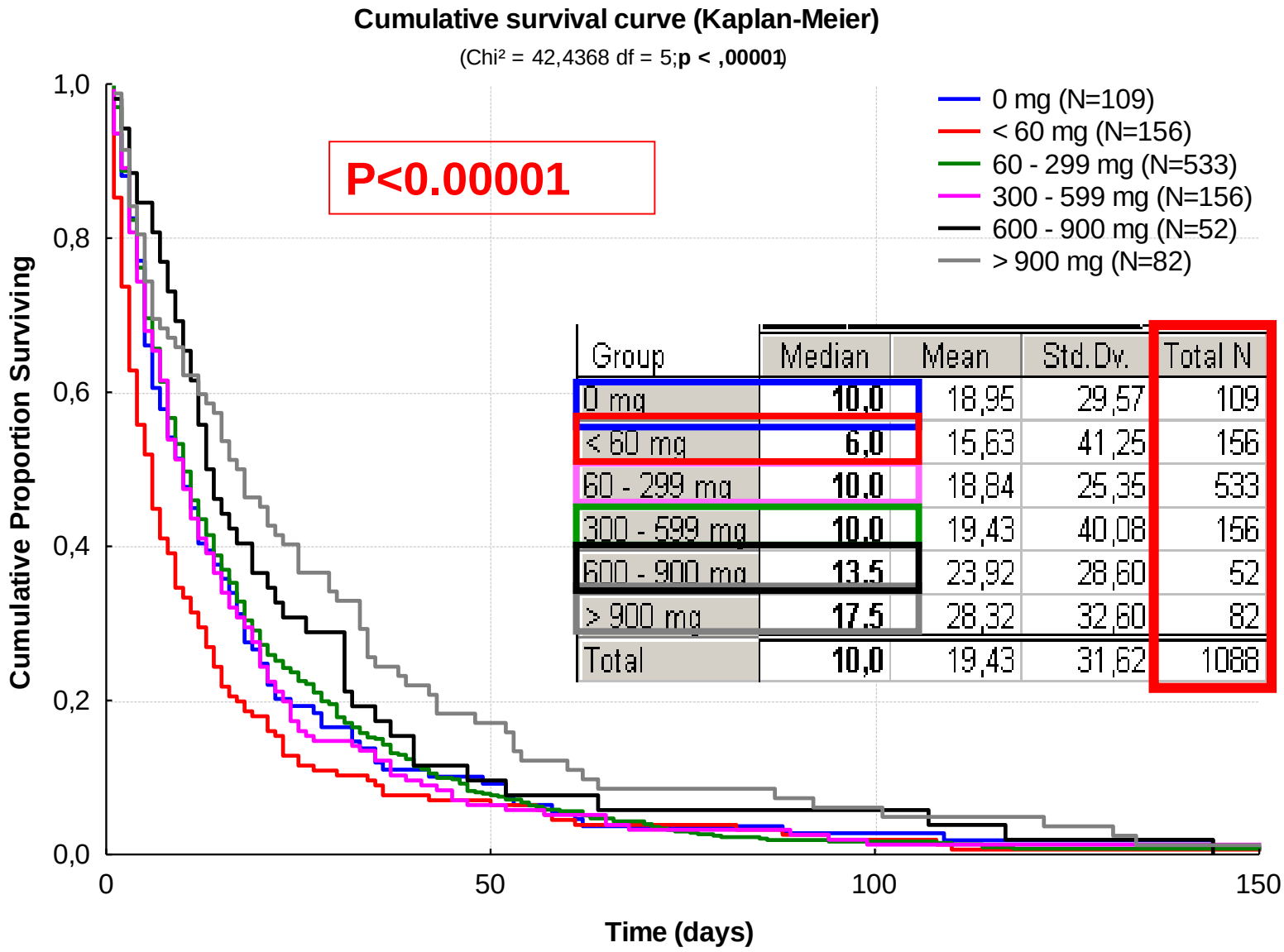
P = 0,002 Mantel-Cox

P=0,029 Breslow-analysis

Duration of stay in PCU until † ifo. oral morphine equivalent dose in mg/d for palliative cancer patients >65y. (PCU - Leuven)



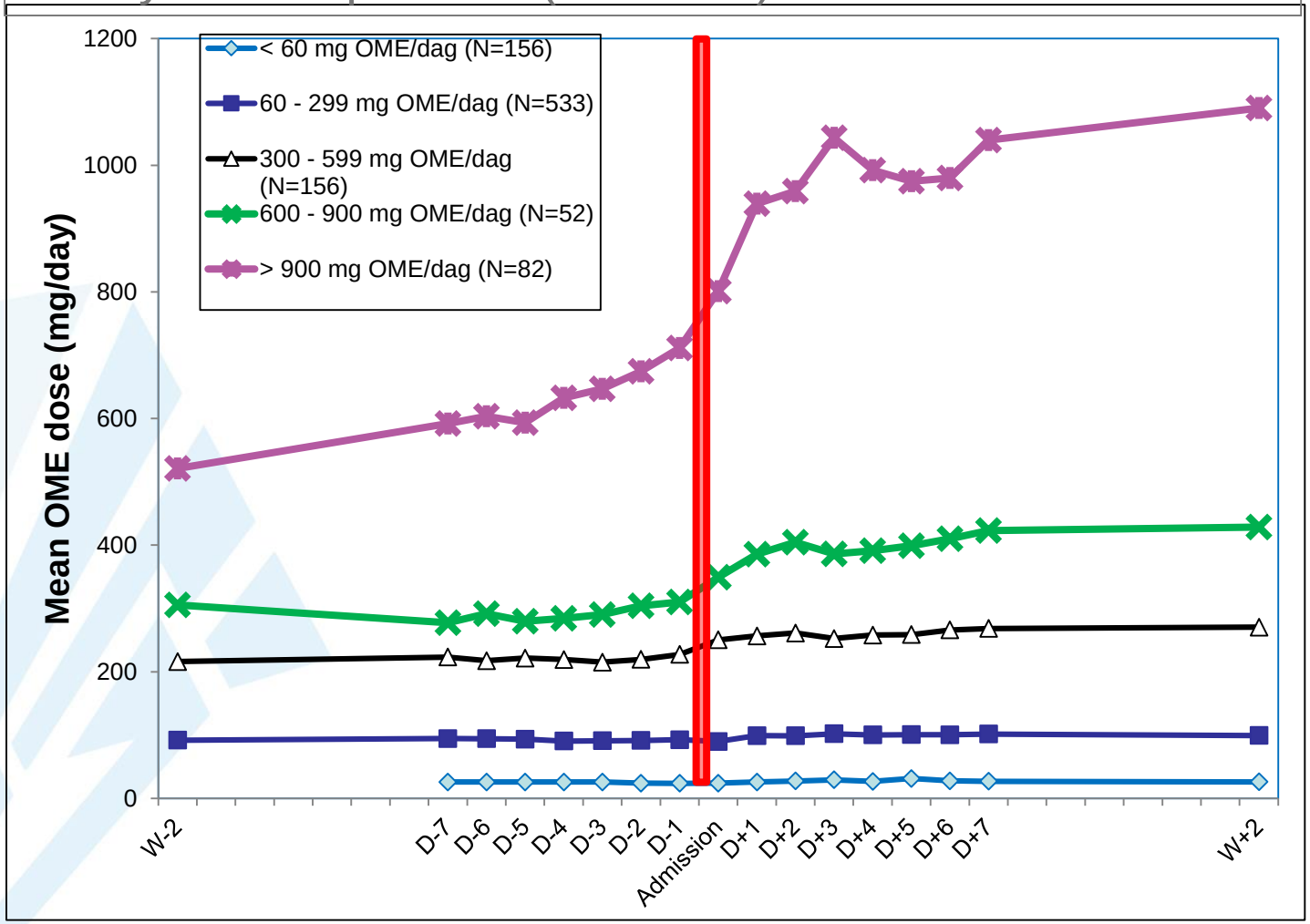
Survival in function of the morphine equivalent dose For >65y palliative cancer patients (died in the PCU- Leuven)



Group	Median	Mean	Std.Dv.	Total N
0 mg	10,0	18,95	29,57	109
< 60 mg	6,0	15,63	41,25	156
60 - 299 mg	10,0	18,84	25,35	533
300 - 599 mg	10,0	19,43	40,08	156
600 - 900 mg	13,5	23,92	28,60	52
> 900 mg	17,5	28,32	32,60	82
Total	10,0	19,43	31,62	1088

Fear for *opioid tolerance* can not justify to withhold effective pain treatment

- palliative care unit UH Leuven
- >65y cancer patients (n = 1088)

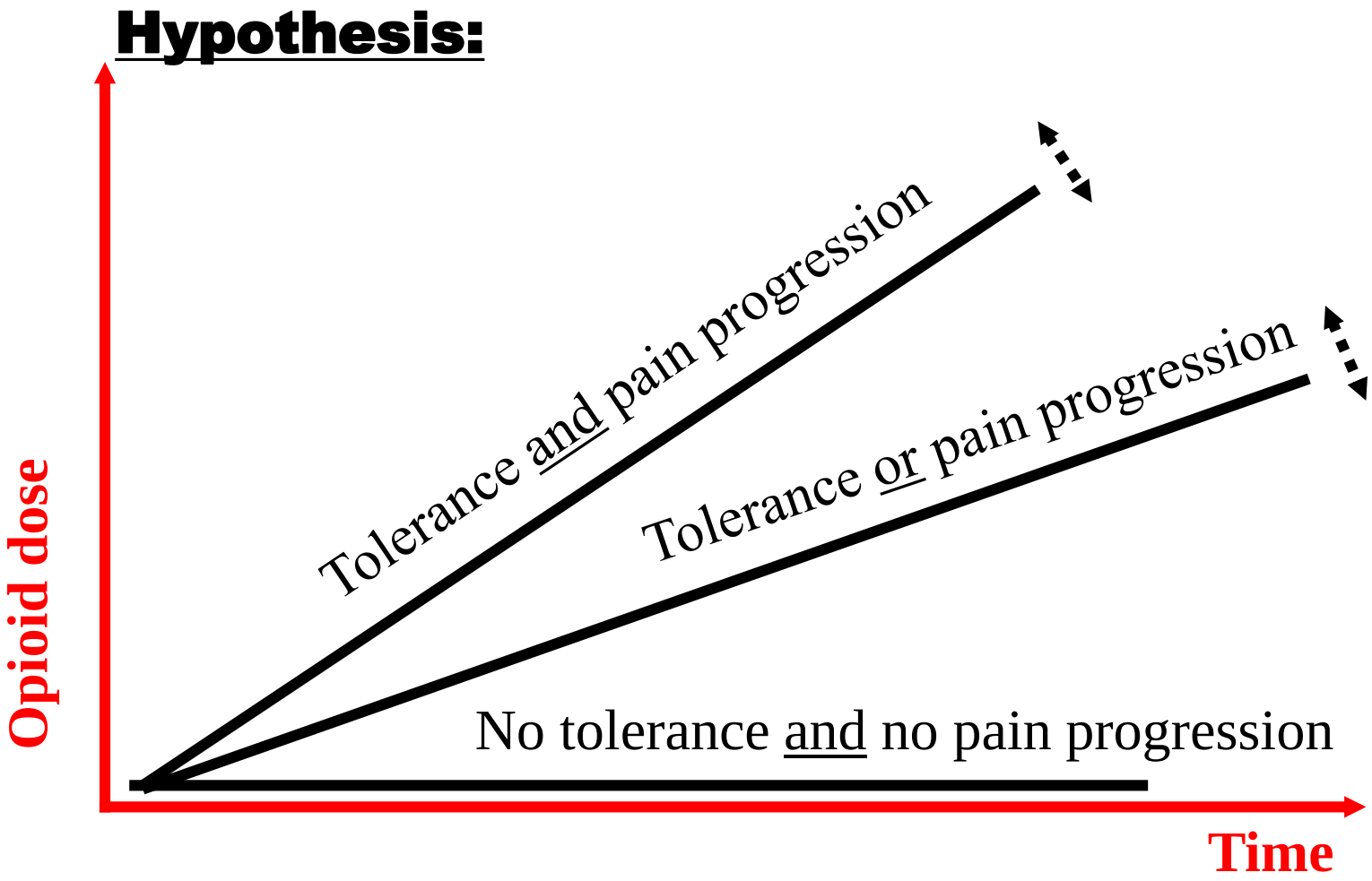


Opioid tolerance in advanced cancer patients

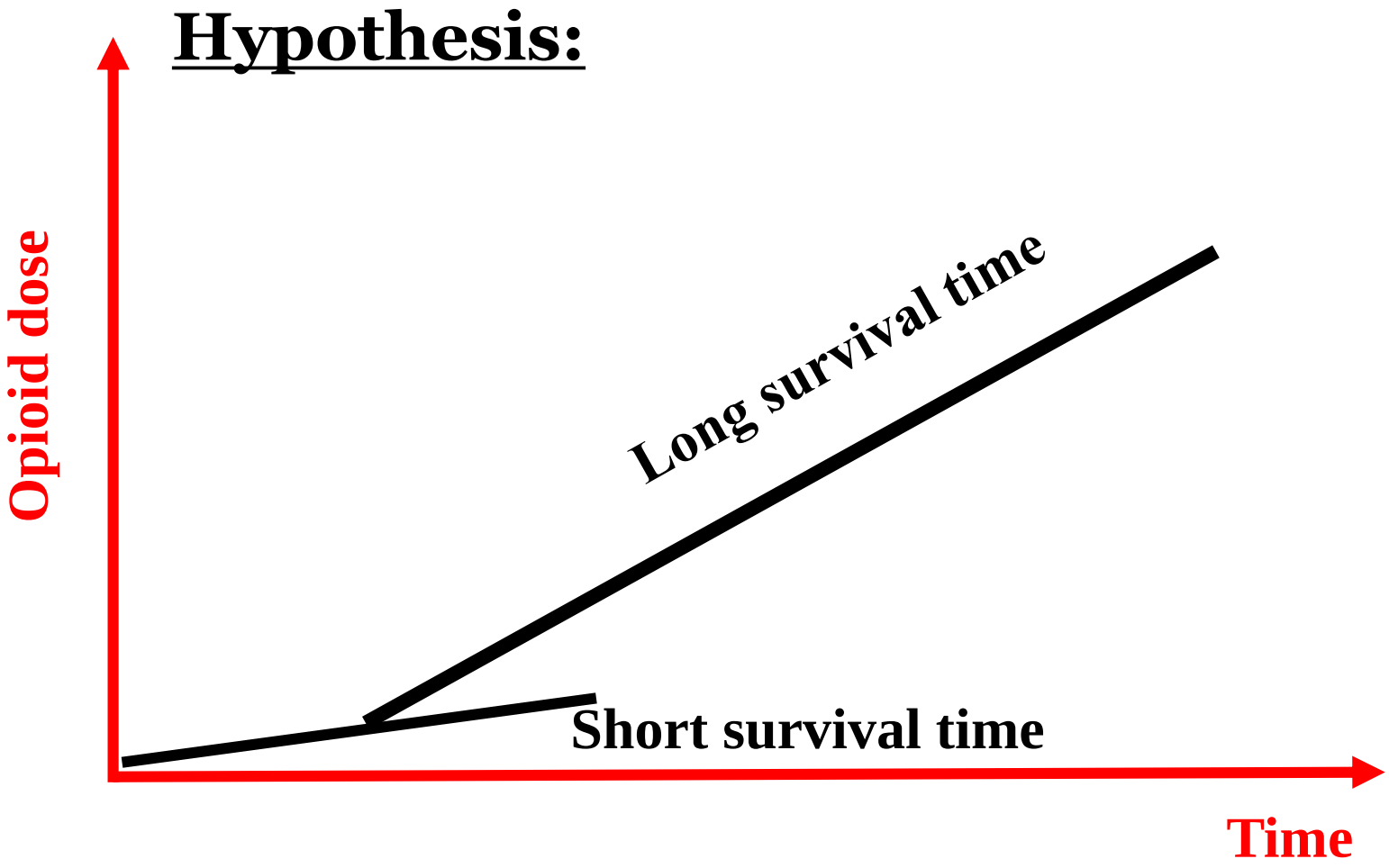
Open label multicenter study (Fen-Bel 5 study)
compassionate use TTS-fentanyl in Belgium (59 physicians)

Palliative untreatable cancer patients
with a assessed life expectancy of ≥ 3 months
that need opioids for pain relief could be included (inform. cons)

Strong opioids will cause tolerance ?

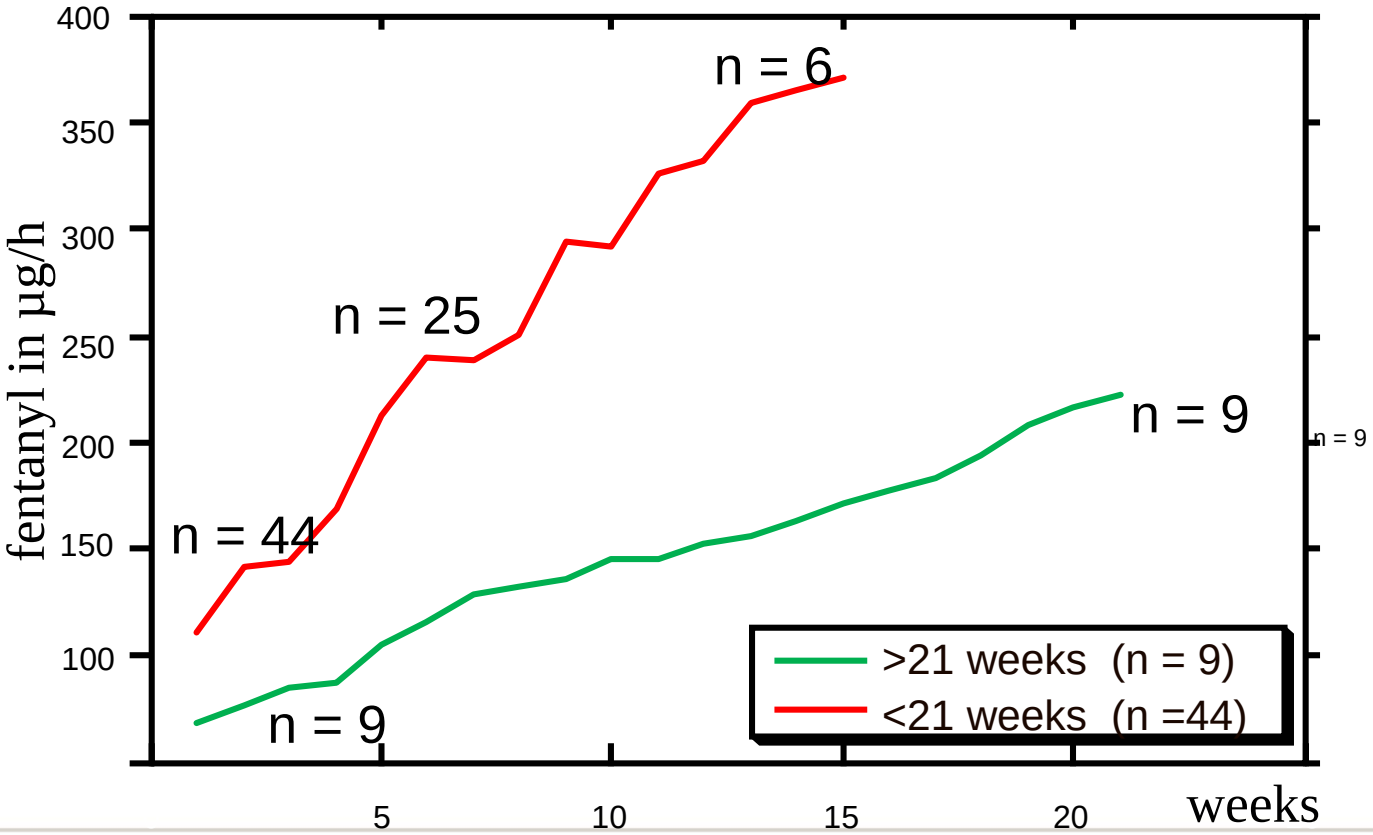


4 Strong opioids will cause tolerance ?



Fentanyl consumption in palliative oncological patients with survival <21 and >21 weeks

Data Palliative support team UH Leuven



Fen-Bel 5 study (Leuven patients = 53)

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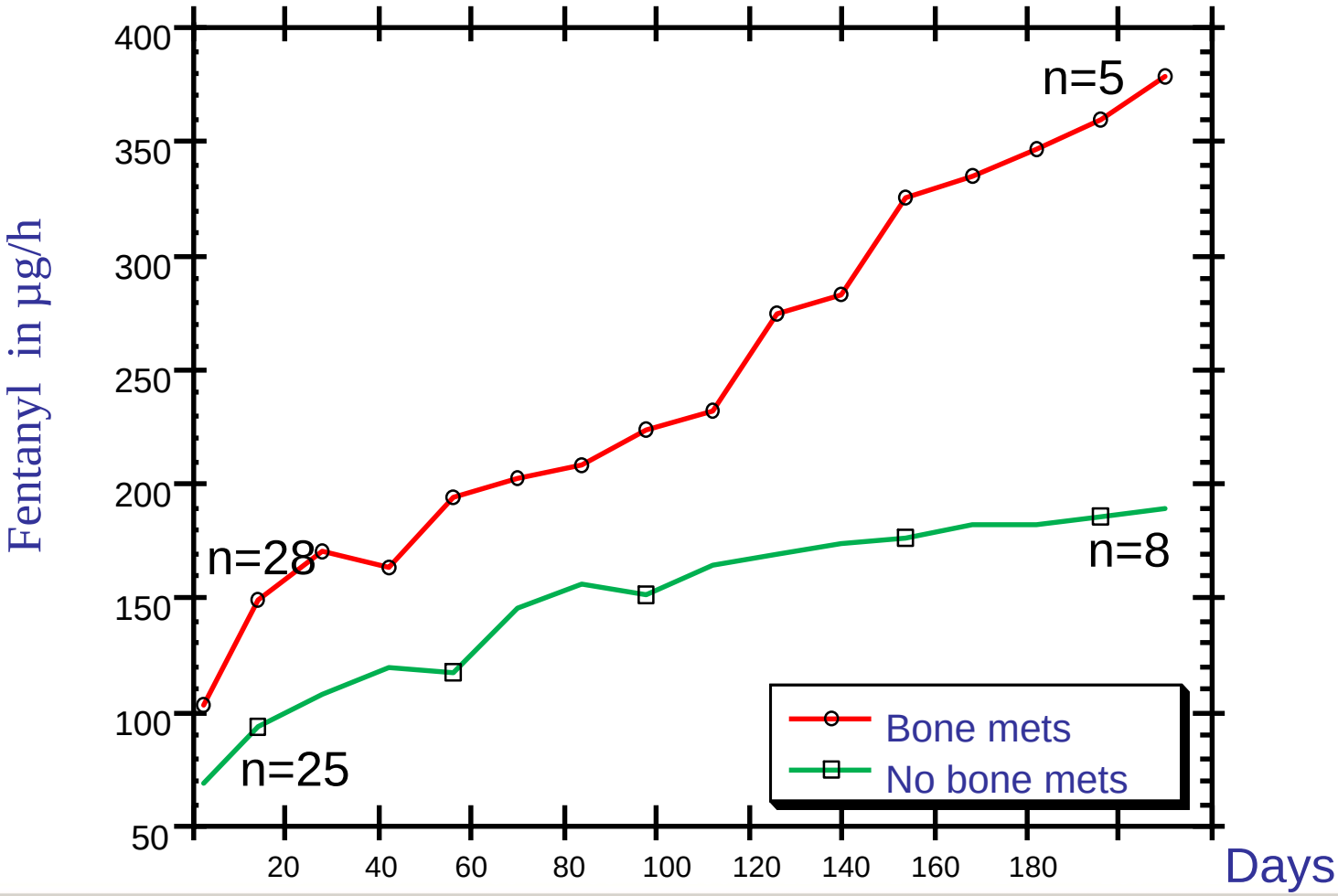
Opioïd consumption in oncological palliative patients with or without bone metastases



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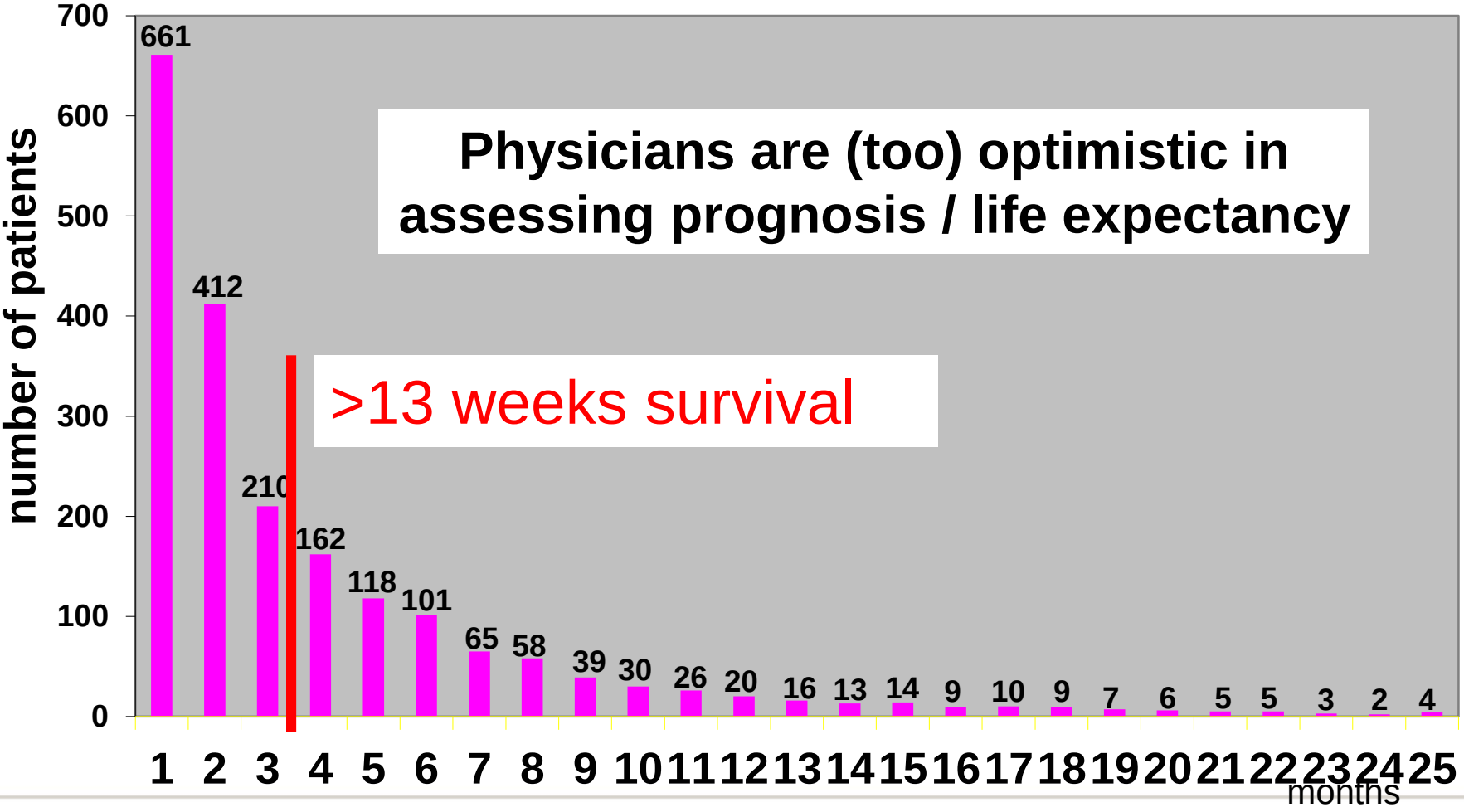
Opioid tolerance in advanced cancer patients: a self limiting phenomenon?

(in months: 1= start, 2-25 are the months 1-24).



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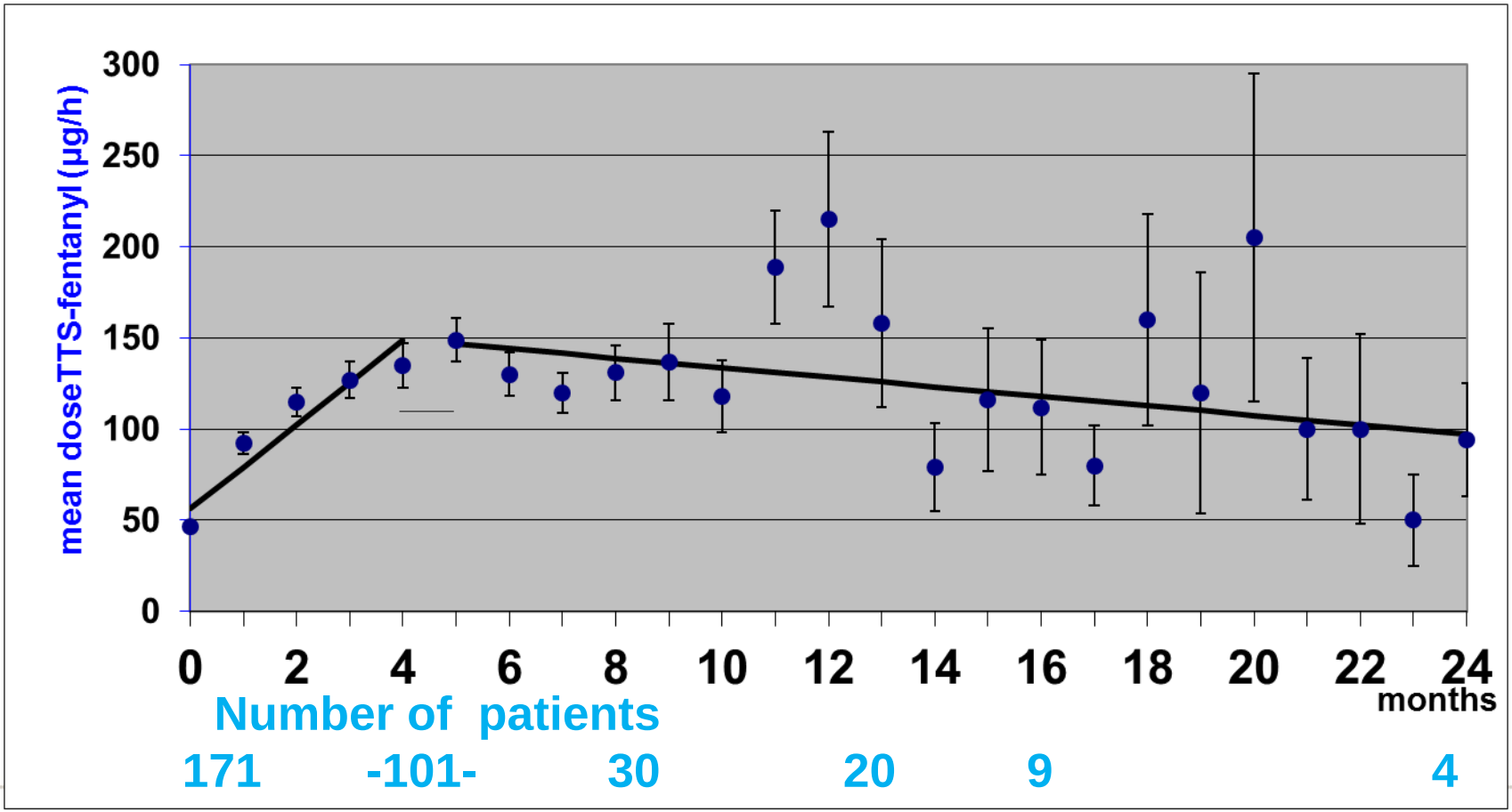
Opioid tolerance in advanced cancer patients



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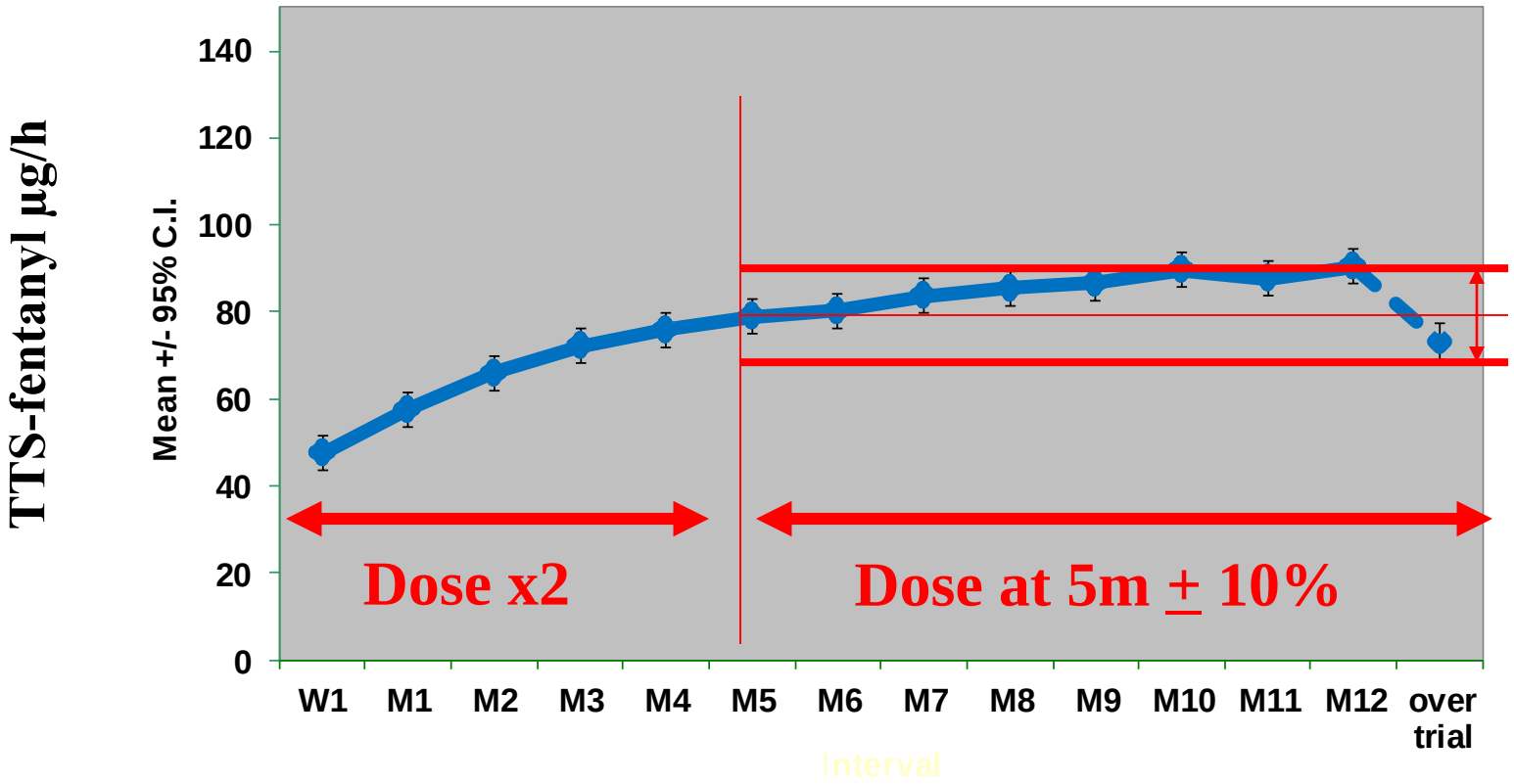
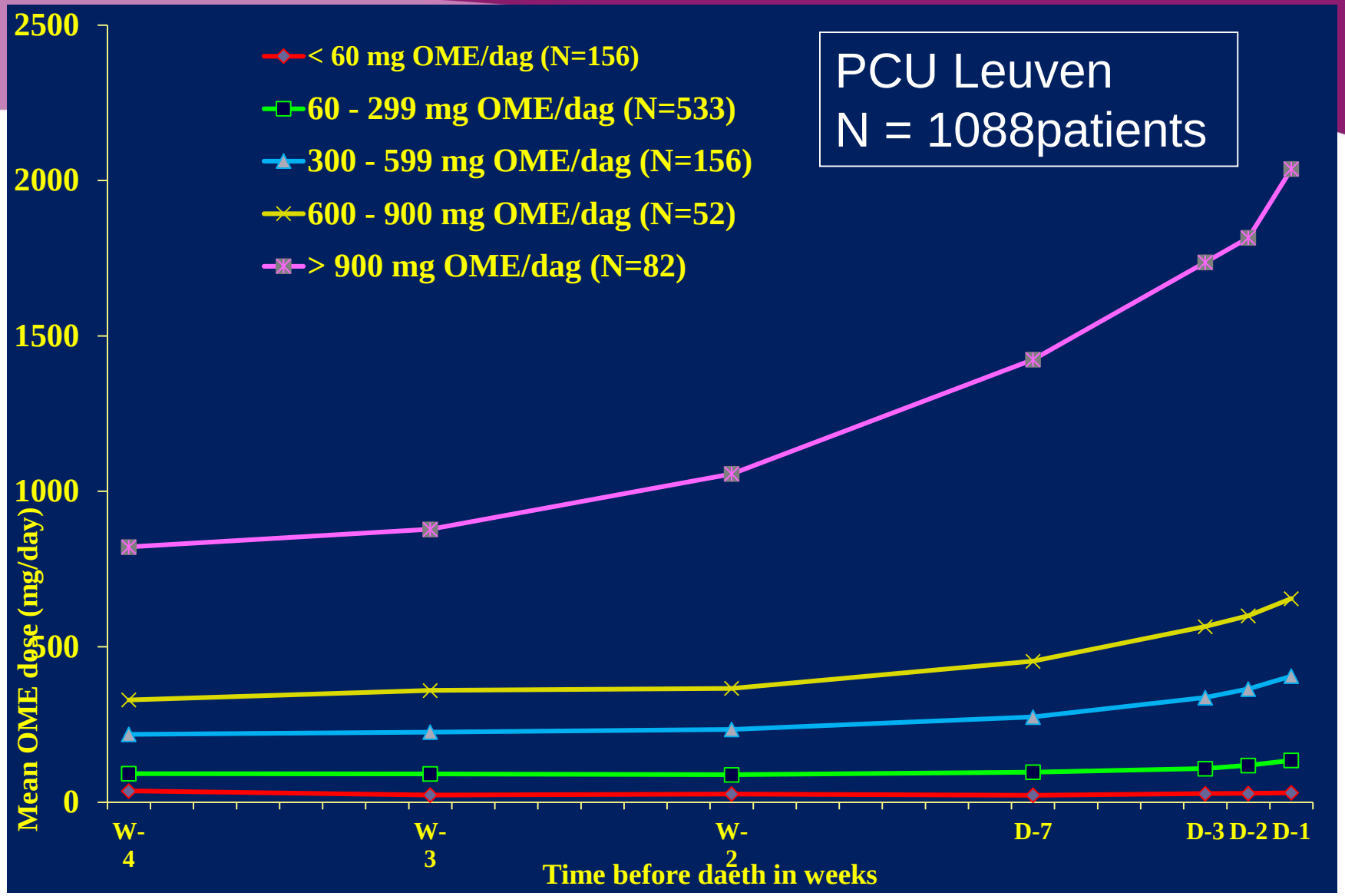
Chronic non-cancer pain

K Milligan et al. , J of Pain, Vol 2, No 4, 2001, 197-204





Morphine, early provided in the disease trajectory, is not automatically leading to tolerance/addiction!!

TABLE 3. CLINICAL PROBLEMS ASSOCIATED WITH EUTHANASIA AND PHYSICIAN-ASSISTED SUICIDE.*

VARIABLE	NO. OF CASES	TECHNICAL PROBLEMS†	P VALUE	COMPLICATIONS‡	P VALUE	PROBLEMS WITH COMPLETION§	P VALUE
		no./total no. (%)		no./total no. (%)		no./total no. (%)	
Intended intervention			0.03		0.03		0.001
Euthanasia	535	24/529 (5)		16/532 (3)		28/528 (5)	
Assisted suicide	114	11/112 (10)		8/111 (7)		16/110 (15)	
Type of physician			<0.001¶				0.04¶
General practitioner	356	28/353 (8)		15/354 (4)		30/351 (9)	
Specialist	256	4/253 (2)		6/253 (2)		11/252 (4)	
Nursing home physician	37	3/35 (9)		3/36 (8)		3/35 (9)	
Type of drug initially administered‖							
Barbiturate	320	21/317 (7)		11/317 (3)		19/315 (6)	
Opioid	142	10/141 (7)		8/141 (6)		15/140 (11)	
Other	171	3/169 (2)		5/171 (3)		10/169 (6)	
Route of administration of initial drug**			0.003				<0.001
Oral or rectal	116	14/115 (12)		8/113 (7)		15/113 (13)	
Parenteral	327	14/325 (4)		12/326 (4)		11/324 (3)	
All cases	649	35/641 (5)		24/643 (4)		44/638 (7)	

New England Journal of Medicine 2000; Vol 342 no8, 551556.

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Opioiden ~ Respiratory depression?

	Total n=661 (%)	Elderly n=341(%)	Opioid naïve n=55(%)
Any adverse event	460 (69.6)	255 (74.8)	38 (69.1)
General disorders	423 (64.0)	232 (68.0)	35 (63.6)
Nervous system disorders	23 (3.5)	16 (4.7)	2 (3.6)
Gastro-intestinal disorders	54 (8.2)	37 (10.9)	4 (7.3)
Psychiatric disorders	34 (5.1)	24 (7.0)	2 (3.6)
Respiratory system disorders	9 (**1.4**)	6 (**1.8**)	1 (**1.8**)
Skin & appendages disorders	10 (1.5)	8 (2.3)	1 (1.8)
Urinary system disorders	7 (1.1)	6 (1.8)	0 (0)

Menten 2003, PhD Thesis

More & better treatment…?

A Scottisch survey suggests that

of the 8%–20% of cancer patients

who have indications for treatment by anesthesiology pain specialists,

…few patients are ever referred for specialty pain consultation

Linklater GT, Leng ME, Tiernan EJ, et al.
Pain management services in palliative care: a national survey.
Palliative Medicine 2002; 16: 435-9

"total analgesia" for refractory pain

(different from "anesthesia")

is defined as a state of minimal / absent pain perception in the face of a potent neuropathic or nociceptive pain stimulus without intentional alteration in awareness.

Therapeutic goal = pain relief
-not sedation, amnesia or unconsciousness.

➔ketamine given in subanesthetic doses

Fine PG.
Low-dose ketamine in the management of opioid non responsive terminal cancer pain.
J Pain and Symptom Manage 1999; 17: 296 –300.

More & better treatment…?

In practice

➔ketamine , administered in **subanesthetic** doses

An IV or SC continuous infusion is initiated at a rate determined by the total dose and duration of effect of bolus doses.

For example,

if sufficient pain relief for 15 min with 5 mg of ketamine,
➔ infusion of 20 mg/h would be appropriate.

In patients receiving large-dose opioids,

it is often possible (& desirable) to immediately reduce the opioid by 25%–50%

Typical effects of **anesthetic** doses of ketamine do not pose problems when given in subanesthetic doses

(e.g., salivation, sedation, loss of airway reflexes, and hallucinations)

Patients with advanced COPD have similar complaints as advanced cancer patients

C. Bausewein et al.
J Pal Med 2010; 13(9): 1109-1118

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JRSM
JOURNAL OF THE ROYAL SOCIETY OF MEDICINE

J R Soc Med. 2007 May; 100(5): 225–233.
doi: 10.1258/jrsm.100.5.225

Major provider of postgraduate medical education.
Independent and apolitical

Palliative care in chronic clinicians

David A Seamark,[1] Clare J Seamark,[2] and David M G Halpin[3]

Box 2 **Drug therapy of COPD in palliative care**

- Benzodiazepines to control anxiety
- Antidepressants to improve mood
- Opioids and oxygen to control breathlessness
- Consider continuous subcutaneous infusion therapy of opioids, anti-emetics and anxiolytics

Journal of the American Geriatrics Society

Chronic Obstructive Pulmonary Disease Diagnosis and Management in Older Adults

Nalaka S. Gooneratne, MD, MSc; Nirav P. Patel, MD, MPH; Amy Corcoran, MD

Disclosures

J Am Geriatr Soc. 2010;58(6):1153–1162

Table 4. Management of Symptoms of End-Stage Chronic Obstructive Pulmonary Disease in Older Adults

Symptom	Management
Dyspnea	Opioids: morphine 2.5–5 mg orally or SL every 3–4 hours as needed or 1 mg IV/SC every 10–15 minutes as needed would be recommended starting dose in an opioid-naïve older adult. Nebulized opioids: nebulized morphine 2 mg or fentanyl 25 μg in 5 mL normal saline every hour as needed can be used. Conflicting data exist regarding efficacy of nebulized opioids, and there is the risk of bronchospasm with nebulized morphine. Humidified oxygen Nebulizers (albuterol or ipratropium) Steroids Fan placed near patient to increase air flow Breathing techniques: breathing control strategies, pacing, relaxation techniques
Anxiety	Benzodiazepines: lorazepam 0.5–1 mg every 4 hours orally, SL, or IV as needed would be recommended starting dose in a benzodiazepine naive older adult
Secretions	Anticholinergics: glycopyrrolate 0.1 mg IV or IM every 4 hours as needed or scopolamine 1.5 mg patch every 3 days as needed would be recommended starting dose. Glycopyrrolate IV/IM will have a more-rapid onset and may be more appropriate for patients in their final 24 hours of life. Position changes: position patient on their side or semiprone if tolerated Suctioning for oral secretions may be helpful, but this may also be uncomfortable if attempt deep suctioning

IV=intravenously; SL= sublingually; SC=subcutaneously; IM=intramuscularly.

British Journal of Clinical Pharmacology Volume 81, Issue 5, 17 JAN 2016 DOI:10.1111/bcp.12856

Letter to the Editor

Opioids and COPD

American College of Chest Physicians consensus on dyspnoea stated:

'with appropriate titration opioids have not caused significant changes in survival after withdrawal of life support

Intern Med J. 2015 Sep;45(9):898-904. doi: 10.1111/imj.12857.

Management of refractory breathlessness with morphine in patients with chronic obstructive pulmonary disease.

Smallwood N[1], Le B[2], Currow D[3], Irving L[1], Philip J[4].

[1]Department of Respiratory and Sleep Medicine, [2]Palliative Care, The Royal Melbourne Hospital, Melbourne, Victoria, Australia.

[3]Palliative and Supportive Services, Division of Medicine, Flinders University, Adelaide, South Australia, Australia.

[4]Centre for Palliative Care, St Vincent's Hospital, Melbourne, Victoria, Australia.

-**Breathlessness** is common in advanced COPD and **remains undertreated**.

Cancer

-As all reversible causes of breatlessness are being optimally managed, **low dose morphine can reduce safely & effectively breathlessness** in patients with severe COPD and refractory dyspnoea.

-Despite numerous guidelines recommending opioids in this clinical setting, **many barriers limit their uptake by clinicians**.

-**Integration of palliative care earlier in the disease course** can help to improve symptom control for people with severe COPD and refractory breathlessness.

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CHRONIC RESPIRATORY DISEASE

Impact Factor: 2.694 | Ranking: Respiratory System 26 out of 58

Attitudes toward opioids for refractory dyspnea in COPD among Dutch chest physicians

Daisy JA Janssen[1,2]

SM de Hosson[3]

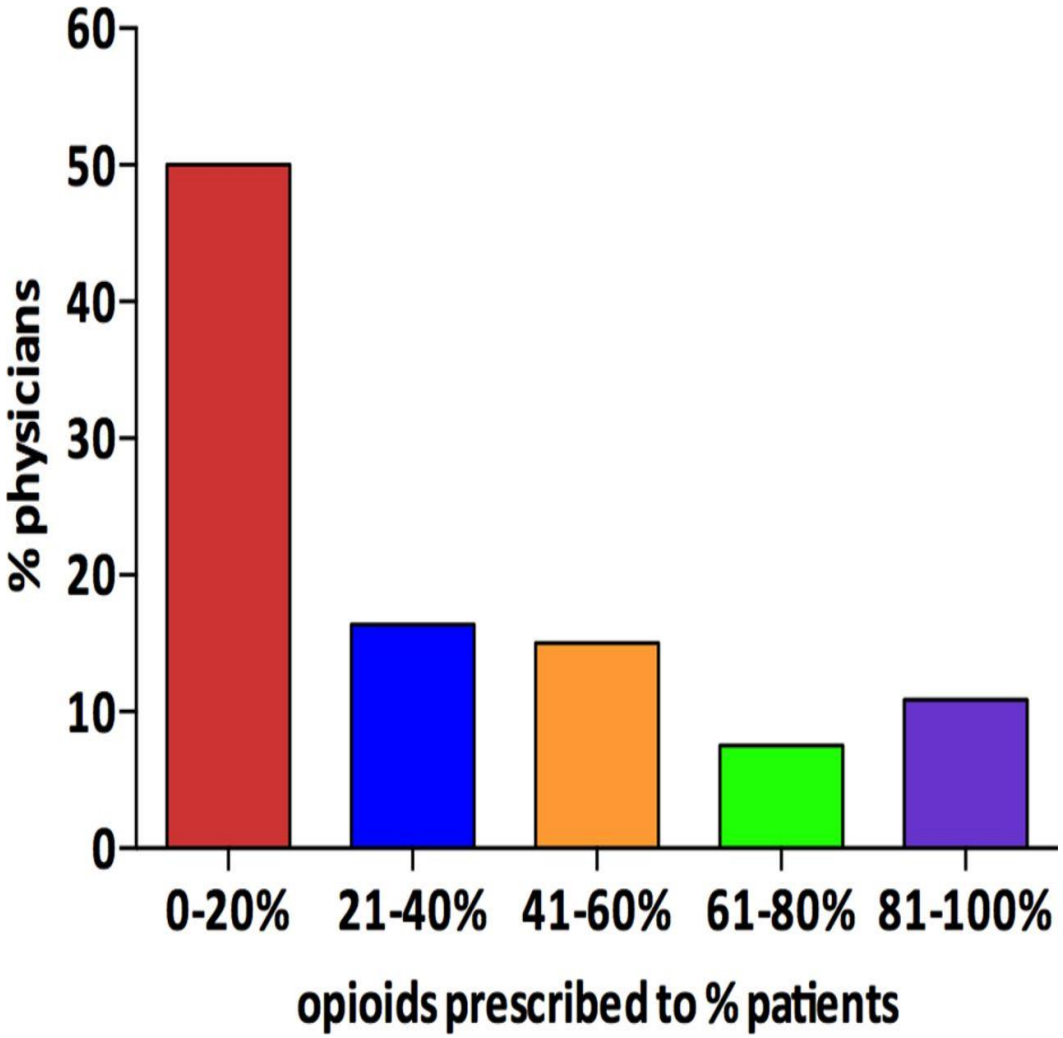
Eline bij de Vaate[4]

Kris JM Mooren[5]

Albert AF Baas[6]

[1]Department of Research and Education, CIRO+, Centre of Expertise for Chronic Organ Failure, Horn, The Netherlands
[2]Centre of Expertise for Palliative Care, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands
[3]Wilhelmina Hospital, Assen, The Netherlands
[4]Merem Asthma Center Heideheuvel, Hilversum, The Netherlands
[5]Kennemer Gasthuis, Haarlem, The Netherlands
[6]Hospital Rivierenland, Tiel, The Netherlands

Figure 1. Attitudes toward opioid prescription.



Daisy JA Janssen et al.
Chronic Respiratory Disease
2015;12:85-92

ESTRO School

Table 2. Determinants of prescribing opioids to 20% or less of the patients with advanced COPD and refractory dyspnea.

	Prescribing to 0-20% ($n = 73$)	Prescribing to 21%–100% ($n = 73$)	Unadjusted p value	OR (95% CI)[b]
Age (years)	45.3 (10.7)	41.9 (8.5)	0.03	1.06 (1.01–1.11)
Male	48 (65.8%)	40 (54.8%)	0.18	1.39 (0.63–3.10)
Physician in academic hospital	23 (69.7%)	10 (30.3%)	0.01	3.80 (1.50–9.60)
Oncology as subspecialty	12 (31.6%)	26 (68.4%)	0.008	0.35 (0.14–0.84)
Palliative care education	38 (52.1%)	48 (65.8%)	0.09	0.57 (0.26–1.26)

[a]Data presented as mean (SD) or number (%).
[b]Based on binary logistic regression analysis, $R^2 = 0.22$.

Daisy JA Janssen et al. Chronic Respiratory Disease 2015;12:85-92

Physician perceived barriers to prescription of opioids.

	Total group ($n = 146$)	Prescribing to 0%–20% ($n = 73$)	Prescribing to 21%–100% ($n = 73$)	p Value
Possibility of respiratory depression	29 (19.9%)	15 (20.5%)	14 (19.2%)	1.00
Side effects such as nausea, constipation, or drowsiness	77 (52.7%)	33 (45.2%)	44 (60.3%)	0.10
Resistance patient	94 (64.4%)	38 (52.1%)	56 (76.7%)	0.003
Unpredictable which patients will respond to opioids	21 (14.4%)	16 (21.9%)	5 (6.8%)	0.02
Insufficient expertise to prescribe opioids	21 (14.4%)	18 (24.7%)	3 (4.1%)	0.001
Insufficient scientific evidence for beneficial effect on dyspnea among patients with advanced COPD	11 (7.5%)	9 (12.3%)	2 (2.7%)	0.06
Insufficient scientific knowledge concerning safety aspects	7 (4.8%)	7 (9.6%)	0 (0%)	0.02
Opioids are only indicated for terminal patients	2 (1.4%)	2 (2.7%)	0 (0%)	0.48
Possibility for development of physical or psychological dependence	10 (6.8%)	4 (5.5%)	6 (8.2%)	0.74

COPD: chronic obstructive pulmonary disease.
[a]Data presented as number (%).

Daisy JA Janssen et al. Chronic Respiratory Disease 2015;12:85-92

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	Number (%)
Preferred long-acting opioid	
Morphine sustained release (oral)	48 (32.9%)
Oxycodone sustained release (oral)	38 (26.0%)
Fentanyl (transdermal)	28 (19.2%)
Other[b] (oral)	5 (3.4%)
Never prescribe long-acting opioid	27 (18.5%)
Prescription of short-acting opioid for breakthrough dyspnea next to long-acting opioid	
Always	54 (37.0%)
As indicated	49 (33.5%)
Never	43 (29.5%)
Preferred short-acting opioid	
Morphine (oral)	73 (50.0%)
Oxycodone (oral)	33 (22.6%)
Fentanyl (transmucosal)	13 (8.9%)
Never prescribe short-acting opioid	27 (18.5%)
Prescription of laxatives and anti-emetics next to opioids	
None	10 (6.8%)
Laxatives only	128 (87.7%)
Anti-emetics only	0 (0%)
Laxatives and anti-emetics	8 (5.5%)

[a] $n = 146$.
[b] Codeine, buprenorphine, or hydromorphone.

chronicOPD ~ chronic pain

3-fold prescription:

1-Maintenance (long acting)
(never on demand,
but around the clock)

2-Breakthrough medication
(short acting)
= 1/12 - 1/6 of the daily dose

3-Laxatifs allways,
anti-emetics if needed

Daisy JA Janssen et al. Chronic Respiratory Disease 2015;12:85-92

Dyspnoea “ladder” in COPD

-Conventional management with **bronchodilatators/steroids.**

-Manage co-morbidities

-**Nonpharmacological** treatments

support /exercise / chest wall vibration / fan,..

~physiotherapy

Supplemental **oxygen** if hypoxic/

consider ambulatory oxygen if desaturation with exercise

opioid therapy for dyspoea

+/- anxiolytics

Some authors suggest

Morfine slow release 5mg po x2/d

Uptitrate to 1-2,5 mg po/4h by the end of the first week

Doses are uptitrated by 25% weekly until adequate symptom relief is achieved

Other authors use sustained release morphine

Starting dose 10 mg/d and titrated weekly to 20 or 30 mg/d without respiratory depression or significant side effects

➔Compliance is highest with once daily dosing or patch/3 days

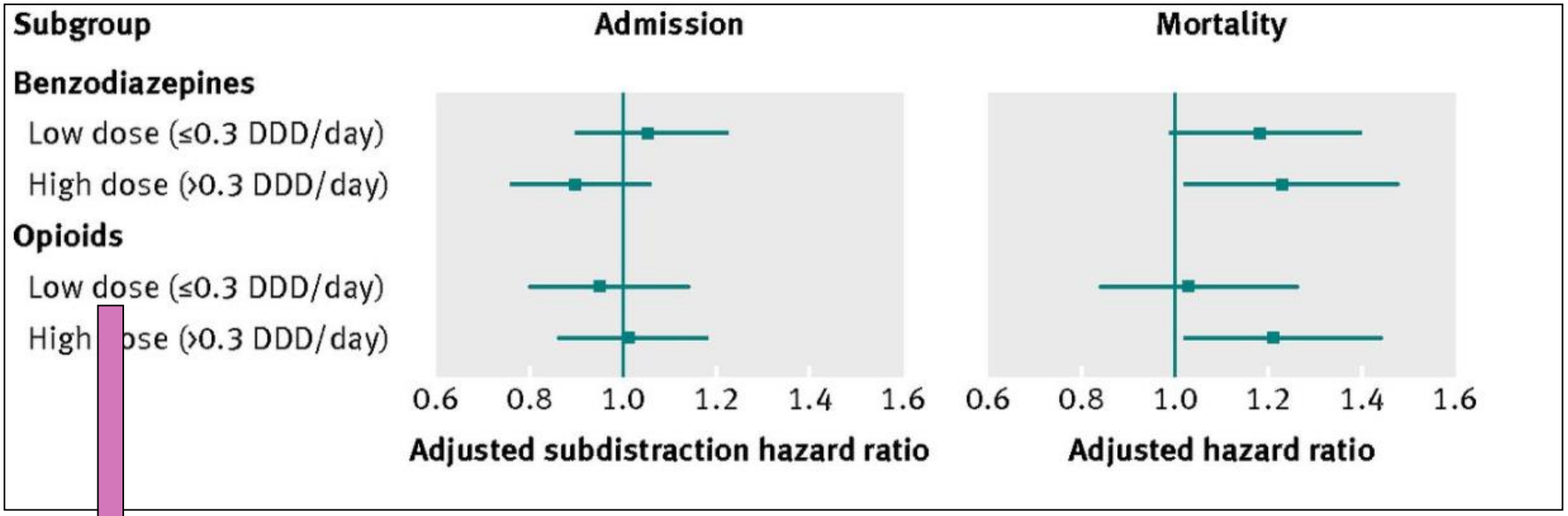
Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study

BMJ 2014;348:g445
M Ekström, Department of Medicine, Blekinge Hospital, SE-37185, Karlskrona, Sweden pmekstrom@gmail.com

- **Objective** To evaluate the safety of benzodiazepines and opioids in patients with very severe chronic obstructive pulmonary disease.
- **Design** Population based longitudinal consecutive cohort study.
- **Setting** Centres prescribing long term oxygen therapy in Sweden.
- **Patients** 2249 patients starting long term oxygen therapy for COPD in Sweden between 2005 and 2009 in the national Swedevox Register.
- **Main outcome measures** Effects of benzodiazepines and opioids on rates of admission to hospital and mortality, adjusted for age, sex, arterial blood gases, body mass index (BMI), performance status, previous admissions, comorbidities, and concurrent drugs.

Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study

BMJ 2014;348:g445
M Ekström, Department of Medicine, Blekinge Hospital, SE-37185, Karlskrona, Sweden
pmekstrom@gmail.com



up to 30 mg oral morphine equivalent dose /d

Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study

BMJ 2014;348:g445
M Ekström, Department of Medicine, Blekinge Hospital, SE-37185, Karlskrona, Sweden pmekstrom@gmail.com

The approach for chronic refractory breathlessness is not different from that of opioid treatment for refractory pain.

Sustained release morphine should be a first line treatment and should be initiated at a low dose and titrated upward over days and weeks, balancing beneficial and adverse effects.

Titration up to 30 mg morphine/d might safely improve breathlessness in > 60% of patients, with a mean decrease of 35% in the intensity of breathlessness from the person's own baseline.

Opioids in oncology

friend:

-used with scientific knowledge

-offered with communicative skills

-titrated according the scientific evidence

*** COPD & IPF up to 30 mg omeq/dag**

*** in cancer: as much as needed to relief the pain ➔NRS <4/10**

enemie:

-if knowledge & prescription experience is lacking

(academic centres have the duty to teach!)

- if communication fails to correct the misconceptions in patients, families, caregivers, volunteers,..

Fatigue

1-Haematological and biochemical urgencies:

1,1 Anaemia

-Hgb <5 + terminal R/ “expectare et sedare ? “

-Hgb <8 + terminal + tachycardia/polypnoe

➔subjective complaints last R/ transfusion

1,2 Hypoglycemia = less apetite

R/less insuline substitution

1,3 Hypercalcemia : to treat or not to treat??

Fatigue

2-Hypotension

R/to withdraw antihypertensiva?
« I had to take that for the rest of my life »

3-Lack of condition ± to muscle wasting

-corticoisteroids needed?
-physical exercise possible?
-good sleep
-uncertainty about the future ➔ communication
-anxiety for death or dying process

Arch Intern Med. 2009 Mar 9;169(5):480-8

Health care costs in the last week of life: associations with end-of-life conversations

Zhang B1, Wright AA, Huskamp HA, Nilsson ME, Maciejewski ML, Earle CC, Block SD, Maciejewski PK, Prigerson HG

603 participants

188 (31.2%) reported EOL discussions at baseline.

the remaining 415 patients did not differ in sociodemographic characteristics, recruitment sites, illness acknowledgment, or treatment preferences.

-the mean (SE) aggregate costs of care (in 2008 US dollars) were:

-$1876 ($177) for patients who reported EOL discussions

Difference = $ 1041

($285) for patients who did not,

Patients with higher costs had worse quality of death in their final week (Pearson production moment correlation partial r = -0.17, *P =.006*).

Conclusion:

1-collaborate in the multidisciplinary palliative teams that exist

-to provide Your knowledge in development of palliative guidelines-expertise bedside when necessary

2-initiate palliative care initiatives in your hospital, in your wards?

about DNR-codes & advanced care planning:

➔what (not or no longer) to do?

3-correct misconceptions about opioids ~ analyse your data

4-help to educate caregivers (physicians, nurses, public,...)

about effective pain & symptom control

↳ Also psycho-social and spiritual care!!

Radiation drug interaction
(in palliative radiotherapy)

Morten Høyer
Professor clinical oncology
Aarhus University Hospital
E-mail: hoyer@aarhus.rm.dk

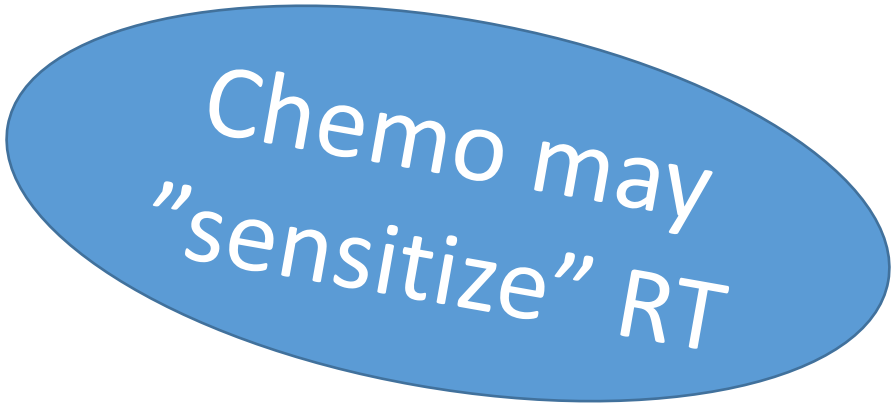
In palliative radiotherapy……..

- Poor level of knowledge
- Imprecise assessment of prevalence of complications
  - Insufficient diagnosis and reporting
- Extrapolation from normo-fractionation
- ……..and from curative therapy
- Sparse knowledge on the importance of timing of drug-radiotherapy

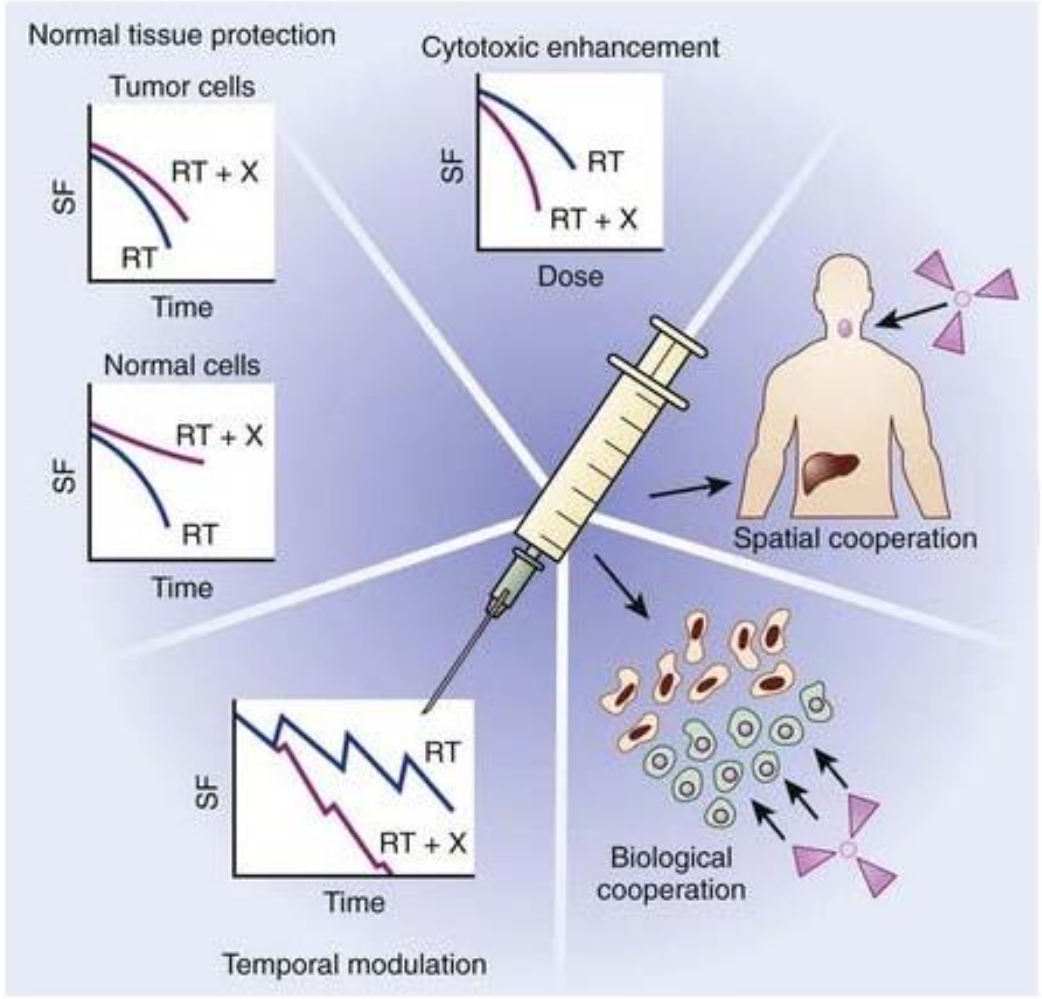
- *Toxicity independence* refers to the concept of combining a drug that caused systemic toxicity with radiation, in which toxicity is expressed locally

Concomitant chemoradiation

- Improves responses/outcomes in
  - Glioma
  - Head and neck cancer
  - Esophageal cancer
  - Lung cancer
  - Pancreas cancer
  - Cervix cancer
  - Rectal cancer
  - Anal cancer
- The price is increased acute toxicity

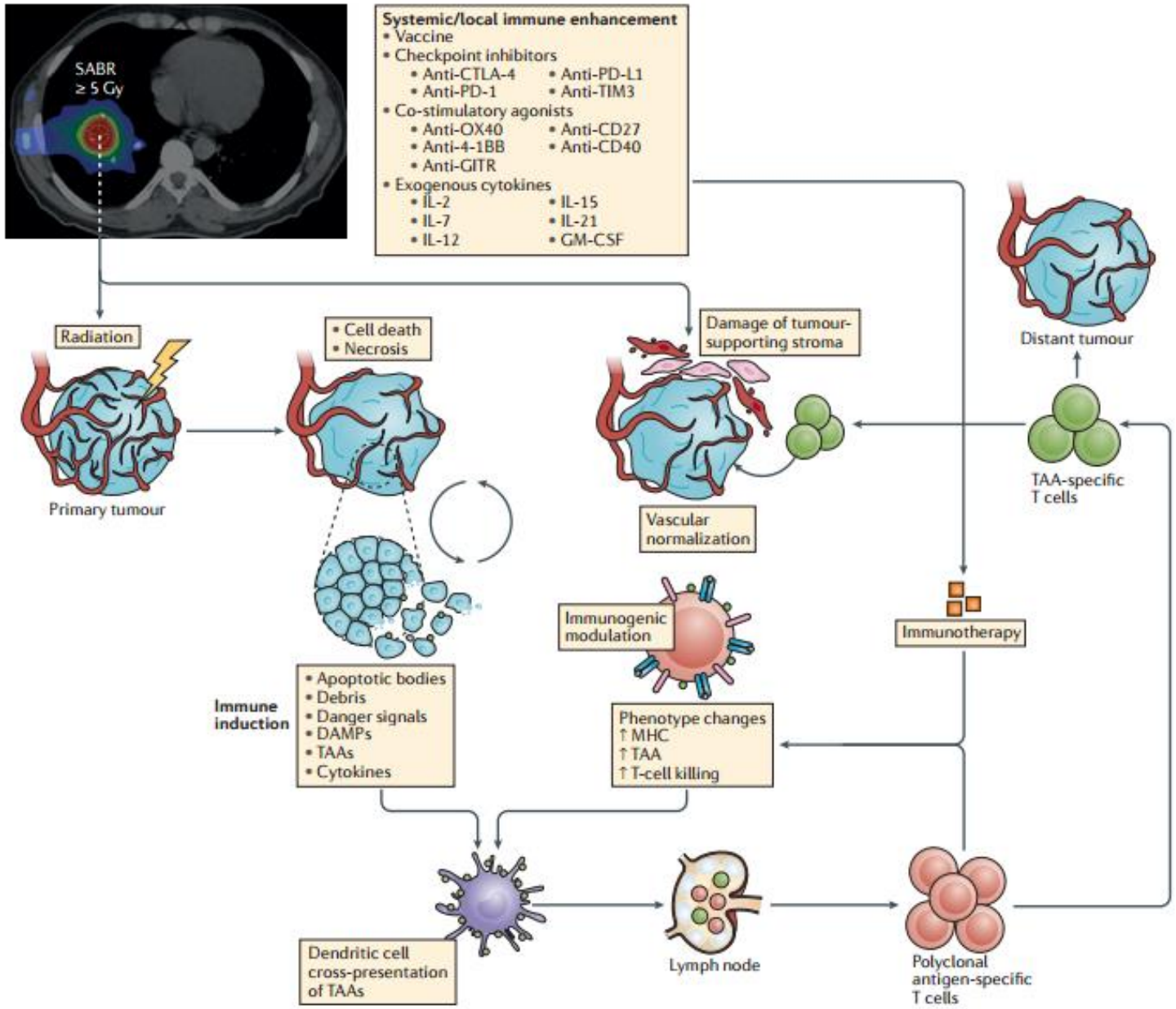


Interplay between spatial cooperation, cytotoxic enhancement, biologic cooperation, temporal modulation, and normal tissue protection



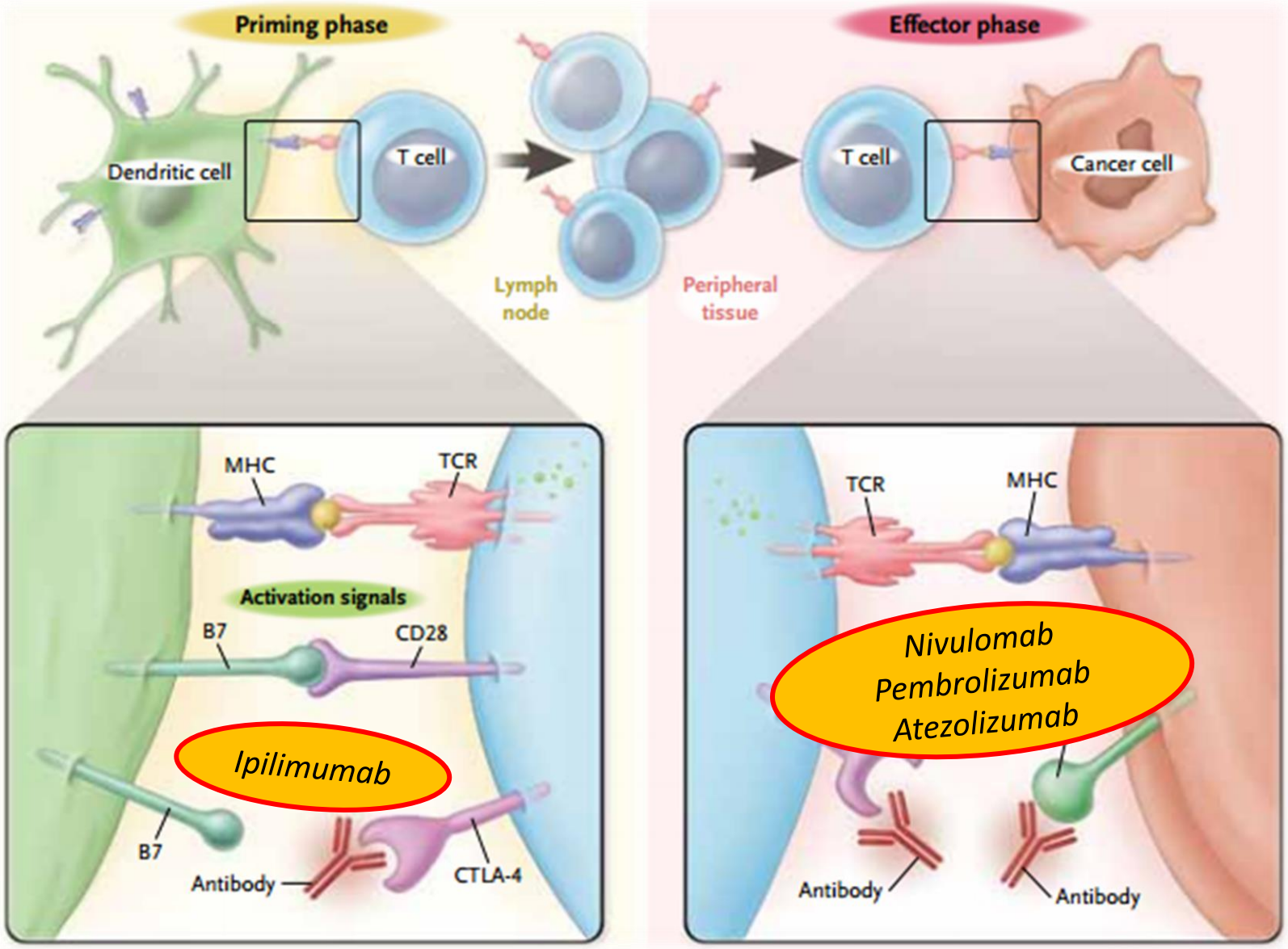
Bentzen et al Nat Clin Pract Oncol 4(3):172–180, 2007

Abscopal immune response



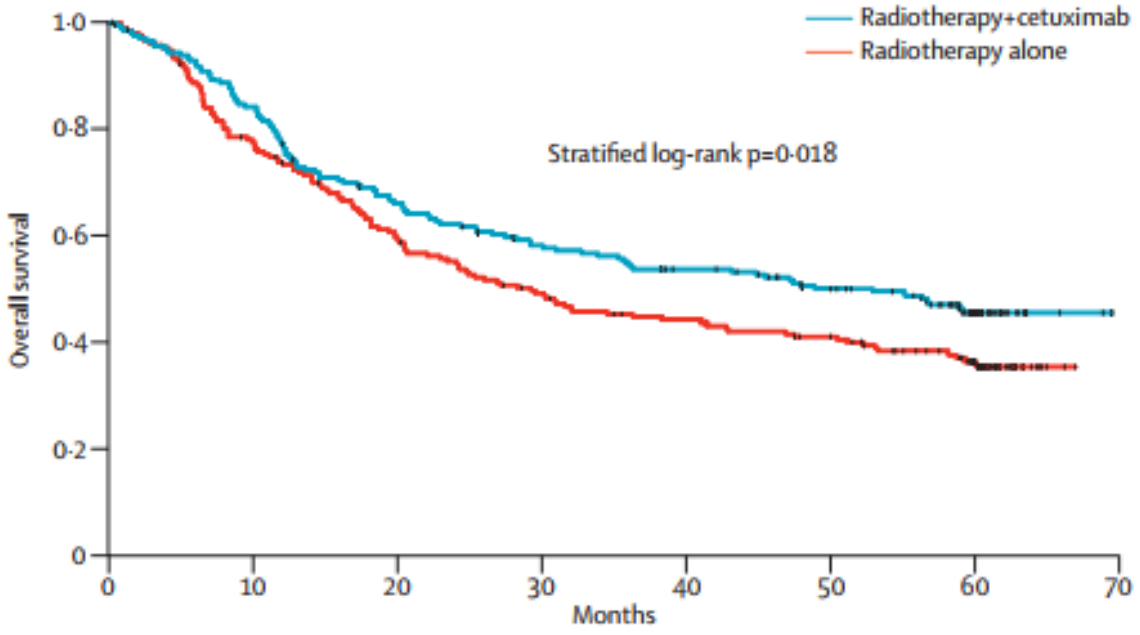
Bernstein et al. Nat. Rev Clin Oncol *e-pub 2016*

Immune check-point inhibitors



Ribas A: N Engl J Med 2012366;26

Cetuximab and RT for advanced stage head and neck squamous cell carcinoma



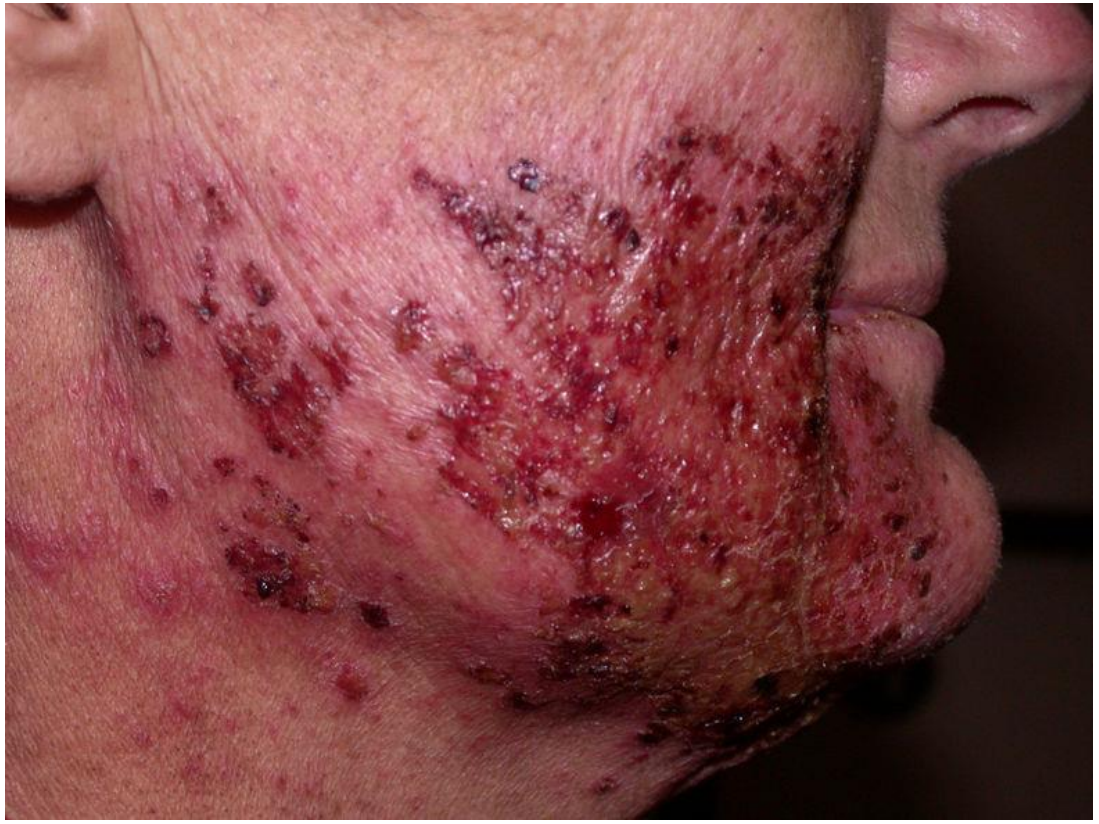
	Radiotherapy (N=212)			Radiotherapy plus cetuximab (N=208)		
	All grades	Grade 3/4	Grade 4	All grades	Grade 3/4	Grade 4
Skin reaction*	200 (94·3%)	45 (21·2%)	3 (1·4%)	204 (98·1%)	73 (35·1%)‖	4 (1·9%)
Mucositis/stomatitis†	199 (93·9%)	110 (51·9%)	9 (4·2%)	194 (93·3%)	116 (55·8%)	13 (6·3%)
Dysphagia	134 (63·2%)	63 (29·7%)	3 (1·4%)	136 (65·4%)	54 (26·0%)	1 (0·5%)
Xerostomia‡	150 (70·8%)	6 (2·8%)	0 (0%)	150 (72·1%)	10 (4·8%)	0 (0%)
Acneiform rash§	21 (9·9%)	3 (1·4%)	0 (0%)	174 (83·7%)‖	35(16·8%)‖	1 (0·5%)
Infusion reaction¶	4 (1·9%)	0 (0%)	0 (0%)	32 (15·4%)‖	6 (2·9%)‖	2 (1·0%)

*Skin reaction includes all Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) terms in the Skin and Appendages body system. †Mucositis/stomatitis includes COSTART terms aphthous stomatitis; gingivitis; glossitis; mouth ulceration; mucous membrane disorder; stomatitis; and ulcerative stomatitis. ‡Xerostomia is COSTART term dry mouth. §Acneiform rash includes COSTART terms acne; rash; maculopapular rash; exfoliative dermatitis. ¶Infusion reaction includes COSTART terms allergic reaction; anaphylactoid reaction; and/or fever; chills; or dyspnoea on the first day of treatment. ‖Statistically significant (p<0·05) difference between the treatment groups; Fisher's exact test.

***Table 2:* Most common adverse events**

Bonner et al Lancet Oncol 2010; 11: 21

A case of enhanced skin toxicity due to concomittant cetuximab-radiotherapy



- 56 year old male, squamous-cell carcinoma of the right base of tongue cT2cN2M0
- Suffered from mucosal toxicity during concomittant 5-FU+ mitomycinC-radiation. Needed feeding tube
- Changed to cetuximab-radiation
- Vesicular and pustular eruptions confined to the irradiated skin

Most frequently used drugs

- 5-FU
- MMC
- Cisplat
- Carboplati
- Oxaliplatin
- Gemcitabine

Long-term experience

- Capecitabine (oral 5FU)
- an
- Temozolamide
- Cetuximab
- Bevacizumab

New agents……..

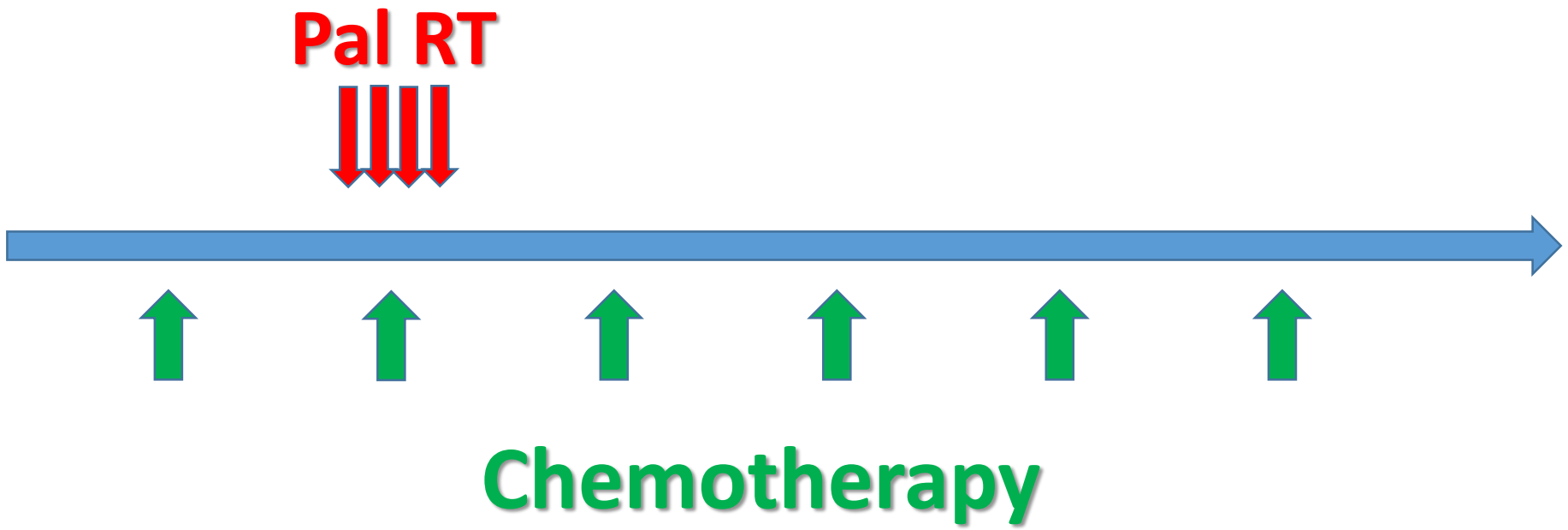
- Trastuzumab (anti-HER-2)
- Panitumumab (a
- Gefitinib (EG
- Erlotinib (EGFR
- PARB inhibitors
- PD-1 and PD-L1 inhibitors

Why not just pause the drug……?

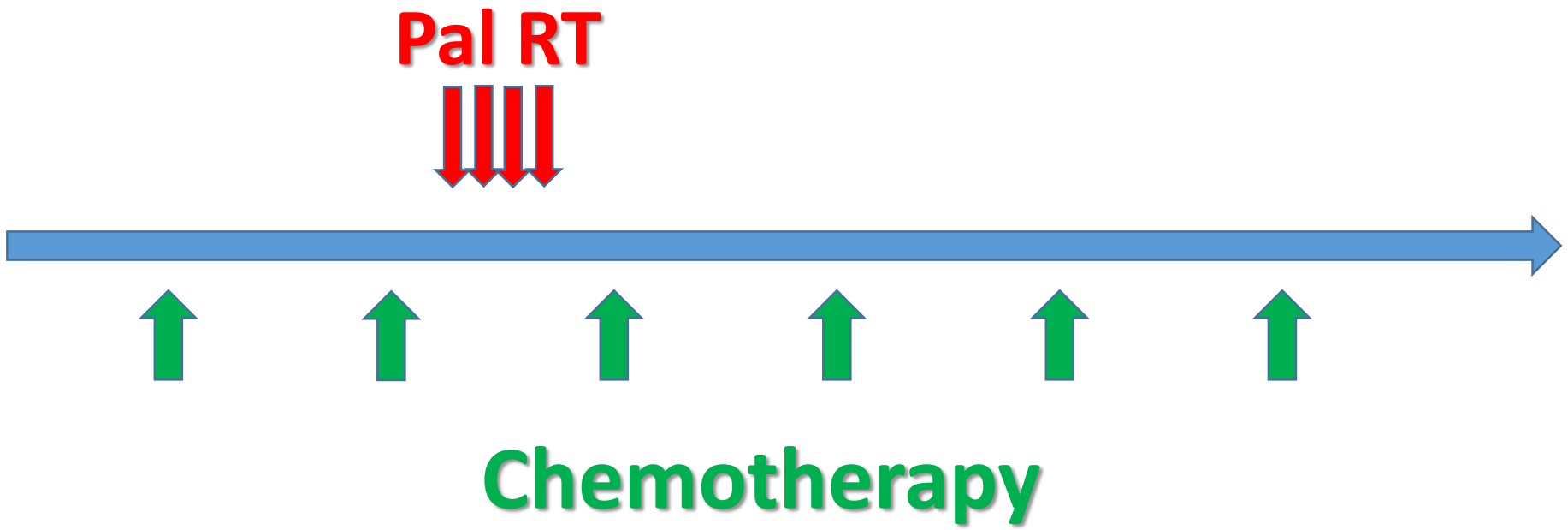
Medical oncologist: ”Because the response rates drops”

”Because tumor flare are frequent”

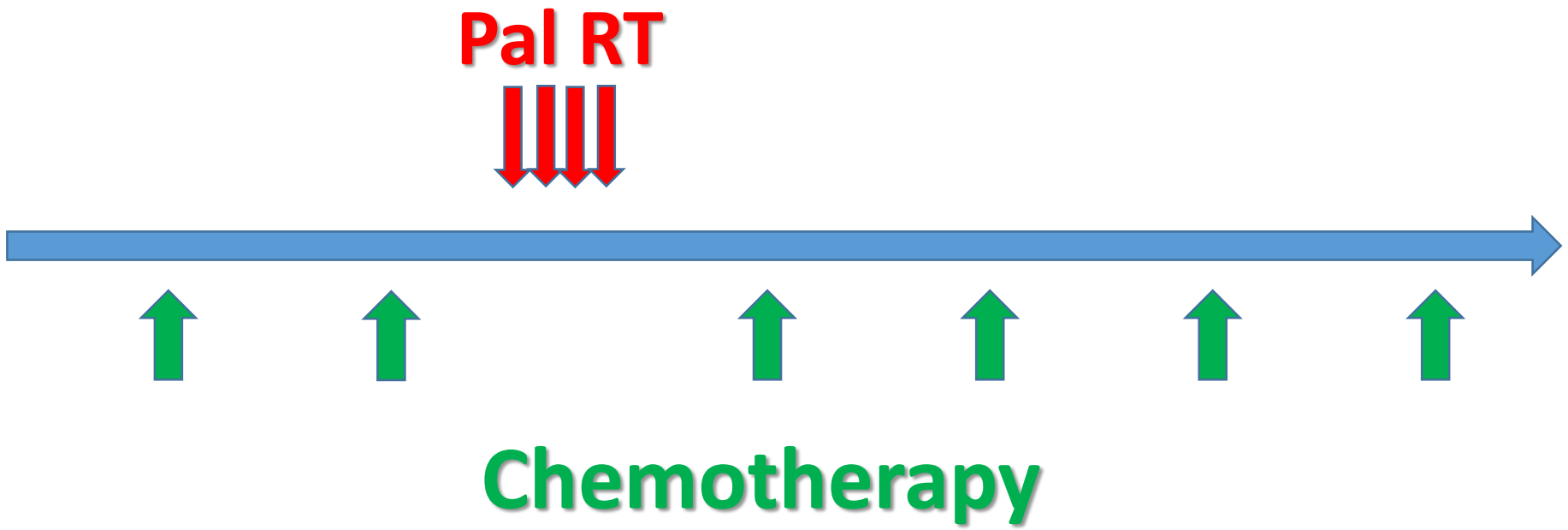
Timing of palliative radiotherapy



Timing of palliative radiotherapy



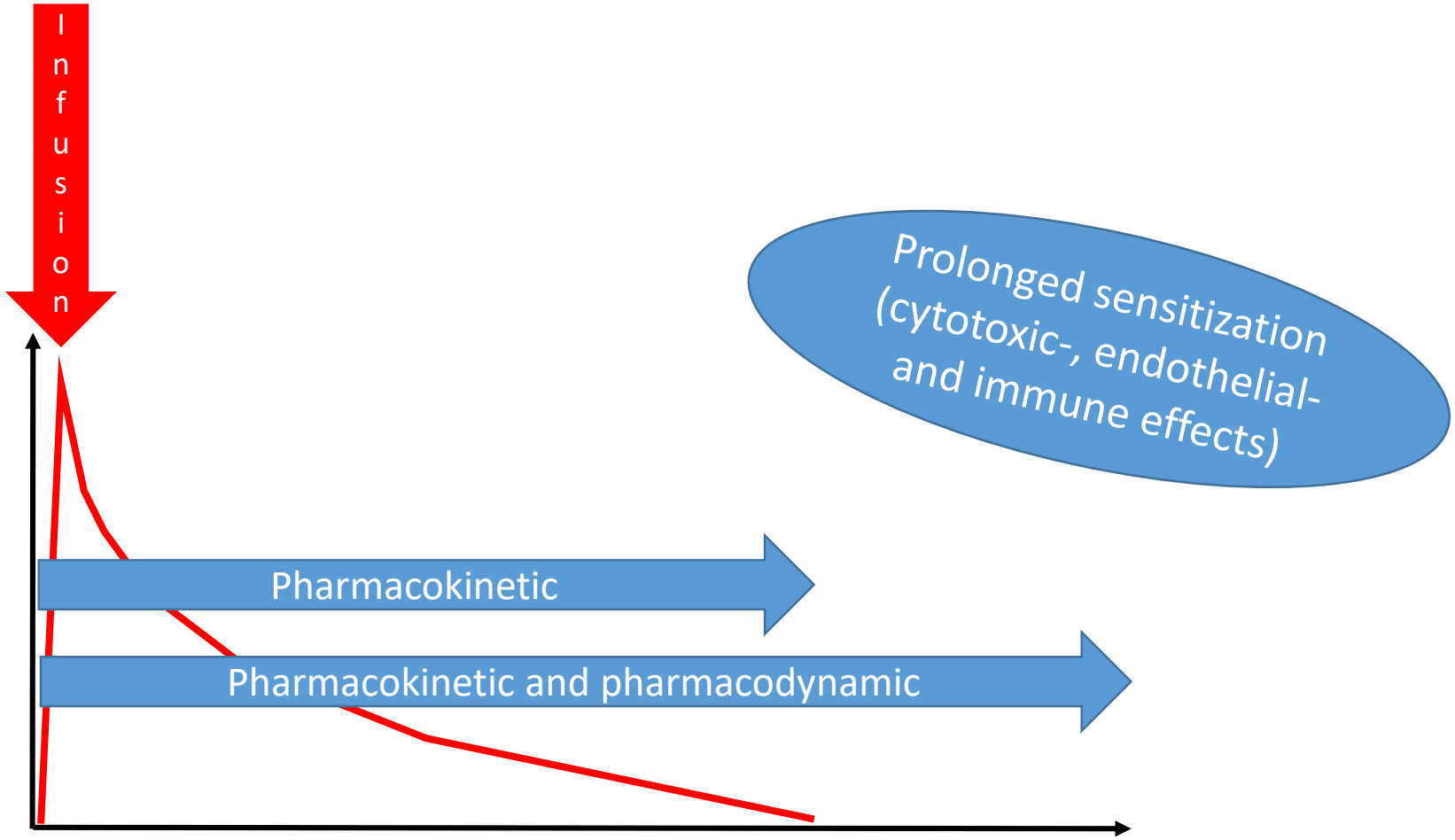
Timing of palliative radiotherapy



Flaire after discontinuation of TKI

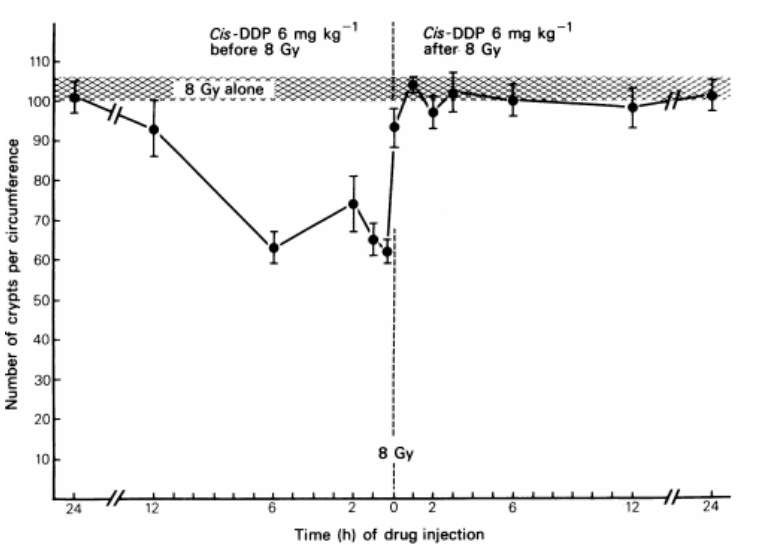
- *Some patients with **EGFR-mutant lung cancer and acquired resistance to erlotinib or gefitinib** (RECIST progression after initial benefit) have accelerated progression of disease after discontinuation of TKI*
- *14/61 patients experienced a disease flair with a median of 8 days (range 3–21) after discontinuation*

Pausing chemotherapy?

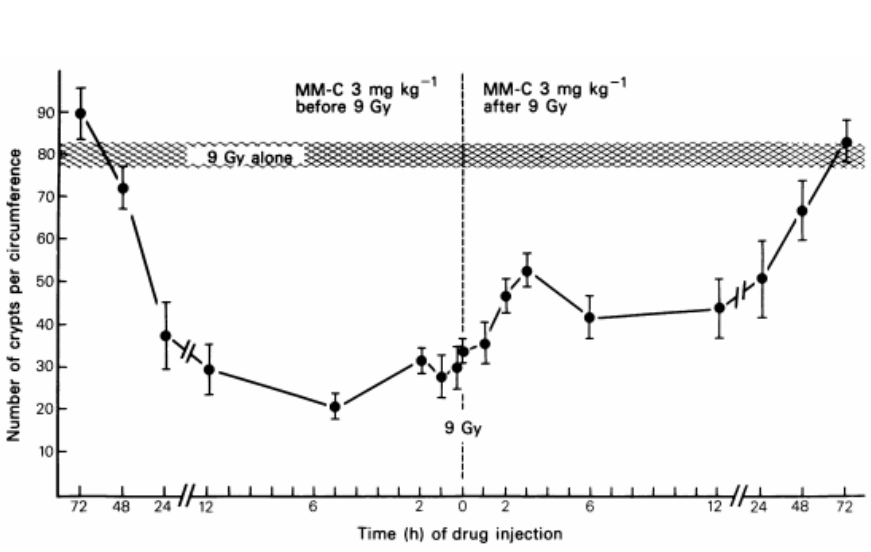


Chemo-radiation interaction (intestinal crypt assay)

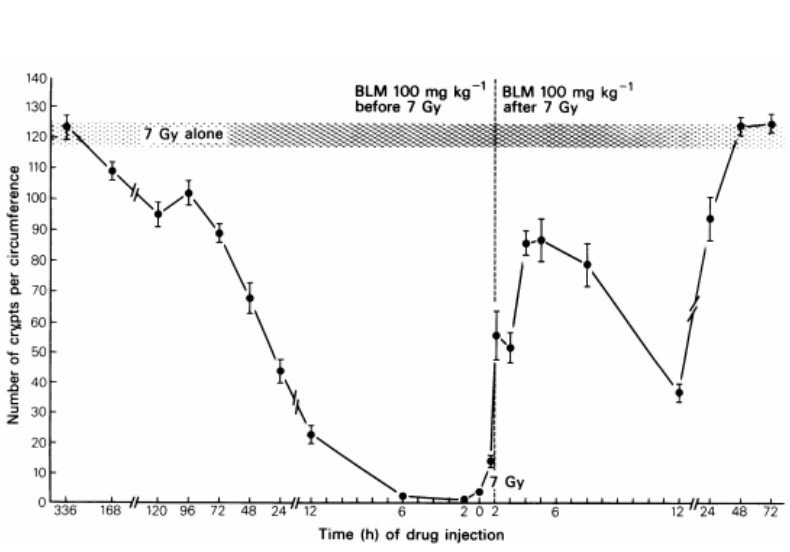
Cisplatin



MitomycinC

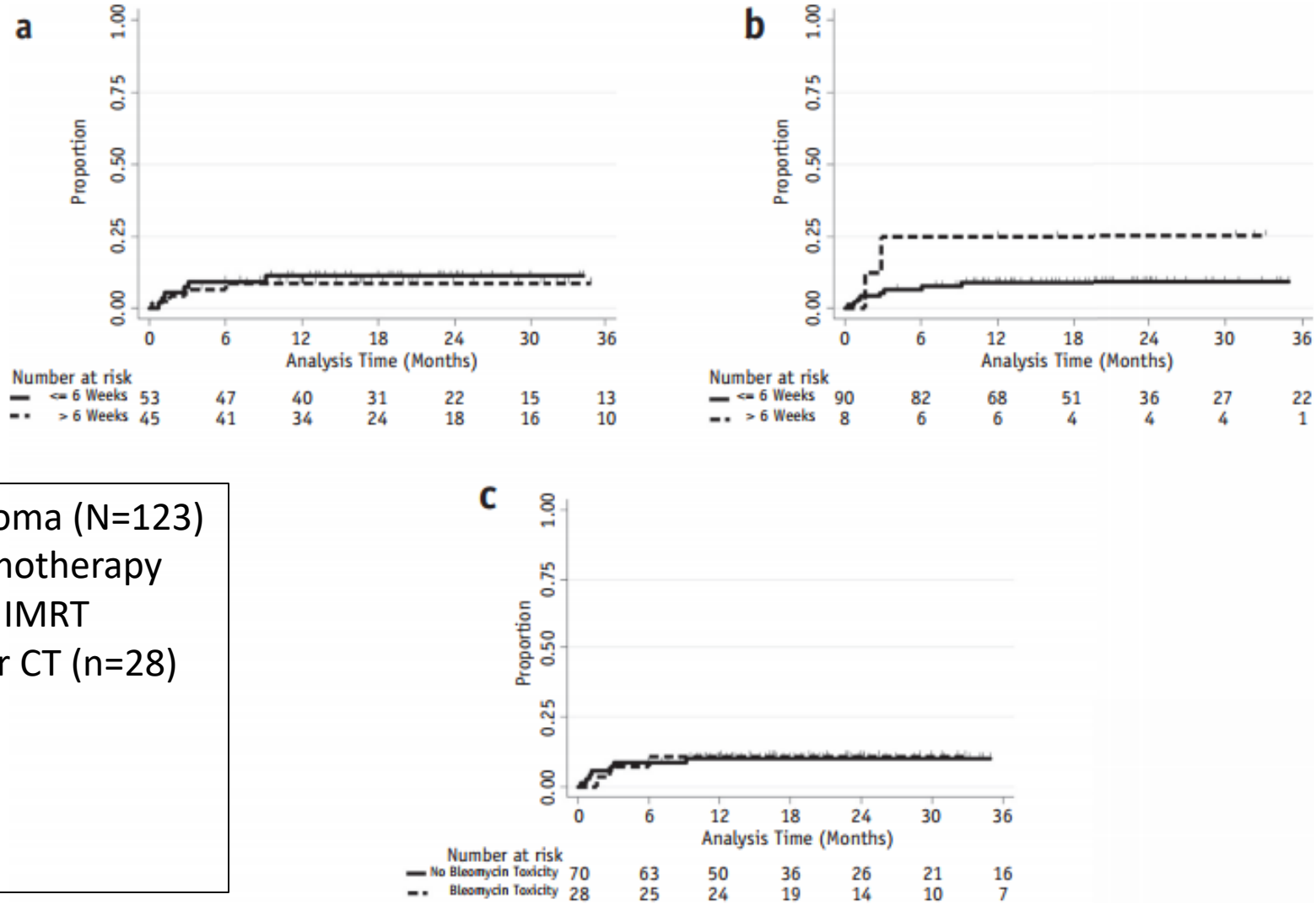


Bleomycin



Von der Maase Br J Cancer (1984), 49, 779

Bleomycin



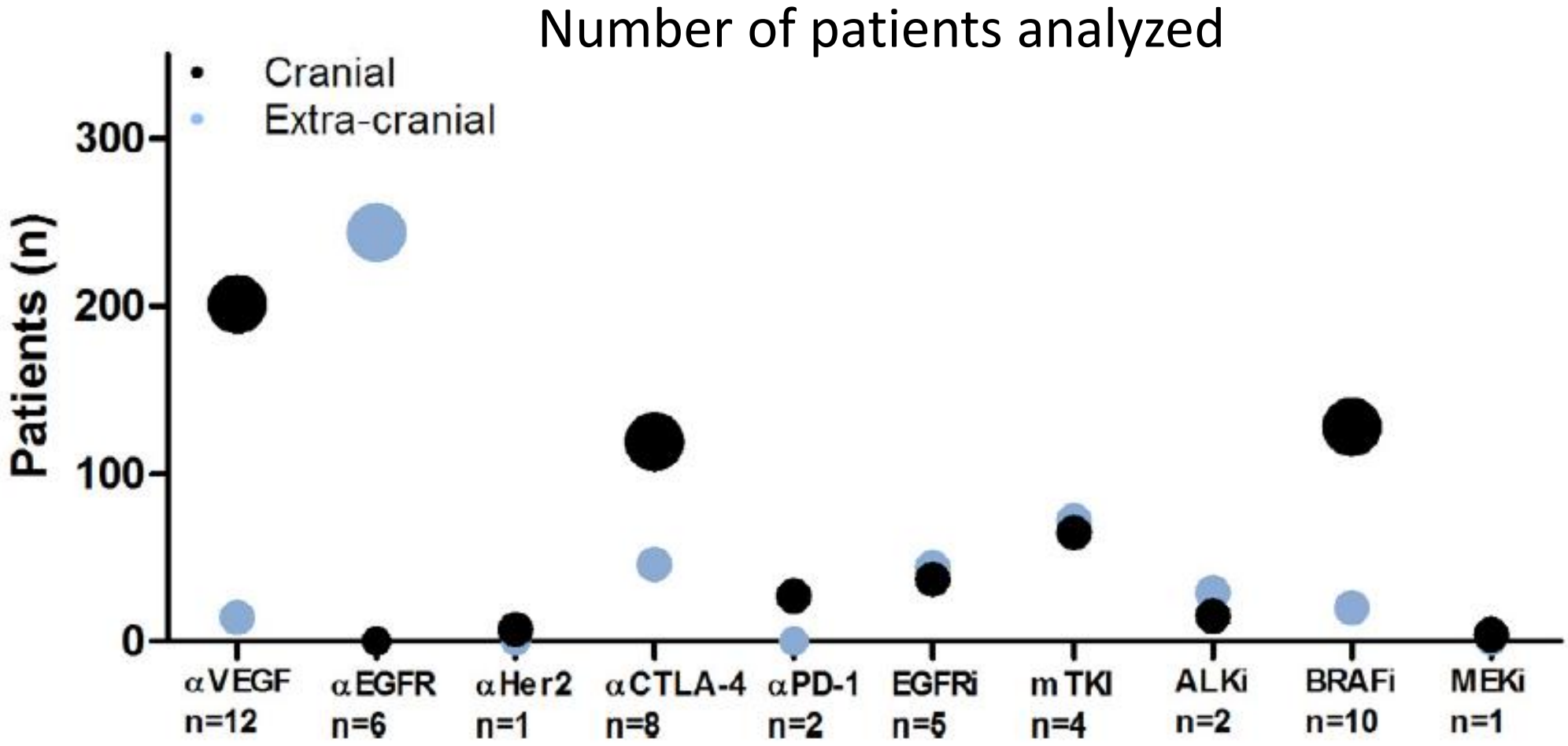
- Mediastinal Hodgkin lymphoma (N=123)
- Average 6 cycles ABVD-chemotherapy
- RT: 30.6 Gy (20-47 Gy); 80% IMRT
- Bleomycin toxicity, clinical or CT (n=28)
- RT-pneumonitis
  - Clinical symptoms
  - Radiological changes
  - Any grade

Yehia et al. IJROBP 2016; 96(5): 951

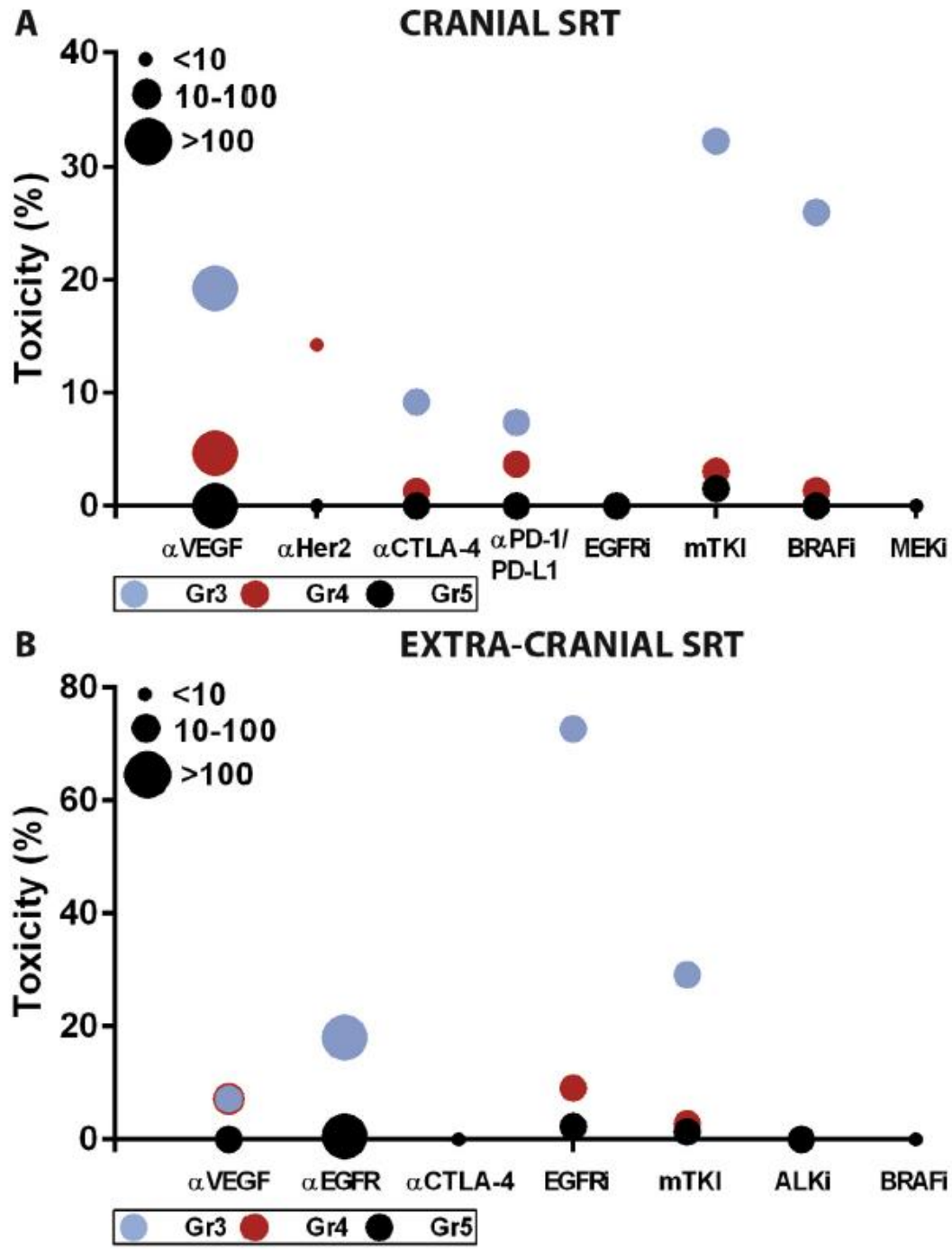
Palliative radiotherapy

- Most palliation is with hypofractionation
- The total dose is low
- Nausea, mucositis, diarrhoea, fatigue and pain-flaire are the most frequent side effects
  - *Relatively mild symptoms. May, however, affect quality of life.*
- And ablative RT (i.e. SBRT) is used more in frequently in palliation

Morbidity in SRT and SBRT



Kroeze et al. Cancer Treat Rev 2017; 53: 25

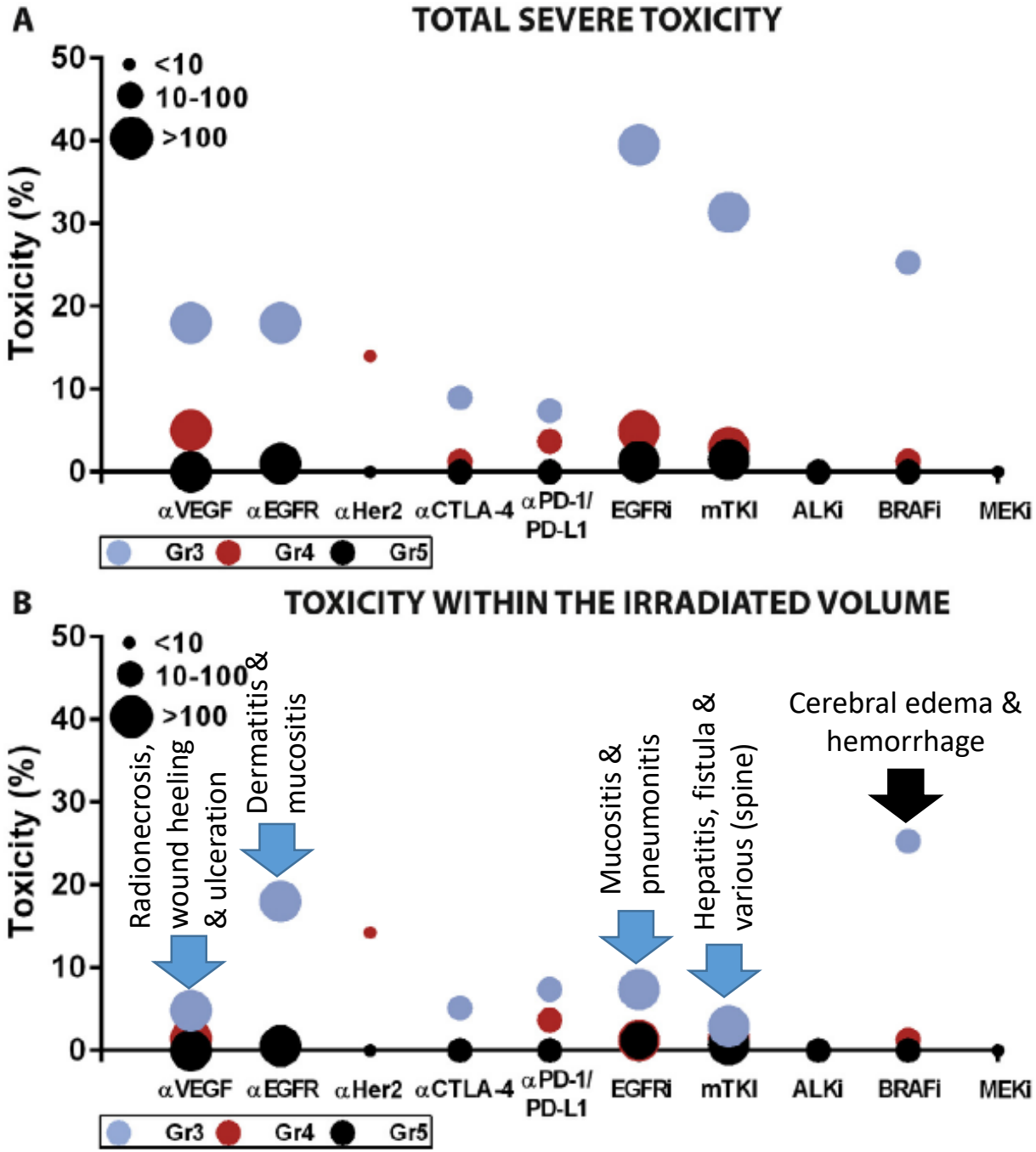


Kroeze et al. Cancer Treat Rev 2017; 53: 25

Caution:

SRT:
BRAFi

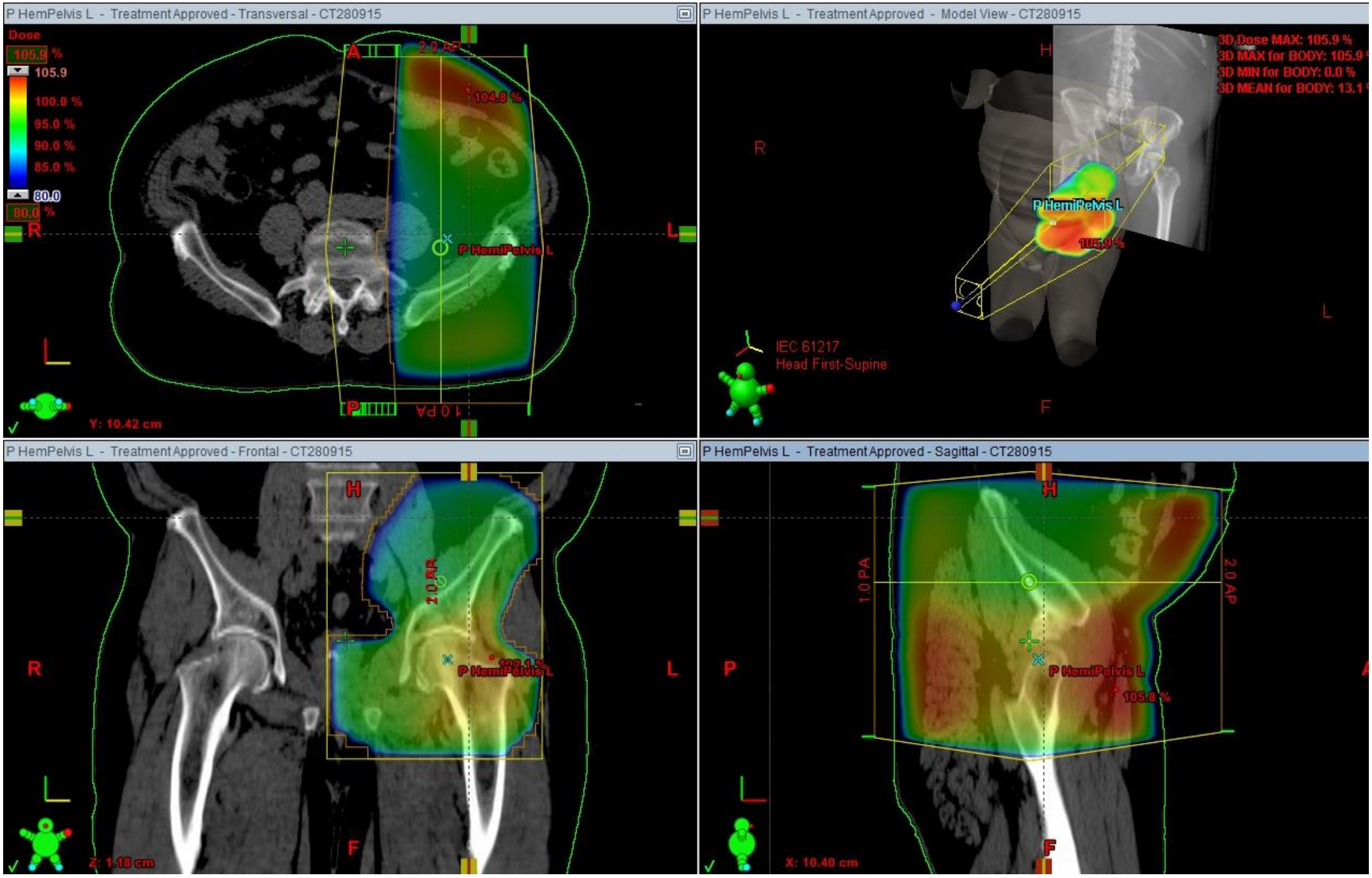
SBRT:
Bevacizumab,
sorafenib, cetuximab
& EGFR-targeting
TKIs



Kroeze et al. Cancer Treat Rev 2017; 53: 25

Case

- 78 year old male with prostate cancer
- Treated for metastatic castrate resistant prostate cancer with docetaxel
- Pain in left hemi-pelvis
- Chemotherapy is scheduled today (Thursday)
- You decide that the patient should have palliative RT
- The patient lives on an island and transportation is an issue


P HemPelvis L - Treatment Approved - Transversal - CT280915
Dose
105.9 %
105.9
100.0 %
95.0 %
90.0 %
85.0 %
80.0
80.0 %
A
2.0 AP
104.8 %
P HemiPelvis L
R
L
P
1.0 PA
Y: 10.42 cm
P HemPelvis L - Treatment Approved - Model View - CT280915
3D Dose MAX: 105.9 %
3D MAX for BODY: 105.9
3D MIN for BODY: 0.0 %
3D MEAN for BODY: 13.1
H
R
P HemiPelvis L
105.9 %
L
IEC 61217
Head First-Supine
F
P HemPelvis L - Treatment Approved - Frontal - CT280915
H
2.0 AP
102.1 %
P HemiPelvis L
R
L
F
Z: 1.18 cm
P HemPelvis L - Treatment Approved - Sagittal - CT280915
H
1.0 PA
2.0 AP
P HemiPelvis L
105.8 %
P
L
F
X: 10.40 cm

Case

- 78 year old male with prostate cancer
- Treated for metastatic castrate resistant prostate cancer with docetaxel
- Pain in left hemi-pelvis
- Chemotherapy is schedu
- You decide that the patient should have palliative RT
- The patient lives on an island and transportation is an issue

α, β and γ half-lives are 4.5 min, 38 min and 12 hrs.

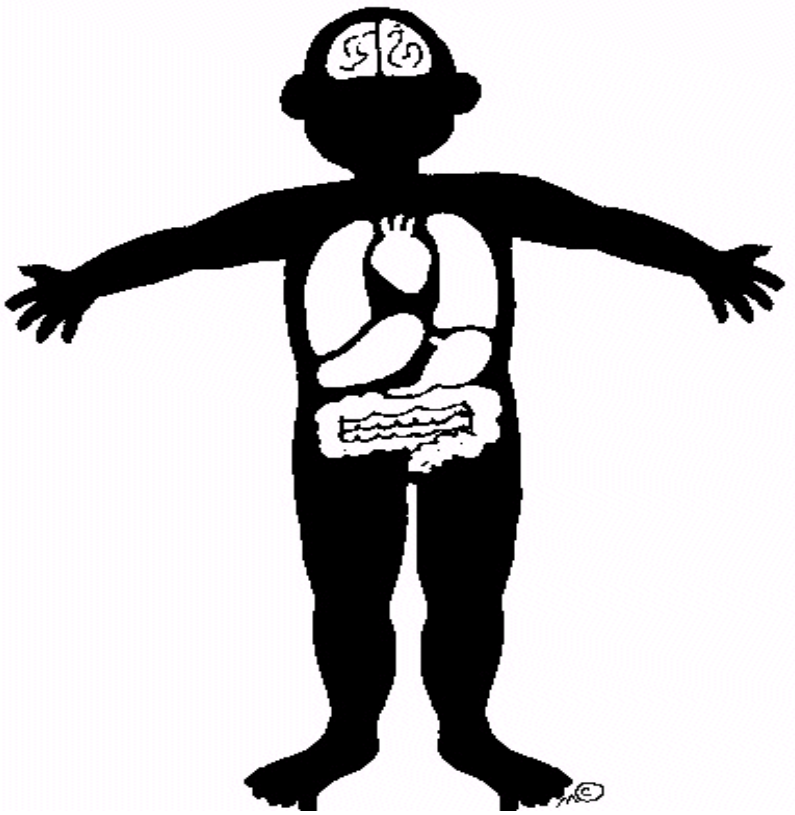
Do not extrapolate directly from conventional fractionated radiation therapy

It is palliation – so stay on the safe side!

- But we take the risk of denying an efficient therapy to a patient who suffers from cancer-related symptoms

Leiden University
Medical Center

Radiotherapy for bone pain

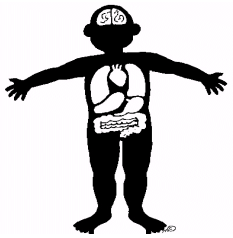


Yvette van der Linden

Centre of Expertise Palliative Care

& Dept. of Radiotherapy

Topics



1. bone metastases
   - pain incl. neuropathic pain
   - retreatment
   - remineralisation
   - other treatment options; radioactive agents, bisphosphonates

2. skin / lymph nodes / soft tissues / organs
   - pain
   - bleeding, ulceration
   - stenoses → edema, dyspnea

oligometastases
use of prognostic models

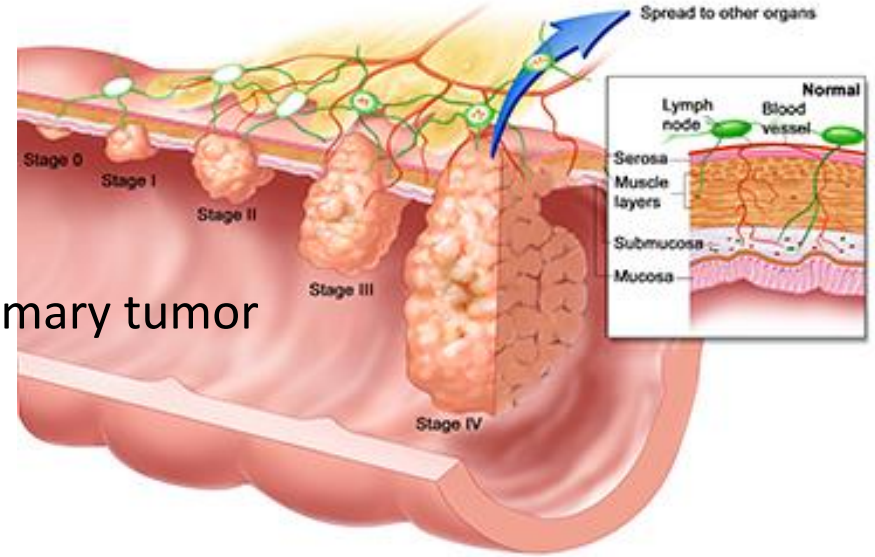
Conclusions radiotherapy as palliative treatment

- patient friendly
  - non invasive
  - quick procedure
  - few side effects
  - effective local treatment → responses about 60-70%
    - pain
    - ulceration, bleeding
    - dyspnea, edema
    - ..

} improvement of QoL

- evidence based outcome → single or short course schedules
- retreatments –always- possible

Pathofysiology of bone metastases



Cascade of events

- progressive growth at the primary site
- tumor neo-vascularization
- detachment of tumor cells from the primary tumor
- invasion in the neighboring tissues
- intravasation into the blood stream
- survival in the circulation

↓

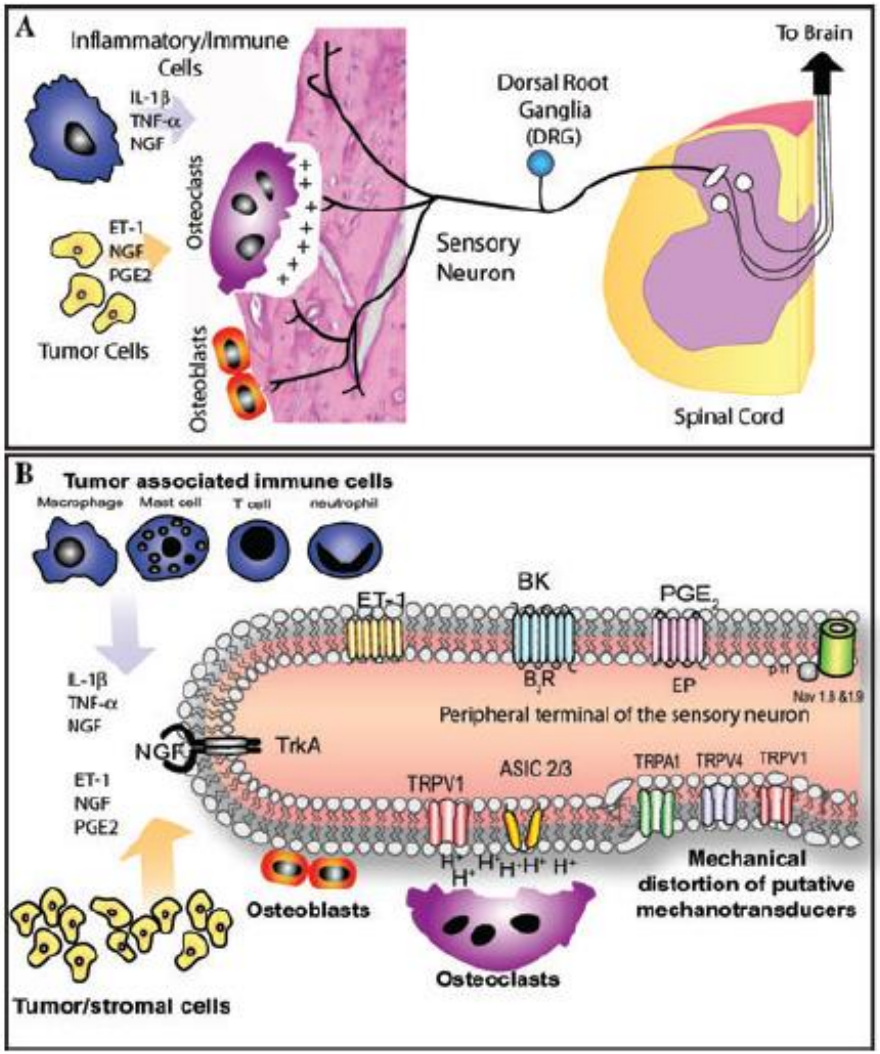
- homing and arrest at the level of the bone marrow
- extravasation
- evasion of the host defence
- growth and stimulation of the osteoclast mediated bone resorption

(Mareel et al., 1991; Choong, 2003; Vakaet et al, 2009)

Pathofysiology of bone metastases

Local mechanisms of bone pain

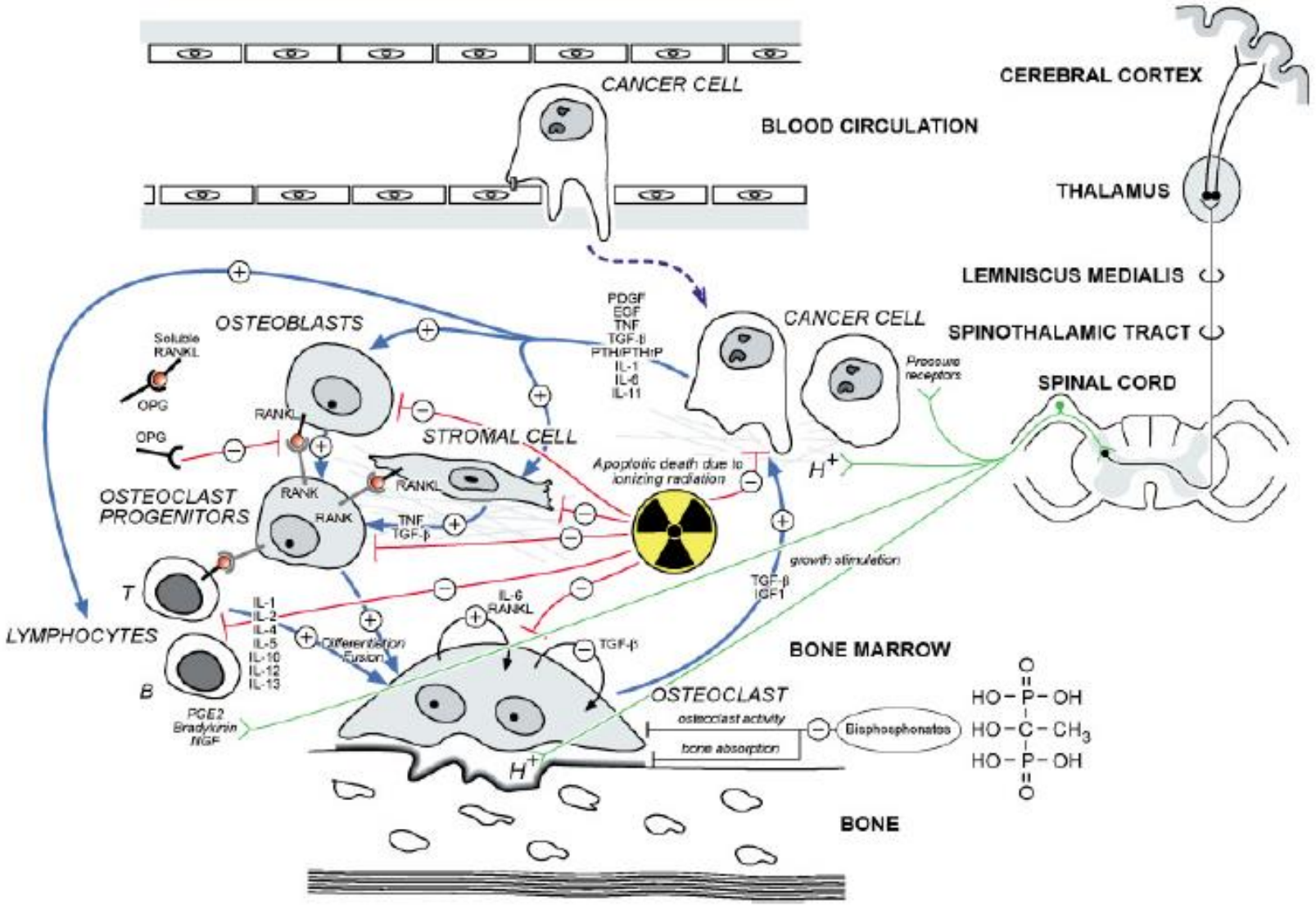
- Release of chemical mediators
- Increased pressure within the bone
- Micro fractures
- Stretching of the periosteum
- Nerve root infiltration
- Compression of the nerves due to collapse of the bone



(Vakaet et al, 2009)

(Jimenez et al, 2010)

Radiation effects several mechanisms



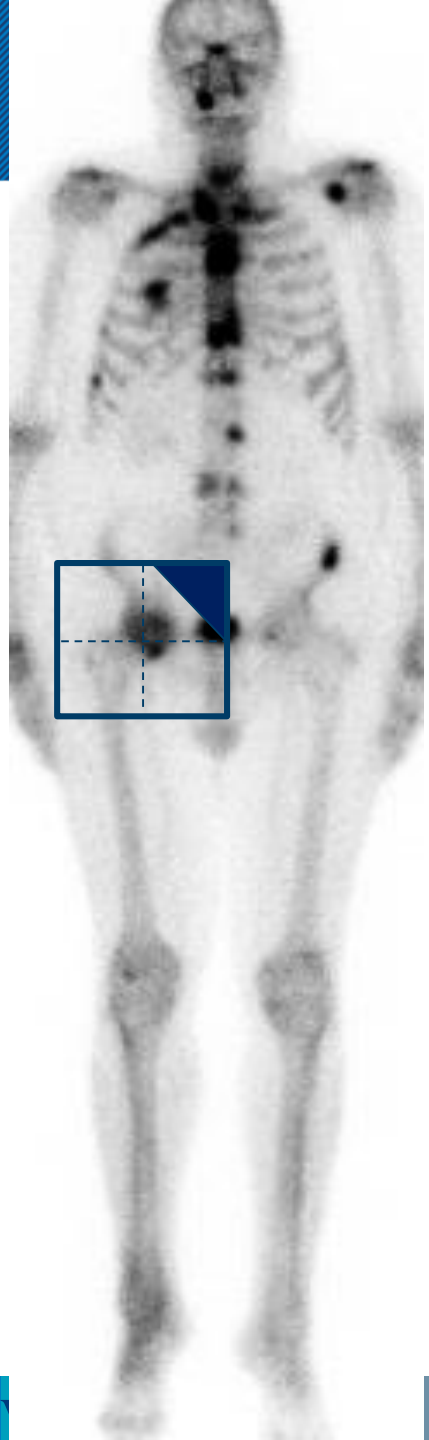
Vakaet et al, Int.J.Dev.Biol.2004

Effectiveness bone pain → two phases

1. Inflammatory cells ↓↓↓

- Chemical pain mediators ↓↓↓
  - prostaglandines
- Edema ↓↓
- ..
- ..

2. Tumor cell kill ↓



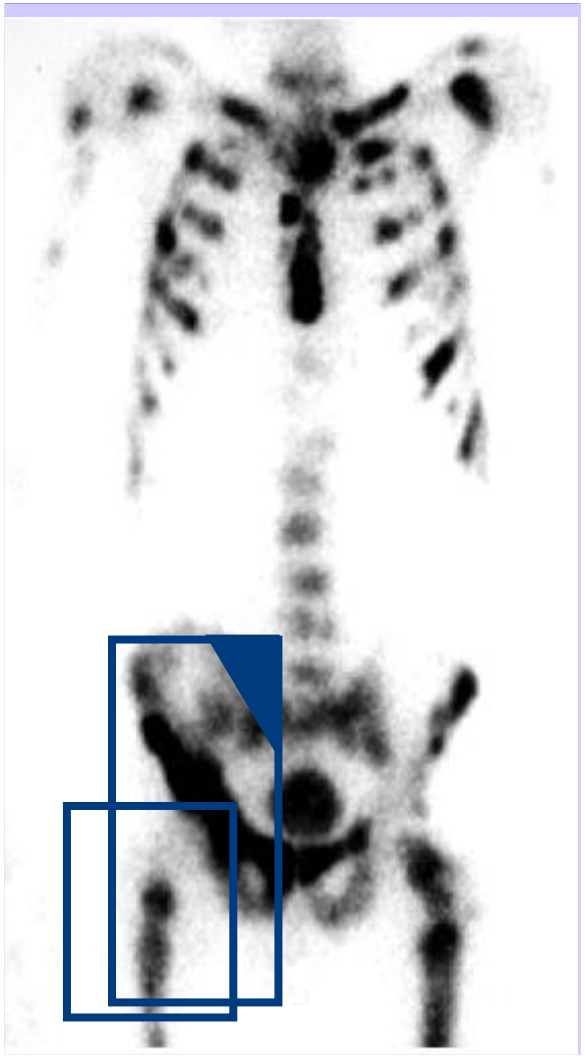
Choices in palliative radiotherapy

Target?

- Lesion only?
- Whole organ / bone?

Dose schedule ?

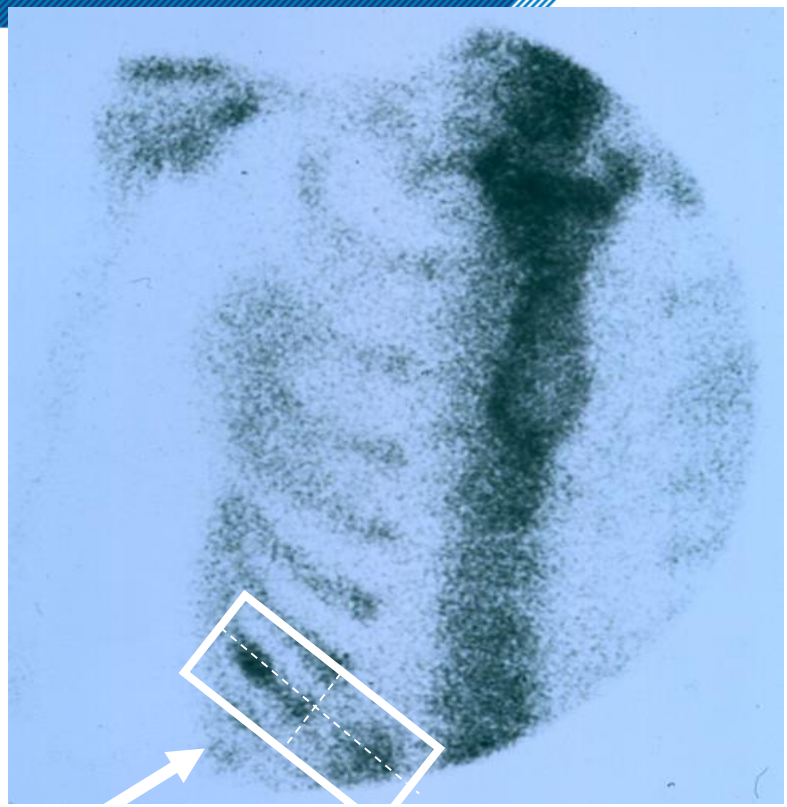
- 12 x 2.5 Gy
- 10 x 3 Gy
- 5 x 4 Gy
- 1 x 8 Gy



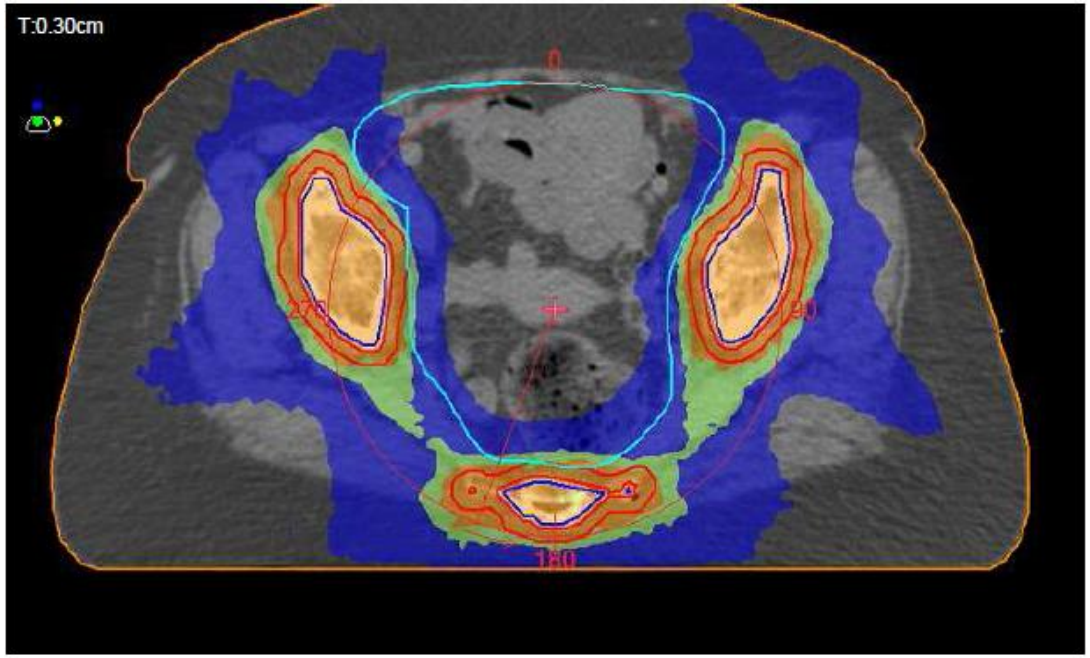
More choices…..

Technique

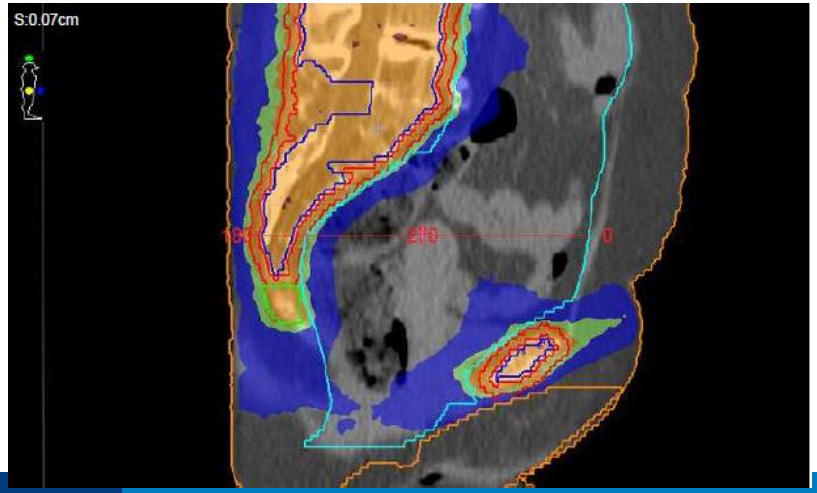
- Simple or advanced?
- Photons of electrons?
- CT or conventional sim?
- Immobilization devices?

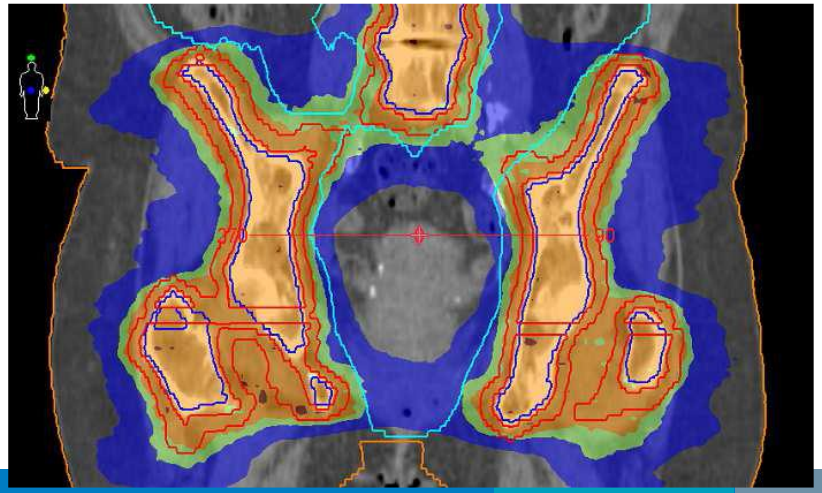


1x 8 Gy in patient with multiple myeloma

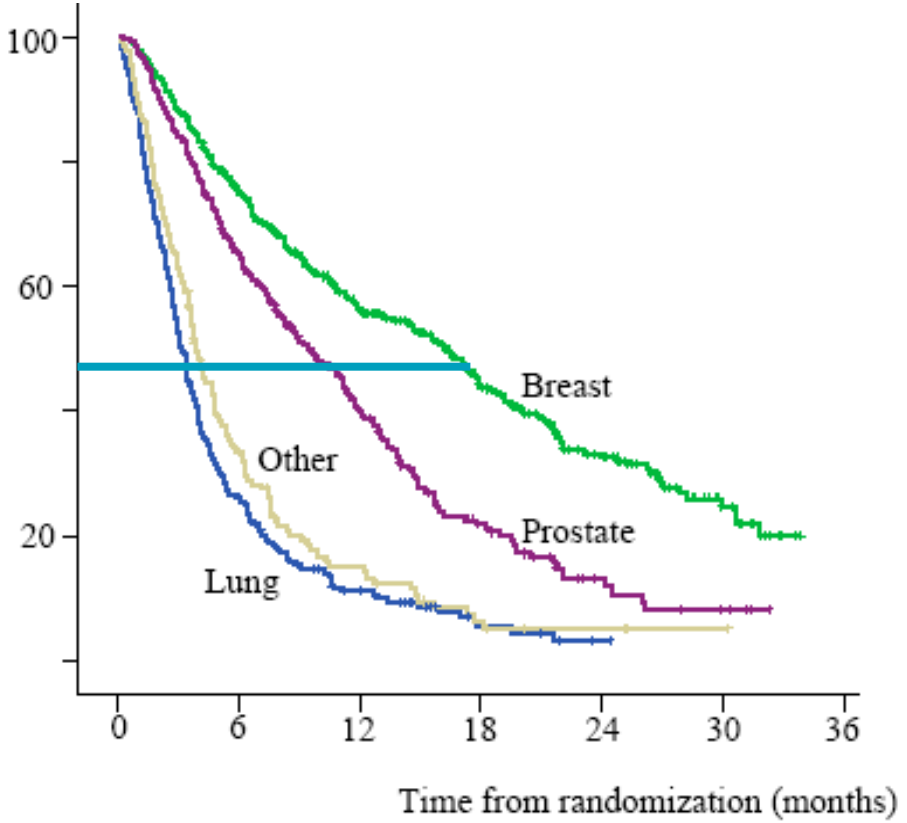


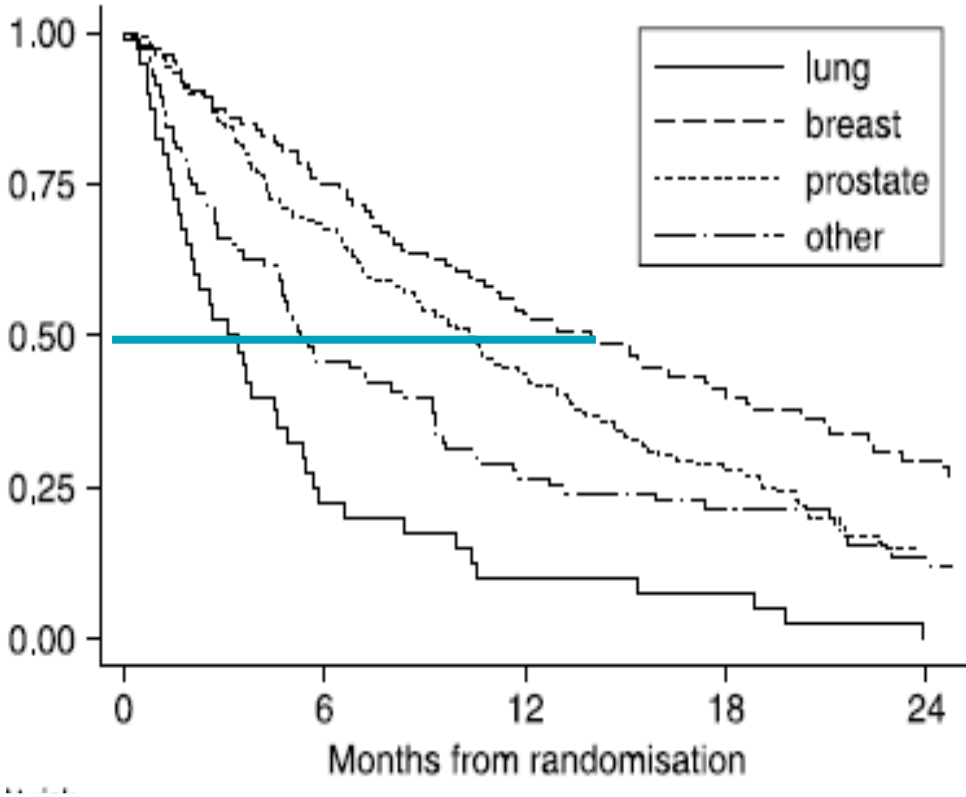
Courtesy dr. Kaspers, UMCU





Survival is dependent on primary tumor





van der Linden et al, R&O 2006

Kaasa et al, R&O 2006

Survival prediction model Dutch Bone Mets Study has reasonable predictivity

Model	Variables	C-statistic
Best	Sex Primary tumor Visceral metastases KPS VAS-general health VRS-valuation of life	0.72
Model	**Variables**	**C-statistic**
Simple	KPS, primary tumor	0.71
Simple	primary tumor, VRS-valuation of life	0.69
Simple	primary tumor, VAS-general health	0.69

Survival prediction model → external validation

Table 3 Observed survival per primary tumor in patients with painful bone metastases in both the derivation dataset and the validation dataset

			Median survival	% Patients with observed survival				
		n	(mo)	3 mo	6 mo	9 mo	12 mo	18 mo
Primary tumor	KPS	D/V	D/V	D/V	D/V	D/V	D/V	D/V
Breast		451/271						
	90-100	22%/23%	20.8/39.7	92/97	82/95	73/91	62/87	58/75
	70-80	51%/52%	16.8/19.9	90/94	79/78	70/71	62/62	46/54
	20-60	27%/24%	8.1/7.8	80/73	60/53	46/47	40/42	28/33
Prostate		267/200						
	90-100	25%/13%	13.9/19.8	95/92	80/84	69/76	59/72	30/56
	70-80	54%/49%	9.1/7.8	85/80	64/59	51/41	39/30	24/23
	20-60	21%/40%	5.6/4.0	67/55	45/32	30/28	17/18	2/10
Lung		287/230						
	90-100	14%/9%	4.7/7.4	65/81	45/57	35/33	29/24	16/0
	70-80	47%/41%	3.6/2.9	58/50	32/27	17/15	12/10	6/5
	20-60	39%/50%	2.0/1.3	39/21	11/8	4/2	4/1	0/0
Other		152/231						
	90-100	11%/12%	7.2/3.6	88/64	50/36	43/29	35/25	16/21
	70-80	54%/41%	4.5/3.5	71/55	37/33	23/23	15/16	7/10
	20-60	35%/47%	2.4/2.1	40/35	21/19	7/11	5/7	0/2

Abbreviations: D = derivation dataset (Dutch Bone Metastasis Study); KPS = Karnofsky performance status; V = external validation dataset.

The continuing story of Fractionation and Total Dose

SF should be standard treatment

Study or Subcategory	Single (n/N)	Multiple (n/N)	RR (random); 95% CI	Weight (%)	RR (random); 95% CI
Price 1986	29/140	34/148		0.90	0.90 (0.58 to 1.40)
Cole 1989	12/16	9/13		0.82	1.08 (0.68 to 1.72)
Kagei 1990	12/14	12/13		2.45	0.93 (0.71 to 1.21)
Gaze 1997	108/151	99/144		7.75	1.04 (0.90 to 1.21)
Foro 1998	19/25	21/25		2.22	0.90 (0.68 to 1.20)
Foro 1998 (2)	19/25	22/25		2.48	0.86 (0.66 to 1.12)
Nielsen 1998	52/122	56/119		2.19	0.91 (0.68 to 1.20)
BPTWP 1999	274/383	257/378		19.66	1.05 (0.96 to 1.16)
Koswig 1999	41/52	45/55		4.88	0.96 (0.80 to 1.16)
Kirkbride 2000*	101/200	95/198		4.33	1.05 (0.86 to 1.29)
Ozsaran 2001	27/36	28/38		2.41	1.02 (0.78 to 1.33)
Ozsaran 2001 (2)	27/36	29/35		2.96	0.91 (0.71 to 1.15)
Sarkar 2001	13/35	16/38		0.53	0.88 (0.50 to 1.56)
Altundag 2002	13/18	12/14		1.35	0.84 (0.59 to 1.20)
Altundag 2002 (2)	13/17	12/14		1.50	0.89 (0.64 to 1.25)
Badzio 2003	53/72	52/74		4.20	1.05 (0.86 to 1.28)
van der Linden 2004	395/579	396/578		28.07	1.00 (0.92 to 1.08)
Hartsell 2005	187/455	188/443		7.23	0.97 (0.83 to 1.13)
Roos 2005	73/137	83/135		4.07	0.87 (0.71 to 1.06)
Total (95% CI)	2,513	2,487		100.00	0.99 (0.95 to 1.03)

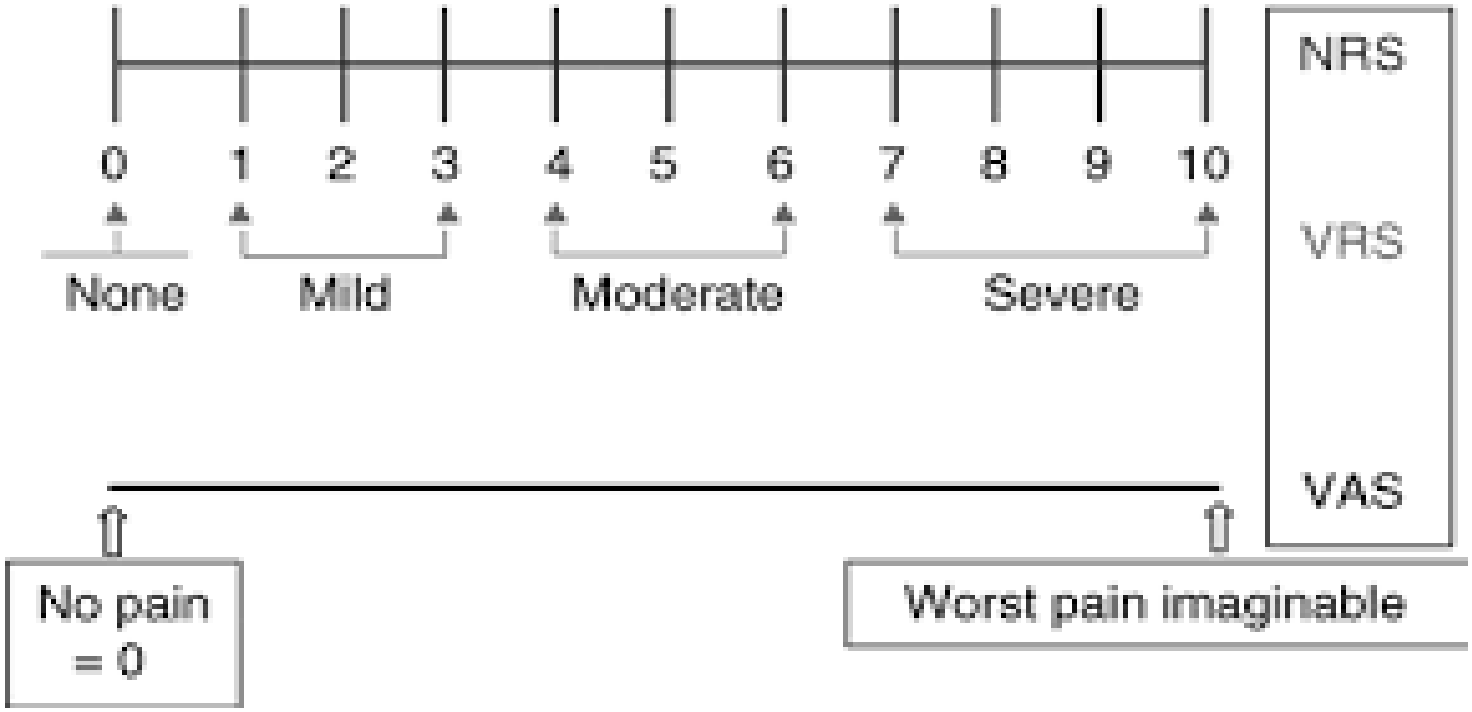
Total events: 1,468 (single), 1,466 (multiple)
Test for heterogeneity: $\chi^2 = 8.72$, $df = 18$ ($P = .97$), $I^2 = 0\%$
Test for overall effect: $z = 0.53$ ($P = .60$)

0.1 0.2 0.5 1.0 2.0 5.0 10.0

Favors Multiple Favors Single

Chow et al. JCO 2007

Response is measured using pain scales

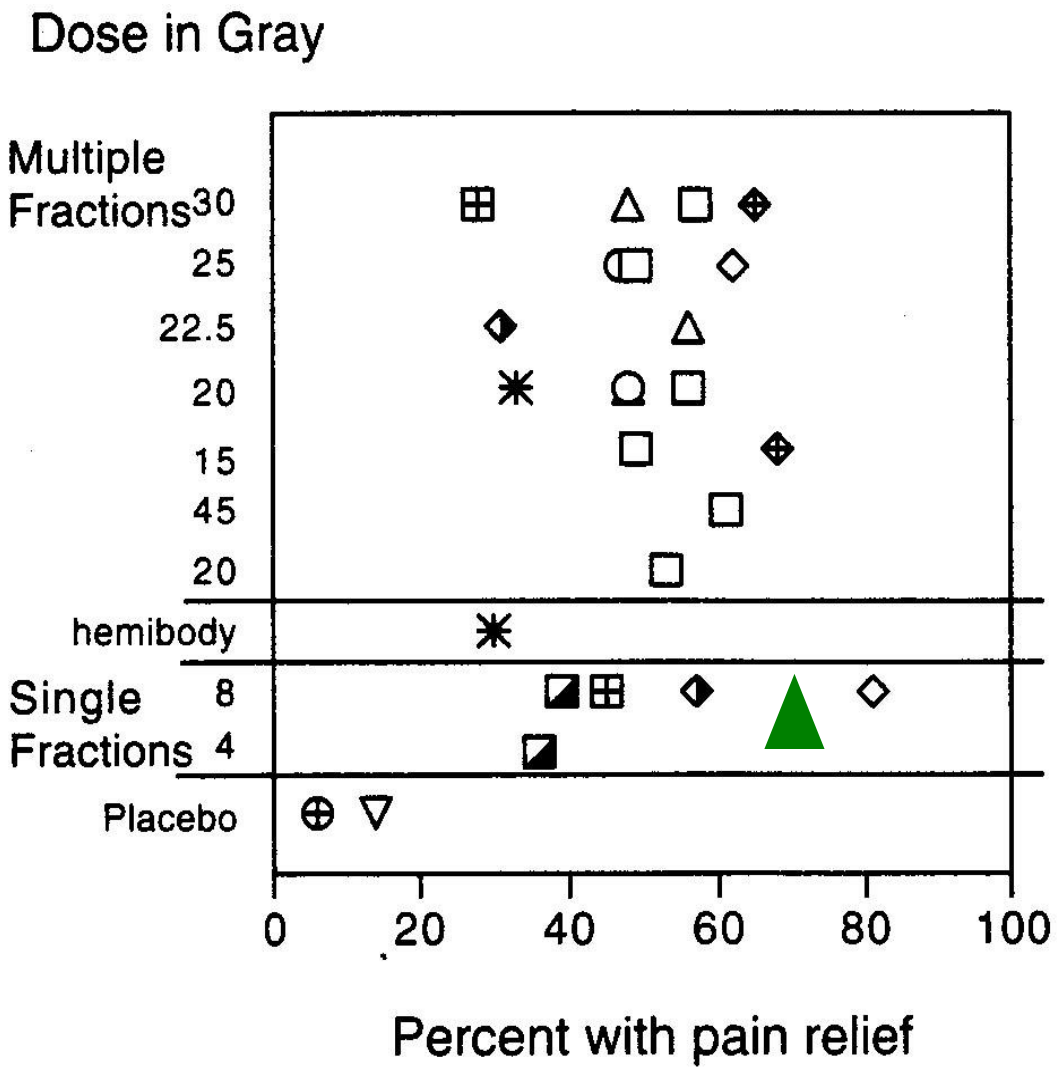


Response criteria International Consensus Group

Term	Definition
Complete response	A pain score of 0 at treated site with no concomitant increase in analgesic intake (stable or reducing analgesics in daily oral morphine equivalent [OMED])
Partial response	Pain reduction of 2 or more at the treated site on a scale of 0 to 10 scale without analgesic increase, or Analgesic reduction of 25% or more from baseline without an increase in pain.
Pain progression	Increase in pain score of 2 or more above baseline at the treated site with stable OMED, or An increase of 25% or more in OMED compared with baseline with the pain score stable or 1 point above baseline
Indeterminate response*	Any response that is not captured by the complete response, partial response, or pain progression definitions

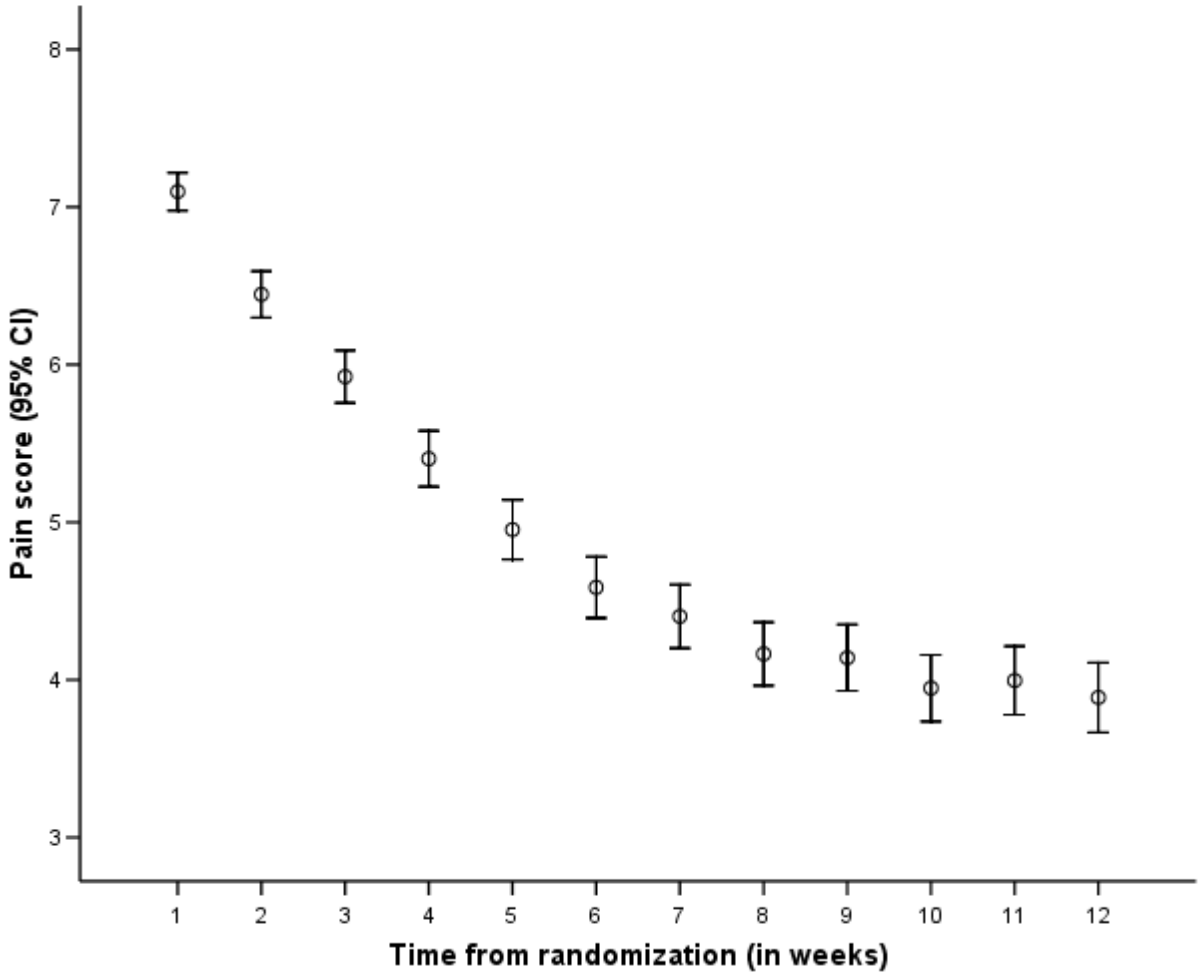
Chow et al IJROBP 2012

Response about 60-70%

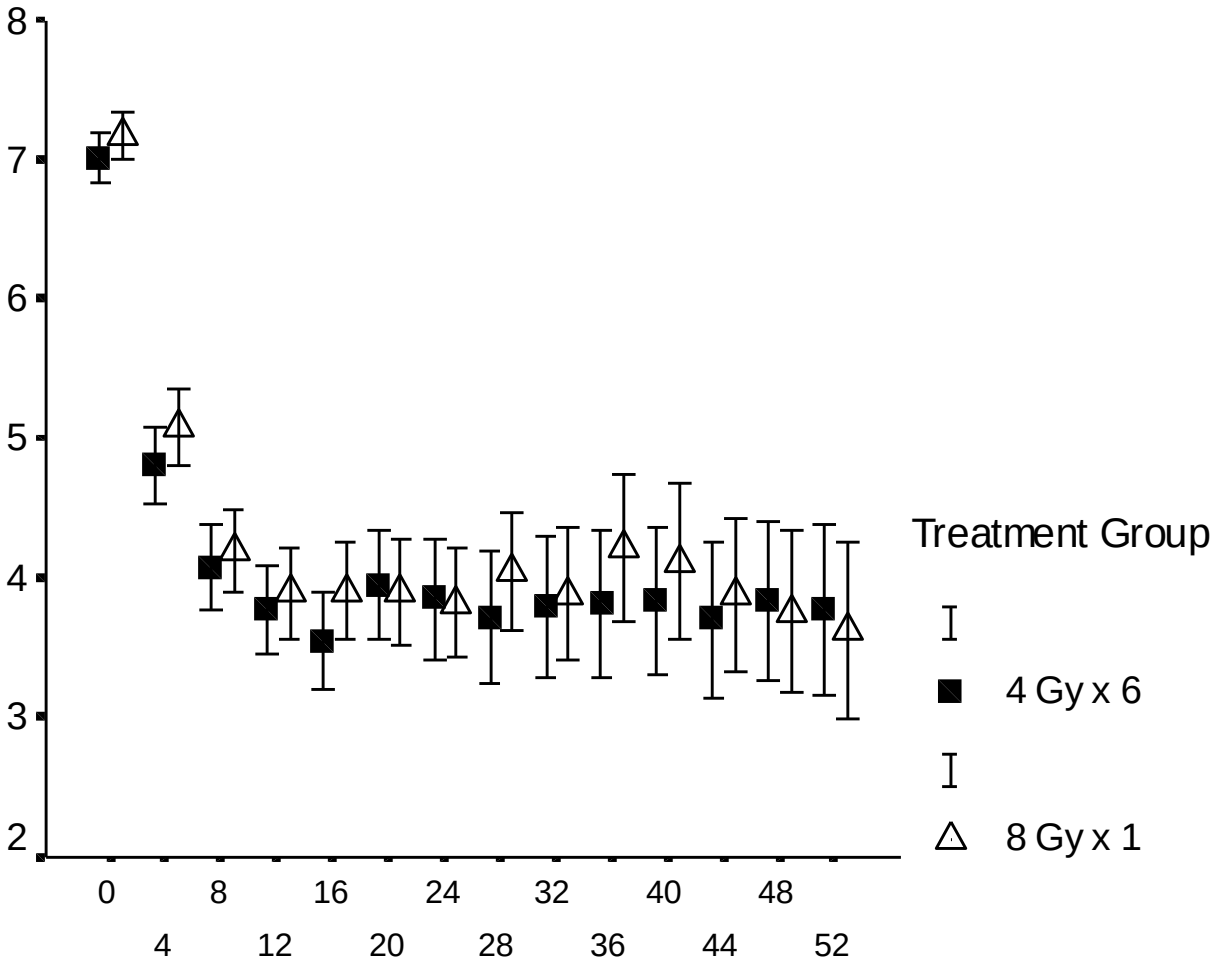


[Cochrane review McQuay et al 1997]

Response within four weeks -> DBMS



Durable response -> DBMS



Individual pain scores → pain flare

2 points increase

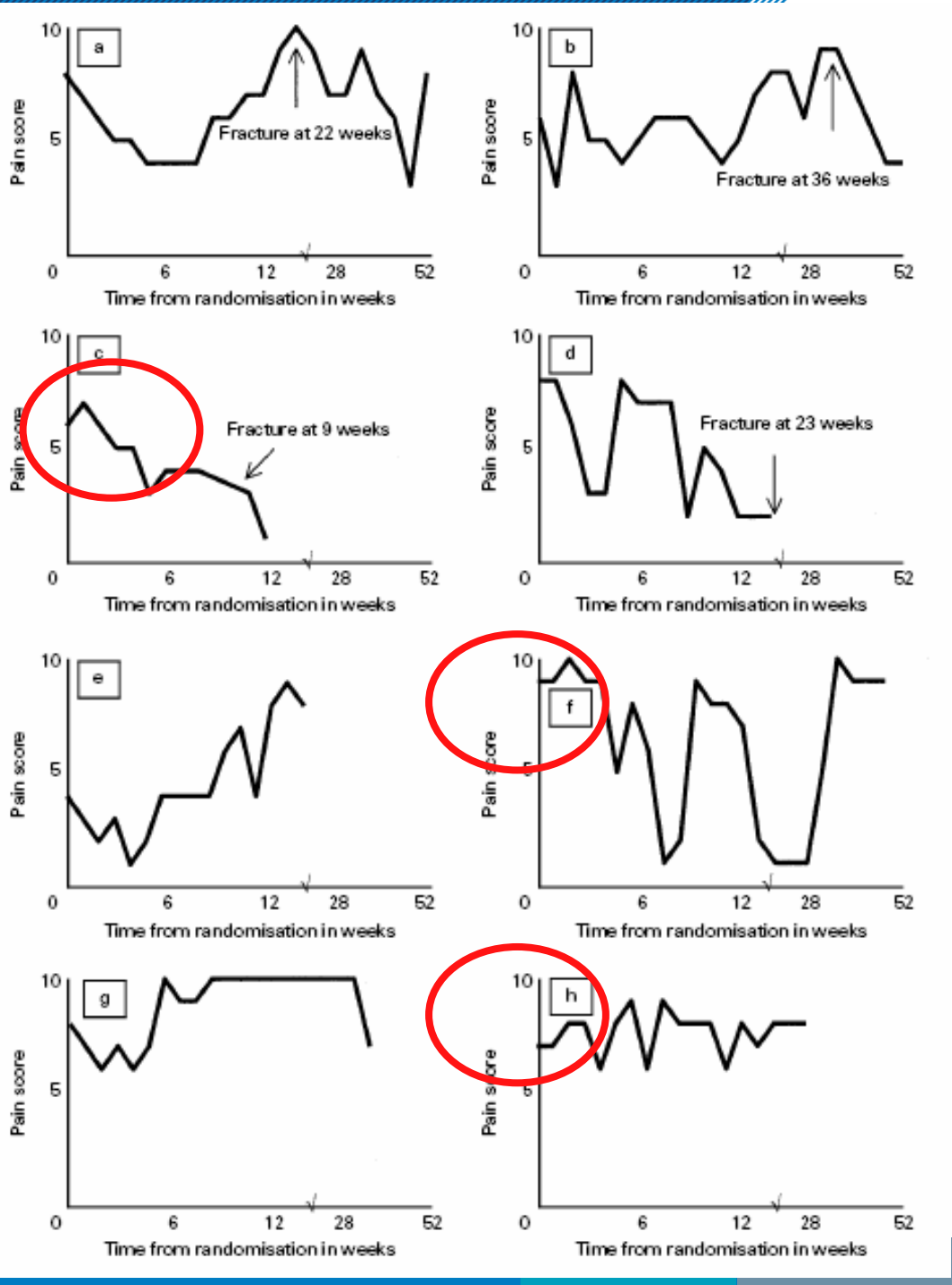
After RT 20-40% pain flare

Phase 3, n= 298

-> dexamethasone 8 mg, 5x

35% to 26%

Chow et al, Lancet Oncol 2015



Single fraction also in subgroups equal

Patient subgroups	Total (in numbers)	Schedule* (in percentages)	Response (in percentages)	p-value†
Primary tumor [4]				0.69
• Breast	434	52% SF	84%	
		48% MF	80%	
• Prostate	253	49% SF	79%	
		51% MF	79%	
• Lung	269	50% SF	62%	
		50% MF	62%	
• Other	143	51% SF	68%	
		49% MF	60%	
Observed survival >52 weeks [5]	320	51% SF	87%	0.54
		49% MF	85%	
Observed survival <12 weeks [6]	247	50% SF	47%	0.58
		50% MF	44%	
Spinal metastasis [7]	342	48% SF	75%	0.52
		52% MF	72%	

Meeuse et al, Cancer 2010; van der Linden et al, Cancer 2005, IJROBP 2004, R&O 2008, ClinOnc 2009

Single fraction effective in elderly patients

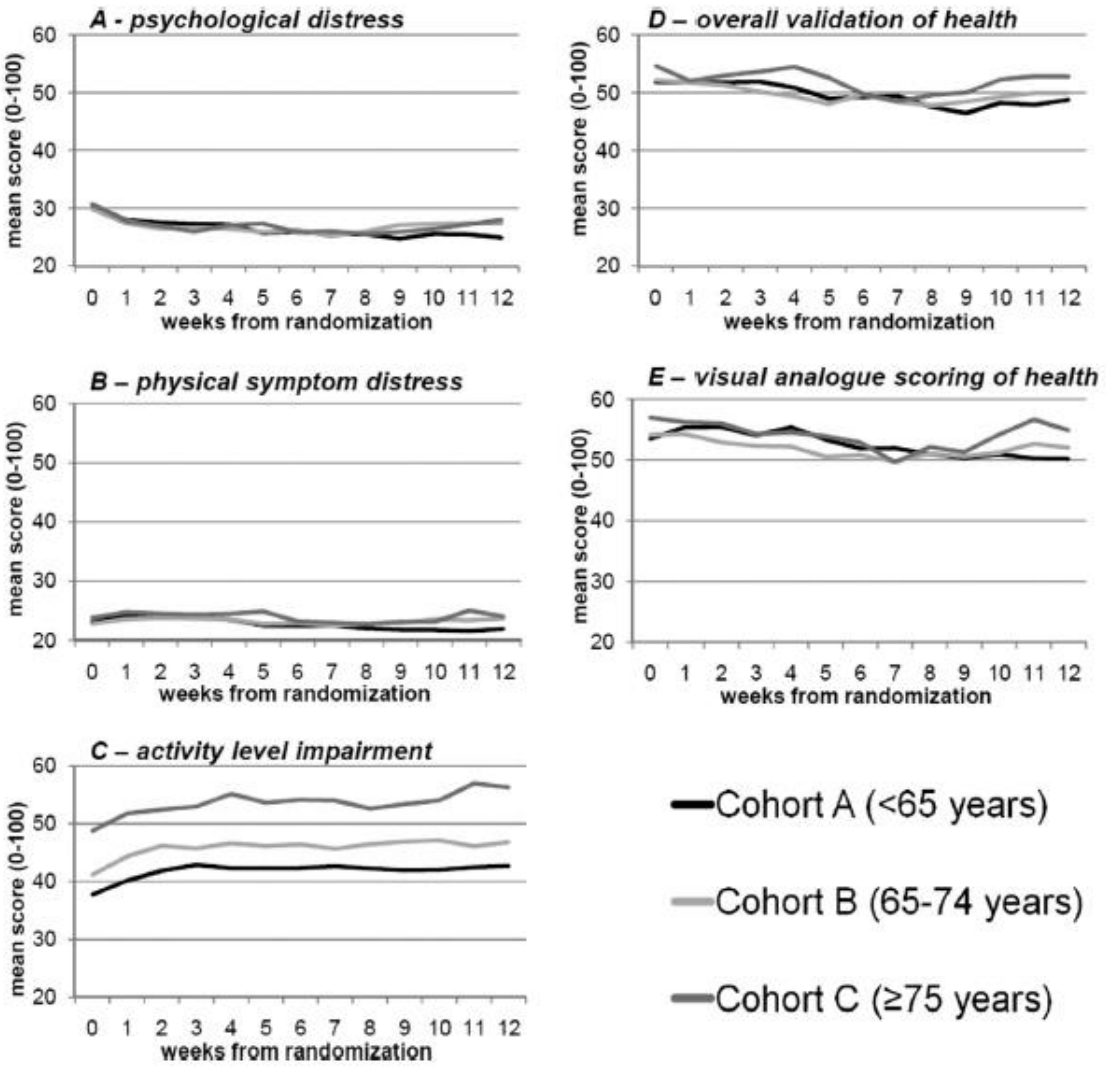
Response

A= 78%

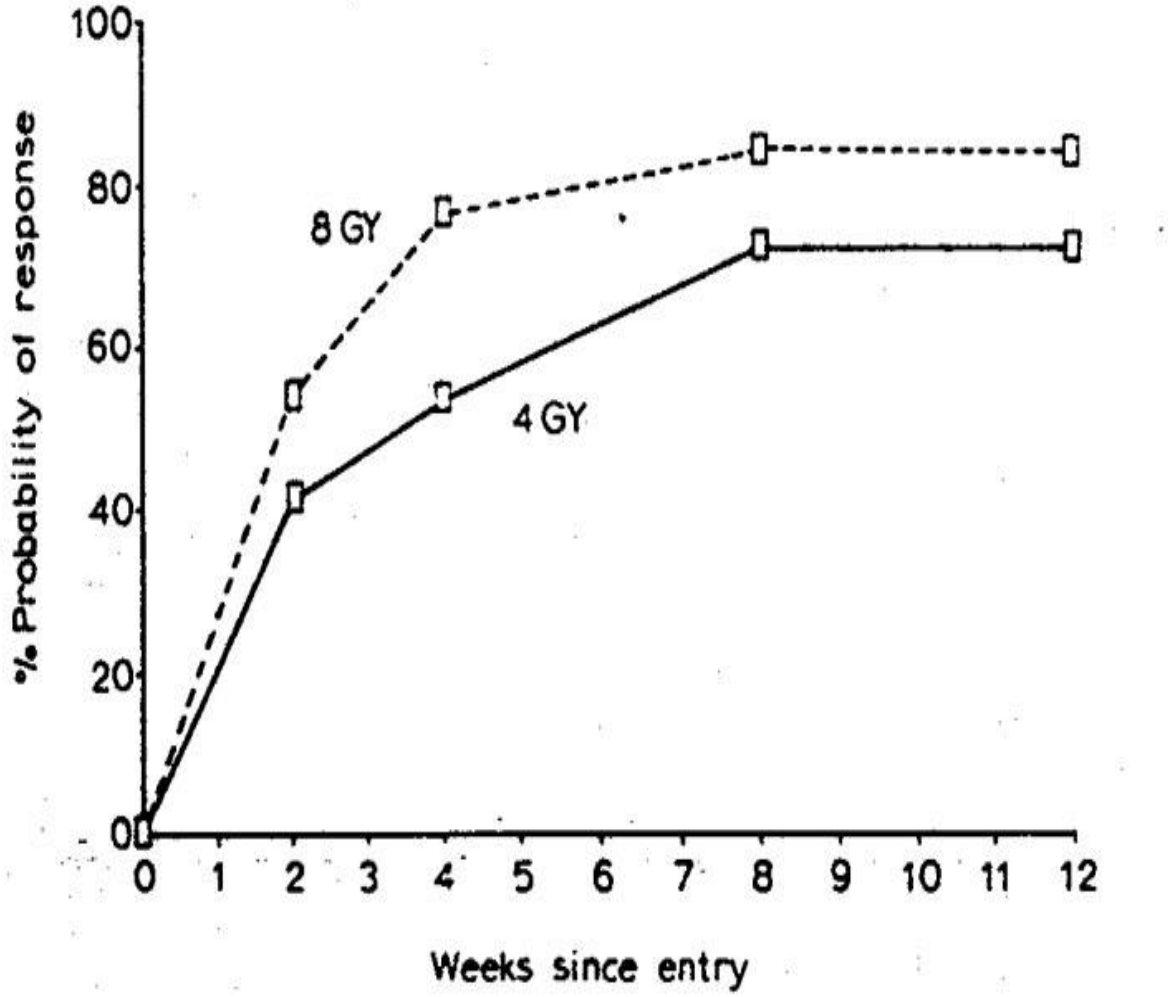
B= 74%

C= 67%

NS



4 Gy less efffective than 8 Gy



270 patients

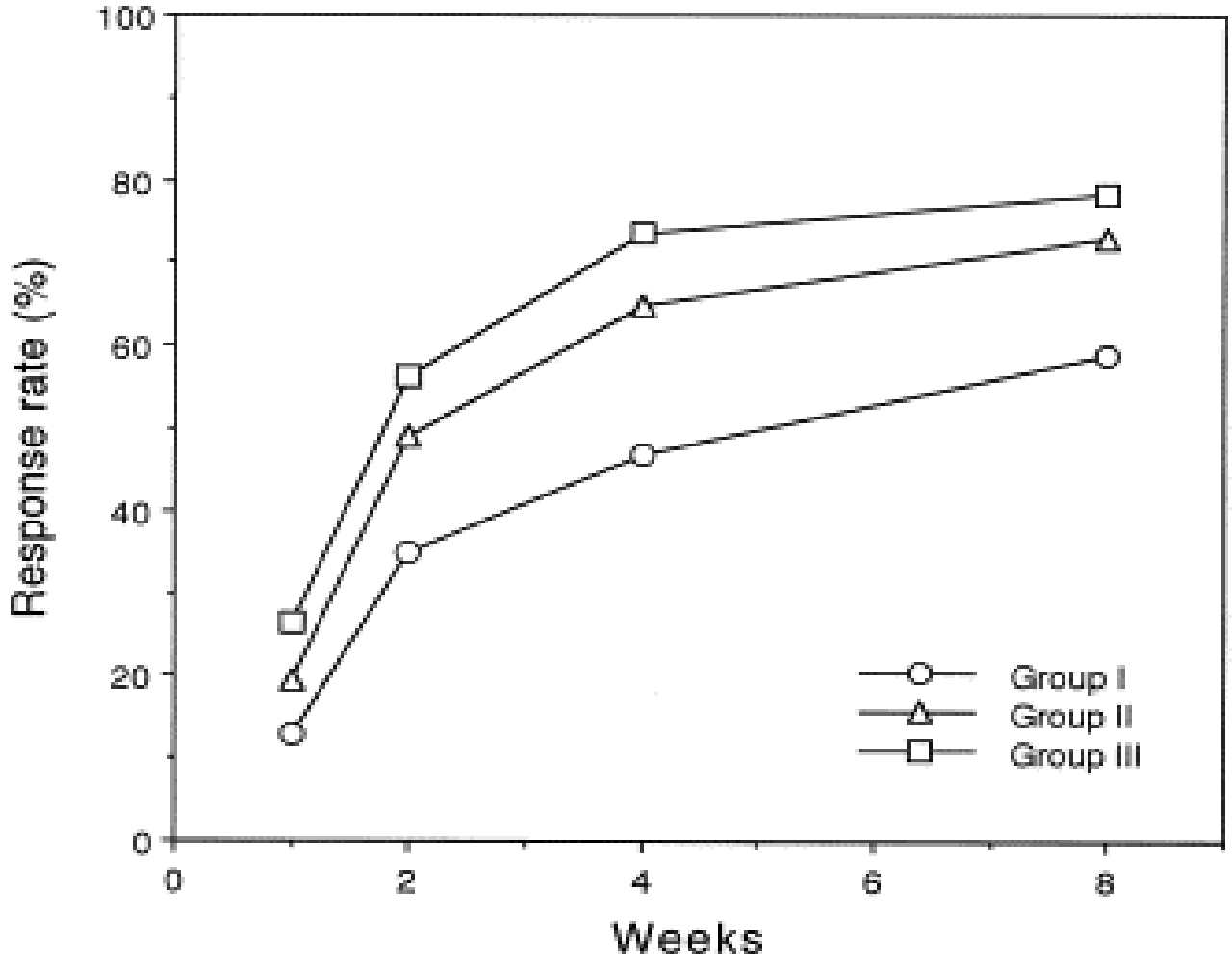
Hoskin et al R&O 1992

6 Gy seems less effective, but outcome non significant

N= 327

I = 4Gy
II = 6Gy
III = 8Gy

P<0.05 for
I vs II except wk 1
I vs III throughout



Jeremic et al IJROBP 1998

Net pain relief = weeks in response / total weeks survival

N= 160

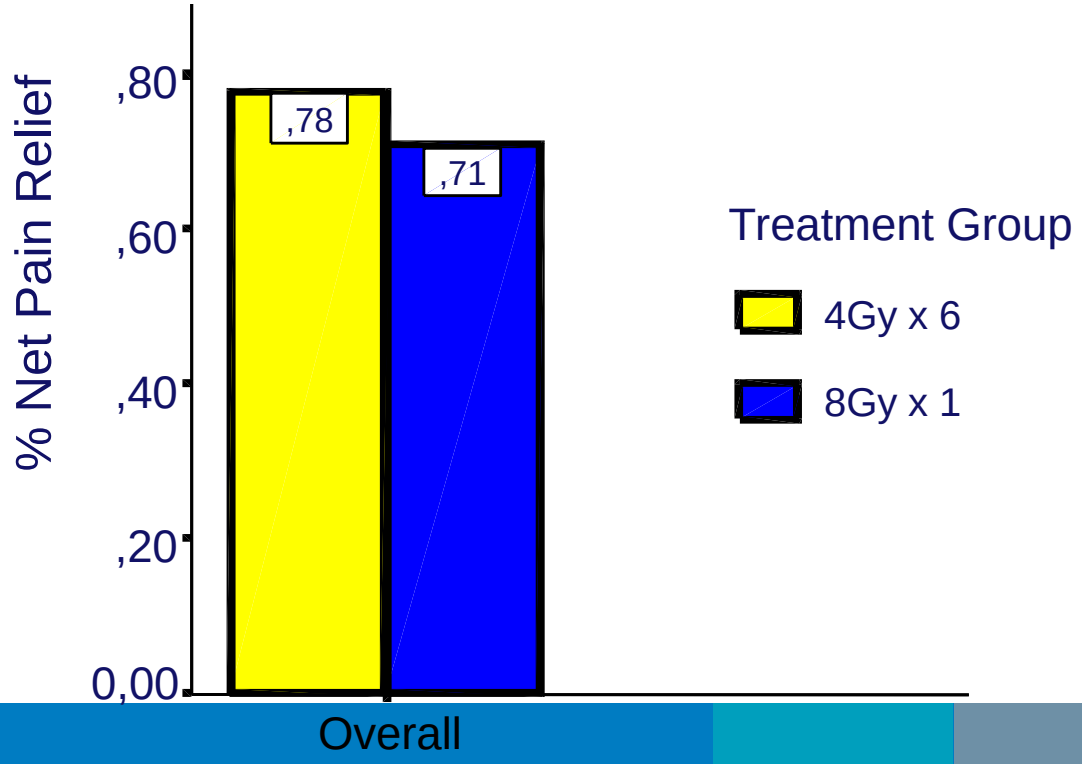
Foro Arnolot, R&O 2008

Table 5
Gain and percentage of pain progression, net pain relief, toxicity, and re-treatment

	30 Gy	8 Gy	*p*
Gain	4	3.5	ns
Pain progression %	43	28	ns
Net pain relief %	71	68	ns
Toxicity %	18	12	ns
Re-treatment %	2	28	0.001

N= 1157

Not published



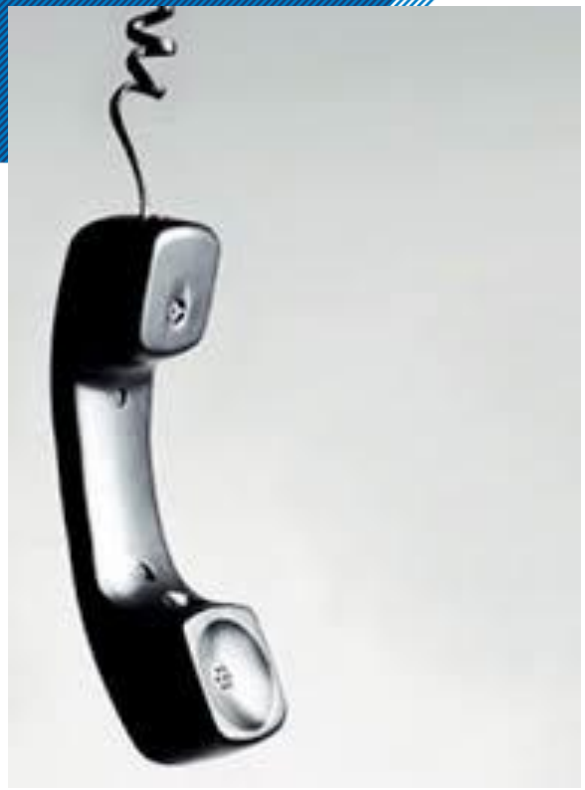
Complete responders about 10-14%

Table 6
Complete response rates in randomised trials where consensus definition is applied

	CR%	
	SF	MF
Hartsell et al. [11]	10	12
Van der linden et al. [22]	13	14
Foro et al.	13	11

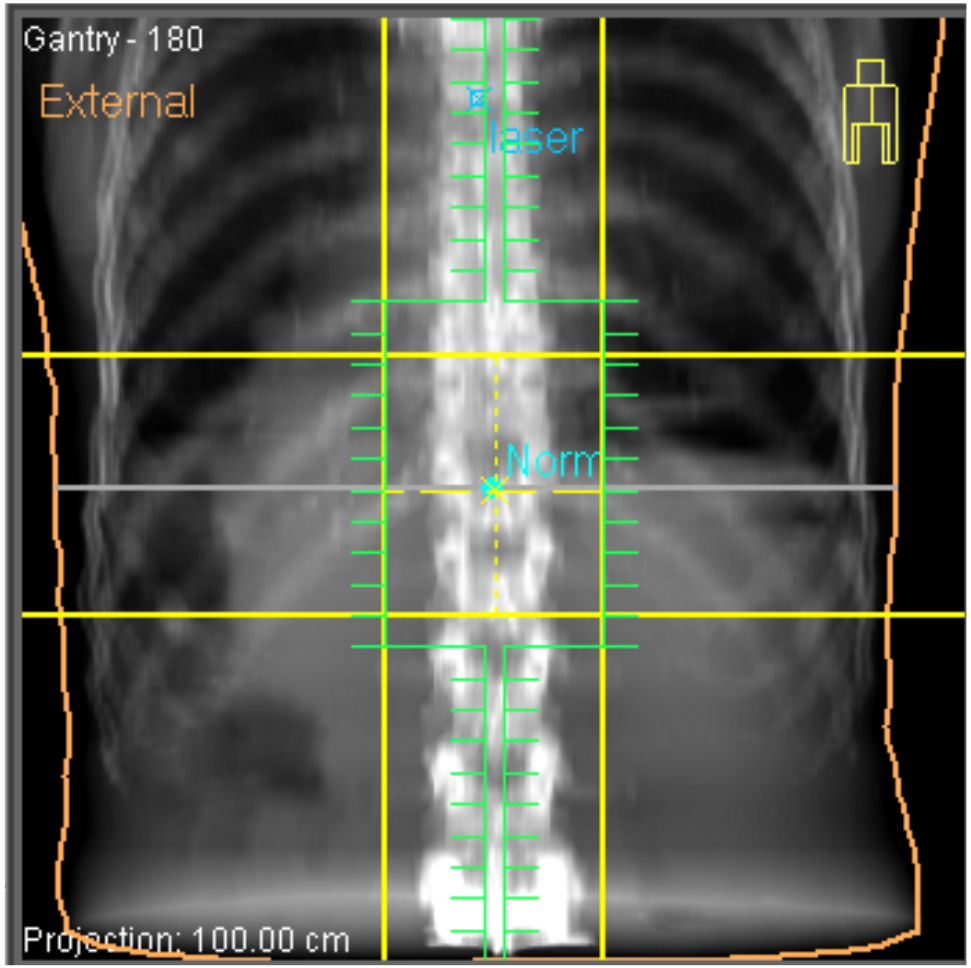
SF, single fraction; MF, multiple fraction; CR, complete response.

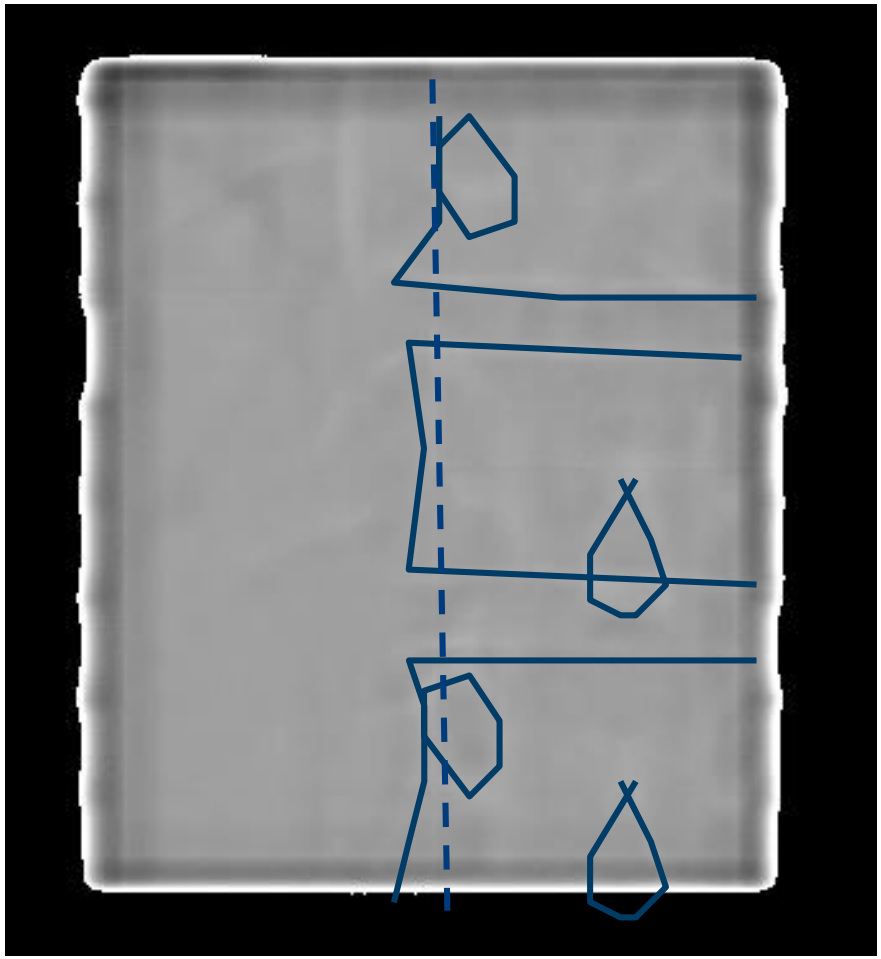
Foro Arnolot, R&O 2008)



Non response, what could be the reason?

Shift during treatment → position verification !





Lateral shift 2 cm

Set up errors are mostly patient dependent

	Patient A	Patient B	Patient C
distress	relaxed	nervous	nervous
performance	good	good	poor
physical complaints	no pain	no pain	highly symptomatic
set up error	1 mm	3 mm	5mm

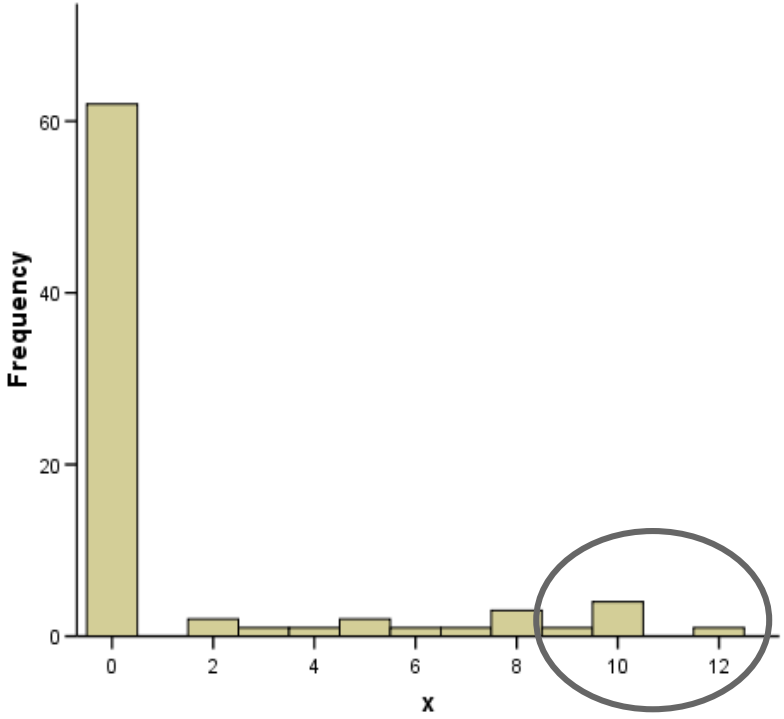
Errors ≥ 10 mm in about 15%

N= 58 spinal bone metastases

simple immobilization with head and knee support

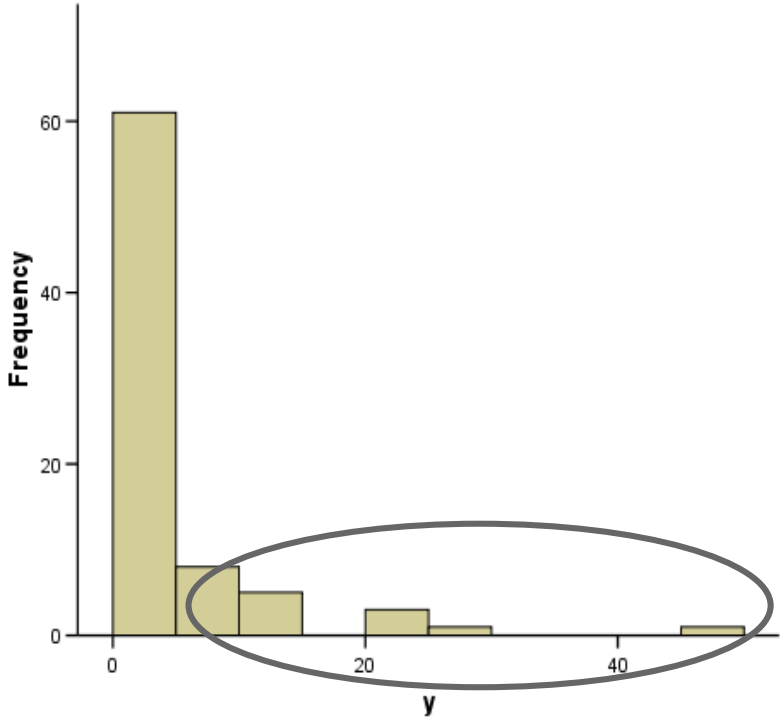
X-axis;

lateral shift

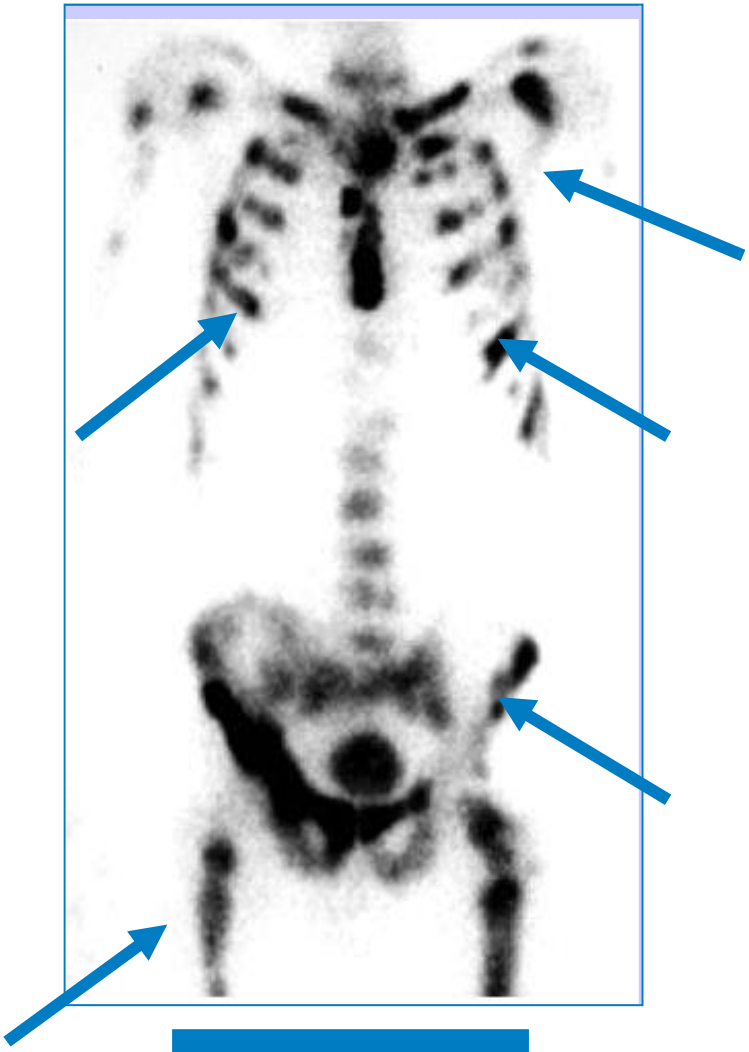


Y-axis;

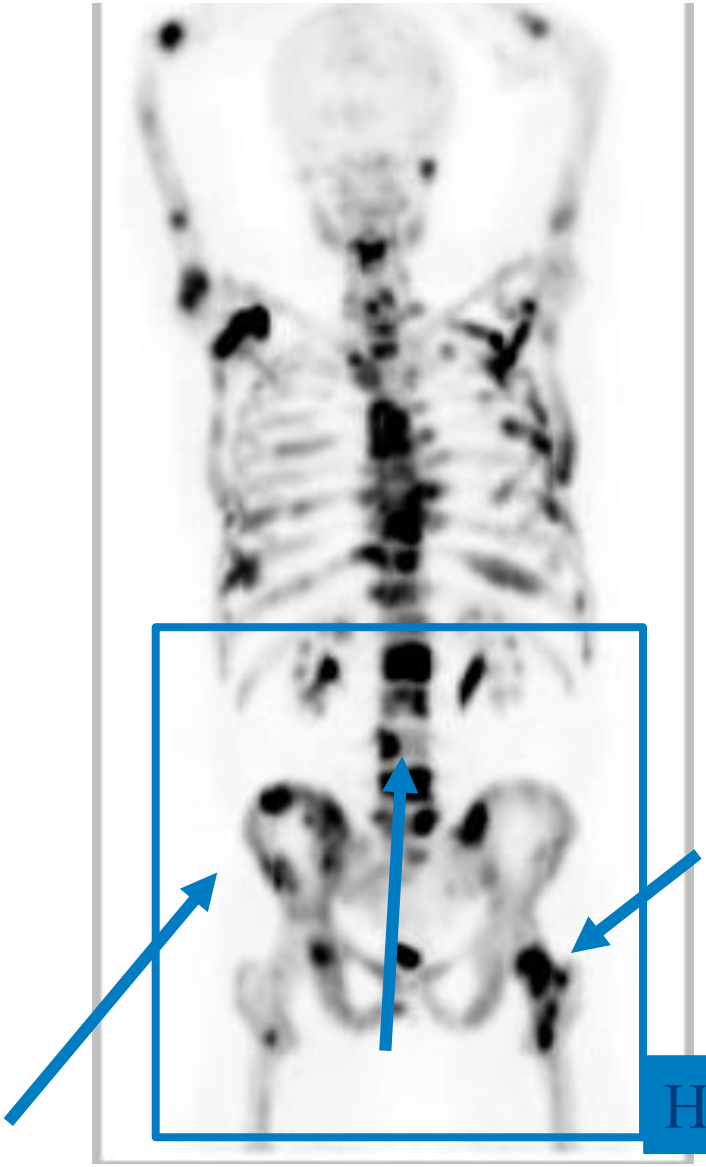
longitudinal shift



Patients with diffuse pain from e.g. prostate cancer



Strontium^{89}



Hemibody

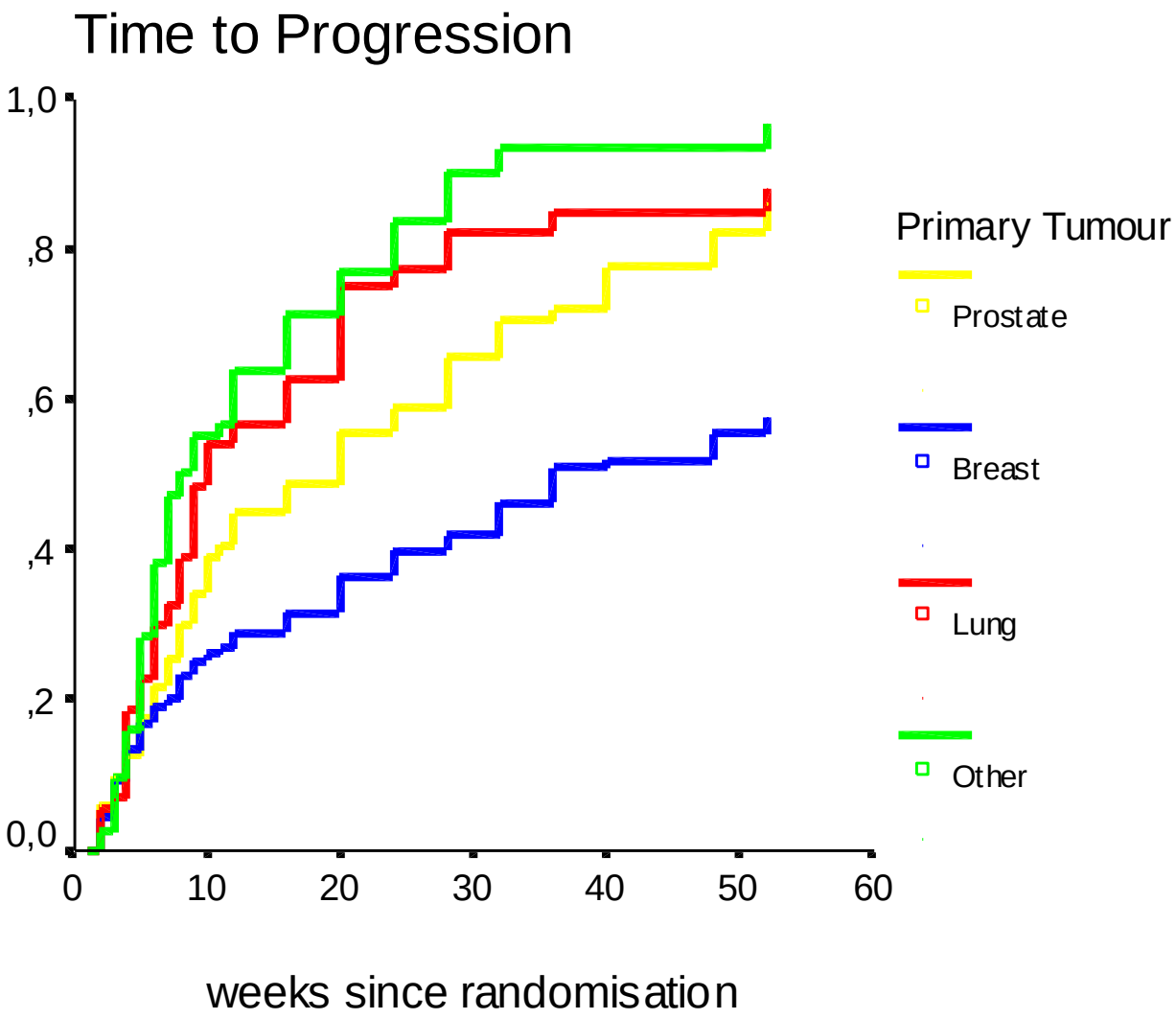
Effectivity of other treatments

RIB study

- Ibandronate single infusion vs. 8 Gy SF
- N= 470, prostate cancer

- Pain response similar at 4 and 12 weeks

Recurrent pain in Dutch trial



How effective is retreatment in painful bone metastases?

Systematic review on re-irradiation

Best research evidence

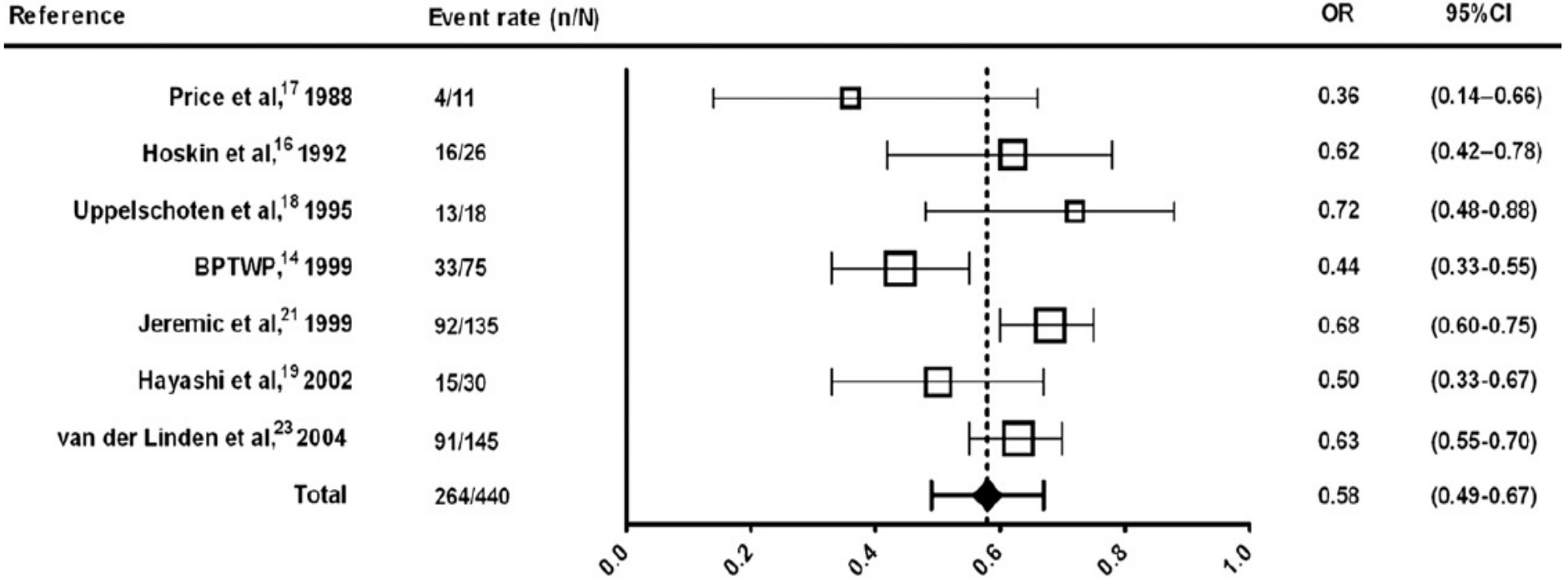
Table 1 Study characteristics

		Study population			Dose schedules		Pain response rates			Time frame		Toxicity
Reference	Study design	Inclusion period	Proportion of initial subjects reirradiated	Proportion of patients with complete follow-up	Initial RT	Reirradiation (% patients)	CR	PR	OR	Time to response (weeks, range)	Duration of remission (weeks, range)	Cases of toxicity in retreated population (%)
Price *et al.* (17) 1988	Prospective cohort	'85	11/26 (42%)	11/11 (100%)	4 Gy	4 or 8 Gy (73%) MF (27%)	NR	NR	4/11* (36%)	NR	NR	NR
Cole *et al.* (15) 1989	Parallel group	NR	4/29 (14%)	4/4 (100%)	8 Gy	NR	NR	NR	4/4* (100%)	NR	NR	NR
Hoskin *et al.* (16) 1992	Parallel group	'86-'90	40/270 (15%)	26/40 (65%)	4 or 8 Gy	8 Gy (100%)	NR	NR	16/26* (62%)	NR	NR	NR
Mithal *et al.* (22) 1994†	Retrospective series	'91	57/280 (20%)	51/57 (89%)	NR	8 or 10 Gy (40%) MF (60%)	8/51‡ (16%)	40/51‡ (78%)	48/51‡ (94%)	NR	NR	NR
Uppelschoten *et al.* (18) 1995	Prospective cohort	'86-'88	18/170 (11%)	18/18 (100%)	6Gy	6Gy (100%)	NR	NR	13/18* (72%)	NR	NR	NR
Jeremic *et al.* (21) 1999	Parallel group	'88-'93	135/327 (42%)	135/135 (100%)	4, 6 or 8Gy	4Gy (100%)	31/109* (28%)	49/109* (45%)	92/135* (68%)	Mean 3 (0-10)	Mean 22 (4-60)	41/135 (30%)
BPTWP, (14) 1999	RCT	'92-'97	115/765 (15%)	75/115 (65%)	8Gy or MF	NR	12/75* (16%)	21/75* (28%)	33/75* (44%)	NR	NR	NR
Hayashi *et al.* (19) 2002	Retrospective series	'94-'00	35/168 (21%)	30/35 (86%)	MF	10Gy/5 to 26Gy/13	5/30§ (17%)	10/30§ (33%)	15/30§ (50%)	NR	Median 20 (8-92)	NR
Jeremic *et al.* (20) 2002	Parallel group	'88-'93	25/327 (8%)	25/25 (100%)	4,6 or 8 Gy	4Gy (100%)	10/25* (40%)	10/25* (40%)	20/25* (80%)	Median 2 (1-3)	Median 5 (2-28)	0
van der Linden *et al.* (23) 2004	RCT	'96-'98	173/1157 (15%)	145/173 (84%)	8Gy or 24Gy/6	8Gy (79%) 24Gy/6 (21%)	NR	NR	91/145‖ (63%)	Mean 5	Mean 15	53/173 (31%)

Huisman et al, IJROBP sept 2012

Overall response 58% to re-irradiation

Best research evidence

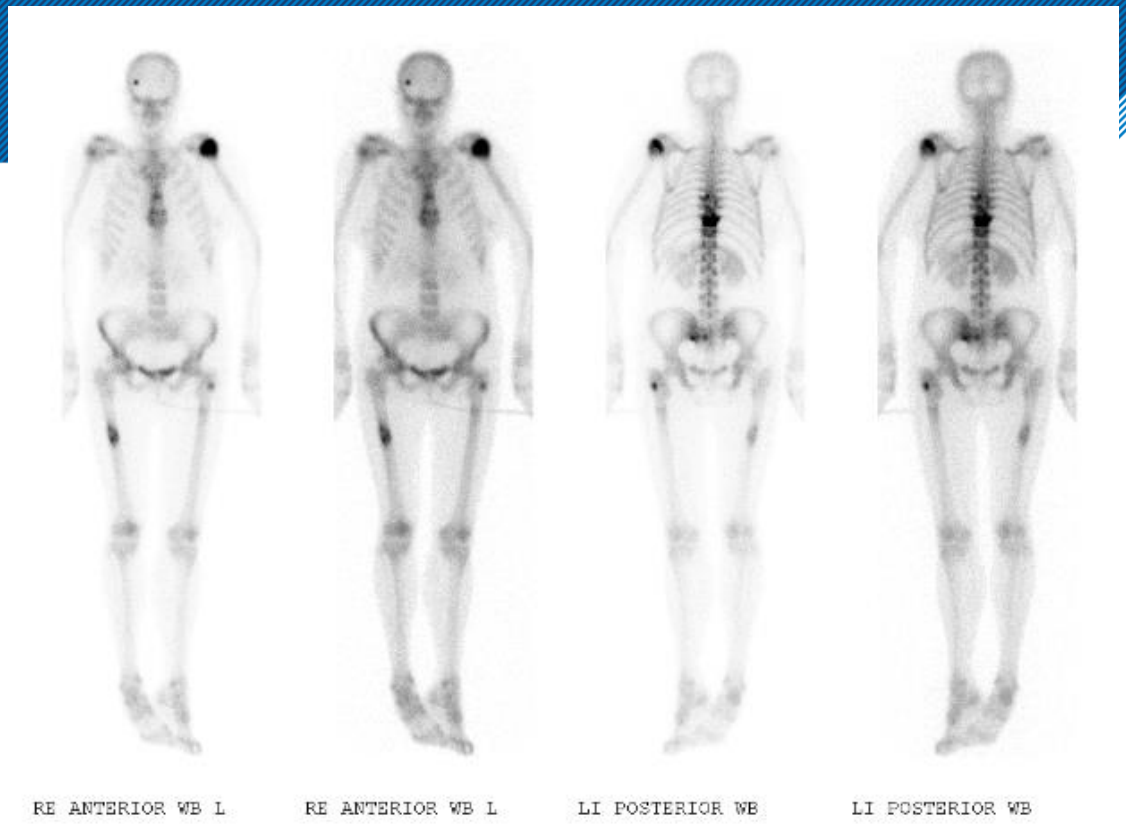


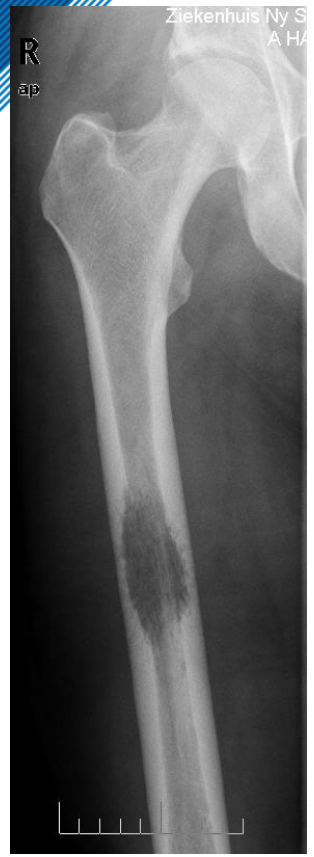
Huisman et al. IJROBP sept 2012

Retreatment fase 3 trial SC20 → 50% responders

Two-month Response	Intention to Treat Analysis		Per-Protocol Analysis	
	8 Gy Single Fraction (N = 425)	*20 Gy Multiple Fractions (N = 425)*	*8 Gy Single Fraction (N = 258)*	*20 Gy Multiple Fractions (N = 263)*
Complete Response	36 (8%)	32 (8%)	35 (14%)	31 (12%)
Partial Response	83 (20%)	104 (24%)	82 (32%)	104 (40%)
Overall Response	**119 (28%)**	**136 (32%)**	**117 (45%)**	**135 (51%)**
Inevaluable	162 (36%)	160 (36%)	0	0
Not Defined	92 (22%)	90 (21%)	91 (35%)	90 (34%)
No Change	7 (2%)	7 (2%)	7 (3%)	7 (3%)
Pain Progression	45 (11%)	32 (8%)	43 (17%)	31 (12%)

Chow et al. Lancet Oncol 2014



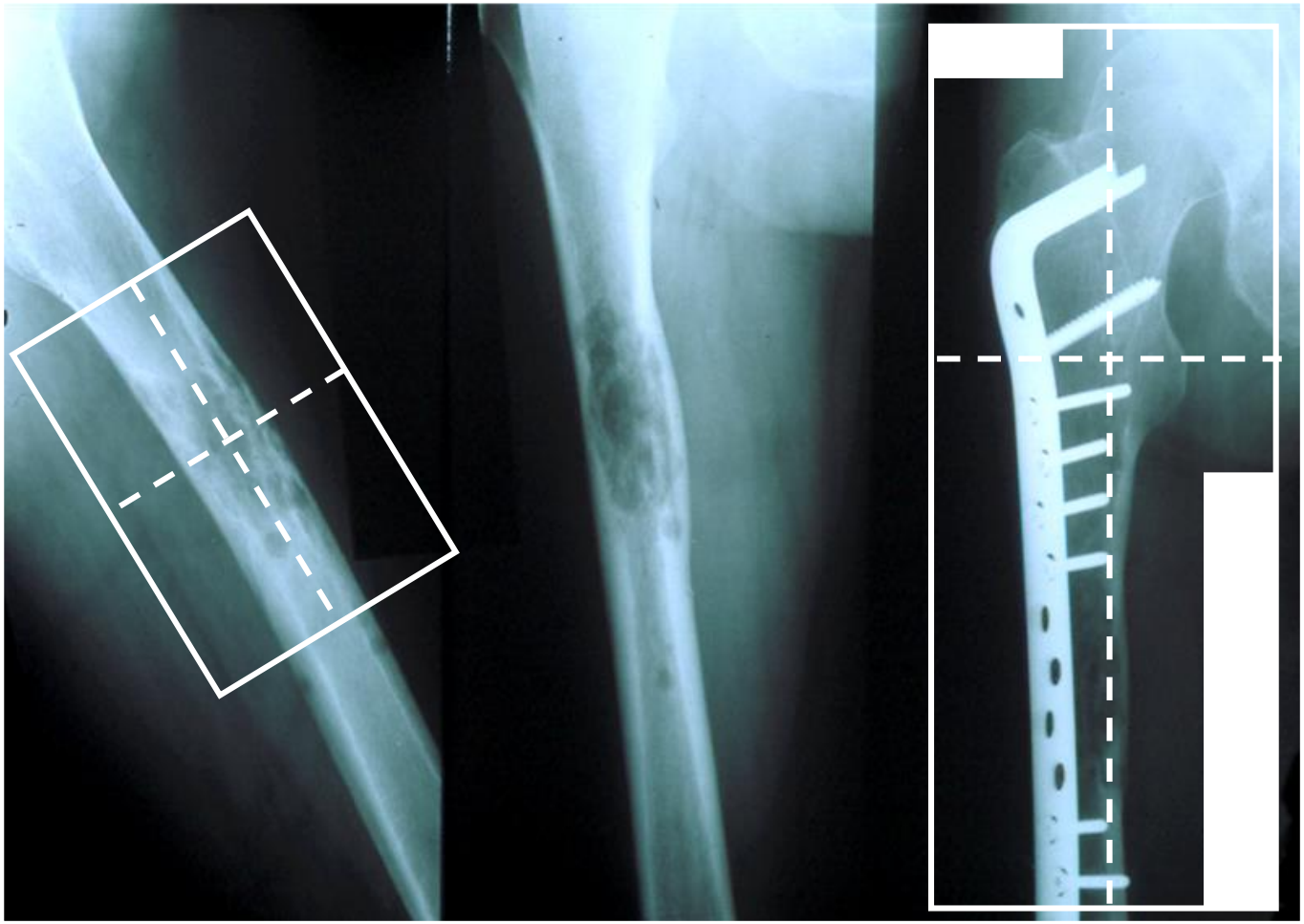


Metastases to the long bones -> chance of fracture

Goals are remineralisation and stabilisation

Prevention

Postoperative



Worry SF leads to more fractures

Analysis 05.04. Comparison 05 Intention-to-treat, Outcome 04 Pathological fracture rate

Review: Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy

Comparison: 05 Intention-to-treat

Outcome: 04 Pathological fracture rate

Study	Single fraction n/N	Multifraction n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
BPTWP 1999	7/383	2/378		9.7	3.50 [0.72, 16.96]
Cole 1989	0/16	1/13		7.8	0.25 [0.01, 6.74]
Nielsen 1998	6/122	6/119		28.3	0.97 [0.31, 3.11]
Price 1986	0/140	1/148		7.1	0.35 [0.01, 8.66]
Steenland 1999	24/579	10/578		47.0	2.46 [1.16, 5.18]
Total (95% CI)	1240	1236		100.0	1.82 [1.06, 3.11]

Total events: 37 (Single fraction), 20 (Multifraction)

Test for heterogeneity chi-square=4.80 df=4 p=0.31 I^2 =16.6%

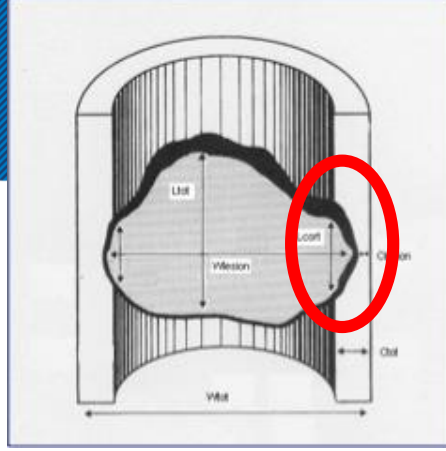
Test for overall effect z=2.16 p=0.03

0.1 0.2 0.5 1 2 5 10

Favours Single Favours Multiple

Cochrane analysis, Sze et al 2002

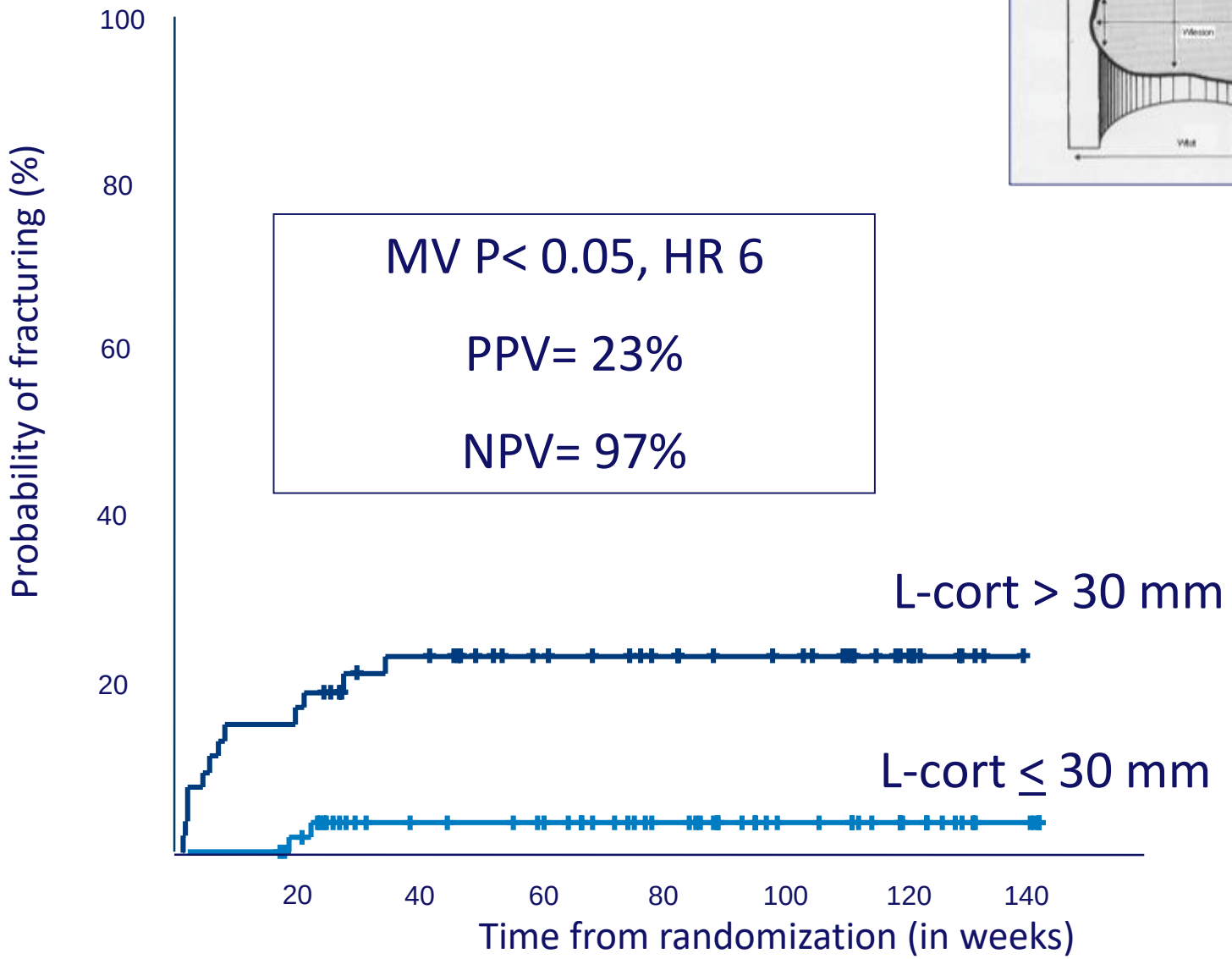
If the axial cortical axila destruction ≤ 30 mm high risk of fracture of the femur



MV P< 0.05, HR 6

PPV= 23%

NPV= 97%



Van der Linden, R&O 2003, JBJS 2004

Predictive models for fracturing lead to surgical overtreatment

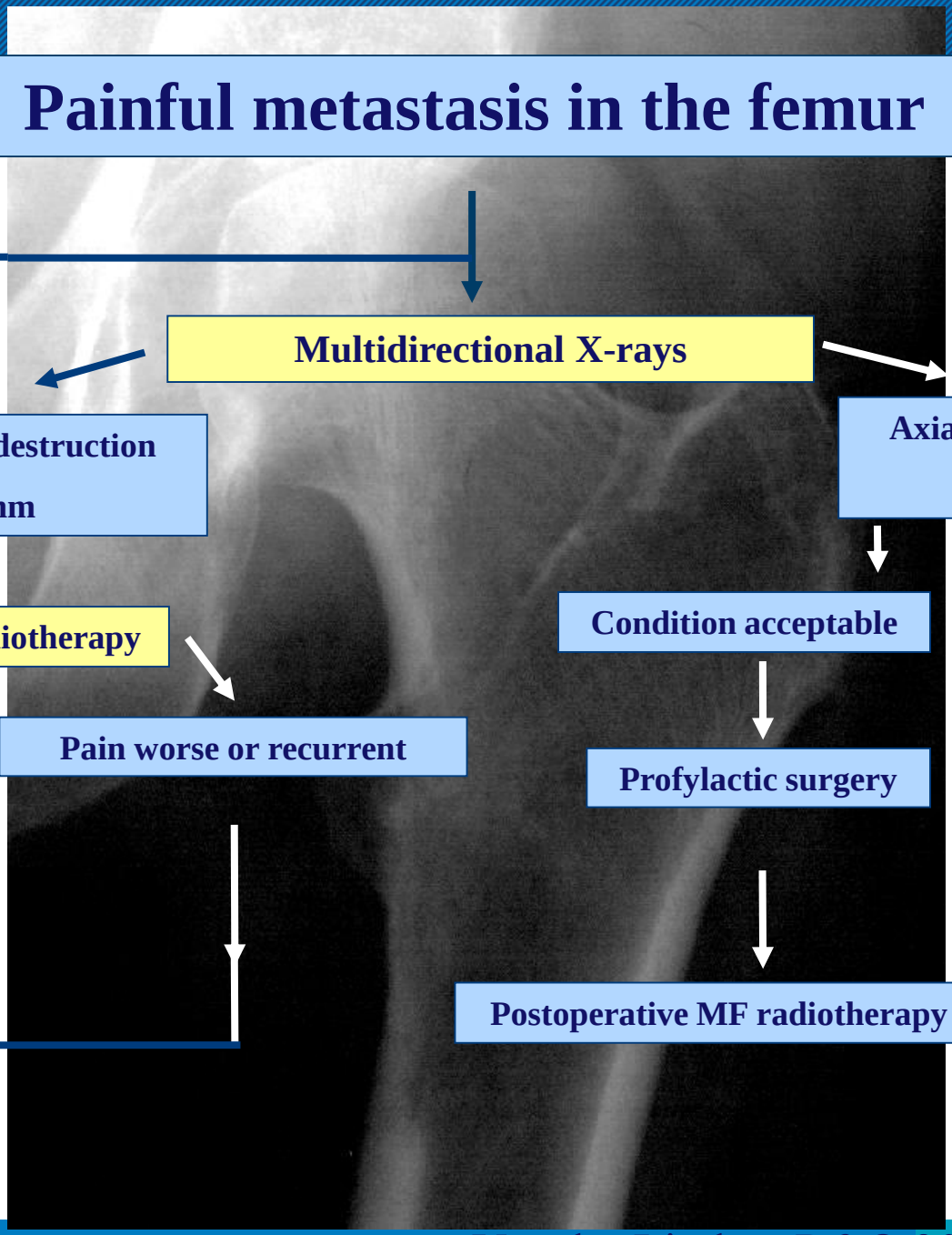
Table II. The modified scoring system of Mirels[7] for the diagnosis of impending pathological fractures

	Score*		
	1	2	3
Site	-	Shaft/distal femur	Proximal femur
Pain†	2 to 4	5 to 7	8 to 10
Lesion	Blastic	Mixed	Lytic
Size	<1/3	≥1/3, ≤2/3	>2/3

	Pathological fracture absent (n = 96)	Pathological fracture present (n = 14)	p value*	SE† (%)	SP† (%)	PPV‡ (%)	NPV‡ (%)
Axial cortical involvement							
≤30 mm	56	2	*0.01*	*86*	*58*	*23*	*97*
>30 mm	40	12					
Circumferential cortical involvement							
≤50%	79	8	*0.03*	*43*	*82*	*26*	*91*
>50%	17	6					
Scoring system of Mirels§							
Score 6 to 8	12	0	*0.36*	*100*	*13*	*14*	*100*
Score 9 to 12	84	14					

Mirels, 1989; Van der Linden, JBJS 2004

Painful metastasis in the femur



Multidirectional X-rays

Axial cortical destruction ≤ 30 mm

SF radiotherapy

Pain response

Follow-up

Pain worse or recurrent

Axial cortical destruction > 30 mm

Condition acceptable

Profylactic surgery

Postoperative MF radiotherapy

Bad condition

MF radiotherapy

Van der Linden, R&O 2003, JBJS 2004

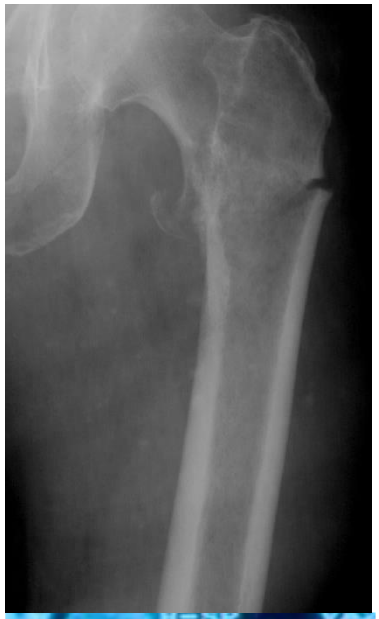
Limited evidence for effectiveness of radiotherapy on bone quality or fracture risk

Fracture -> postoperative RT

- Townsend et al, IJROBP 1995
- N= 64
- 53% vs. 11% (MV, P< 0.01) → function

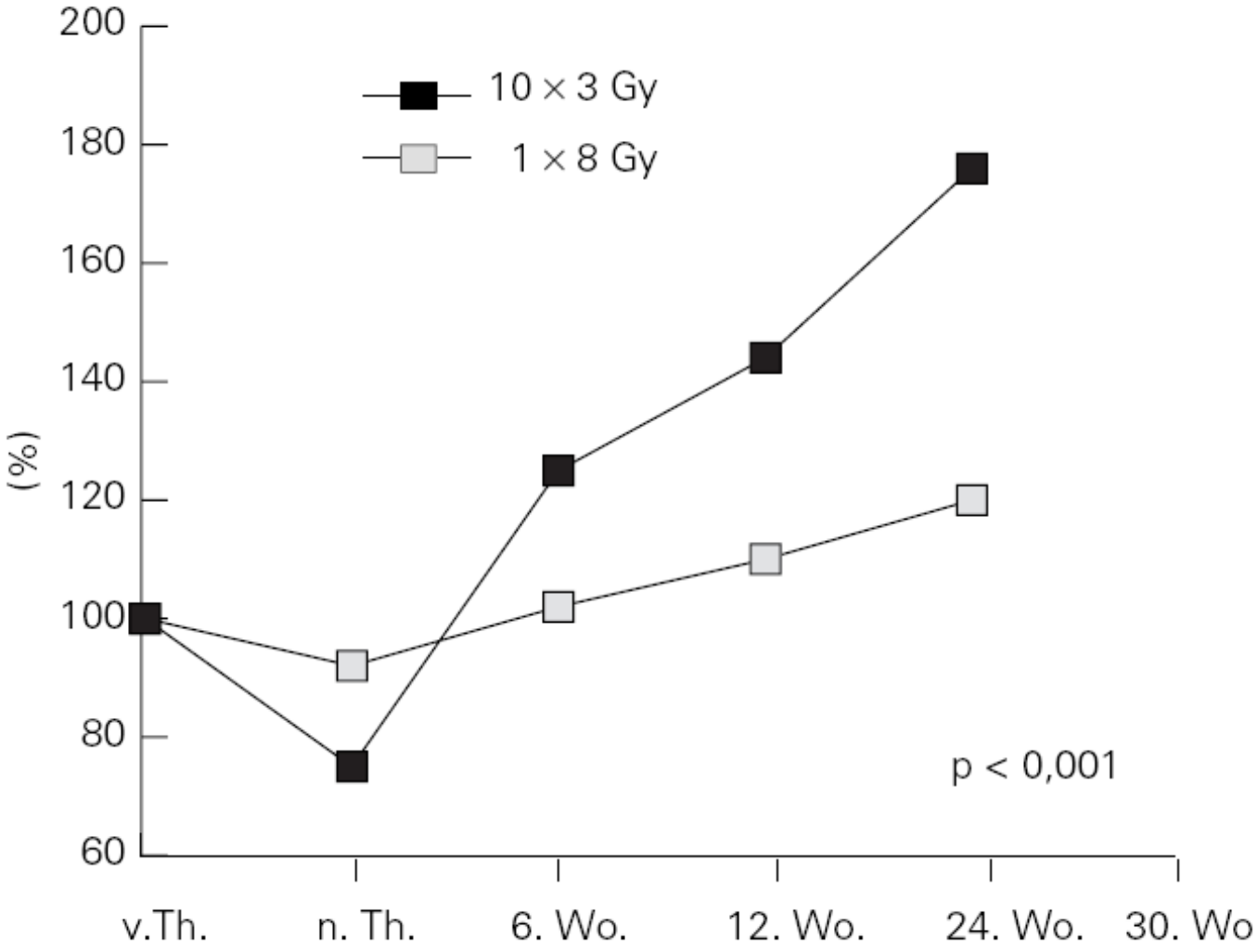
Impending

- Koswig et al, Strahlenther.Onc. 1999
- N= 107
- 8 Gy SF vs. 30 Gy / 10 fr.
- Higher dose -> more recalcification



Groenen et al, R&O 2016, Willeumier et al. R&O 2016

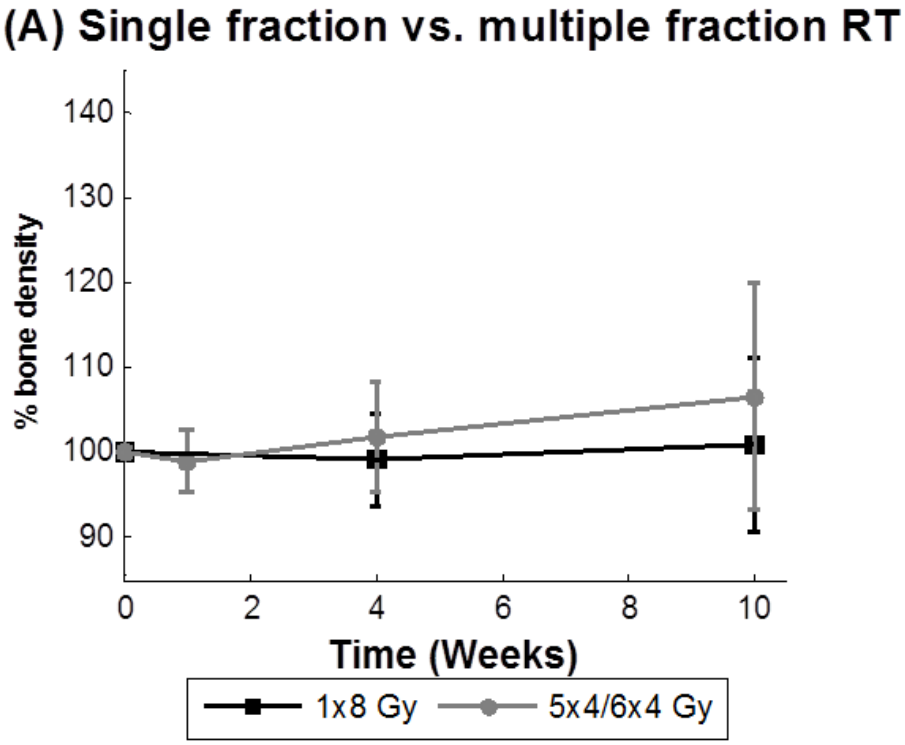
Remineralisation using CT

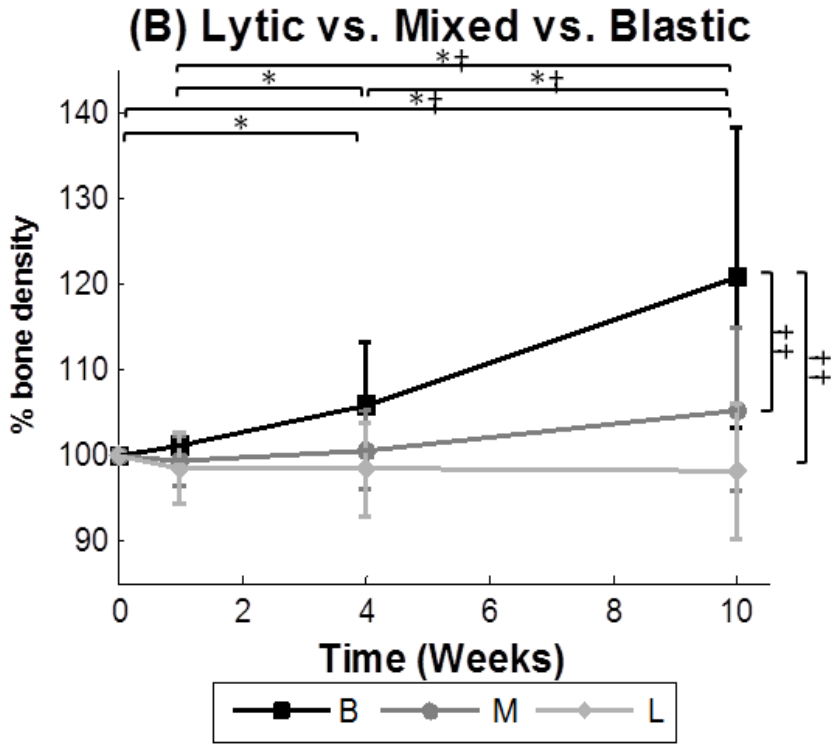


Koswig et al. Strahlenth.Onkol. 1999

Prospective CT femur study shows limited effect on remineralisation

N= 42 with 47 femurs





Eggermont et al, Adv Radiat Oncol. 2016

Consolidation, improved bone strength after RT

Systematic review -> no sufficient evidence for a positive effect or RT on bone quality and fracture risk

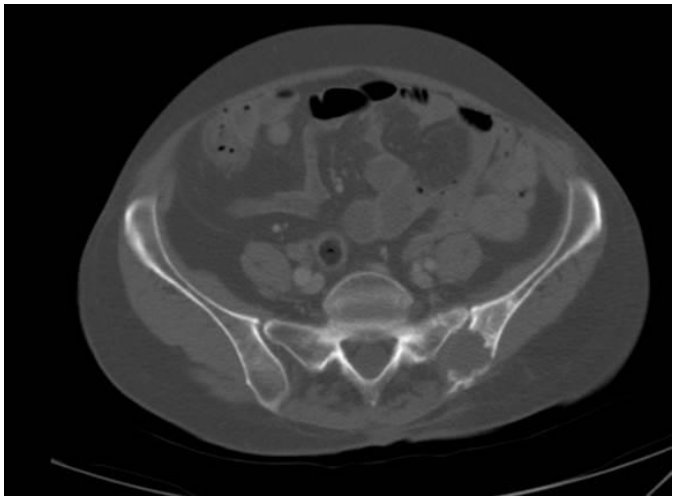
Groenen et al, R&O 2016

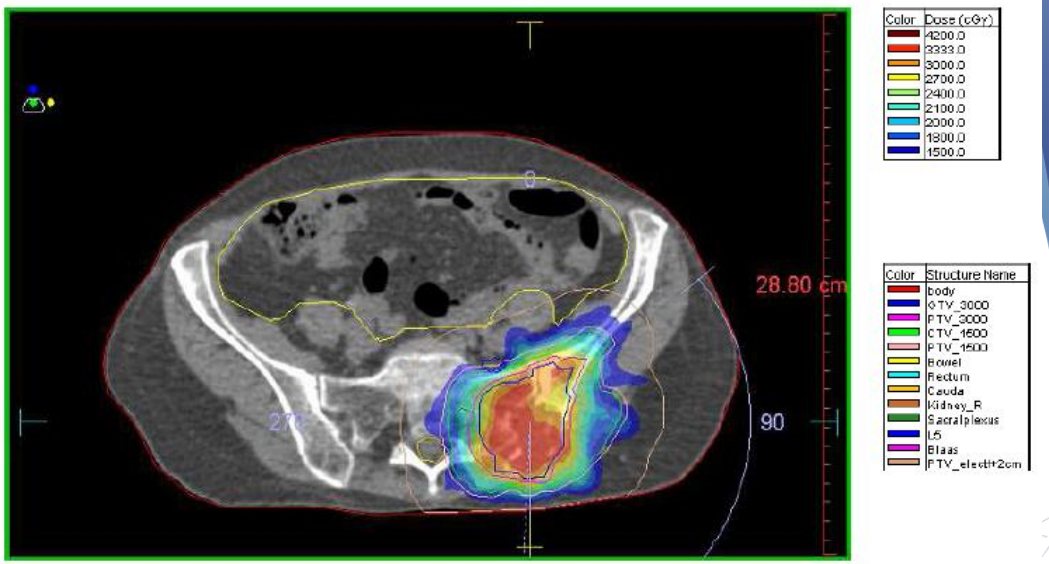
Jan 2016

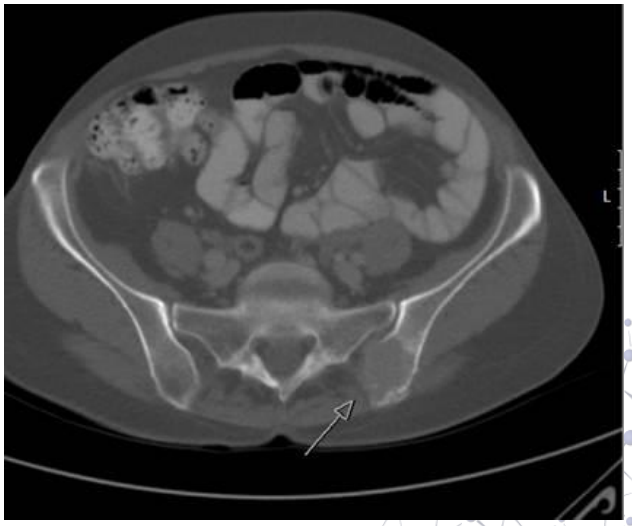
July 2016

Febr 2017

Restoration of bone shortly after 3x 10 Gy







Courtesy dr. Kaspers, UMCU

Systemic treatments prevents bone events

Reduce skeletal related events (SREs)

Fracture, surgical intervention, need for radiotherapy, SCC

- Increase bone mass / strength
- No effect on pain — Porta- Sales et al, Pall Med 2016

- Bisphosphonates
  - Oral
  - IV
- RANK-L inhibitors
  - Denosumab sc 1 per month — Peddi et al, Canc Treat Rev 2013
- Ra 223
  - Phase 3 ALSYMPCA study, prostate cancer, n= 921
  - Outcome 33% SRE vs. 38%
  - Time to first SRE 15,6 vs. 9,8 months — Sartor et al, Lancet Oncol 2014

Has single fraction radiotherapy become the gold standard for bone pain?

Dose fractionation surveys

Implementation of SF

Questionnaires sent out

- Schedules used

- Factors influencing choice for schedules
- Case scenarios
  - Simple clinical problems to more difficult problems

Case scenarios

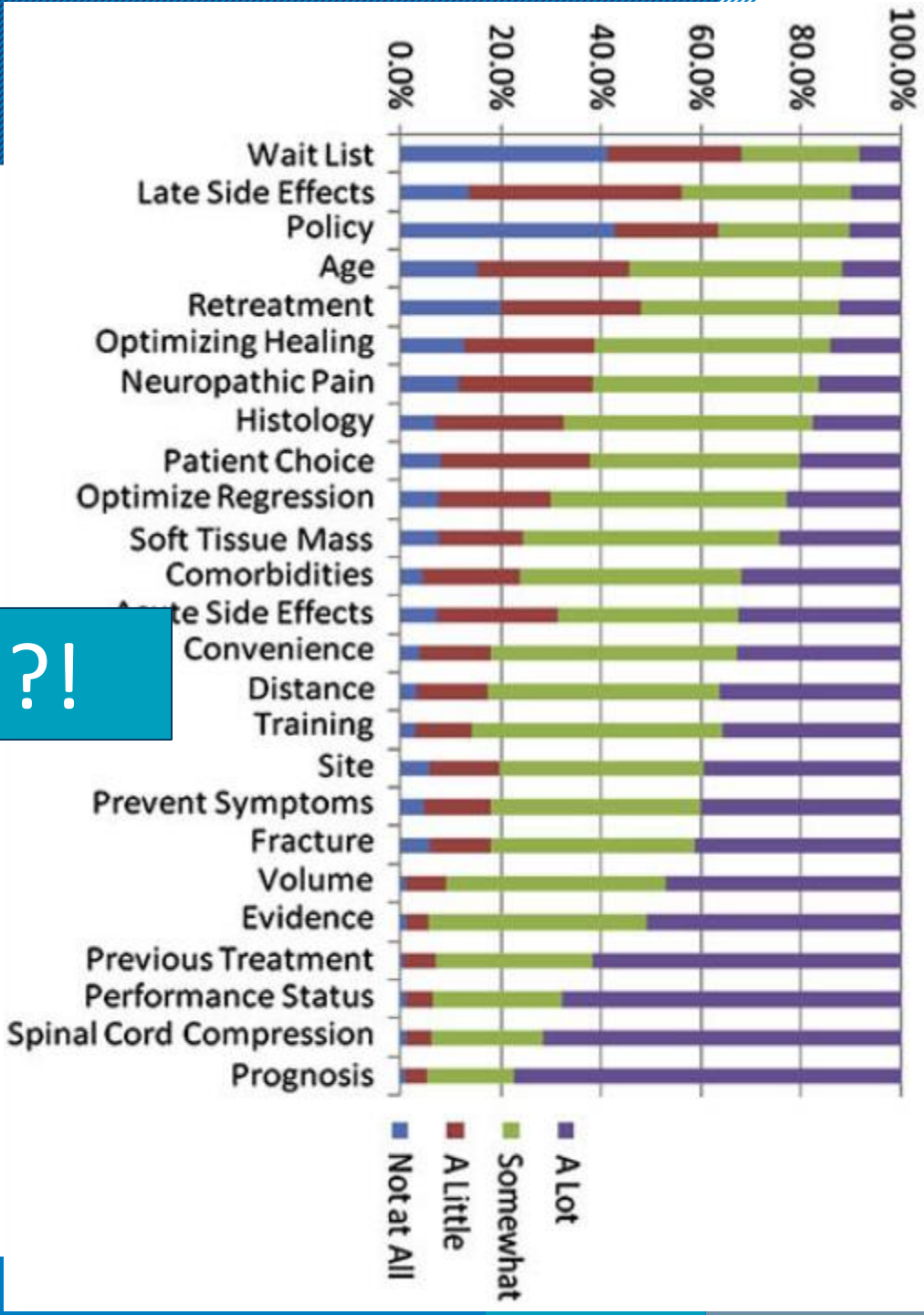
1.	breast cancer;	T6-9, uncomplicated
2.	prostate cancer;	shoulder pain
3.	lung cancer;	L3, mild vertebral collapse
4.	Lung cancer:	+ neuropathic pain
5.	retreatment;	lower thoracic, hip

Overview

	Use of SF-RT (%)	Most common regimen	Range
Europe			
Lawton, 1991 (35)	NR	30 Gy/10	5 Gy/1–50 Gy/25
Lievens, 2000 (40)	11	30 Gy/10	NR
Adamietz, 2002 (43) (Germany)	NR	NR	1 Gy/1–60 Gy/NR
Present study	11–57*	8 Gy/1	4 Gy/1–50 Gy/20
United Kingdom			
Priestman, 1989 (34)	25	20 Gy/5	8 Gy/1–33 Gy/15
Crellin, 1989 (33)	36	NR	NR/1–NR/10
Present study	8–60*	8 Gy/1	8 Gy/1–30 Gy/10
Canada			
Duncan, 1993 (37)	15	20 Gy/5	8 Gy/1–30 Gy/10
Chow, 2000 (39)	16–31*	20 Gy/5	8 Gy/1–30 Gy/10
Barton†, 2002 (44)	26	20 Gy/5	NR
Present study	18–67*	20 Gy/5	6 Gy/1–30 Gy/10
United States			
Maher, 1992 (36)	0	30 Gy/10	10 Gy/7–46 Gy/42
Hartsell, 1998 (38)	0	30 Gy/10	8 Gy/2–50 Gy/25
Ben-Josef, 1998 (1)	<1	30 Gy/10	8 Gy/1–40 Gy/20
Present study	2–20*	30 Gy/10	3 Gy/1–60 Gy/20
Australia/NZ			
Roos, 2000 (42)	15–42*	20 Gy/5	8 Gy/1–50 Gy/25
Present study	9–65*	20 Gy/5	6 Gy/1–40 Gy/20
Asia			
Gupta†, 2004 (45) (India)	24	NR	NR
Present study	9–39*	30 Gy/10	4 Gy/1–50 Gy/25

Fairchild et al. IJROBP 2009

Factors influencing choice for dose fractionation



Reimbursement ?!

Fairchild et al. IJROBP 2009

SF vs. protracted regimens

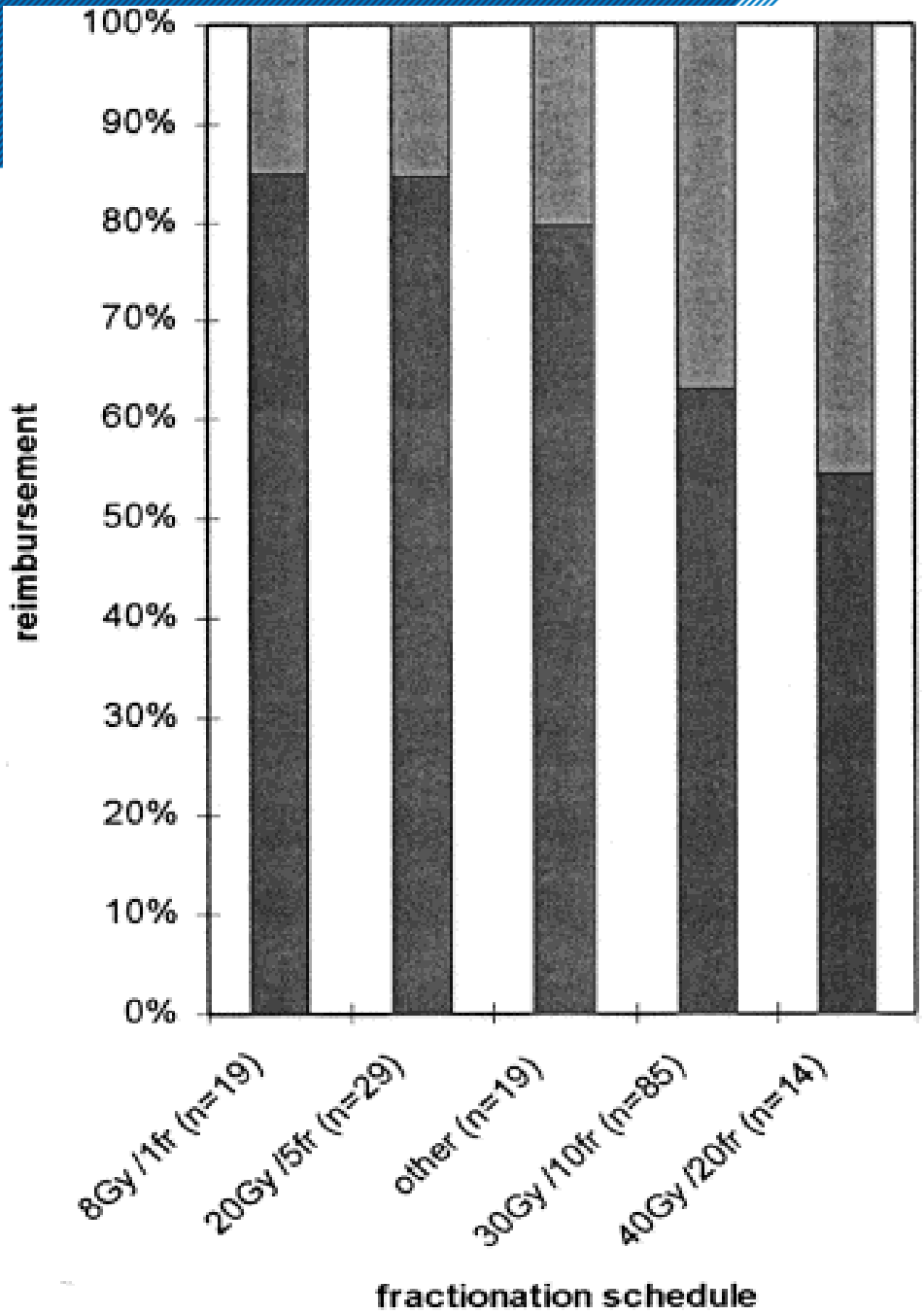
Perspective	Pros	Cons
Patient	Convenience • One stop treatment • Less time in hospital or department • Less side effects	Higher percentage of retreatment; 7–25%
Doctor	Convenience	Reimbursement • Lower revenues
Department	Lower costs [26–28] Less use of available equipment Ease of scheduling among other therapies	Reimbursement • Lower revenues
Society	Lower costs Less use of available equipment	

van der Linden et al. Clin Onc 2009

Payment incentive

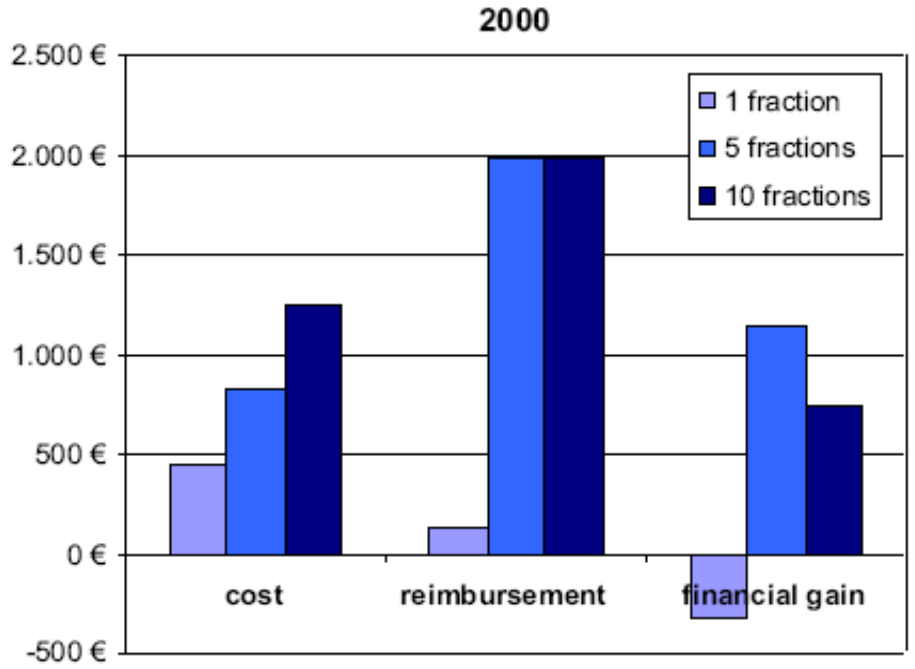
Fee-For-Service

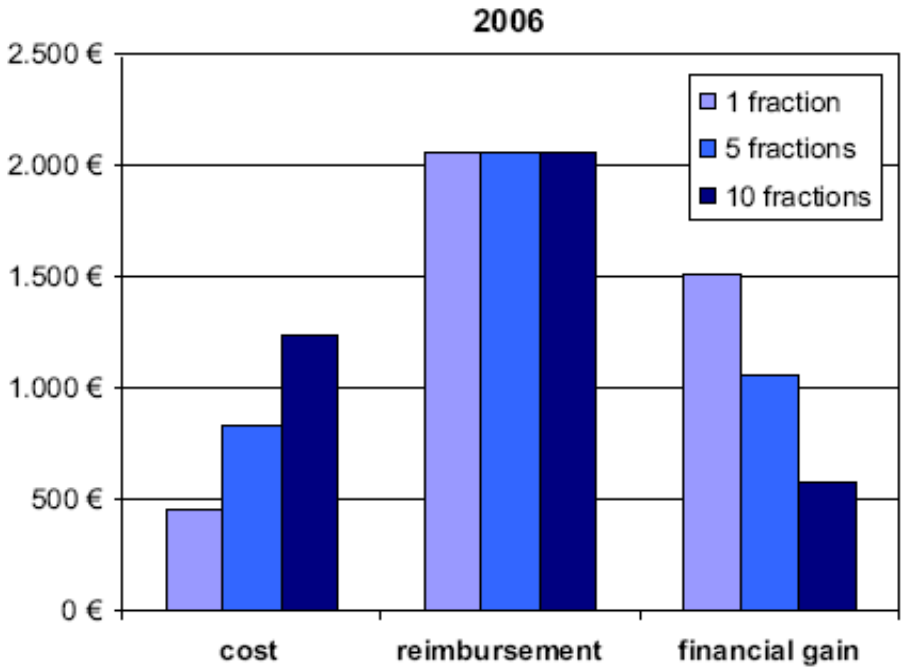
Budget and/or Case Payment



Lievens et al. R&O 2000

Costs vs. reimbursement in Belgium

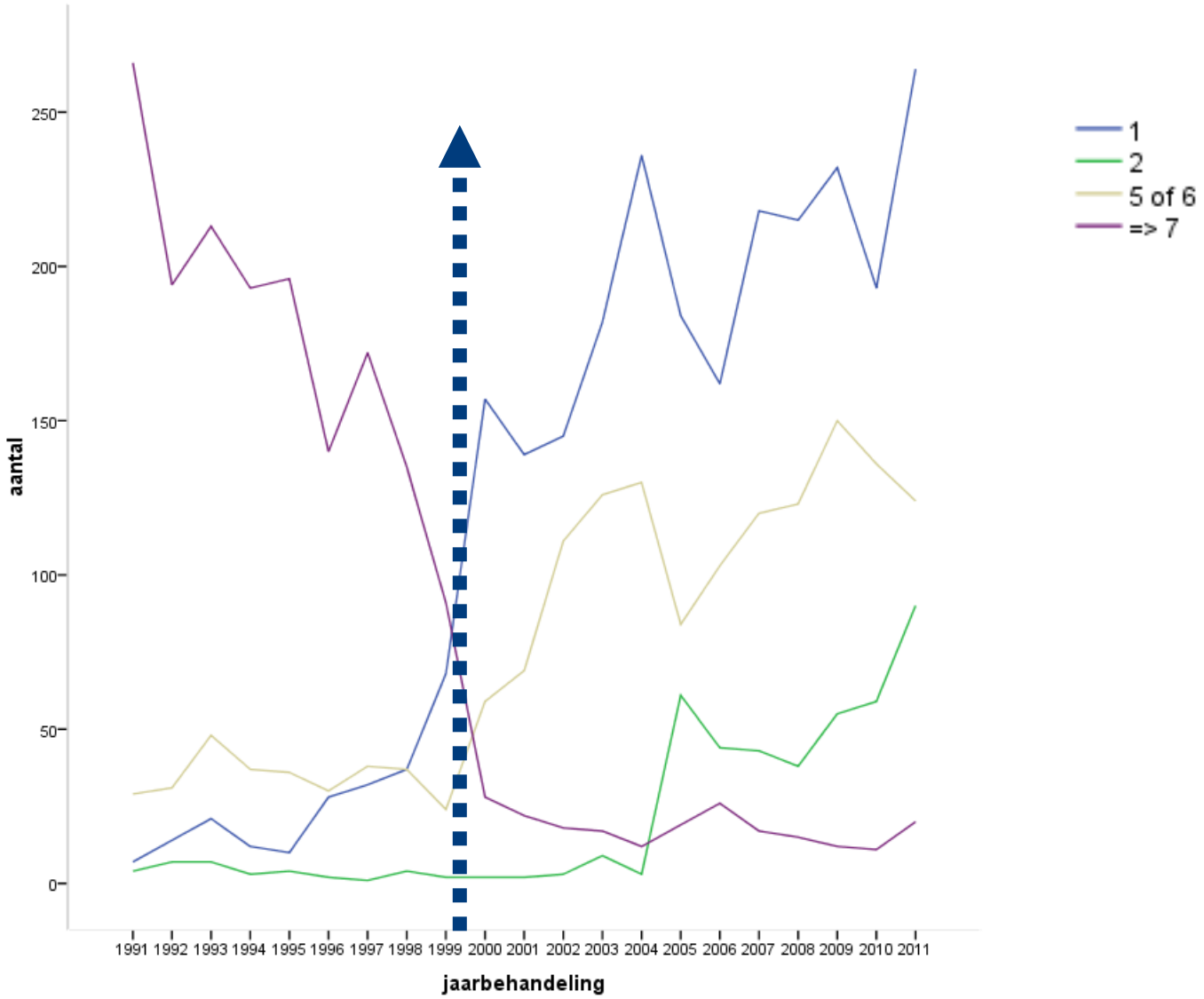




	1998	2004
8Gy single fraction	0%	25%
20Gy/4Gy	14%	22%
30Gy/3Gy	82%	47%
other	4%	6%

Lievens et al. personal communication

Leiden changed its schedules…



Concluding remarks

SF is still underexploited

- Cost effective
- More convenient for patients

Need to optimize usage of SF

- Awareness
- Education
- Change in reimbursement system

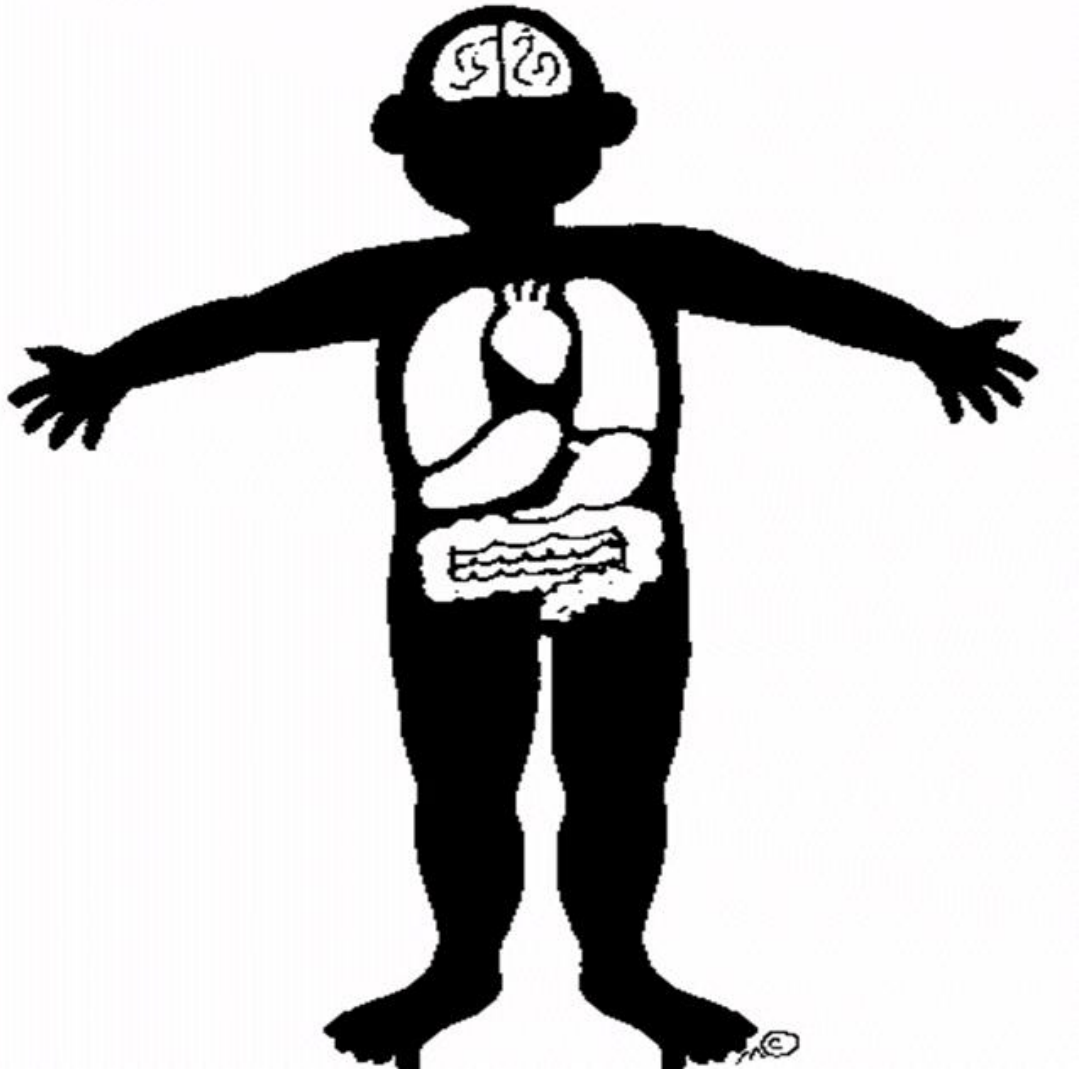
Conclusions radiotherapy for bone pain

- patient friendly
  - non invasive
  - quick procedure
  - few side effects
  - effective local treatment → responses about 60-70%
    - pain
    - ulceration, bleeding
    - dyspnea, edema
    - ..

} improvement of QoL

- evidence based outcome → single or short course schedules
- retreatments –always- possible

Skin / lymph nodes / soft tissues / organs



Radiotherapy in palliative care

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Outline

- Symptoms: Bleeding, Dyspnea
- Thorax: Airway obstruction,SVCS, breast
- Abdomen: Upper GI, liver
- Pelvis: bladder cancer
- Head and neck

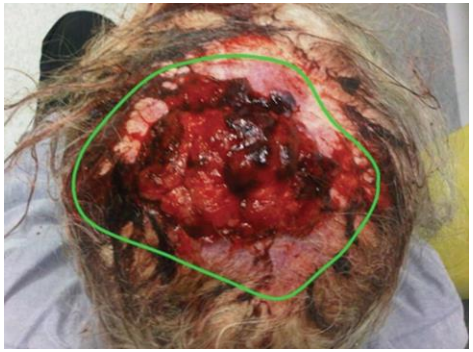
Outline

- ✓ Symptoms: Bleeding, Dyspnea
- Thorax: Airway obstruction, SVCS, breast
- Abdomen: Upper GI, liver
- Pelvis: bladder cancer
- Head and neck

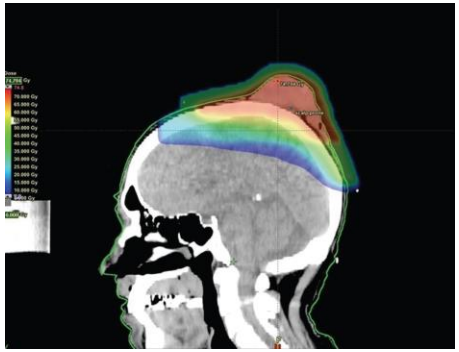
Bleeding

- From different sites: hemoptysis, hematuria, vaginal bleeding, melena, hematochezia, hematemesis, bleeding from ulceration of skin

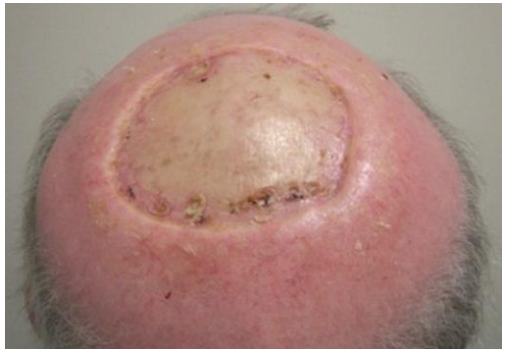
- Why: infiltration of vessels by cancer, bleeding from pathological tumor's vessels, ulceration and inflammation



Malignant Fibrous Histiocytoma MFH



Radiotherapy



4 mts after treatment RT +surgery

JK 4/49

Jang H Case Rep Med 2012

Radiotherapy in bleeding

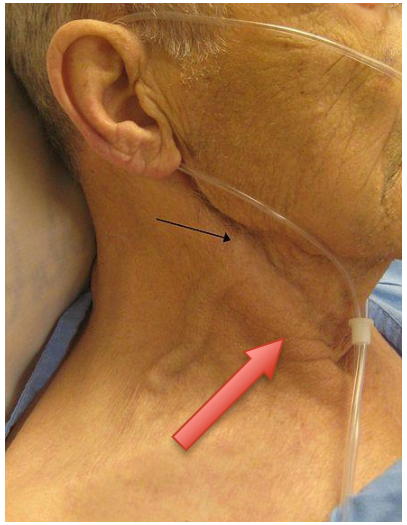
- RT helps in 24-48 h (think about transfusion if massive bleeding!)
- Schedules – preferred hypofractionation:
  - 1x 8-10 Gy,
  - 3-5 x 4-8 Gy,
  - 10 x 3 Gy
- Different definition of succes:
  - no further bleeding,
  - increased level of Hb
  - less transfusions
  - RT effective in vaginal bleeeding almost 100%, hemoptysis 86%, upper GI - 90%

Dyspnea

- Main symptom in many malignancies, not only in thorax
- 29-74% patients in terminal state complains of dyspnea, especially when KPS<60
- Experienced together with pain and psychosocial distress which inrease dyspnea
- Central, neural and mechnical reasons
- Interfere with acid base homeostasis

Dyspnea – when you are on call

- Evaluate possible reason of dyspnoea. Sudden onset and evolution?
- Symptoms presents at rest? Positional?
- Tachypnea? Cyanosis? Hemoptysis? Cough?
- Lung examination – sounds? Signs of pleural effusion? X-ray, CT, angiogram (embolisation!)
- Cardiac examination: tamponade? Jugular Venous Pressure?
- Bronchoscopy?
- Malignacy in abdomen (pressure on diaphragm)?

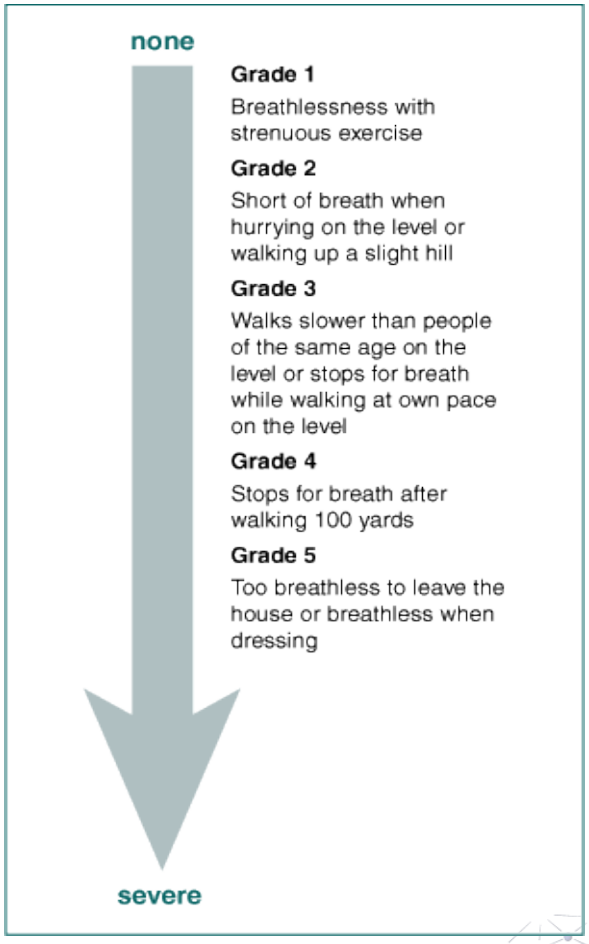


Visible external jugular vein, JVP raised, no pulsation = SVCS

Evaluation of dyspnea

- Lab:
  - oxygen saturation,
  - arterial gases,
  - acid- base balance

- Scales:
  - Modified Medical Reasearch Council Cancer Dyspnea Scale 1-5 functional
  - Stanford Anatomical Scale for SVCS



Nursing Best Practice Gudelines

Dyspnea - intervention

- Risk and benefits of intervention - balance!

- Pharmacotherapy (opioids, benzodiazepin)
- Oxygen therapy

- Steroids –no EBM proof for use, except first days of radiotherapy

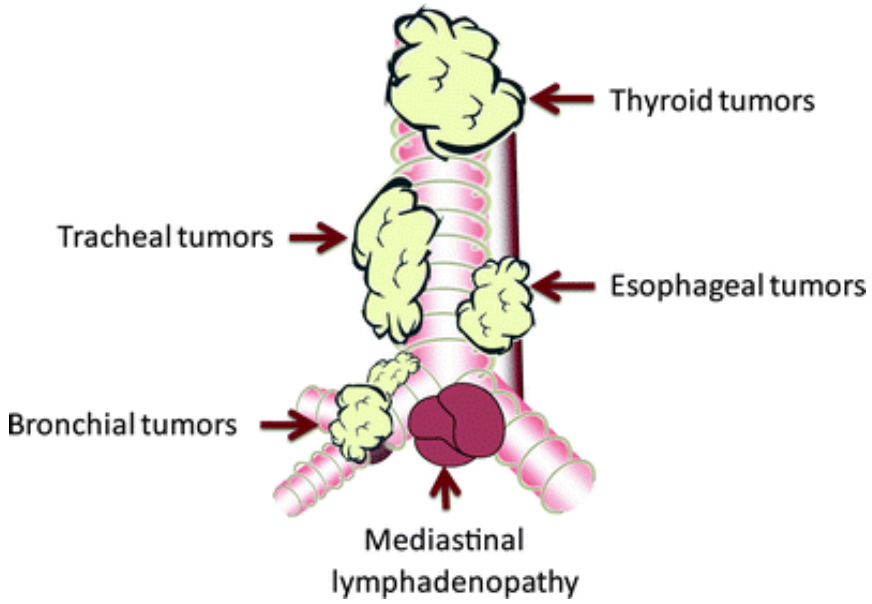
- Further intervention depends on main cause of dyspnea – MAO? Upper airway obstruction?

Outline

- ✓ Symptoms: Bleeding, Dyspnea
- ✓ Thorax: Airway obstruction, SVCS, breast
- Abdomen: Upper GI, liver
- Pelvis: bladder cancer
- Head and neck

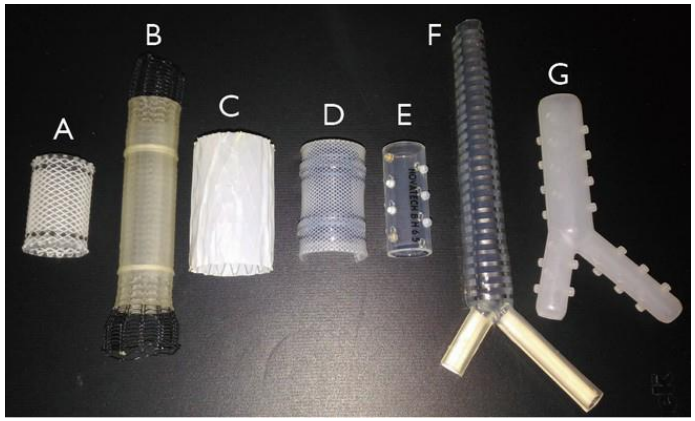
Malignant problems in Thorax

- Malignant airway obstruction (MAO)
- Superior Vena Cava Syndrom



Malignant Airway Obstruction (MAO)

- Symptoms: dyspnea, pneumonia, cough, hemoptysis
- Diagnosis: CT with bronchial reconstruction + bronchoscopy
- Tratment: stents and baloons, laser, surgery, cryotherapy and
- Radiotherapy – including EBRT and BT



Stents used in different types of MAO from *Guibert N JDT 2016*

RT for MAO – what really matters?

- RT schedules:
  - 1 x 8Gy
  - 10 x 3 Gy
  - 5 x 4 Gy
  - 15 x 3 Gy
- Important for response: size of the tumour < 6cm (p=0.04)
- BED_{10} >= 39 Gy (p=<0.01)
- Response for treatment important for OS!

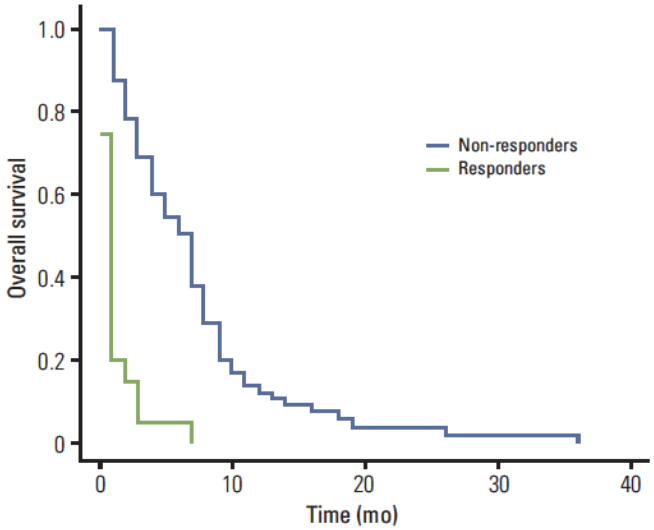
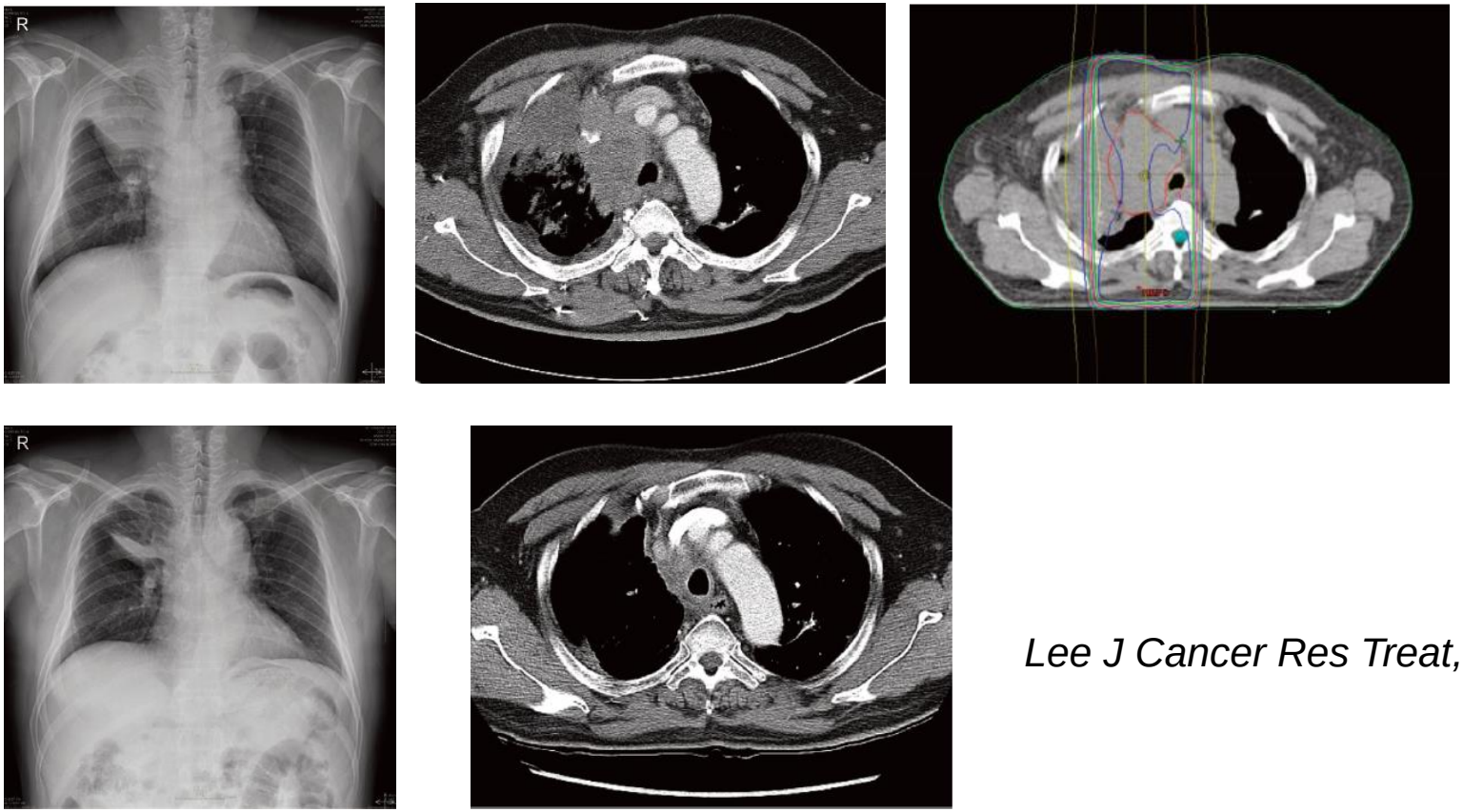


Fig. 2. The 1-year survival rate for responders to the irradiation was significantly higher than non-responders (12.5% vs. 0%, p < 0.001).

Lee J. Cancer Res Treat, 2015

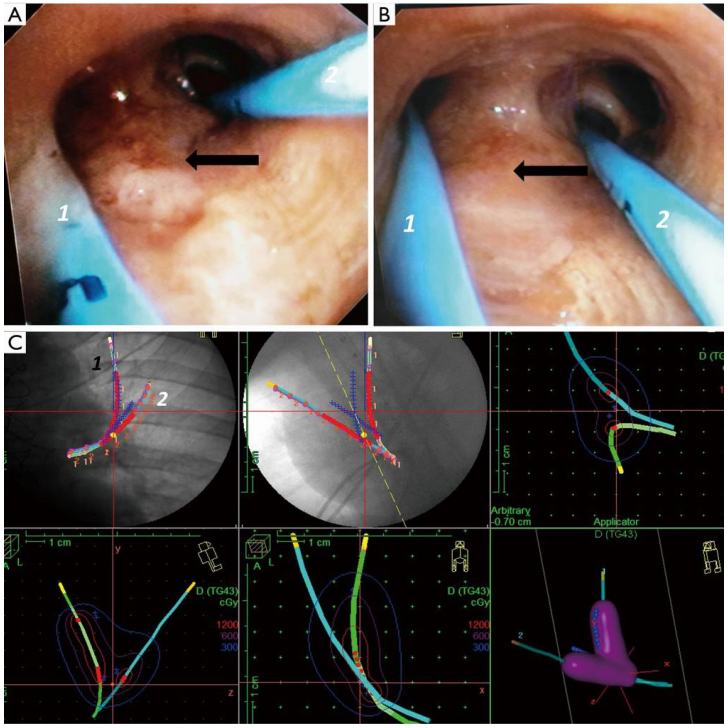
MAO – an example of EBRT



Lee J Cancer Res Treat, 2015

Fig. 3. A patient with small cell carcinoma had obstructive pneumopathy in right upper lobe and received a radiation dose of 30 Gy in 10 fractions. (A) There was an obstructive lesion in right upper lobe at the initial chest X-ray and computed tomography (CT). (B) Radiation-dose distributions in axial and coronal planning CT image. (C) Follow-up chest X-ray and CT showed an improvement of obstruction in right upper lobe 7 days after external beam radiotherapy.

MAO – an example of BRT



Guibert N JDT 2016

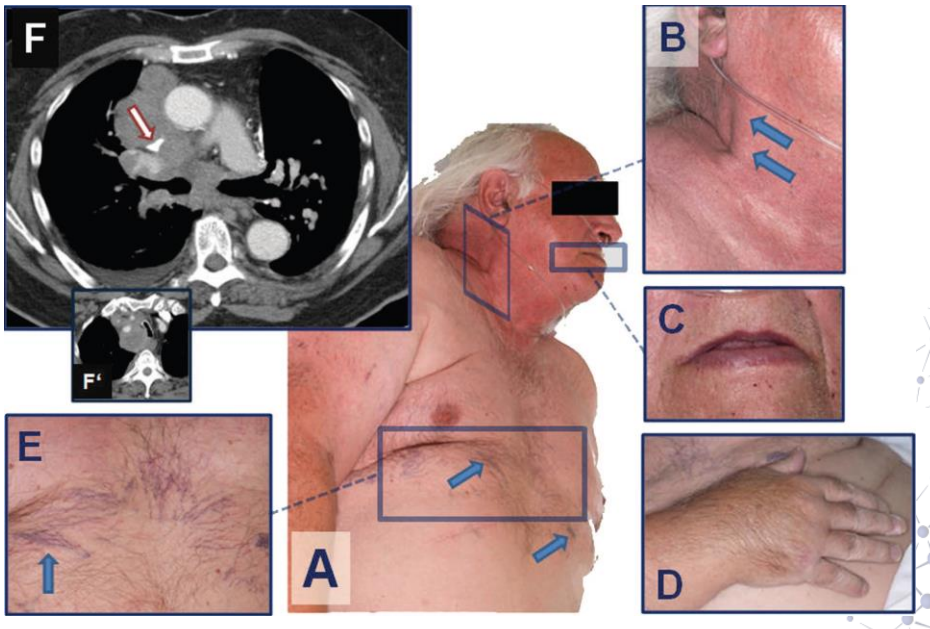
Example of brachytherapy for an endobronchial infiltration of the upper left lobe.

Bronchoscopic view of the two catheters showing local improvement.

(A) before
(B) after the three first fractions (6 Gy)
(C) planning of dose distribution from radiographic images

Superior Vena Cava Syndrome - SVCS

- Obstruction of SVC, reduction of blood flow and increased blood pressure in proximal vessels
- Signs:
  - Dyspnea
  - Edema of face, neck chest, upper extremities
  - cyanosis
  - Stridor, headeache (2-10%)
  - Visible collateral blood flow network in the chest wall
  - Sympoms are worse in horizontal position



Lepper M. Resp Care 2011

SVCS

- Lung cancer (2-4% all, SCLC -10%), lymphadenopaty, other
- First described by William Hunter in 1757
- Management depends on severity of symptoms and whole strategy of treatment: including diagnosis and staging
- Traditionally – immediate intervention, but be careful- the reason and pathological diagnosis **is** important!
- RT can affect biopsy results

SVCS - Scoring system

Clinical signs (Lacout et al. 2012; Kishi et al. 1993)	Weighting
Neurological signs	
Awareness disorders or coma	4
Visual disorders, headache, vertigo or memory disorders	3
Mental disorders	2
Malaise	1
Thoracic or pharyngeal-laryngeal signs	
Orthopnea or laryngeal edema	3
Stridor, dysphagia or dyspnea	2
Coughing or pleurisy	1
Facial signs	
Lip edema, nasal obstruction or epistaxis	2
Facial edema	1
Vessel dilation	
Neck, face or arms	1

Presence of any of the symptoms in the left column give the points indicated in the right column. The total points are added to together. A score of 4 or higher indicates a need for percutaneous stent placement

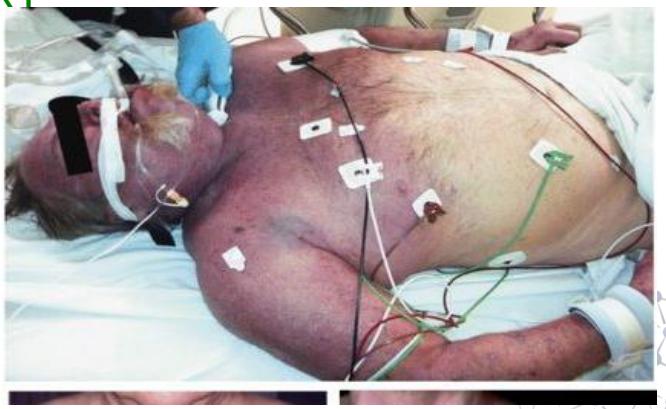
SVCS treatment recommendations I

- Asses life threatening symptoms:
  cerebral or laryngeal oedema (5%),
  tracheal obstruction and
  pericardial effusion
  (Yu 2008 Thorac Oncol, Soufe Intervent Radiol, 2013)

  - If yes: endovascular stenting (optimal, fast relief), or immediate RT or CHT

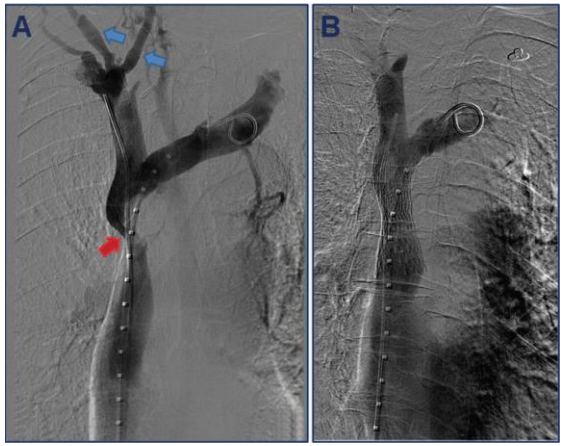
  - If less severe: histology first, staging , MDT.
    - SCLC, DLBCL – CHT **and** RT
    - NSCLC and other – stenting **and** RT

- RT vs CHT similar response rate
  - For SCLC 76,9% vs 77.6%
  - For NSCLC 59% vs 63%

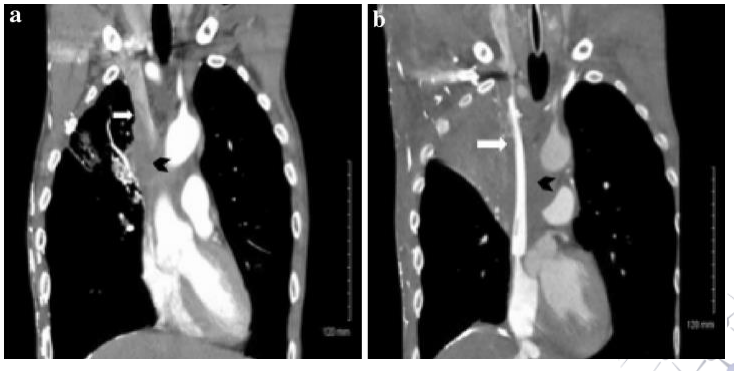


SVCS treatment recomendations II

- Stenting of SVCS – final diagnosis not necessary, but needs **techical expertise**
- No studies on: use of steroids alone. Helpful in first days of RT
- **Immediate RT**: *(Soufe, Intervent Radiol, 2013, Taguchi Cancer Chemoter 2011)*
  - Brain edema
  - Laryngeal edema
  - Tracheal obstruction
  - Pericardial efusion



Lepper M. Resp Care 2011



Straka C Springer Plus 2016

Radiotherapy for SVCS I

- **RT schedules**: fractions 3-4 Gy.
- SVCS in lung cancers is **dose dependent**, dose should be above 20Gy!
  - 10 x 3 Gy,
  - 5 x 4 Gy,

- Improvement ~ 72h

- Symptoms - 77% response but only 11% of full recanalisation and 24%-partial in imaging

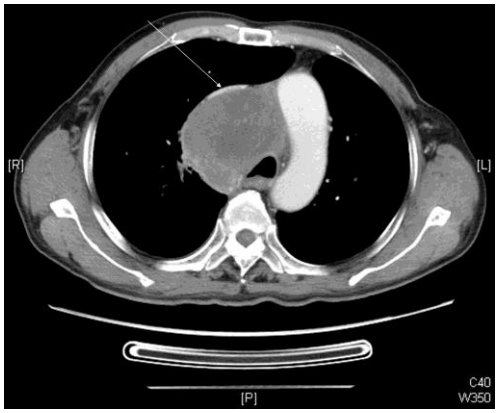
- Why such discrepancy?
  - RT decrease tumor size what allows for better collateral circulation

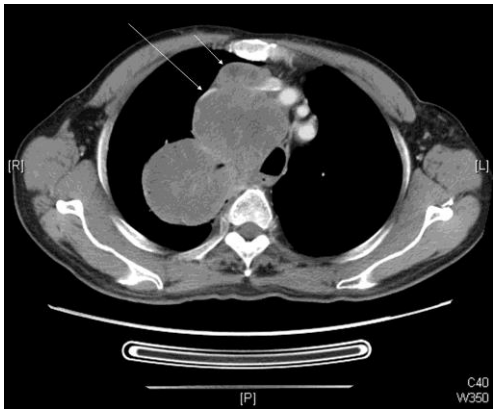
  (Wilson NEJM 2007)

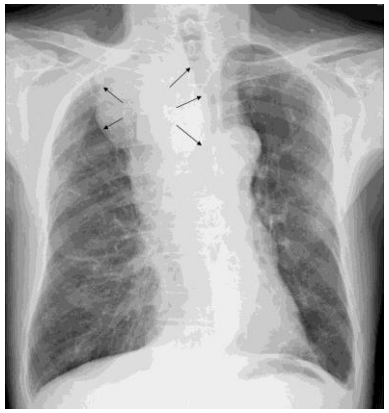
Radiotherapy for SVCS II

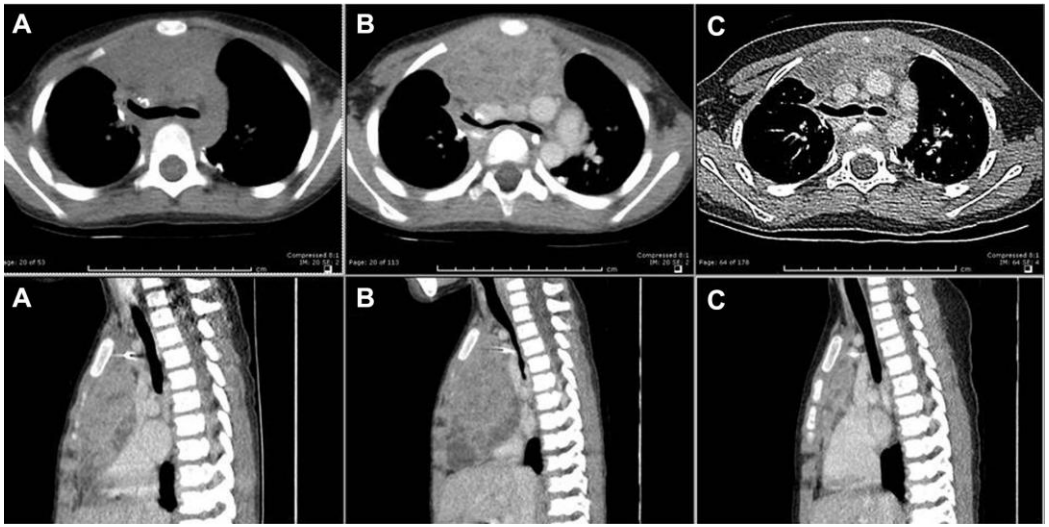
- SBRT – promising but so far no proven benefit, for highly selected patients in better condition *(Mc Kenzie Rep Pract Radiot Oncol 2013)*
- Always think about the future of patient and doses – some patients may be further treated with RT!
- BT- HDR, following stenting or as a salvage after EBRT for intraluminal recurrence
- Addition endobronchial BT to EBRT – no benefit
- Concurrent chemotherapy – no added benefit

SVCS two examples





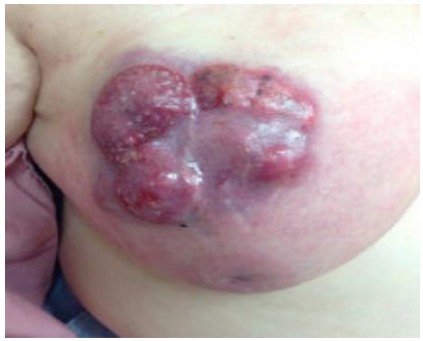


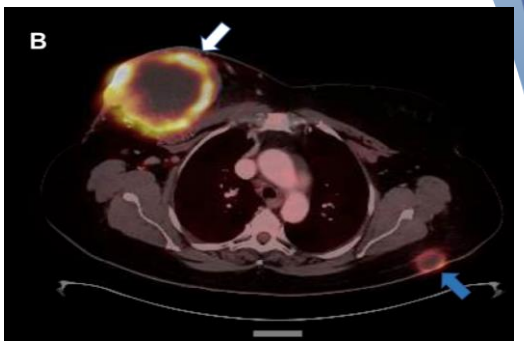


Rvigema C Advances in Radiation Oncology 2017

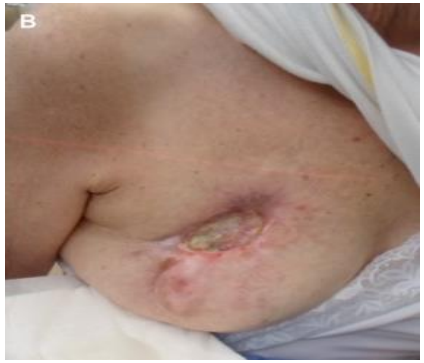
Breast – palliative treatment

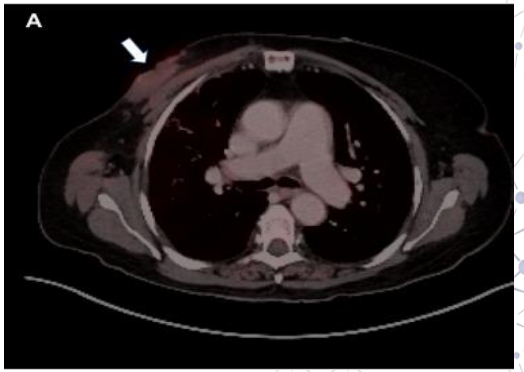
- Locally advanced cancer (LABC) symptoms: pain, ulceration, infection, bleeding, brachial plexopathy
- Very important: decision should be made in MDT,
  no single best solution for everyone
- Palliative RT effective not only in LABC, also in recurrences, metastases





Before treatment



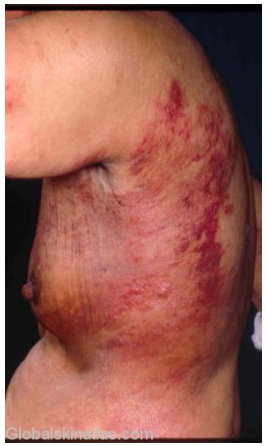


4 months after treatment

Gao R, Cureus 2017

Breast – palliative radiotherapy

- LABC – rarely RT alone, if yes 27-35% long term respons.
- Doses in palliative LABC – 50-60 Gy
- Bleeding – 8-20 Gy in 2-5 fractions
- Ulceration, infection, malodor – 20-30 Gy in 5-10 fractions
- Whole chest recurrence „brestplate pattern ”- photons or electrons, tangential fields.
- Lymph nodes - supraclavicular 71% subjective respons after RT



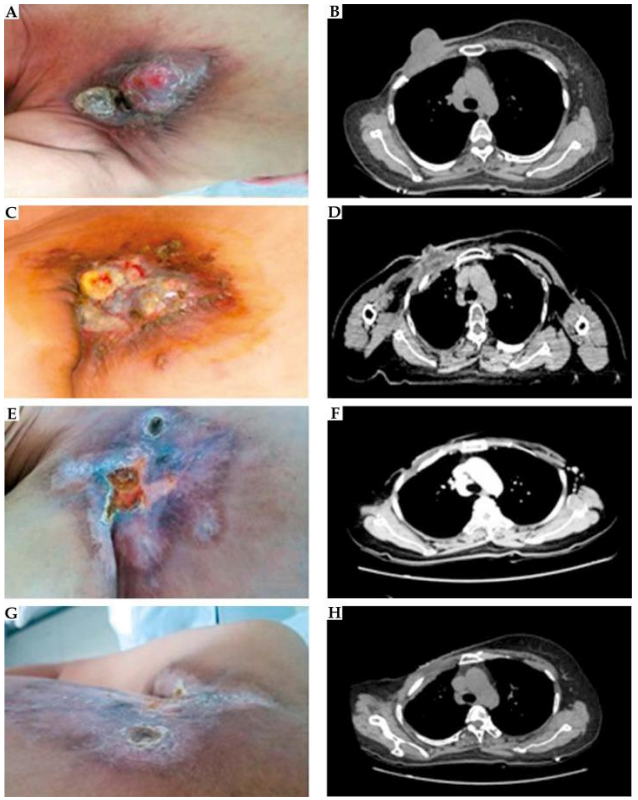
globalskinatlas.com

Breast re-irradiaton

- Role unclear – individual decisions in reurrence in skin, ribs, subcutaneous tissue, limiting factor: doses for lungs and heart

- EBRT : Combined dose to 100 Gy for local control *(Wurschmidt F Radiat Oncol 2008, Harkenrider M Clin Breast Cancer 2011)*
- BT: *(Harms W IJROBP 2001)*

- Hypertermia enhaces effect of RT 41 vs 59% of CR *(Koulalais V, Clin Cance Res 2002)*



Before and 7 mts after BT: 5 x 6 Gy

Wu N, JCB 2015

Outline

- ✓ Symptoms: Dyspnea, Bleeding
- ✓ Thorax: Airway obstruction,SVCS, breast
- ✓ Abdomen: Upper GI, liver
- Pelvis: bladder cancer
- Head and neck

Upper GI malignacies

- 50% patients presents in advanced stage
- Symptoms: dysphagia, bleeding, obstruction, nausea, malnutrition and pain

Gastric cancer

- Bleeding from gastric cancer = melena, hematemesis causing anemia
- RT alone 1 x 8 Gy or 5 x 4 Gy, improvements in 50-73% of patients: increase Hb, decrease number of transfusions *(Chaw C ecancer, 2014)*
- The pooled overall response rates for bleeding, pain and obstruction symptoms were 74%, 67% and 68% *(meta-analysis Tey J,Ocotarget 2017)*

Radiotherapy in gastric bleeding

- There was no difference in response rate of bleeding between regimens with high BED of ≥ 39Gy versus regimens with low BED < 39Gy
- Thus, low dose regiments 1 x 8Gy, 5 x 4Gy, 10 x 3Gy, 3 x 6Gy most beneficial and repeatable *(Kawabata, H, J Palliat Med 2017)*
- Conflicting results: *(Lee Y, BMC Cancer 2017)*, BED10 >36Gy most significant factor for EBRT response for gastric bleeding
- Grade 3 to 4 toxicities occurred in up to 15% of patients when treated with RT alone and up to 25% of patients treated with chemoradiotherapy: gastritis, anorexia, neutropenia
- Health-related quality of life (HRQL) outcomes **were not reported**

Gastric bleeding RT OS – responders vs non - responders

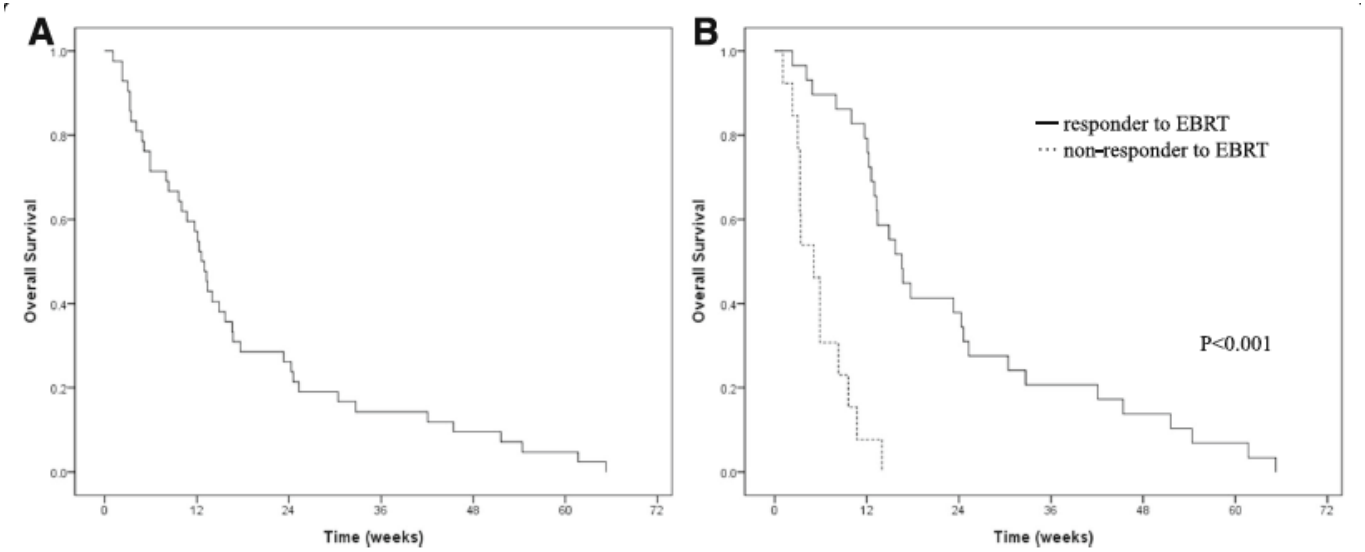
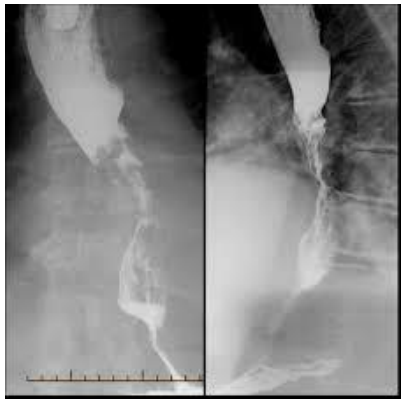


Fig. 1 Overall survival of all patients (**a**) and based on the response to radiotherapy (**b**)

Lee Y, BMC Cancer 2017

Dysphagia in esophageal cancer - treatment

- Dysphagia mostly in esophageal cancer, but also in head and neck cancer
- Risk of cachexia, dehydratation, aspiration pneumonia
- Procedures used:
  - endoscopic dilatation,
  - stenting,
  - PhotoDynamicTherapy,
  - APC laser and
  - Radiotherapy

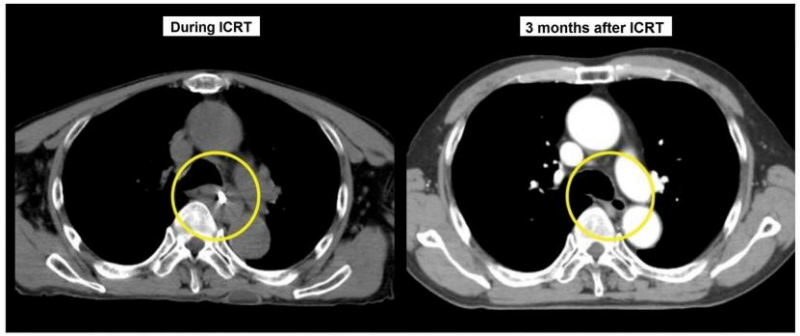


- CONSORT1a,b: best results in recanalisation, days to recurrence dysphagia and QoL for combination of APC and HDR (88 days vs 35 days, p=0.002) *(Rupinski M, Am J Gastroenter 2011)*

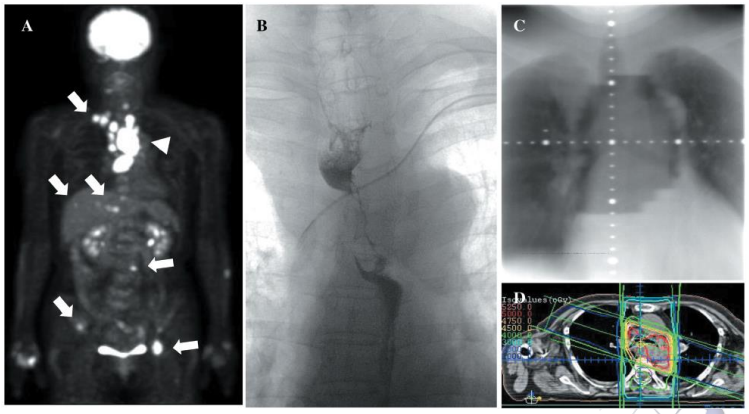
- Respons after RT lasts longer than stenting due to decrease of tumor volume.
- Single fraction BT bettter than stenting alone in long term relief, toxicity and QoL *(Homs M. Lancet 2004 SIREC)*

Dysphagia in esophageal cancer - radiotherapy

- Combination of EBRT 10 x 3 Gy and stenting prove to be better for sustained relief vs stenting alone in randomized study (7 vs 3 months)
- No difference in mortality and OS. *(Javed A, J Gastroin Cancer 2012)*
- Combination HDR 1 x 8 Gy i EBRT 10 x 3 Gy was better in duration of relief all symptoms: dysphagia (p<0.0001), chest pain, odynophagia and PS. Benefit in OS 18% in 200 days *(Rosenblatt E, R&O 2010, Welsch J Journal of Cancer 2016)*



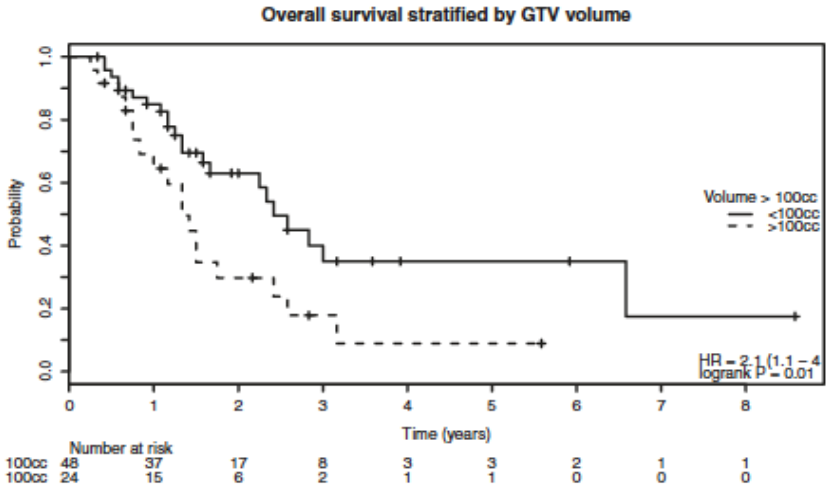
Yamashita M, Oncoclogy Lettres 2015

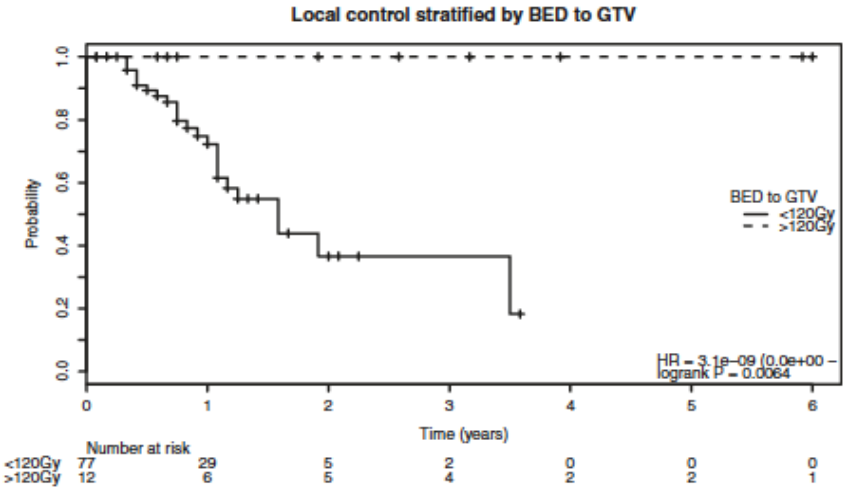


Suzuki G. Anticanc Res 2017

Liver metastases

- From **any site**, but most common: breast, lung, colorectal cancer
- **Symptoms**: pain, nausea, vomiting, fever
- **Options:** surgery, ablations (chemo-, radiofrequency RFA, radioembolization, SIRT: Y-90-SIRFLOX,
- **RT-SBRT:** 1-3 lesions, < 6cm, 60 Gy in 5 fraction,
  small lesion <3 cm - 2y control 100%, OS depends on histology fav vs unfav. *(Rusthoven K, JCO 2009)*

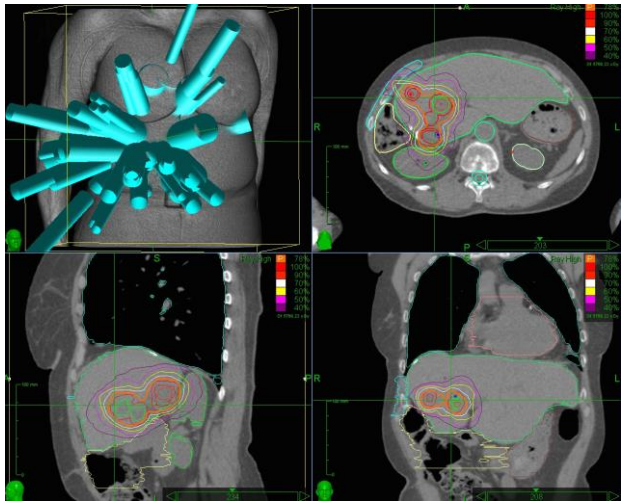




Andratschke N, Radiation Oncol 2015

Example of liver metastases SBRT

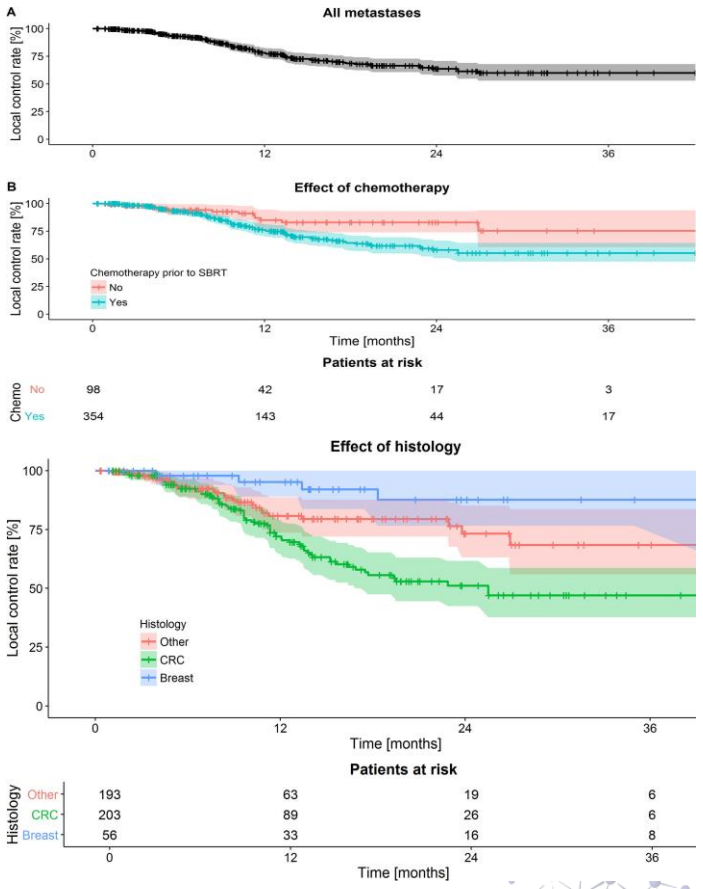
CK treatment 4 liver metastases
Courtesy
A. Skrobala, WCO



- Progress in technology allows for better targeting, better management tumor motions, high dose gradient
- Whole spectrum of lesions including metastases not accesible for surgery
- SABR for oligometastatic comparable to surgery, 5yOS 49 vs 41% (p=0.43)
- No added mortality: grade 3 toxic effects often reported in 1-10% of patients

Liver SBRT- modeling of response

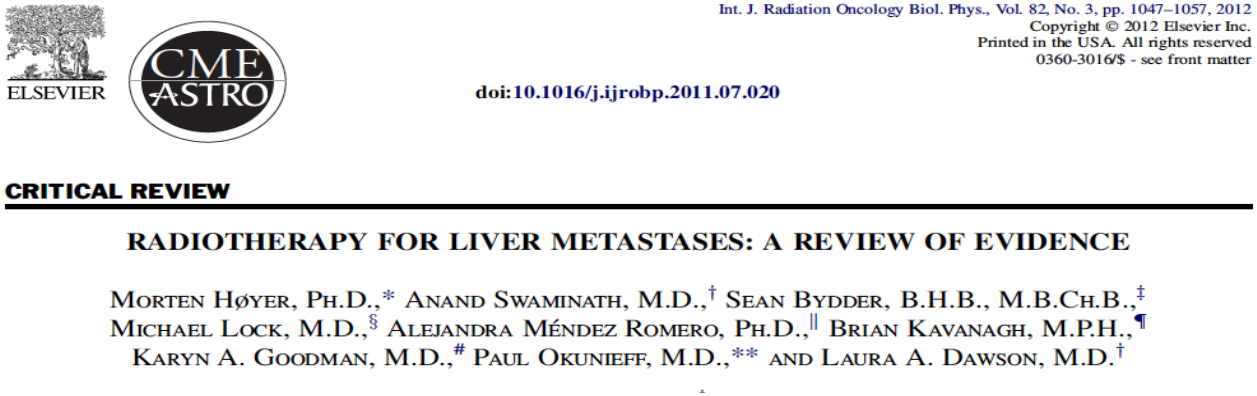
- TCP modeling for alfa/beta of 10Gy (BED max)
- 90% TCP at 2 y needs BED 209 Gy_{10} for patients never treated with chemo and inreases to 286 Gy_{10} after chemo.
- Larger PTV(>70.4 cc) and simple motion managemnet predicted signifantly lower TCP
- Favourable histology: breast cancer: 157 Gy_{10} with prior chemo or 80 Gy_{10} without chemo
- SBRT for liver metastases yields a strong dose–response relationship that is modified by factors such as chemotherapy and metastases histology.*(Klement RJ, R&O 2017)*



Klement RJ, R&O 2017

Liver SBRT guidelines and toxicity

- Generally, doses 30-60 Gy in 1-6 fraction, tumor size about 6 cm, not more than 5 mets
- RILD –rare, transient elevation liver ezymes
- No more than 700 cc uninvolved liver received 15 Gy in 3 fraction (QUANTEC) *(Pan CC IJROBP 2010)*
- Rib fracture, subcutaneous tissue damage, duodenal ulceration –very rare



Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 3, pp. 1047–1057, 2012

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2011.07.020

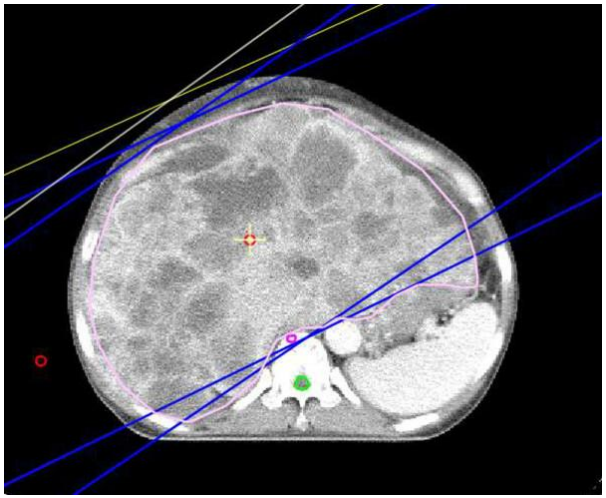
CRITICAL REVIEW

RADIOTHERAPY FOR LIVER METASTASES: A REVIEW OF EVIDENCE

Morten Høyer, Ph.D.,* Anand Swaminath, M.D.,† Sean Bydder, B.H.B., M.B.Ch.B.,‡ Michael Lock, M.D.,§ Alejandra Méndez Romero, Ph.D.,‖ Brian Kavanagh, M.P.H.,¶ Karyn A. Goodman, M.D.,# Paul Okunieff, M.D.,** and Laura A. Dawson, M.D.†

Whole Liver Irradiation (WLI)

- EBRT- for pain from infiltration of capsule
- Relief in pain 60-90%, other symptoms: anorexia, fever, sweating- about 20-30%
- Low doses 21-30 Gy in 7-19 fractions 1,5 -3 Gy or 1 x 8Gy
- Improvement of PS -25%
- Survival advantage – unclear
- No evidence for better results in combination with chemotherapy or readiosensitizers *(see review M.Hoyer IJROBP 2012)*



Yeo SG Radiation Oncol 2010

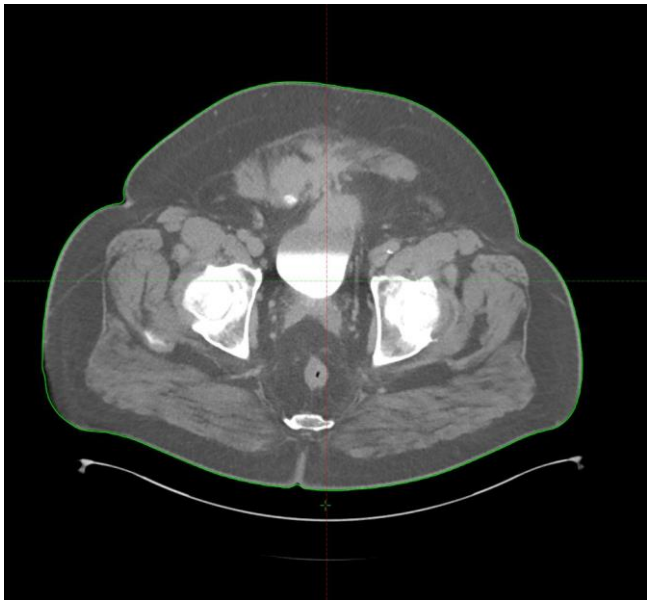
Outline

- ✓ Symptoms: Dyspnea, Bleeding
- ✓ Thorax: Airway obstruction,SVCS, breast
- ✓ Abdomen: Upper GI, liver
- ✓ Pelvis: bladder cancer
- Head and neck

Bladder cancer – role of palliative RT

- Symptoms: hematuria, pelvic pain, dysuria

- Example of palliative schedules:
  - 5 x 4 Gy,
  - 10 x 3 Gy,
  - 6 x 5.75 Gy to a total dose of 34.5 Gy in six fraction given once a week
    (*Dirix P Support Care Cancer 2016)*
  - 35 Gy in 10 fractions over two weeks versus 21 Gy in 3 fractions over one week *(MRC BA09, Duchesne IJROBP 2000)*



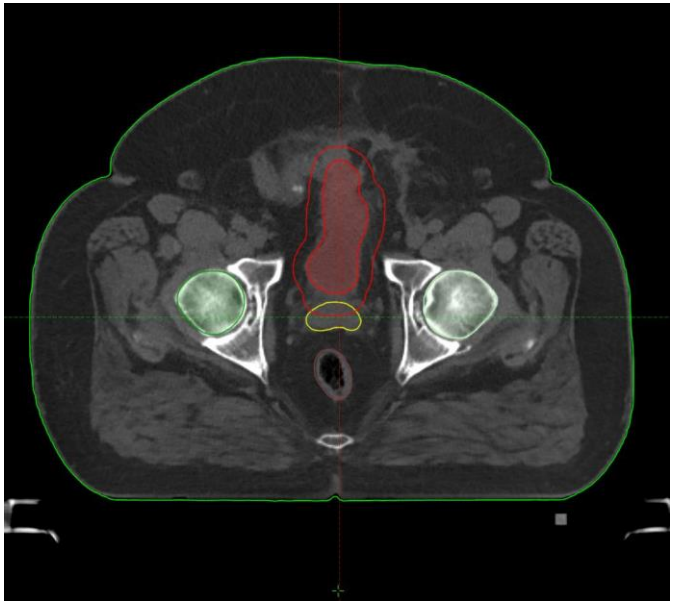
Bladder cancer – role of palliative RT

- 58 - 91% of response (hematuria), 47% (dysuria)

  No significant difference between schedules

- Mean hematuria - free survival of 10-13 months. Severe (≥ grade 3) acute and late urinary toxicity was observed in 9 and 19% of patients, respectively.

  (*Dirix P Support Care Cancer 2016)*

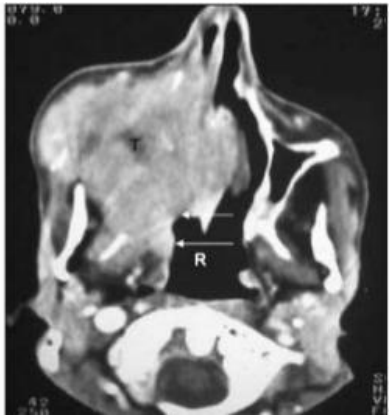


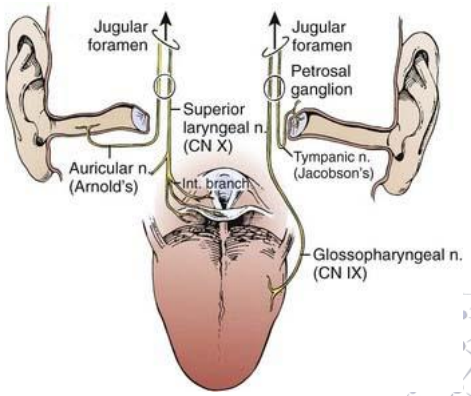
Outline

- ✓ Symptoms: Dyspnea, Bleeding
- ✓ Thorax: Airway obstruction,SVCS, breast
- ✓ Abdomen: Upper GI, liver
- ✓ Pelvis: bladder cancer
- ✓ Head and neck

Head and neck

- Different types of symptoms:
  - Pain: somatic, neuropatic
  - otalgia from infiltration of clivus
  - bleeding, ulceration, direct infiltration of vessel wall, exposure of extratumoral vessel
  - airway obstruction
  - speech and swallowing difficulties
  - aspiration, cough





Before start of palliative RT, let's look at the patient

- Tracheotomy
- Feeding tube
- PEG
- Nutrition and hydratation
- Pain management
- Smoking cesation
- Treating of infections
- Local management of ulceration
- Charlson comorbidity index

Mercurynews.com

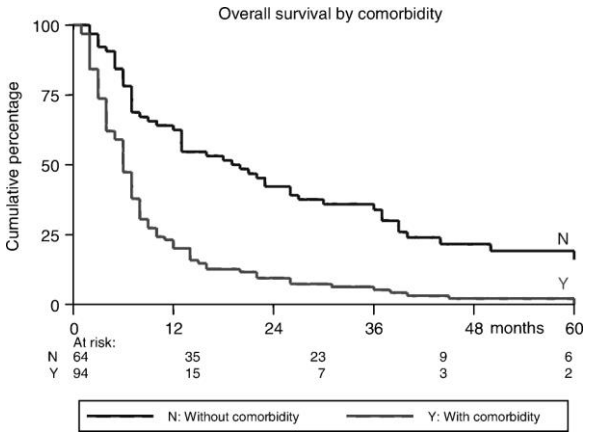
Classic palliative schedules

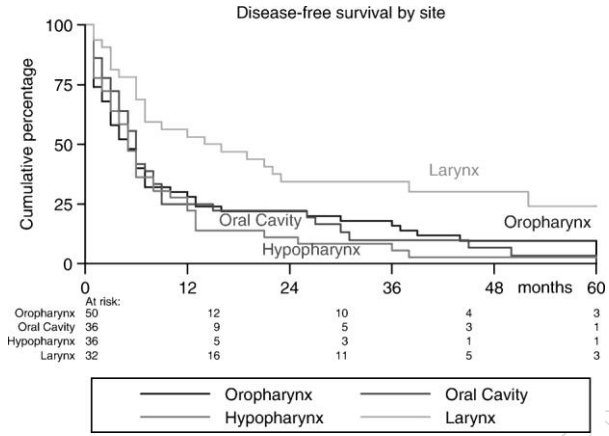
- No difference in results between conventional and hypofractionated schedules *(Porccedu S R&O 2007, Cory J R&O 2006)*

- Schedules:
- 5 x 4 Gy
- 10 x 3 Gy
- 16 x 3 Gy
- Split course: 2 x 25 Gy in 10 fraction separated by two weeks

- Overall response rate: 73%
- Median survival time was average 17 months

- Acute grade 3 skin and mucosal toxicities were observed in 45% and 65% of patients, respectively. *(Al. Mamgani A, Acta Oncol 2009)*



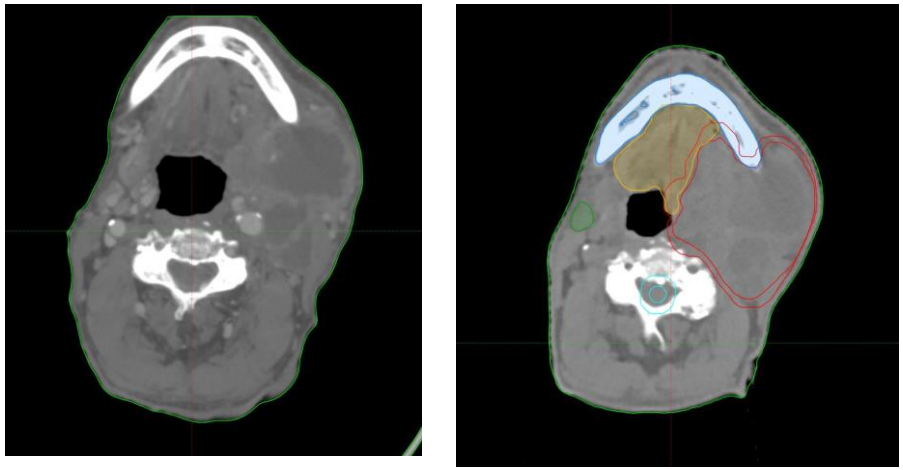


Beyond classic palliative schedules

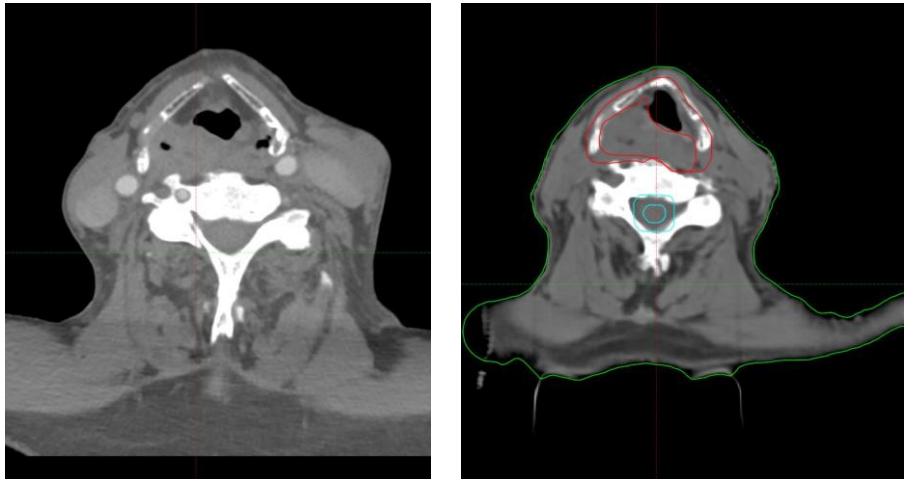
- RTOG 85-02: 3,7Gy twice daily over 2 consecutive days at 2 to 3 week intervals up to a total dose of 44 Gy
- 37% completed three cycles of the regimen.
- 65% palliative response.
- Median OS was 5.67 months *(Lok B. Oral Oncol 2015)*

- „0-7-21”: 3 x 8 Gy day 0,7,21
- 31% complete tumor response
- 40% complete symptoms response
- OS 50% patients survive at least 6 mts
- Tumor volume predictive for OS and PFS, TNM stage for response level. *(Nguyen A BJR 2014)*

Examples of palliation in head and neck cancer



Oropharyngeal cancer
76yo, CCI 7, symptoms:
pain, anemia, malnutrition
due to pain and ulceration



Hypopharyngeal cancer
86yo, CCI 8, symptoms:
pain, hemoptysis

Summary I

- Radiotherapy is an effective method of palliative treatment of symptoms of different cancers.
- There are almost no detailed guidelines (except bone mets) for doses and scheduling, due to often complicated clinical situation of the patient.
- Therefore, treatment choices and decisions are more individual than ever before.
- Generally shorter, hypofractionated courses are recommended as convenient for patient, highly effective and minimally toxic.
- Some symptoms are dose dependent (liver metastases) others –not (gastric cancer)

Summary II

- Radiotherapy is effective in emergencies: SVCS, MAO, bleeding, dyspnea and dysphagia.
- In life threating symptoms – be fast, but careful, detailed physical examination +/- other test are necessary to prepare optimal plan of tretment (*stent first?, transfusion? Is there time for pathology? Immediate RT?)*
- Remember, RT is not a knife – relief takes time (hours to days). Make sure your patient is safe.
- Carefull planning, delineation and consultation are VERY IMPORTANT in palliative treatment, don’t be afraid to use modern technology if necessary! (see SBRT for liver, IGRT for re-irradiation etc.)
- Communicate with your patients in whole process to find the best way of treatment together.

- **Thank you!**

Stereotactic body radiation therapy for oligo-metastases

Morten Høyer
Danish Center for Particle Therapy
Aarhus University Hospital, Denmark

CIRRO AARHUS UNIVERSITET

SBRT in palliation

- SBRT for
  - *Lung, liver, abdominal nodes and adrenal gland*
  - *Vertebral metastases (Spinal SBRT)*
- SBRT for
  - *Colorectal and prostate metastases*

Aim for eradication of oligo-metastases

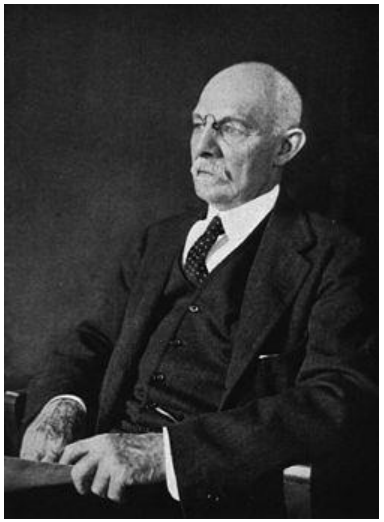
Oligometastases: Reduction of tumor burden to achieve long-term survival

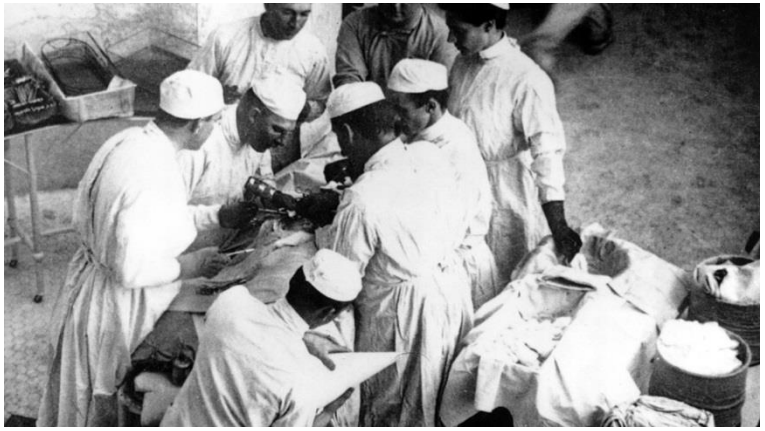
Oligoprogression: Maintaining chemosensitivity

Metastases: Preventing cancer related symptoms

W.S. Halsted at Johns Hopskins 1894

The Halsted theory proposed that cancer spread is orderly, extending in a contiguous fashion from the primary tumor through the lymphatics to the lymph nodes and then to distant sites.





Cancer progression

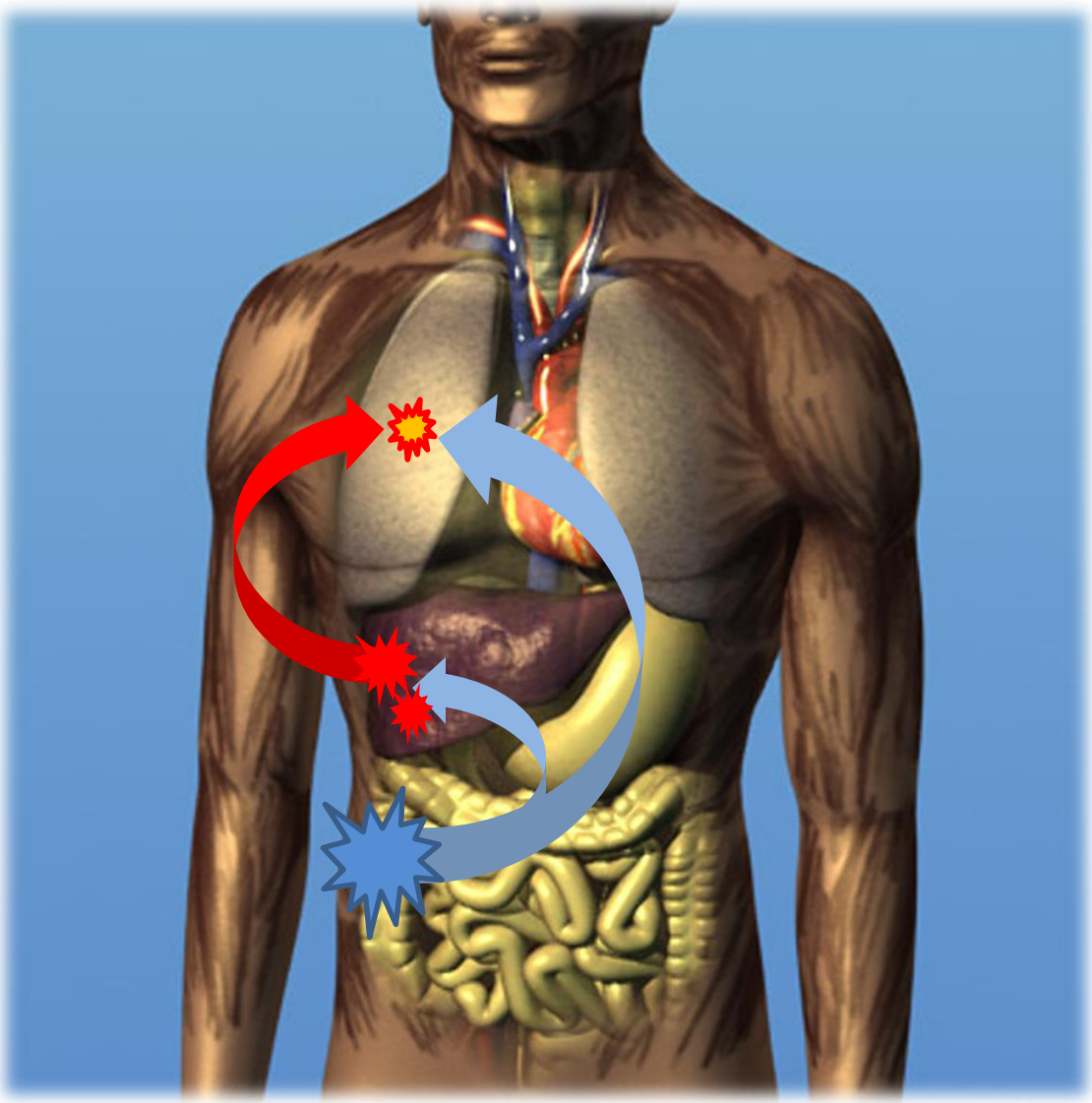
Localized (primary tumor)

Oligometastases (one/few)

Multiple metastases (widespread)

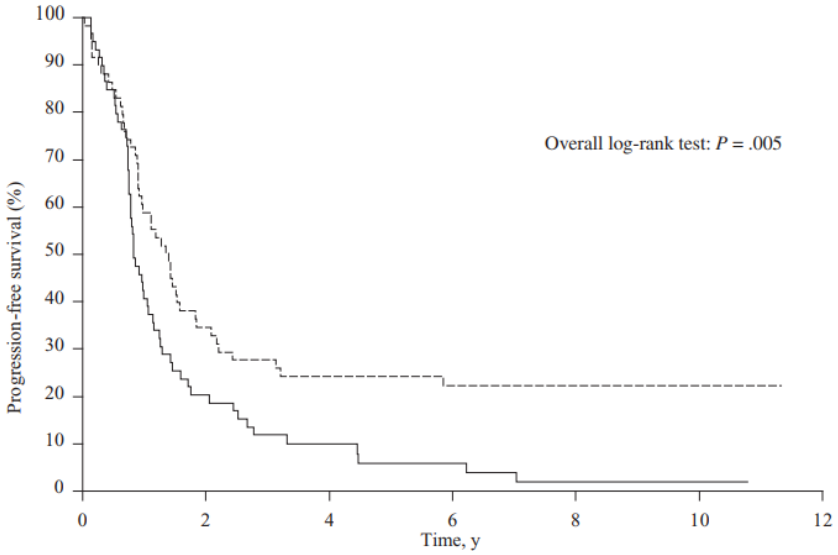
Hellman & Weichselbaum JCO 1995

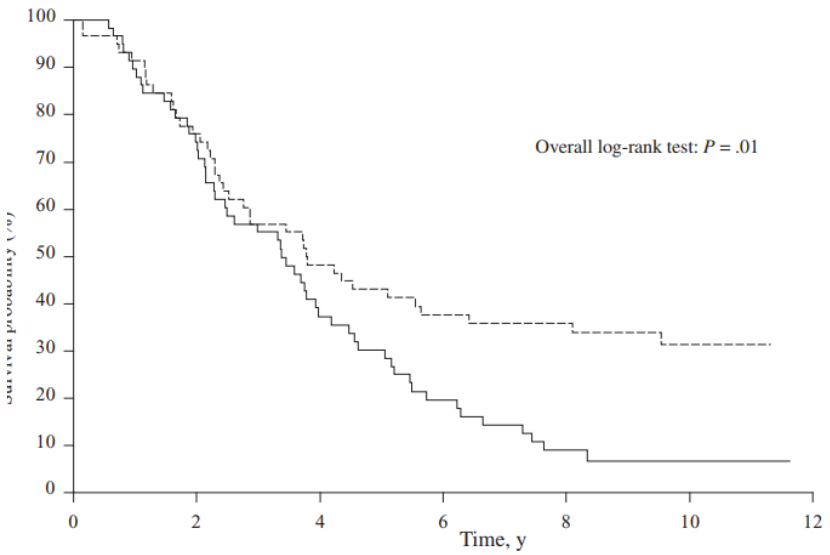
Natural history of metastasis



CLOCC/EORTC 40004

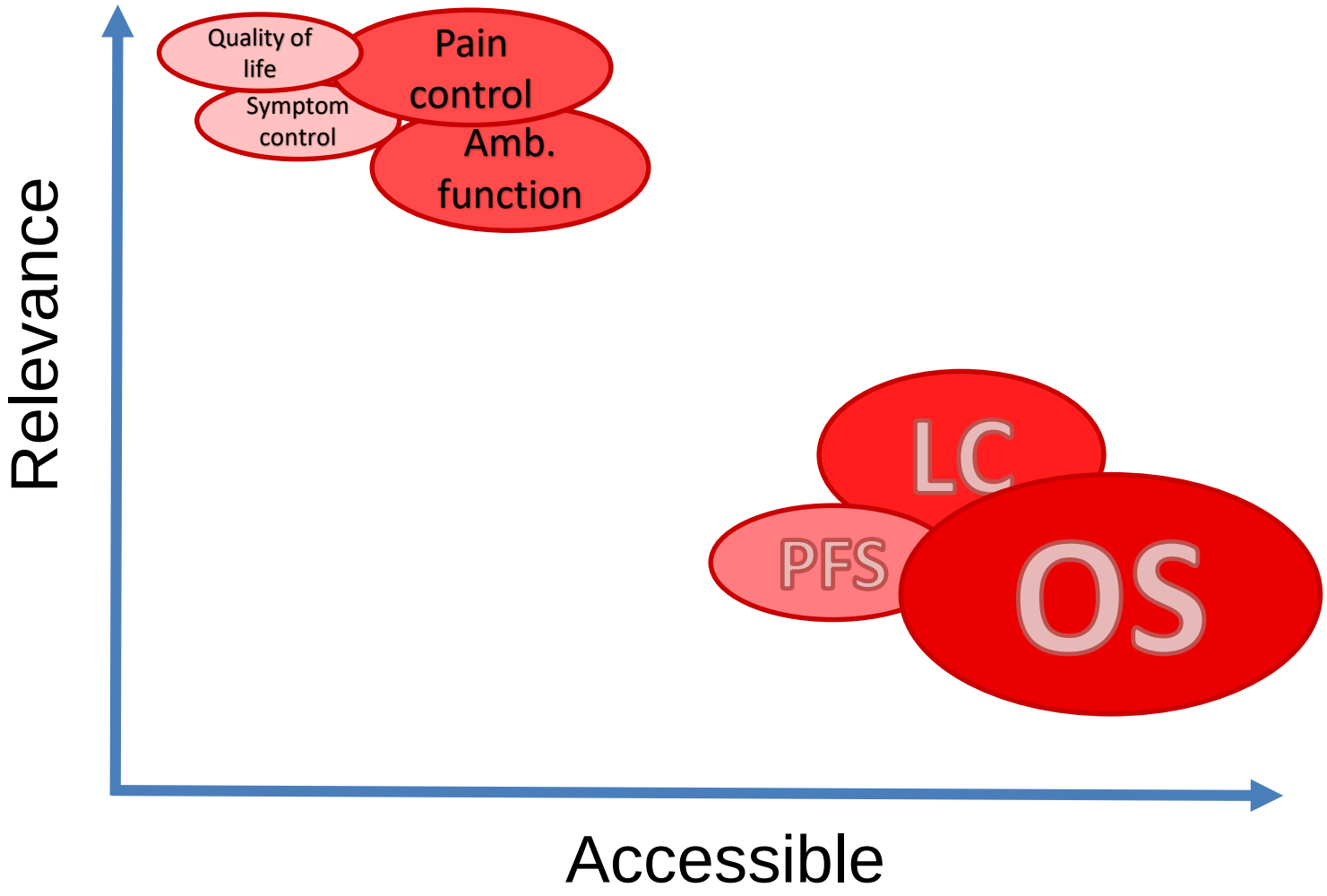
Chemotherapy +/- RFA of 1-10 liver metastases
Phase II (2002); N=119



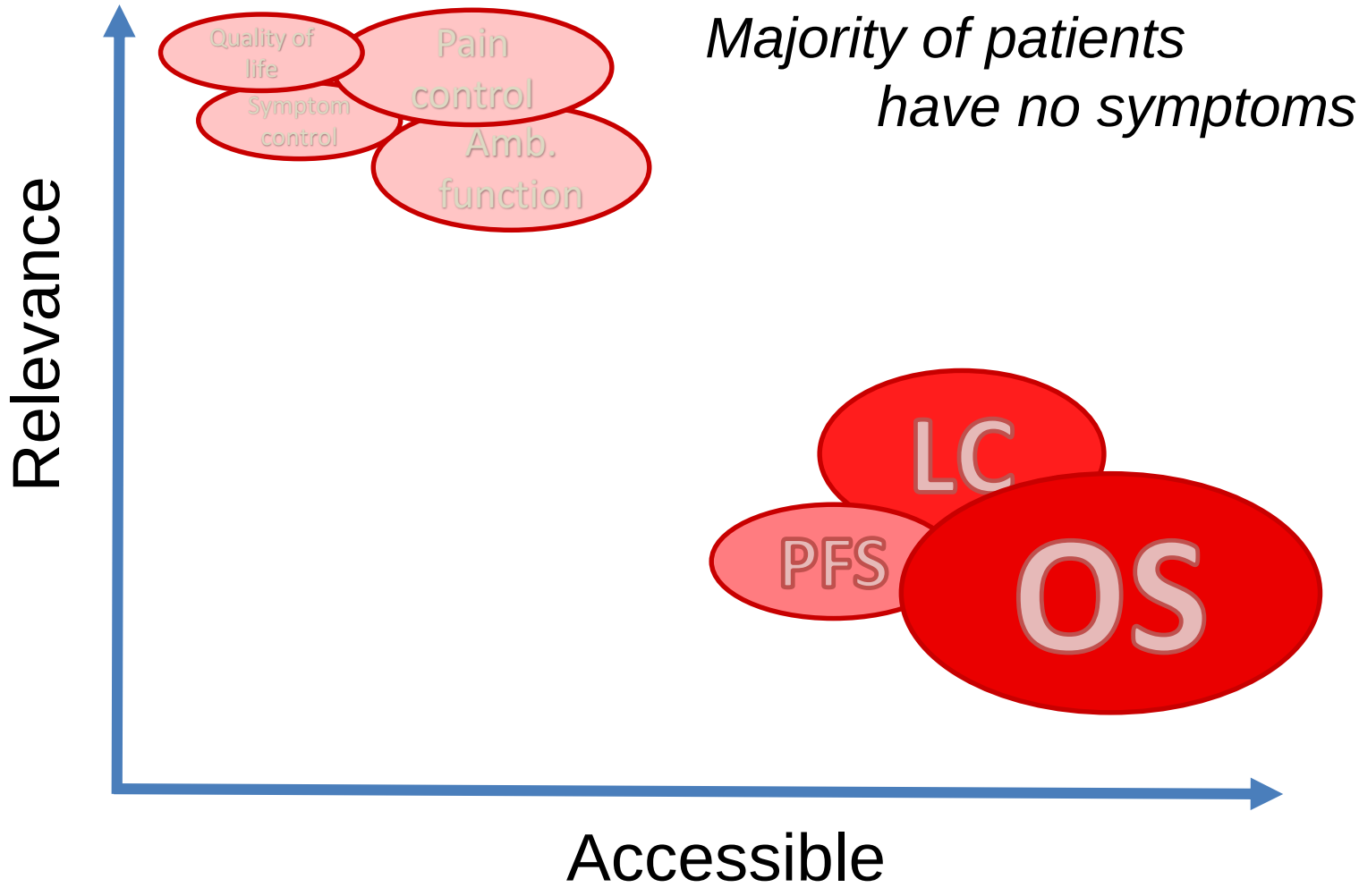


Ruers et al. CI J Natl Cancer Inst (2017) 109(9): djx015

Endpoints in palliative care

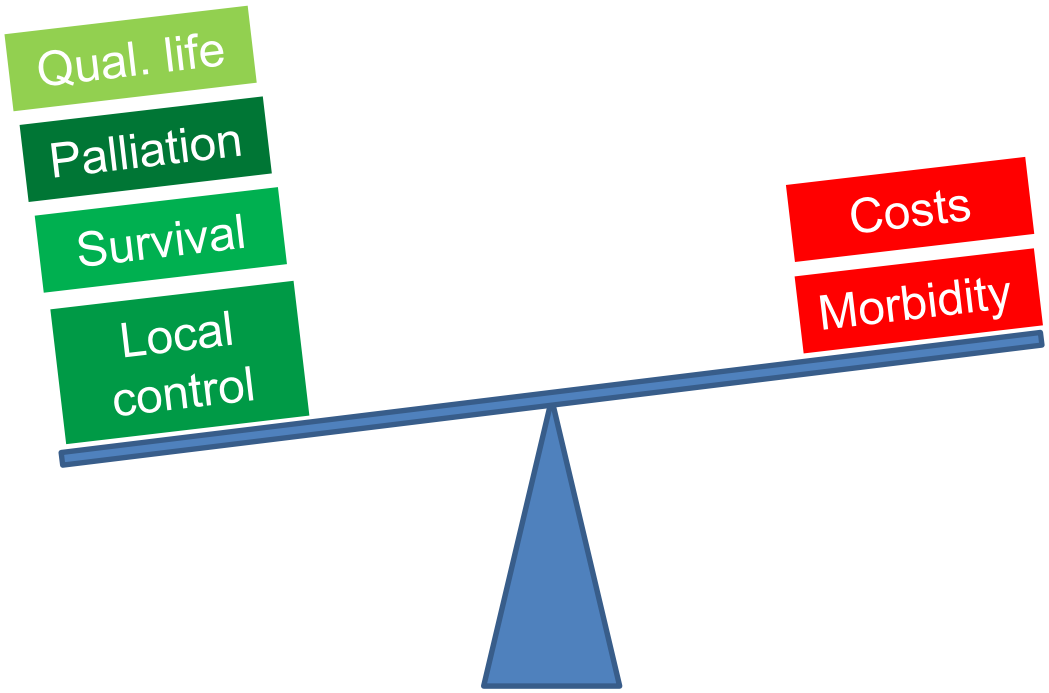


Endpoints in SBRT

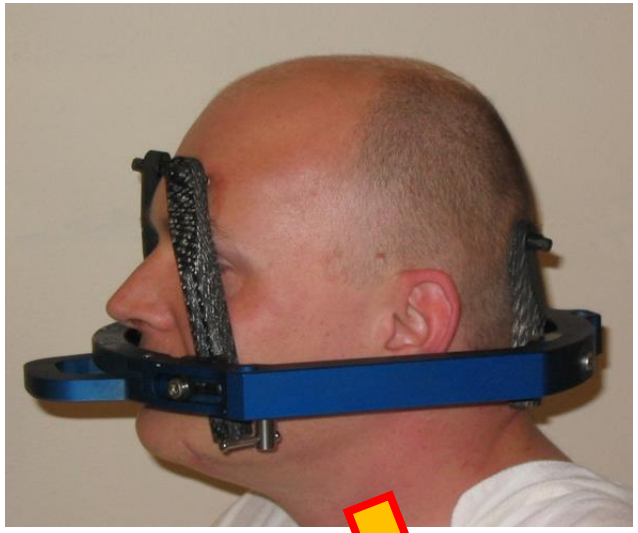


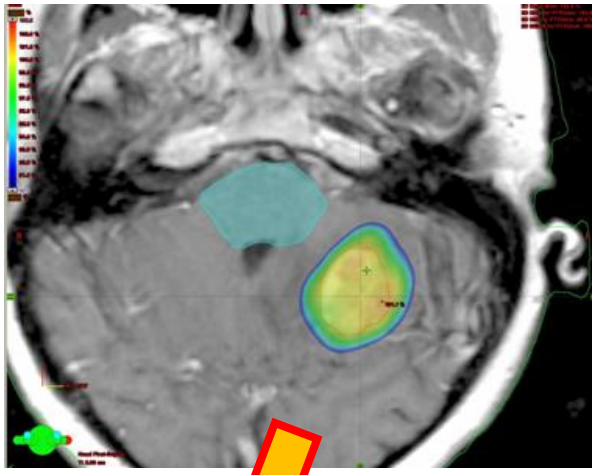
Majority of patients have no symptoms

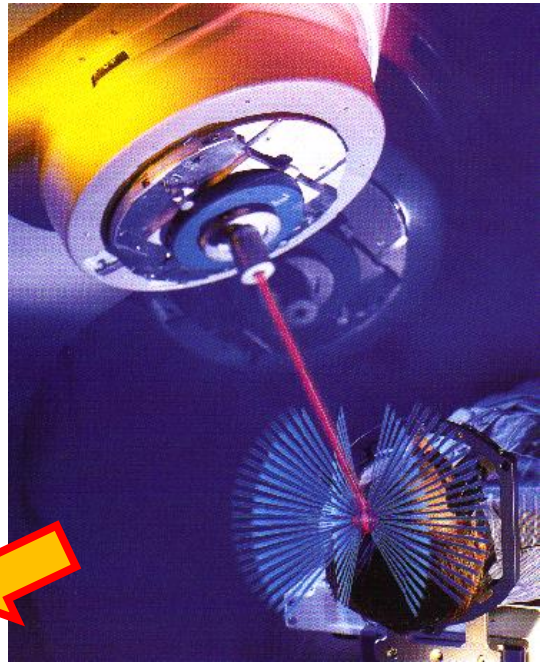
Therapeutic ratio

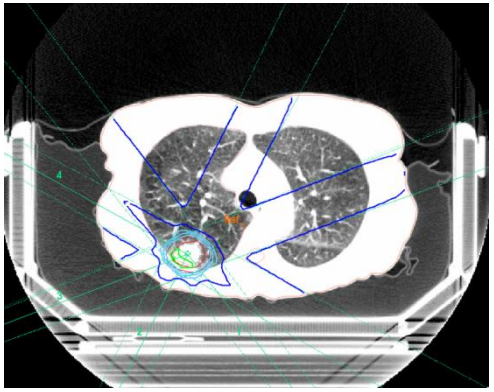


From brain to body

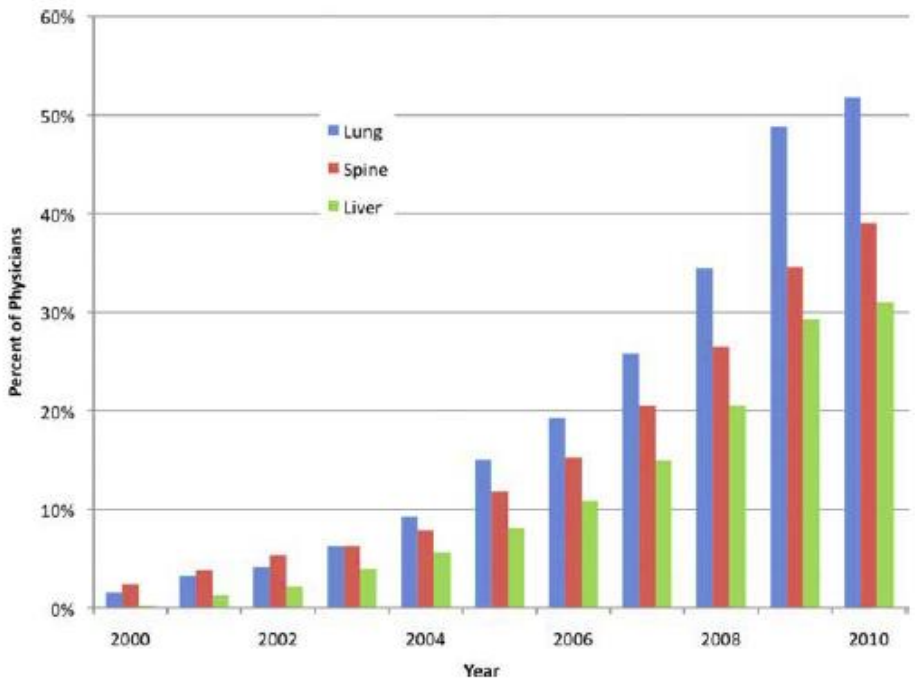






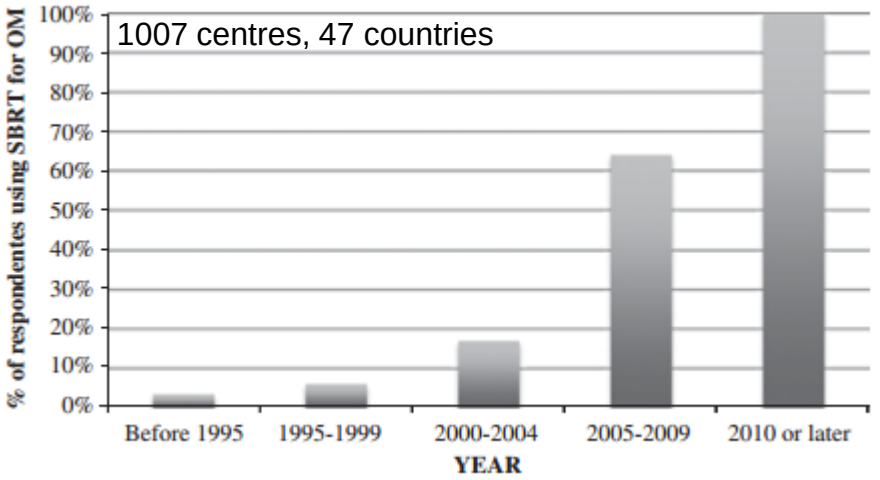


Survey: The use of SBRT



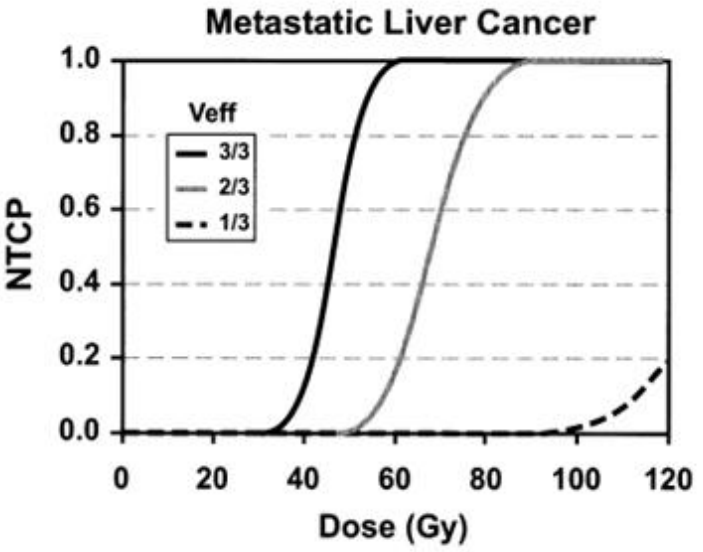
Pan et al. Cancer 117: 4566-72; 2011

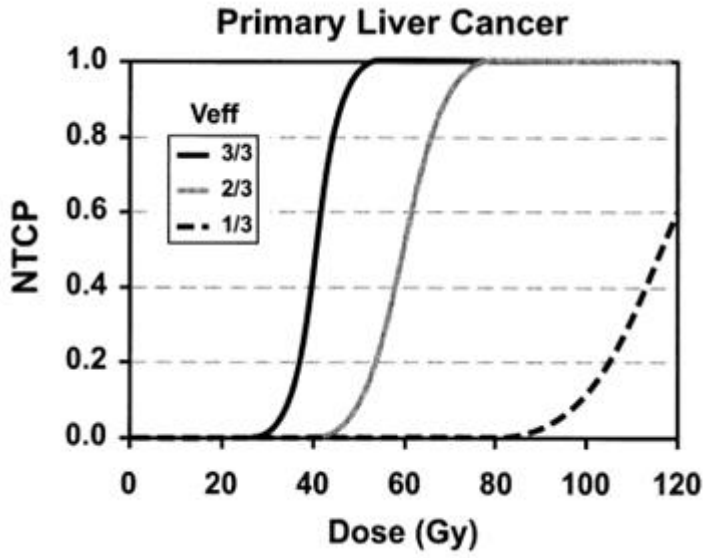
Lung (90%), spine (68%), liver (63%), bones (58%), and adrenals (39%)



Lewis et al. Am J Clin Oncol e-pub; 2015

Challenge I: Risk of morbidity (RILD)



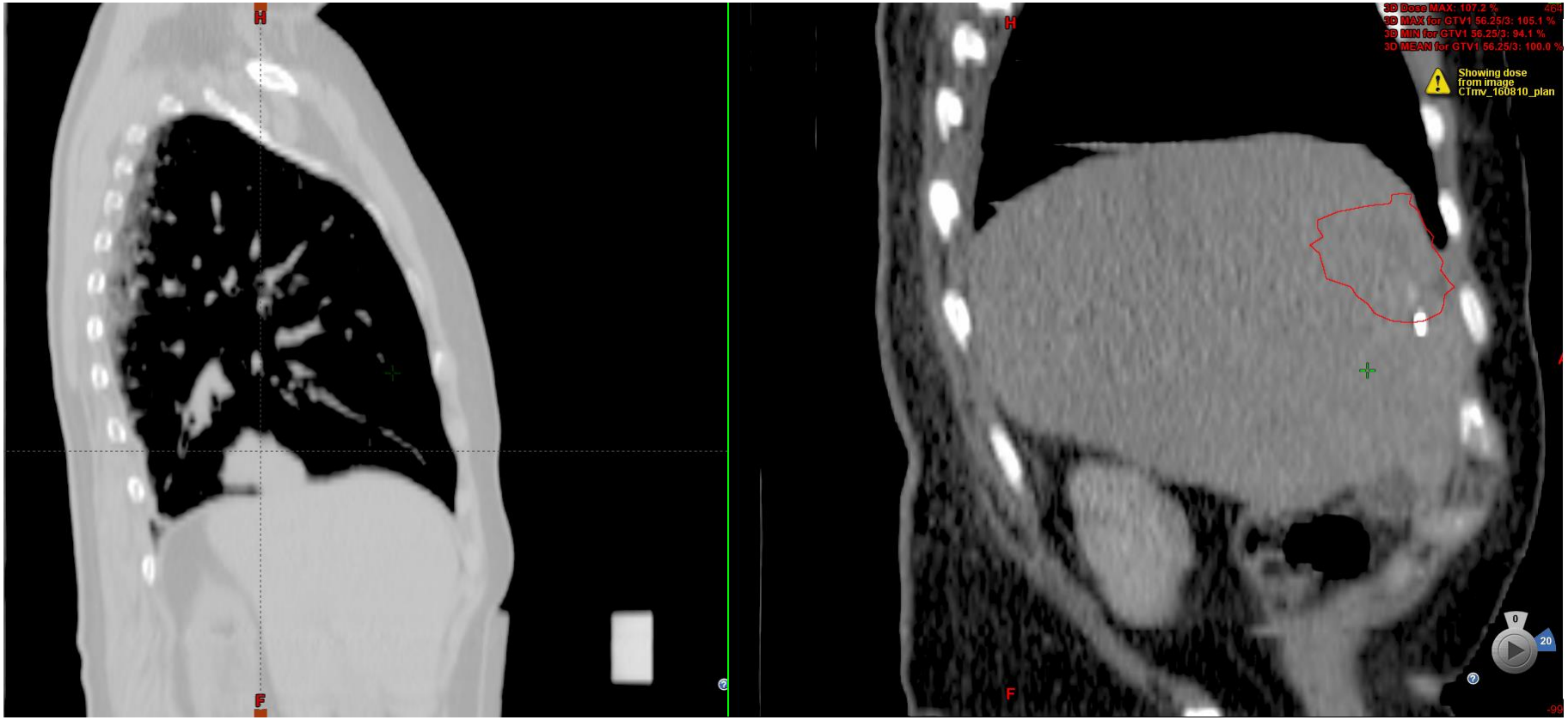


Dawson et al. 2002

Conventional fractionation:

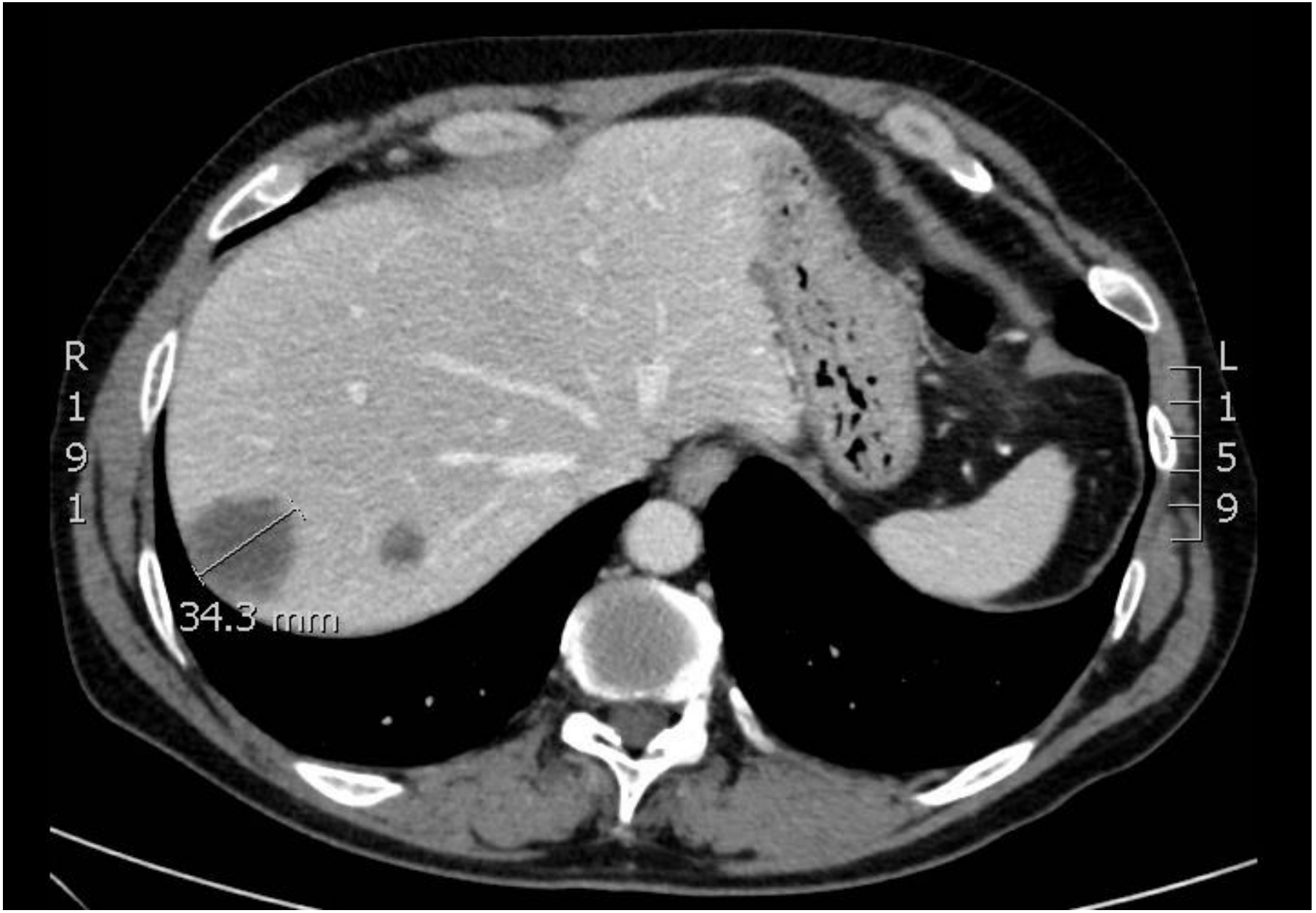
- TD_{50} in metastases patients < 46 Gy
- TD_{50} in primary liver cancer < 40 Gy
  - Dawson et al. IJROBP 53: 810; 2002
- TD_{50} in non-HBV carriers: 50 Gy
- TD_{50} in HBV carriers: 46 Gy
  - Cheng et al. IJROBP 60:1502; 2004

Challenge II: Moving target



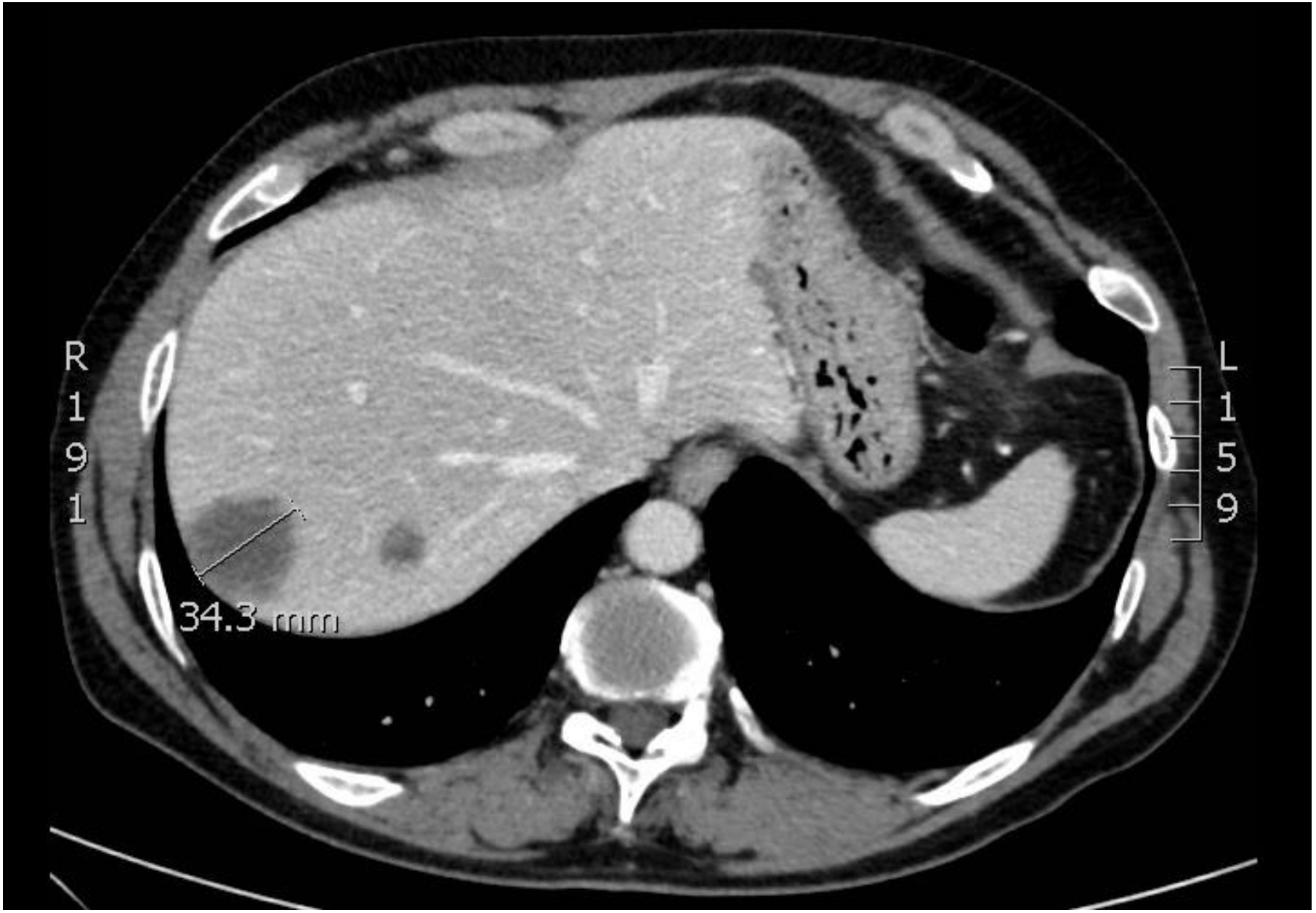
Case: colorectal metastases

- 68 year old man with T4N1M0 rectal cancer
- Chemo-radiation of the rectum nov 2014
- Coronary artery stenosis and angina during chemotherapy
- Liver metastases may 2015


R
1
9
1
34.3 mm
L
1
5
9

Treatment options

- Chemotherapy
- Surgical resection
- Radiofrequency ablation
- SBRT


R
1
9
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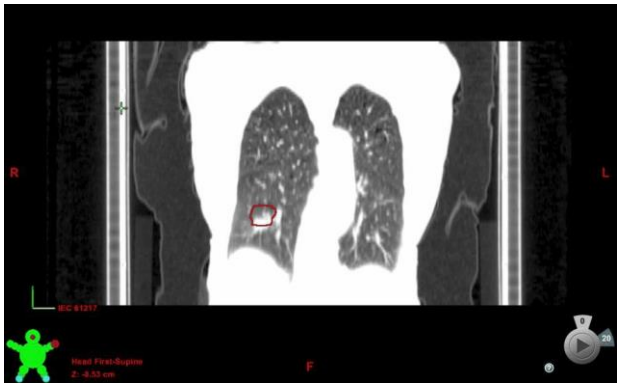
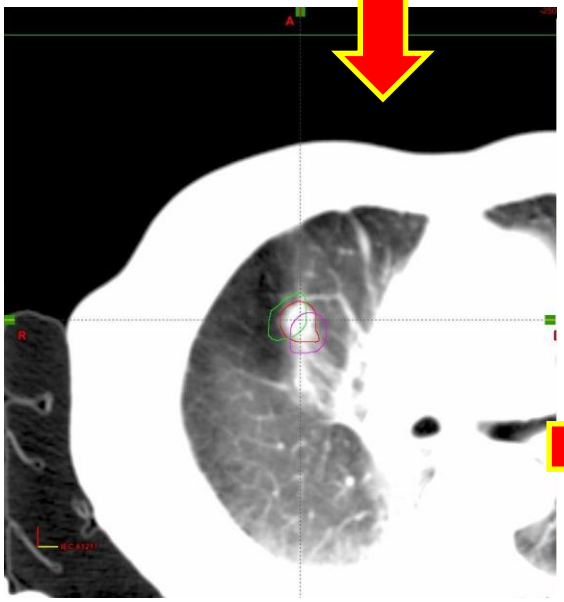
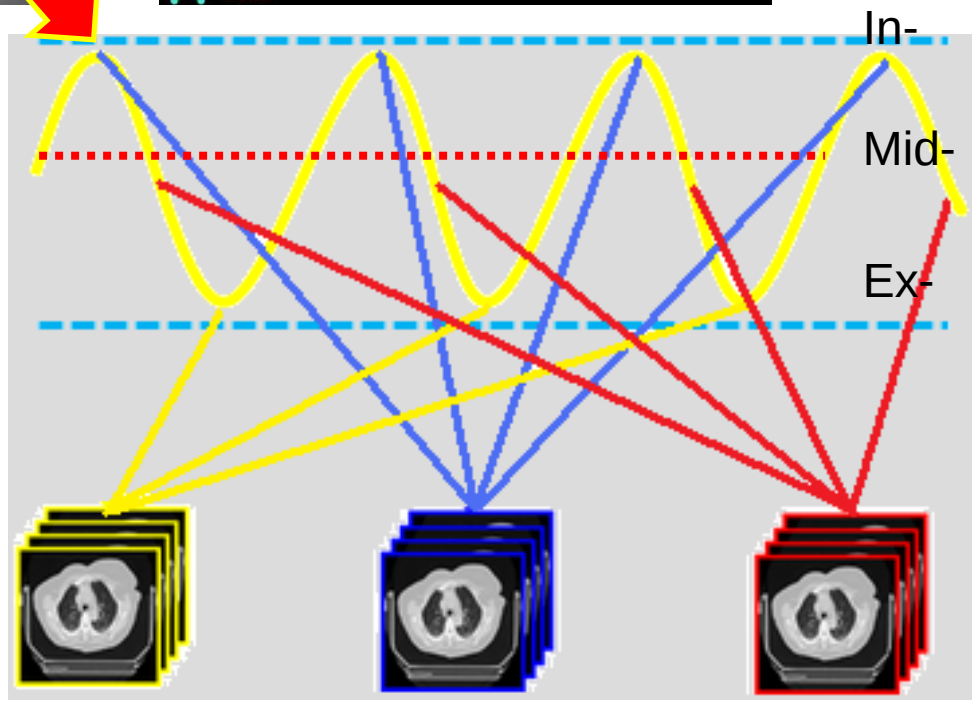
34.3 mm
L
1
5
9

Full body vac-loc

Motion management:
4DCT scan and mid-vent strategy





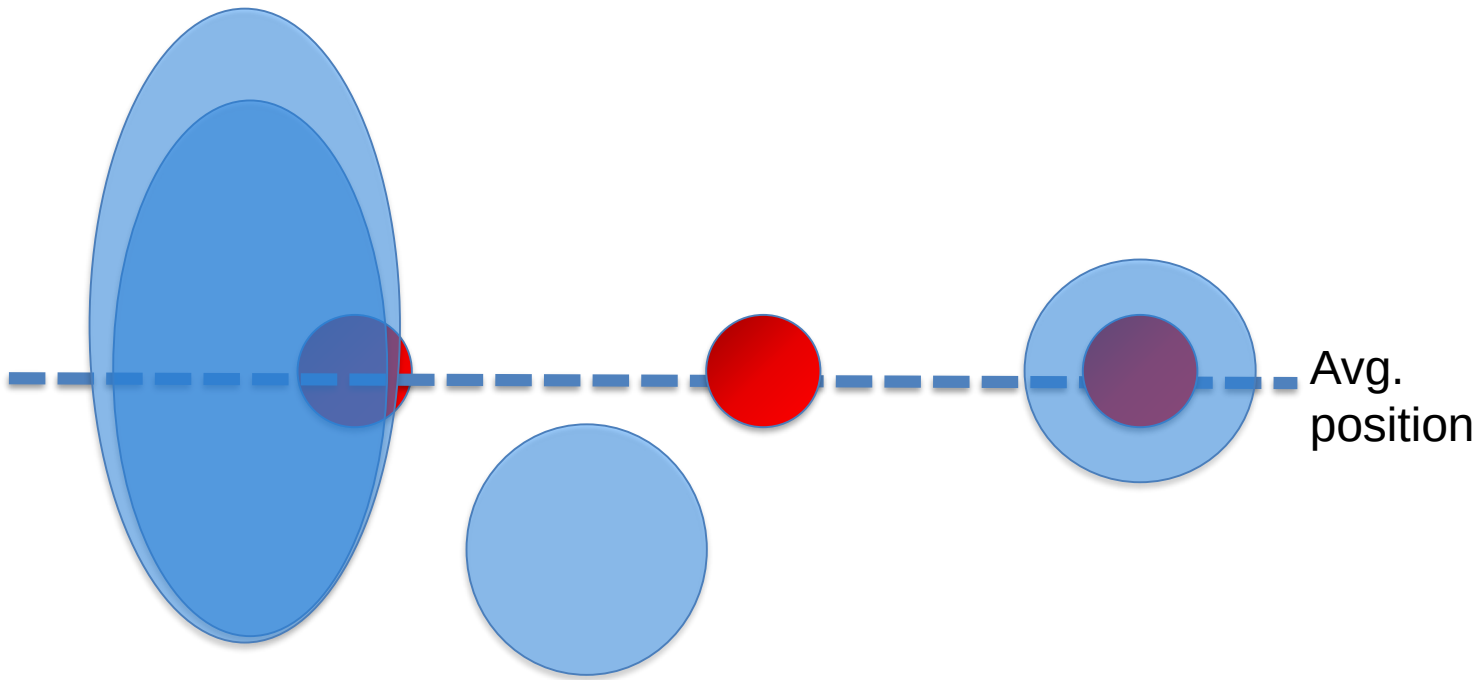


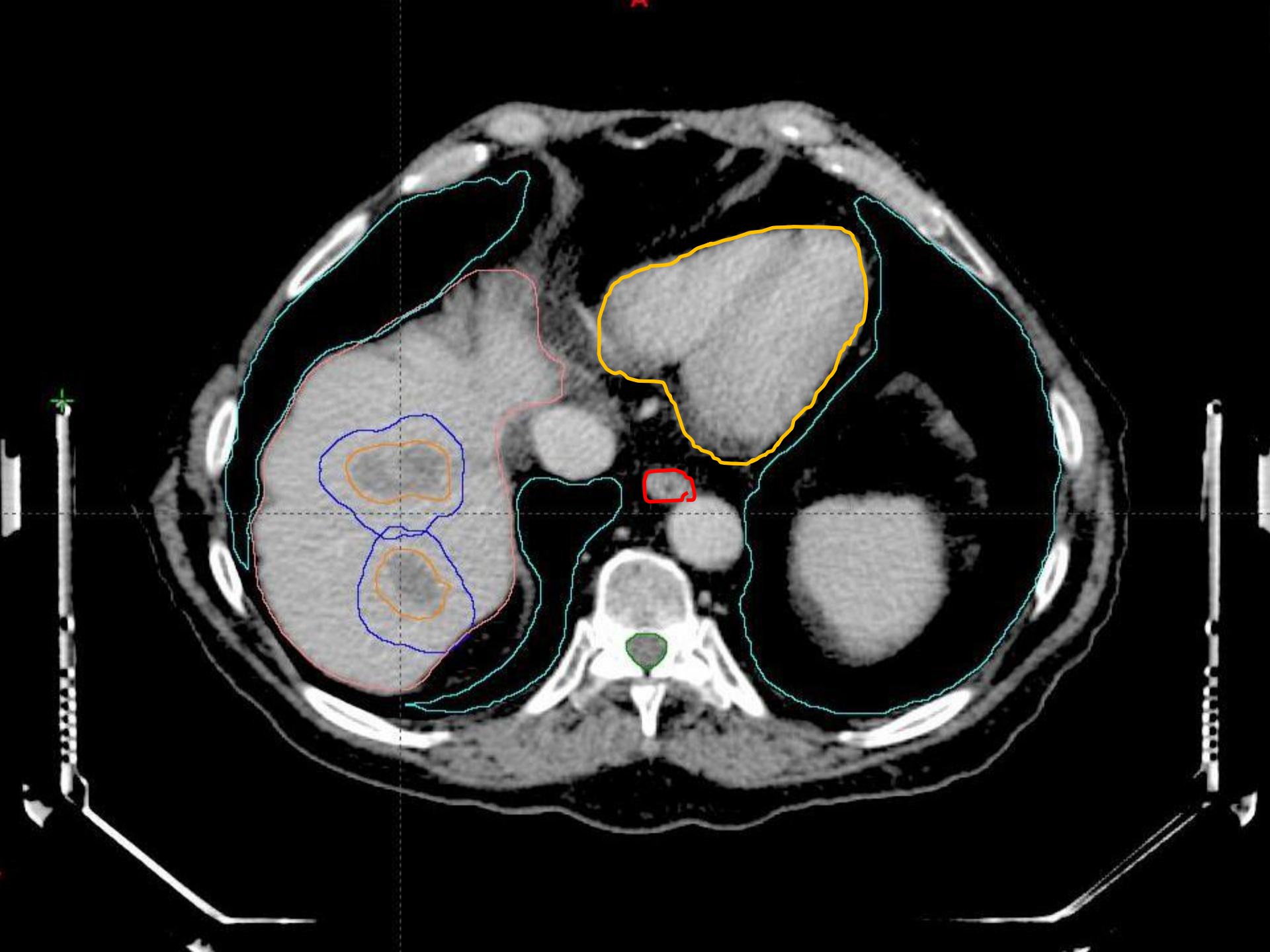
General concepts in motion management

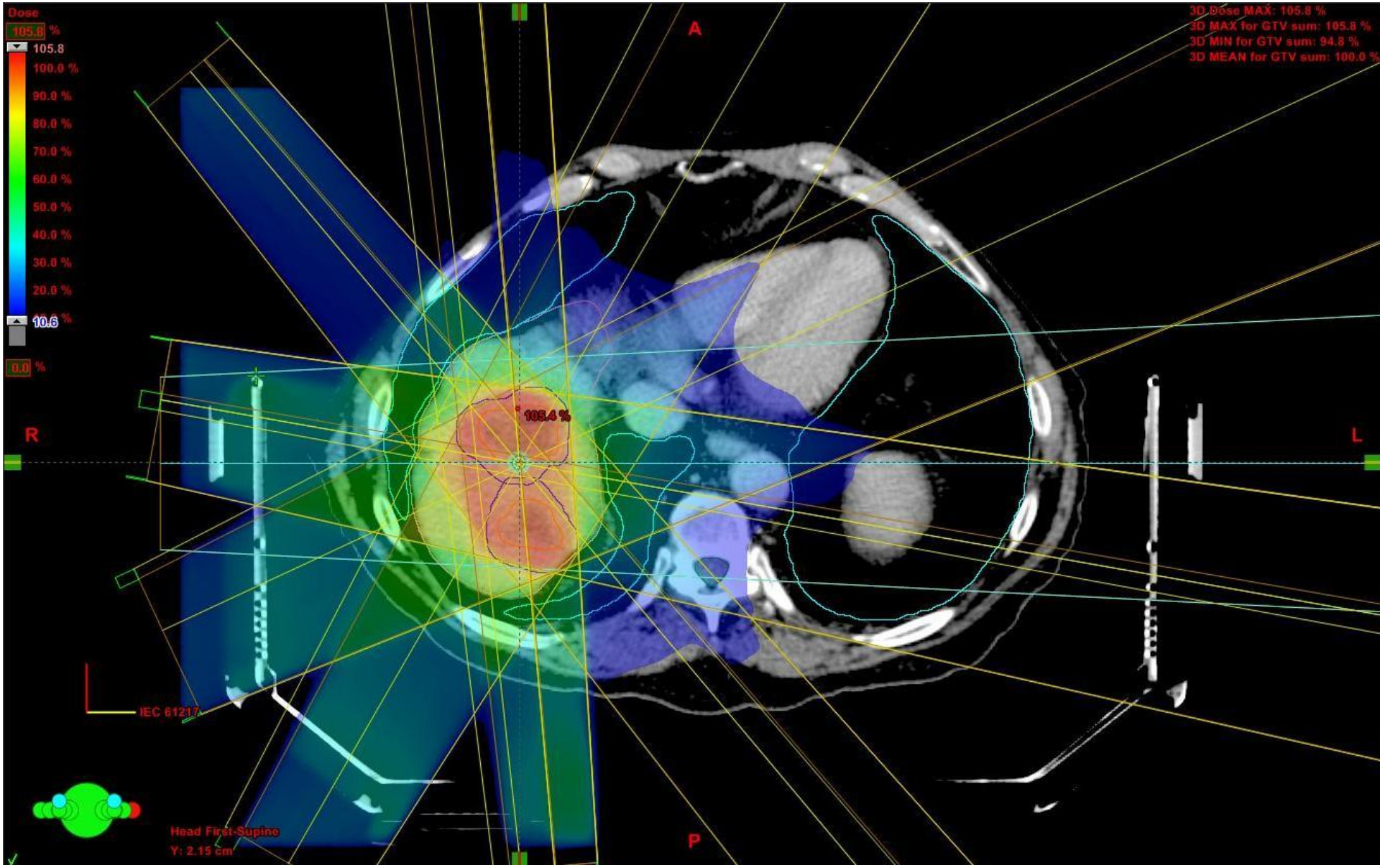
1) Mid-ventilation
or
2) ITV approaches

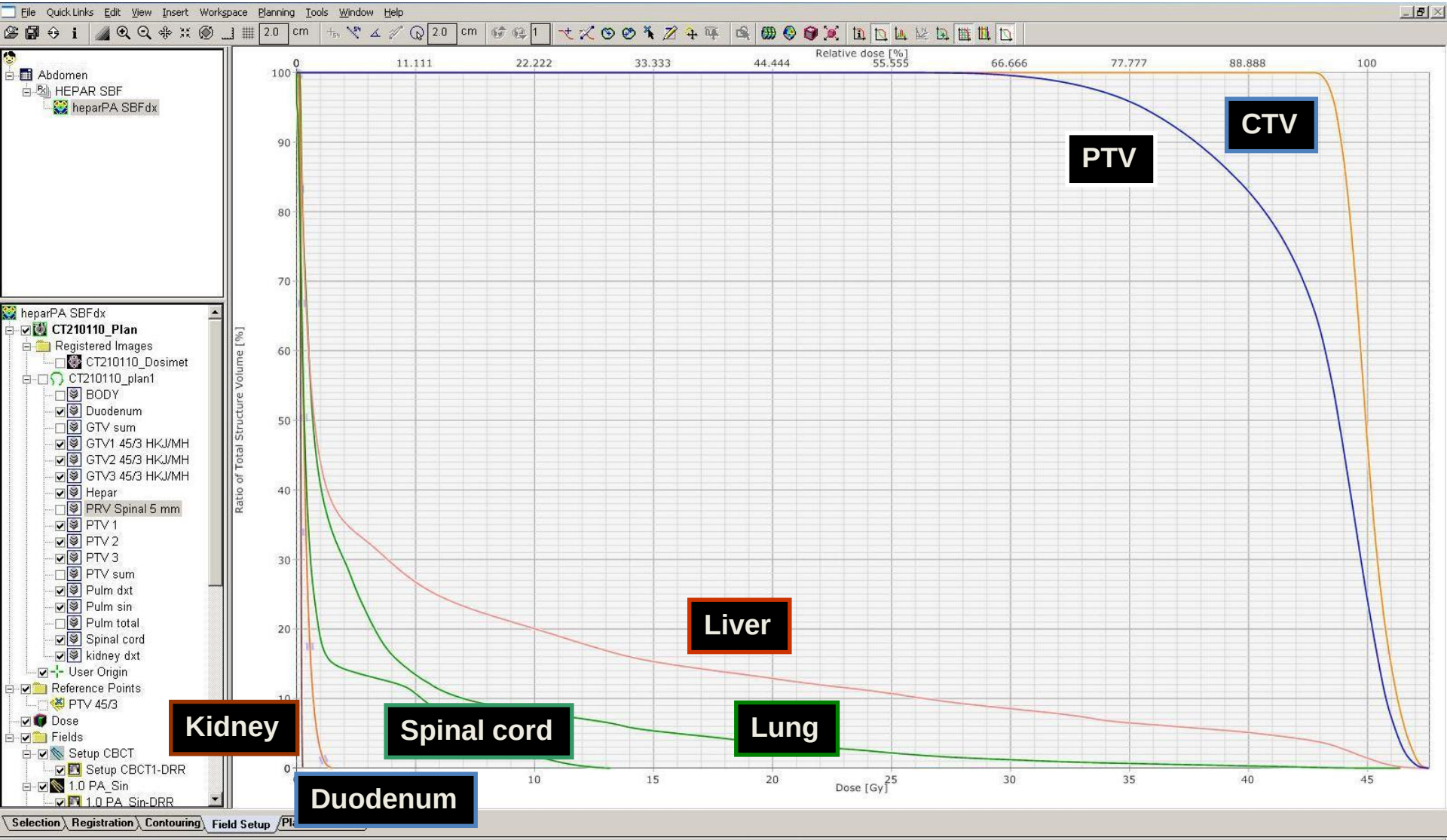
3) Gating

4) Tracking






Dose
105.8 %
105.8
100.0 %
90.0 %
80.0 %
70.0 %
60.0 %
50.0 %
40.0 %
30.0 %
20.0 %
10.6 %
0.0 %
3D Dose MAX: 105.8 %
3D MAX for GTV sum: 105.8 %
3D MIN for GTV sum: 94.8 %
3D MEAN for GTV sum: 100.0 %
A
R
L
P
105.4 %
IEC 61217
Head First-Supine
Y: 2.15 cm

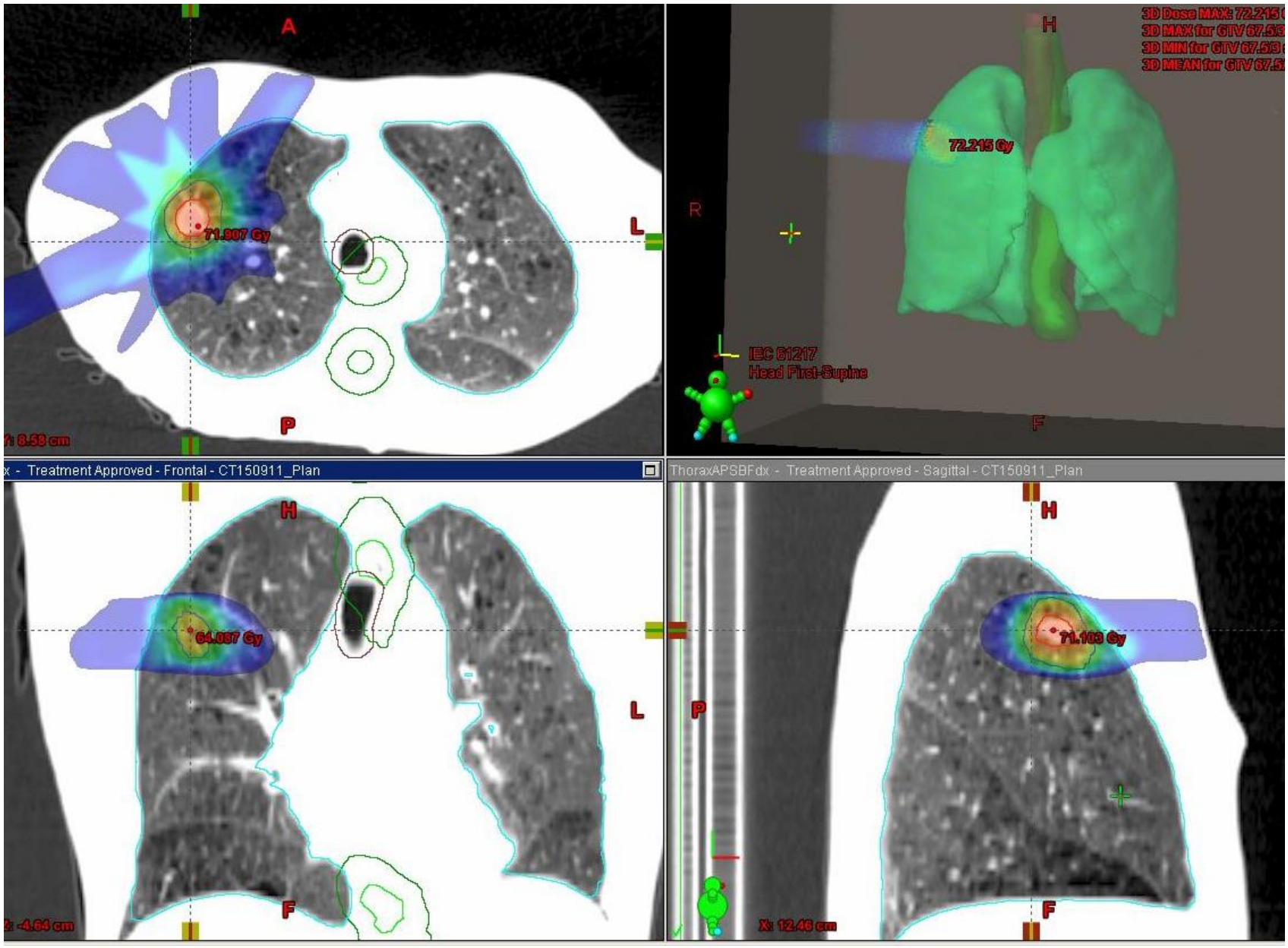


Fields | Dose Prescription | Field Alignments | Plan Objectives | Optimization Objectives | Dose Statistics | Calculation Models | Plan Sum

View	DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [Gy]	Max Dose [Gy]	Mean Dose [Gy]
☑		kidney dxt	Approved	heparPA SBFdx	Abdomen	192.6	100.0	100.0	0.079	1.565	0.363
☐		GTV2 45/3 HKJ/MH	Approved	heparPA SBFdx	Abdomen						
☐		GTV3 45/3 HKJ/MH	Approved	heparPA SBFdx	Abdomen						
☐		PTV 1	Approved	heparPA SBFdx	Abdomen						
☐		PTV 2	Approved	heparPA SBFdx	Abdomen						
☐		PTV 3	Approved	heparPA SBFdx	Abdomen						
☑		PTV sum	Approved	heparPA SBFdx	Abdomen	111.0	100.0	100.0	24.846	47.598	42.744
☑		Hepar	Approved	heparPA SBFdx	Abdomen	2138.6	100.0	100.0	0.000	47.598	6.629

Lung metastases

SBRT of oligometastases to the **lung**



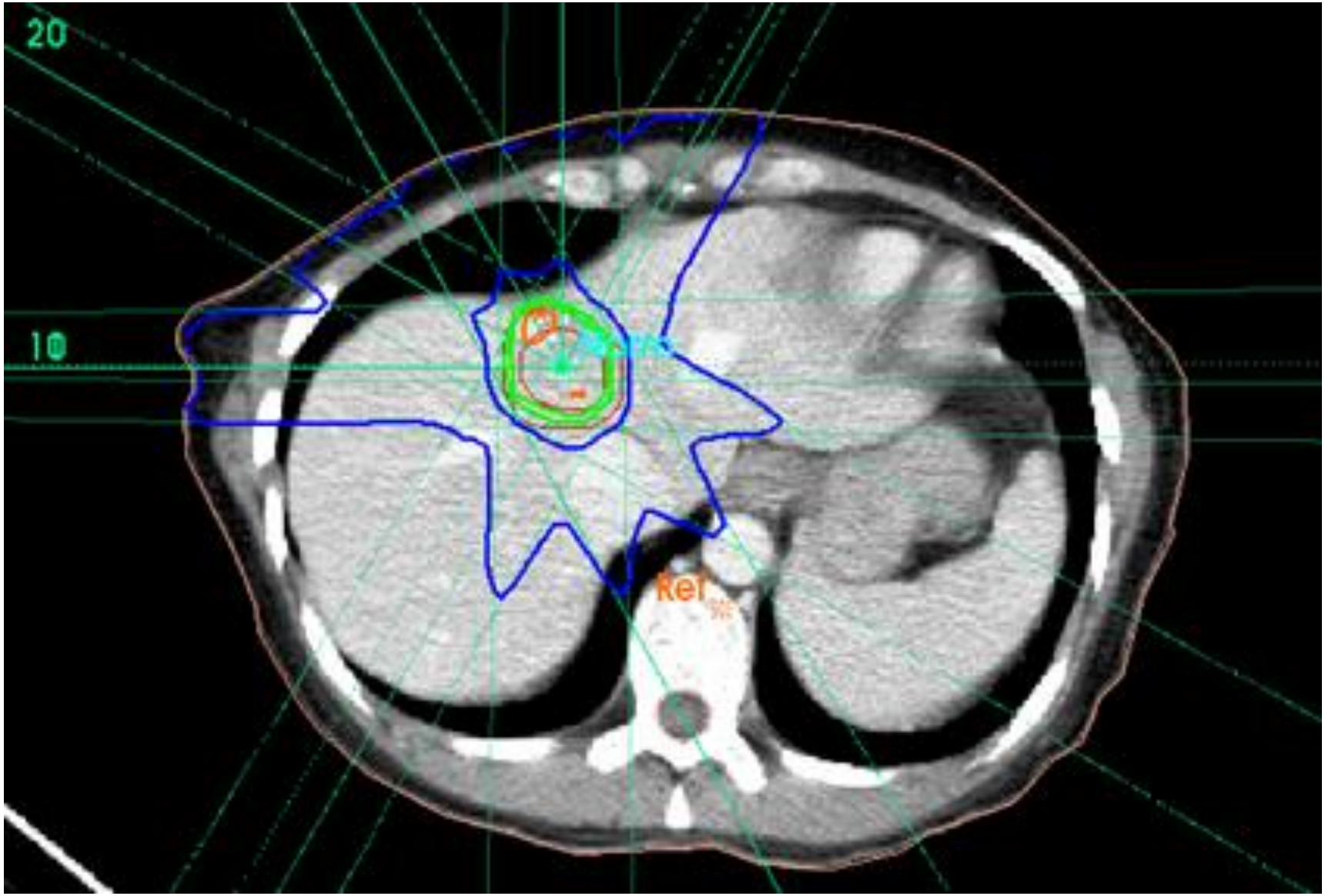
SBRT of oligometastases to the **lung**
Phase II or retrospective cohorts

Author; year	Design	Pts	Dose/frx	m-FU	Locol control (%)	Survival 1,2 years 1, 2 years (%)
Wulf 2004	Dose esc.	41	3x10-12.5 Gy 1x26 Gy	9 mts	80	85, 33
Hof 2007	Phase I/II	61	1x12-30 Gy	14 mts	83 (>26 Gy and <10cc)	78, 65
Rusthoven 2009	Phase I/II	38	3x16-20 Gy			
Zhang 2011	Retrospect				97, 89	79, 41 (3 yr)
Ric[illegible]			3x15 Gy, 4x9 Gy	20 mts	89	79, 67
C[illegible] 2014	Phase II	40	4x12 – 3x25 Gy	24	80	80, 65
DeVin 2014	Retrospect	56	10x4-5 Gy	12 mts	33 (incl brain)	55 (2 yr)
Takahachi 2014	Carbon ions Feasibility	34	12x5 Gy 1x44 Gy	24 mts	85	90, 65
Fode 2015	Retrospect	92	3x15-22.5 Gy	29	LR: 13	80, 58
Guckenberger/ DEGRO (abstract)	Retrospect Multi-inst	715	NA	NA	NA	53 (2 yr) 24 (5 yr)

Lung mets: Local control rates 80-96%

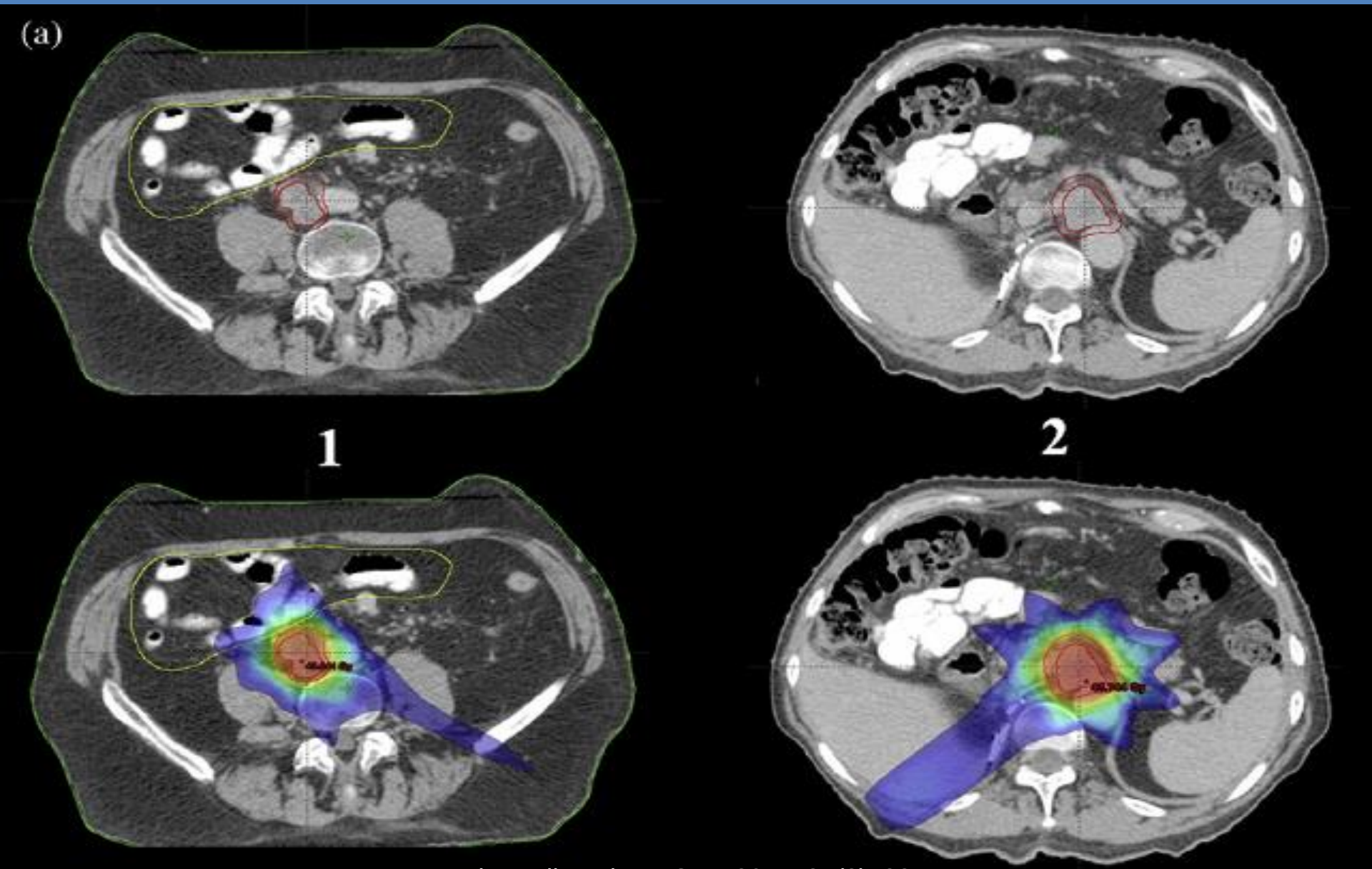
Liver metastases

SBRT of oligometastases to the **liver**



And abdomino-pelvic lymph node-, adrenal metastases and……..

Examples: SBRT for abd. lymph node mets.



Bignardi et al. IJROBP 2011; 81(3): 831

Vertebral metastases (spinal SBRT)

RADIATION ONCOLOGY

RESEARCH Open Access

Safety and efficacy of stereotactic body radiotherapy as primary treatment for vertebral metastases: a multi-institutional analysis

Matthias Guckenberger[1,12*], Frederick Mantel[1], Peter C Gerszten[2,3], John C Flickinger[2,3], Arjun Sahgal[4], Daniel Létourneau[5], Inga S Grills[6], Maha Jawad[6], Daniel K Fahim[7], John H Shin[8], Brian Winey[9], Jason Sheehan[10] and Ron Kersh[11]

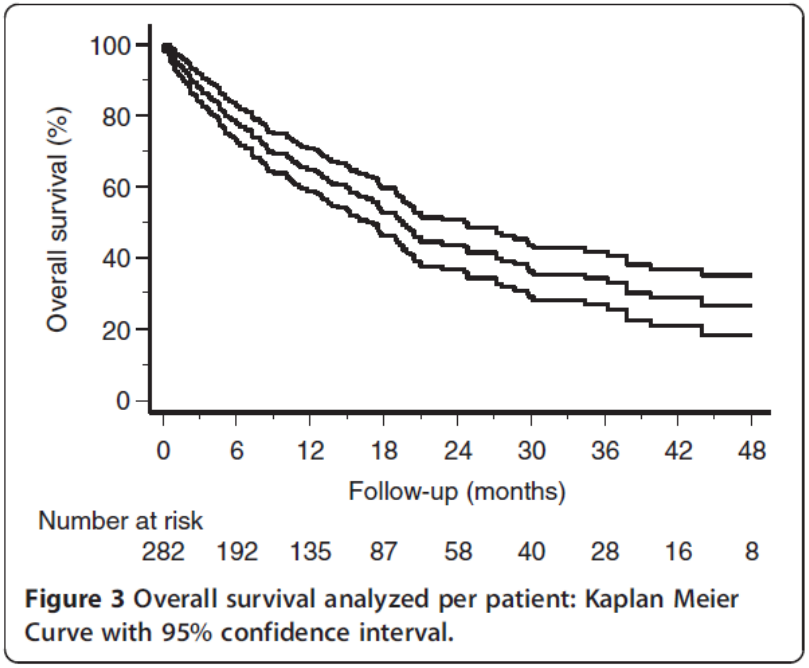


Figure 3 Overall survival analyzed per patient: Kaplan Meier Curve with 95% confidence interval.

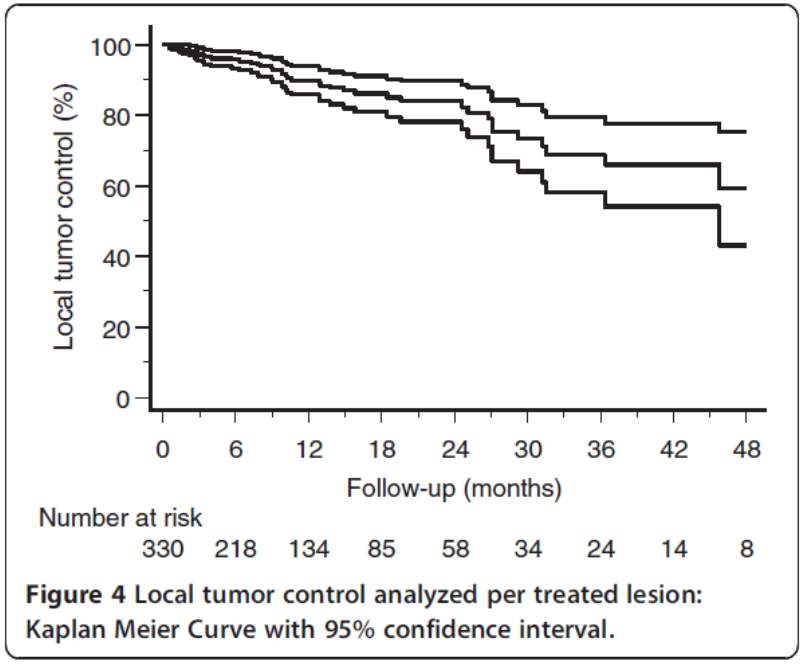


Figure 4 Local tumor control analyzed per treated lesion: Kaplan Meier Curve with 95% confidence interval.

Guckenberger et al. Radiation Oncology 2014, 9:226
http://www.ro-journal.com/content/9/1/226

RADIATION ONCOLOGY

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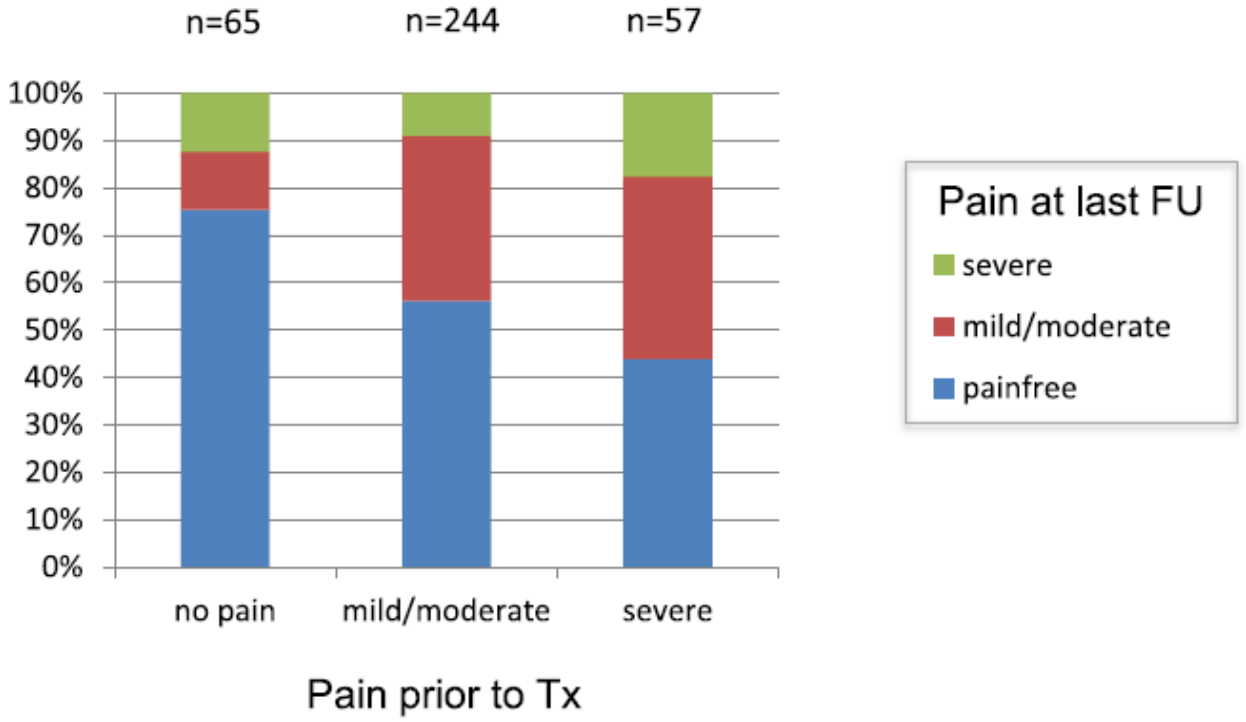


Spinal Instability Neoplastic Score (SINS)

(1) location: 3 points for C0-C2, C7-T2, T11-L1, L5-S1; 2 points for C3-C6, L2-L4; 1 point for T3-T10, 0 for S2-S5

(2) pain relief with recumbency and/or pain with movement/ loading of the spine: 3 points for yes, 1 point for no, 0 points if pain-free lesion

(3) lesion characteristic: 2 points for lytic bone lesion, 1 point for mixed lytic/blastic, 0 points for blastic

(4) radiographic spinal alignment: 4 points f… …ion/ translation, 2 points for de… …sis), 0 points fo…

(5) v… …2 p… …th gr… …absence of tho…

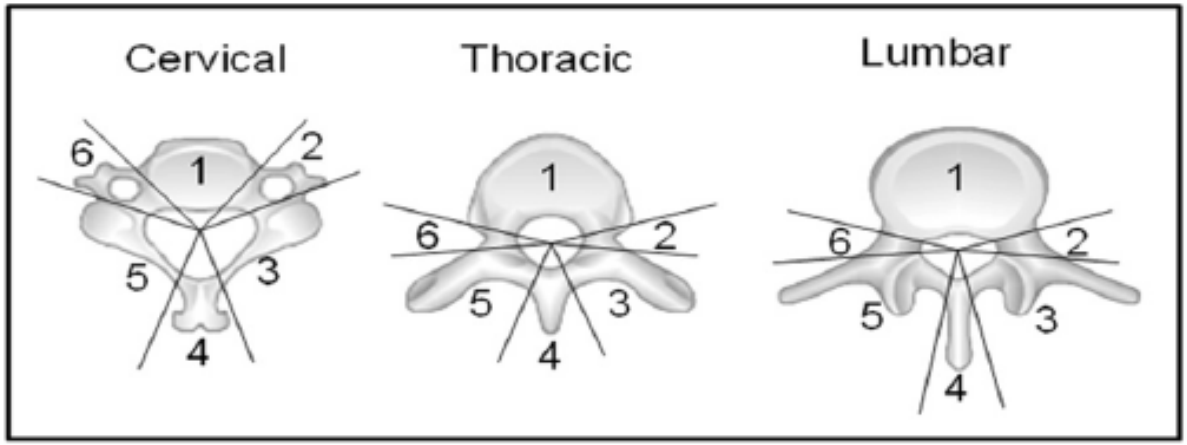
(6) pos… …involvement of the spinal elements (facet, pedicle, or costovertebral joint fracture or replacement with tumor): 3 points if bilateral, 1 point if unilateral, 0 points if neither.

A painful lytic metastasis of L5 (without compression fracture)
SINS-score: 8

1-6 no-minimal instability; 7-12 potential instability; 13+ instability

CTV

International Spine Radiosurgery Consortium Consensus Guidelines for Target Volume Definition in Spinal Stereotactic Radiosurgery *Cox IJROBP 2012*



Segmentation of the vertebra

GTV involvement	ISRC GTV anatomic classification	ISRC bony CTV recommendation	CTV description
Any portion of the vertebral body	1	1	Include the entire vertebral body
Lateralized within the vertebral body	1	1, 2	Include the entire vertebral body and the ipsilateral pedicle/transverse process
Diffusely involves the vertebral body	1	1, 2, 6	Include the entire vertebral body and the bilateral pedicles/transverse processes
GTV involves vertebral body and unilateral pedicle	1, 2	1, 2, 3	Include entire vertebral body, pedicle, ipsilateral transverse process, and ipsilateral lamina
GTV involves vertebral body and bilateral pedicles/transverse processes	3	2, 3, 4	Include entire vertebral body, bilateral pedicles/transverse processes, and bilateral laminae
GTV involves unilateral pedicle	2	2, 3 ± 1	Include pedicle, ipsilateral transverse process, and ipsilateral lamina, ± vertebral body
GTV involves unilateral lamina	3	2, 3, 4	Include lamina, ipsilateral pedicle/transverse process, and spinous process
GTV involves spinous process	4	3, 4, 5	Include entire spinous process and bilateral laminae

CTV definition based on involved segments

Spinal cord tolerance

Review of radiation myelopathy

Table 1 SBRT point maximum dose limits to thecal sac

Prior radiation	*1 fx SBRT* P_{max} *limit*	*2 fx SBRT* P_{max} *limit*	*3 fx SBRT* P_{max} *limit*	*4 fx SBRT* P_{max} *limit*	*5 fx SBRT* P_{max} *limit*
None	12.4 Gy	17 Gy	20.3 Gy	23 Gy	25.3 Gy
20 Gy in 5 fx to 45 Gy in 25 fx	9 Gy	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
50 Gy in 25 fx	N/A	11 Gy	12.5 Gy	14 Gy	15.5 Gy
>50 Gy in 25 fx	N/A	N/A	N/A	N/A	N/A

Abbreviations: fx, fractions; N/A, not applicable, insufficient data to make SBRT dose limit recommendations; P_{max}, point maximum volume.

Wong et al. Spinal Cord (2015) 53, 574

Influence of SINS score on risk of pathological fracture

32 fractures (15 symptomatic) in 79 patients
Median 3.3 (0.4-34) months

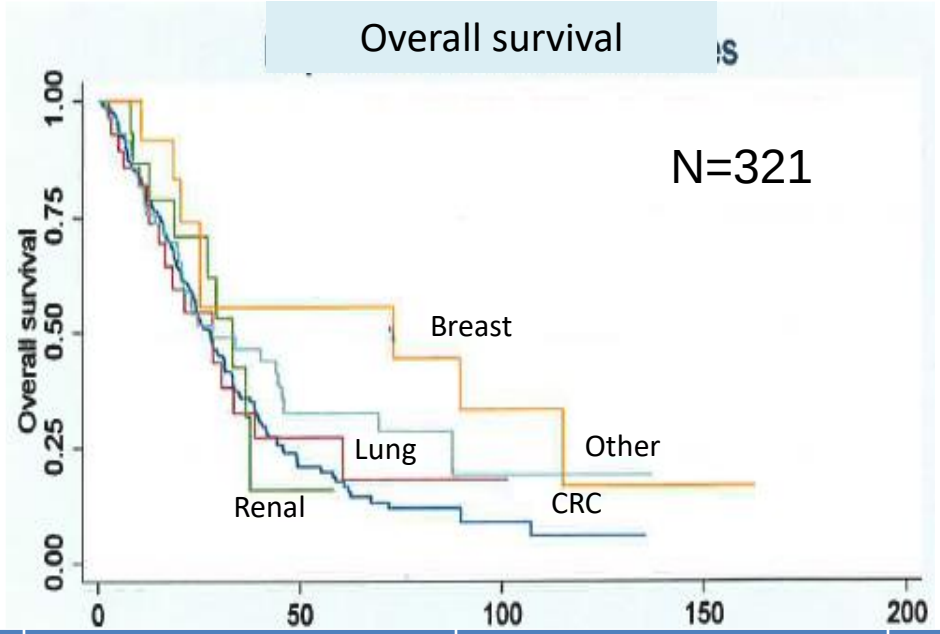
	SINS 1-6	SINS 7-12	SINS>12
Risk of PF	17%	67%	No

High risk of fracture…….
24 Gy/1 fraction

Lee et al IJROBP 2016; 126(3):509

Turn it around:
How about different cancers (primaries)

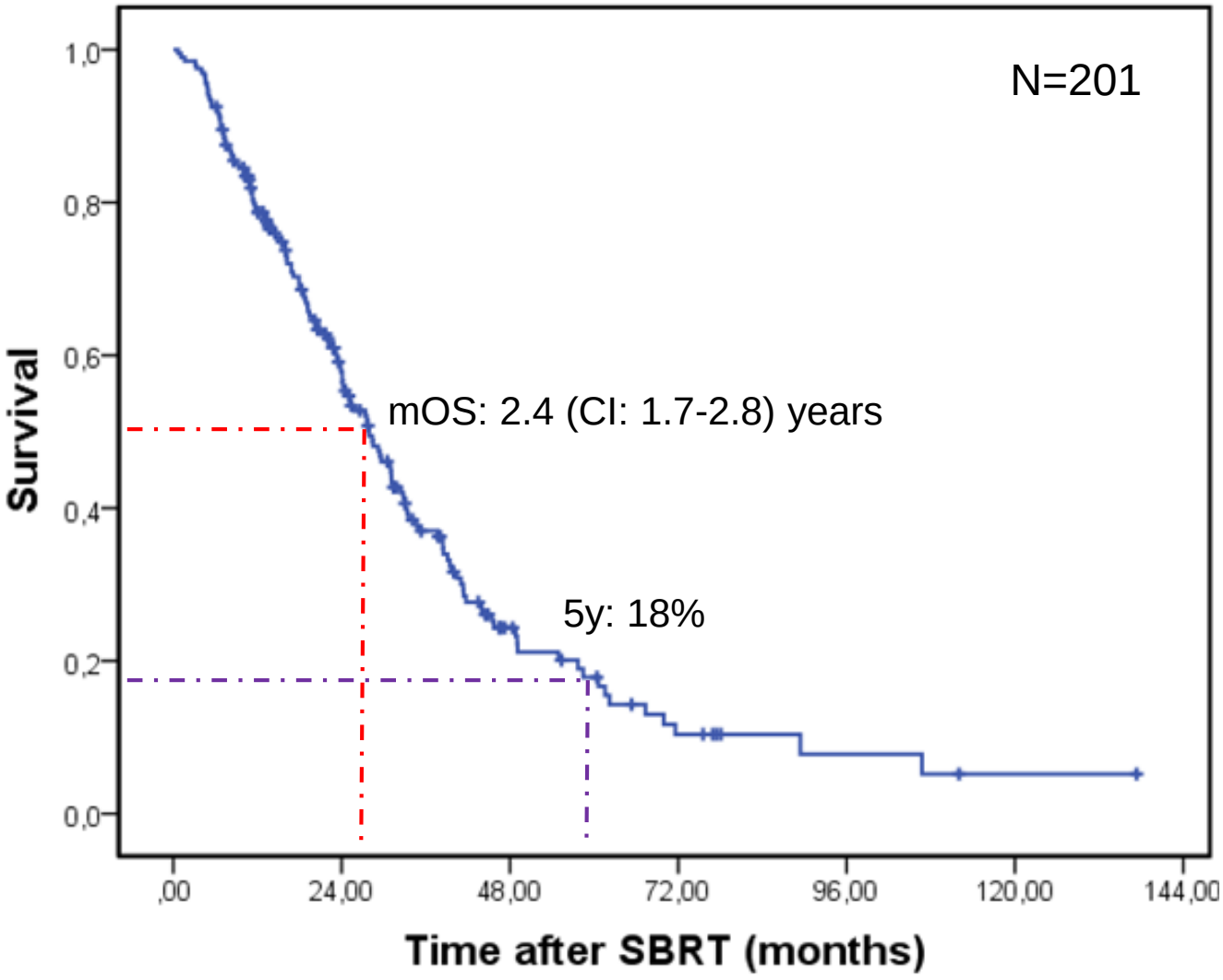
Survival by histological type



	No.	Med. OS (years)	95% C.I. (years)
Colorectal	201	2.4	1.7-2.8
Lung	31	1.5	1.2-2.5
Renal	17	2.4	1.1-3.1
Breast	12	6.1	1.5-9.6

MM Fode et al. Radiother Oncol 2015; 114(2):155

Overall survival after SBRT for mCRC



MM Fode et al. Radiother Oncol 2015; 114(2):155

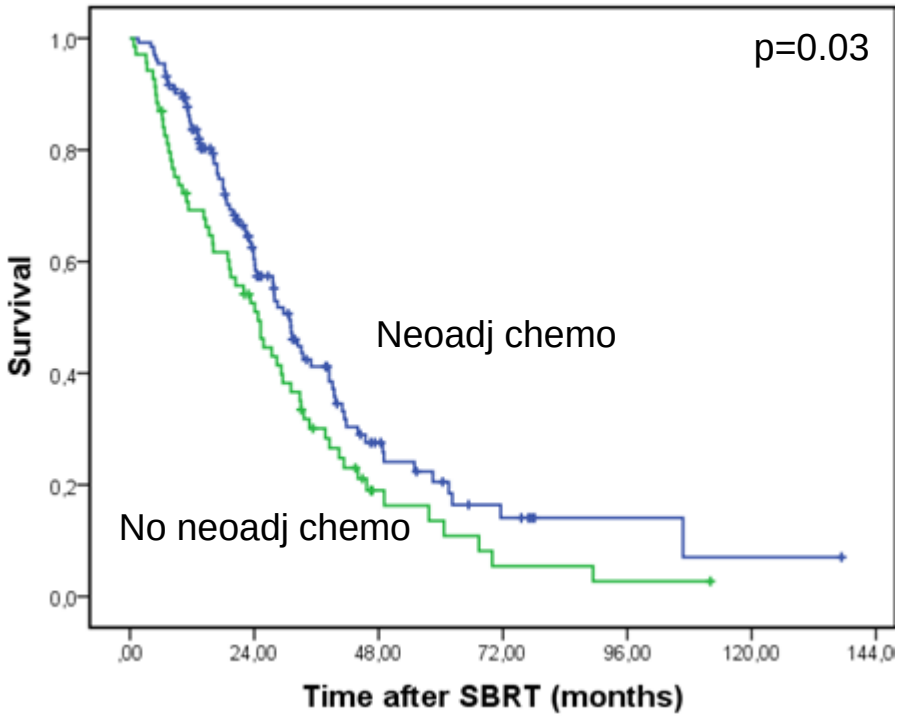
Prognostic factors related to survival after SBRT for mCRC

Covariate	Categories (n)	Median OS years (95 % CI)	HR	P- value
Performance status	0-1 (187) 2-3 (14)	2.5 (2.1 – 2.8) 1.2 (0.3- 1.9)	2.54	<0.01
Gender	Males (136) Females (65)	3.0 (2.4-3.6) 3.5 (2.8-4.2)	0.65	0.03
Age	<71 (101) ≥72 (100)	3.2 (2.6-3.8) 2.9 (2.6-3.6)	1.10	0.38
Size of largest metastases	≤ 30 mm (102) >30 mm (98)	2.8 (2.5 – 3.4) 1.9 (1.5 – 2.1)	1.67	<0.01
Number of metastases	1 metastasis (86) 2-6 metastases (115)	2.8 (2.3 – 3.4) 2.0 (1.8 – 2.5)	1.49	0.02
Treatment site	Lung (30) Liver, other (171)	3.4 (2.3 – 5.1) 2.1 (1.9– 2.6)	1.74	0.03
Prior chemotherapy	Yes (132) No (69)	2.6 (2.0 – 3.2) 2.1 (1.3 – 2.5)	1.44	0.03
Prior local therapy	Yes (98) No (103)	2.6 (2.0- 2.8) 2.1 (1.9- 2.8)	1.16	0.39
Timing of metastasis	Metachronous (70) Synchronous (131)	2.5 (2.0 – 3.3) 2.3 (1.8 – 2.7)	1.14	0.48

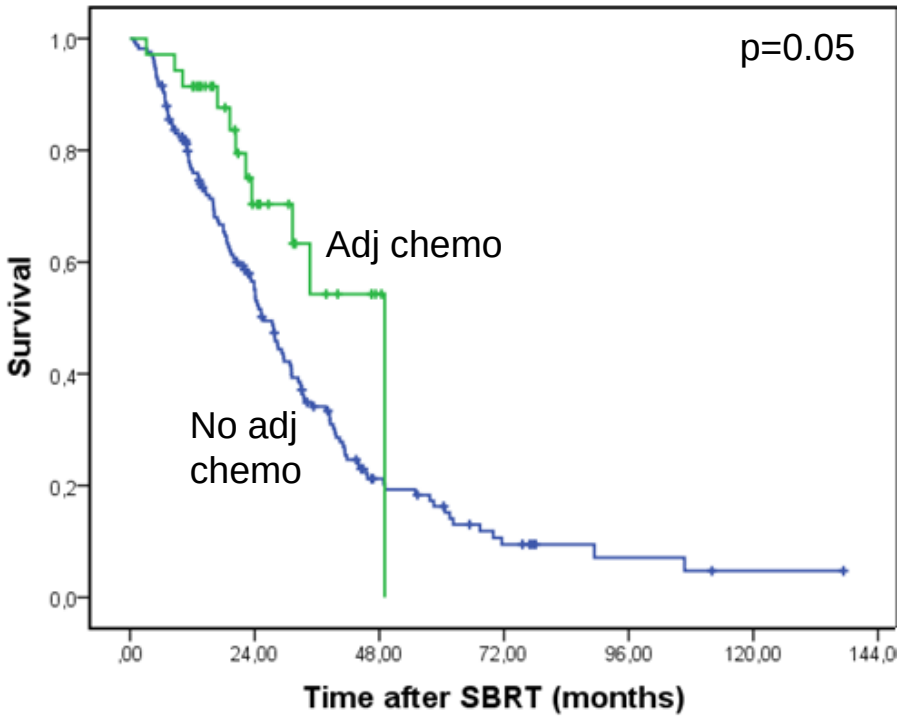
MM Fode et al. Radiother Oncol 2015; 114(2):155

SBRT and chemotherapy for mCRC

Chemotherapy before SBRT



Chemotherapy after SBRT



MM Fode et al. Radiother Oncol 2015; 114(2):155

SBRT for prostate cancer metastases

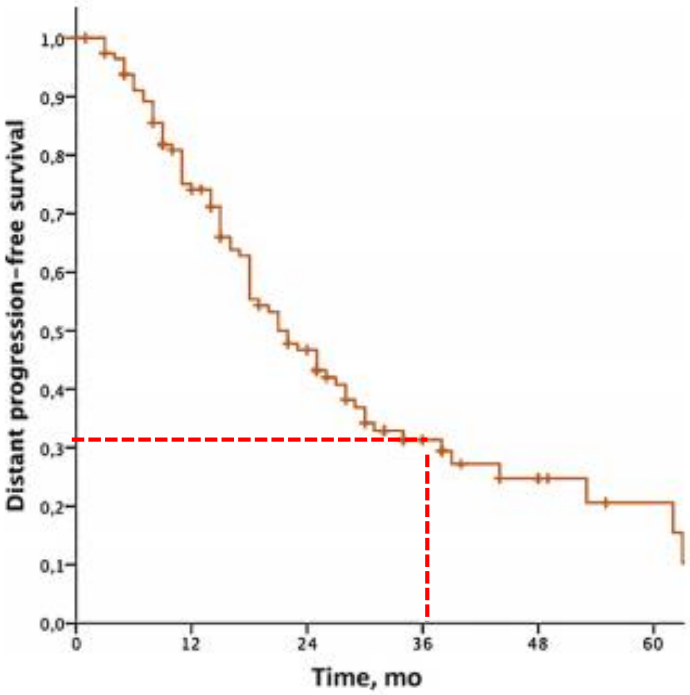


Fig. 1 – Kaplan-Meier analysis depicting time to distant progression.

- Multi-institutional database (n=119)
- Hormone naïve with metastases in:
  - Lymph nodes (n=72)
  - Bone (n=43)
  - Viscera (n=2)
- Number of metastases (1-3; 1 met.: 72%)
- LPFS 79% (BED<100 Gy) and 99% (BED≥100 Gy)
- The median time to start of palliative ADT was 28 months (95% CI, 16.2–69.7)
- The 3- and 5-yr OS was 95% and 88%, respectively

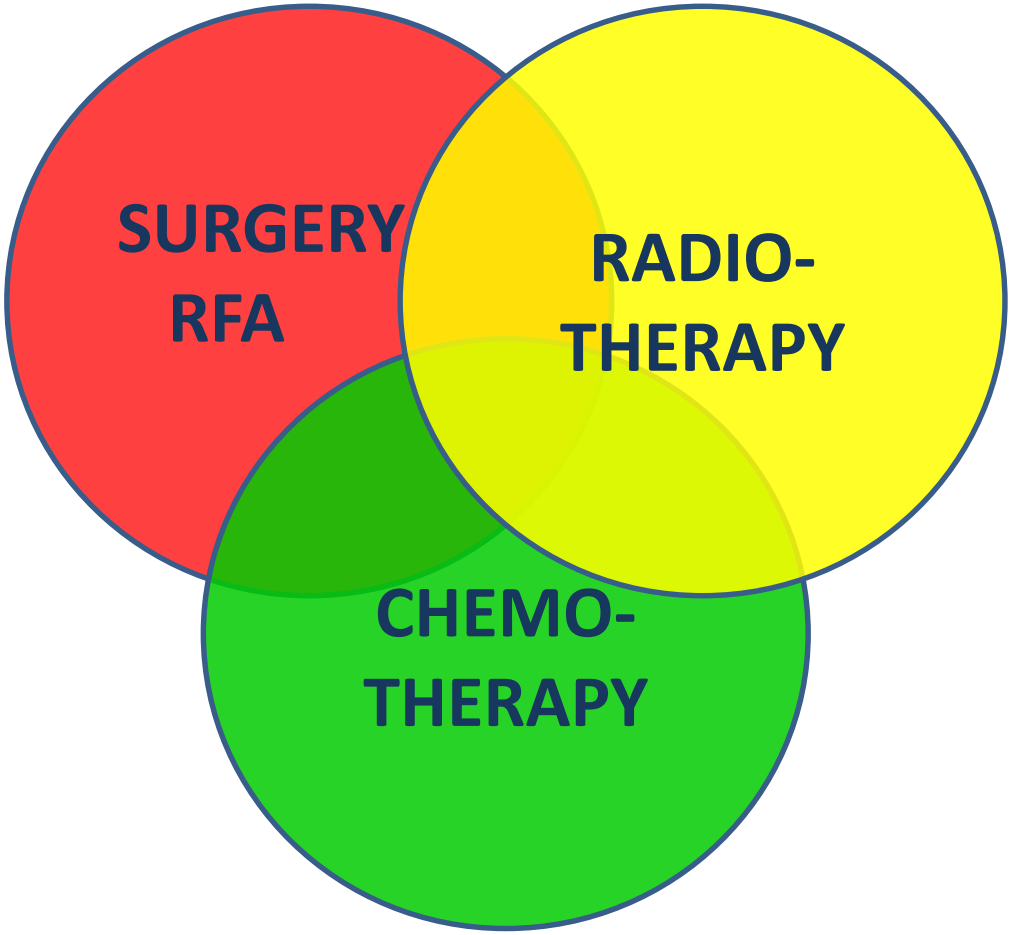
P. Ost et al. Eur Urol 2016; 69(1): 9-12

SBRT of prostate cancer and systemic therapies

- *Is SBRT replacing systemic therapy?*
- *Or should they be combined?*

- ***TOAD trial*** *(Duchesne et al, ASCO 2015): immediate versus delayed ADT at PSA relapse after definitive therapy*
  - *HR=0.55 (CI: 0.30-1.00)*
- ***CHAARTED-*** *(Sweeney et al NEJM 2015): ADT+docetaxel versus ADT alone in advanced stage hormone sensitive PCa*
  - *HR=0.61 (CI: 0.47-0.80)*
  - *m-OS: 58 and 44 months, respectively*
- ***STAMPEDE*** *(James et al Lancet 2016): SOC+docetaxel versus SOC in advanced stage hormone sensitive PCa*
  - *HR=0·78 (CI: 0·66–0·93)*
- *Combination with immune stimulating agents*

Treatment of cancer in a Multidisciplinary Team



Conclusions – SBRT in palliation

……, but evidence is still lacking

- We may cure a few. At least, we observe long-term survivors after SBRT for metastases
- Some patients may benefit in terms of prolonged survival
- Ablation of metastases may prevent cancer related symptoms

Conclusions – SBRT in palliation

Experience based on selected patients

- Long-term survival after SBRT may be achieved in patients with favorable prognostic factors:
  - Colorectal and prostate primaries
  - Good performance status
  - Small size of the metastases
  - Low number of metastases
- Few patients with grade $\geq$ 3 morbidities
- Candidates for SBRT should enter phase III trials

AARHUS UNIVERSITET

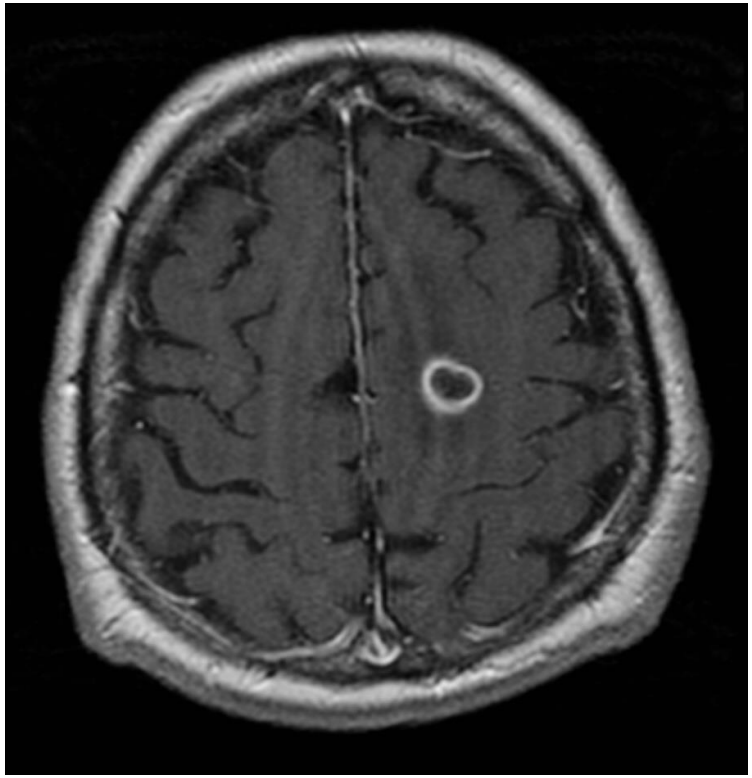
CIRRO

Treatment of patients with solitary brain metastasis

Morten Høyer

Aarhus University Hospital

hoyer@aarhus.rm.dk



ESTRO School

Epidemiology of brain metastases

Accounting for 50% of all brain tumors

Most common brain tumor

Increasing incidence

- More use of MRI
- Some patients live longer with targeted therapy with limited activity in the brain (i.e. HER-2 pos breast cancer)

Epidemiology of brain metastases

Primary sites	
Lung	50-60%
Breast	15-20%
Melanoma	5-10%
Gastrointestinal	4-6%
Genitourinary	3-5%
Other	3-5%
Unknown primary	4-8%

Newton: *Am Fam Physician.* 1999 Feb 15;59(4):878-886.

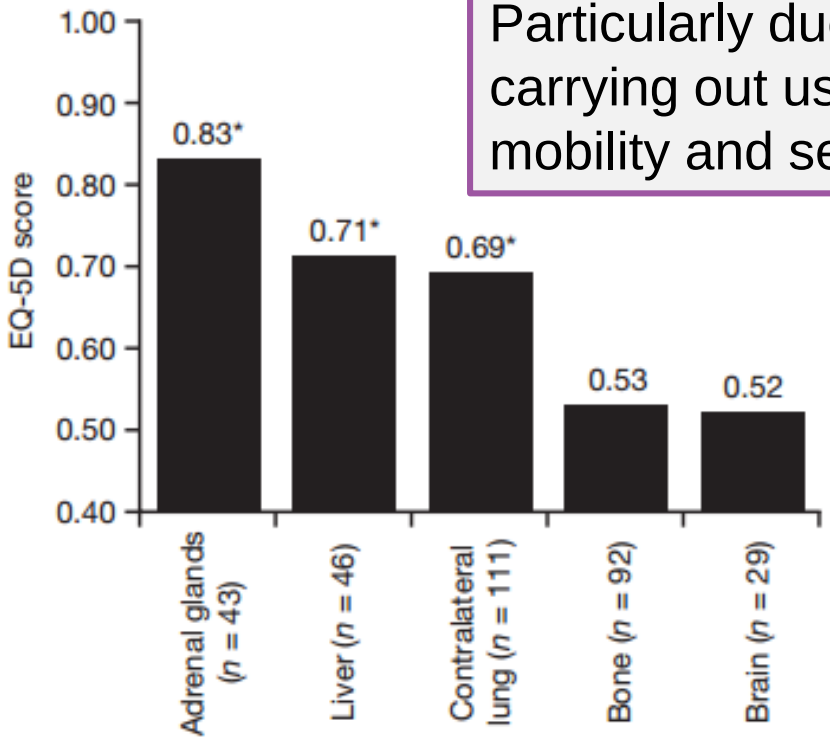
Symptoms and signs of brain metastases

Symptoms	
Headache	49%
Mental problems	32%
Focal weakness	30%
Ataxia	21%
Seizures	18%
Speech problems	12%

Clinical signs	
• Hemiparesis	59%
• Cognitive deficit	58%
• Sensory deficit	21%
• Papillary edema	20%
• Ataxia	19%
• Apraxia	18%

Impact of brain metastasis on qol

Advance stage NSCLC patients with one metastasis site
France and Germany; N=365 pts.



Particularly due to difficulty in carrying out usual daily activities, mobility and self-care

Roughley et al ISPOR 2014

Management patients with brain metastases

Metastasis directed therapy

(Systemic therapy)

Supportive management of metastasis-related conditions

- *Edema*
- *Seizures*
- *Venous thrombosis*

Cortico-steroids on brain metastasis patients

Reduces peritumoral vasogenic edema

Antiemetic and analgesic effects

Improve appetite and mood

Why not high-dose steroids in all brain metastasis patients?

Cortico-steroids to patients with brain metastases

No evidence for corticosteroids patients without symptoms (mass effects)

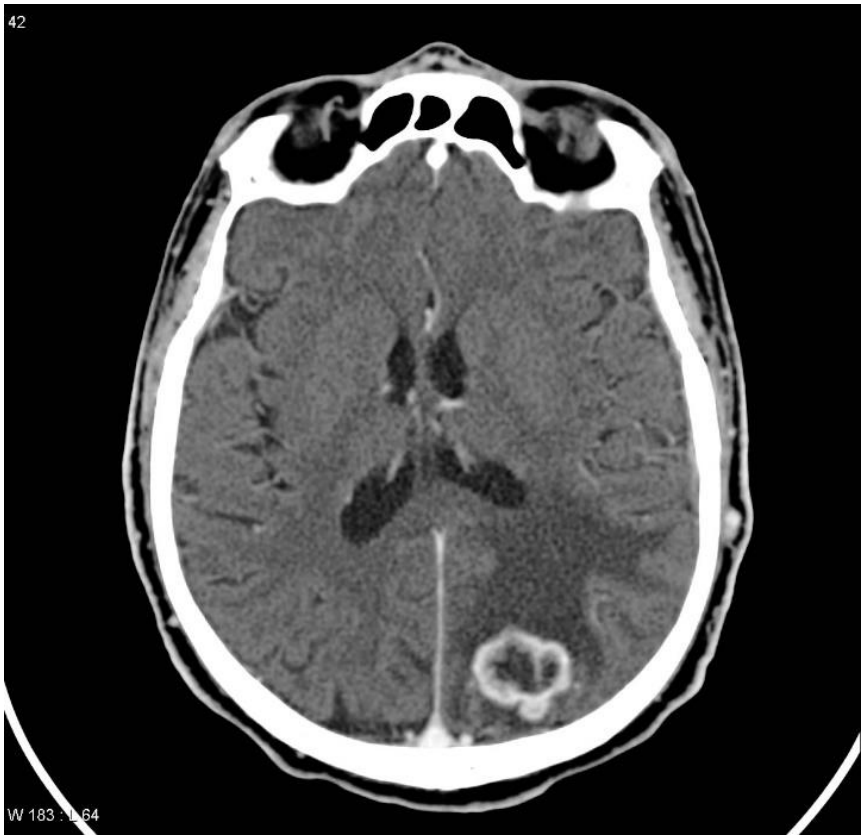
Corticosteroids are recommended to provide temporary symptomatic relief of symptoms related to increased intracranial pressure and edema secondary to brain metastases

Dexamethasone is the best choice

a starting dose of 4 – 8 mg/day of dexamethasone be considered severe symptoms consistent with increased intracranial pressure, it is recommended that higher doses such as 16 mg/day or more be considered

Ryken et al. J Neurooncol (2010) 96:103–114
Vecht et al Neurology 44(4): 675; 1994

Treatment of solitary brain metastasis



Which is best?

Surgery or WBRT?

Surgery+WBRT or WBRT alone?

Surgery+WBRT or surgery alone?

Surgery or SRT?

SRT+WBRT or SRT alone?

SRT+WBRT or WBRT alone?

……..

……..

Which is best?

Surgery or WBRT?

Surgery+WBRT or WBRT alone?

Surgery+WBRT or surgery alone?

Sur…

SI…

SF… alone?

A: One metastasis
B: Oligo-metastases
C: Multiple metastases

……..

……..

Definition: solitary brain metastasis

- Only **ONE** metastasis in the brain on contrast enhanced T1W-MRI
- Symptoms and clinical signs consistent with findings on MRI

65% die from intra-cranial progression

End-points:
- Quality of life
- Neurocognitive function
- Functional independency
- Overall survival
- Brain control
- Distant brain control
- Local control

Is SRT better than surgical resection?

Endpoints:

- Failure free survival
- Overall survival

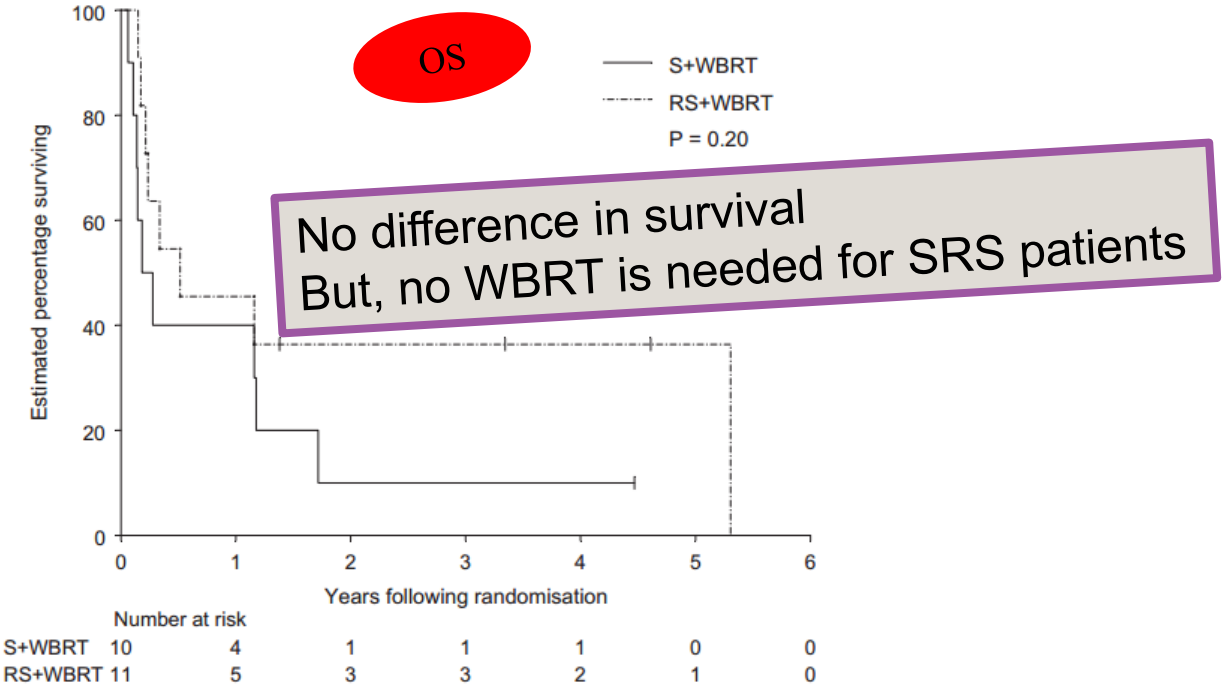


Fig. 2. Overall survival by arm, intention-to-treat, 21 patients. S + WBRT, surgery + whole brain radiotherapy; RS + WBRT, radiosurgery + whole brain radiotherapy.

Ross et al. Clinical Oncology 23 (2011) 646

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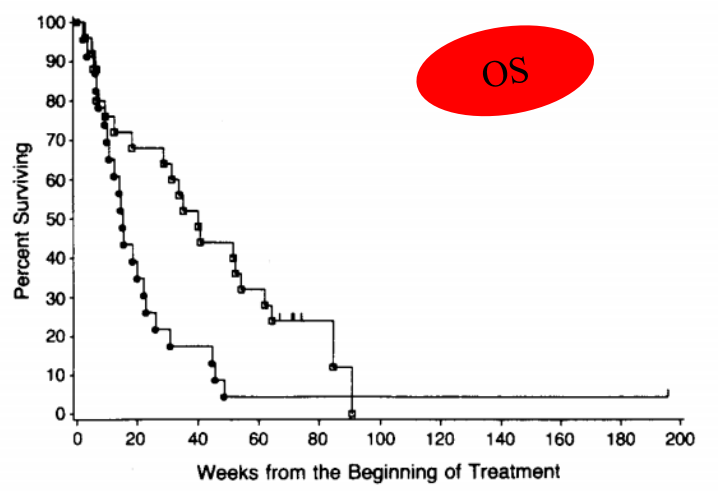
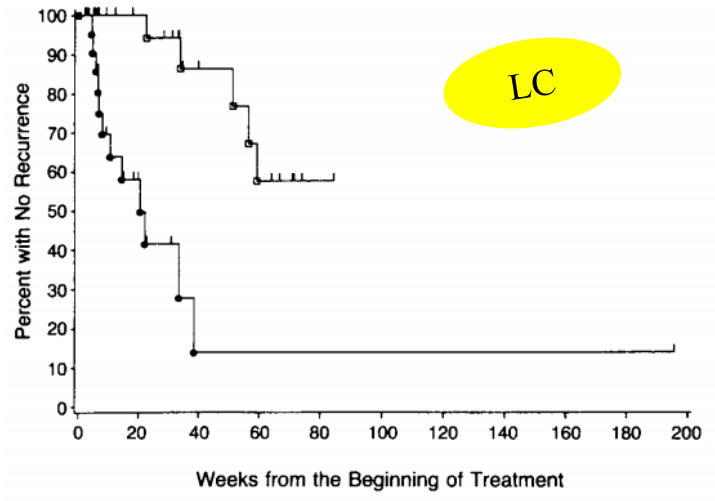
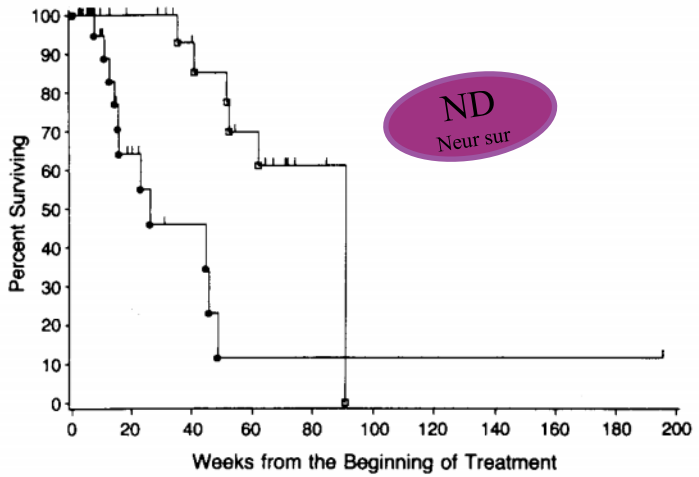
Surgical resection versus WBRT

48 patients with a single brain metastasis





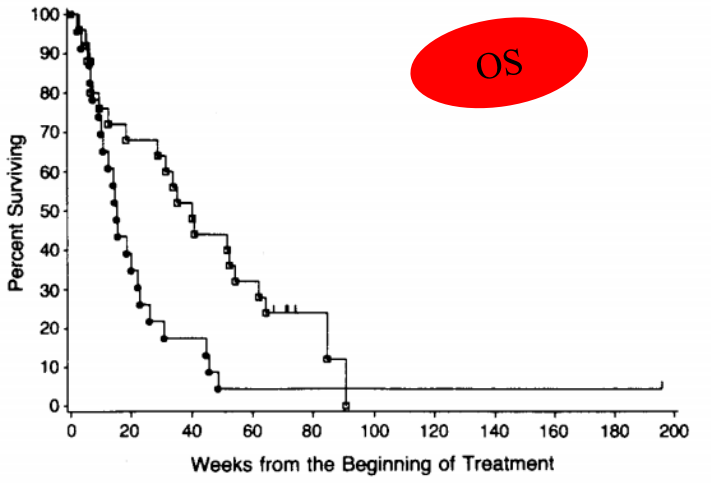


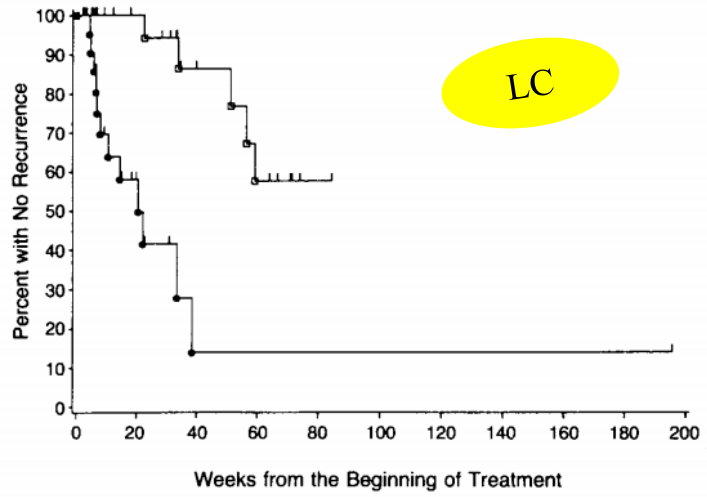
Patchell et al NEJM 1990; 322: 494

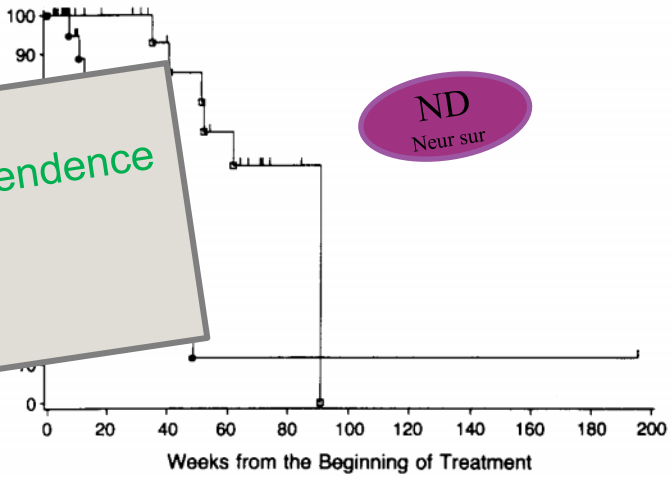
ESTRO School

Surgical resection versus WBRT

48 patients with a single brain metastasis







Vecht 1993 (63 pts.)
- Longer functional independence
- Longer overall survival

Mintz 1998 (84 pts.)
- No difference

Patchell et al NEJM 1990; 322: 494

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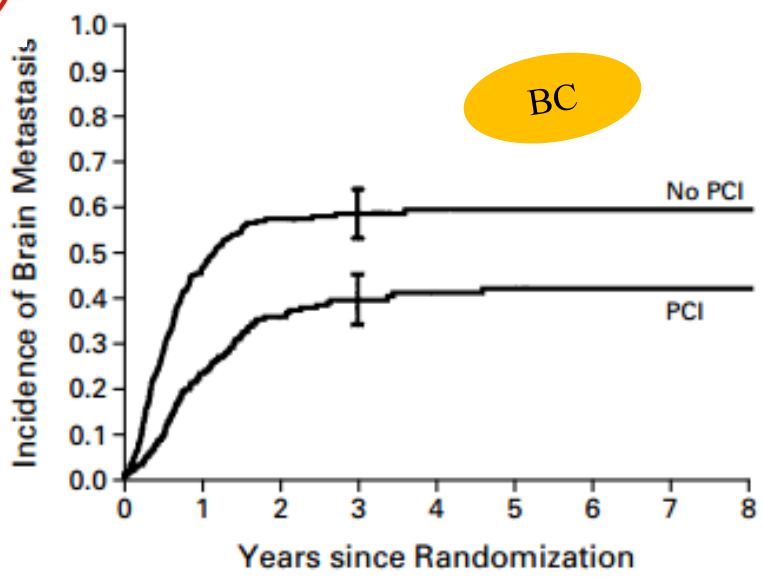
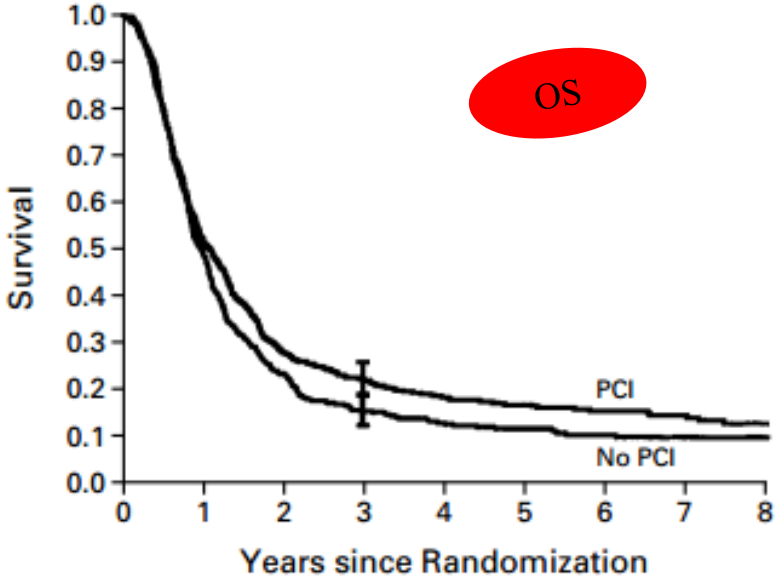
PCI or no PCI in patients with SCLC





- Meta-analysis of 6 RTC with a total of 987 patients
- RR of death reduced by **0.84** (95% CI 0.73-0.97; P= 0.01)
- Corresponds to a **5% (**absolute) increase in the rate of survival at 3 years

Auperin et al NEJM 1999; ;341:476

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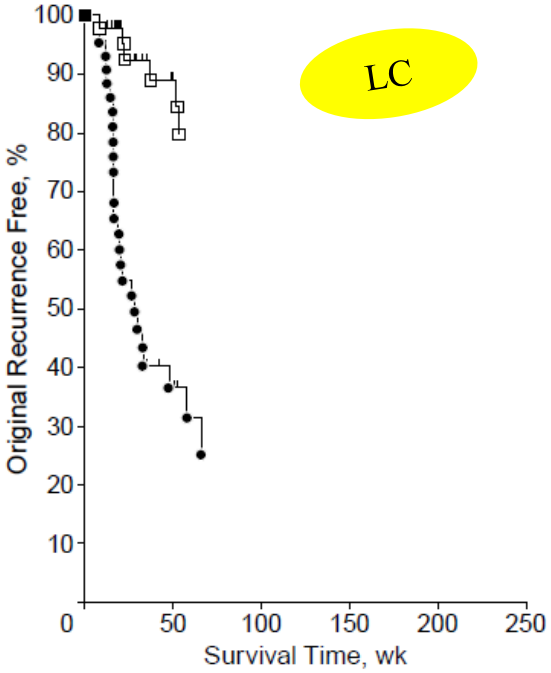
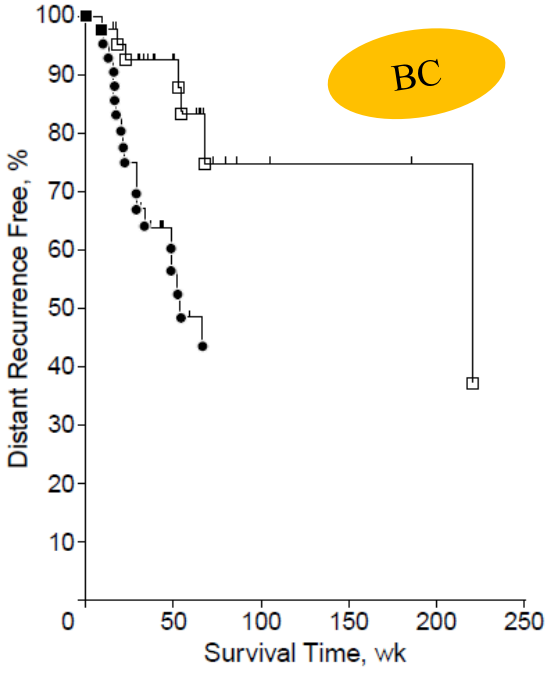
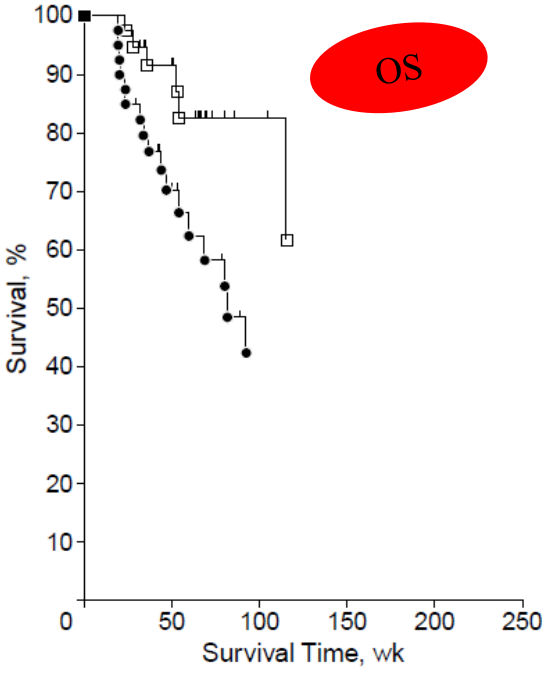
Surgical resection+WBRT versus surgical resection alone?





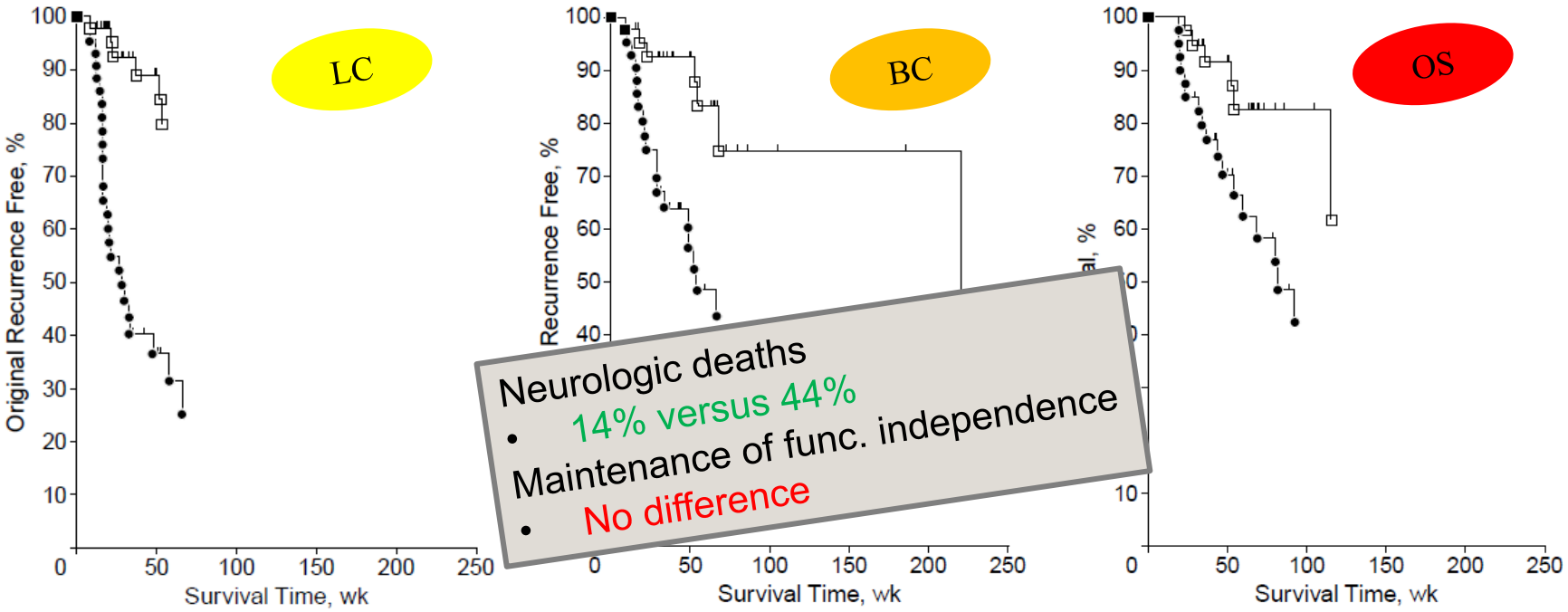


- 95 pts; single BM
- complete resection
- MRI at baseline and every 3 mts
- No neurocognitive tests

Patchell et al JAMA 1998; 280: 1485

ESTRO School

Surgical resection+WBRT versus surgical resection alone?



- 95 pts; single BM
- complete resection
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Patchell et al JAMA 1998; 280: 1485

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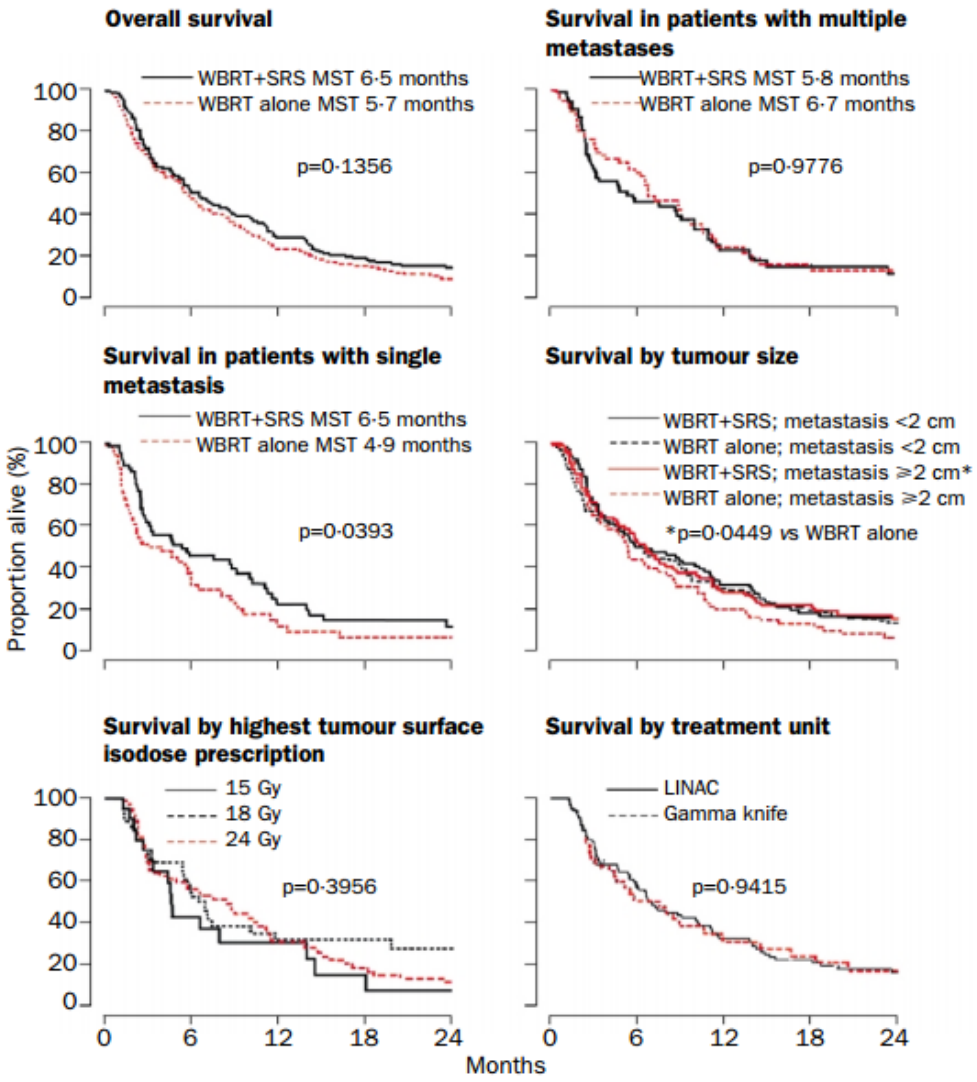
Is SRS+WBRT better than WBRT alone?



MST=mean survival time.

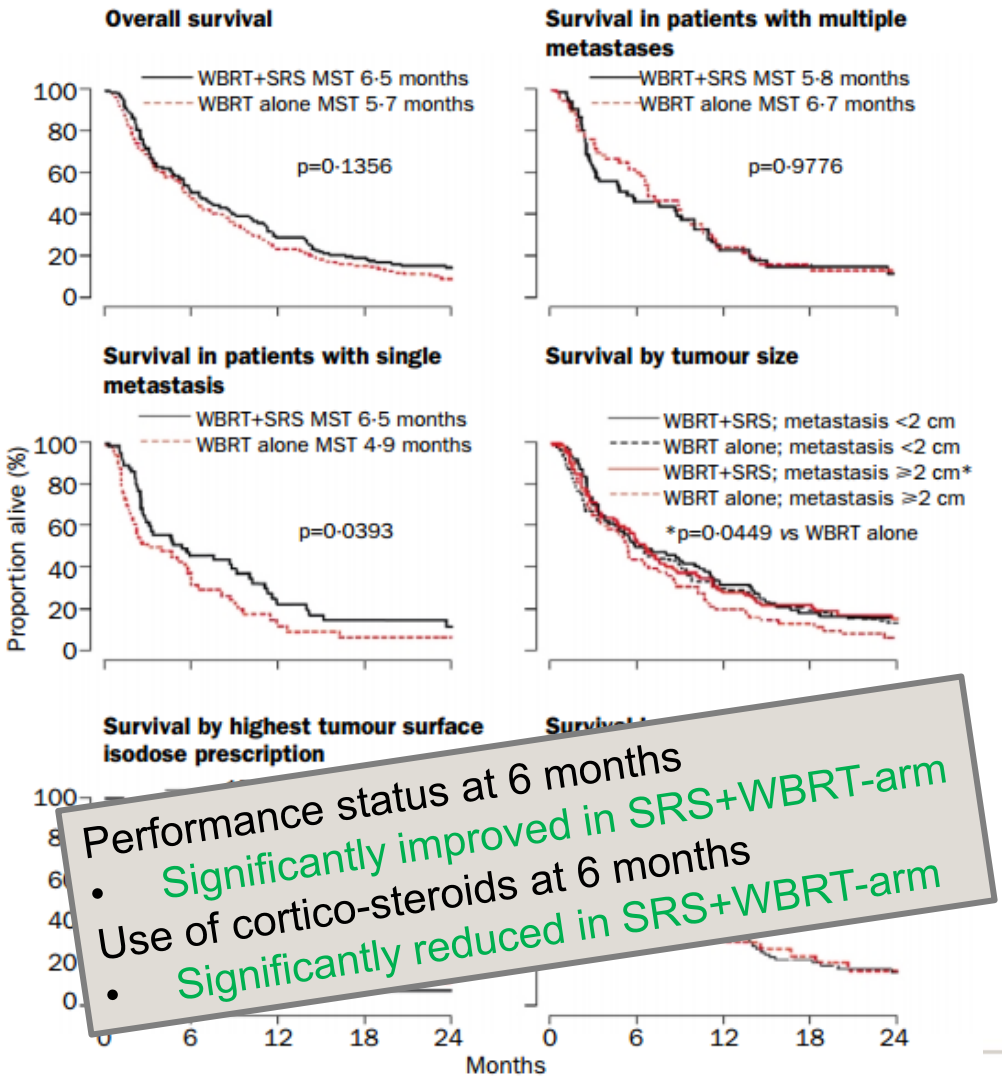
Figure 2: **Intention-to-treat outcomes by tumour size, extent of intracranial disease, radiation dose, and treatment technique**

Andrews et al Lancet 2004;363:1665

OS

Is SRS+WBRT better than WBRT alone?

N=333 pts; 1-3 BMs
RTOG 9505



Performance status at 6 months
- Significantly improved in SRS+WBRT-arm

Use of cortico-steroids at 6 months
- Significantly reduced in SRS+WBRT-arm

MST=mean survival time.

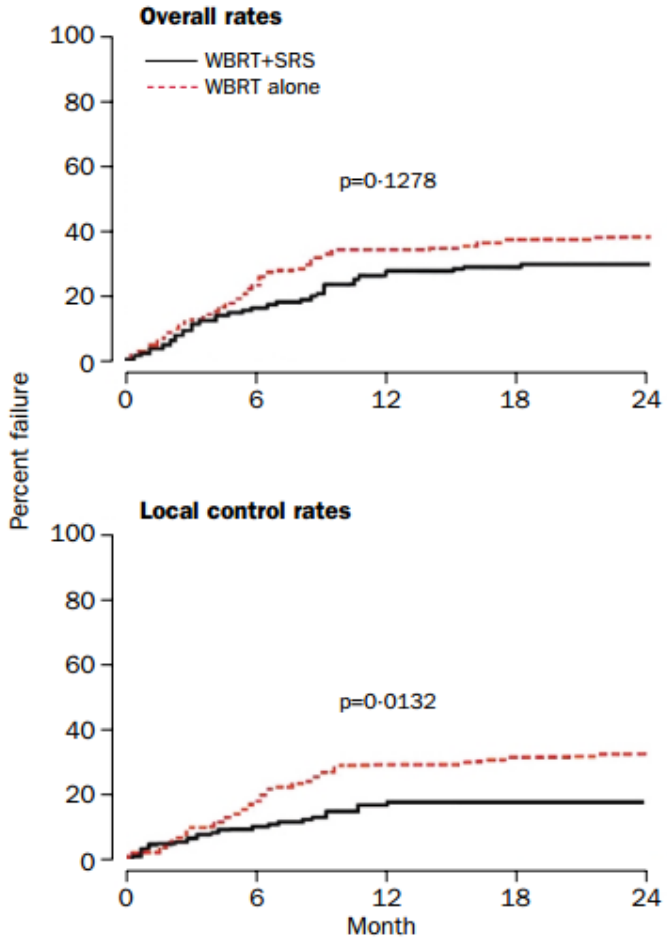
Figure 2: **Intention-to-treat outcomes by tumour size, extent of intracranial disease, radiation dose, and treatment technique**

Andrews et al Lancet 2004;363:1665

OS

ESTRO School

Is SRS+WBRT better than WBRT alone?



BC

LC

Figure 3: **Intention-to-treat intracranial disease control rates**
SRS=stereotactic surgery.

N=333 pts; 1-3 BMs
RTOG 9505
Andrews et al. Lancet 363 (9422): 1665 (2004)

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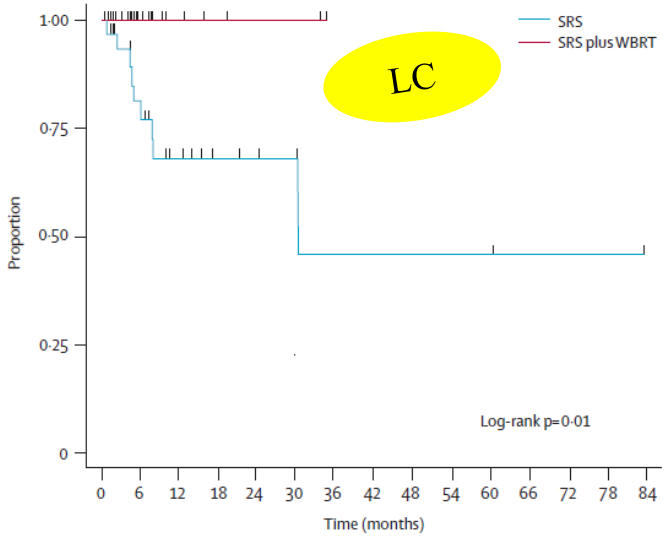
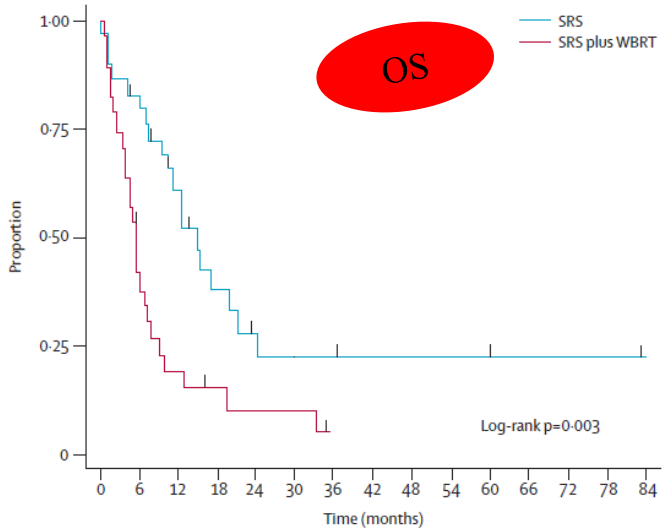
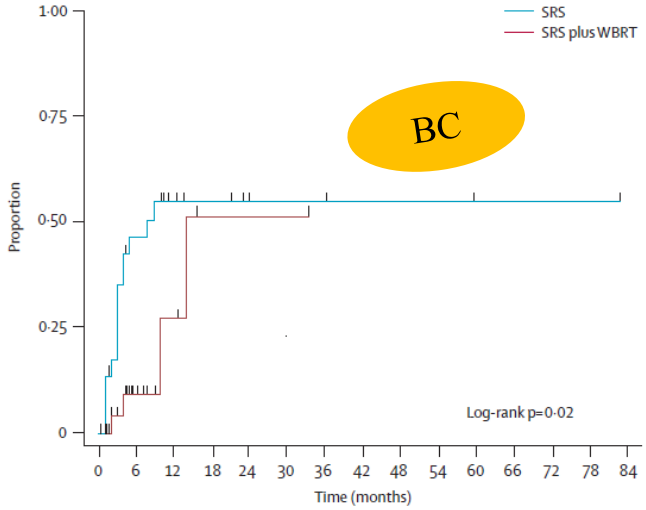
Is SRT+WBRT better than SRS?

End-point: Neurocognitive function HVLT-R (4 mts.)
N=58 (90 planned)







Imbalance in tumor volume between the two arms

Only reported at 4 mts.

Chang et al. Lancet Oncol 2009; 10: 1037

ESTRO School

Is SRT+WBRT better than SRS?

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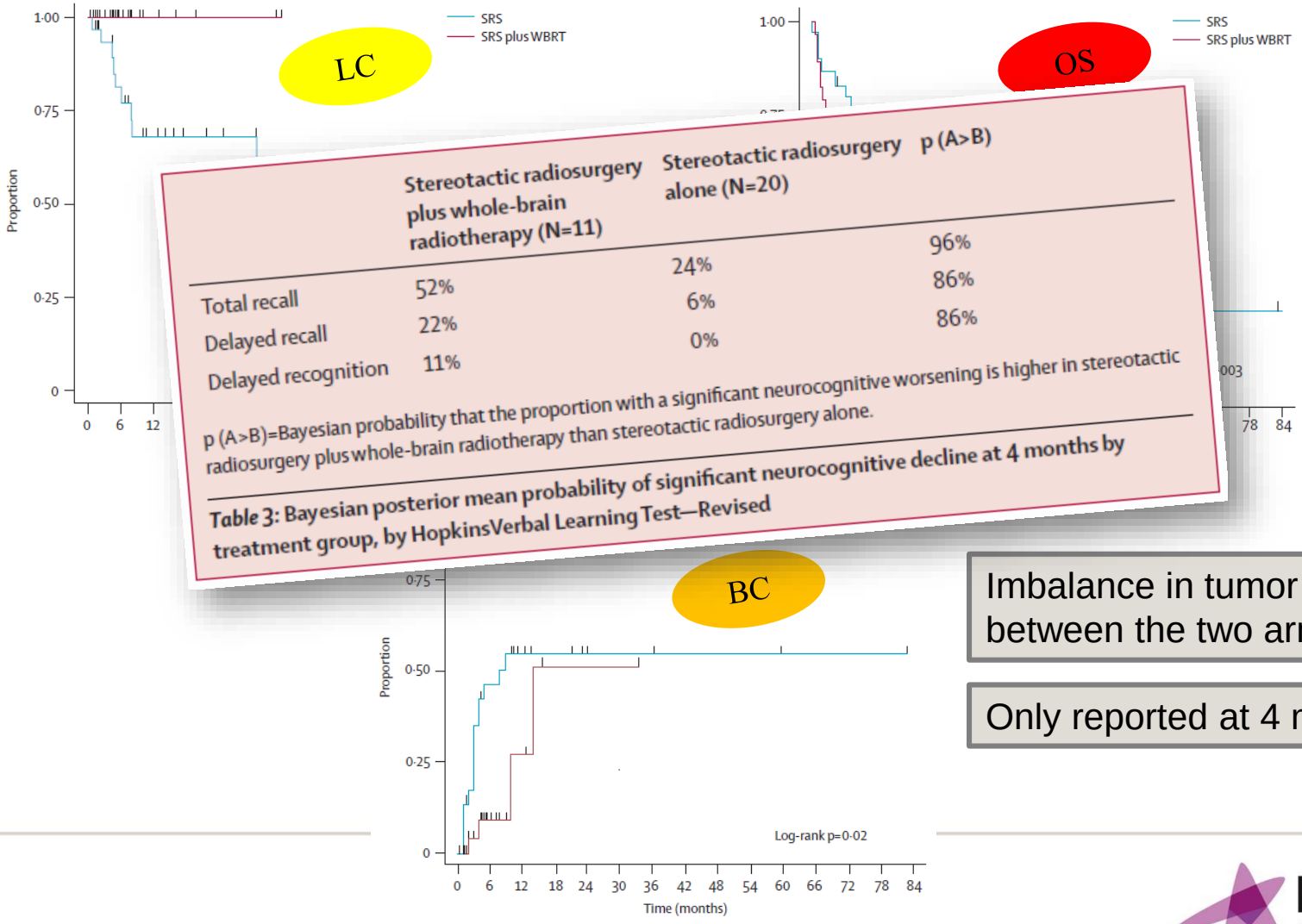

	Stereotactic radiosurgery plus whole-brain radiotherapy (N=11)	Stereotactic radiosurgery alone (N=20)	p (A>B)
Total recall	52%	24%	96%
Delayed recall	22%	6%	86%
Delayed recognition	11%	0%	86%

p (A>B)=Bayesian probability that the proportion with a significant neurocognitive worsening is higher in stereotactic radiosurgery plus whole-brain radiotherapy than stereotactic radiosurgery alone.

Table 3: Bayesian posterior mean probability of significant neurocognitive decline at 4 months by treatment group, by HopkinsVerbal Learning Test—Revised

Imbalance in tumor volume between the two arms

Only reported at 4 mts.

Chang et al. Lancet Oncol 2009; 10: 1037

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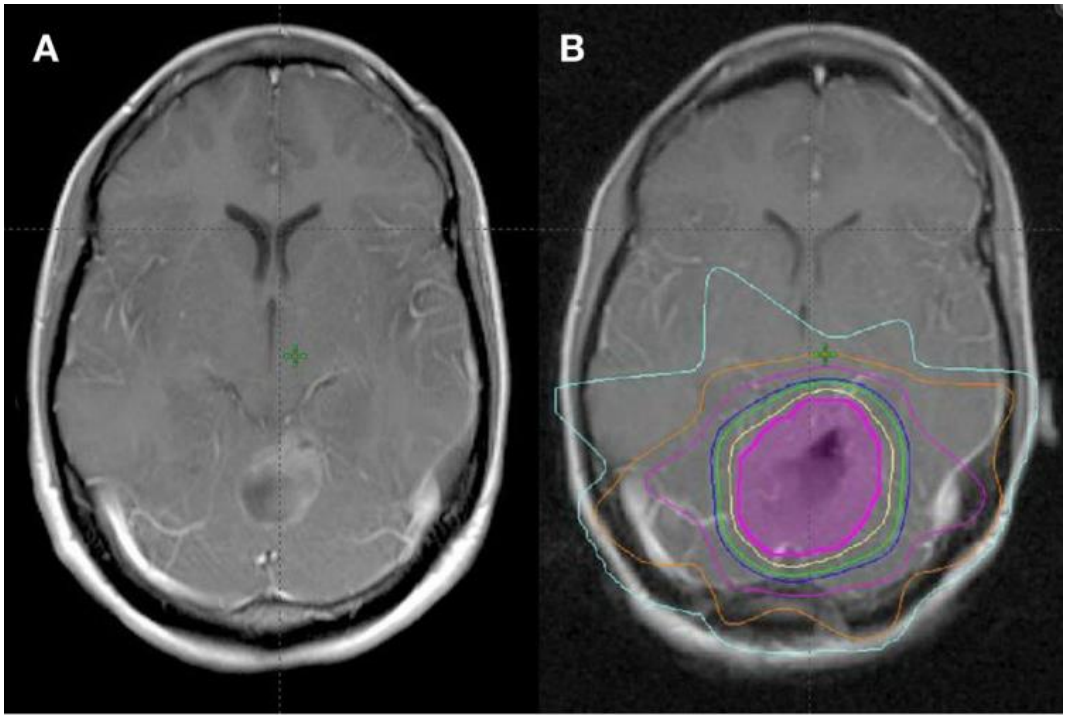
F-IMRT to the resection cavity



Fractionation examples:
40 Gy/15 frx (3 weeks)

n=58 pts

LC

LC 85% at 2 years

Shin et al.
Front Oncol. 2015; 5: 206.

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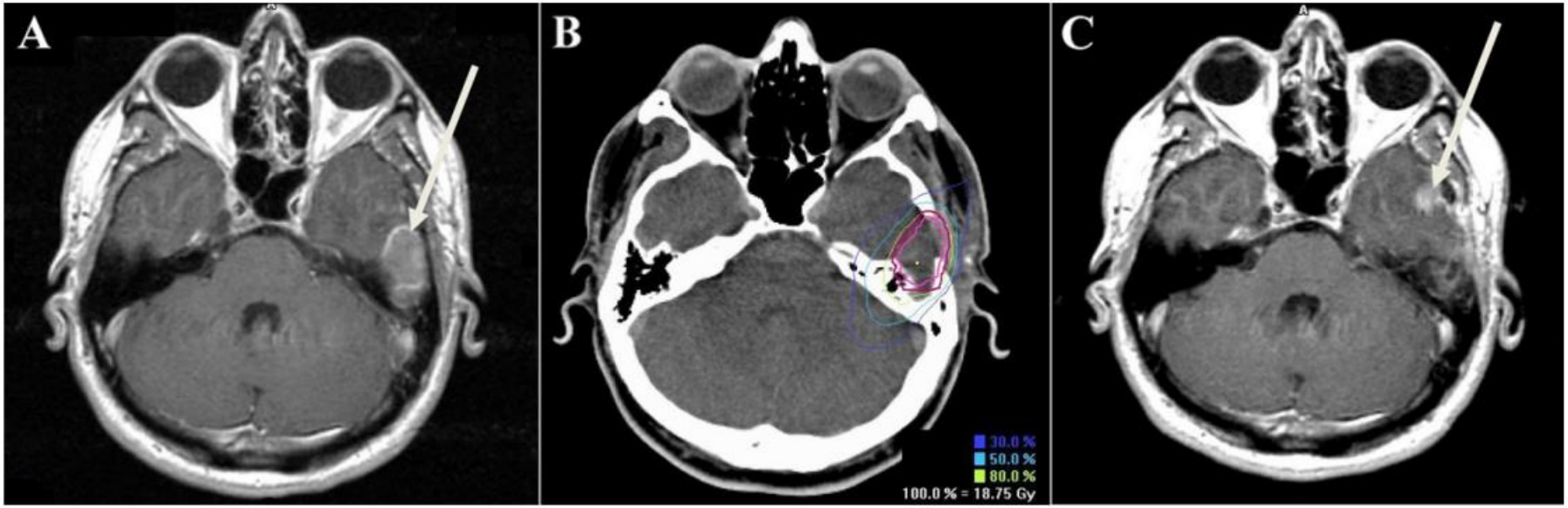
SRT of the resection cavity



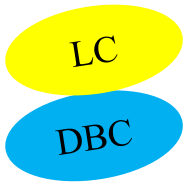
44 year-old man w. melanoma and solitary brain metastasis (A). Treated with surgical resection and SRT to the resection cavity (B). Recurrence adjacent to the treated volume (C)

Phase II, 49 pts

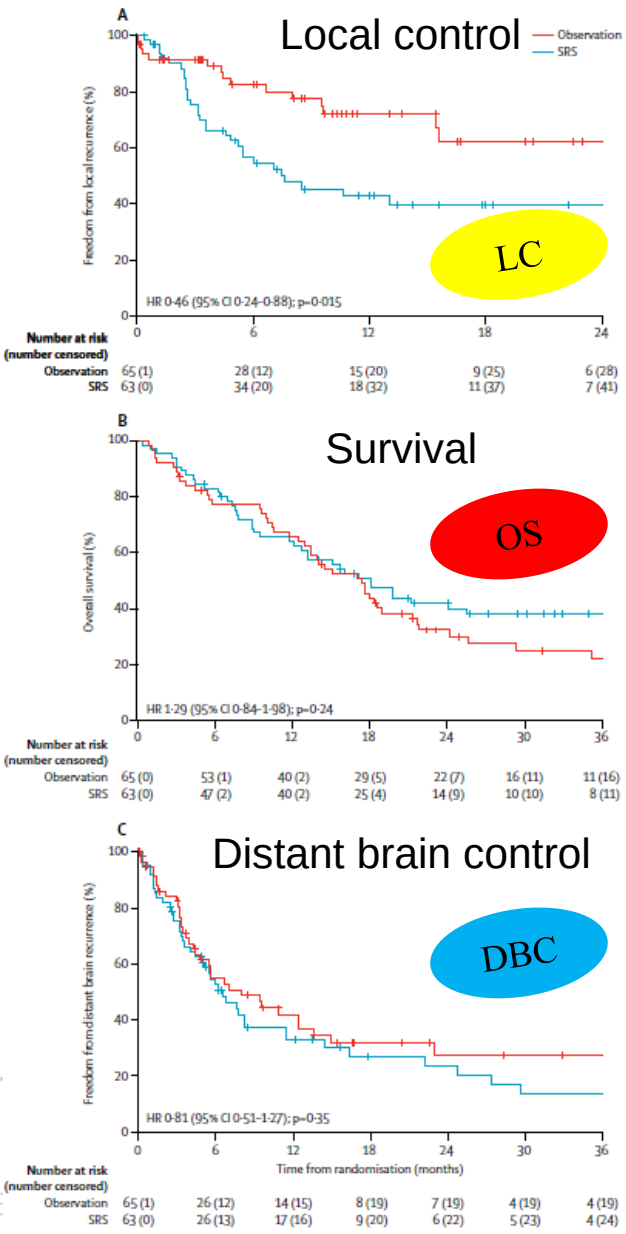
Failure rates after SRT

LF = 22%

DBF = 44%



SRS to the resection cavity



- SRT vs no SRT to resection cavity
- Complete resection of 1-3 brain mets
- Local recurrence was 43% vs. 72%
  HR 0·46 [95% CI 0·24–0·88]; =0·015
- No adverse events in the two groups
- MD Anderson; N=132

Mahajan et al Lancet Oncol 2017, in press

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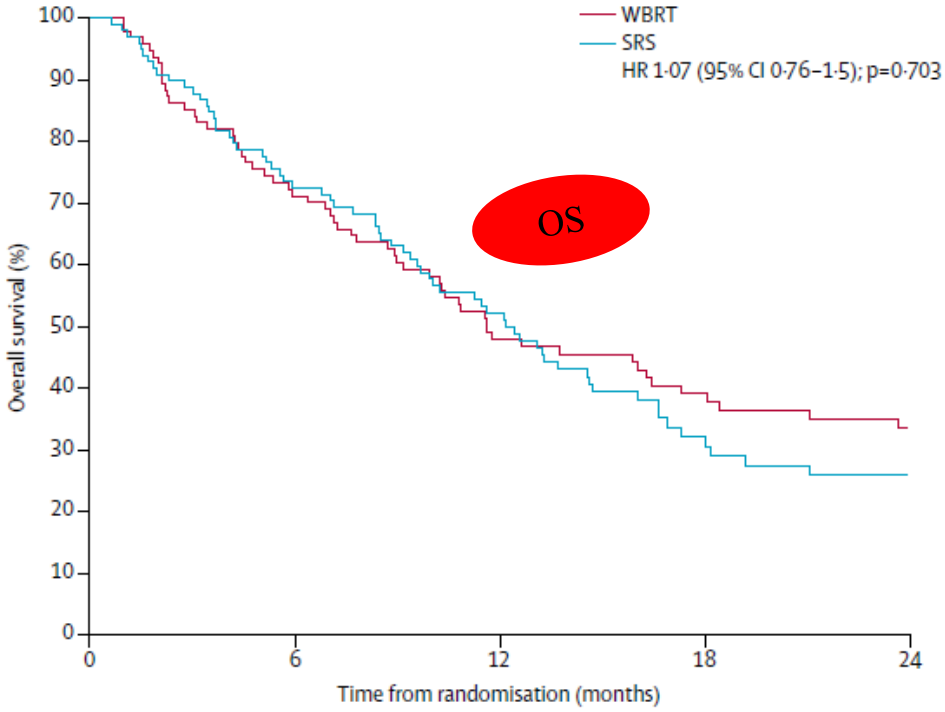
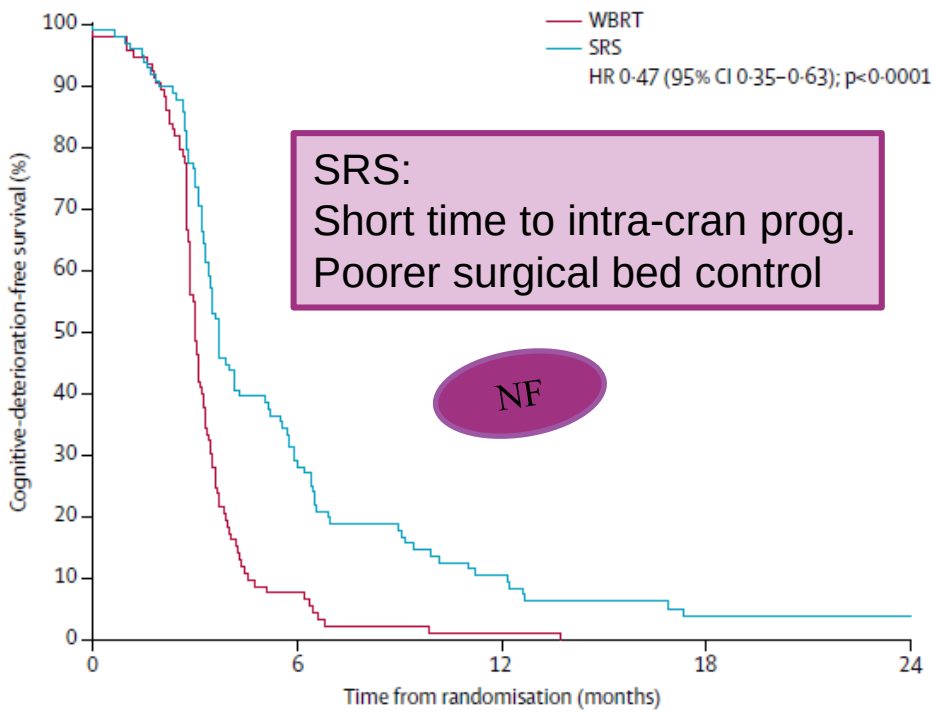
SRS to resection cavity

SRT to resection cavity vs WBRT
Complete resection of solitary brain mets
Multi-Inst (48); N=132
Neurocognitive testing, QoL





Brown et al Lancet Oncol 2017, in press

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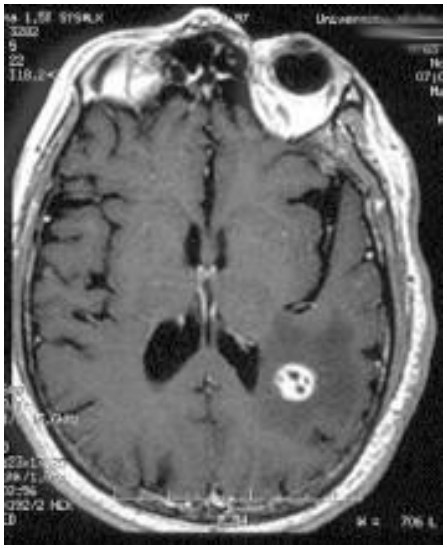
SRT or surgical resection?

SRS

Metastases < 3 cm

(Deep/central)



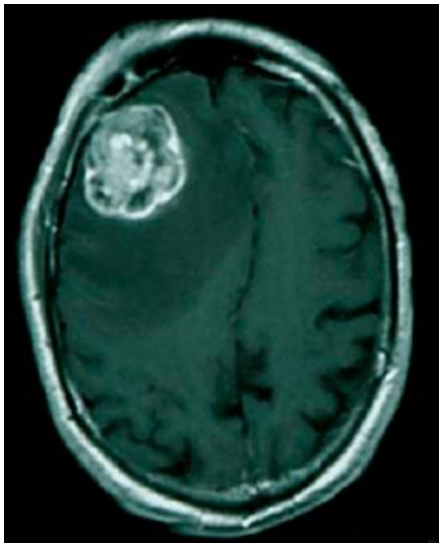
Resection

Metastases > 3-4 cm

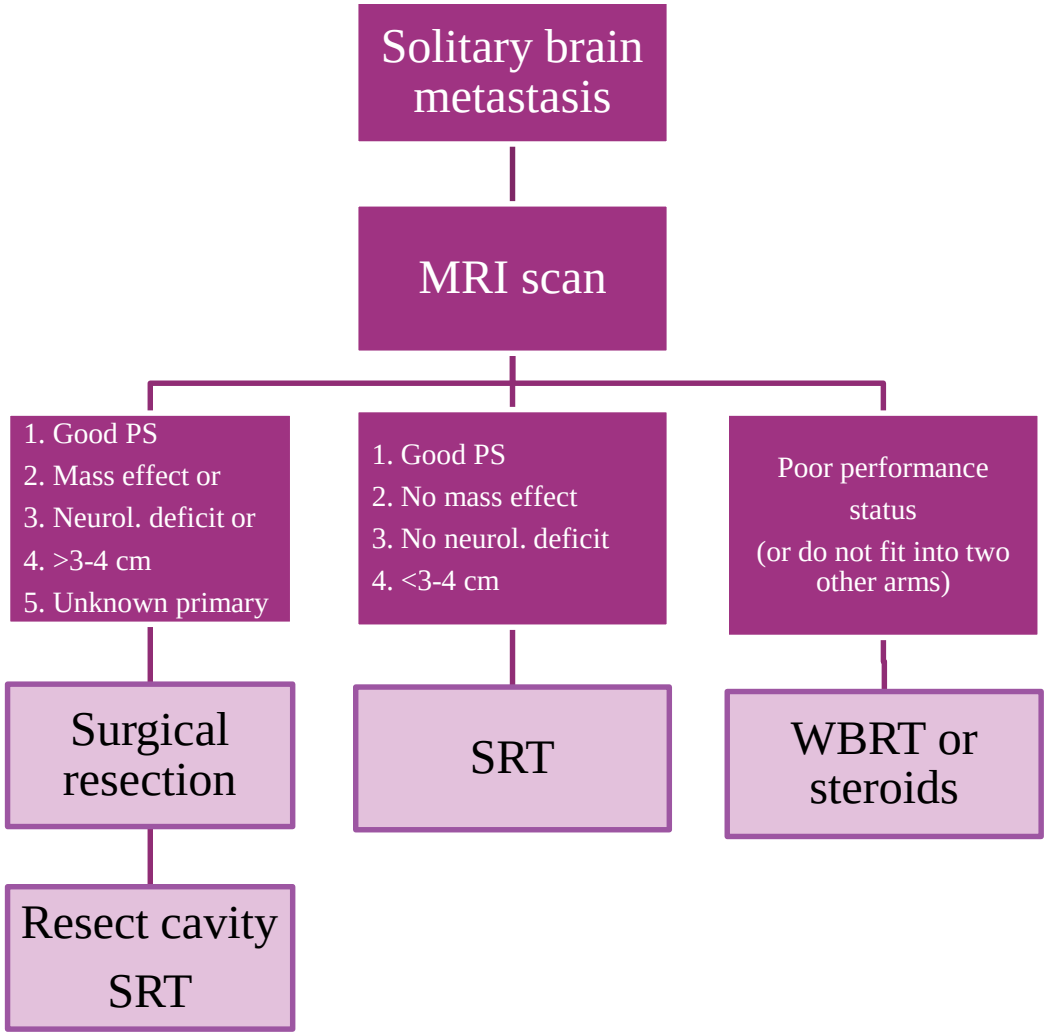
Mass effects

Neurological deficits

(Superficial and eloquent)



Algoritm for therapy of solitary brain metastasis at AUH



Addtional factors:

- Age
- Performance status
- Metastasis localization
- Patient's preferences

- Highly chemosensitive cancers with brain mets should be treated with chemotherapy

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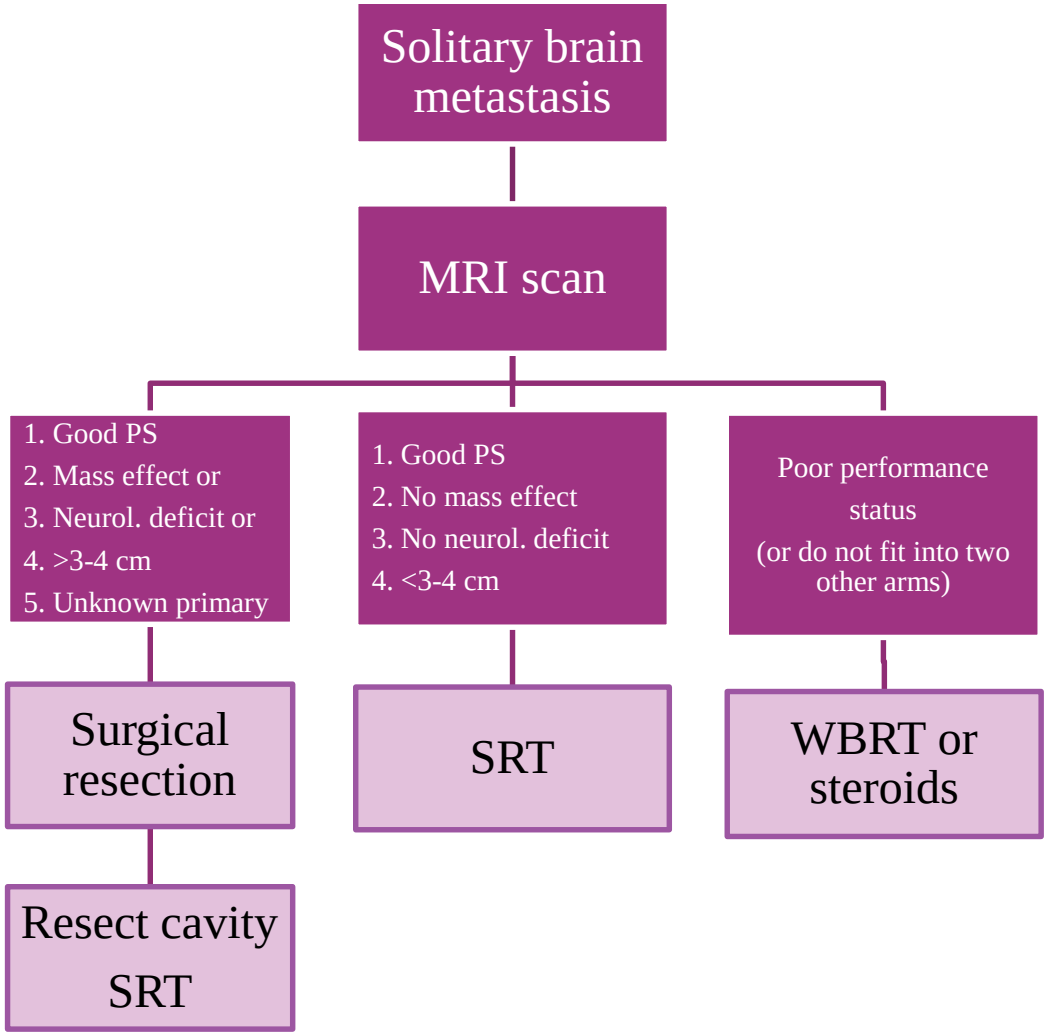
Algoritm for therapy of solitary brain metastasis at AUH



Addtional factors:

- Age
- Performance status
- Metastasis localization
- Patient's preferences

- Highly chemosensitive cancers with brain mets should be treated with chemotherapy

End of talk!

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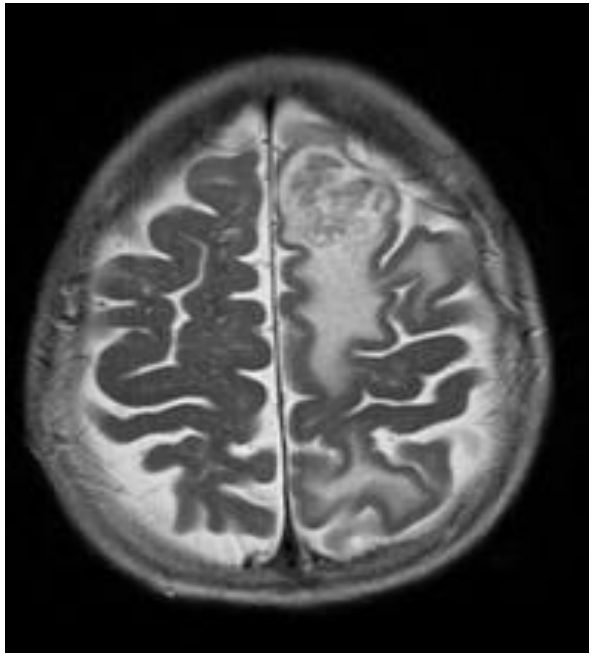
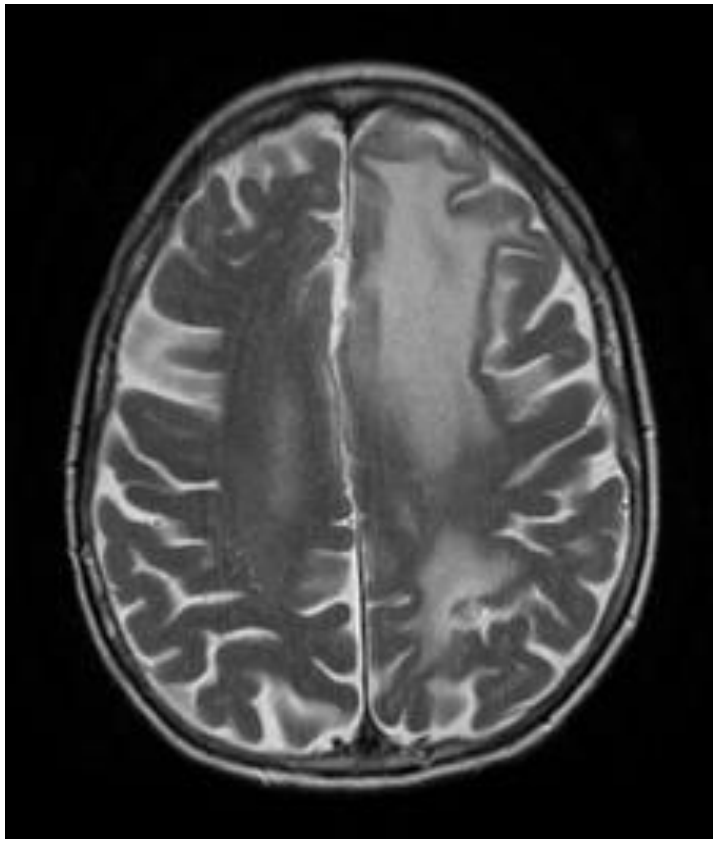
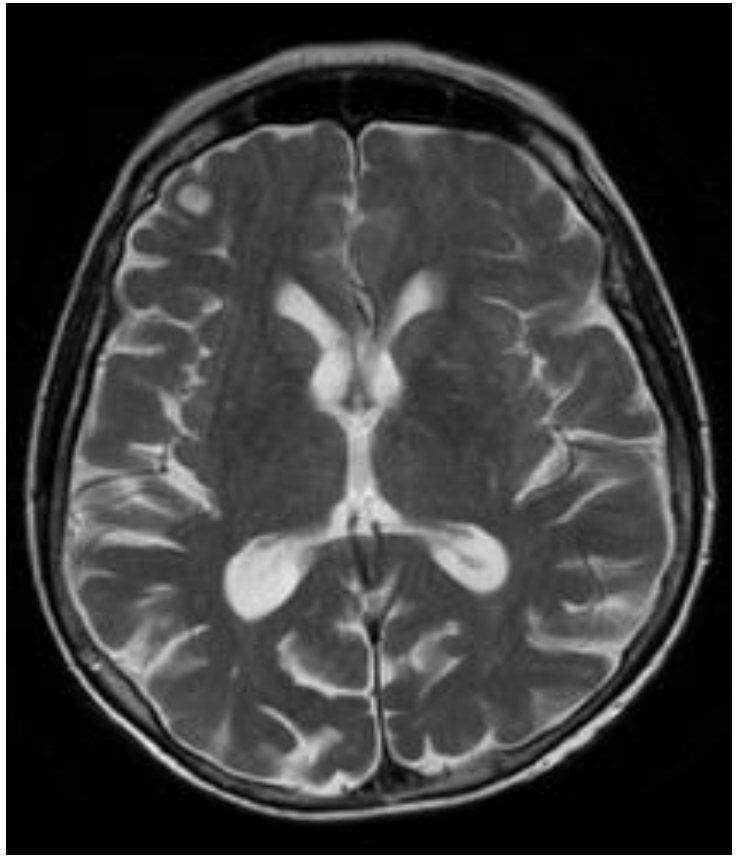
Management of multiple brain metastases

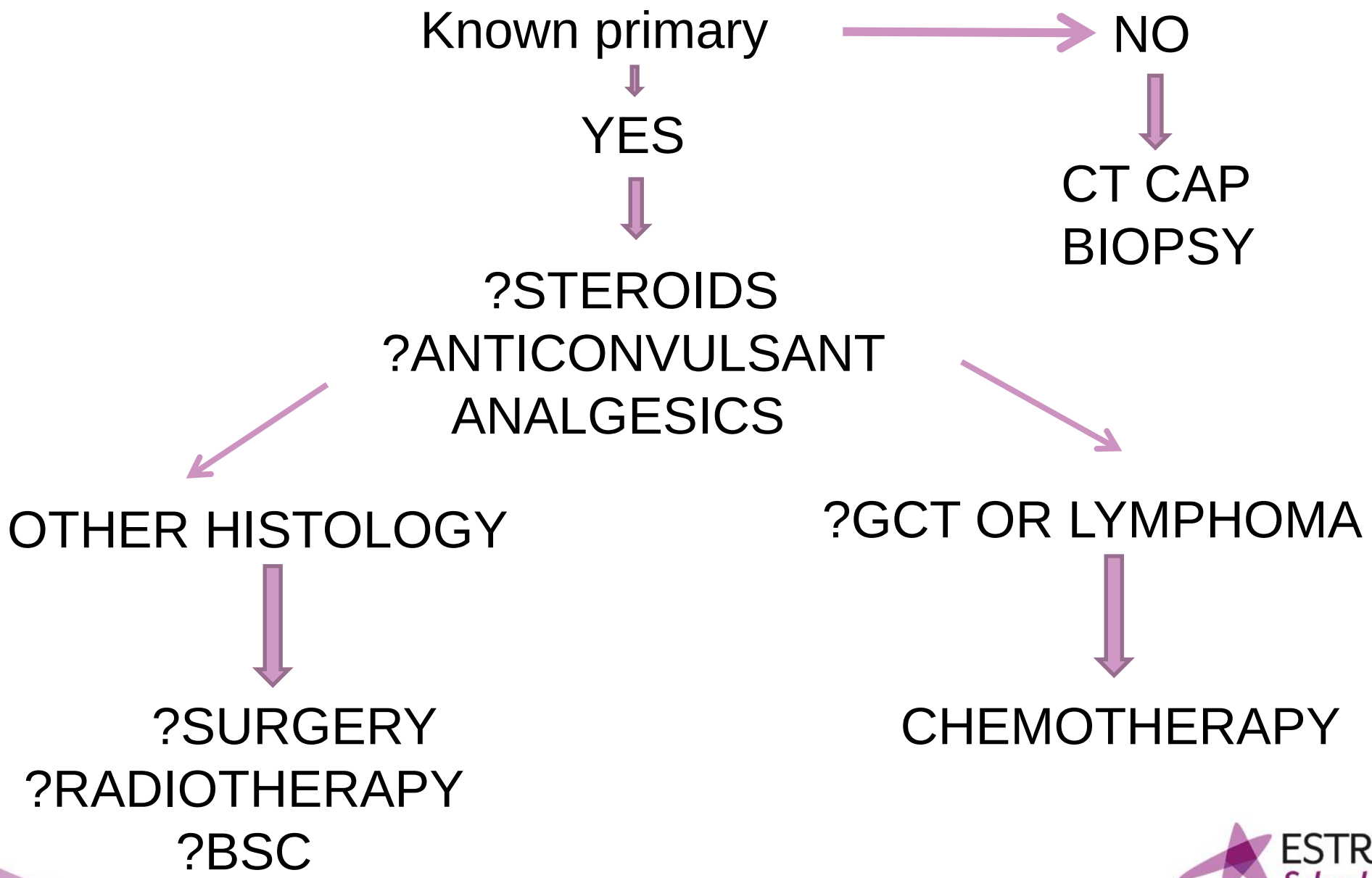
By
Peter Hoskin







Suspicious symptoms
radiological diagnosis of
brain metastases



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Multiple brain metastases

Radiotherapy

- Dose fractionation
- Patient selection

Chemotherapy

- Patient selection

Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases (Review)

Tsao MN, Lloyd N, Wong RKS, Chow E, Rakovitch E, Laperriere N, Xu W, Sahgal A

Dose >30Gy/10f vs 30Gy/10f control

SURVIVAL

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Chatani 1985	-0.7487 (0.2907)		6.9 %	0.47 [0.27, 0.84]
Chatani 1994	0.0435 (0.2169)		12.4 %	1.04 [0.68, 1.60]
Kurtz 1981	-0.0747 (0.1367)		31.2 %	0.93 [0.71, 1.21]
Murray 1997	0.0698 (0.1085)		49.5 %	1.07 [0.87, 1.33]
Total (95% CI)			**100.0 %**	**0.97 [0.83, 1.12]**

Dose <30Gy/10f vs 30Gy/10f control

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Chatani 1994	0.0171 (0.239)		10.0 %	1.02 [0.64, 1.63]
Harwood 1977	0.3461 (0.199)		14.4 %	1.41 [0.96, 2.09]
Priestman 1996	0.179 (0.087)		75.5 %	1.20 [1.01, 1.42]
Total (95% CI)			**100.0 %**	**1.21 [1.04, 1.40]**

Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases (Review)

Tsao MN, Lloyd N, Wong RKS, Chow E, Rakovitch E, Laperriere N, Xu W, Sahgal A

Dose >30Gy/10f vs 30Gy/10f control

LOCAL CONTROL

Study or subgroup	Higher dose n/N	Control dose n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Borgelt 1980	346/741	156/359		74.1 %	1.14 [0.88, 1.47]
Chatani 1985	25/34	26/35		4.1 %	0.96 [0.33, 2.82]
Chatani 1994	32/46	57/81		7.7 %	0.96 [0.44, 2.12]
Kurtz 1981	45/86	44/98		14.1 %	1.35 [0.75, 2.41]
Total (95% CI)	**907**	**573**		**100.0 %**	**1.14 [0.92, 1.42]**

Dose <30Gy/10f vs 30Gy/10f control

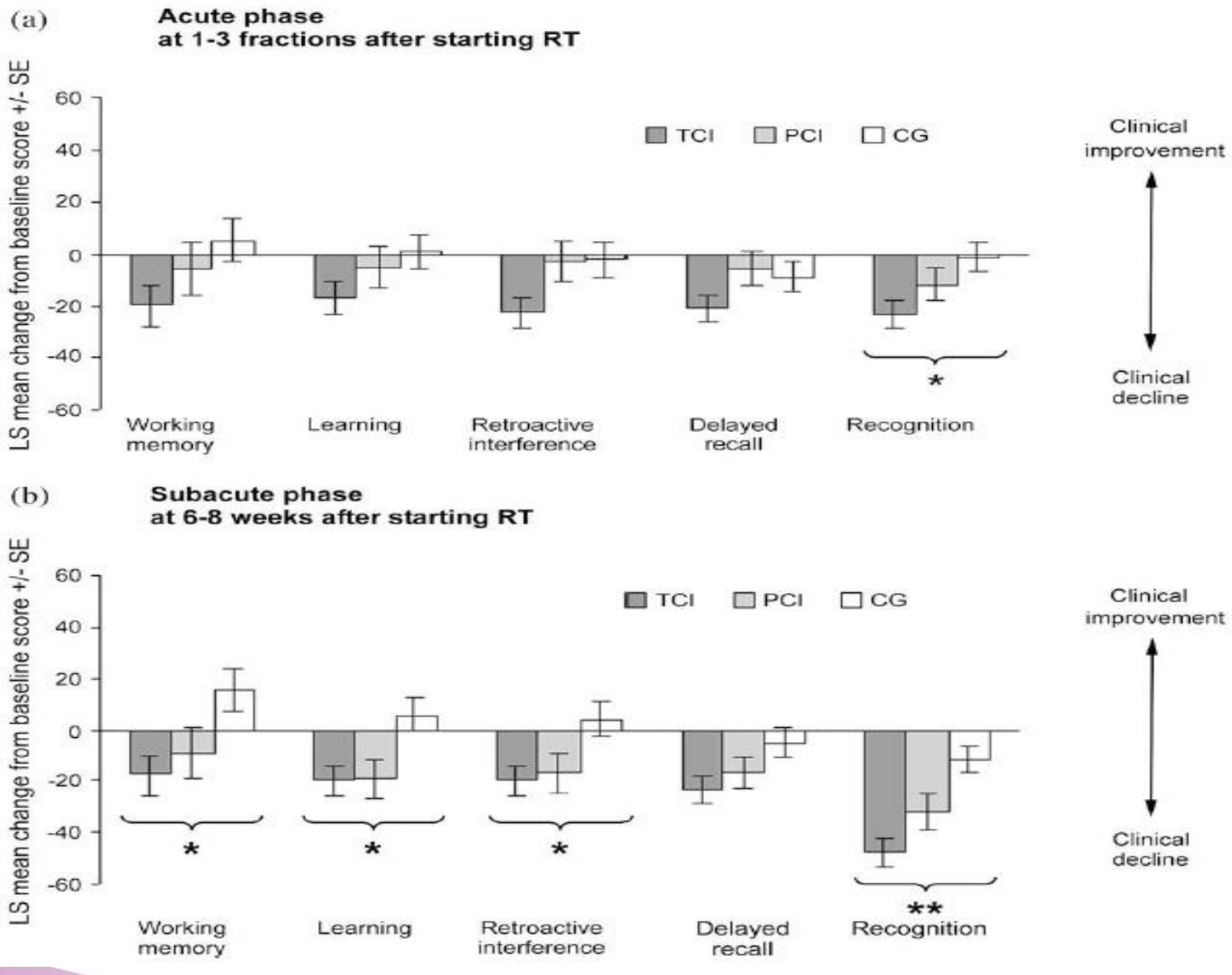
Study or subgroup	Lower dose n/N	Control dose n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Harwood 1977	22/51	18/50		16.3 %	1.35 [0.61, 3.00]
Borgelt 1980	250/353	156/359		25.9 %	3.16 [2.32, 4.31]
Borgelt 1981	38/68	41/82		19.3 %	1.27 [0.66, 2.42]
Chatani 1994	29/35	57/81		13.1 %	2.04 [0.75, 5.53]
Priestman 1996	163/270	142/263		25.3 %	1.30 [0.92, 1.83]
Total (95% CI)	**777**	**835**		**100.0 %**	**1.74 [1.06, 2.84]**

MEMORY FUNCTION BEFORE AND AFTER WHOLE BRAIN RADIOTHERAPY IN PATIENTS WITH AND WITHOUT BRAIN METASTASES

GRIT WELZEL, M.SC.,* KATHARINA FLECKENSTEIN, M.D.,*† JÖRG SCHAEFER, M.D.,* BRIGITTE HERMANN, M.D.,* UTA KRAUS-TIEFENBACHER, M.D.,* SABINE K. MAI, M.D.,* AND FREDERIK WENZ, M.D.*

*Department of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany; and †Department of Radiation Oncology, Duke University Medical Center, Durham, NC

Int. J. Radiation Oncology Biol. Phys., Vol. 72, No. 5, pp. 1311–1318, 2008

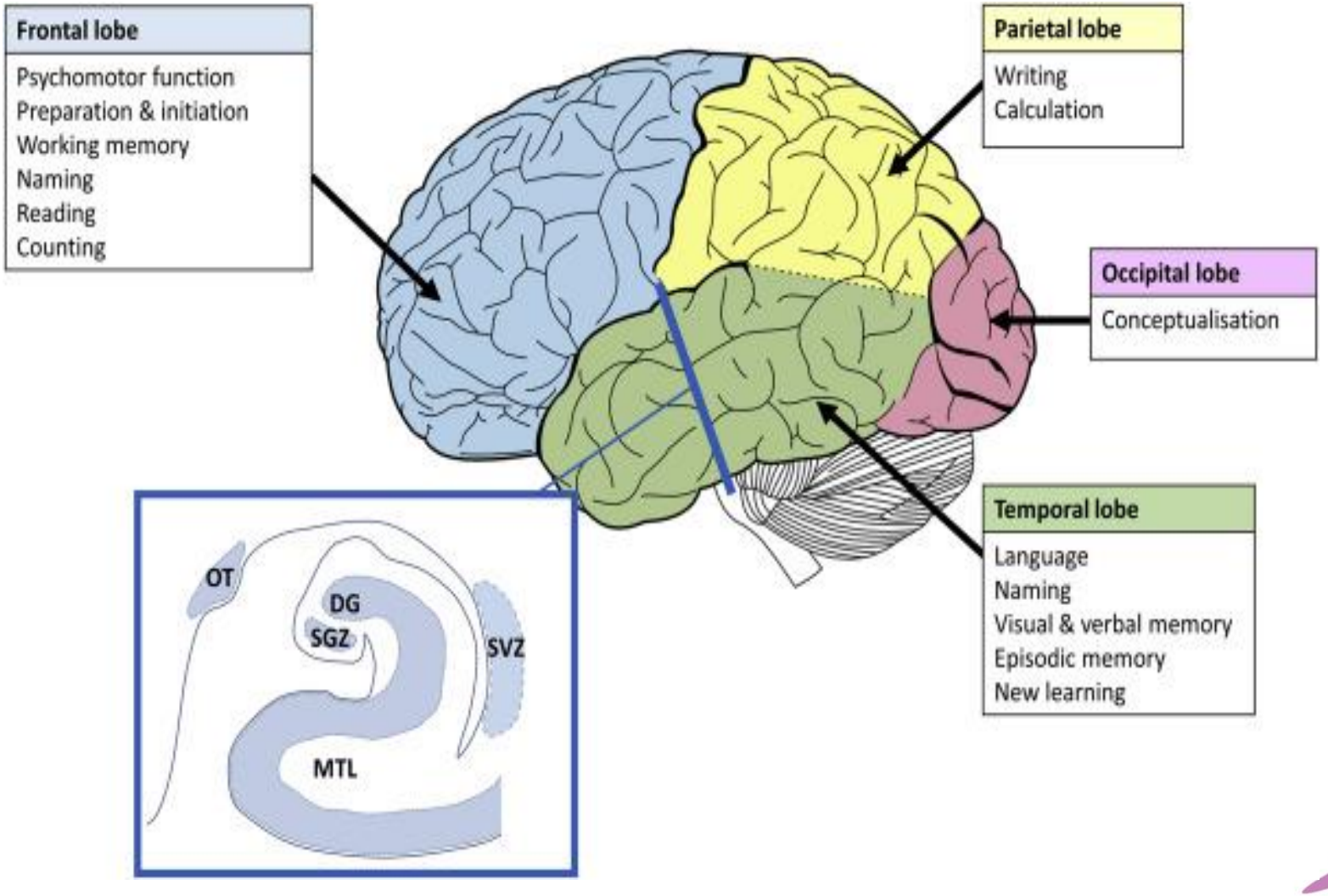


Neurocognitive Effects Following Cranial Irradiation for Brain Metastases

Clinical Oncology 27 (2015) 630–639

M.B. Pinkham *†, P. Sanghera ‡, G.K. Wall §, B.D. Dawson §, G.A. Whitfield *

Hippocampal sparing



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Neurocognitive Effects Following Cranial Irradiation for Brain Metastases

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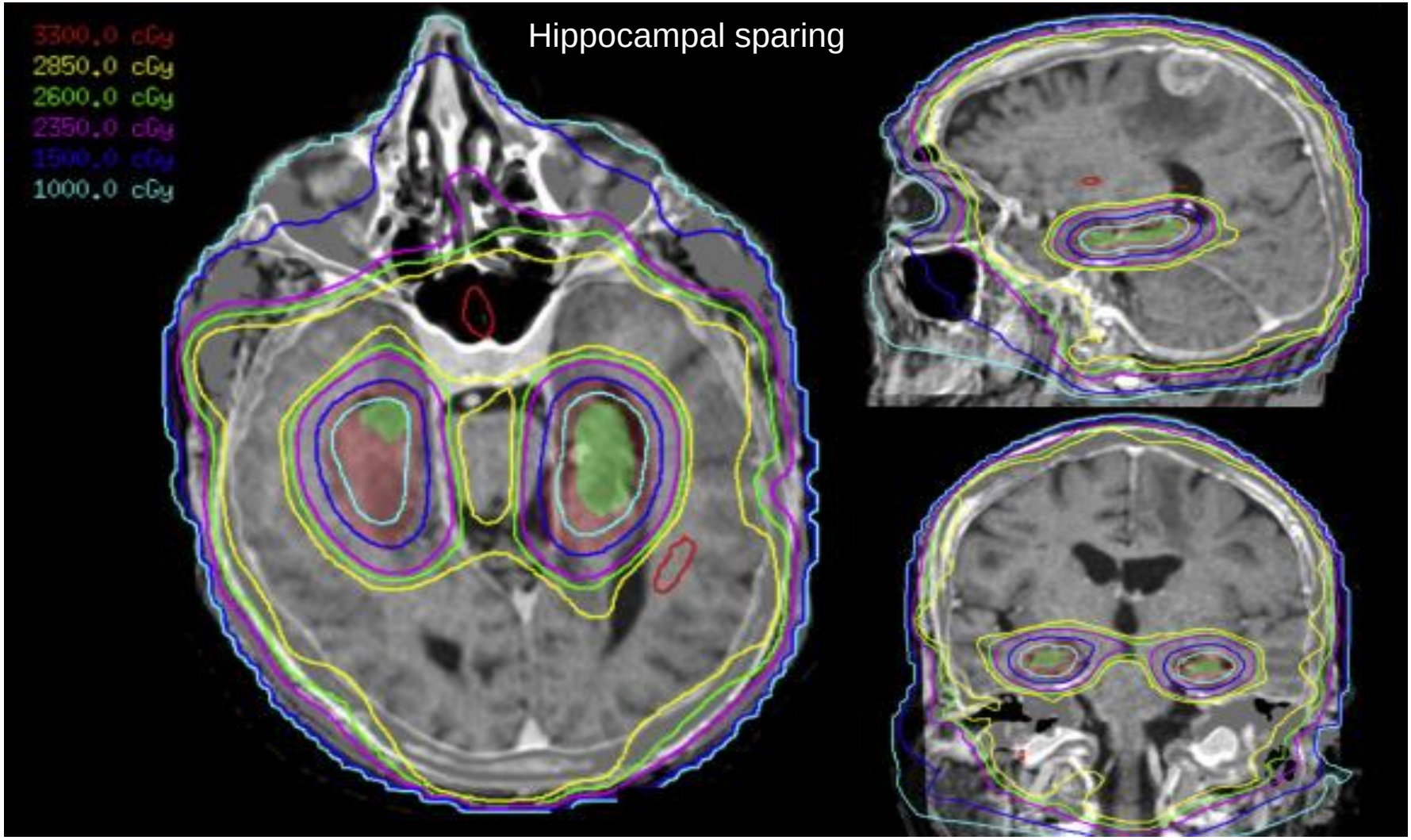
M.B. Pinkham *†, P. Sanghera ‡, G.K. Wall §, B.D. Dawson §, G.A. Whitfield *



Delayed recall after EQD2 >7Gy to 40% of hippocampus

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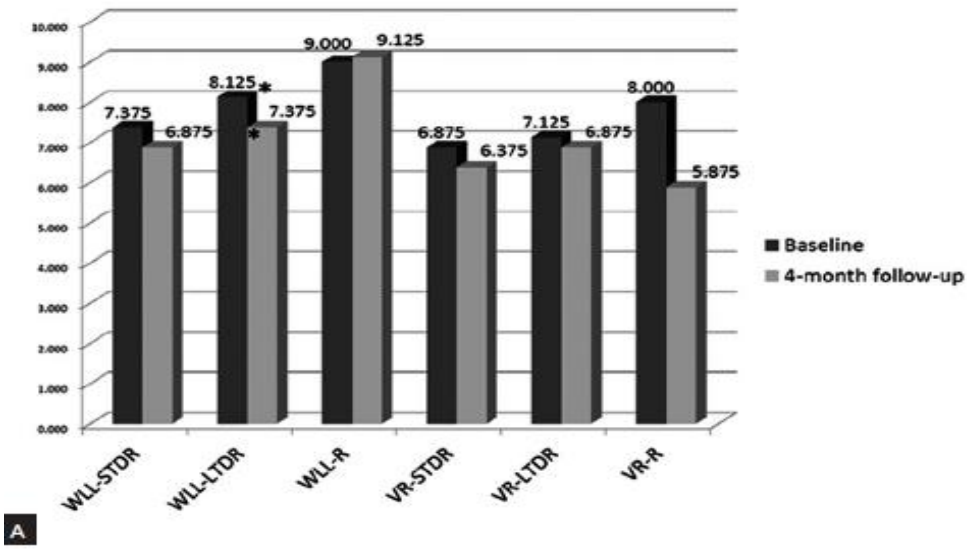
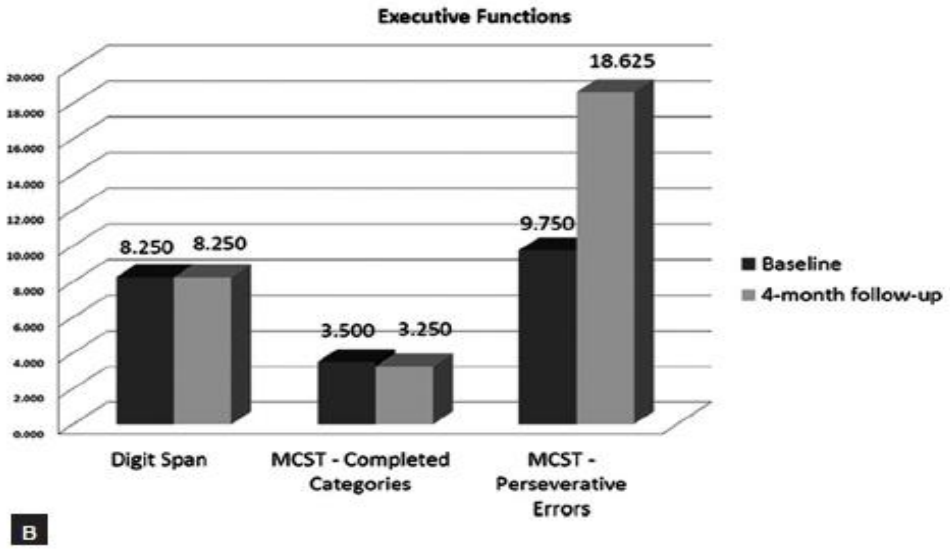
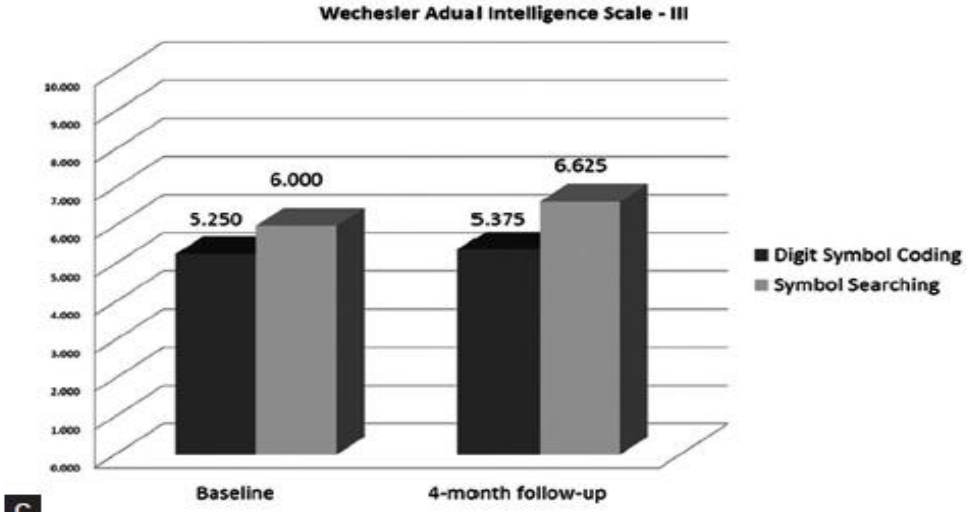
Evaluating the Impact of Hippocampal Sparing During Whole Brain Radiotherapy on Neurocognitive Functions: A Preliminary Report of a Prospective Phase II Study

(Biomed J 2015;38:439-449)

Shinn-Yn Lin[1,2,3], Chi-Cheng Yang[4], Yi-Ming Wu[5], Chen-Kan Tseng[1,2], Kuo-Chen Wei[6], Yi-Chuan Chu[7], Hsiang-Yao Hsieh[7], Tung-Ho Wu[1,2], Ping-Ching Pai[1,2], Peng-Wei Hsu[6], Chi-Cheng Chuang[6]







Chemotherapy for brain metastases

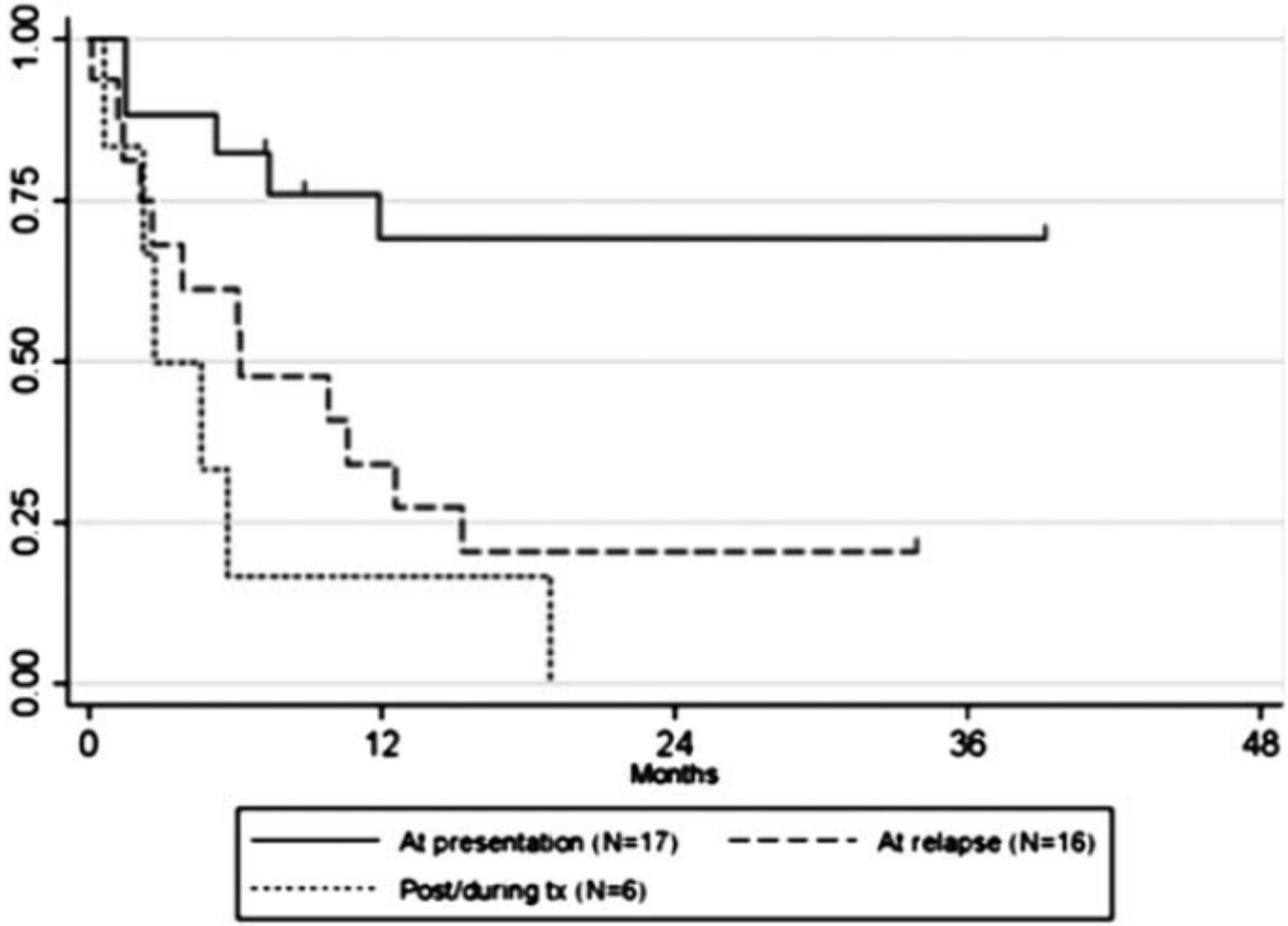
Highly chemosensitive tumours:

- Germ cell, Lymphoma

Brain Metastases Associated With Germ Cell Tumors May Be Treated With Chemotherapy Alone

Cancer 2014;120:1639–46.

Anna Hardt, MRCP[1]; Jonathan Krell, MRCP[2]; Peter D. Wilson, FRCP[1]; Victoria Harding, MRCP[3]; Simon Chowdhury, FRCP[3]; Danish Mazhar, FRCP[4]; Dan Berney, FRCP[1]; Justin Stebbing, FRCP[2]; and Jonathan Shamash, FRCP[1]



n=39

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Systemic treatments for brain metastases from breast cancer, non-small cell lung cancer, melanoma and renal cell carcinoma: An overview of the literature

Cancer Treatment Reviews 40 (2014) 951–959

Breast

Author	PTS	Regimen	RR (%)	PFS (ms)	OS (ms)
Cytotoxic drugs					
Freedman et al. [7]	15	Sagopilone	13.3	1.4	5.3
Siena et al. [5]	51	Temozolomide	4	1.9	NR
Cassier et al. [3]	25	Cisplatin + vinorelbine + RT	76	3.7	6.5
Rivera et al. [6]	24	Capecitabine + temozolomide	18	12 wks	NA
Franciosi et al. [4]	56	Cisplatin + etoposide	38	4	8
Targeted therapies					
Brufsky et al. [8]	258	Trastuzumab vs. no use	NA	NA	17.5 vs. 3.9
Lin et al. [11]	39	Lapatinib	2.6	3	NR
	242	Lapatinib	6	2.4	6.4
Lin et al. [12]	(50)	(Lapatinib + capecitabine)	(20)	(3.6)	
Lin et al. [13]	22	Lapatinib + capecitabine vs. lapatinib + topotecan	38 vs. 0	NA	NA
Bachelot et al. [14]	44	Lapatinib + capecitabine	66	5.5	17
Lin et al. [15]	35	Lapatinib + RT	79	4.8	19

Lung

Author	PTS	Regimen	RR (%)	mPFS (ms)	OS (ms)
Franciosi et al. [4]	43	Cisplatin–etoposide	30	4	8
Cortes et al. [20]	26	Cisplatin–taxol	38	3.2	5.3
Cotto et al. [77]	31	Cisplatin–fotemustine	23	5	4
Fujita et al. [78]	30	Cisplatine–ifosfamide–CPT11	50	4.6	12
Dinglin et al. [19]	42	Pemetrexed–cisplatin	68	10.6	12.6
Kleisbauer et al. [21]	24	Cisplatin	30	NA	NA
Siena et al. [5]	53	TMZ	NA	66 days	172 days
Giorgio et al. [24]	30	TMZ	10	3.6 ms	6 ms
Quantin et al. [22]	23	RT + vinorelbine–ifosfamide–cisplatin	30	NA	7.6

Non-small cell lung cancer patients with brain metastases treated with first-line platinum-doublet chemotherapy: Analysis from the European FRAME study☆

Lung Cancer 90 (2015) 427–432

Denis Moro-Sibilot[a,*], Egbert Smit[b], Javier de Castro Carpeño[c], Krzysztof Lesniewski-Kmak[d], Joachim G. Aerts[e,f], Rosa Villatoro[g], Kees Kraaij[h], Karim Nacerddine[i], Yulia Dyachkova[j], Karen T. Smith[k], Allicia Girvan[k], Carla Visseren-Grul[h], Philipp A. Schnabel[l]

A *post-hoc* subgroup analysis was performed for patients with brain metastases

Survival data.

	Patients with brain metastases					All patients in FRAME
	Pem + Plt (n = 117)	Gem + Plt (n = 49)	Tax + Plt (n = 54)	Vin + Plt (n = 38)	Total (n = 258[a])	Total (n = 1524[a])
Median (95% CI) OS, months	9.3 (6.2–11.9)	5.6 (4.1–8.4)	6.6 (3.7–7.8)	6.7 (5.2–9.3)	7.2 (6.1–8.2)	10.3 (9.5–11.2)
Median (95% CI) PFS, months	4.0 (3.0–5.8)	3.5 (2.4–5.6)	2.9 (2.1–4.1)	3.7 (2.6–5.2)	3.6 (3.1–4.4)	5.6 (5.1–6.1)
1-year survival rate (95% CI), %	39 (29–48)	25 (13–37)	19 (8–30)	22 (8–36)	30 (24–36)	45 (42–48)

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Systemic treatments for brain metastases from breast cancer, non-small cell lung cancer, melanoma and renal cell carcinoma: An overview of the literature

Cancer Treatment Reviews 40 (2014) 951–959

Melanoma

Author	PTS	Regimen	RR (%)	mPFS (wks)	mOS (wks)
Jacquillat et al. [39]	36	Fotemustine	25	NA	NA
Avril et al. [40]	22	Fotemustine	5.9	NA	NA
Mornex et al. [41]	37	Fotemustine + RT	10	8	15
Margolin et al. [42]	31	Temozolomide + RT	9	8	24
Atkins et al. [43]	39	Temozolomide + RT + Talidomide	7.6	7	16
Margolin et al. [50]	51	Ipilimumab	16	10.7	28
Queirolo et al. [51]	146	Ipilimumab	11	11.2	17.2
Falchook et al. [54]	10	Dabrafenib	90	16.8	32
Dummer et al. [56]	24	Vemurafenib	52	16	30

Renal

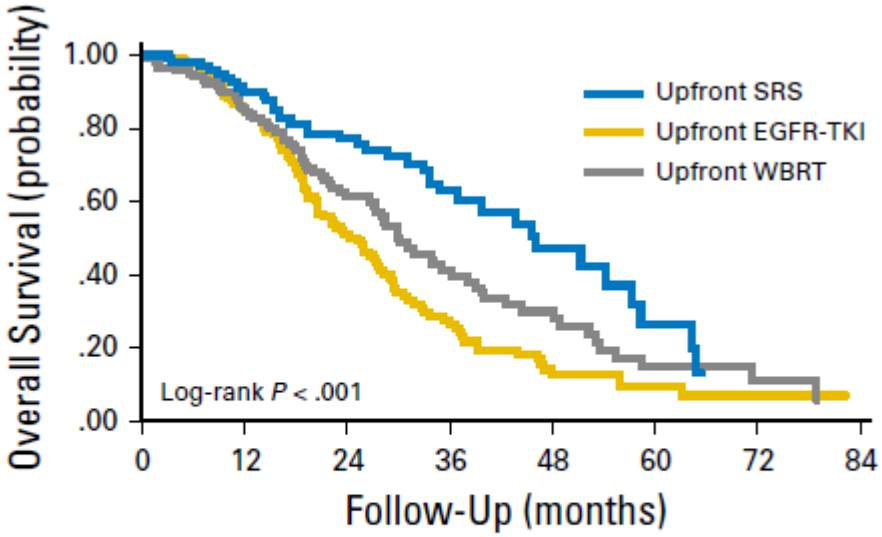
Authors	PTS	Regimen	RR (%)	mPFS (ms)	mOS (ms)
Gore et al. [66]	213	Sunitinib	12	5.6	9.2
Stadler et al. [68]	70	Sorafenib	4	NA	NA
Zustovich et al. [76]	4	Bevacizumab	75	26.3*	33.2*

Management of Brain Metastases in Tyrosine Kinase Inhibitor–Naïve Epidermal Growth Factor Receptor–Mutant Non–Small-Cell Lung Cancer: A Retrospective Multi-Institutional Analysis

J Clin Oncol 35:1070-1077. © 2017

William J. Magnuson, Nataniel H. Lester-Coll, Abraham J. Wu, T. Jonathan Yang, Natalie A. Lockney, Naamit K. Gerber, Kathryn Beal, Arya Amini, Tejas Patil, Brian D. Kavanagh, D. Ross Camidge, Steven E. Braunstein, Lauren C. Boreta, Suresh K. Balasubramanian, Manmeet S. Ahluwalia, Niteshkumar G. Rana, Albert Attia, Scott N. Gettinger, Joseph N. Contessa, James B. Yu, and Veronica L. Chiang

351 patients; 6 institutions



No. at risk								
Upfront SRS	100	76	51	29	13	5	1	1
Upfront WBRT	120	97	52	27	15	6	3	1
Upfront EGFR-TKI	131	103	54	24	8	4	2	0

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Management of Brain Metastases in Tyrosine Kinase Inhibitor–Naïve Epidermal Growth Factor Receptor–Mutant Non–Small-Cell Lung Cancer: A Retrospective Multi-Institutional Analysis

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	Univariable Analysis			Multivariable Analysis		
Variable	HR	95% CI	*P*	HR	95% CI	*P*
Upfront WBRT *v* upfront EGFR-TKI	0.72	0.53 to 0.98	.039	0.70	0.50 to 0.98	.039
Upfront SRS *v* upfront EGFR-TKI	0.45	0.31 to 0.66	< .001	0.39	0.26 to 0.58	< .001
Age at brain metastases, years						
50- < 60 *v* < 50	1.35	0.88 to 2.06	.18	1.51	0.98 to 2.34	.062
60- < 70 *v* < 50	1.47	0.97 to 2.50	.071	1.48	0.96 to 2.27	.074
> 70 *v* < 50	1.65	1.04 to 2.59	.032	1.69	1.06 to 2.69	.028
Stage at diagnosis						
IV *v* I-III	1.25	0.78 to 2.00	.346			
ECOG performance status						
2-3 *v* 0-1	2.12	1.57 to 2.87	< .001	2.45	1.78 to 3.67	< .001
EGFR mutation						
Exon 20 *v* exon 19	0.68	0.34 to 1.35	.266	0.62	0.31 to 1.25	.185
Exon 21 *v* exon 19	1.51	1.11 to 2.02	.008	1.75	1.29 to 2.38	< .001
Extracranial metastases at time of brain metastases						
No *v* yes	2.69	1.87 to 3.86	< .001	3.12	2.09 to 4.64	< .001

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Management of Brain Metastases in Tyrosine Kinase Inhibitor–Naïve Epidermal Growth Factor Receptor–Mutant Non–Small-Cell Lung Cancer: A Retrospective Multi-Institutional Analysis

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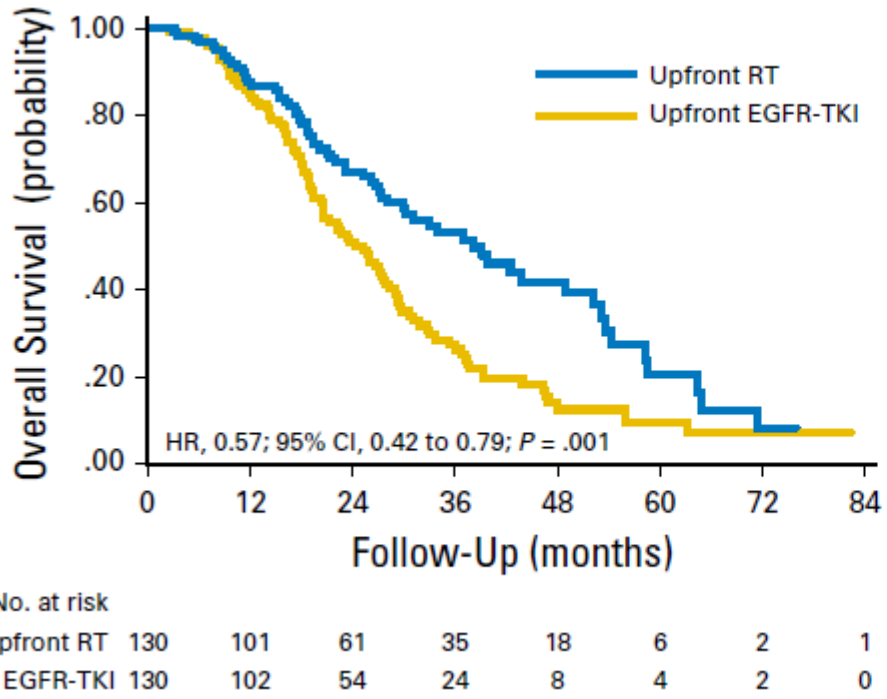
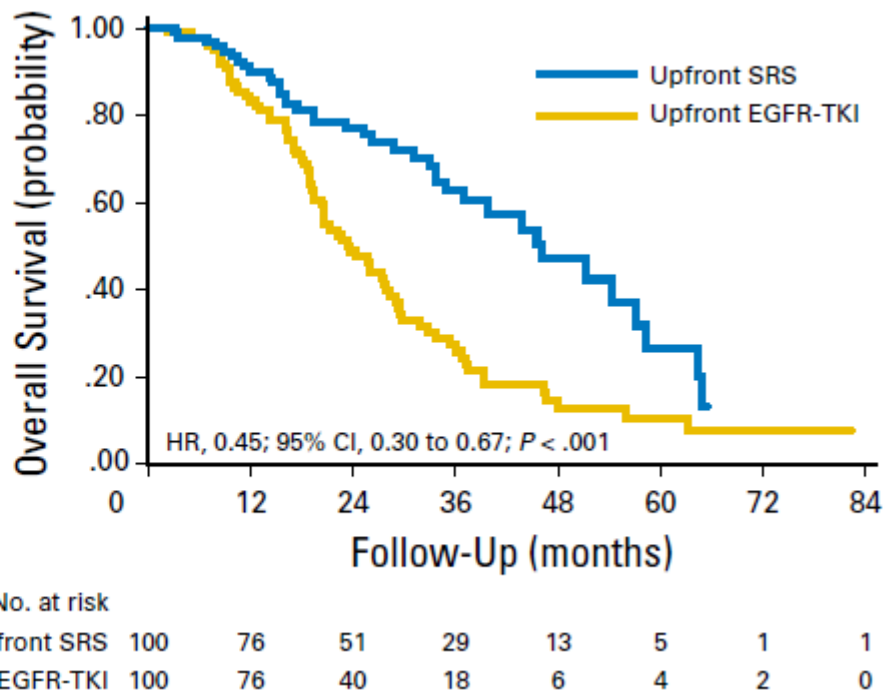
William J. Magnuson, Nataniel H. Lester-Coll, Abraham J. Wu, T. Jonathan Yang, Natalie A. Lockney, Naamit K. Gerber, Kathryn Beal, Arya Amini, Tejas Patil, Brian D. Kavanagh, D. Ross Camidge, Steven E. Braunstein, Lauren C. Boreta, Suresh K. Balasubramanian, Manmeet S. Ahluwalia, Niteshkumar G. Rana, Albert Attia, Scott N. Gettinger, Joseph N. Contessa, James B. Yu, and Veronica L. Chiang

351 patients; 6 institutions





Propensity score matched cohorts
RT=SRS + WBRT

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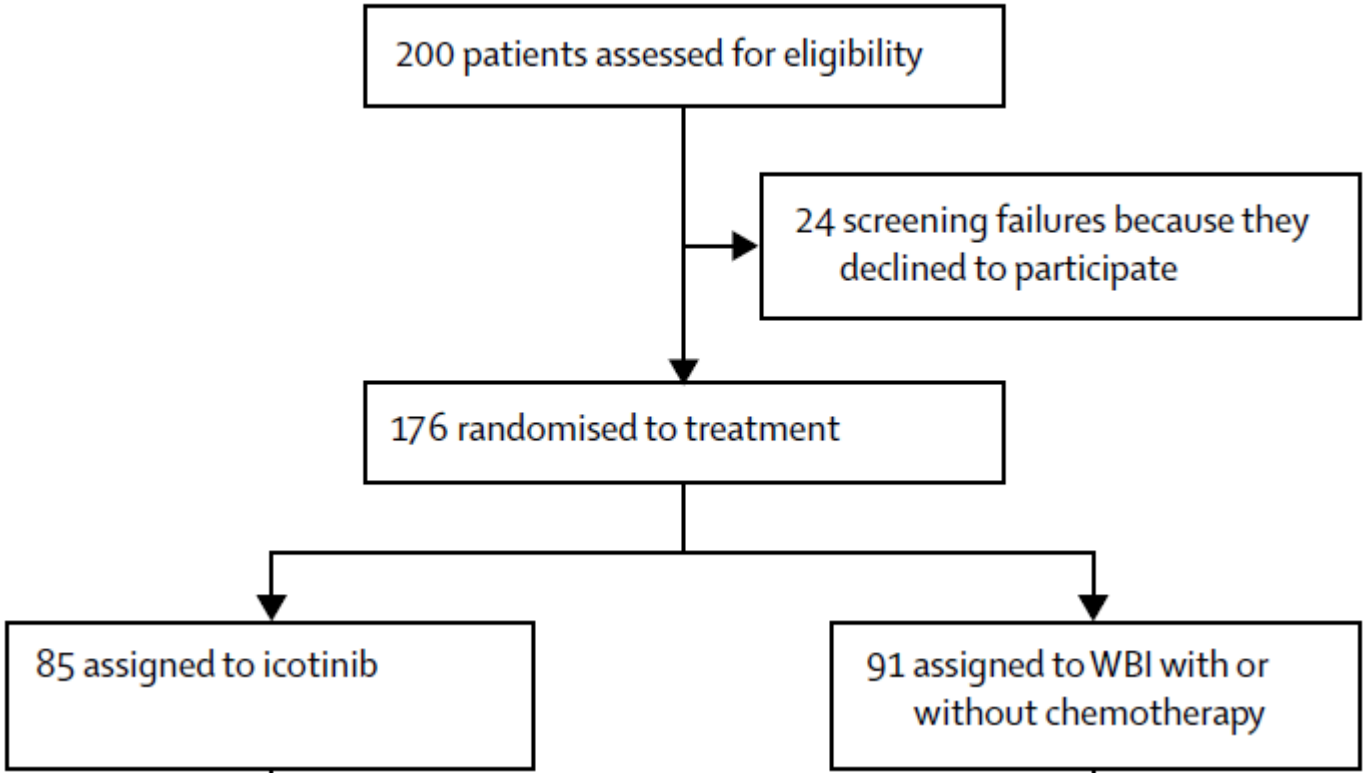
Icotinib versus whole-brain irradiation in patients with *EGFR*-mutant non-small-cell lung cancer and multiple brain metastases (BRAIN): a multicentre, phase 3, open-label, parallel, randomised controlled trial

Lancet Respir Med 2017

Jin-Ji Yang, Caicun Zhou, Yisheng Huang, Jifeng Feng, Sun Lu, Yong Song, Cheng Huang, Gang Wu, Li Zhang, Ying Cheng, Chengping Hu, Gongyan Chen, Li Zhang, Xiaoqing Liu, Hong Hong Yan, Fen Lai Tan, Wenzhao Zhong, Yi-Long Wu



Icotinib versus whole-brain irradiation in patients with *EGFR*-mutant non-small-cell lung cancer and multiple brain metastases (BRAIN): a multicentre, phase 3, open-label, parallel, randomised controlled trial

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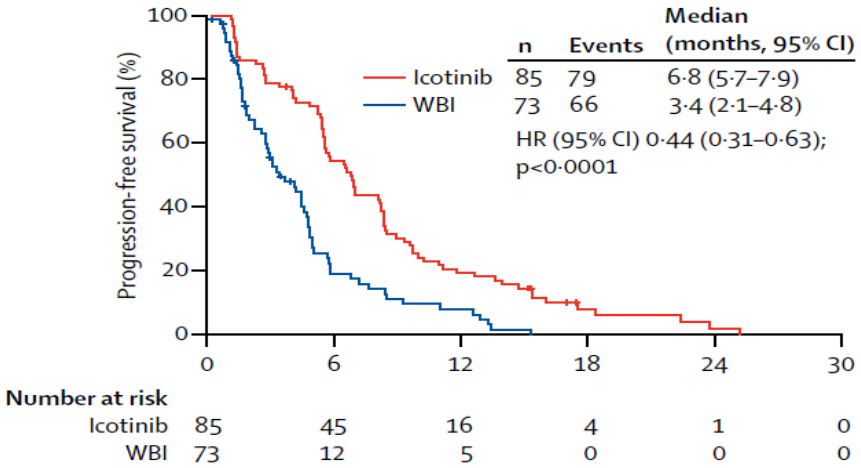

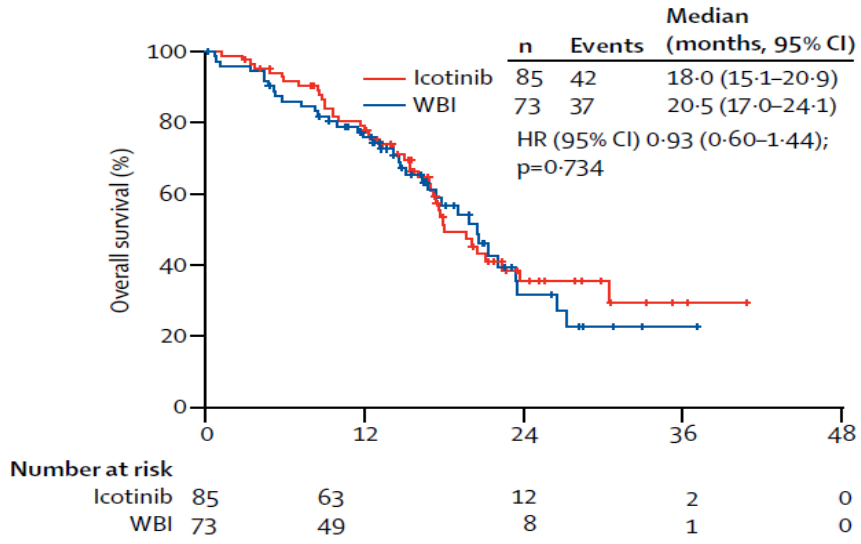

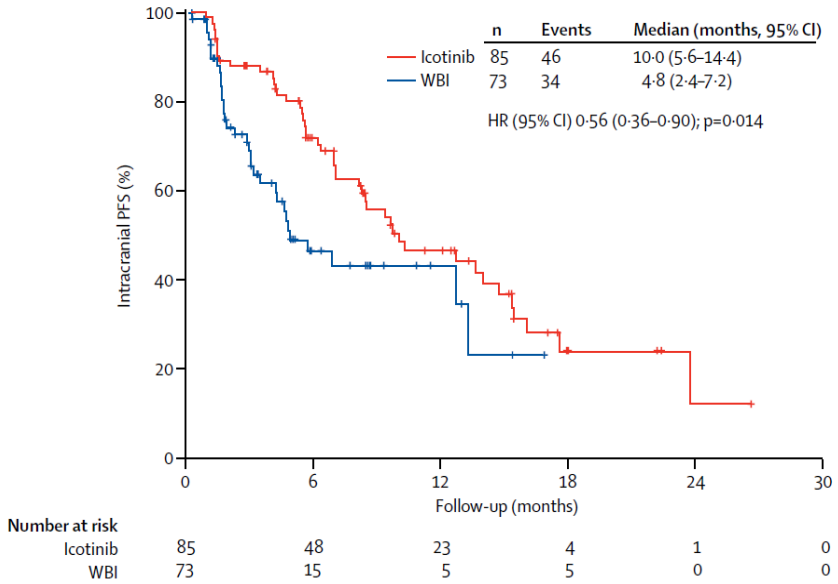

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JAMA Oncology Clinical Evidence Synopsis

Targeted Therapy as an Alternative to Whole-Brain Radiotherapy in *EGFR*-Mutant or *ALK*-Positive Non–Small-Cell Lung Cancer With Brain Metastases

Pablo Martínez, MD, PhD; Raymond H. Mak, MD; Geoffrey R. Oxnard, MD

JAMA Oncology Published online May 18, 2017

Evidence Profile

No. of randomized clinical trials: 3

Comparisons: Icotinib vs whole-brain radiotherapy plus chemotherapy; ceritinib vs chemotherapy; alectinib vs crizotinib

No. of patients randomized: 176; 376; 207

Patients with brain metastases, %: 100%; 32%; 20%

Brain metastases characteristic: 3 or more; stable with or without any symptoms; asymptomatic

Primary outcome: Intracranial progression-free survival; overall progression-free survival; overall progression-free survival

Benefit primary end point: Hazard ratio (HR) 0.56; HR 0.55 (0.70 with brain metastases); HR 0.34 (0.08 with brain metastases)

CLINICAL APPLICATION Patients with *EGFR*-mutant or *ALK*-positive non–small-cell lung cancer with brain metastases now have the potential to achieve a prolonged survival. Through use of highly active targeted therapies, whole-brain radiotherapy can be safely postponed, diminishing toxic effects that could impair quality of life.

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Recommendations on Disease Management for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer and Brain Metastases: American Society of Clinical Oncology Clinical Practice Guideline

J Clin Oncol 32:2100-2108. © 2014

Key Recommendations

- For patients with a favorable prognosis for survival and a single brain metastasis, treatment options include surgery with postoperative radiation, stereotactic radiosurgery (SRS), whole-brain radiotherapy (WBRT; ± SRS), fractionated stereotactic radiotherapy (FSRT), and SRS (± WBRT), depending on metastasis size, resectability, and symptoms. After treatment, serial imaging every 2 to 4 months may be used to monitor for local and distant brain failure.
- For patients with a favorable prognosis for survival and limited (two to four) metastases, treatment options include resection for large symptomatic lesion(s) plus postoperative radiotherapy, SRS for additional smaller lesions, WBRT (± SRS), SRS (± WBRT), and FSRT for metastases > 3 to 4 cm. For metastases < 3 to 4 cm, treatment options include resection with postoperative radiotherapy. In both cases, available options depend on resectability and symptoms.

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Multiple brain metastases

Radiotherapy

- Patient selection

Chemotherapy

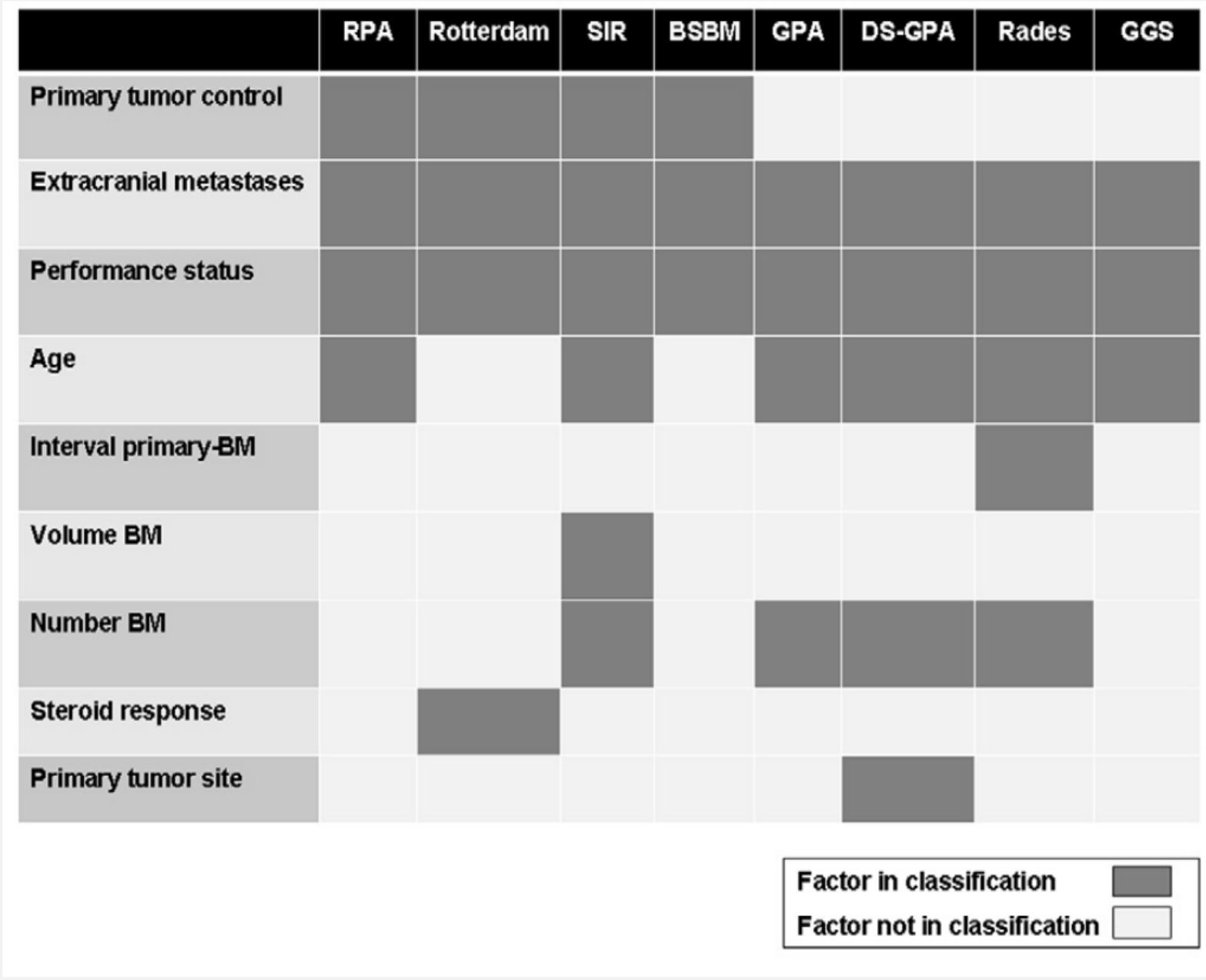
- Patient selection

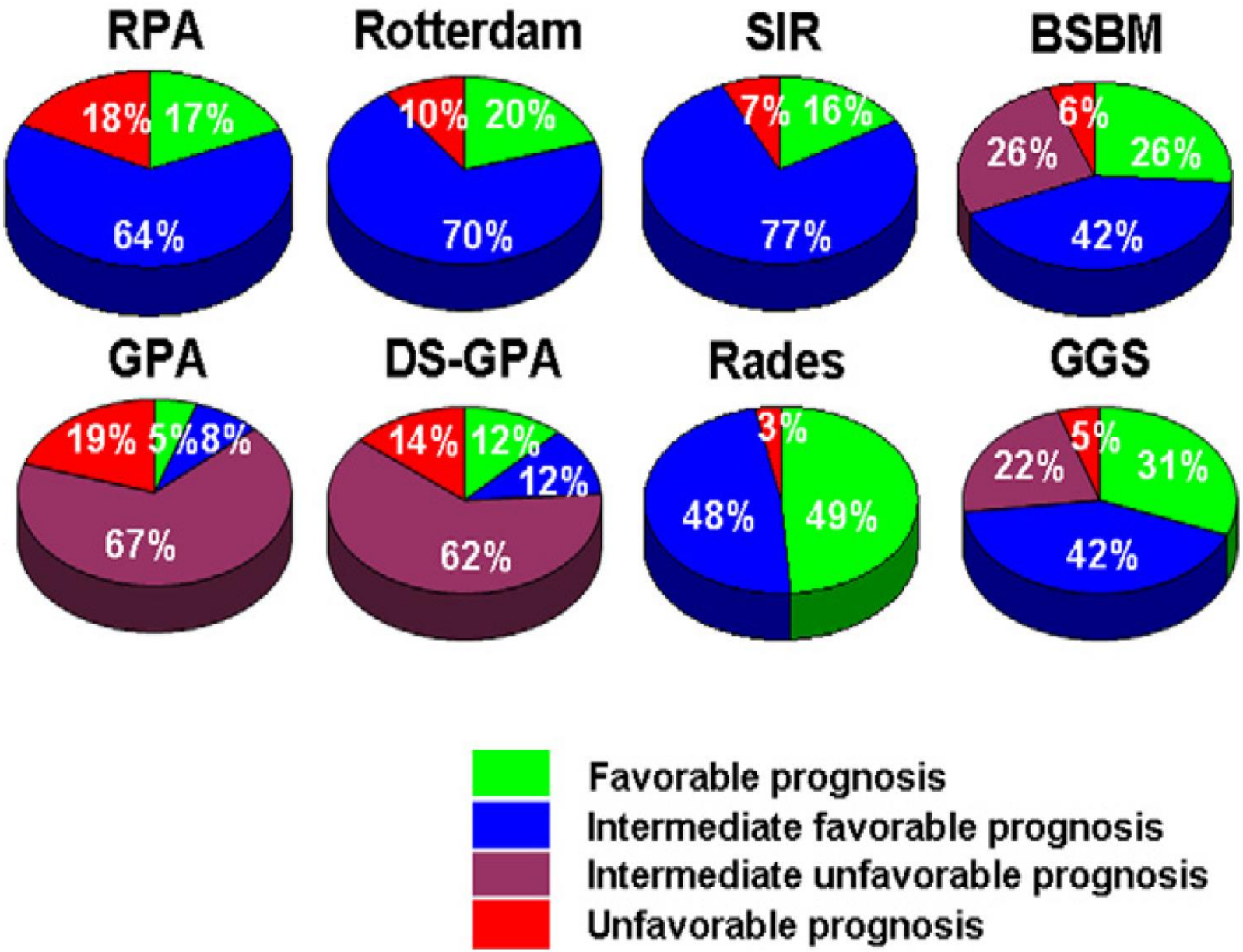
The clinical utility of prognostic scoring systems in patients with brain metastases treated with radiosurgery

Jaap D. Zindler[a], George Rodrigues[b], Cornelis J.A. Haasbeek[a], Patricia F. De Haan[a], Otto W.M. Meijer[a], Ben J. Slotman[a], Frank J. Lagerwaard[a,*]

Radiotherapy and Oncology 106 (2013) 370–374

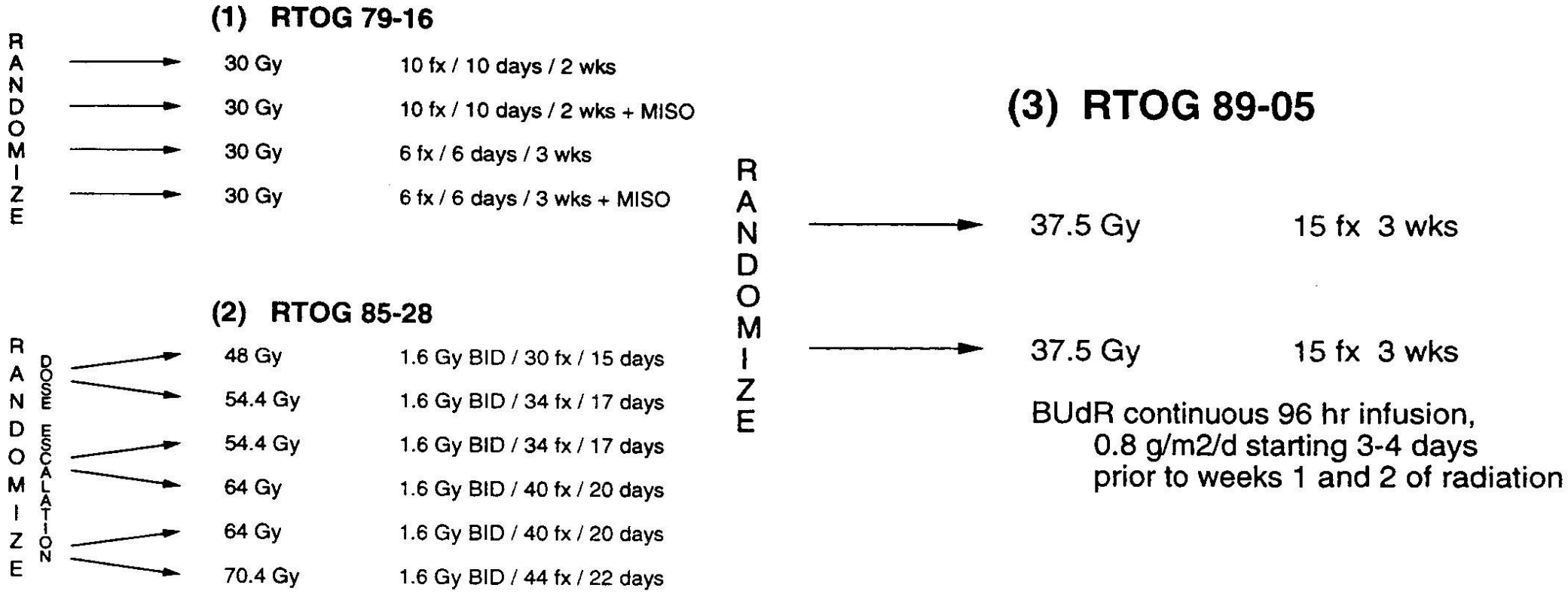
Baseline characteristics included in various prognostic scoring systems for patients with brain metastases.




RPA
18%
17%
64%
Rotterdam
10%
20%
70%
SIR
7%
16%
77%
BSBM
6%
26%
26%
42%
GPA
19%
5%
8%
67%
DS-GPA
14%
12%
12%
62%
Rades
3%
48%
49%
GGS
5%
22%
31%
42%
Favorable prognosis
Intermediate favorable prognosis
Intermediate unfavorable prognosis
Unfavorable prognosis

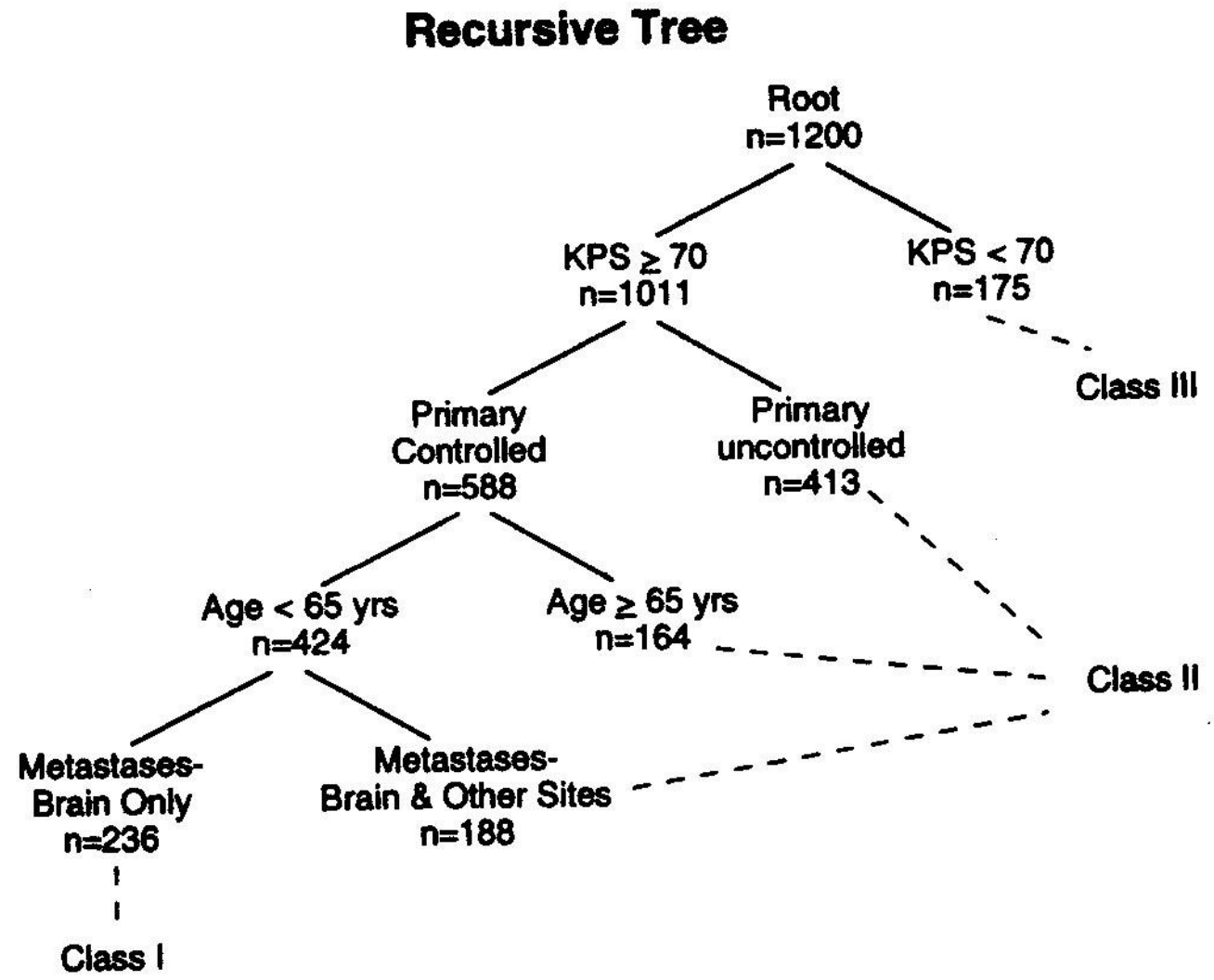
Recursive partitioning of prognostic factors in RTOG trial

1200 patients



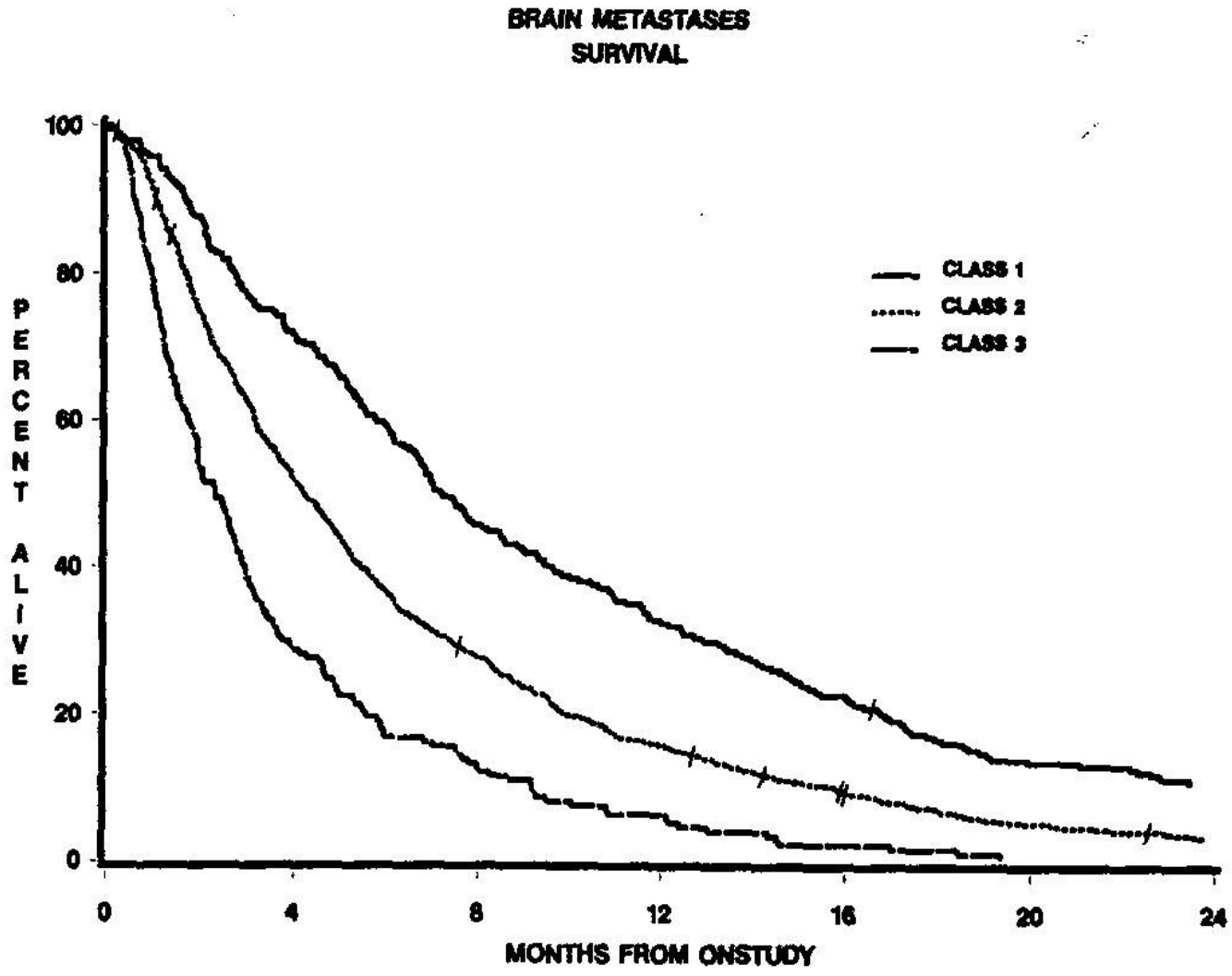
Recursive partitioning of prognostic factors in RTOG trial

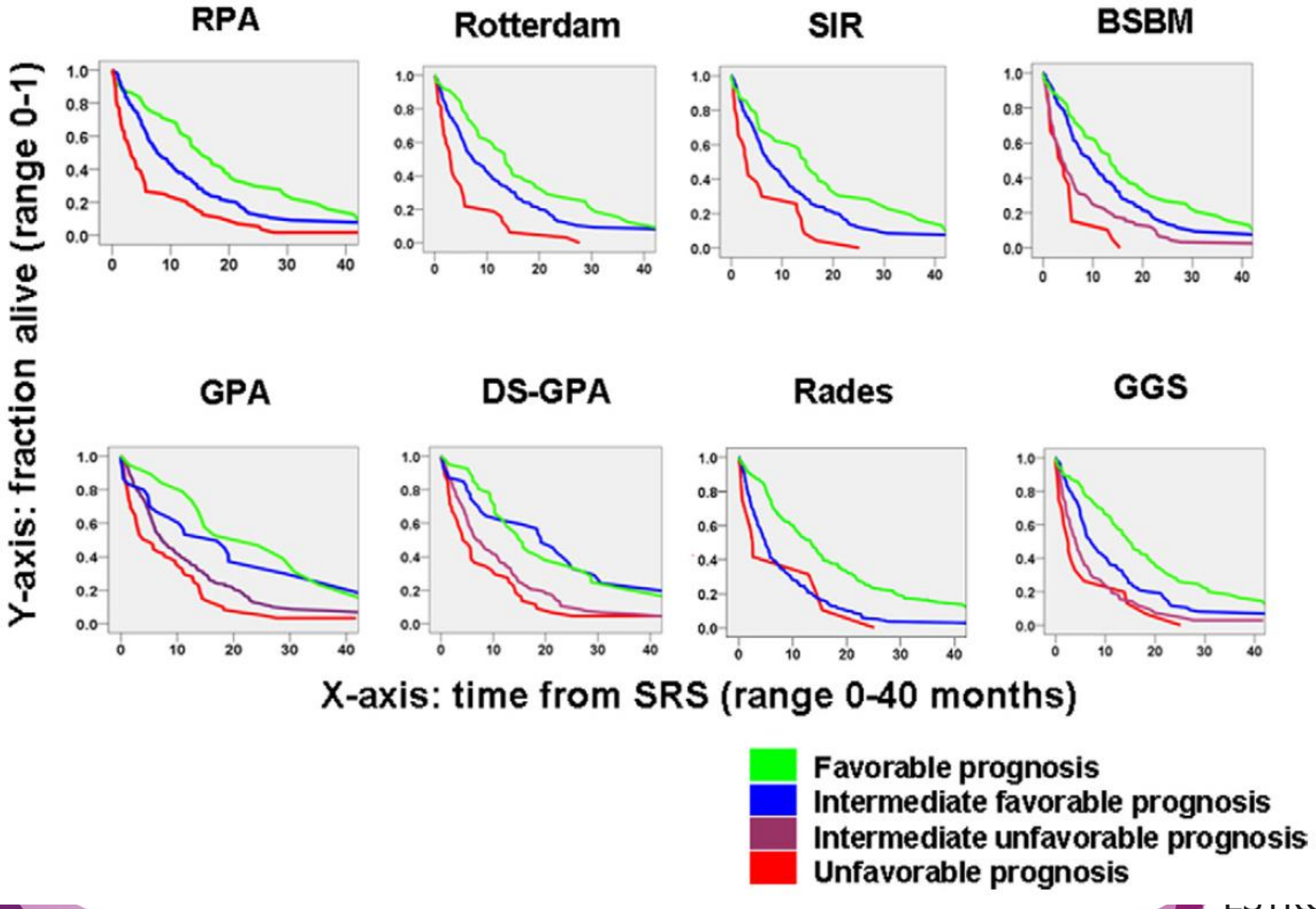
1200 patients



Recursive partitioning of prognostic factors in RTOG trial

1200 patients





Zindler et al. Radiotherapy and Oncology 106 (2013) 370–374

Prognostic Indexes for Brain Metastases: Which Is the Most Powerful?

Int J Radiation Oncol Biol Phys, Vol. 83, No. 3, pp. e325–e330, 2012

Gustavo Arruda Viani, M.D., Lucas Godói Bernardes da Silva, M.D., and Eduardo Jose Stefano, M.D.

Variable	Overall survival at 1 y (%)	*p* (log-rank test)
Rotterdam score		.001
Class I	31	
Class II	18	
Class III	11	
BSBM		.002
Class I	26	
Class II	17	
Class III	13	
Class IV	8	
Germany score		<.0001
Class I	42	
Class II	35	
Class III	26	
Class IV	14	
RPA		<.0001
Class I	44	
Class II	30	
Class III	16	
GPA		<.0001
Class I	49	
Class II	27	
Class III	13	
Class IV	9	

Abbreviations: BSBM = basic score for brain metastases; RPA = recursive partitioning analysis; GPA = graded prognostic assessment.

ESTRO School

If the only tool you have is a hammer then you tend to see every problem as a nail’

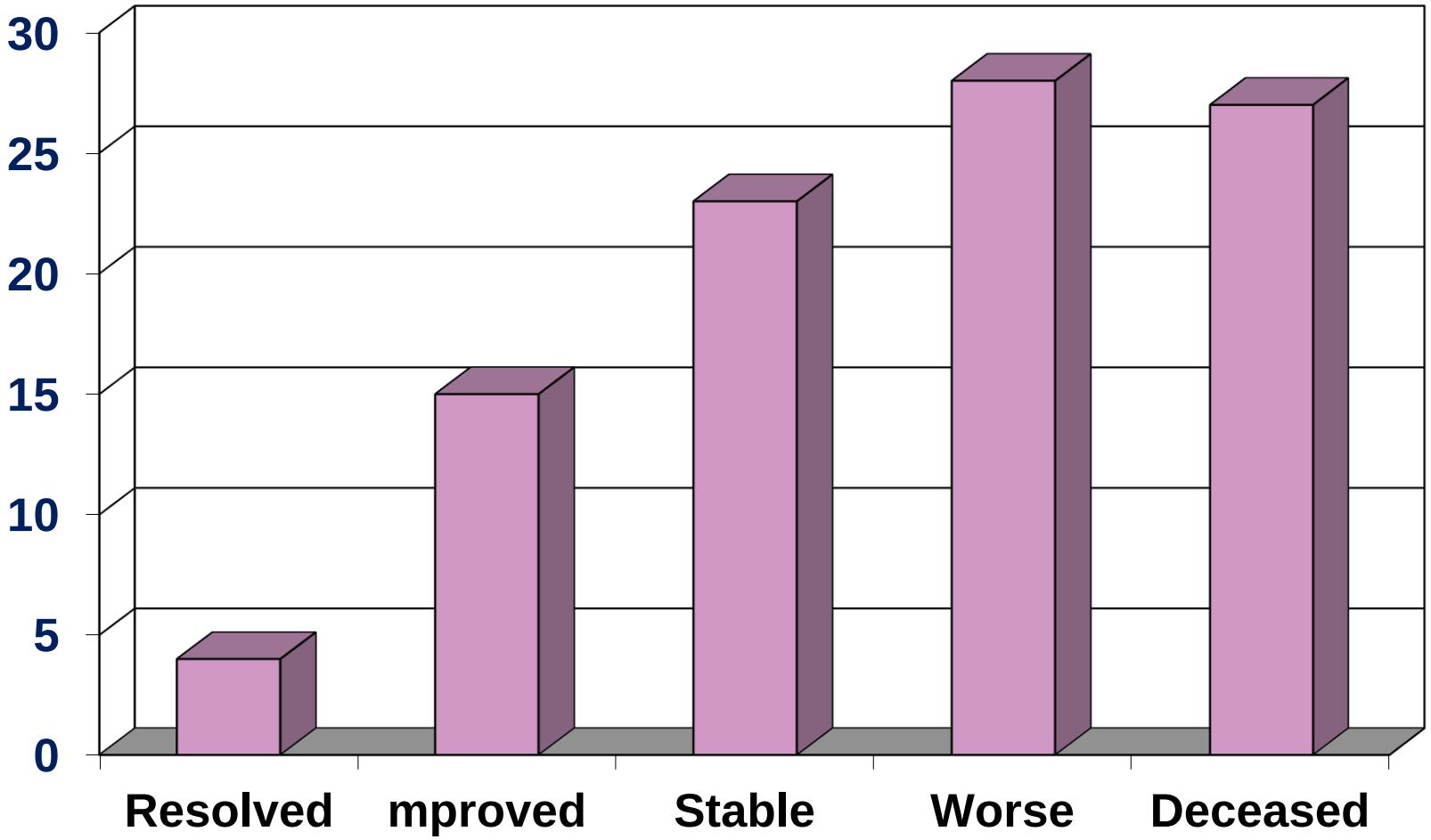
Abraham Maslow

ESTRO School

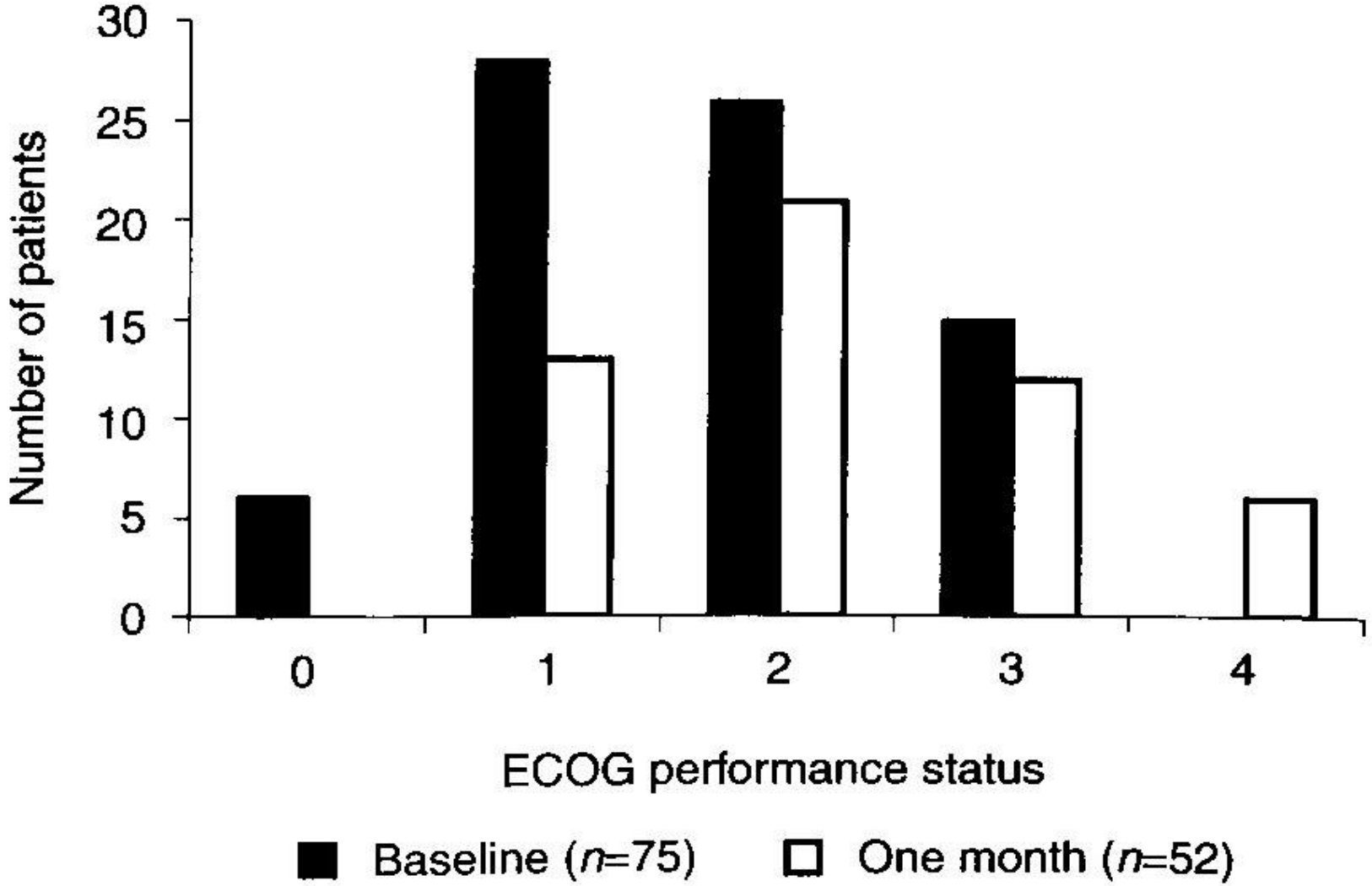
Supportive care management of brain metastases: what is known and what we need to know [Tsao et al 2003]

‘the optimal management of brain metastases remains elusive. The magnitude of benefit of using WBRT above supportive care alone is uncertain’

Symptom response after palliative radiotherapy for patients with brain metastases [Bezjak et al 2002]



Symptom response after palliative radiotherapy for patients with brain metastases [Bezjak et al 2002]



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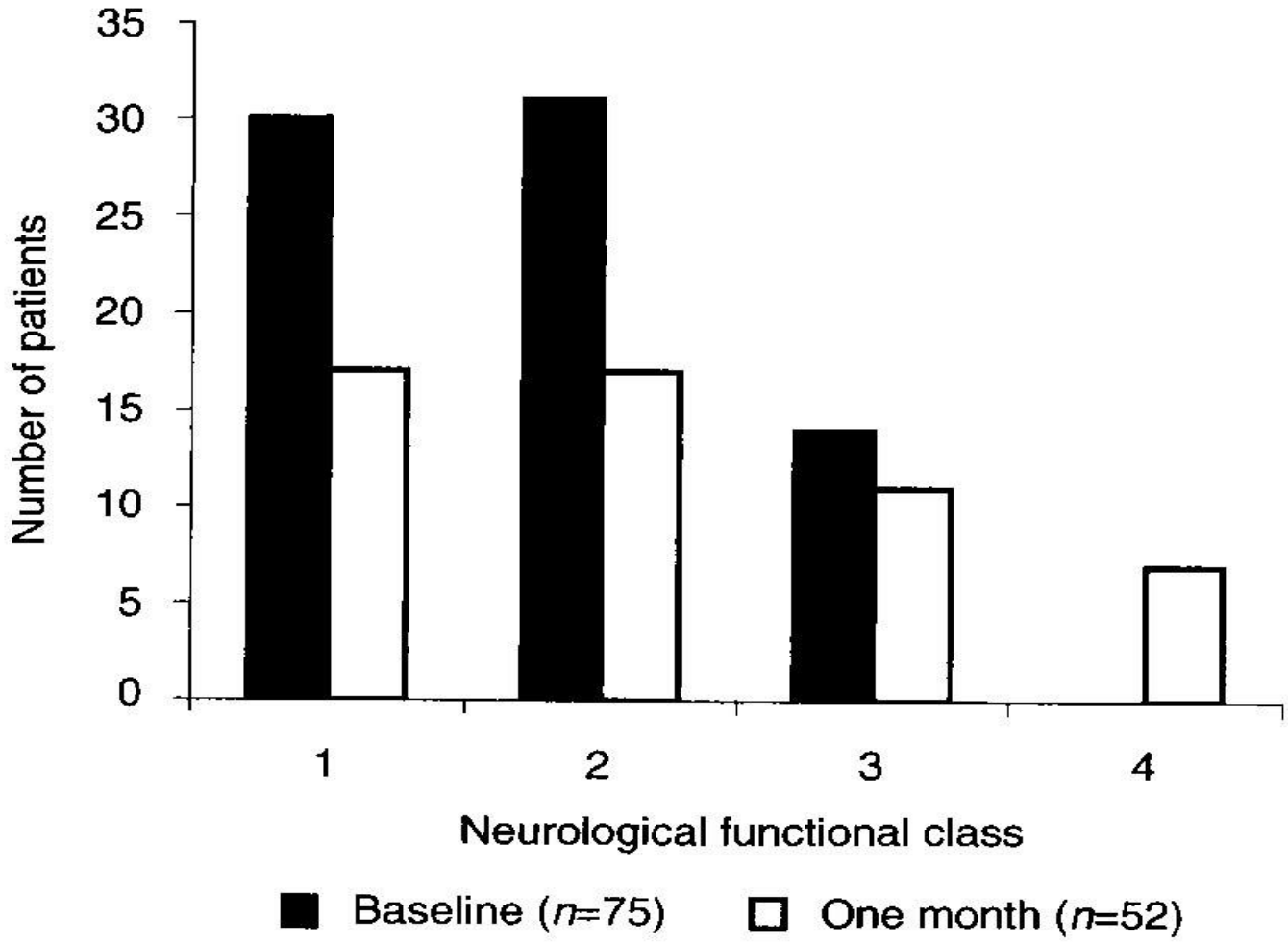
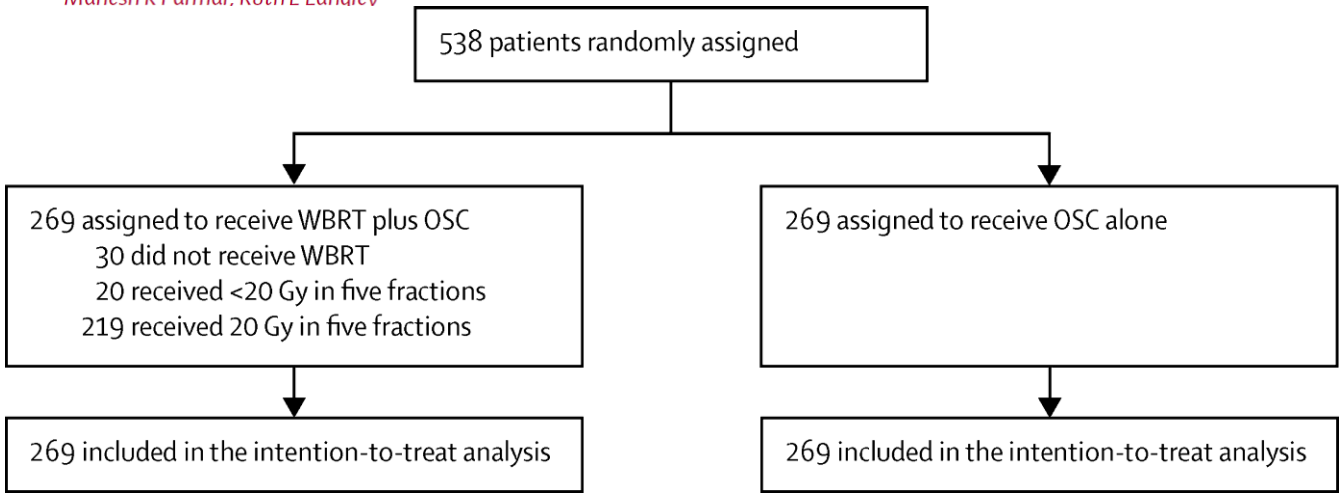
Symptom response after palliative radiotherapy for patients with brain metastases [Bezjak et al 2002]



Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial

Paula Mulvenna, Matthew Nankivell, Rachael Barton, Corinne Faivre-Finn, Paula Wilson, Elaine McColl, Barbara Moore, Iona Brisbane, David Ardron, Tanya Holt, Sally Morgan, Caroline Lee, Kathryn Waite, Neil Bayman, Cheryl Pugh, Benjamin Sydes, Richard Stephens, Mahesh K Parmar, Ruth E Langley



Extracranial metastases		
No	122 (45%)	124 (46%)
Yes†	147 (55%)	145 (54%)
NSCLC histology		
Adenocarcinoma	148 (55%)	138 (51%)
Squamous	53 (20%)	66 (25%)
Large cell	7 (3%)	5 (2%)
NSCLC NOS	61 (23%)	60 (22%)
RPA prognostic class		
1	22 (8%)	8 (3%)
2	145 (54%)	156 (59%)
3	100 (37%)	102 (38%)
Data unavailable	2	3

ESTRO School

Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial

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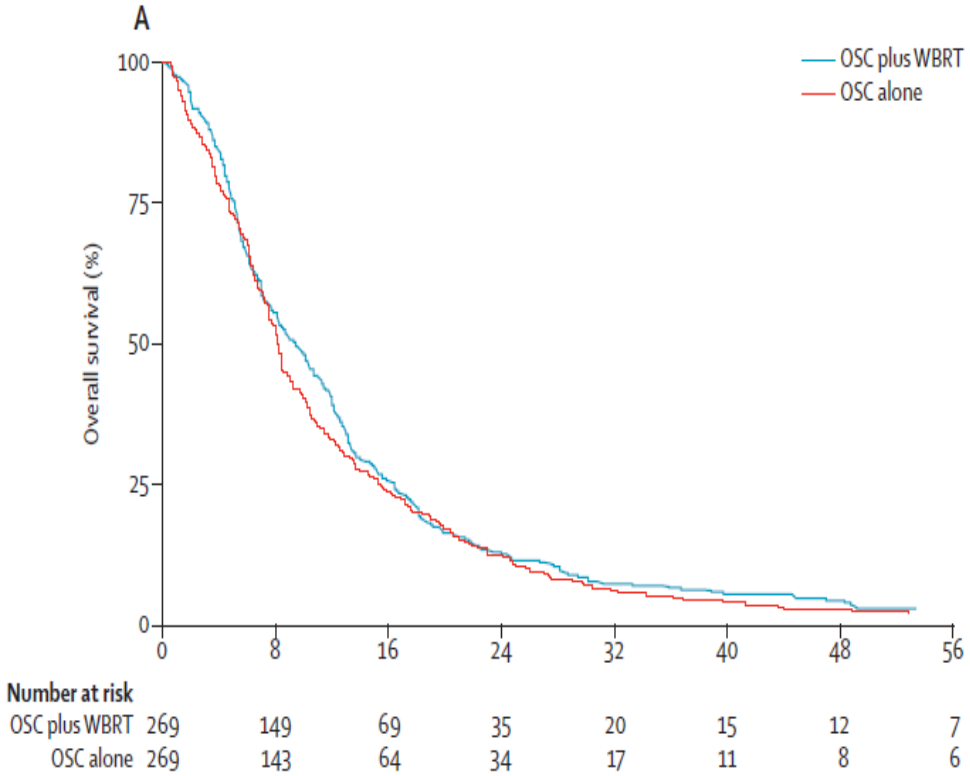

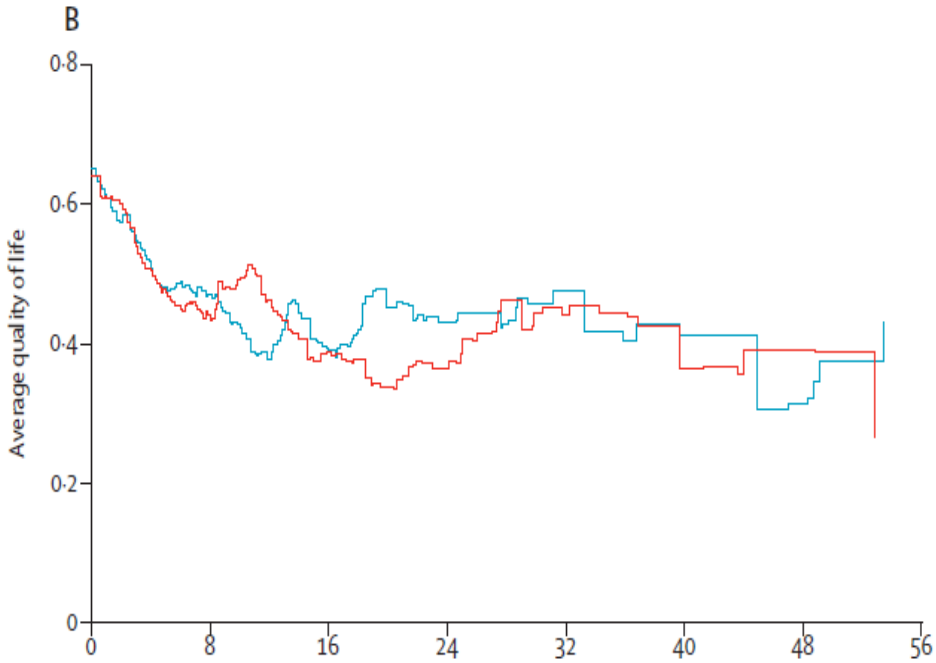

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Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial

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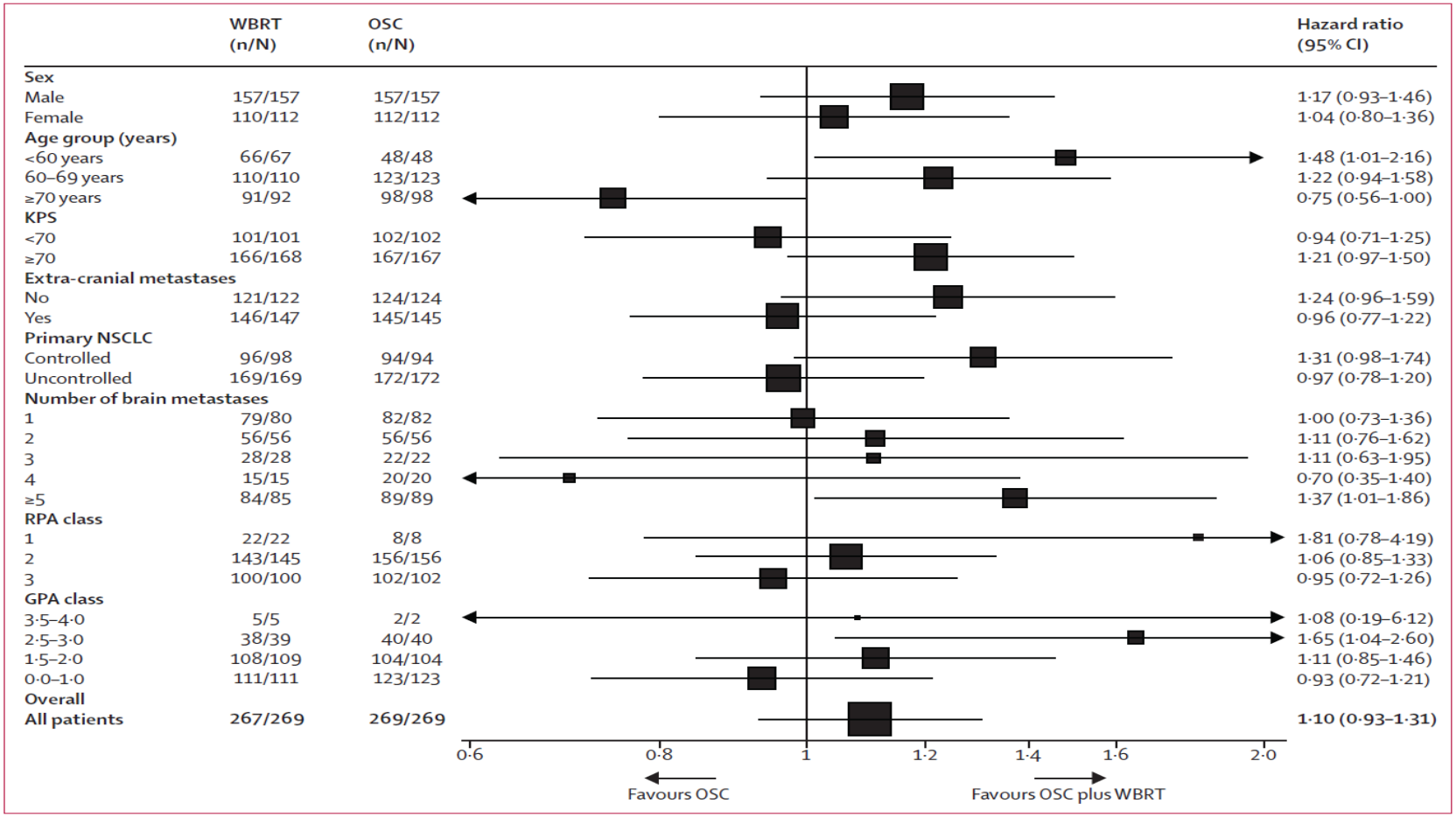

Cochrane meta-analysis 2007 & 2012

Supportive care versus whole brain radiotherapy

There is a lack of high quality randomized evidence to clarify the value of WBRT versus supportive care alone

Supportive care alone is an option (for example, for patients with poor performance status or widely disseminated cancer based on short life expectancy).

There is lack of contemporary high quality trials to guide practitioners as to which subsets of patients with brain metastases should be managed with supportive care alone without whole brain radiotherapy.

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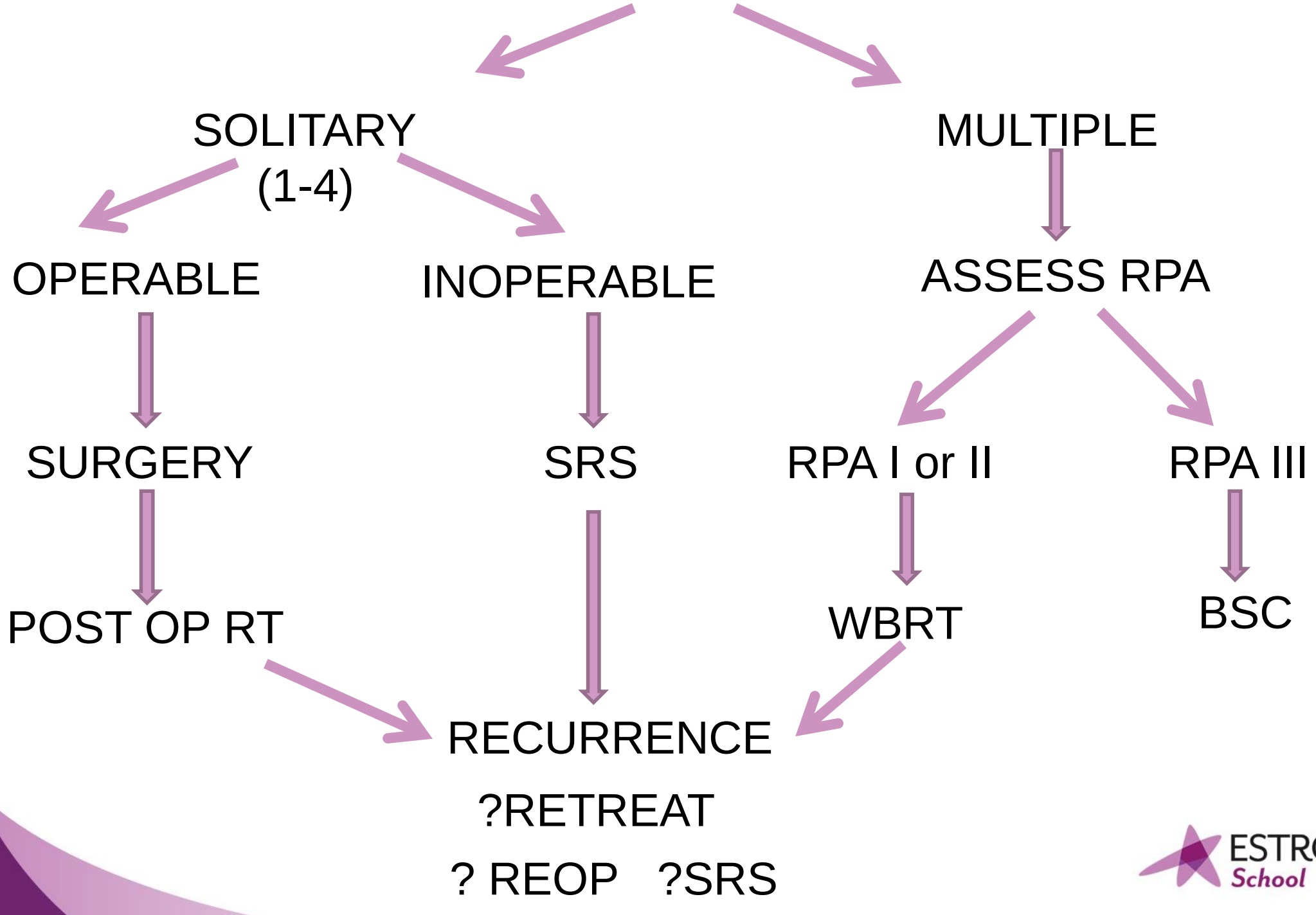
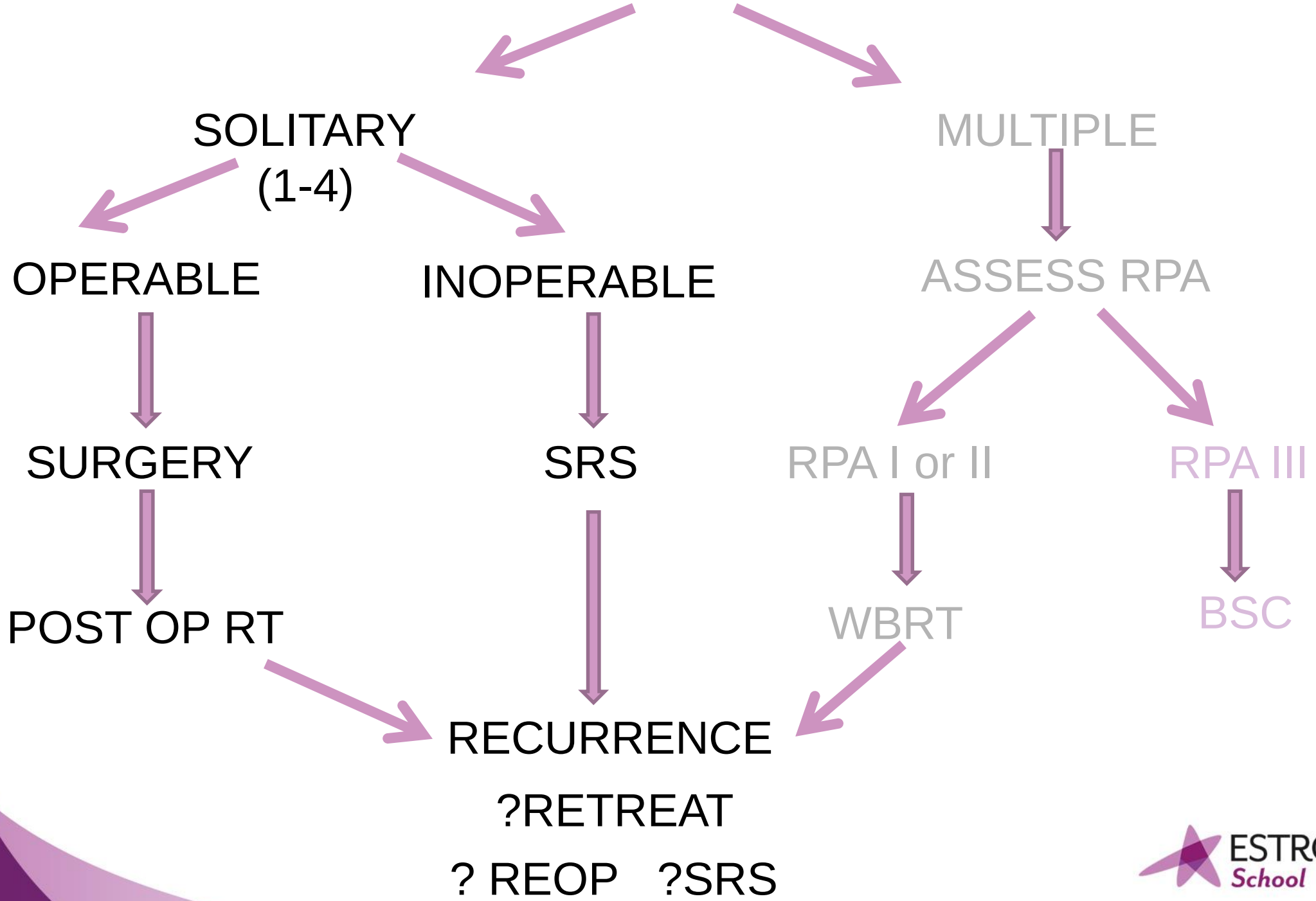
Management of brain metastases



ESTRO School

Management of brain metastases



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Conclusion

- Chemotherapy for
  - GCT, lymphoma
  - ?breast, SCLC,
  - ??alk+ve NSCLC, b-raf+ve melanoma
- WBRT
  - RPA I/II
- BSC
  - RPA III

Leiden University
Medical Center

Complications of spinal disease

Pain, progressive instability, neurological symptoms

Yvette van der Linden

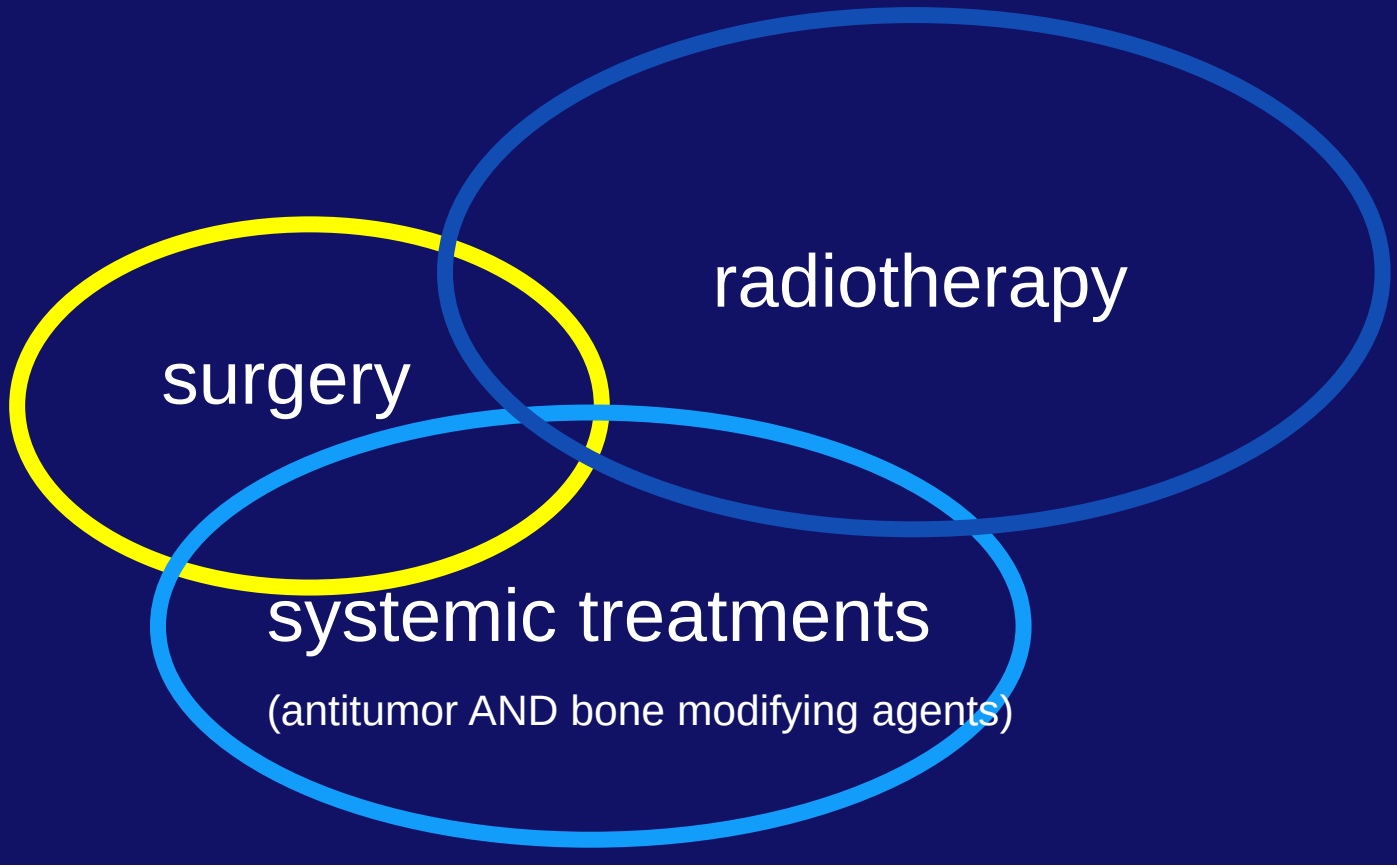
Centre of Expertise Palliative Care

& Dept. of Radiotherapy

Important factors when deciding on spinal treatment

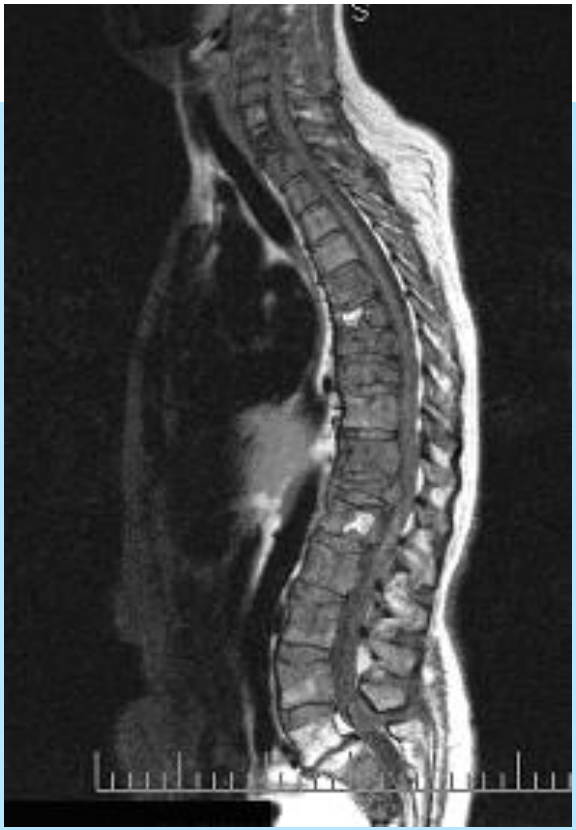
Expected

- survival
- instability
- outcome



Selecting patients for treatment

- Easy
  - Pain only, stable spine
  - Progressive instability with neurological complaints on 1 level
- Less easy
  - Favourable prognosis, pain only, but MSCC on MRI on 1 level
- Difficult
  - Neurological complaints on 3 not-adjacent levels
  - Radiosensitive primary tumor
  - Young age / expected prolonged prognosis (years?)



Spinal metastases causing pain

Single fraction also in subgroups equal

Patient subgroups	Total (in numbers)	Schedule* (in percentages)	Response (in percentages)	p-value†
Primary tumor [4]				0.69
• Breast	434	52% SF	84%	
		48% MF	80%	
• Prostate	253	49% SF	79%	
		51% MF	79%	
• Lung	269	50% SF	62%	
		50% MF	62%	
• Other	143	51% SF	68%	
		49% MF	60%	
Observed survival >52 weeks [5]	320	51% SF	87%	0.54
		49% MF	85%	
Observed survival <12 weeks [6]	247	50% SF	47%	0.58
		50% MF	44%	
Spinal metastasis [7]	342	48% SF	75%	0.52
		52% MF	72%	

Meeuse, van der Linden et al, Cancer 2010

van der Linden et al, Cancer 2005, IJROBP 2004, R&O 2008, Clin Onc 2009

Beware of spinal cord toxicity when re-irradiating spinal mets

- Risc scores

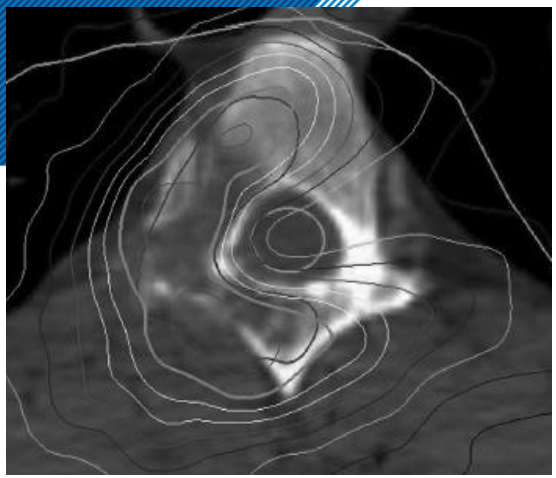
Factor	0 points	1 point	2 points	3 points	4 points	5 points	6 points	7 points	8 points	9 points
Cumulative BED in Gy_2	≤120	120.1–130	130.1–140	140.1–150	150.1–160	160.1–170	170.1–180	180.1–190	190.1–200	>200
Interval <6 months					× (4.5)					
BED of one course ≥102 Gy_2					× (4.5)					

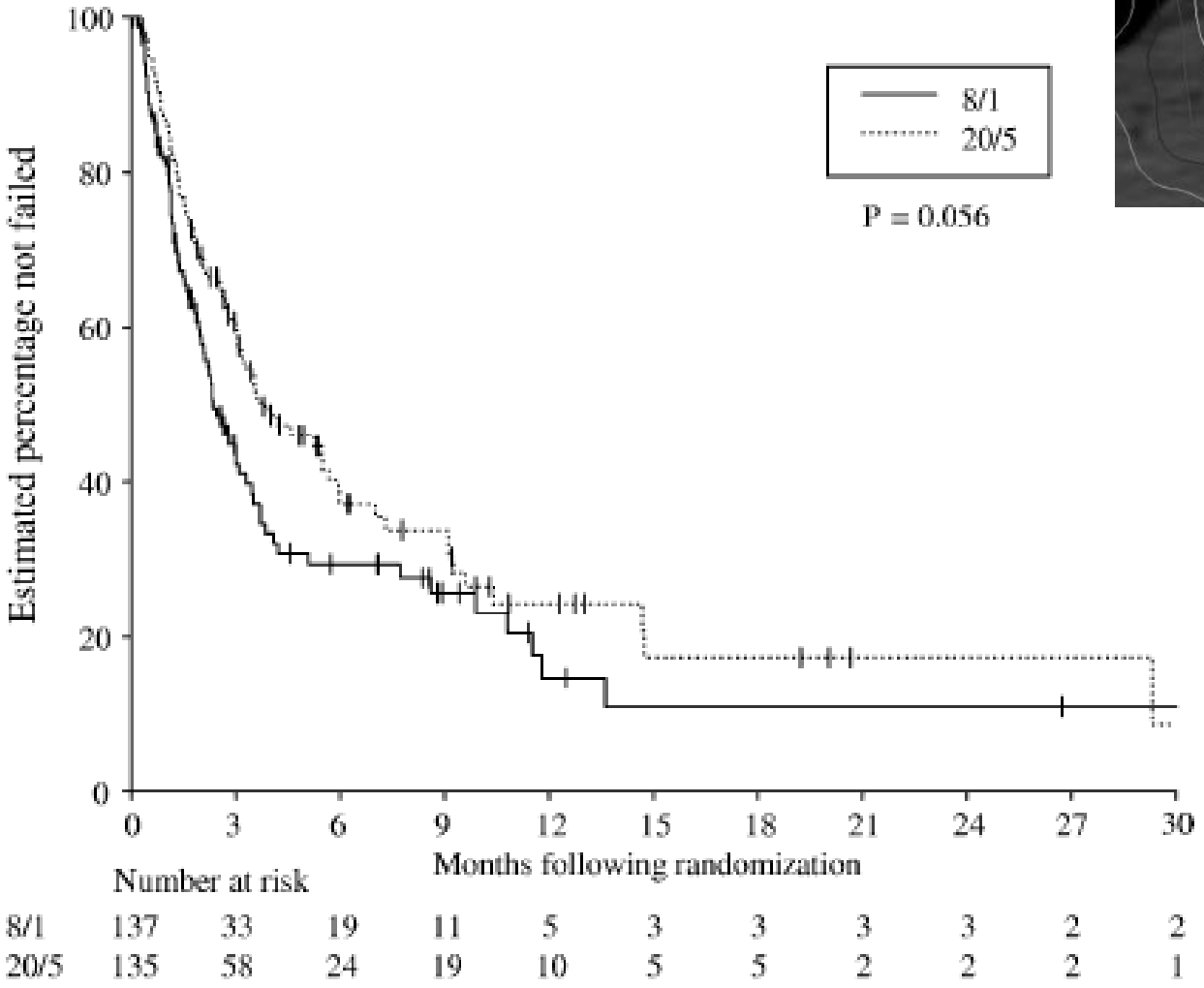
Group	Points	Myelopathy 2005 (1)	**Myelopathy updated**	% Myelopathy 2005 (1)	**% Myelopathy updated**
Low risk	≤3	0/24	**1/30**	0	**3**
Intermediate risk	4–6	2/6	**2/8**	33	**25**
High risk	>6	9/10	**9/10**	90	**90**

- Two times 1x 8 Gy → BED2 40 Gy total → 3rd time -> 60 Gy
- Two times 5x 4 Gy → BED2 60 Gy total → …
- 10 x 3 Gy → BED2 75 Gy total

Nieder et al. IJROBP 2005 & 2006

Higher doses for neuropathic pain?

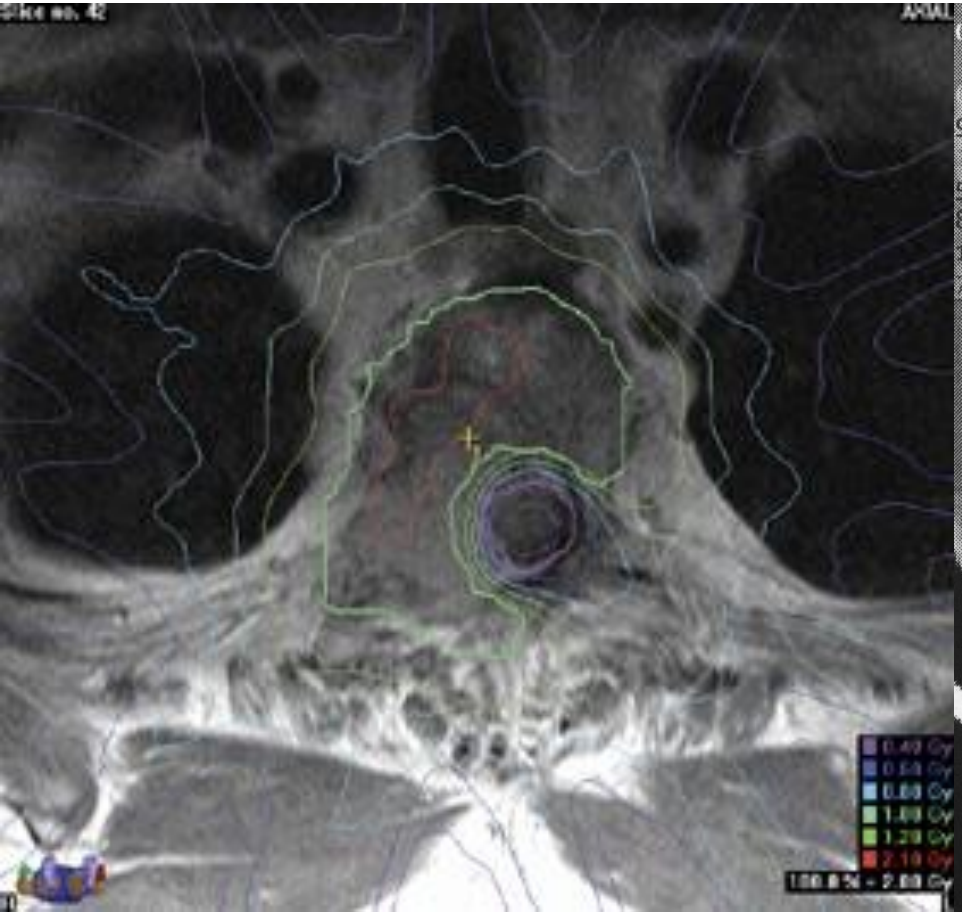


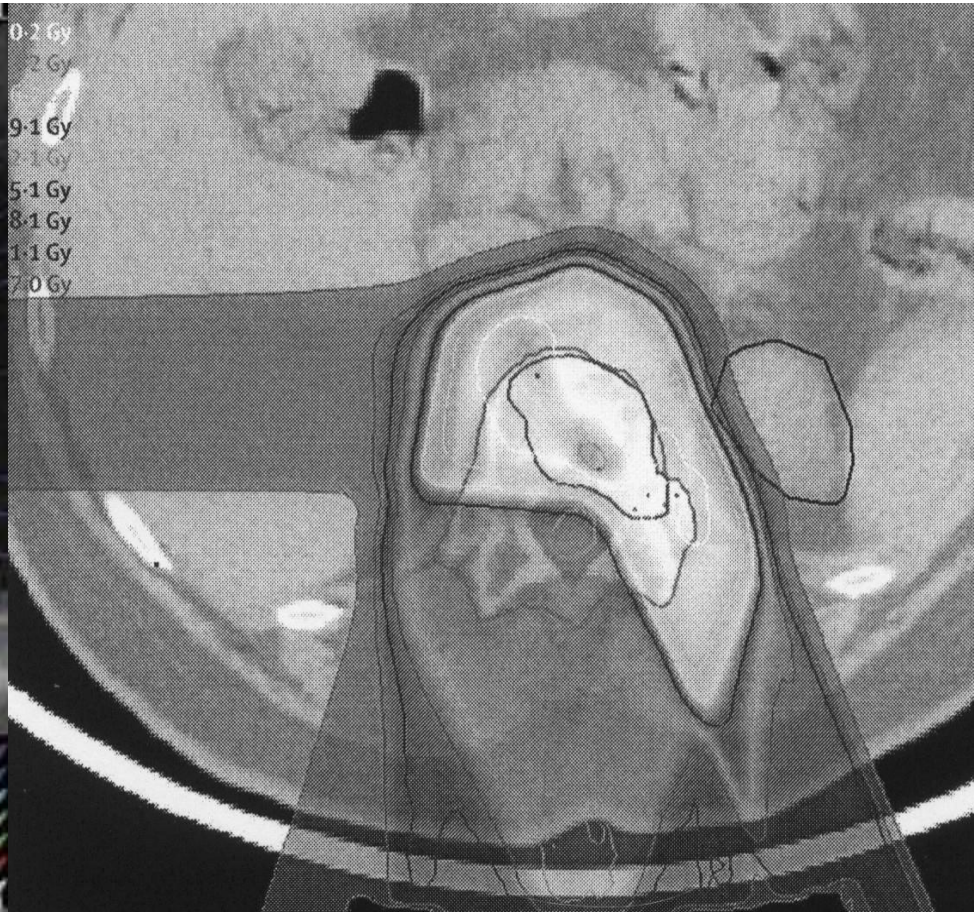


Roos et al R&O 2005

Improve outcome? Higher doses? Apply more conformal techniques with less toxicity to OARs?

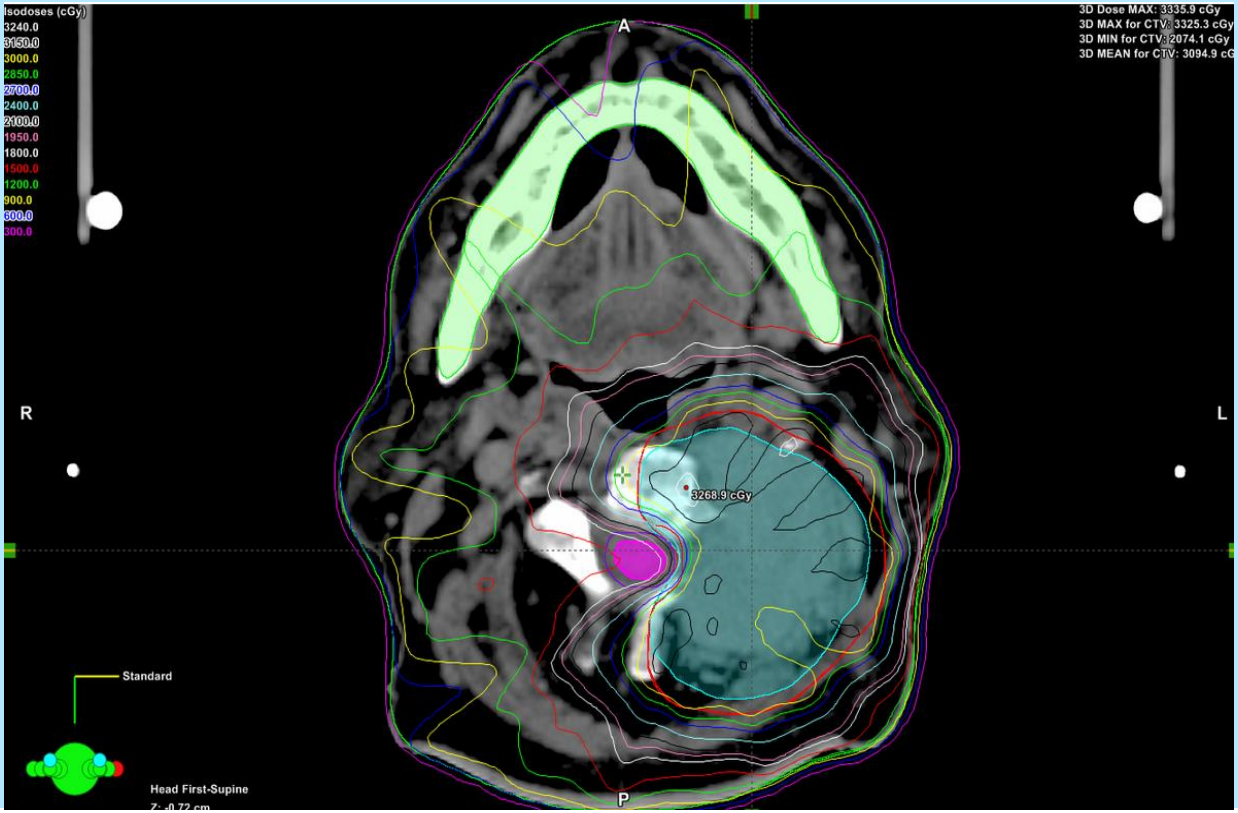
IMRT, VMAT, stereotactic procedures? Protons??





Spine SBRT

- Deliver ablative dose to target volume
- Steep dose fall off beyond
- 40-90 minutes on linac couch



Lo et al, Disc Med 2010

SBRT- proper patient selection

Inclusion

- Able to lie flat for extended period of time 40-50 minutes
- Reasonable performance status
- Lesion clearly identified on CT or MRI
- Limited number of lesions ≤ 2-3 spinal levels
- Gross tumor ≥ 3-5 mm from spinal cord

Exclusion

- MSCC
- no MRI possible
- recent ^{89}S
- prior RT to 45 Gy2
- spinal instability

	Patient A	Patient B	Patient C
distress	relaxed	nervous	nervous
performance	good	good	poor
physical complaints	no pain	no pain	highly symptomatic
set up error	1 mm	3 mm	5mm

Lo et al, Disc Med 2010

“PROMISES“

Radiosurgery vs. Conventional RT

Higher rates of pain relief

More rapid pain relief

Longer duration of pain relief

Less side effects

Superior particularly for less radiosensitive tumors

Superior particularly for re-irradiation

Guckenberger et al., “Clinical practice of image-guided spine radiosurgery – results from an international research consortium”. Radiat Oncol 2011;6:172. [Charlottesville/VA, Newport News/VA, Pittsburgh/PA, Toronto, Wuerzburg]

SBRT for pain only

Table 2: Pooled results of spinal radiosurgery series.

Description	Values
Total patients	1388
Total lesions	1775
Patients with previous RT	888
Mean F/U time (months)	15
Pain improvement rate (n=902)	79%
Local control rate (n=1169)	90%
Myelopathy rate (n=1388)	0.4%

Abbreviations: RT, radiation therapy; F/U, followup.

Hall et al, Int J. Surg Oncol 2011

Toxicities SBRT

- Radiation myelopathy
- Fatal esophageal necrosis
- Bronchial stenosis
- Fracture progression

} Despite optimal immobilization and patient set up with CBCT.

- RTOG 0631 2009

PHASE II COMPONENT	
R	
E	
G	**Radiosurgery/SBRT**:
I	Single fraction dose of 16 Gy
S	
T	
F	

Patient Population: (See Section 3.0 for Eligibility)
Patients with localized spine metastasis from the C1 to L5 levels (a solitary spine metastasis; 2 separate spine levels; or up to 3 separate sites); each of the separate sites must have a maximal involvement of 2 contiguous vertebral bodies.

Required Sample Size: **Phase II component: 43 patients**
Phase III component: 240 patients

			urgery/SBRT:
			fraction dose of 16 Gy
I		U	Arm 2: External Beam Radiation Therapy:
I		M	Single fraction dose of 8 Gy
F		I	
Y		Z	Randomization ratio (Arm 1: Arm 2) = 2:1
		E	

Ongoing phase 3 trials in spinal metastases -> pain

- RTOG 0631 -> USA

Single dose SBRT 16 Gy vs. single dose external beam radiotherapy 8 Gy

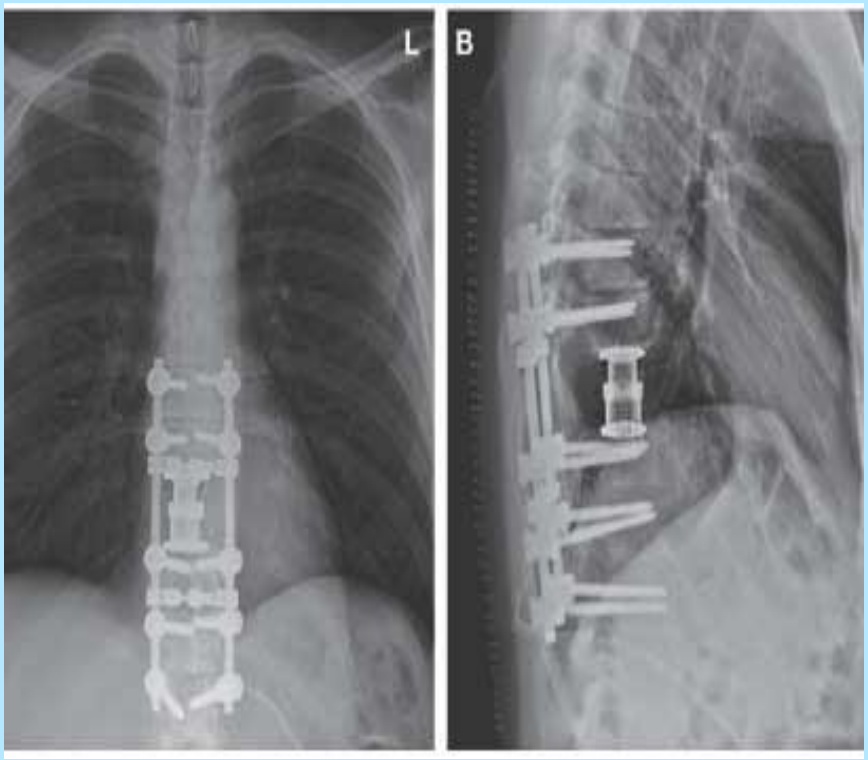
  - n= 240, nov 2017

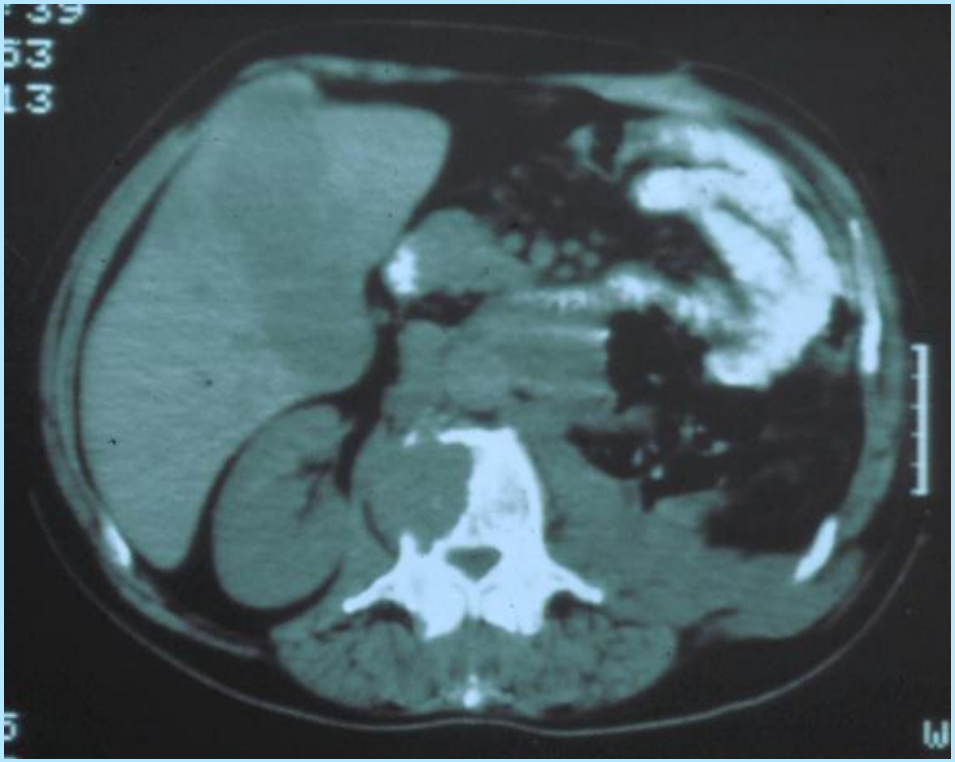
- RACOST -> 2015 Dutch trial

8 Gy SF conventional technique vs. 20 Gy SBRT

  - n= 386

Surgery for pain?





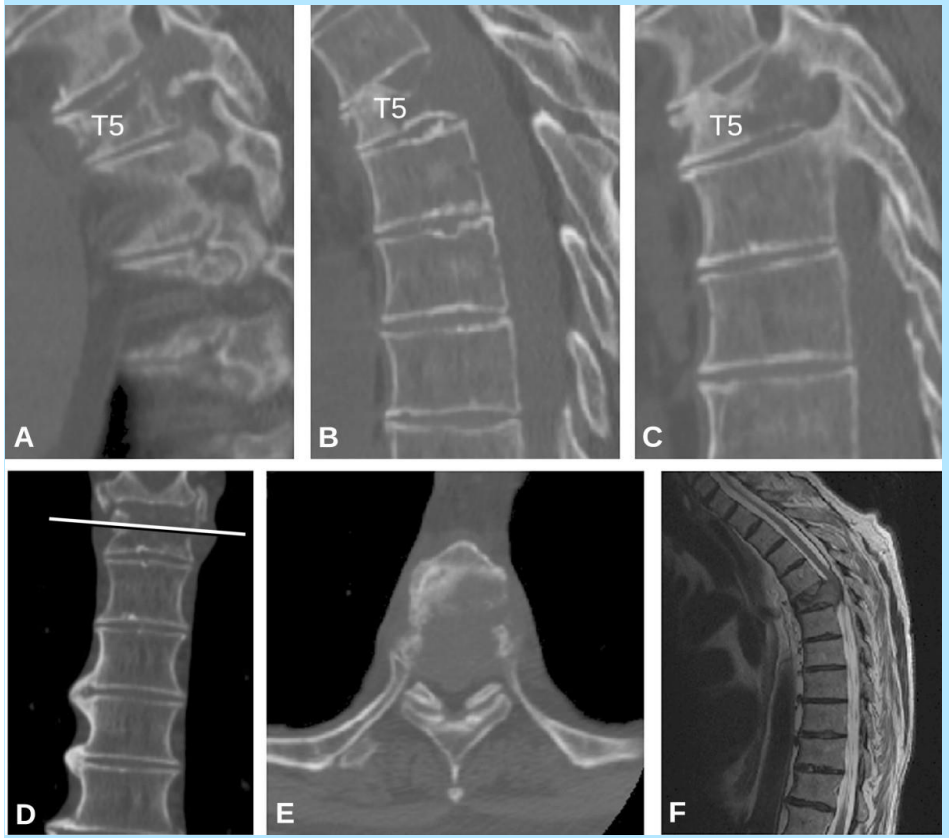
Spinal Instability Neoplastic Score

Table 1 Spinal instability neoplastic score (SINS) (6)

SINS component	Score
Location	
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	3
Mobile spine (C3-C6, L2-L4)	2
Semirigid (T3-T10)	1
Rigid (S2-S5)	0
Pain	
Yes*	3
Occasional pain but not mechanical	1
Pain-free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
≥50% collapse	3
<50% collapse	2
No collapse with ≥50% body involved	1
None of the above	0
Posterolateral involvement of spinal elements†	
Bilateral	3
Unilateral	1
None of the above	0

* Pain improvement with recumbency and/or pain with movement or loading of spine.

† Facet, pedicle, or costovertebral joint fracture or replacement with tumor.

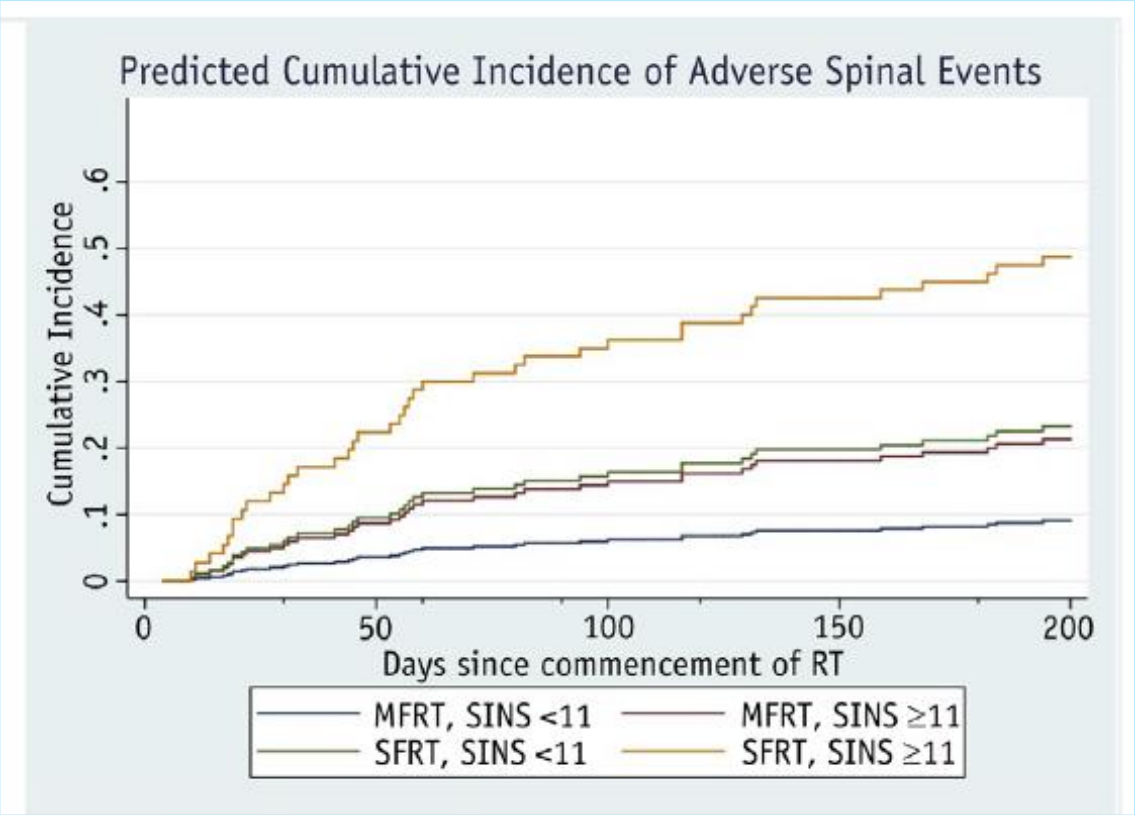


Note! All subsequent studies are about interobserver variability, not on outcome prediction

Fisher et al, Spine 2010

Use of SINS maybe of help to predict probability of complications after palliative radiotherapy

- n= 299



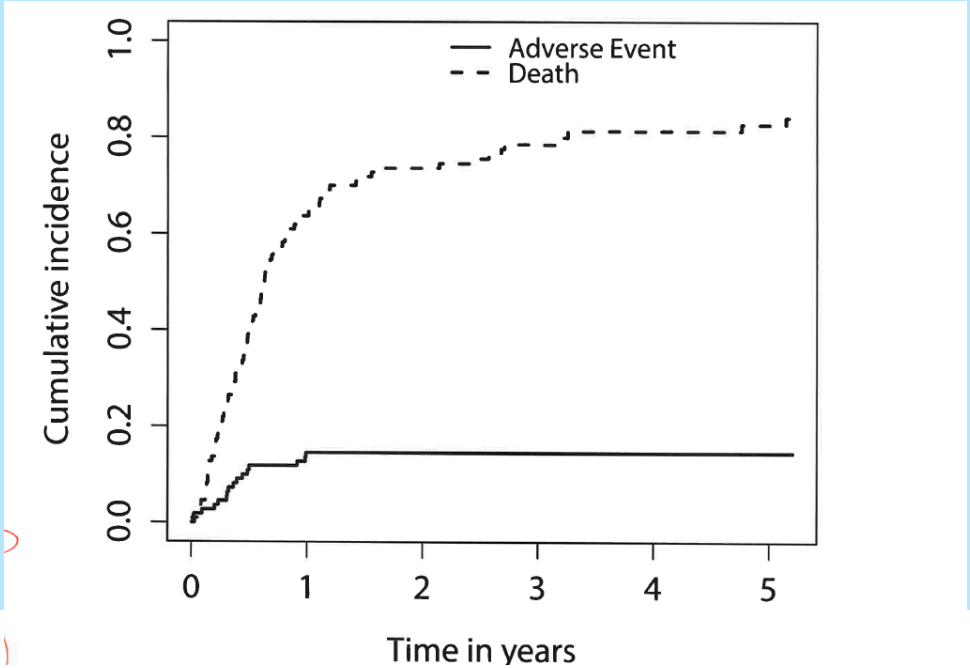
Baseline factors	Hazard ratio for first adverse event* (95% CI)	*P* value	Hazard ratio for death† (95% CI)	*P* value
SINS ≥11 (vs < 11)	2.52 (1.29-4.92)	.007	1.15 (0.80-1.67)	.44
Single-fraction RT (vs multifraction RT)	2.78 (1.51-5.15)	.001	1.95 (1.42-2.68)	<.001
BMI‡	1.04 (1.00-1.09)	.04	0.96 (0.94-0.98)	<.001
Neuropathic pain	1.82 (0.96-3.44)	.07	1.21 (0.93-1.57)	.15

Lam et al. IJROBP 2015

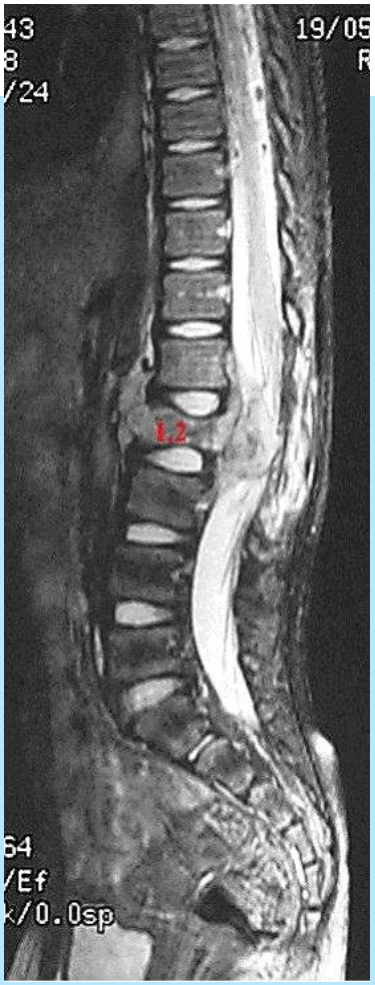
SINS score in some studies not easy to reproduce….

- N=110, 15% during FUP neurological complaints
- Retrospective cohortstudy

	Sensitivity	Specificity	PPV	NPV
Observer 1	69%	48%	18%	90%
Observer 2	35%	27%	7%	71%
Observer 3	35%	18%	6%	63%
Observer 4	41%	25%	8%	71%



Bollen et al, Spine 2017



Spinal metastases causing neurological complaints

Spinal cord compression -> published papers

- Expected short survival
  - Maranzano et al R&O 2009
    - 2x 8 Gy vs. 15 Gy /3fr + 15 Gy /5fr
    - N= 300
    - Outcome =
  - Maranzano et al JCO 2005
    - 1x 8 Gy vs. 2x 8 Gy
    - N= 305
    - Outcome =
  - SCORAD (Peter Hoskin) -> ASCO 2017
    - 1x 8 Gy vs. 5x 4 Gy
    - N= 688
    - Outcome =
- Prolonged survival ?



60% improvement after RT

Motor and sphincter function before and after treatment according to radiotherapy regimen.

	8 Gy × 2 short-course No. of patients (%)	8 Gy single-dose No. of patients (%)	Total No. of patients (%)
Motor function			
1. Walking pretreatment	101 (67)	98 (64)	199 (65)
Walking	91 (90)	86 (88)	177 (89)
Not walking	10 (10)	12 (12)	22 (11)
2. Not walking pretreatment	49 (33)	55 (36)	104 (35)
Ambulation regained	13 (26)	9 (16)	22 (21)
Not walking	36 (74)	46 (84)	82 (79)
Total of responders	104 (69)	95 (62) p = N.S.	199 (66)

Maranzano et al. R&O 2009

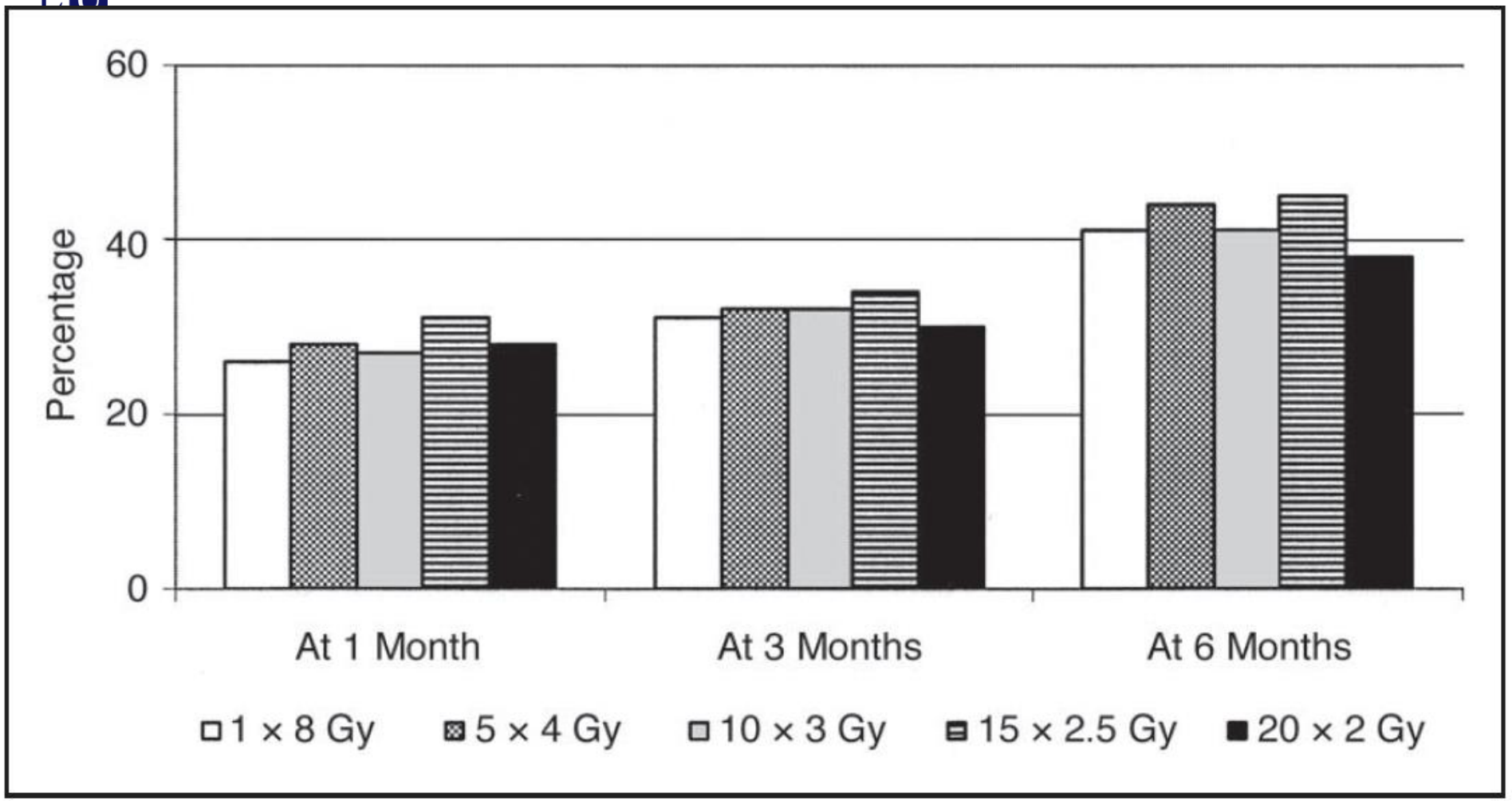
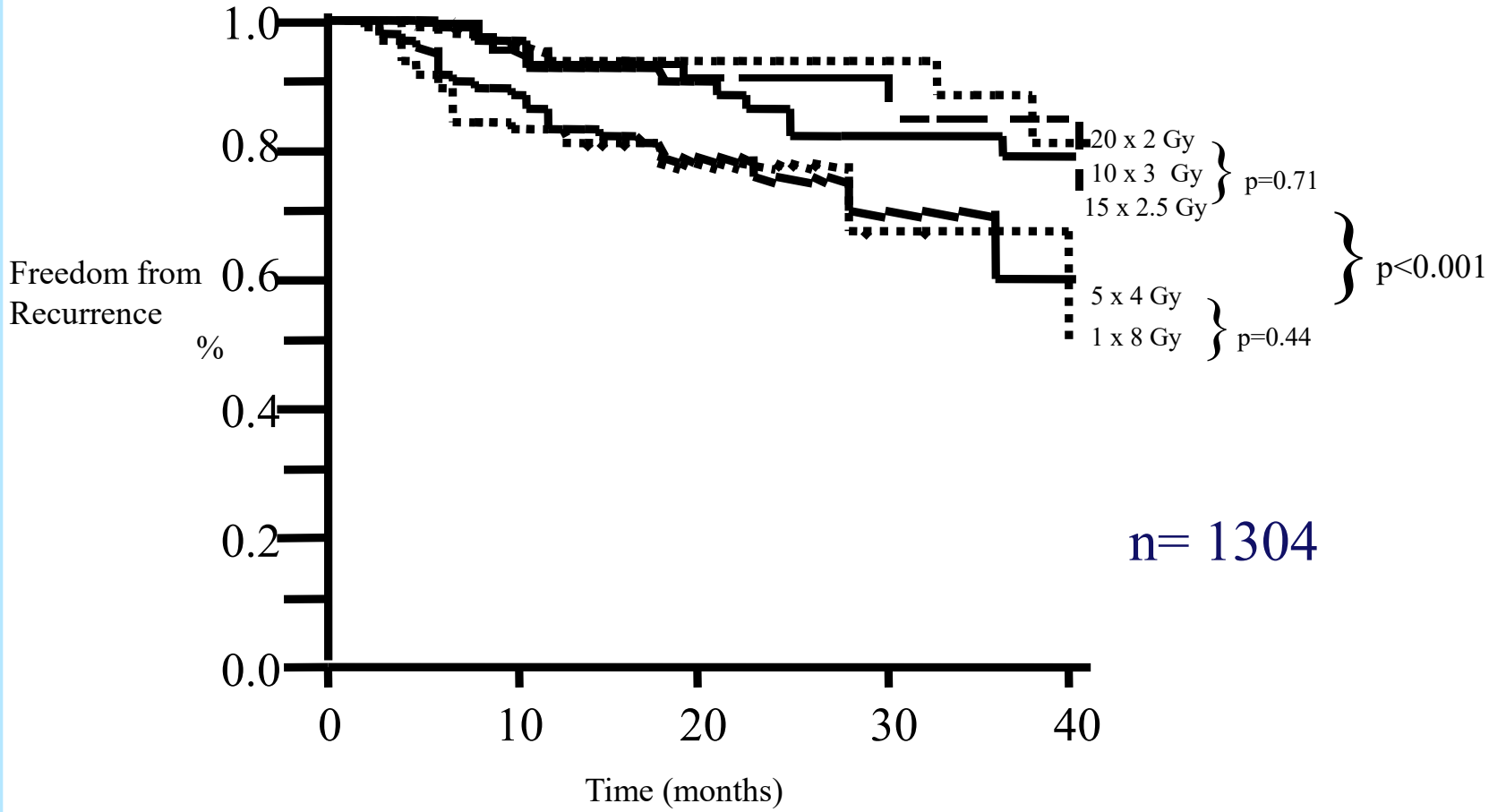


Fig 1. Comparison of the five treatment groups with respect to improvement of motor function after radiotherapy.

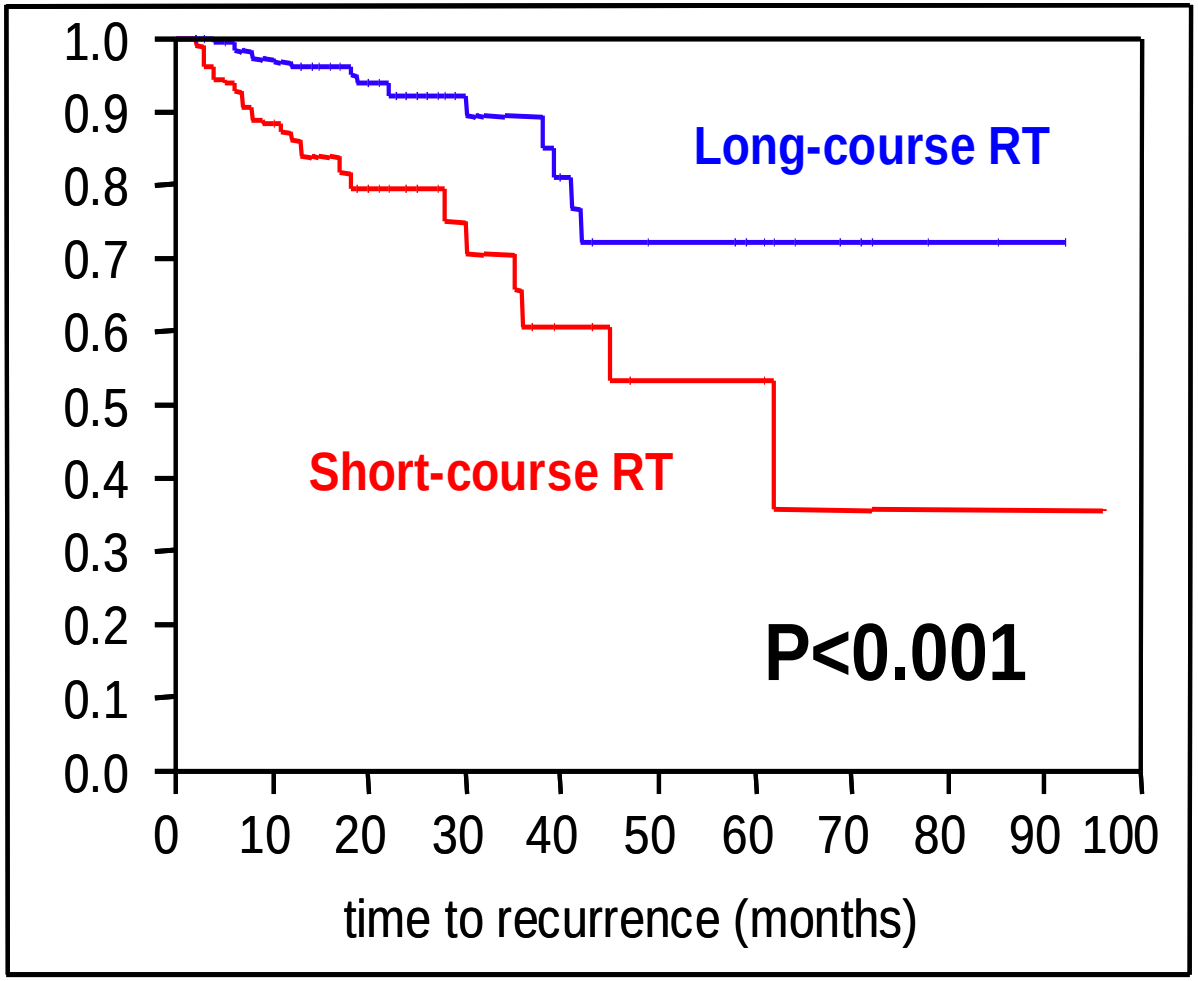
Rades et al. JCO 2005

Local control better with higher total doses



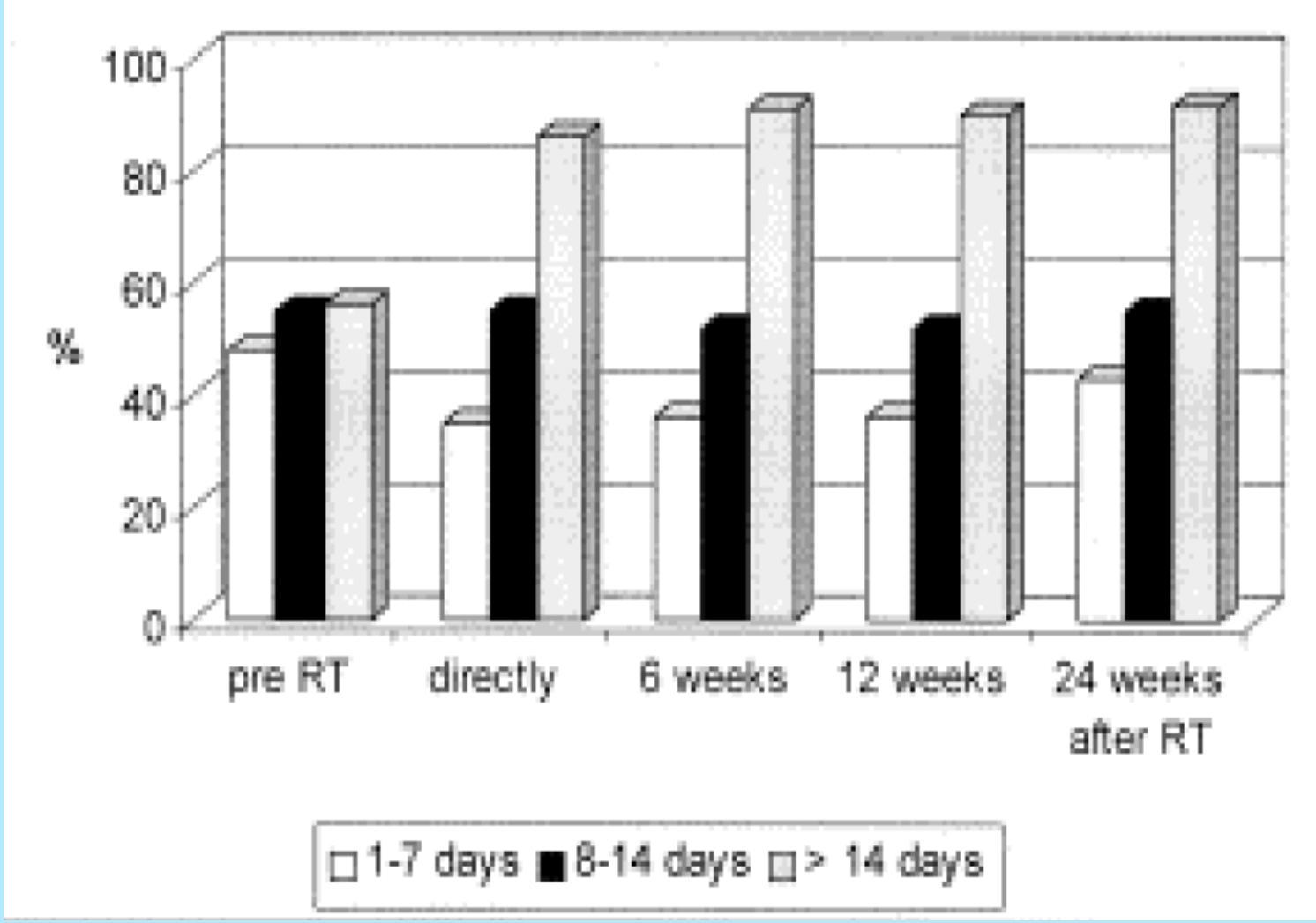
Rades et al JCO 2005

Oligometastases (N=521): Local Control



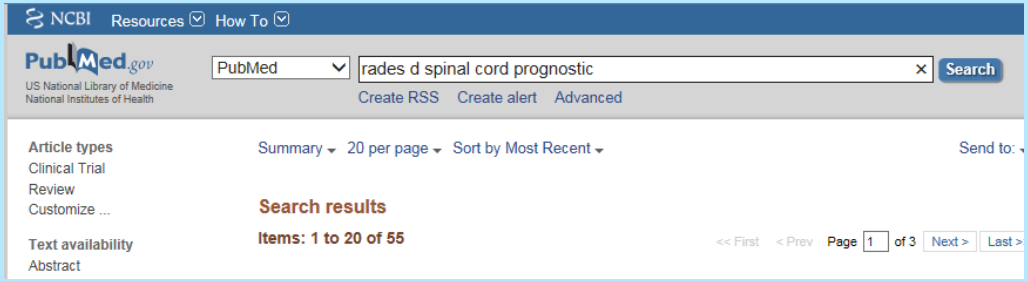
Rades et al., JCO, 2007

Treatment effective only if slow development of complaints -> duration > 14 days



Spinal cord compression -> survival & outcome

- Rades et al
- *N= 274*
- *N= 136, prognostic*
- *N= 55, spinal cord prognostic*



- Prognostische factoren
  - *tumor type*
  - *interval tumor diagnosis to MSCC*
  - *visceral metastases*
  - *pre-RT motor function*
  - *time developing motor deficits*
  - *no other bone metastases*
  - *number of involved vertebrae*
  - *RT dose*

Neurological complaints -> use prognostic system to choose appropriate treatment

	Survival at 6 months (%)	Score
Type of primary tumor		
Breast cancer	78	8
Prostate cancer	66	7
Myeloma/lymphoma	85	9
Lung cancer	25	3
Other tumors	40	4
Other bone metastases at the time of RT		
Yes	48	5
No	65	7
Visceral metastases at the time of RT		
Yes	17	2
No	80	8
Interval from tumor diagnosis to MSCC		
≤15 months	41	4
>15 months	71	7
Ambulatory status before RT		
Ambulatory	71	7
Non-ambulatory	31	3
Time of developing motor deficits before RT		
1-7 days	26	3
8-14 days	55	6
>14 days	78	8

	Puntentotaal	6 months survival probability	12 months survival probability
A	≤ 28	4%	0%
B	29-31	11%	6%
C	32-34	48%	23%
D	35-37	87%	70%
E	≥38	99%	89%

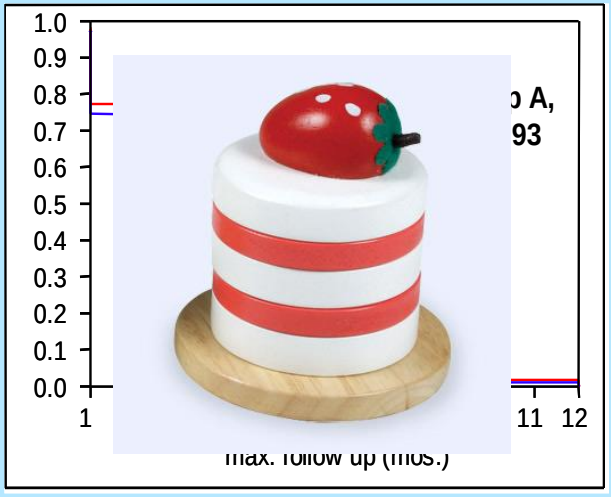
Treatment

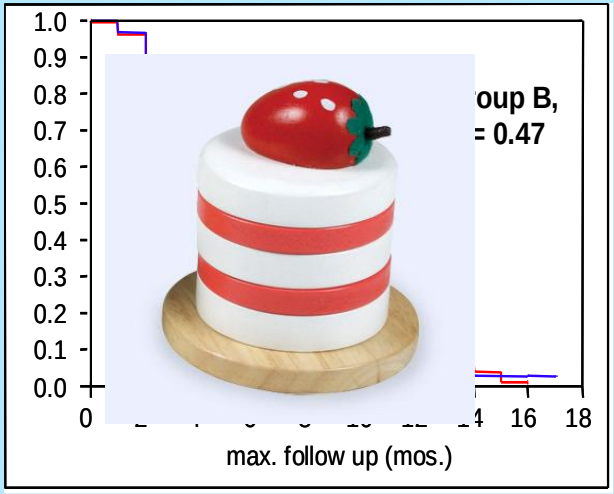
A, B, C -> 1x 8 Gy

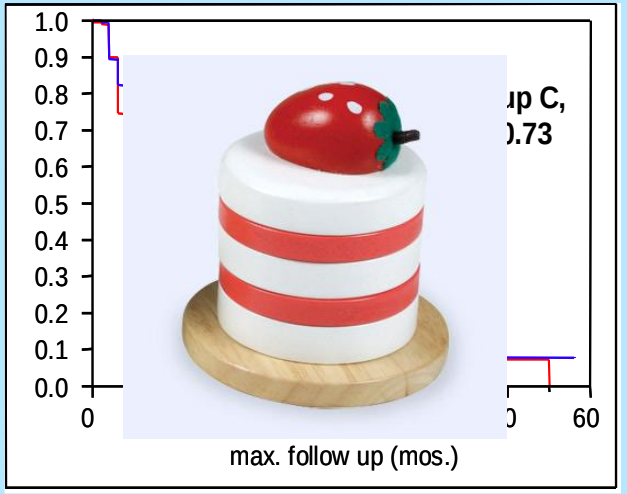
D, E -> 10x 3 Gy

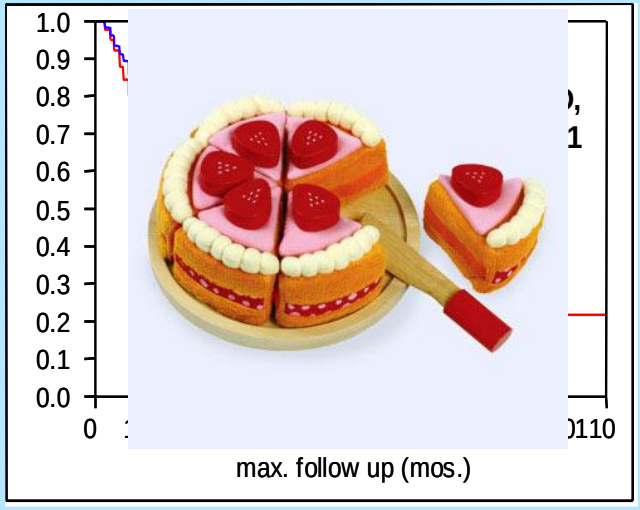
Rades et al. Cancer 2008, IJROBP 2011

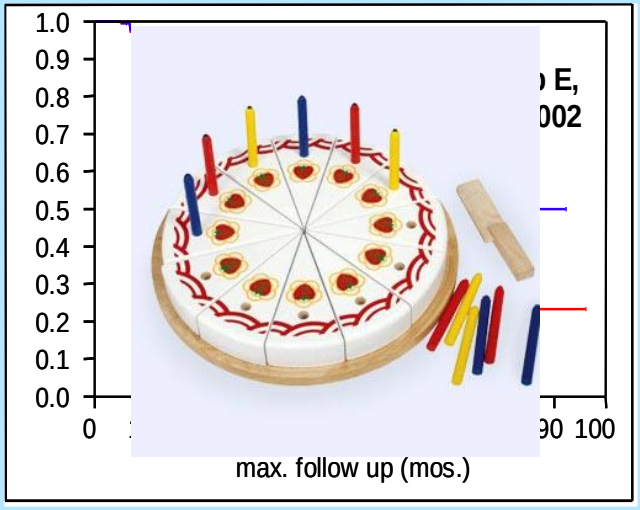
Treatment categories based on expected survival





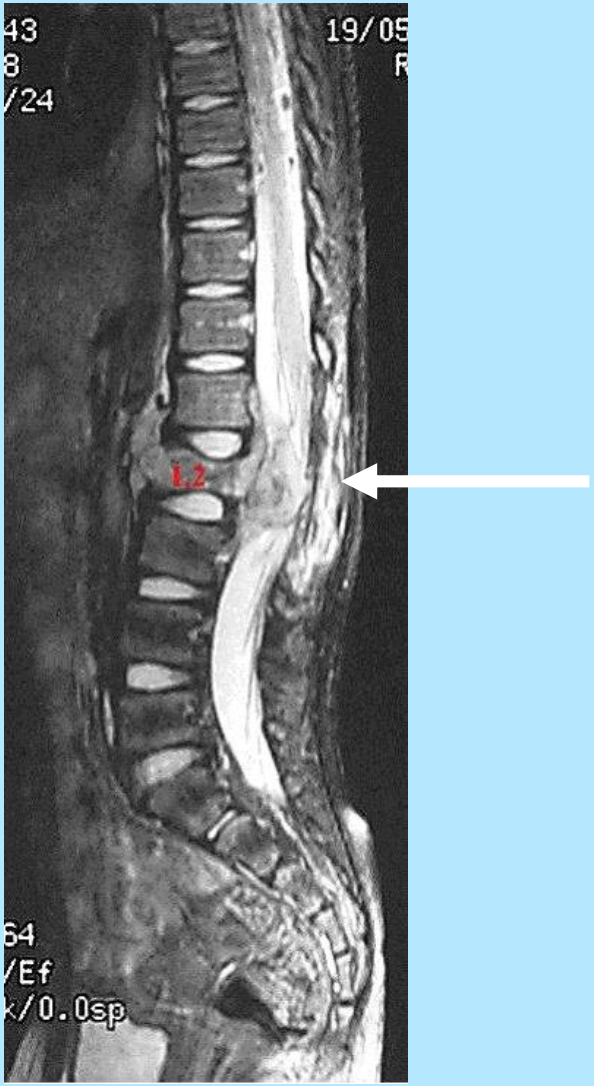


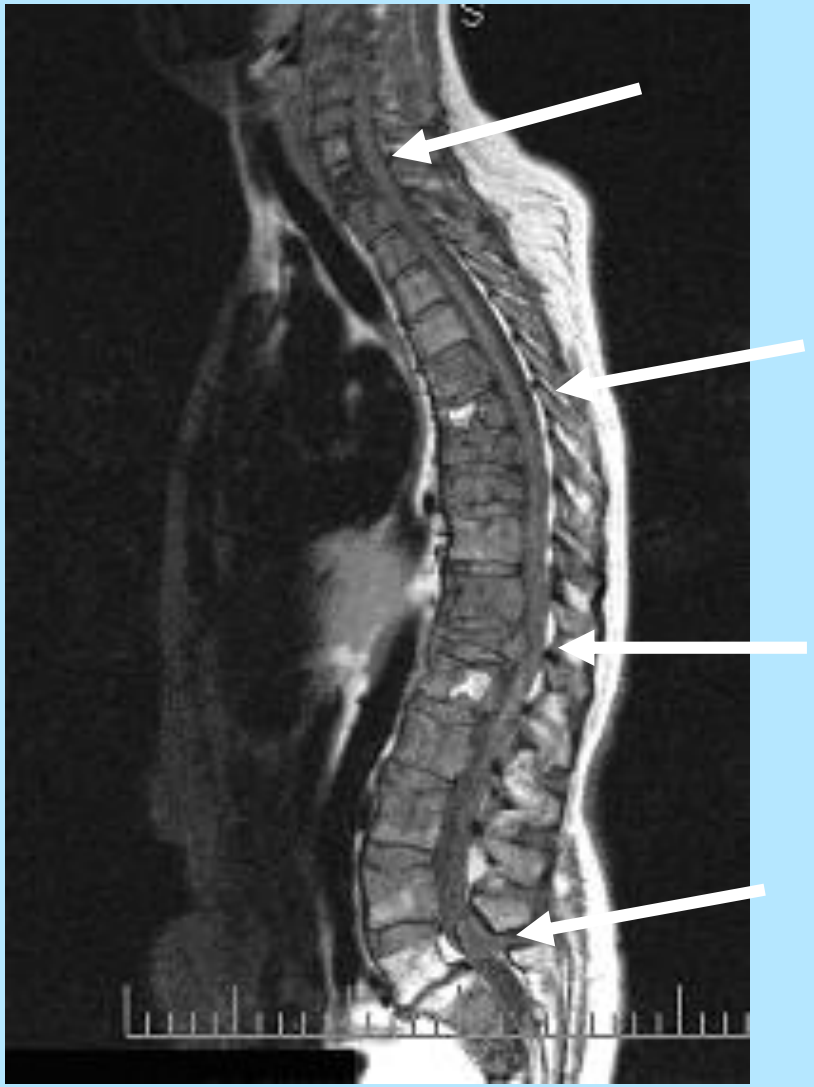




Rades et al., Cancer 2008

Surgery in MSCC and / or radiotherapy?





The Patchell-Study

randomized trial, stopped after interim analysis *(Patchell, Lancet, 2005)*

surgery plus 10 x 3 Gy (N=50) vs. 10 x 3 Gy alone (N=51)

ability to walk after treatment: 42/50 (84%) vs. 29/51 (57%), p=0.001

Surgery only for selected patients (10-15%):

KPS ≥ 70 , OS ≥ 3 mos., no paraplegia > 48 hrs., 1 spinal segment, no myeloma

- **10 years to accrue (not all eligible patients included?)**
- **≥10% more ambulatory patients than in other series**
- **small number of patients (statistical power?)**
- **surgery-related complications: 17% (primary 12%; salvage 40%)**

Matched pair analysis -> No difference performing laminectomy prior to RT

	LE+RT ($n = 24$)	RT ($n = 48$)	p value
Ambulatory following treatment	33%	50%	0.41
Regaining ambulatory status	15%	19%	0.97
Treatment effect on motor function			
Improvement	13%	13%	0.15
No change	46%	65%	
Deterioration	42%	23%	
Local control of MSCC			
At 6 months	89%	92%	0.60
At 12 months	71%	92%	
Survival			
At 6 months	38%	44%	0.67
At 12 months	27%	14%	

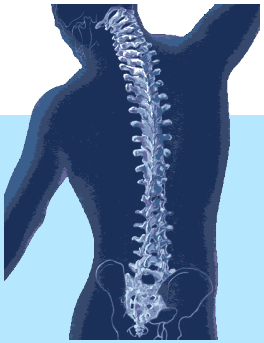
Rades et al. JCO 2010

Direct decompressive surgery adds little……

	DDSS+RT ($n = 43$)	RT ($n = 86$)	p value
Ambulatory following treatment	86%	67%	0.30
Regaining ambulatory status	45%	18%	0.29
Treatment effect on motor function			
Improvement	28%	19%	0.024
No change	60%	53%	
Deterioration	12%	28%	
Local control of MSCC			
At 6 months	94%	94%	0.78
At 12 months	94%	88%	
Survival			
At 6 months	57%	47%	0.18
At 12 months	45%	29%	

Rades et al. JCO 2010

Conclusions



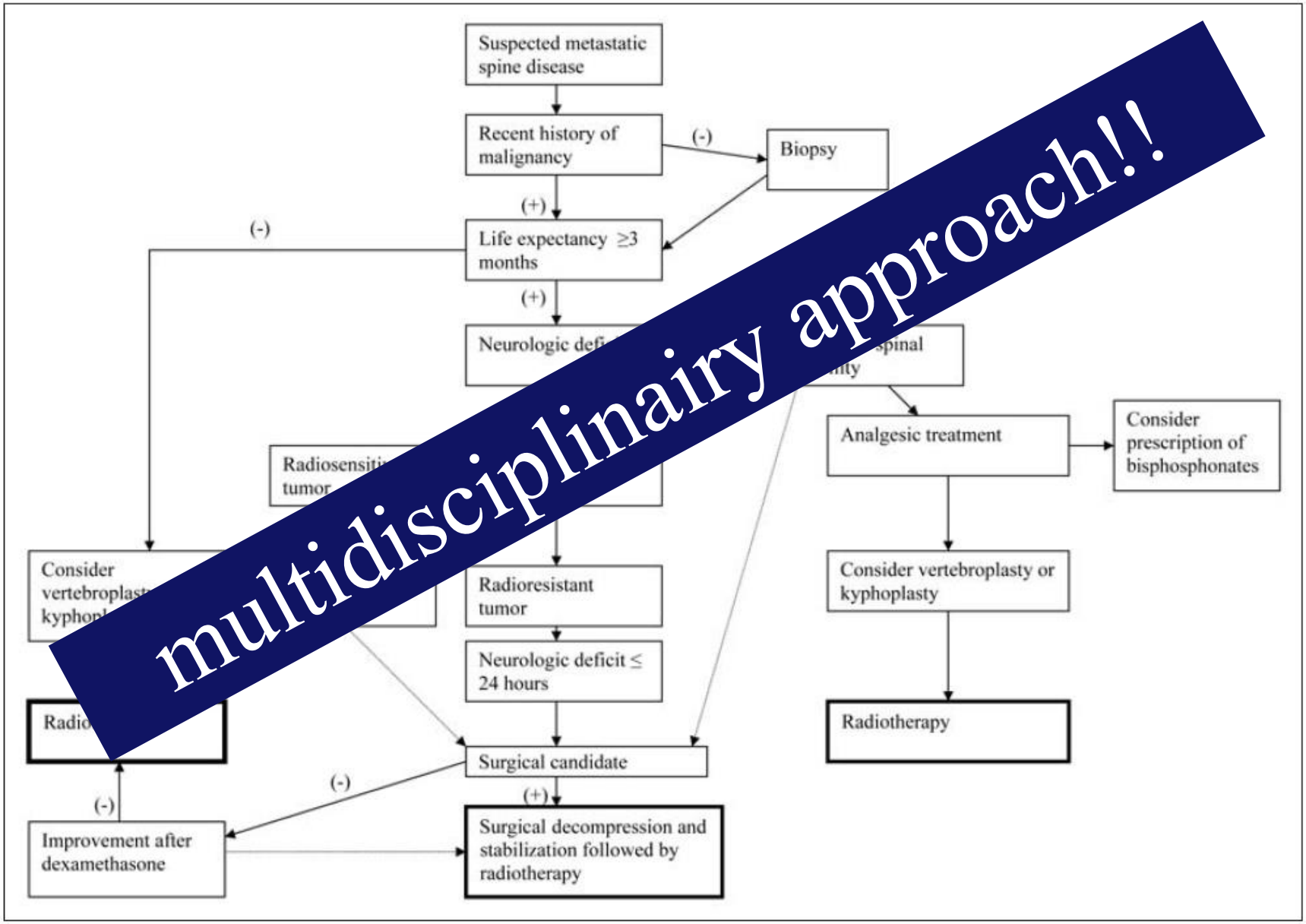
Pain

- RT SF
  - Simple techniques, await outcomes high dose trials
- If progressive pain; consider surgery
- SINS?
- Advanced techniques for retreatment

Neurological symptoms

- RT SF, or, if prolonged prognosis (single metastasis); consider higher doses
- Surgery
  - Survival > 6 months
  - Progressive complaints despite RT
  - New combinations -> preop RT followed by immediate surgery

Decision making protocol for spinal metastases



multidisciplinairy approach!!

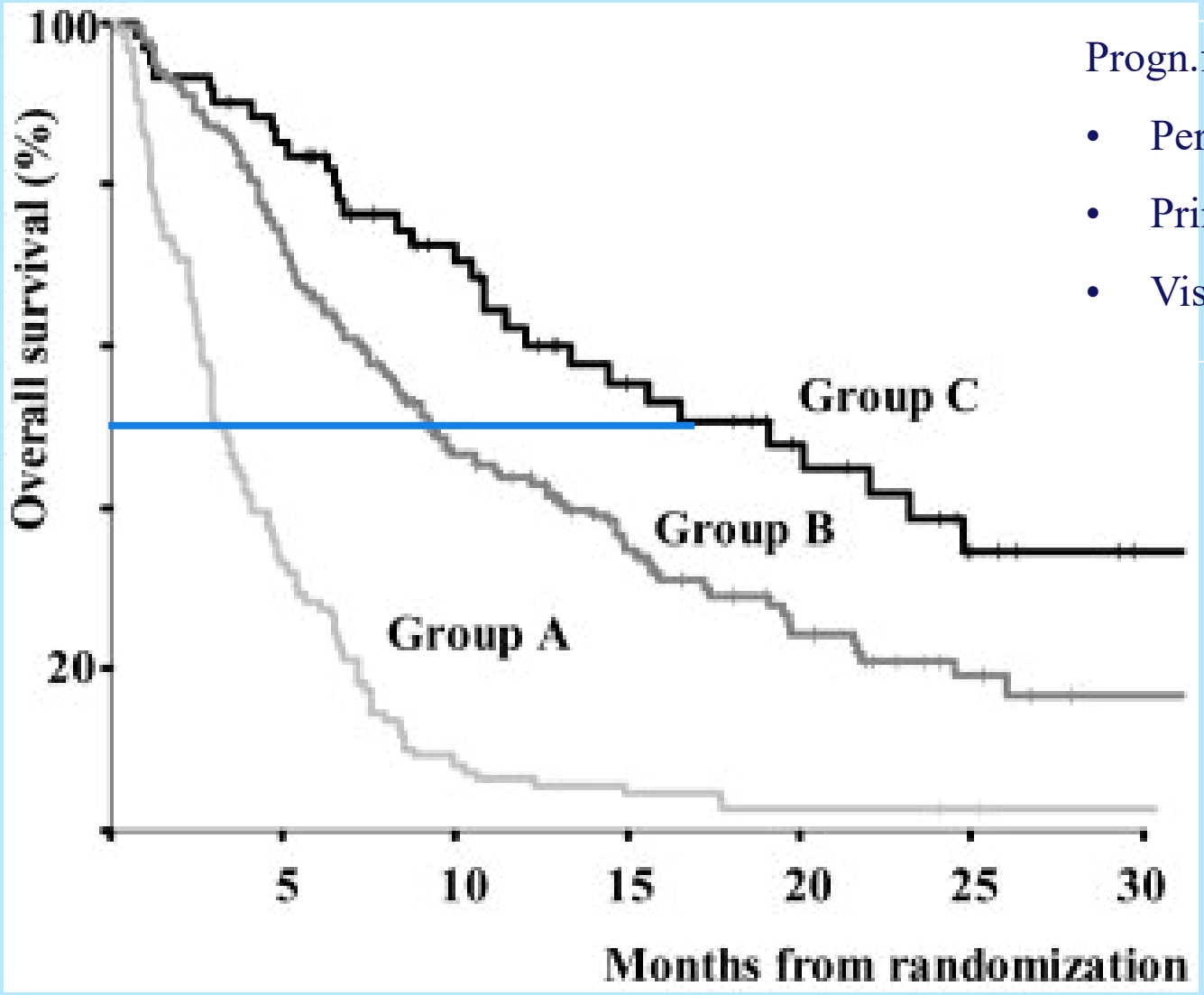
R.Bartels, Y van der Linden , W. de Graaf, Ca Cancer J Clin, 2008

Research ongoing

- Prognostic value of SINS
- Finite element modeling to predict fracturing
- New combinations -> pre op RT followed by immediate surgery

Can we correctly estimate the prognosis of palliative patients with spinal metastases ?

Survival prediction model in 342 patients with spinal metatases

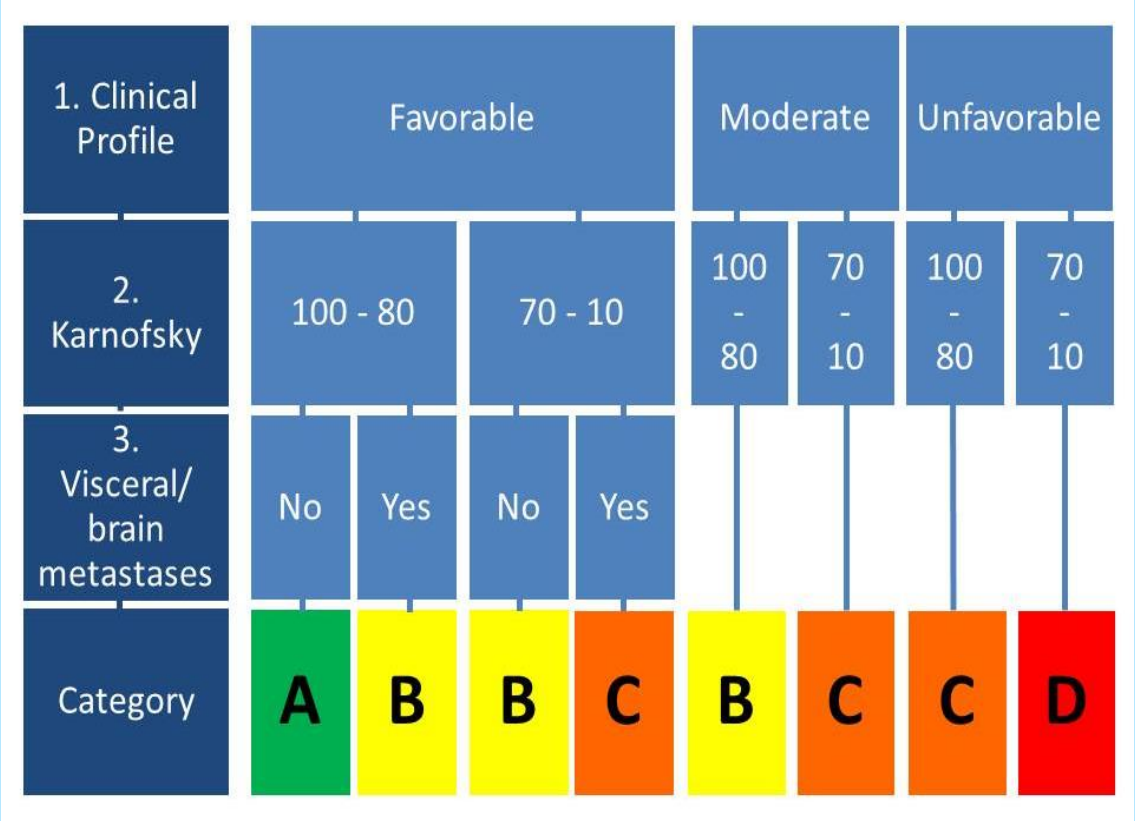


Progn.fact. MV

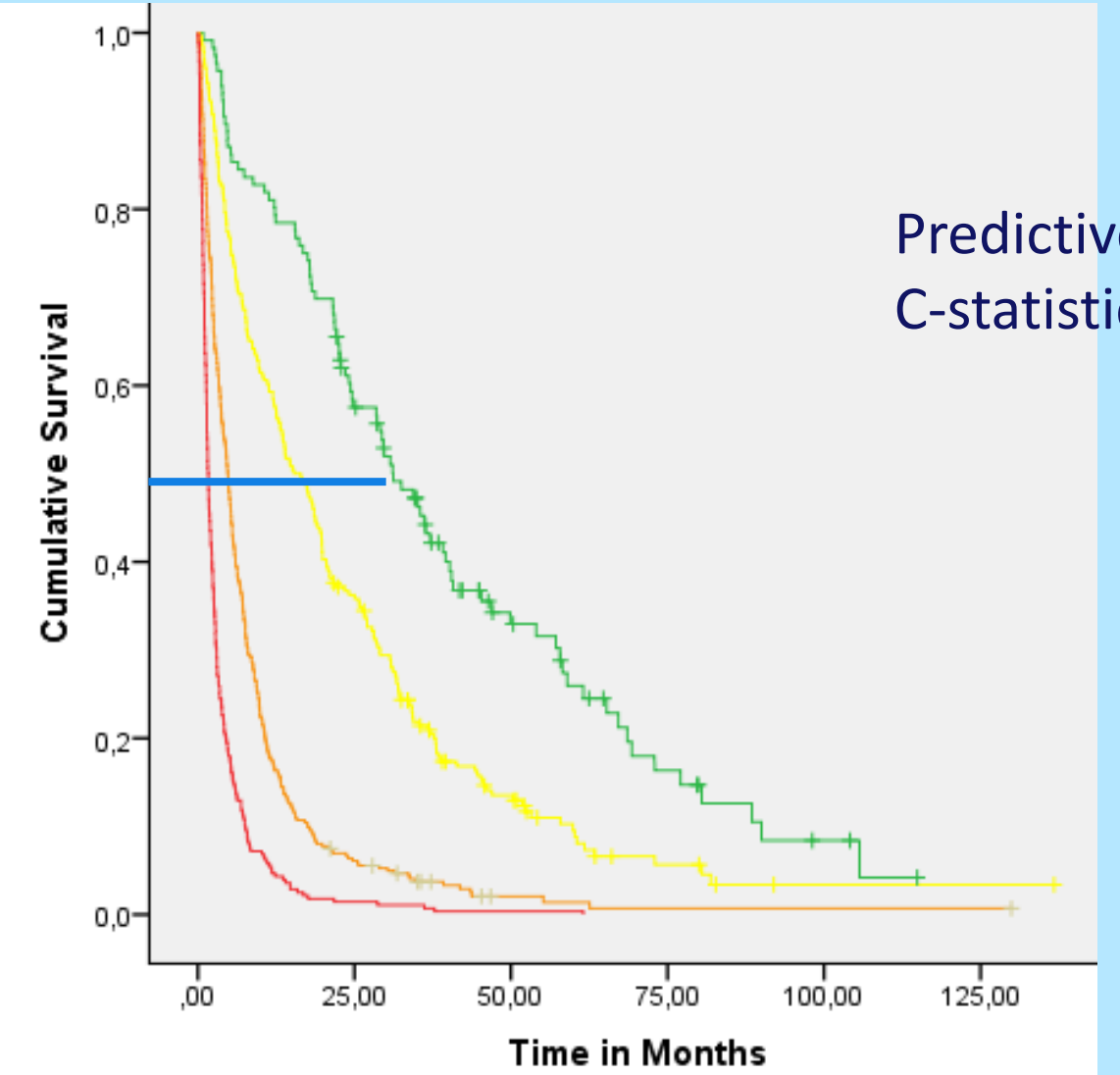
- Performance
- Prim tumor
- Visceral mets

N= 1043 spinal mets patients, 2001-2011

- **Significant Predictors**
  - **Favourable**
    - Performance
    - Visceral metastases
    - Brain metastases
  - **Intermediate**
    - Performance
  - **Unfavourable**
    - Performance



Survival categories A-D for spinal mets

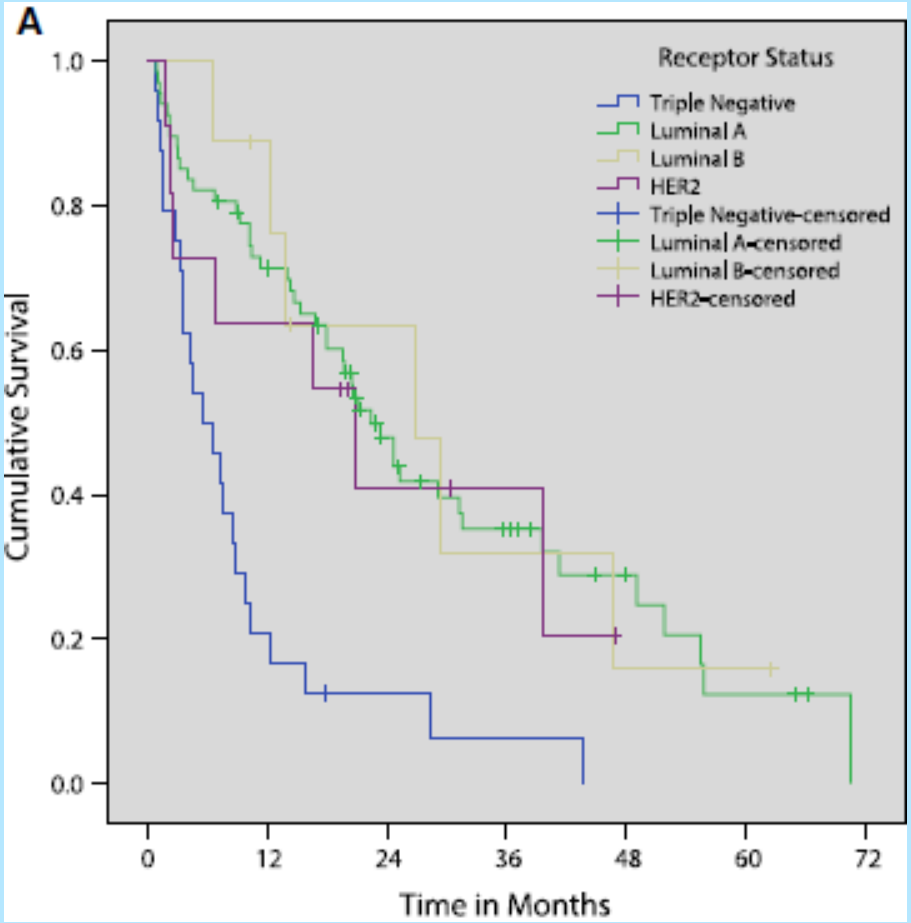


Predictive power
C-statistic 0.72

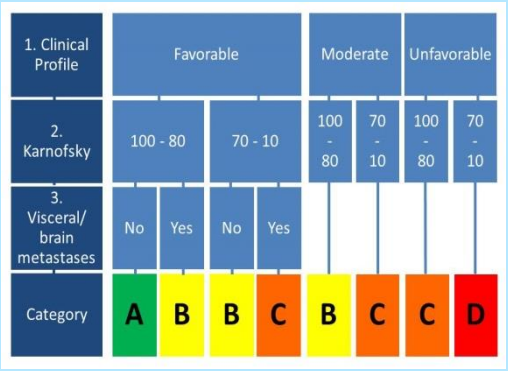
Bollen, Neuro Oncol 2014

Subtyping breast cancer improves survival prediction

n= 111



Predictive category	N (%)	MOS (95 %CI)	HR	95 %CI	p value
Before adjustment					
A	32 (29)	31.2 (14.6–47.9)	–	–	0.007
B	48 (44)	15.9 (8.7–23.1)	1.8	1.0–3.1	0.046
C	30 (27)	9.8 (7.6–12.0)	2.7	1.5–4.9	0.002
D	None	N/A	N/A	N/A	N/A
After adjustment					
A	27 (25)	39.6 (19.2–60.0)	–	–	0.001
B	51 (46)	14.7 (9.9–19.5)	2.5	1.3–4.7	0.004
C	32 (29)	9.3 (7.1–11.5)	3.8	1.9–7.3	<0.001
D	None	N/A	N/A	N/A	N/A



C-statistic 0.61 → 0.64

Bollen et al. Clin Exp Met 2015

Proceed with RT
Practical considerations → patient comfort

- Quick procedure
- Minimize transfers
- Minimize pain during treatment

- Minimize toxicity

- Influence our choice for
  - Dose
  - Technique

Special palliative clinics

Rapid Radiotherapy Response Program

- Since 1996 -> provide timely palliative radiotherapy to relieve symptoms in patients with advanced cancer.

Specialized clinics and programs

- The RRRP clinic runs daily, Monday through Friday.
- Patients are seen within a week of referral and often treated on the same day of their consultation.
- This clinic has shortened waiting time for radiation treatment in patients with limited life expectancies
- RRRP has been well received by physicians who refer their patients to this service.
- Ongoing palliative care is provided by the referring physician during and after radiotherapy.
- The program is active in research and teaching.

www.sunnybrook.ca

Radiotherapy treatment -> minimum transfers

1. Patient's bed to ambulance stretcher
2. Ambulance stretcher to RT stretcher
3. RT stretcher to CT couch
4. CT couch on to stretcher
5. RT stretcher to linac couch
6. Linac couch to ambulance stretcher
7. Ambulance stretcher to patient's bed

Probably tiring and painful exercise !!

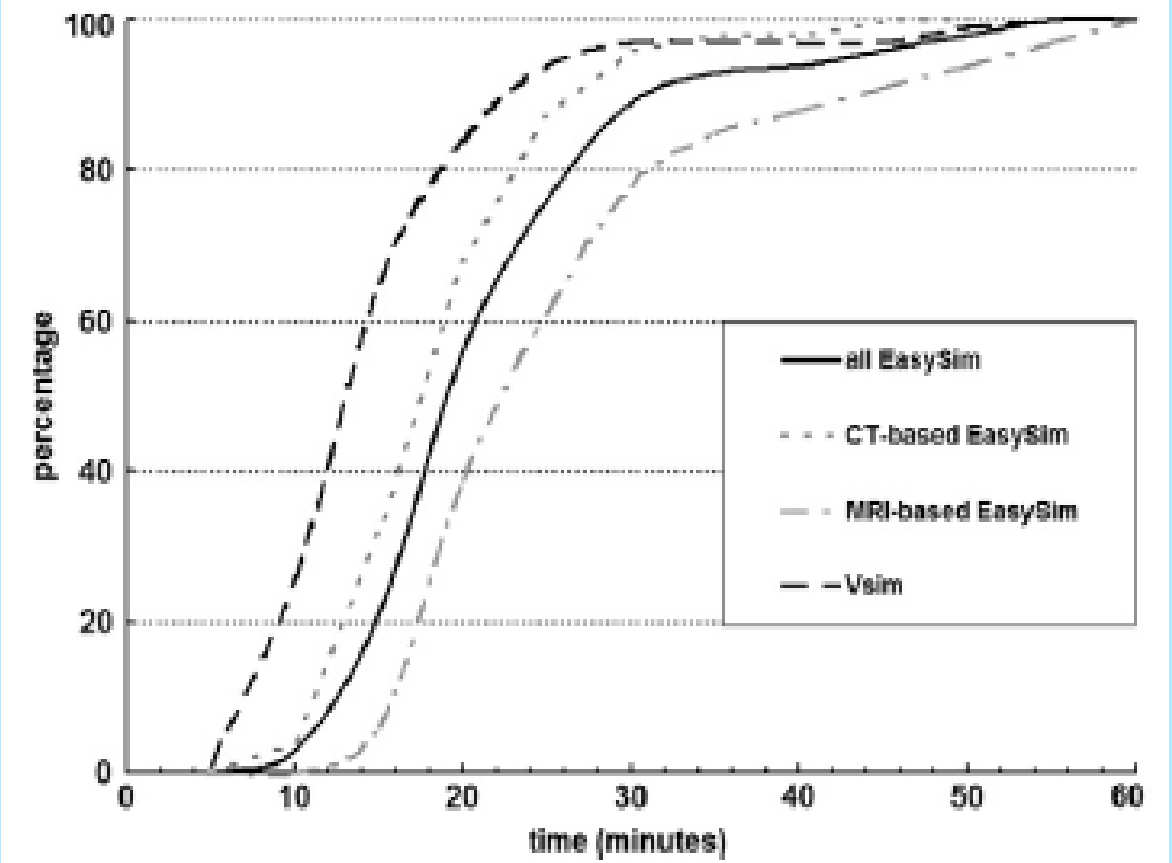
CBCT assisted RT without V-SIM

+ quick procedure

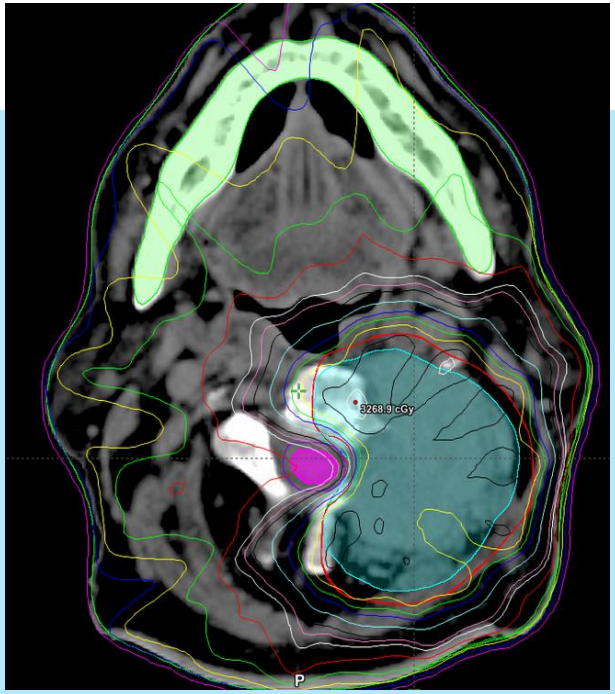
+ ambulance can wait

- No MLC

- Standard dose 5 cm

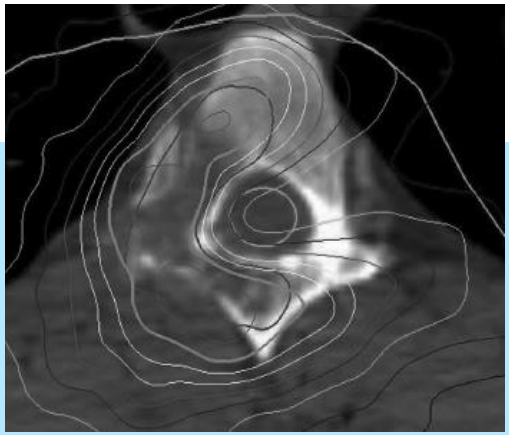


Haas et al R&O 2013



What are the costs of spinal radiotherapy?

SBRT for spinal metastases is costly



	Conventional radiotherapy ($)	Single-fraction stereotactic body radiosurgery ($)	3-fraction stereotactic body radiosurgery ($)
Hospital and clinic	3,119	9,440	14,681
Physician	1,013	2,204	2,204
Total	4,132	11,644	17,065

Saghal et al, IJROBP 2008

SBRT takes time

Table 1. Average duration of the online treatment strategy performed on phantom

Procedures	Time
Phantom Setup (aligned with lasers)	3.0 min
Cone-beam CT acquisition and processing	3.3 min
Cone-beam CT reconstruction	4.0 min
Transfer to planning system	1.2 min
On-line planning (outlining, beam arrangement and plan evaluation)	6.4 min
Transfer plan to record and verify	0.5 min
Treatment delivery (8 Gy)	4.7 min*
Total	**23.1 min**

Letourneau et al IJROBP 2007

Correction protocols: MVI EPI or CBCT

Off line → conventional EBRT

- single fraction → recording actual delivered radiotherapy field
- multiple fractions → No Action Level protocol

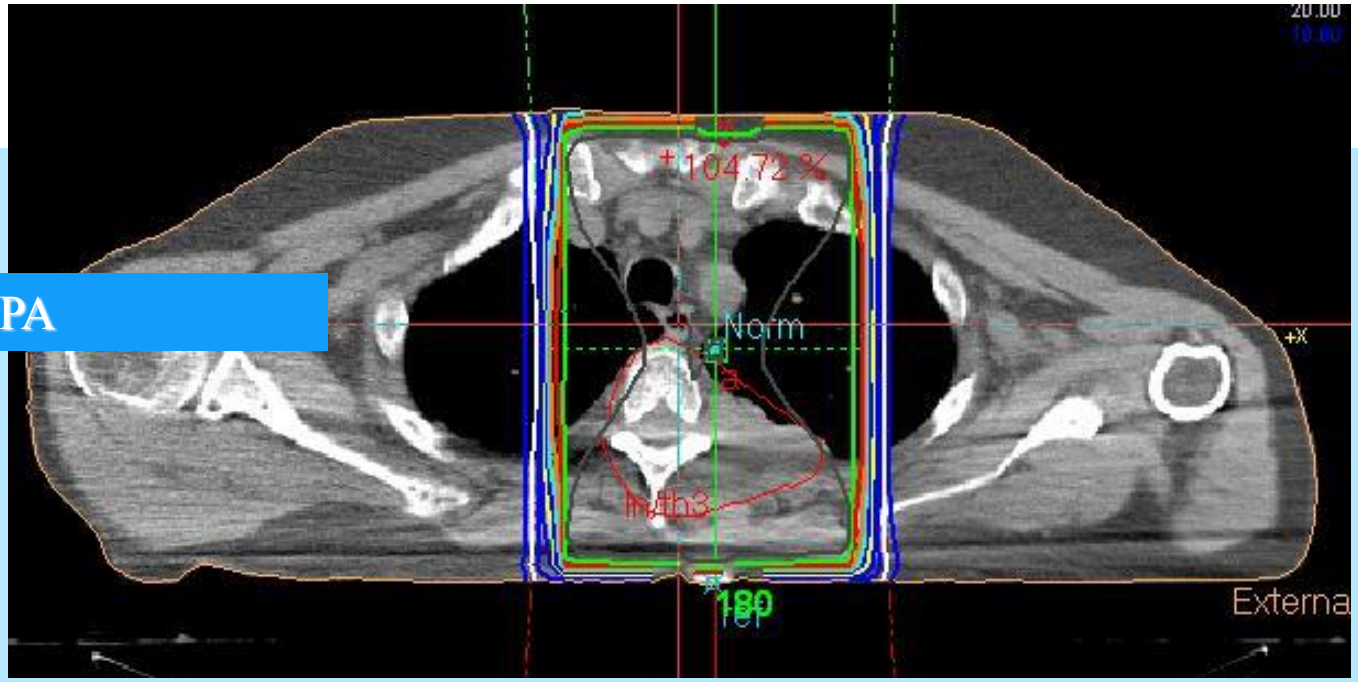
On line

- essential for stereotactic RT; high dose, high precision, risk of myelopathy
- if conventional EBRT; prevention of geographic miss; more time needed at LINAC
- poor man’s online; visual check if PTV is in treatment field
- helpful; automatic remote couch set up

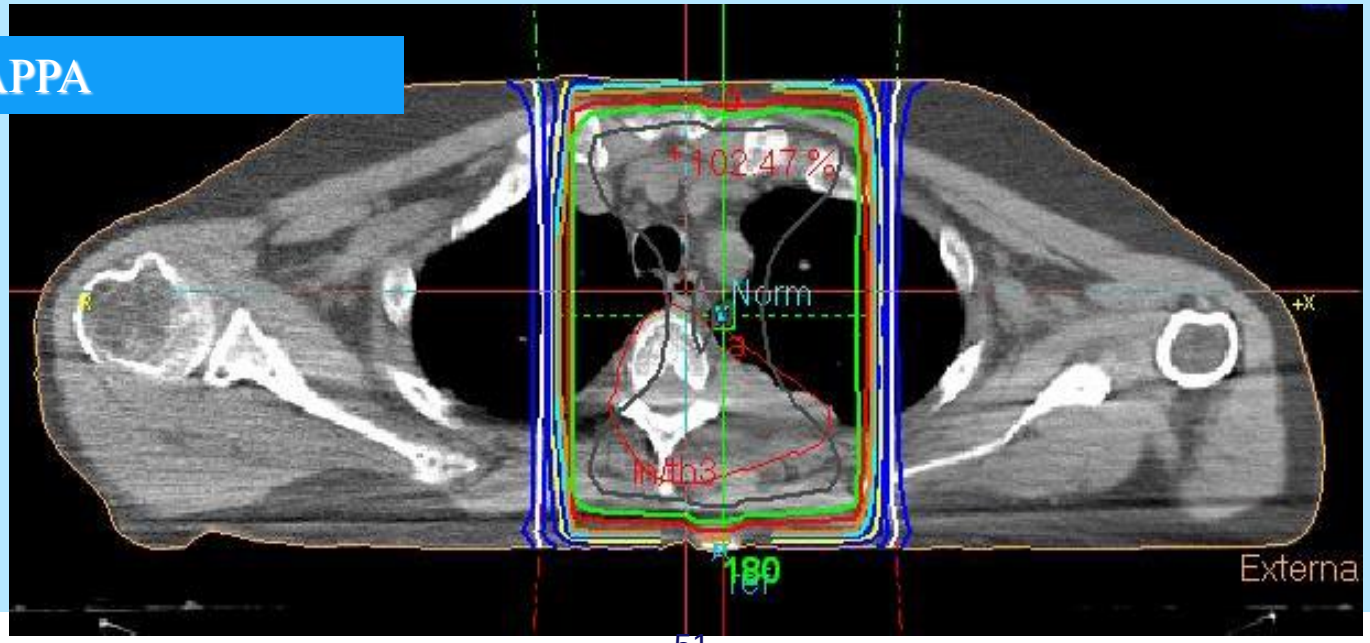
Choice for simulation technique / radiation technique

- Availability of personnel, equipment
- Goal of RT
  - patient selection → short or long term palliation
- Patient comfort
  - mobility, level of pain, other complaints (level of conciousness, nausea, involuntary muscle contractions)

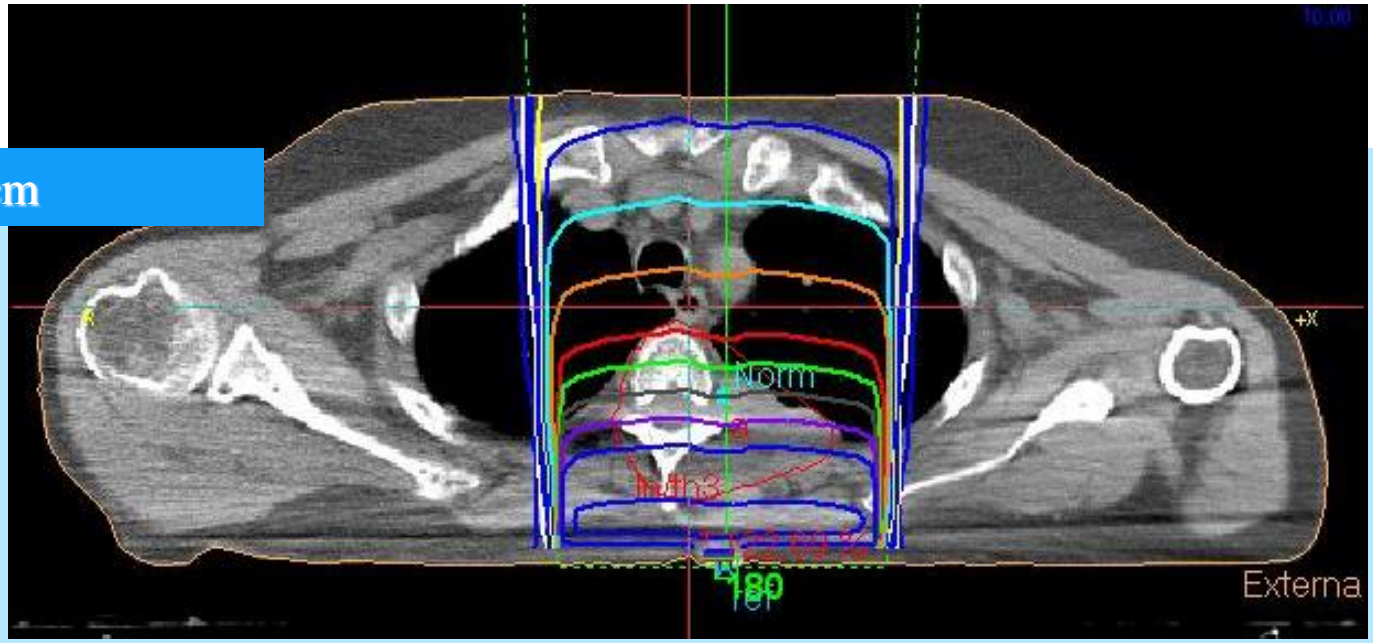
6 MV- APPA



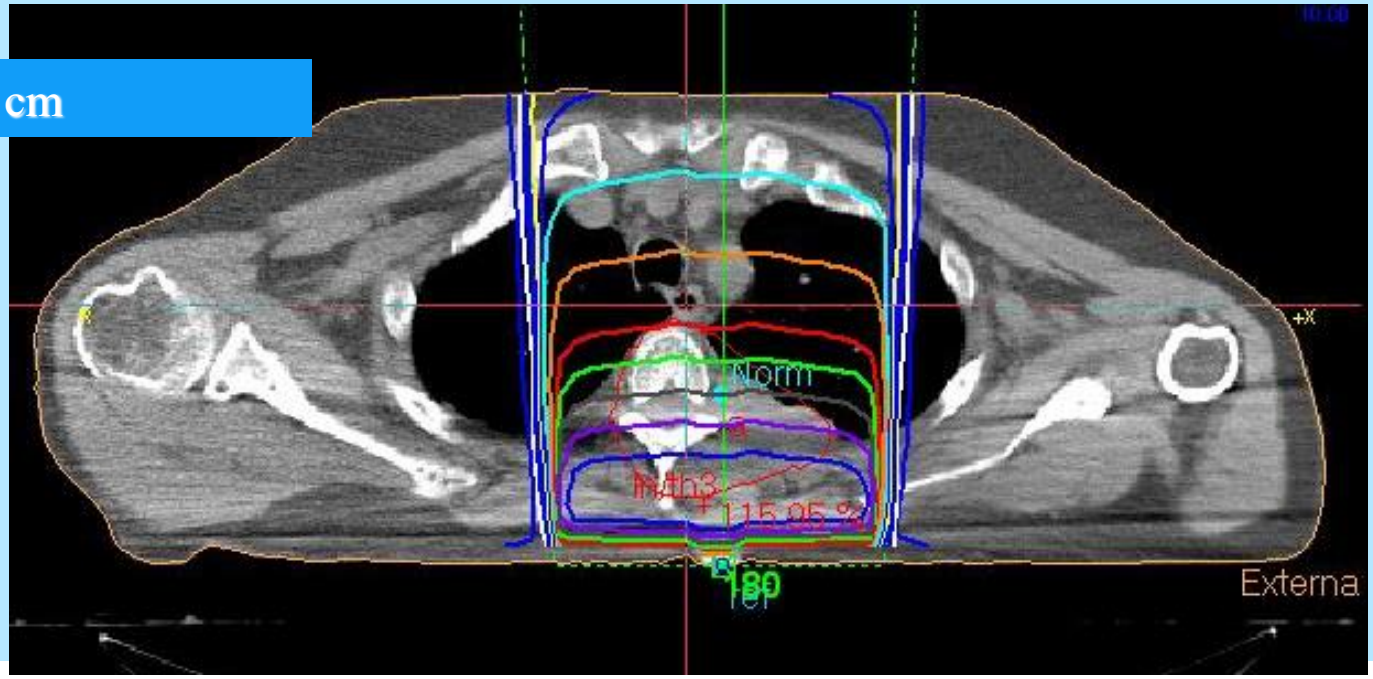
10 MV- APPA



6 MV-6 cm

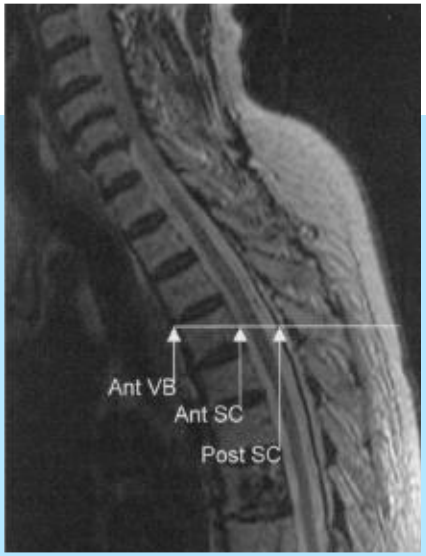


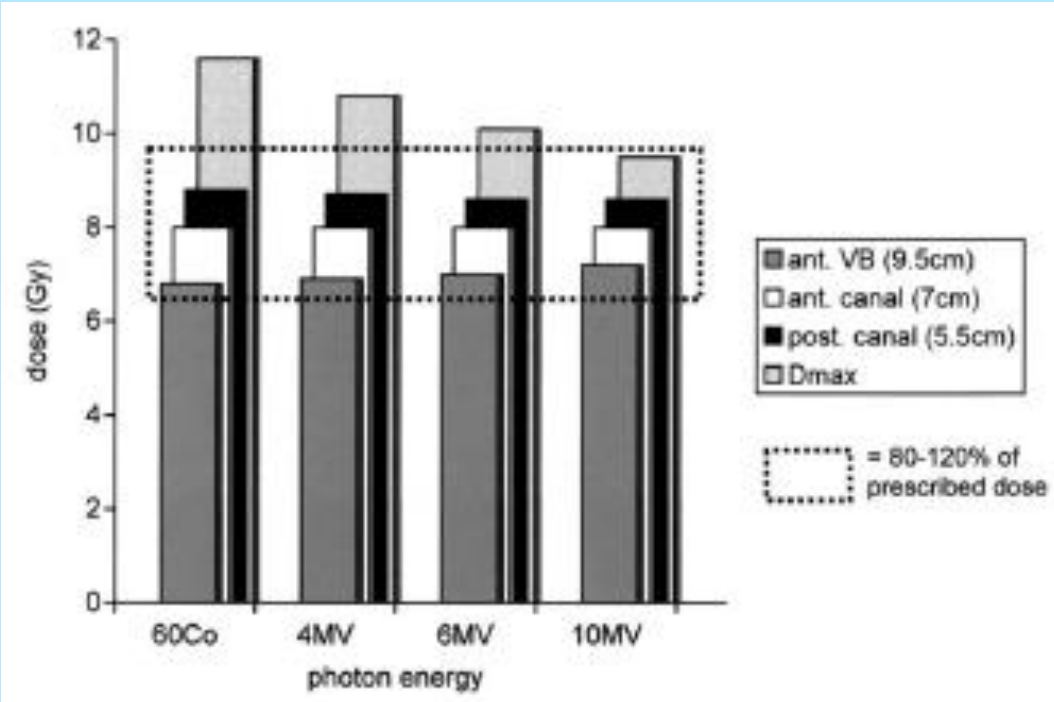
10 MV-6 cm

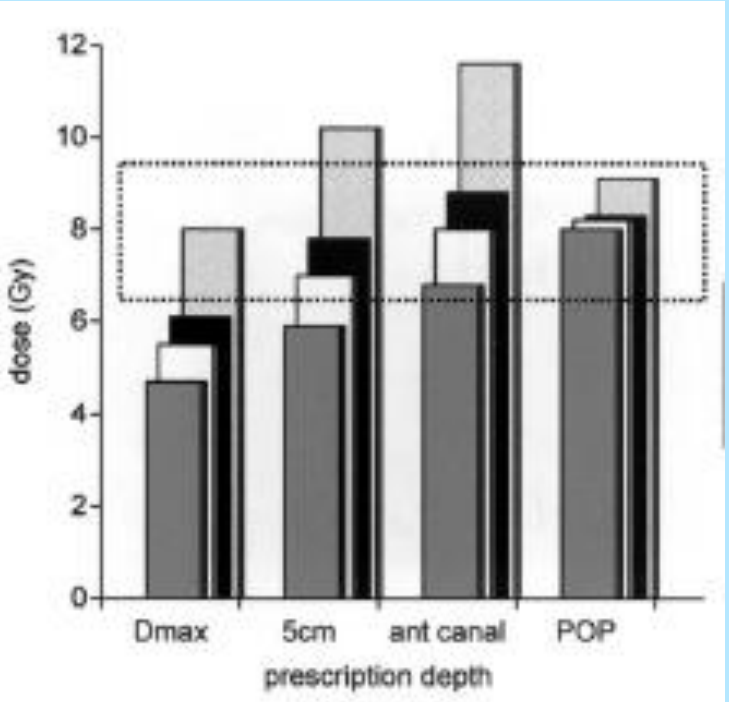


Doseren

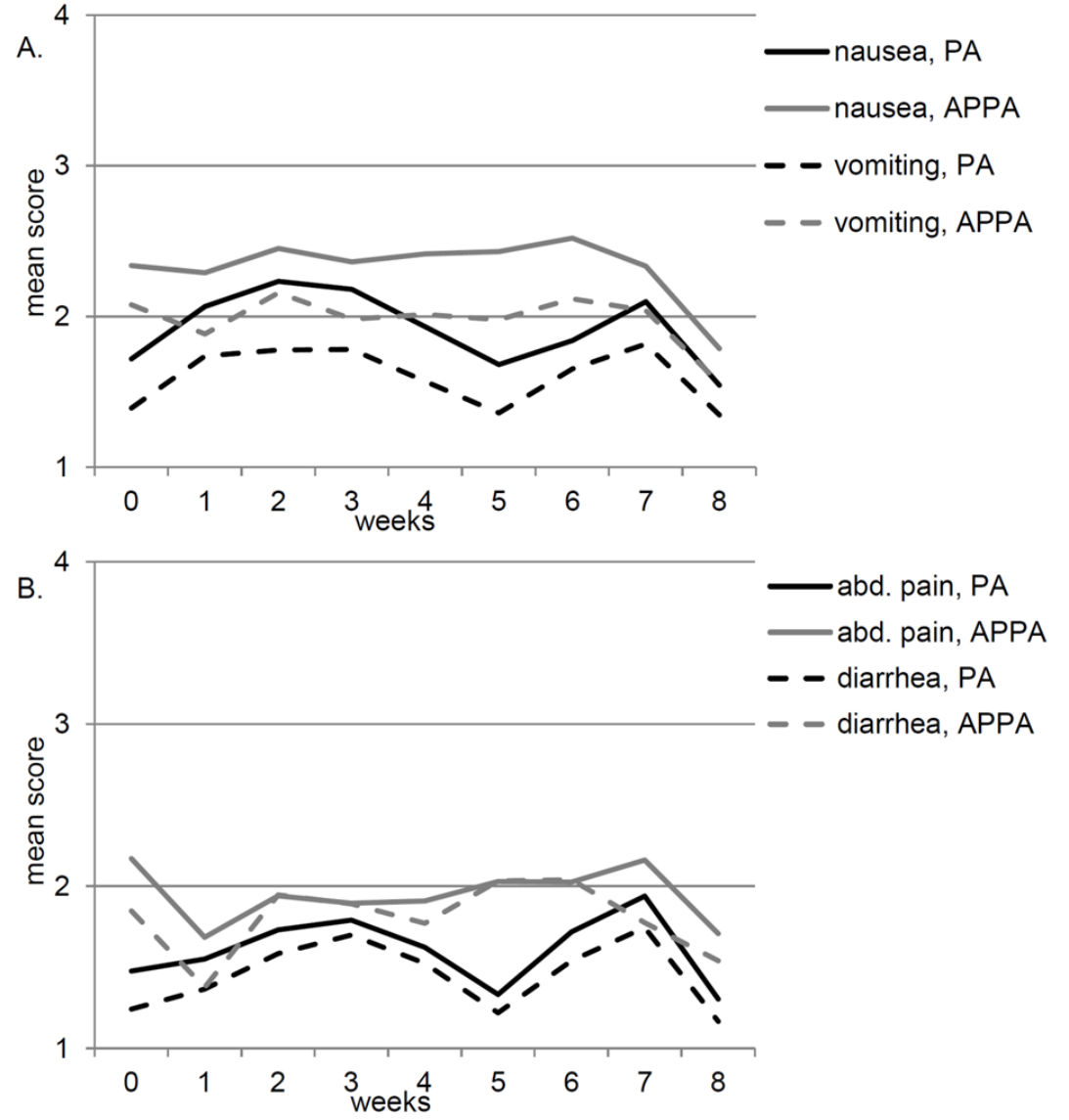
- Barton et al, IJROBP 2002
  - Varying MV
  - PA vs APPA







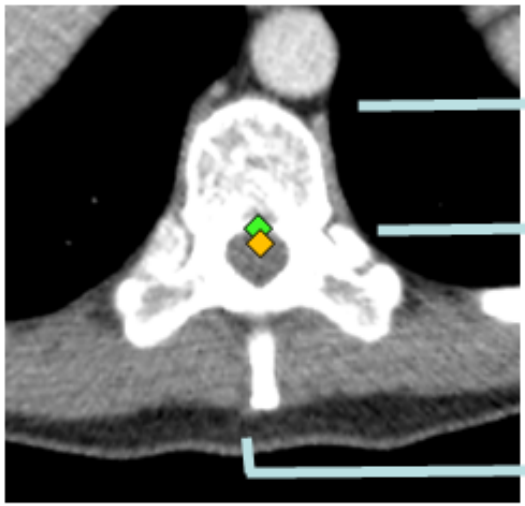
Toxicity after EBRT seems limited; results from DBMS



Westhoff et al, accepted Rad Onc

Optimal settings for simple dose planning -> V-SIM

- Dmax 115%
- Dmin 80%



Initial beam set up for all patients

- 10 MV
- PA veld

Poster ESTRO 2010

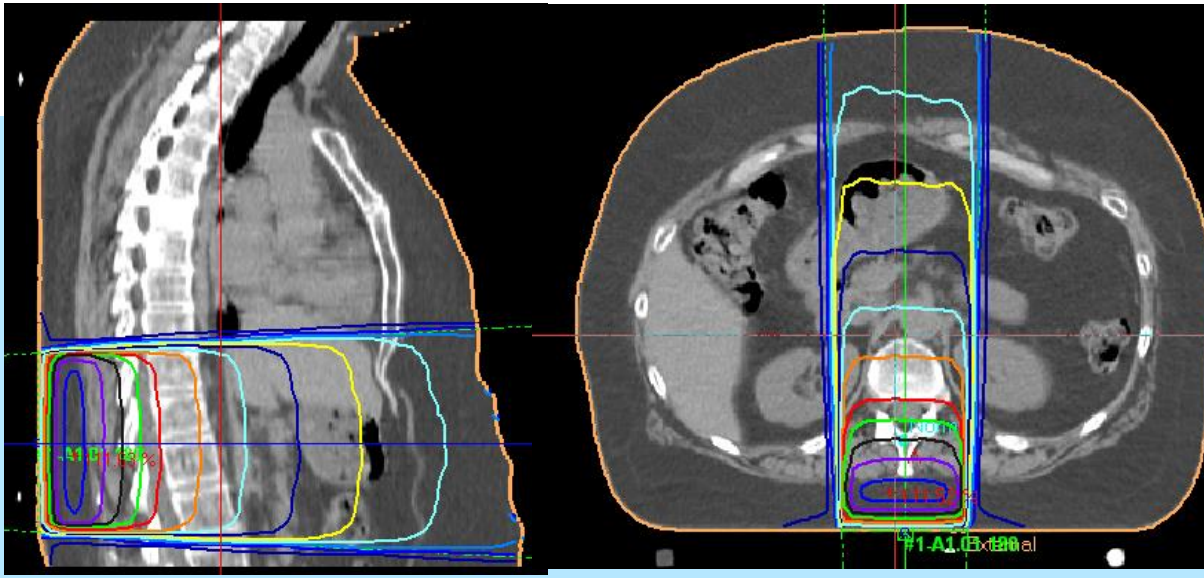
Modifications

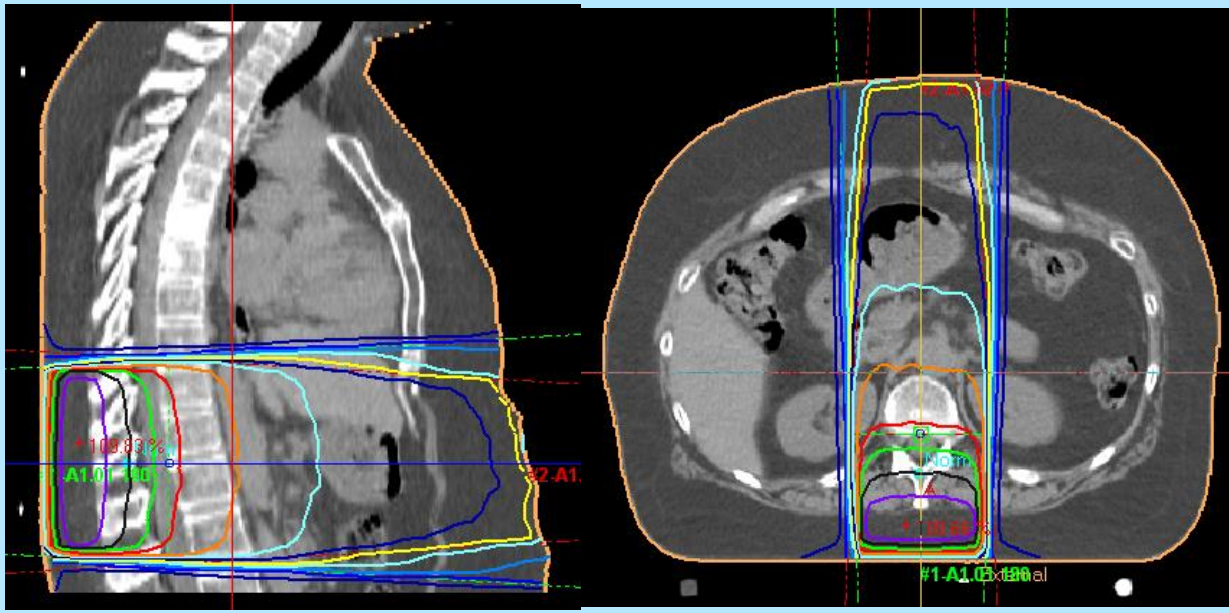
- If Dmax > 115%, and/or Dmin < 80%

↓

Add AP beam with increasing weight until 80% of total dose ventrally

Time= 10 minutes



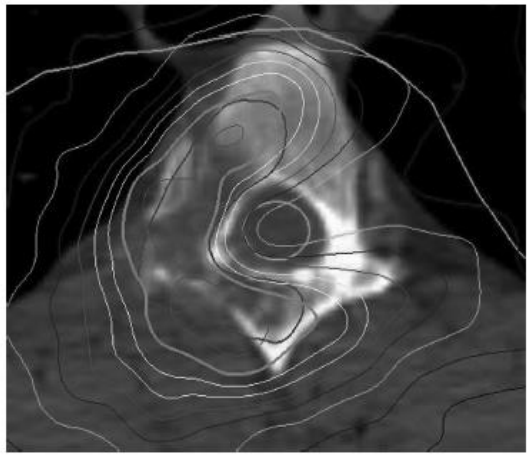


Ideal situation

MDT meetings

Optimally equipped radiation centre

1. proper patient selection
2. availability of EBRT and stereotactic RT
3. simulation and planning on CT or CBCT
4. online correction protocol



Gerstzen et al, Spine 2007

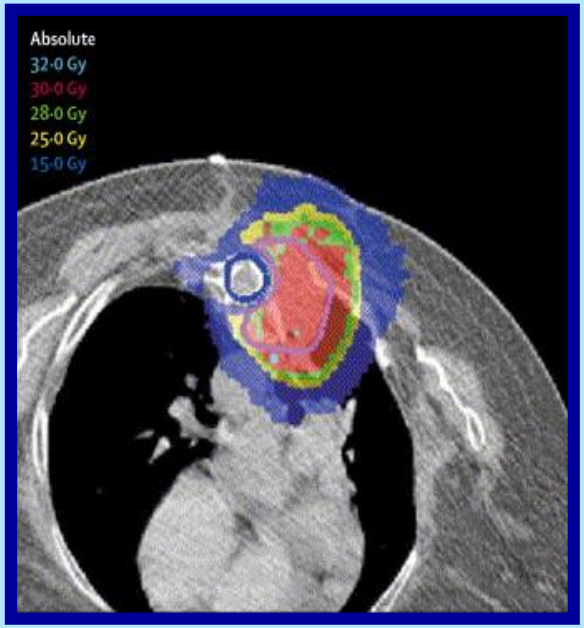
SUMMARY 1

	RS / SBRT	conv. RT
Higher rates of pain relief:		
Overall response:	82%	75%
Complete response:	43%	15%
More rapid pain relief:	1-4 wks.	1-4 wks.
Less side effects:		
Grade ≥3 acute toxicity:	mostly 0%	mostly 0%
Vertebral fractures:	2-39%	0-3%

In-field Recurrence after Long-course RT

Surgery ? Re-RT ? (=> new RT-Techniques)

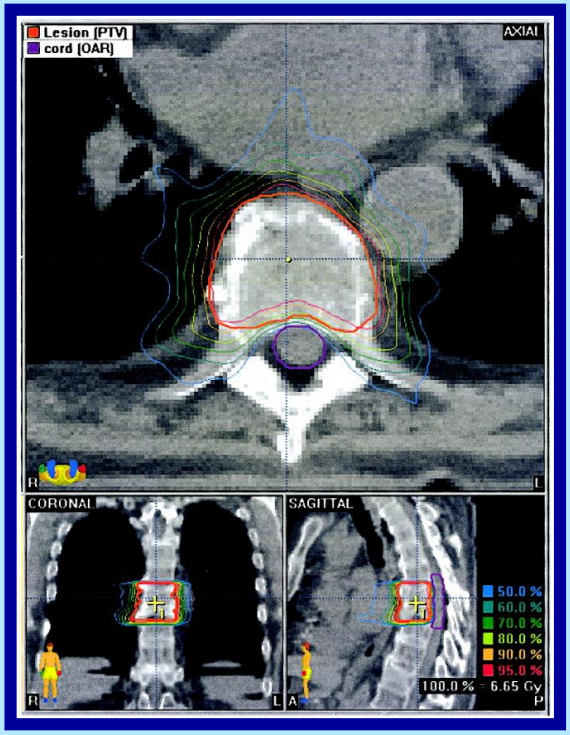
IMRT / Tomotherapy



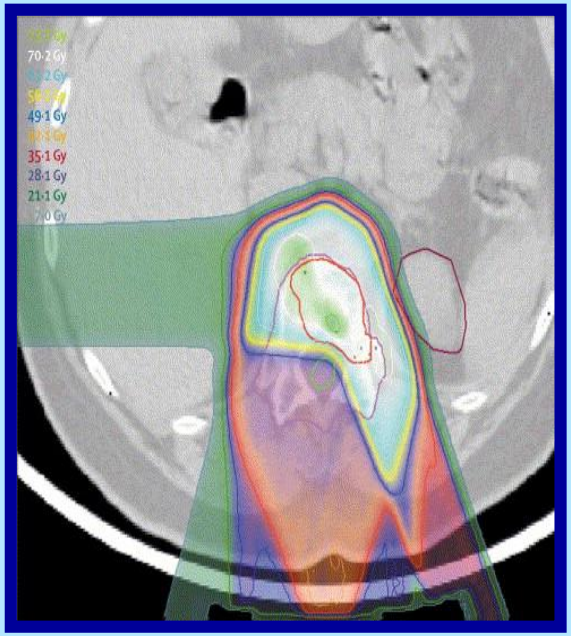
Milker-Zabel et al., IJROBP, 2003

Ryu et al., Cancer, 2003

Intensity-modulated RS

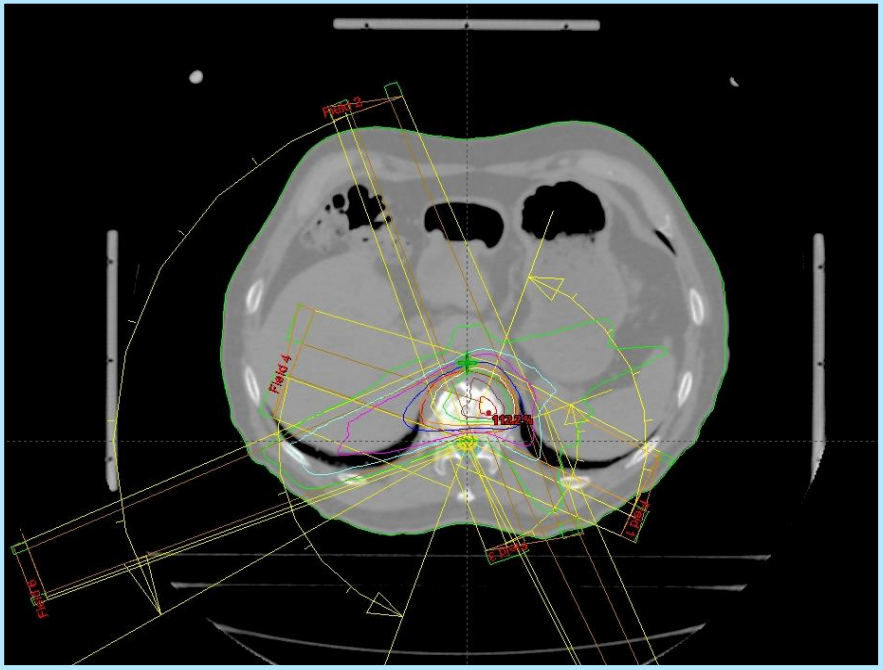


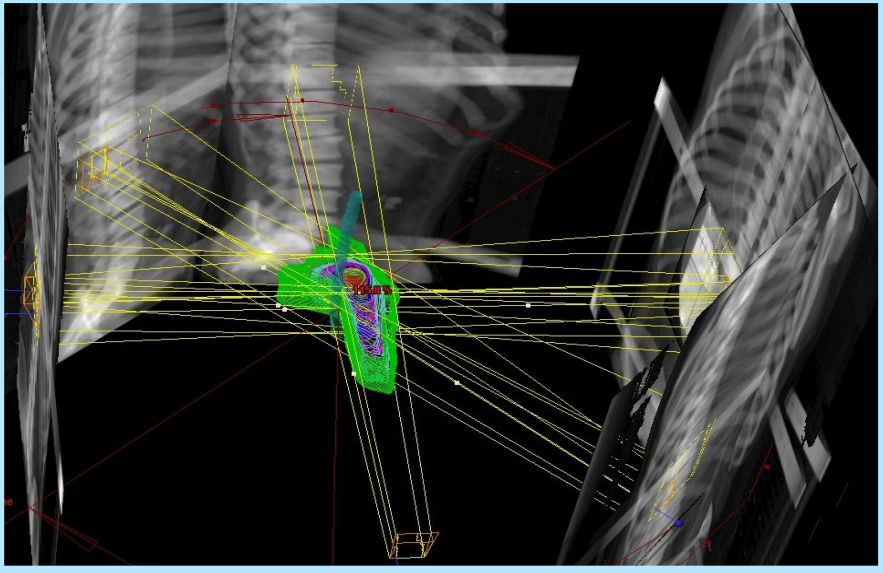
Protons

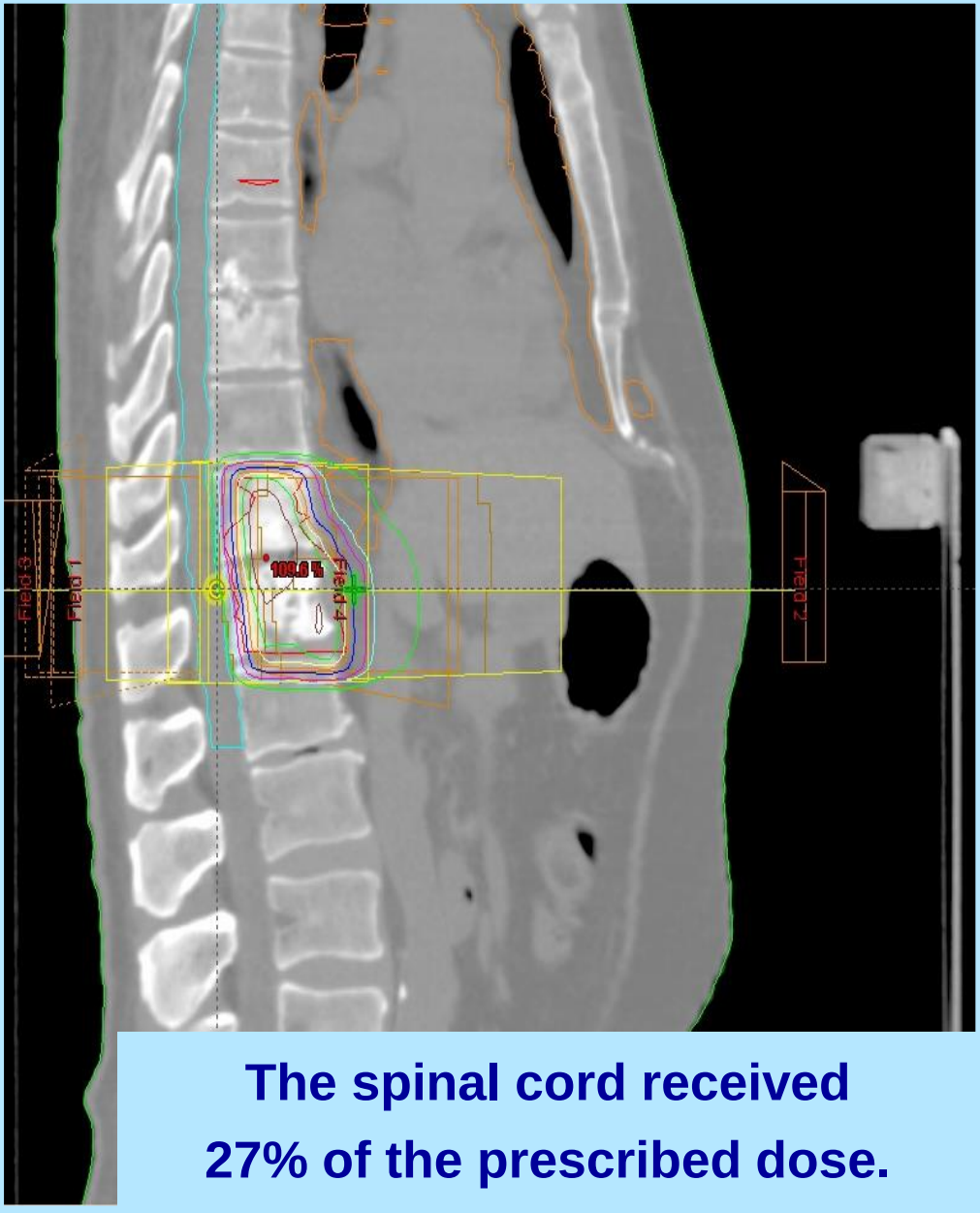


Prasad, Lancet Oncol, 2005

Fractionated SBRT: Re-RT (12x2 Gy) 12 mos. after

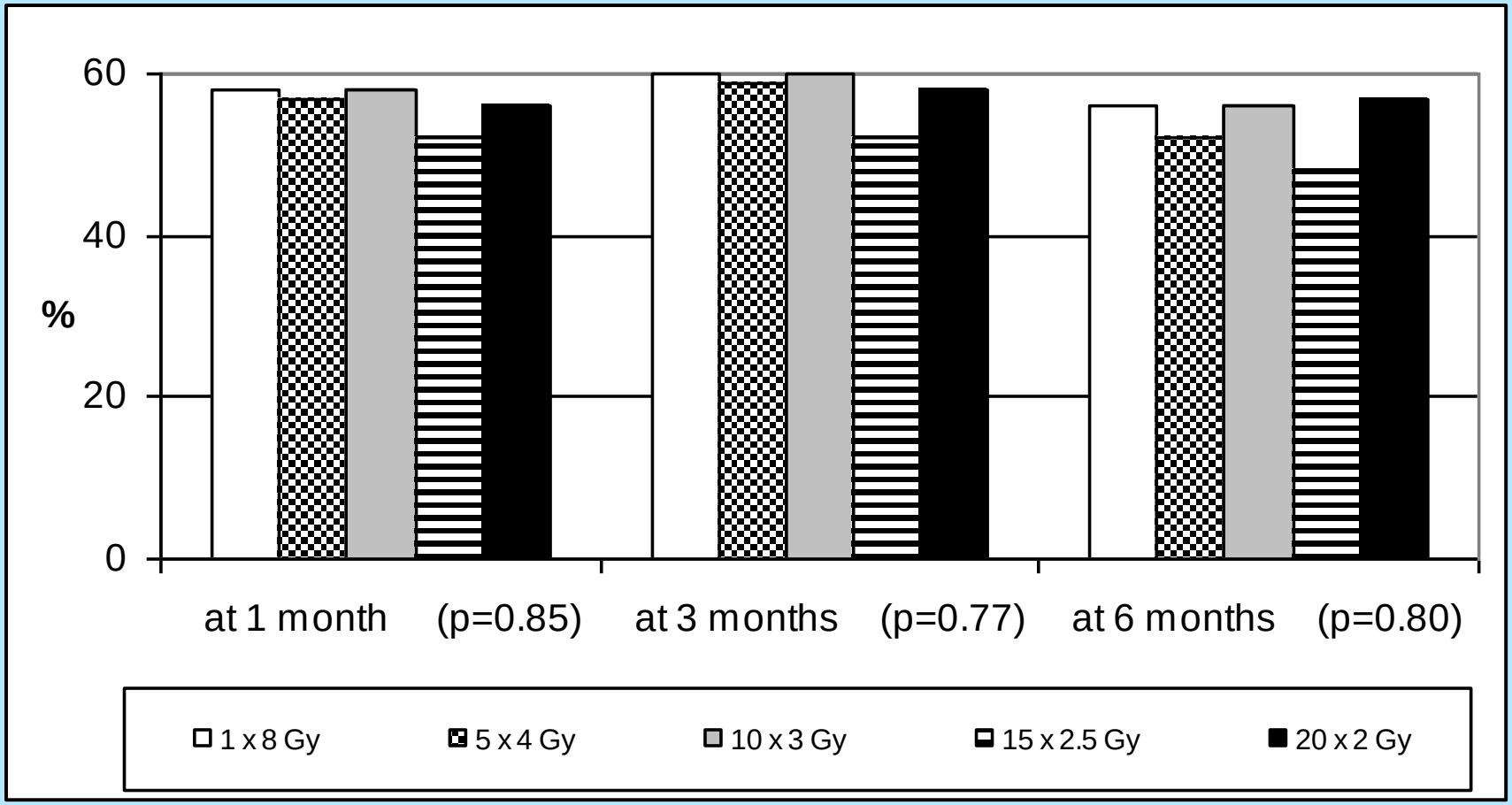






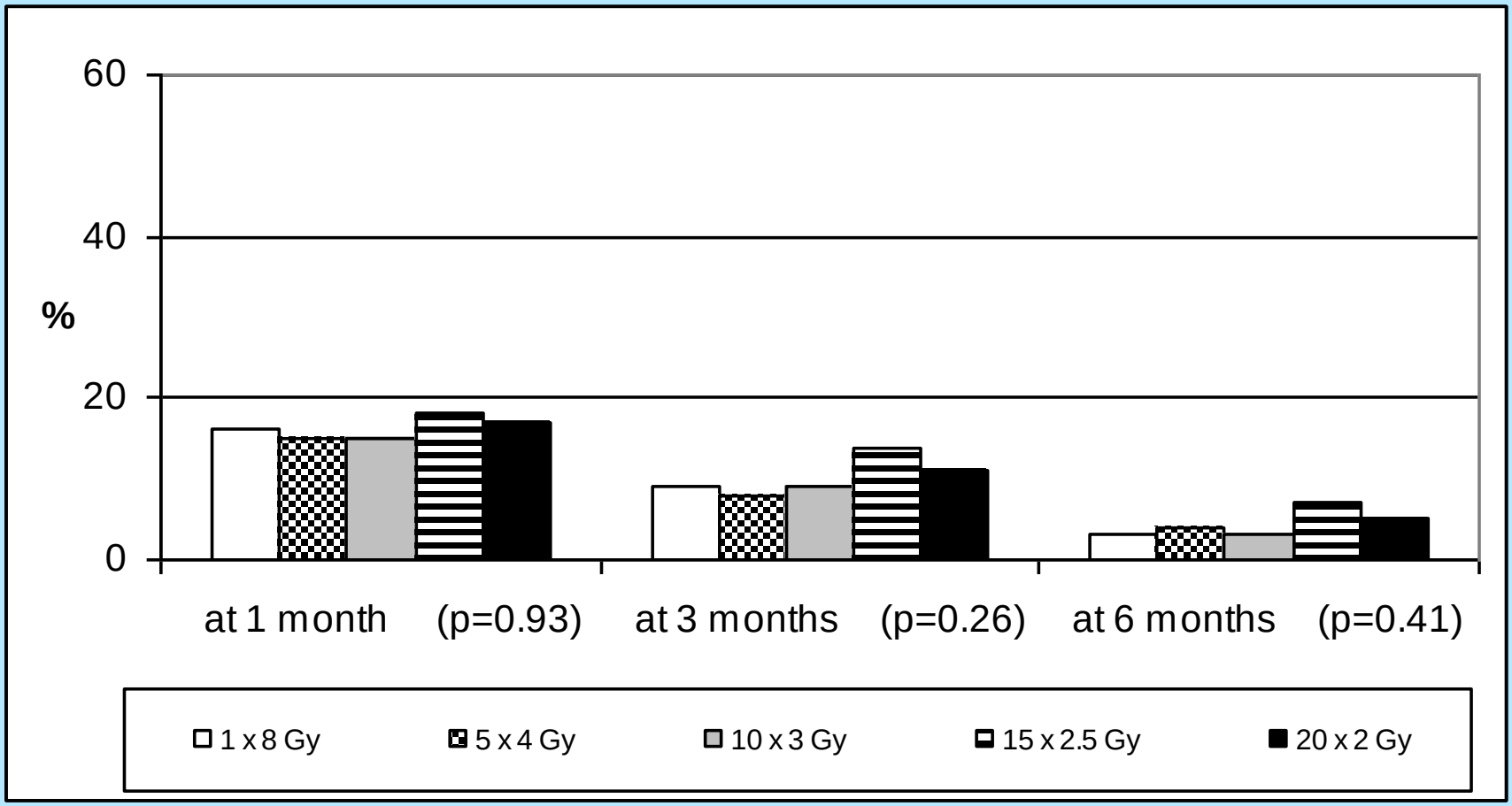
The spinal cord received 27% of the prescribed dose.

Motorische functies: no change



Rades et al JCO 2005

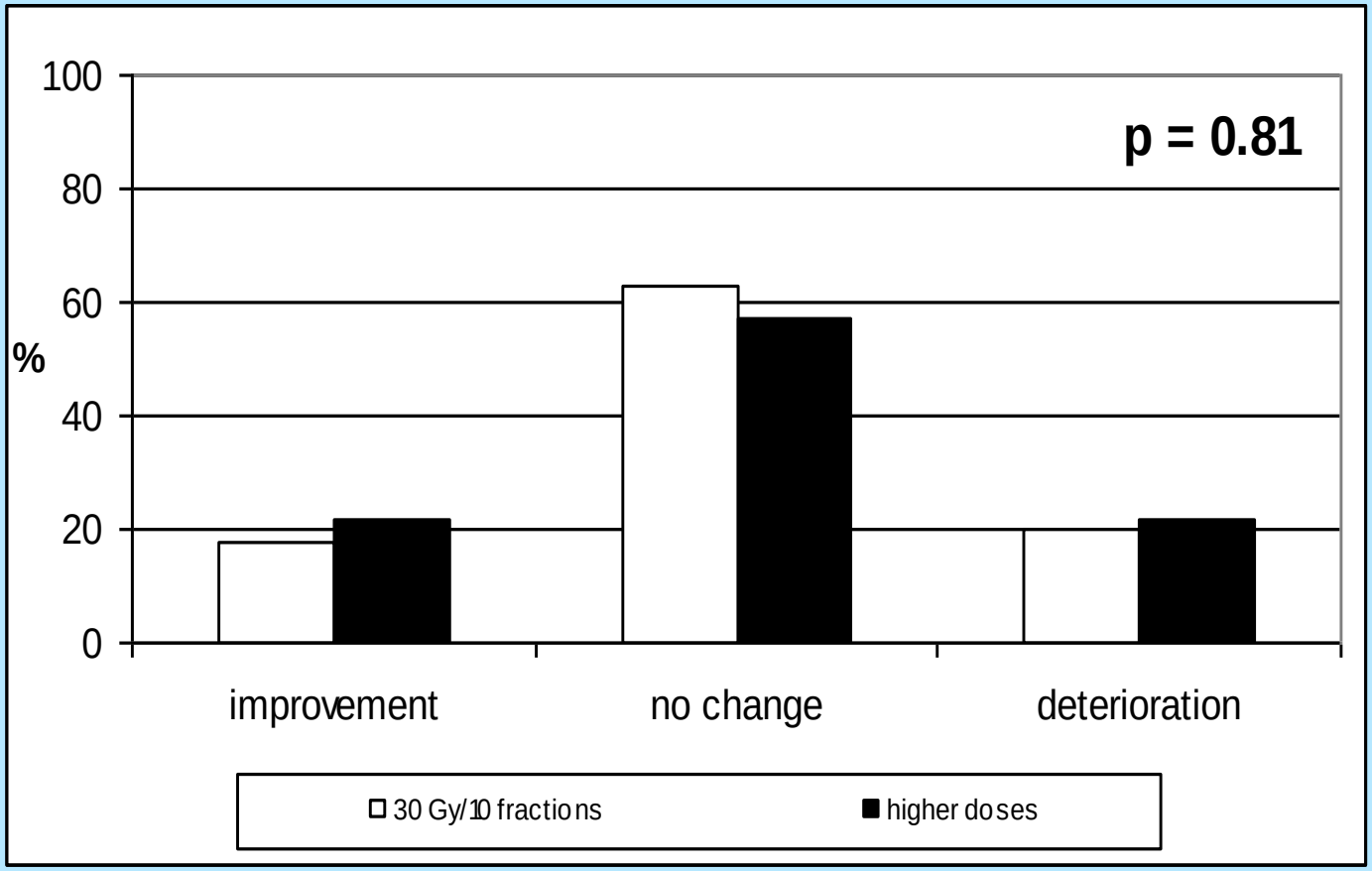
Motorische functies: decrease



Rades et al JCO 2005

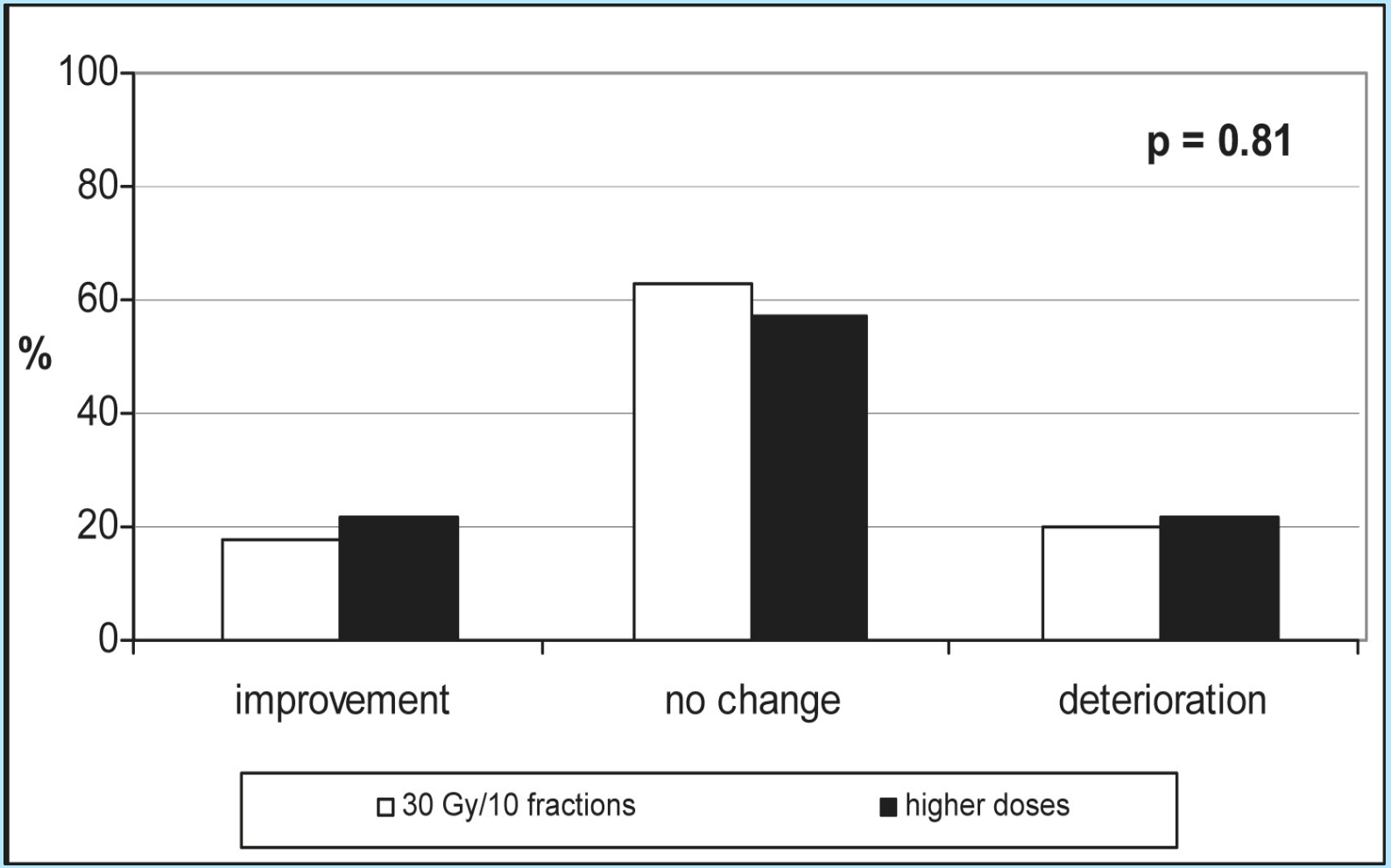
Less Radiosensitive Tumors: Dose Escalation

RCC (N=100), CRC (N=84), MM (N=22)



Rades et al., IJROBP, 2012

MSCC; > 30 Gy is not improving outcome



Rades D. et al. IJROBP 2011

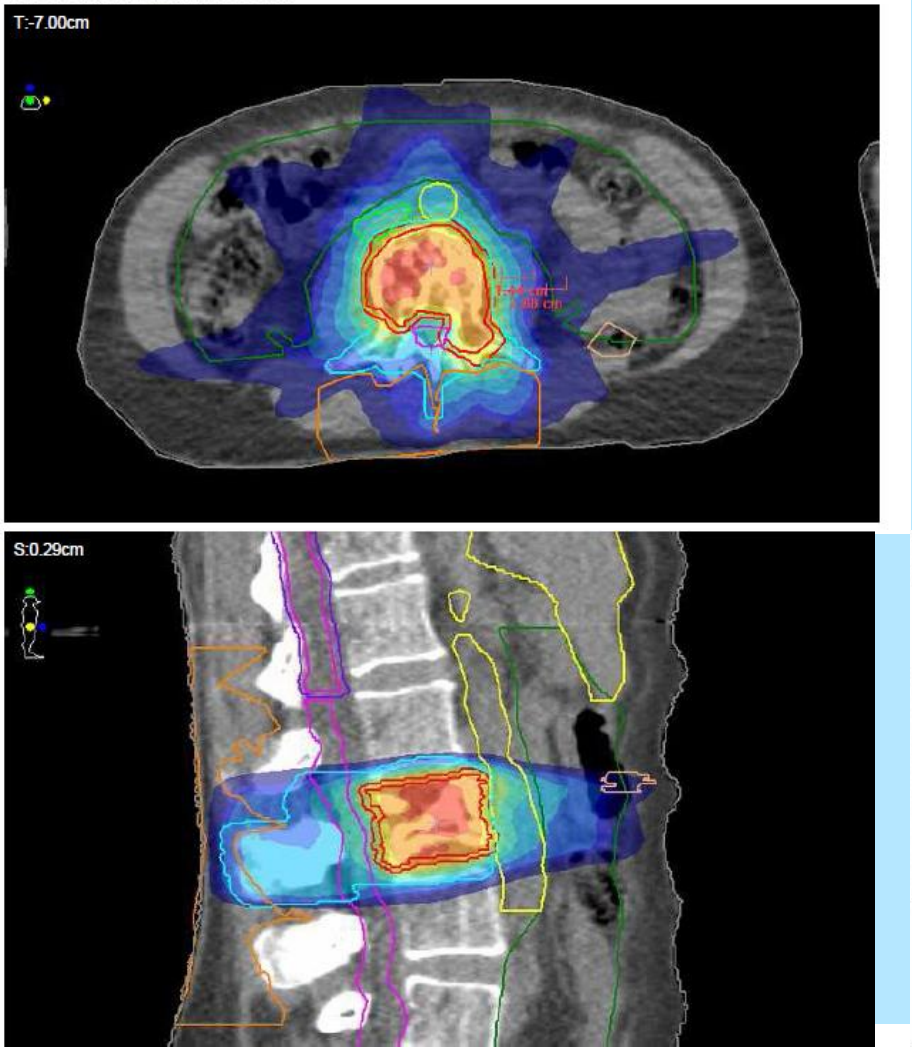
SUMMARY 2

MSCC RT	RS / SBRT	conv.
Improvement, less selected:	23%	40%
Improvement, myeloma:	71%	76%
Improvement, ambulatory:	63%	62%

Potential Benefit of RS / SBRT for:

- Long-term Survivors (SBRT instead of RS to reduce late toxicity)
- Less Radiosensitive Tumors
- Re-RT, in particular after previous longer-course RT

1x 18 Gy solitairy lesion breast ca
FUP -> PET/CT negative 1 year later



Courtesy dr. Kaspers, UMCU

Pros and cons of different techniques

		EBRT		SBRT
		CT / MVI EPI	CBCT	
Time investment	Patient	+	+++	++
	Linac	+++	++	+
Comfort	Pain with movement	+	++	++
	Pain when lying still	+++	++	+
Costs		+++	++	+
Planning	Margins	wide	in between	small

Leiden University
Medical Center

Practical application

Logistics and implementing research outcome

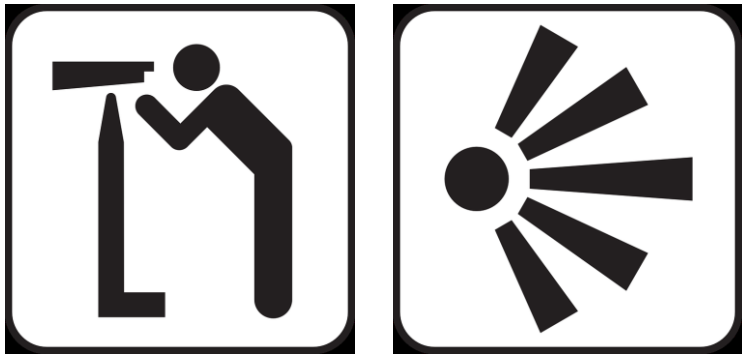
Yvette van der Linden

Centre of Expertise Palliative Care

& Dept. of Radiotherapy

Levels of influence

What viewpoints must we tackle?

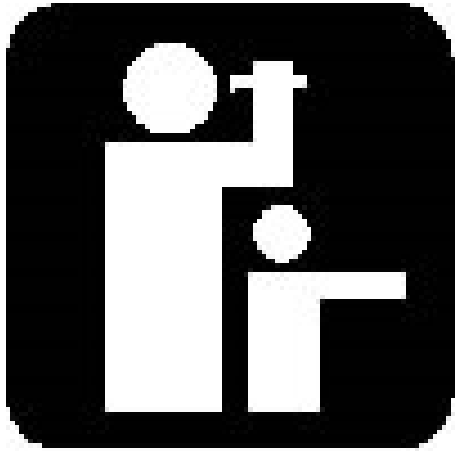


Personal

- As a person, as a doctor

Team

- Monodisciplinary -> RTs only
- Multidisciplinary team
  - Home & Hospital



Patient & carers

Public

Politics

Public & Politics → create awareness

From another point of view.

Campaigns

- Yearly donations
- Incidental
  - Hair donations
  - ALS ice bucket challenge

Implementation on (inter-) national agenda

- Guidelines, education

Reimbursement

- Fee for talking

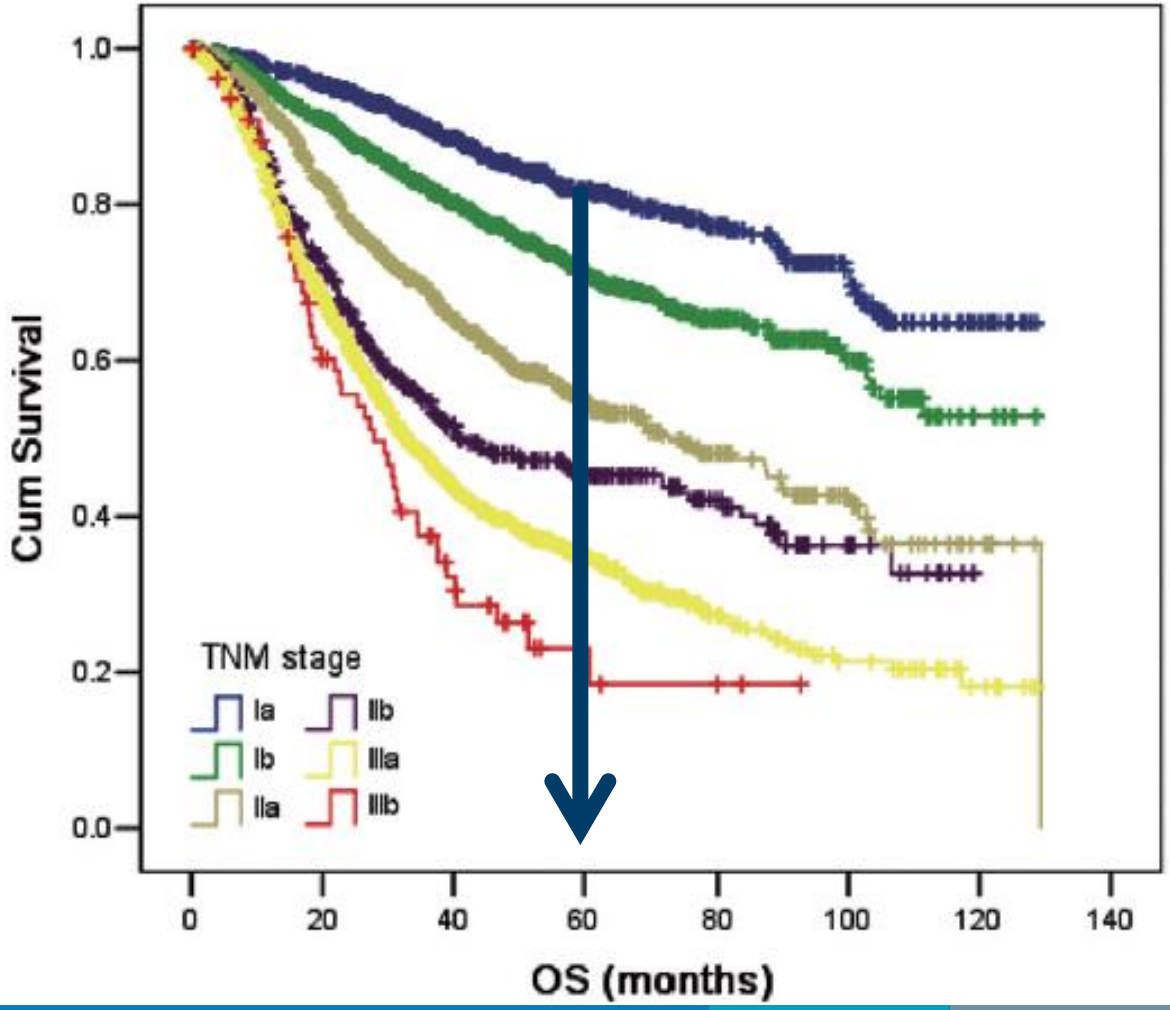
Treatment with curative intent ≠ cure

Survival in NSCLC is dependent on stage at diagnosis

N= 5853

treated with radical surgery

2001-2008

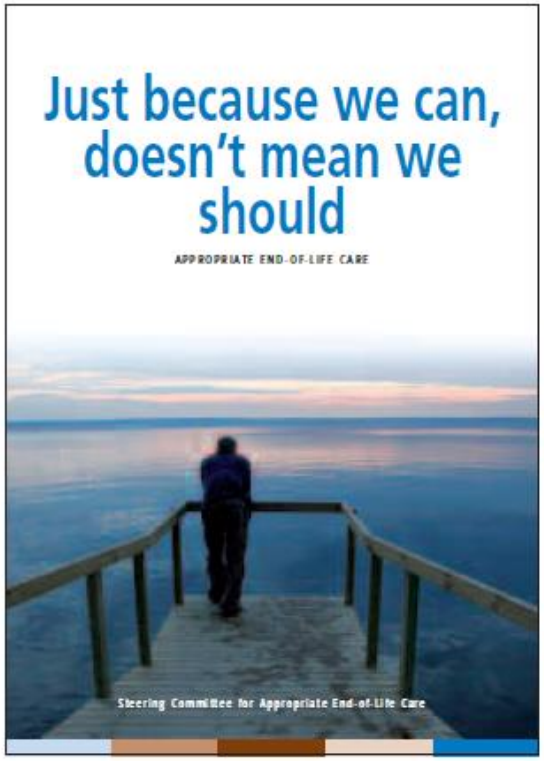


Dutch national steering committee for appropriate End of Life care 2015

" To treat is golden standard *unless*….. you have good reasons not to treat"

Mechanisms

- Discussing EoL is unusual and time costly
- Default attitude = do not give up
- Guidelines focus on 'action'
- Education focuses on 'action'
- Payment for treatment
- No holistic view
- Doing nothing = incompetence



23 Measures towards better care

Top 5

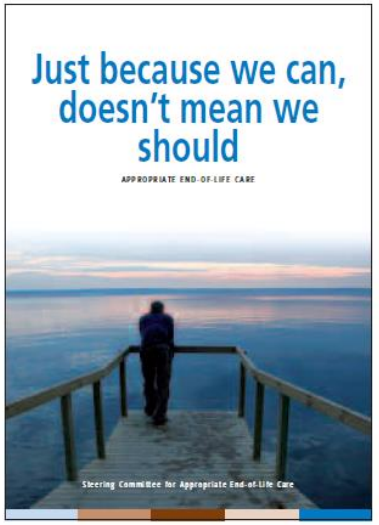
1.Make end-of-life acceptance and talking about death more common

2.Greater clarity on patients' wishes and improved coordination, including handover

3.Shared and improved decision-making

4.Guidelines directed also at 'inaction' or alternative action

5.Shift focus of healthcare system from production to appropriateness



Traditional versus early palliative care

For both curative and palliative phase apply a two track approach

Prerequisites for a true multidisciplinary team

Team multidisciplinary

MDTs

-Discuss all patients → curative / palliative intent

-Rad onc → Speak up! Educate!

- a broad scope
- large knowledge of diseases & treatment options

-Incorporate a multidisciplinary attitude

- List possible treatment options
- Prevent 'action' attitude only
  - Offer a meeting with the medical specialist

NB if you have a PCT in your hospital → join !

National level → participate in guidelines, implementation of EBM outcome

Team monodisciplinairy

RTs

- Appoint experts in palliative RT
- Write protocols on palliative RT using EBM
  - Background information
  - Schedules
  - Techniques

Changing goals….. even in palliation

Short Course

- Simple, effective
- Time efficient

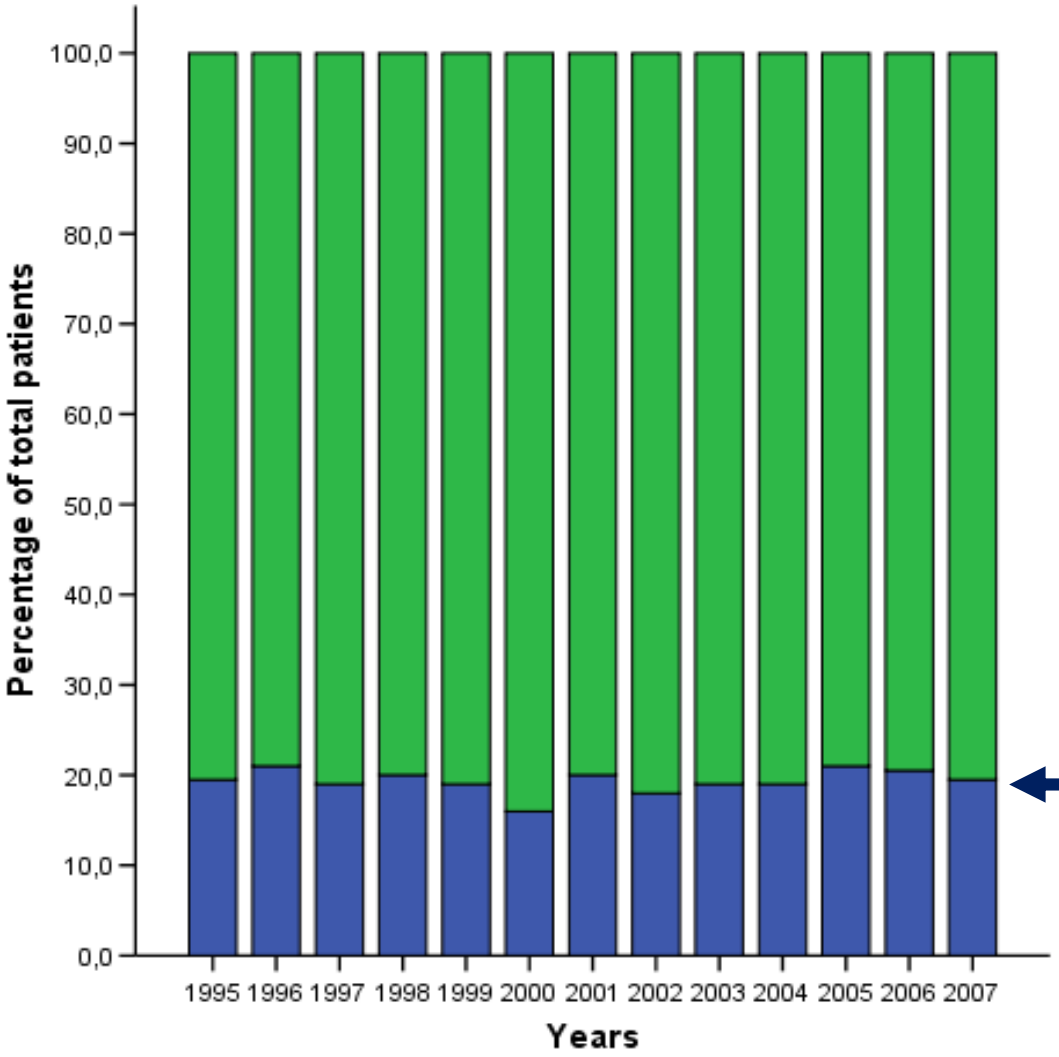
Radical

- More protracted, higher overall dose fractionation schedules for more durable symptom relief
- High dose hypofractionation using new technologies

Prophylactic

- Treatment in *asymptomatic* patients given with the intention of preventing symptoms, extending life

Palliative indications make up to 40% of our total



20% bone metastases

Team monodisciplinairy

RT department

-Appoint experts in palliative RT -> doctors and RTTs / PAs

-Write protocols on palliative RT using EBM

- Background information
- Schedules
- Techniques

- Patient discussions → debate treatment options considering
  - Wishes & goals of patient
  - Expected toxicity vs. expected outcome
  - Life expectancy
- Education of residents
  - Apply two track approach
  - Inform patients and carers
- FUP → evaluate your outcome, start prospective database

Educate your colleagues on the Key elements of palliative care

7 Key Elements
Relationship and rapport building
Addressing symptoms
Symptom assessment and review
Symptom management
Addressing coping
Ability to cope
Spirituality and faith
Emotional status
Referral to social work, psychiatry, or psychology
Establishing illness understanding
Information preference
Prognostic awareness
Current illness status
Discussing cancer treatments
Effect of cancer treatments
Decision making about cancer treatment
End-of-life planning
Resuscitation preferences
Hospice discussion or referral
Practical or personal plans
Health care proxy
Engaging family members

Young et al, 2013, JAMA

Get to know viewpoints

Five questions that you ask every patient who faces a life threatening incurable disease.

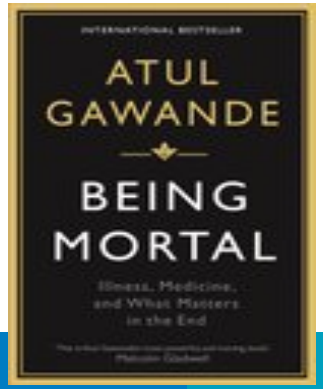
1. *What do you know of your illness and how far advanced it is?*

2. *What are your fears and uncertainties regarding your future?*

3. *What are your goals and priorities in life?*

4. *What are you willing to give up or not , and what will you accept?*

5. *What makes a day a good day for you?*



Learn the basic skills for Palliative Care

Primary Palliative Care

- Basic management of pain and symptoms
- Basic management of depression and anxiety
- Basic discussions about
  - Prognosis
  - Goals of treatment
  - Suffering
  - Code status

Specialty Palliative Care

- Management of refractory pain or other symptoms
- Management of more complex depression, anxiety, grief, and existential distress
- Assistance with conflict resolution regarding goals or methods of treatment
  - Within families
  - Between staff and families
  - Among treatment teams
- Assistance in addressing cases of near futility

Helpful for generalist doctors

- Practical palliative guidelines -> www.pallialine.nl -> per symptom
- PalliArts app

Presence of symptoms in palliative phase

	Palliative phase	Last two weeks of life
	N= 25.074	N= 2219
Tiredness	74%	88%
Pain	71%	45%
Loss of energy	69%	-
Weakness	60%	74%
Loss of appetite	53%	56%
Anxiety	48%	-
Weight loss	46%	86%
Dyspnea	35%	39%

Teunissen S et al, JPSM 2007

pallialine
richtlijnen palliatieve zorg

reageer zoeken

overzicht documenten contact disclaimer over deze site

Richtlijnen
- ☐ Algemeen
- ☐ **Symptomen**
- ☐ Ziektegerelateerd
- ☐ Rondom levenseinde
- ☐ Overigen

Overig
- ☐ Algemene principes van palliatieve zorg
- ☐ Folders
- ☐ Samenvattingskaarten
- ☐ Handreikingen

U kunt hier een selectie maken uit het totale aanbod van de richtlijnen.

KNL integraal kankercentrum Nederland

Richtlijn	Methodiek	Laatst gewijzigd
Anorexie en gewichtsverlies (3.0)	Evidence based	30-09-2014
Ascites (2.0)	Consensus based	19-01-2010
Decubitus (2.0)	Evidence based	01-11-2011
Dehydratie en vochttoediening (2.0)	Consensus based	27-07-2010
Delier (3.0)	Consensus based	10-05-2010
Delirium (3.0)	Consensus based	10-05-2010
Depressie (2.0)	Consensus based	22-06-2010
Diarree (2.0)	Consensus based	21-02-2010
Diepe veneuze trombose en longembolie (2.0)	Consensus based	27-07-2010
Dyspneu in de palliatieve fase (3.0)	Evidence based	22-12-2015
Hersenmetastasen (2.0)	Consensus based	29-07-2010
Hik (2.0)	Consensus based	28-09-2009
Hoesten (2.0)	Consensus based	18-06-2010
Hypercalciemie (2.0)	Consensus based	24-03-2010
Ileus (2.0)	Consensus based	29-01-2009
Jeuk (2.0)	Consensus based	27-07-2010
Klachten van de mond (2.0)	Consensus based	29-07-2010
Koorts (2.0)	Consensus based	23-07-2008
Lymfoedeem (1.0)	Evidence based	01-05-2014
Misselijkheid en braken (4.0)	Consensus based	16-06-2014
Misselijkheid en braken in de palliatieve fase (verpleegkundig) (1.0)	Evidence based	01-12-2007
Nausea and vomiting (4.0)	Evidence based	16-06-2014
Nierfalen - in ontwikkeling (1.0)	Evidence based	01-06-2015
Obstipatie (2.0)	Consensus based	28-09-2009
Oncologische ulcera (2.0)	Consensus based	11-08-2010
Palliatieve Zorg voor Kinderen (1.0)	Evidence based	01-08-2013
Pijn (2.1)	Consensus based	02-07-2010
Pijnmeting en behandeling van pijn bij kinderen (1.0)	Evidence based	01-10-2007
Slaapproblemen (1.0)	Consensus based	02-10-2008
Urogenitale problemen, fistels, loze aandrang en tenesmi (2.0)	Consensus based	08-05-2010

Laxatives

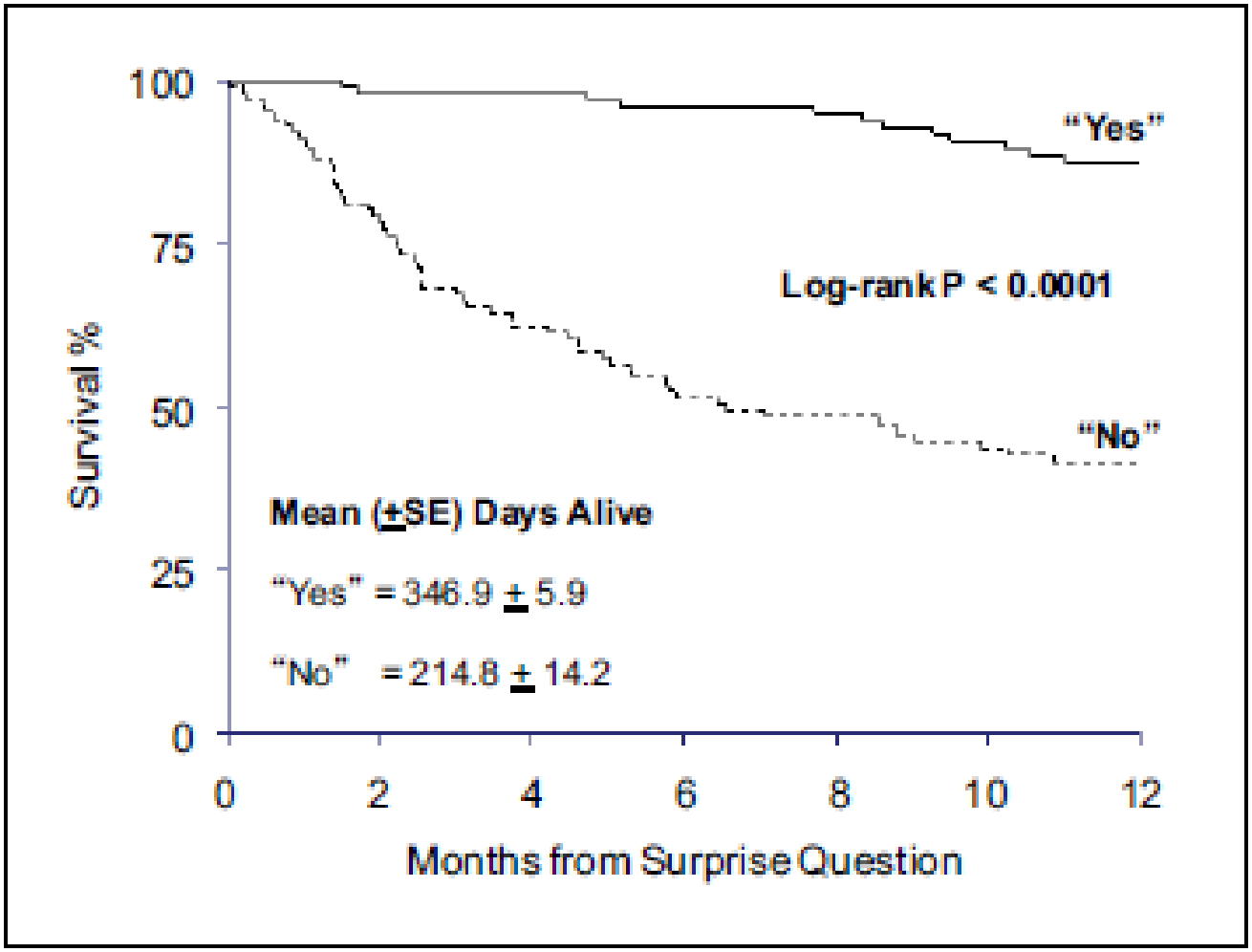
Laxans	Werking	Dosis	Werkzaamheid	Opmerkingen
Macrogol/ elektrolyten	Osmotisch	1-2 sachets dd Bij fecale impactie: 8 sachets dd binnen 6 uur gedurende maximaal 3 dagen	1-2 dagen	Sommige preparaten hebben een vieze smaak (minder bij oplossen in ijswater)
Magnesiumoxide Magnesium-hydroxide	Osmotisch	3 dd 500-1000 mg 3 dd 724-1448 mg	2-8 uur	Grote tabletten Niet bij ernstig gestoorde nierfunctie Niet gelijktijdig innemen met tetracyclines, ijzer of chinolonen
Lactulose (stroop of poeder)	Osmotisch	1-2 dd 15-30 ml (stroop) of 12-24 g granulaat	1-2 dagen	Voor sommigen: vieze smaak, opgeblazen gevoel, flatulentie
Lactitol	Osmotisch	1-2 dd 20-30 ml of 10-20 g granulaat	1-2 dagen	Flatulentie
Magnesiumsulfaat (bitterwater)	Osmotisch	10-30 g 's morgens op de nuchtere maag	1-3 uur	Alleen voor incidenteel gebruik
Psyllium	Volume-vergrotend	1 sachet of 1 maatdop 1-3 dd	2-3 dagen	Vochtopname meer dan 1500 ml per dag!
Sterculiagom	Volume-vergrotend	1-2 maatlepels of 1 sachet 1-2 dd	2-3 dagen	Vochtopname meer dan 1500 ml per dag!
Bisacodyl	Contactlaxans	10-20 mg p.o. voor de nacht of 10 mg supp. 's morgens	Oraal: 5-10 uur Rectaal: 15-60 minuten	Soms buikkrampen Niet gelijktijdig gebruiken met antacida of melk
Sennosiden A + B	Contactlaxans	10-20 ml	6-12 uur	Vieze smaak, soms buikkrampen
Natriumlauryl-sulfoacetaat	Emolliens	1 microklysma (5 ml)	5-20 minuten	Bij vol rectum
Natriumfosfaat-klysma	Osmotisch	1 klysma (133 ml), 1-3 dd	10-20 minuten	Bij harde feces in het rectum, gebruiksklaar wegwerpklysma
Natriumdocusaat + sorbitol klysma	Emoliens	1 klysma (120 ml), 1-3 dd	5-20 minuten	Bij harde feces in het rectum, kan voorafgaand aan fosfaatklysma worden gegeven

Tabel 1. Dosering en werking van veel gebruikte laxantia

Use the Surprise question to mark imminent death

'Would I be surprised if my patient died within the next year?'

N= 231



When should I ask for specialized care ?

Critical decision moments

- **Surprise question 1 year**
- **Considering yes / no disease modifying treatments**
- **Symptom control phase**
- **Admittance for symptom management**
- **Start dying phase**
- **Death**

Generalist care

Symptom-management (pro active)

Council and advise (multidisciplinairy)

Inform GP + coordinate care

Specialist care

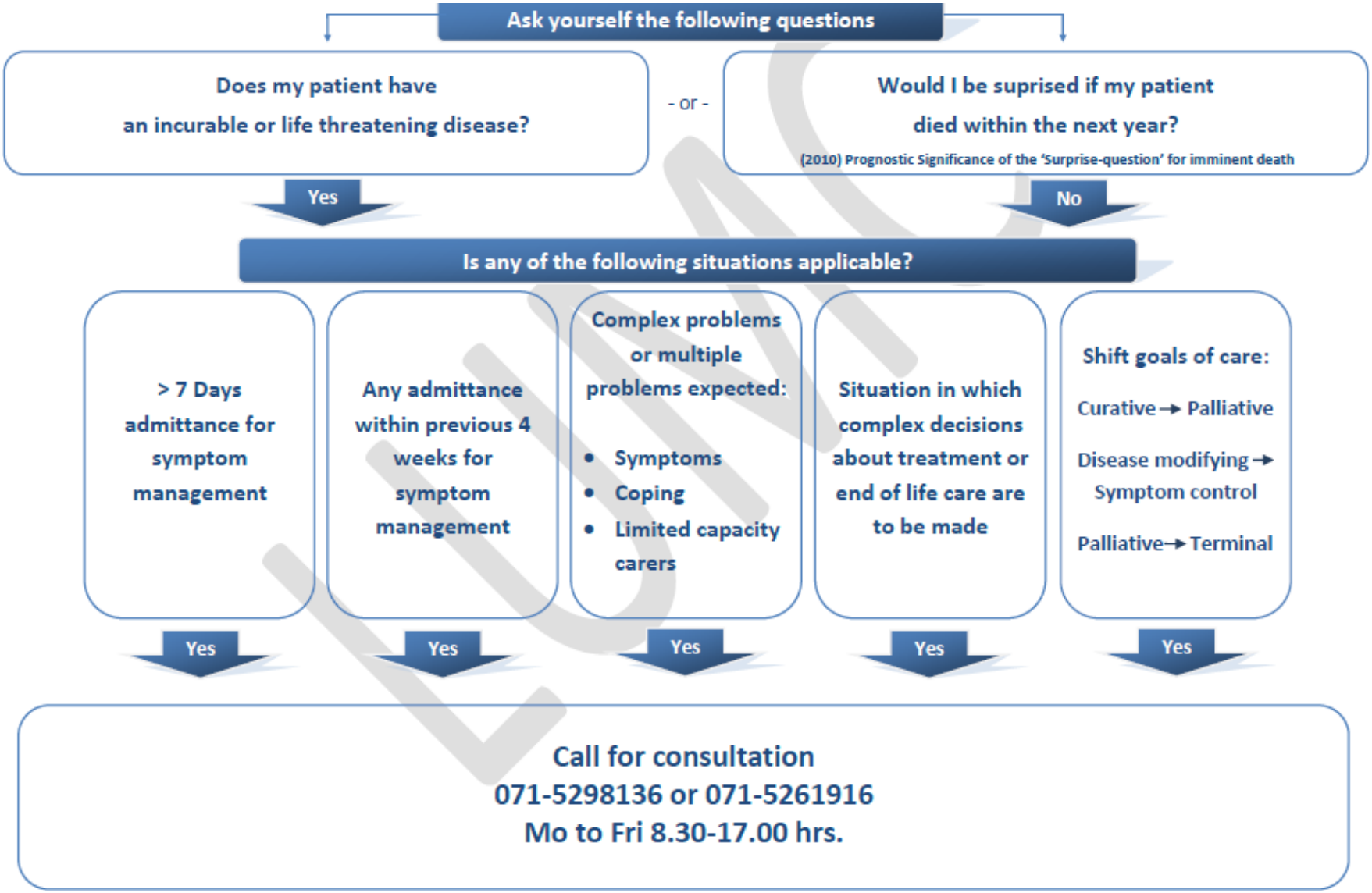
Symptoms that are difficult to treat, complex or rare

Hampered communication eg. treatment goals

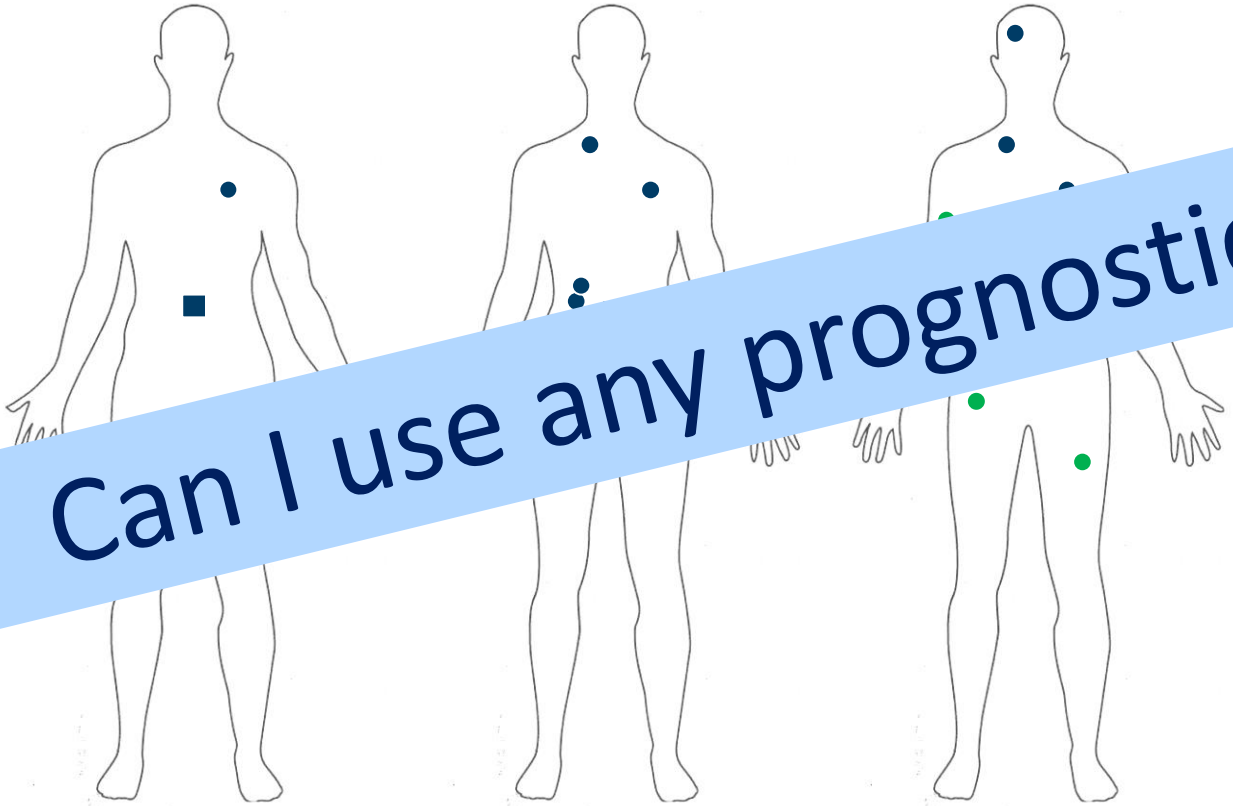
Shortcomings in knowledge and experience of generalists

→ After care

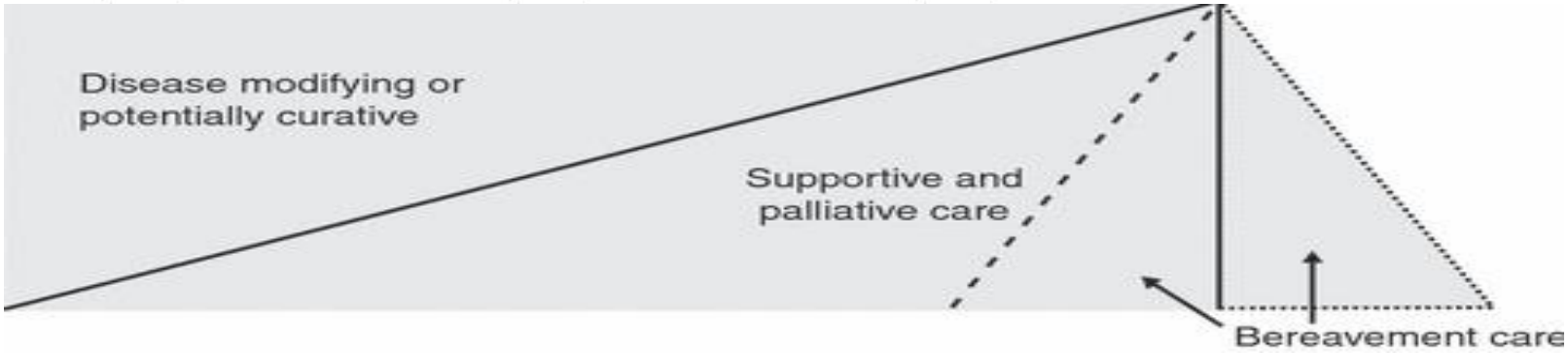
Use of a triggercard when to consult the PCT



Where in the trajectory is my patient?



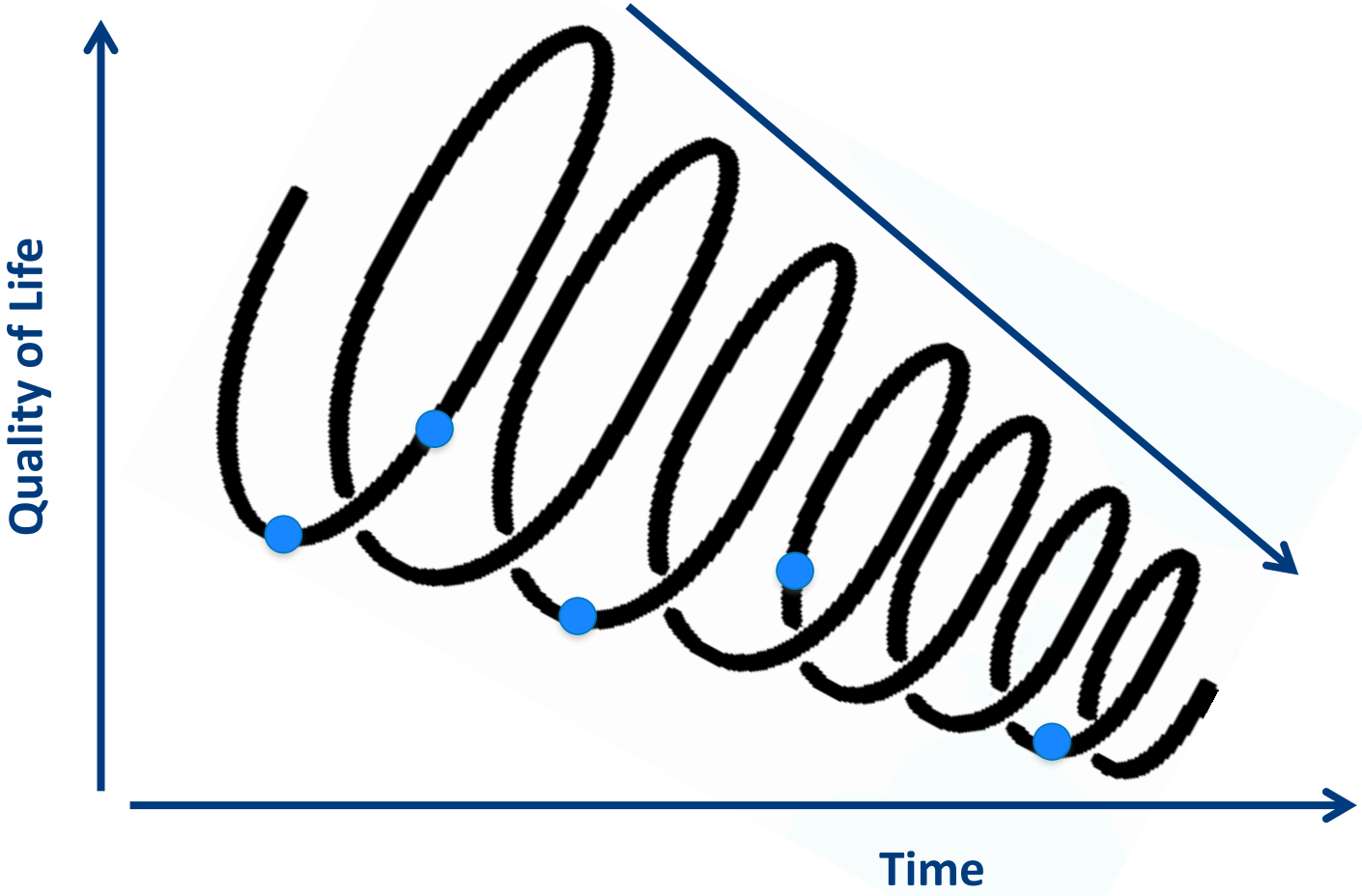
Can I use any prognostic tool?



Decision making needs multiple input

- Expected toxicity vs. expected outcome
- Life expectancy

Decision making needs repetition



- Consultations with health care professional

ESTRO School

Lung palliative management

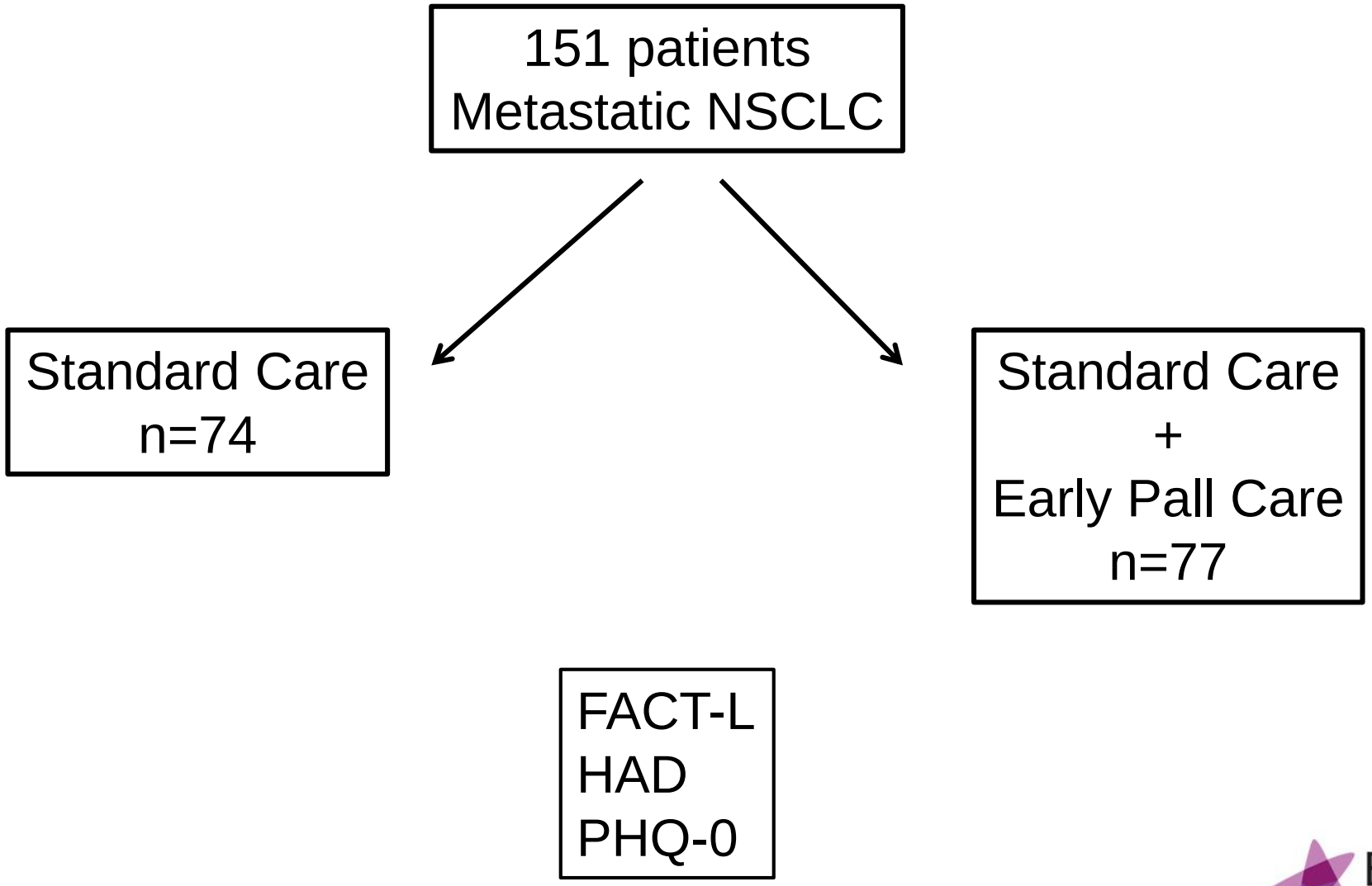
by

Peter Hoskin

Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer

N Engl J Med 2010;363:733-42.

Jennifer S. Temel, M.D., Joseph A. Greer, Ph.D., Alona Muzikansky, M.A., et al



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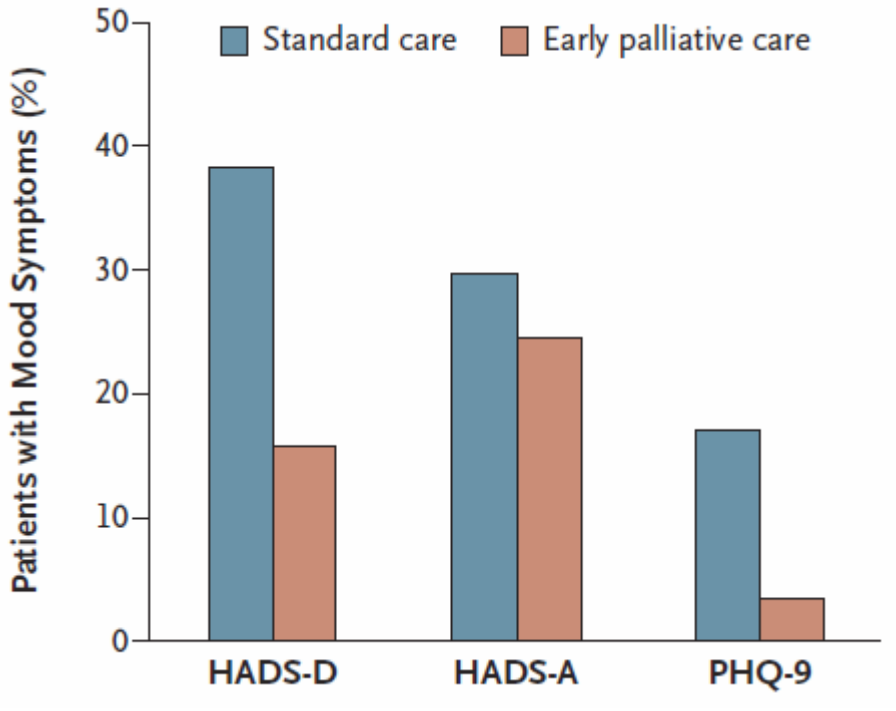
Quality of life outcomes at 12 weeks

Variable	Standard Care (N=47)	Early Palliative Care (N=60)	Difference between Early Care and Standard Care (95% CI)	P Value†	Effect Size‡
FACT-L score	91.5±15.8	98.0±15.1	6.5 (0.5–12.4)	0.03	0.42
LCS score	19.3±4.2	21.0±3.9	1.7 (0.1–3.2)	0.04	0.41
TOI score	53.0±11.5	59.0±11.6	6.0 (1.5–10.4)	0.009	0.52



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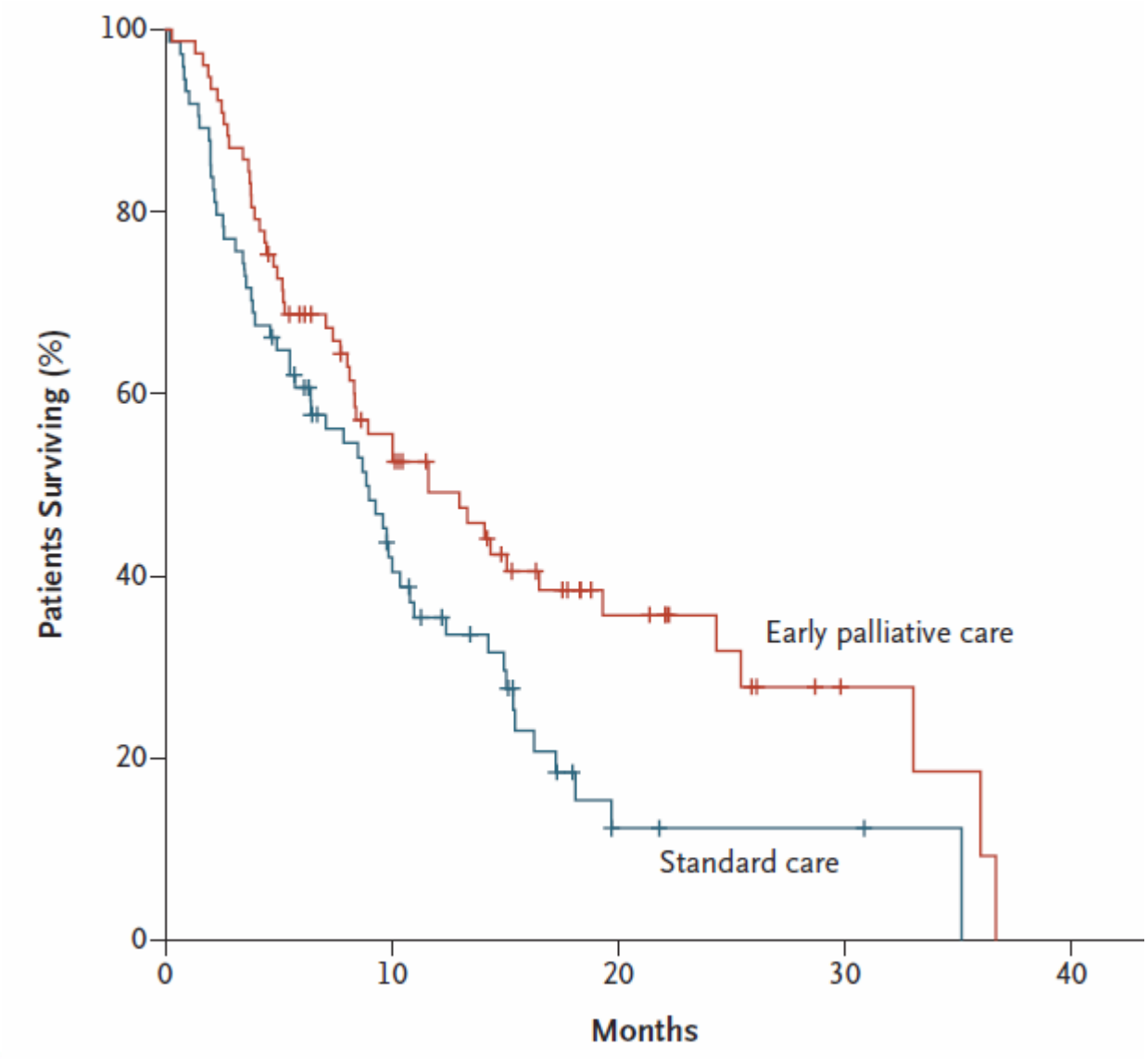
N Engl J Med 2010;363:733-42.

Jennifer S. Temel, M.D., Joseph A. Greer, Ph.D., Alona Muzikansky, M.A., et al



ESTRO School

What is the role of active oncological treatment in inoperable NSCLC

- Symptom control
  - Cough
  - Haemoptysis
  - Dyspnoea
  - Chest pain
  - Anorexia
- Improved QoL
- Survival

ESTRO School

Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

PS ≥2 patients:

- Chemotherapy prolongs survival and possibly improves the QoL in NSCLC patients with PS 2, when compared with BSC [I, B]. Single-agent chemotherapy with gemcitabine, vinorelbine, and taxanes represents an option [I, B].
- Carboplatin-based combination chemotherapy should be considered in eligible PS 2 patients [II, A].
- Poor PS (3–4) patients should be offered BSC [II, B] in the absence of tumours with activating (sensitising) EGFR mutations.

- Radiotherapy plays a major role in symptom control in the case of bone and brain metastases and is also effective in treating pain related to chest wall, soft tissue, or neural invasion.
- Neurological symptoms from spinal compression can be relieved by early radiotherapy.
- Radiotherapy is indicated in cases of haemoptysis, symptomatic airway compression or obstruction, and following CNS and, sometimes, bone surgery [II, B].

ESTRO School

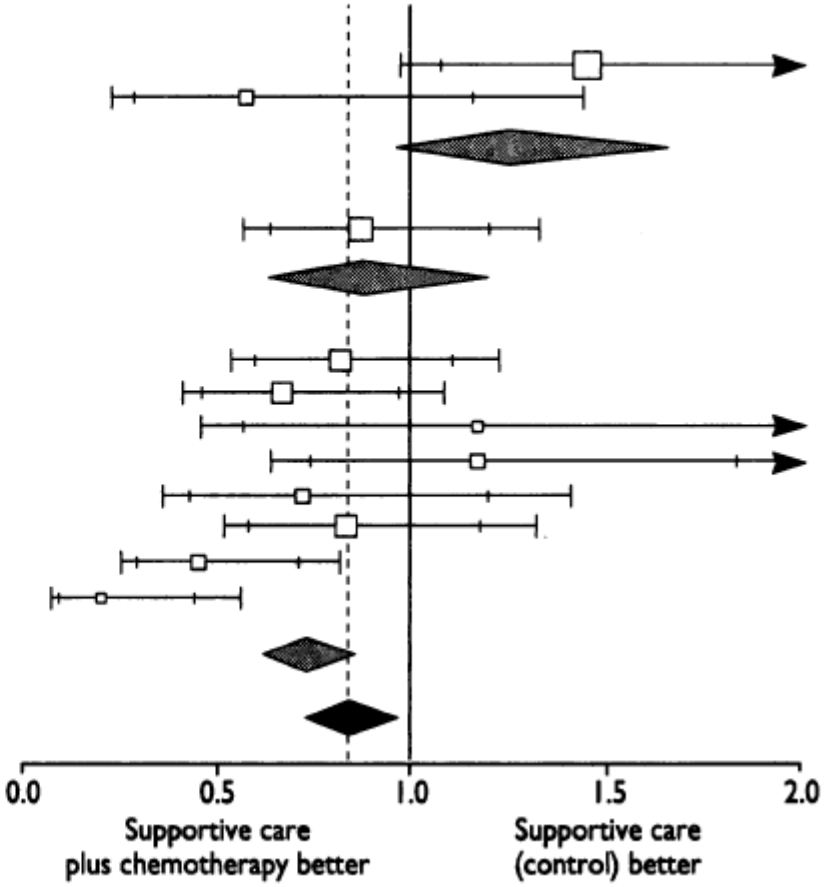
Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials

Non-small Cell Lung Cancer Collaborative Group

BMJ 1995;311:899-909

Trial	No of events/ No of patients entered: Supportive care plus chemotherapy	Supportive care	Observed – expected deaths	Variance
Long term alkylating agents:				
Oxford	120/121	62/67	16.40	43.80
Quebec	20/20	18/18	-4.38	7.99
Subtotal	140/141	80/85	12.02	51.79
Vinca alkaloids/etoposide:				
Gwent 2	96/111	67/75	-5.15	38.00
Subtotal	96/111	67/75	-5.15	38.00
Cisplatin based:				
RLW 8351	84/86	80/81	-8.06	39.94
NCIC CTG	95/97	51/53	-11.28	28.24
Southampton	17/17	15/15	1.16	7.55
NRH	44/44	40/43	2.93	18.72
UCLA	31/32	30/31	-4.83	14.53
Ancona I	63/63	65/65	-5.72	30.95
AOI-Udine	52/52	50/50	-14.98	18.77
CEP-85	23/25	21/24	-10.52	6.61
Subtotal	409/416	352/362	-51.31	165.31
Total	645/668	499/522	-44.44	255.09

Overall survival



ESTRO School

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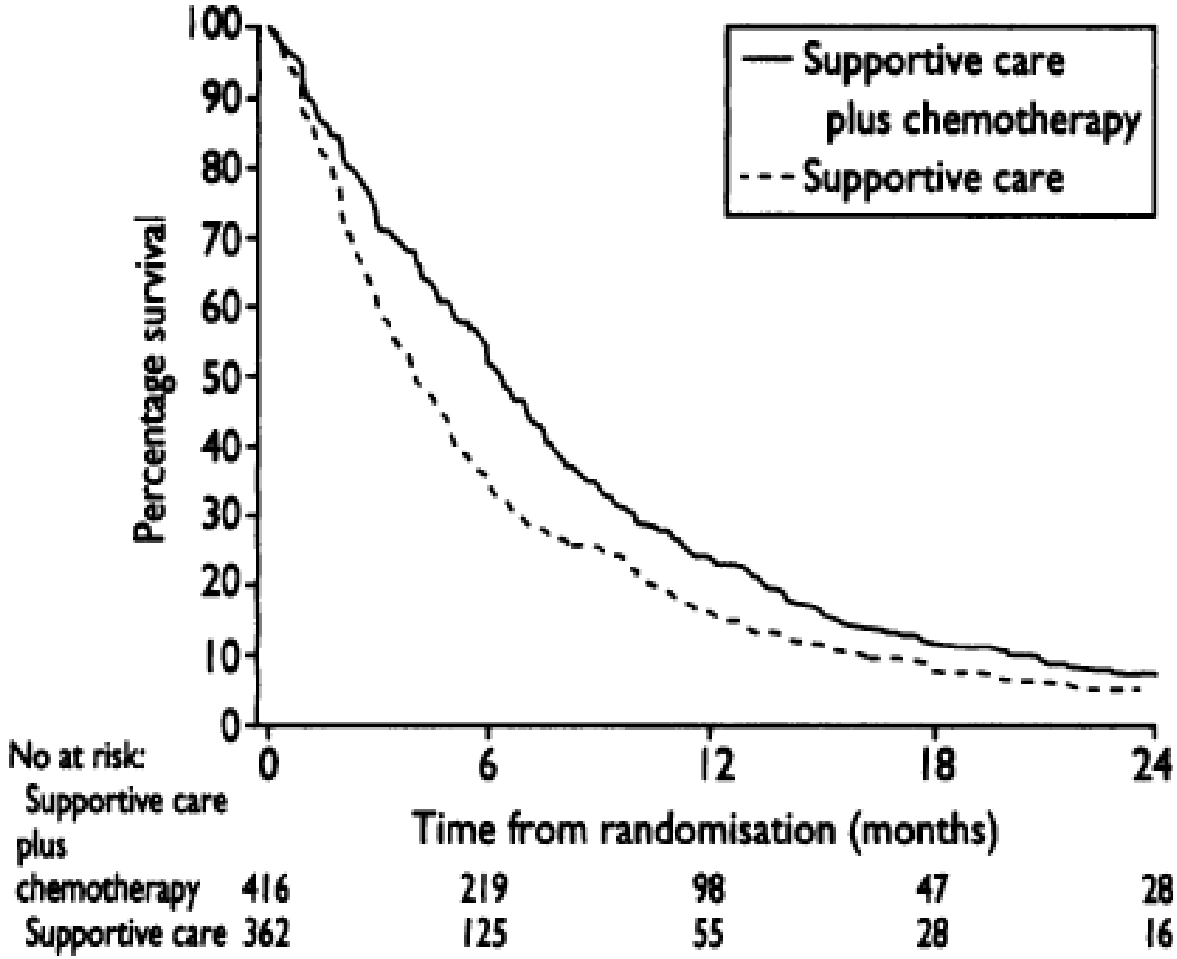
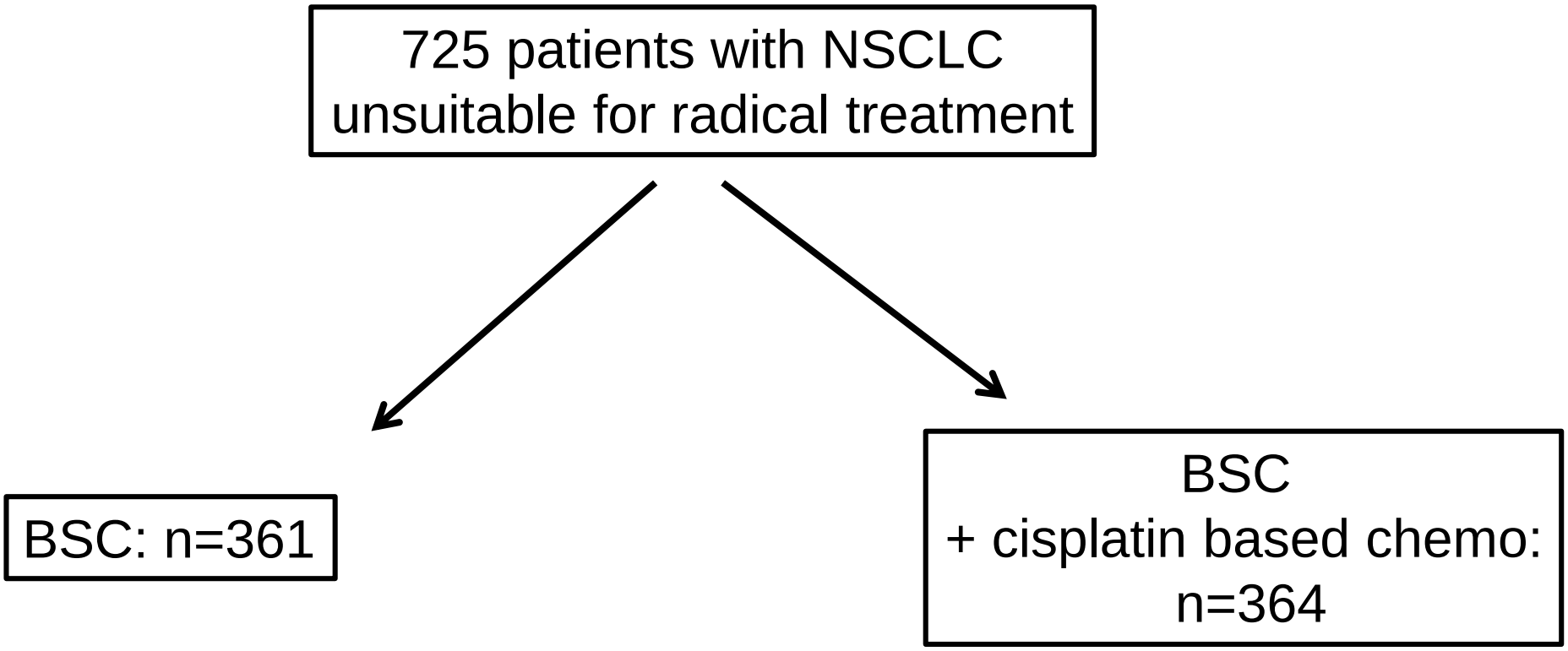


Chemotherapy versus supportive care in advanced non-small cell lung cancer: improved survival without detriment to quality of life

Thorax 2004;59:828–836

S G Spiro, R M Rudd, R L Souhami, J Brown, D J Fairlamb, N H Gower, L Maslove, R Milroy, V Napp, M K B Parmar, M D Peake, R J Stephens, H Thorpe, D A Waller, P West, on behalf of all the Big Lung Trial participants



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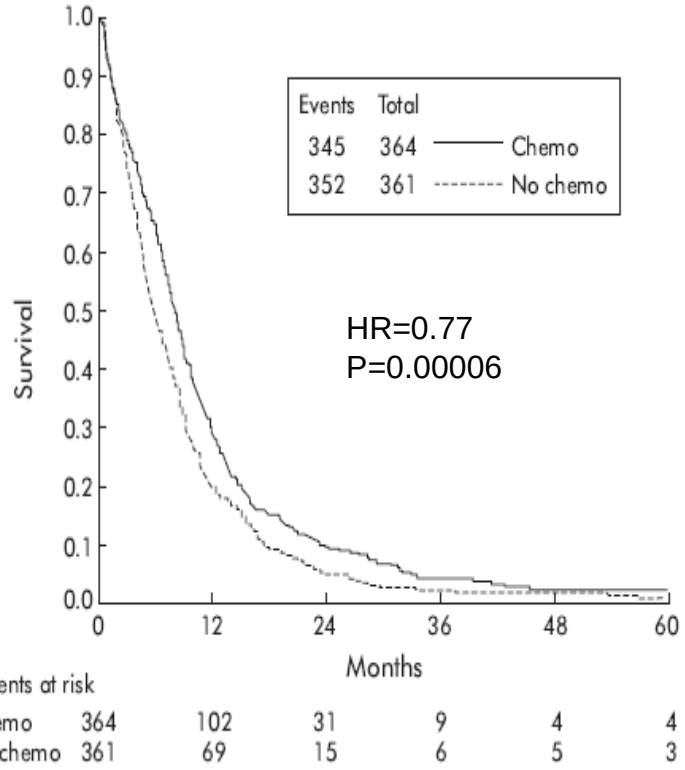
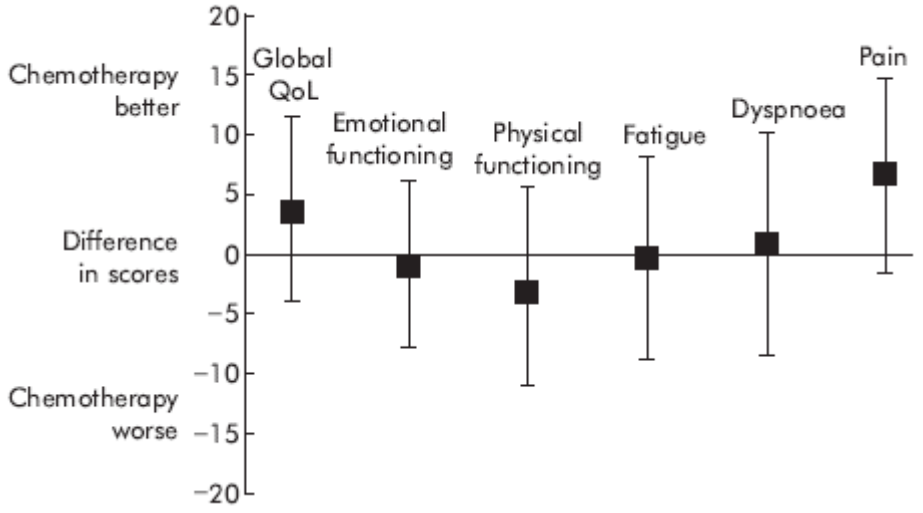


	C		NoC	
	Baseline	12 weeks	Baseline	12 weeks
Global quality of life*	57.8	52.1	53.5	48.2
Emotional functioning*	70.5	68.6	64.8	69.3
Physical functioning*	66.8	51.0	60.0	53.5
Fatigue†	40.1	48.2	45.0	48.1
Dyspnoea†	39.1	46.5	48.2	47.6
Pain†	25.0	24.8	30.1	31.5



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Improving Health-Related Quality of Life in Non–Small-Cell Lung Cancer with Current Treatment Options

David F. Cella,[1-3] Jyoti D. Patel[2,3]

Clinical Lung Cancer, Vol. 9, No. 4, 206-212, 2008

Drug	Target	Improved Health-Related QOL Reported
Docetaxel	Microtubules	Yes
Pemetrexed	Folic acid–dependent metabolism	No change
Erlotinib	Receptor TK	Yes
Gefitinib	Receptor TK	Yes

EORTC LC13 or FACT-L

ESTRO School

Chemotherapy versus best supportive care for extensive small cell lung cancer (Review)

Pelayo Alvarez M, Westeel V, Cortés-Jofré M, Bonfill Cosp X

Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD001990.

First line chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Supportive care	First-line chemotherapy			
Overall survival	The mean survival ranged across control groups from 56-93 days [1]	The mean survival in the intervention groups was 134-172 days [1]	Not estimable	65 (2 studies)	⊕○○○ very low[2,3]
Adverse effects	Haematological: 0% Leucopenia:0% Vomiting and hair loss: 0% Other: 0%	Haematological: 94.1% Leucopenia:15% ifosfamide; 15.8% ifosfamide + CCNU Vomiting and hair loss: 70% ifosfamide; 68.4% ifosfamide + CCNU Other: 55% ifosfamide; 52.6% ifosfamide + CCNU	Not estimable	65 (2 studies)	⊕○○○ very low[2,3]

ESTRO School

Chemotherapy versus best supportive care for extensive small cell lung cancer (Review)

Pelayo Alvarez M, Westeel V, Cortés-Jofré M, Bonfill Cosp X

Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD001990.

Second line chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	BSC	Second-line chemotherapy			
Overall survival	The median survival ranged across control groups from 97.3-138 days[1]	The median survival in the intervention groups was 144-181.3 days[2]	HR: 0.73 (0.55, 0.96)	542 (2 studies)	⊕⊕◯◯ **low** [4,5]
Toxic death	0%	6% topotecan 0% picoplatin	Not estimable	542 (2 studies)	⊕⊕⊕◯ **moderate** [4]
Adverse effects	Dyspnoea 3% Fatigue 4% Non sepsis infection 12% sepsis 1%	Haematological: 18%-61% neutropenia, 38%-41% Thrombocytopenia, 25%-29% anaemia, Non sepsis infection 14% Sepsis 4% Asthenia 11%	Not estimable	542 (2 studies)	⊕⊕⊕◯ **moderate** [4]
Quality of life	See footnotes 3	See footnotes 3	Difference in rate of deterioration per 3-month intervals in the EQ-5D score: 0.15 (95% CI 0.05, 0.25)	141 (1 study)	⊕⊕◯◯ **low** [4,5]

ESTRO School

A randomised trial of planned versus as required chemotherapy in small cell lung cancer: a Cancer Research Campaign trial

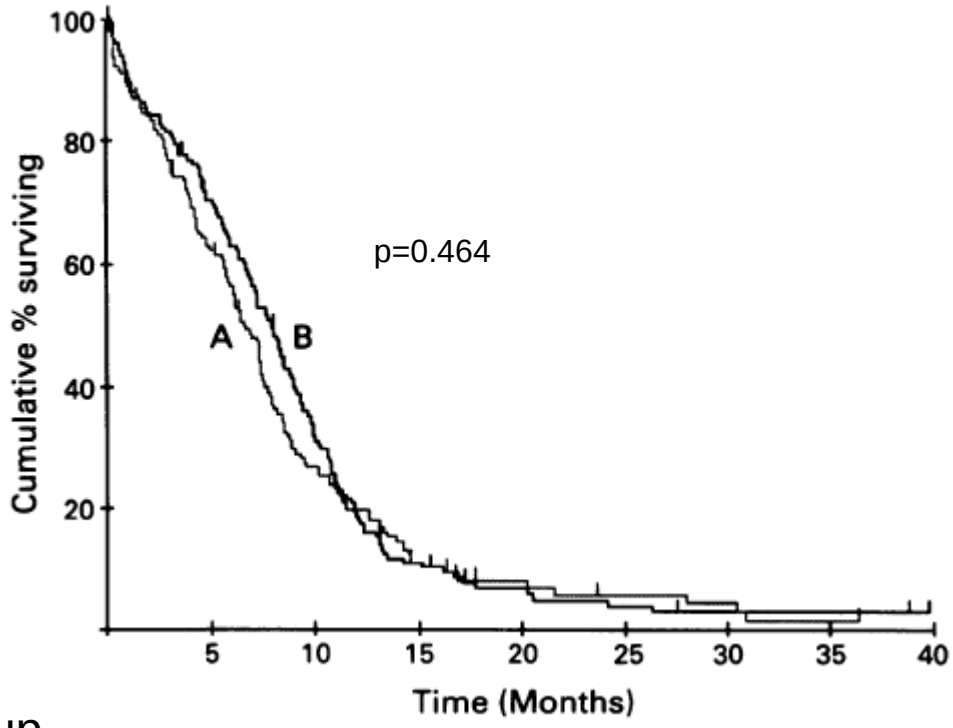
Br. J. Cancer (1991), **64**, 566–572

H.M. Earl[1], R.M. Rudd[2], S.G. Spiro[3], C.M. Ash[1], L.E. James[1], C.S. Law[1], J.S. Tobias[1], P.G. Harper[4], D.M. Geddes[3], D. Eraut[5], M.R. Partridge[6] & R.L. Souhami[1]

Untreated SCLC n=300
LD & ED
Cycle 1 chemo ECV
No progression

Planned chemo
Q3w to 8 cycles

As required chemo



AR group received 50% of total chemo in planned group

ESTRO School

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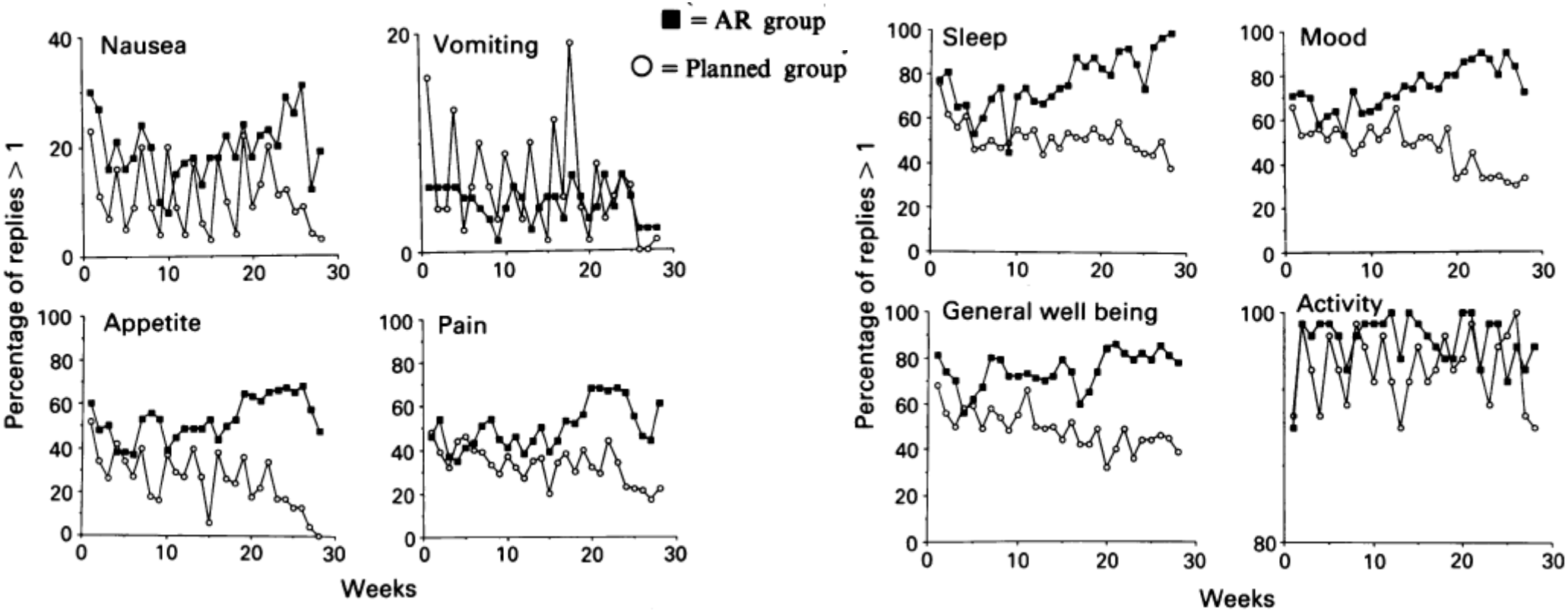

Daily diary cards: high scores = worse symptoms

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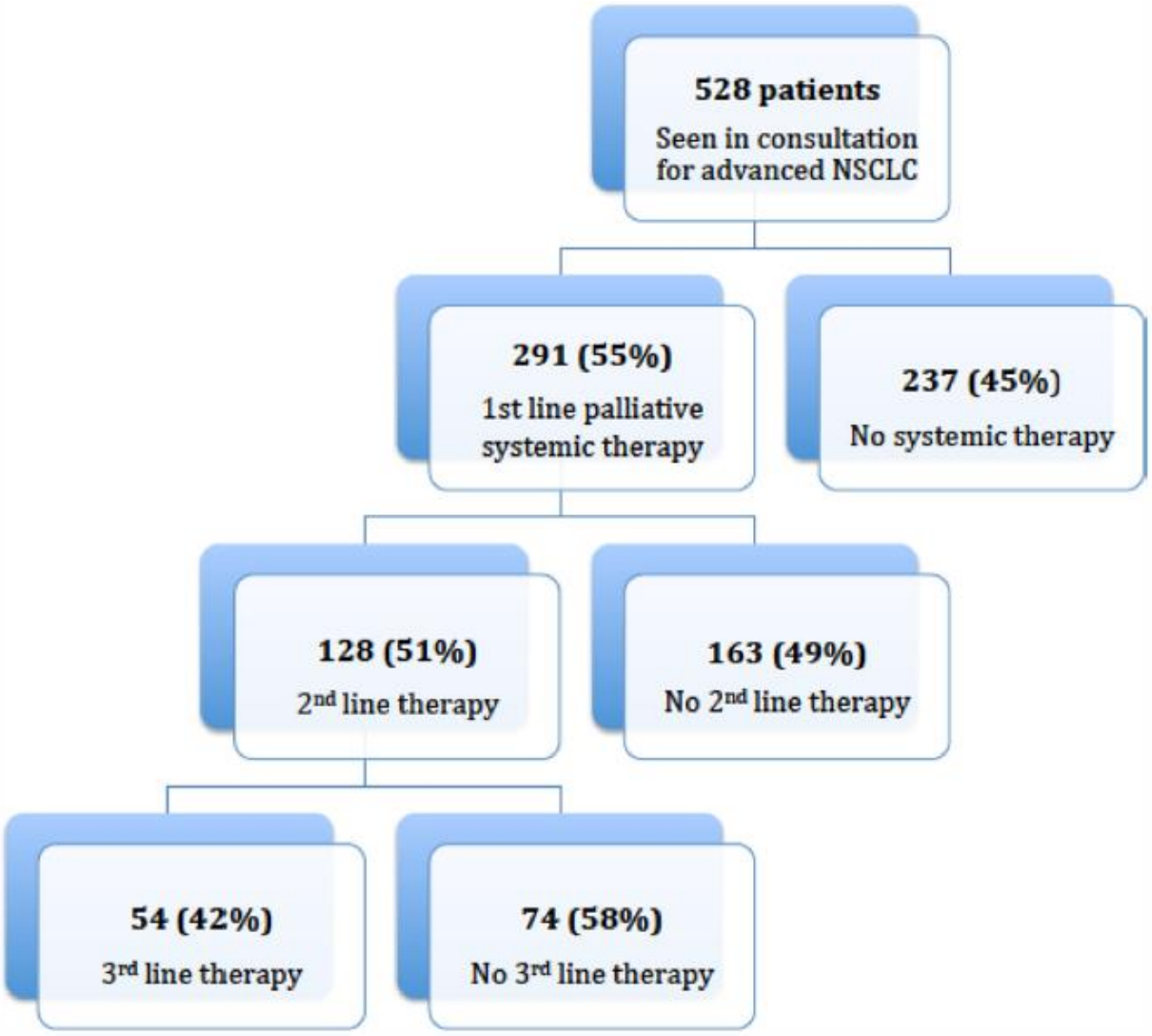
Chemotherapy or radiotherapy …… or both?



Lung Cancer 97 (2016) 15–21

ESTRO School

Palliative systemic therapy for advanced non-small cell lung cancer: Investigating disparities between patients who are treated versus those who are not

Stephanie Y. Brule[a,*], Khalid Al-Baimani[a], Hannah Jonker[a], Tinghua Zhang[b], Garth Nicholas[a,b], Glenwood Goss[a,b], Scott A. Laurie[a,b], Paul Wheatley-Price[a,b]

Reasons for not receiving systemic therapy and associated median overall survival.

Reason for no systemic therapy	N (%)	Median OS (months, [95% CI])
Poor performance status	158 (66.7)	3.4 (3.1–3.9)
Patient choice	49 (22.7)	7.5 (5.9–10.1)
Comorbidities	5 (2.1)	5.7 (3.9-NE)
Age	3 (1.3)	7.6 (4.3–10.9)
Other	22 (9.3)	2.2 (1.8–5.2)

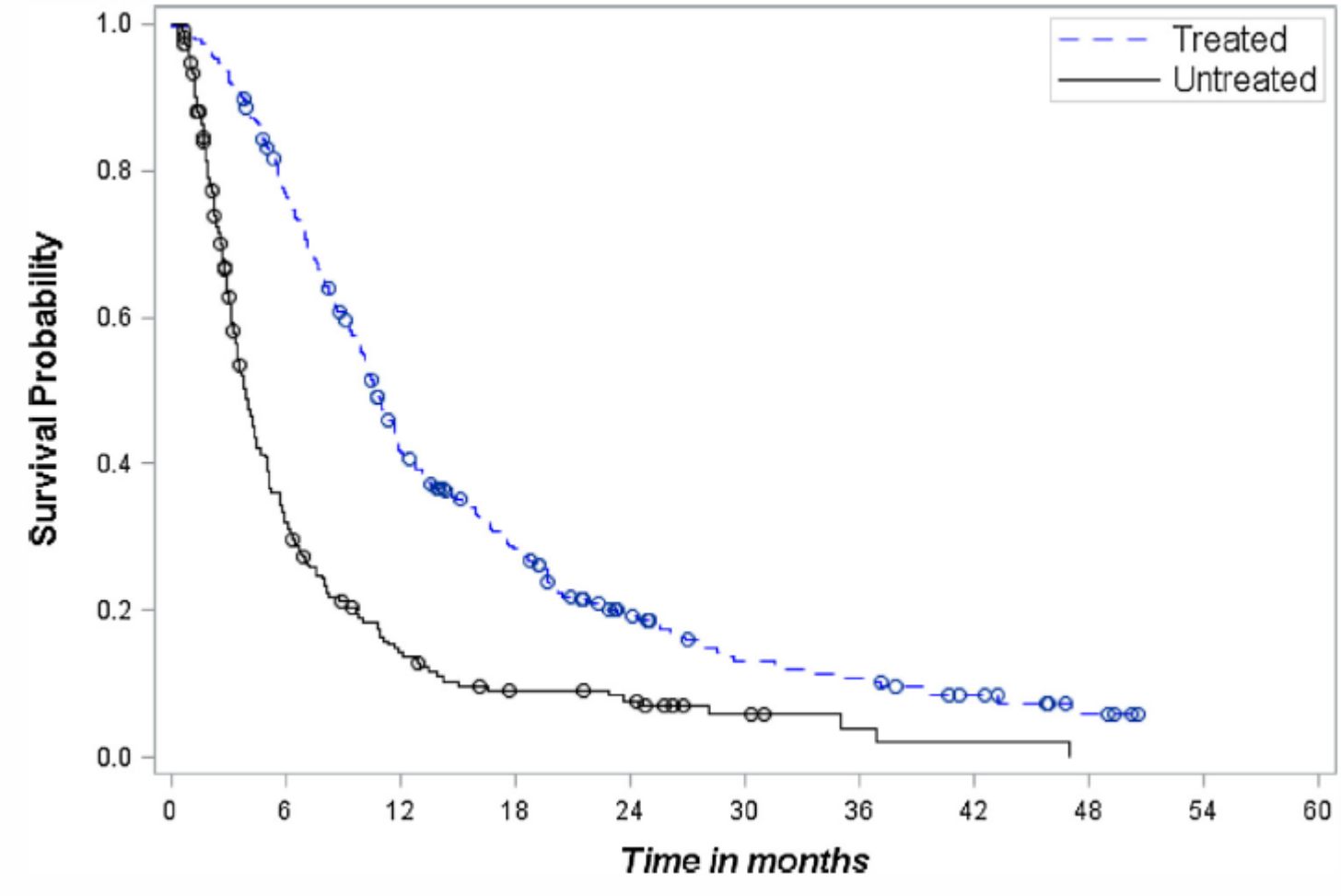
NE = not estimable.

Lung Cancer 97 (2016) 15–21

ESTRO School

Palliative systemic therapy for advanced non-small cell lung cancer: Investigating disparities between patients who are treated versus those who are not

Stephanie Y. Brule[a,*], Khalid Al-Baimani[a], Hannah Jonker[a], Tinghua Zhang[b], Garth Nicholas[a,b], Glenwood Goss[a,b], Scott A. Laurie[a,b], Paul Wheatley-Price[a,b]



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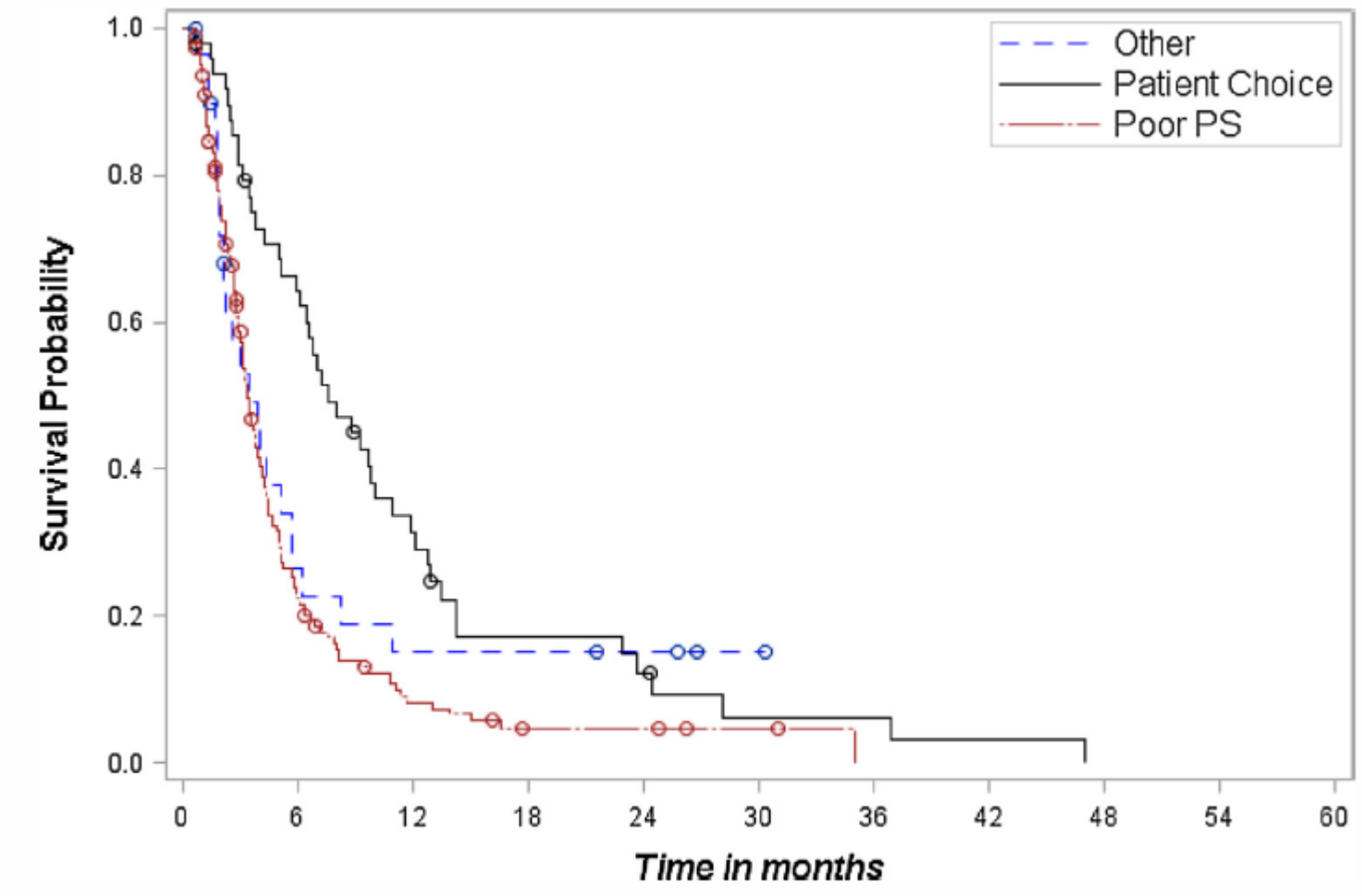


Lung Cancer 97 (2016) 15–21

ESTRO School

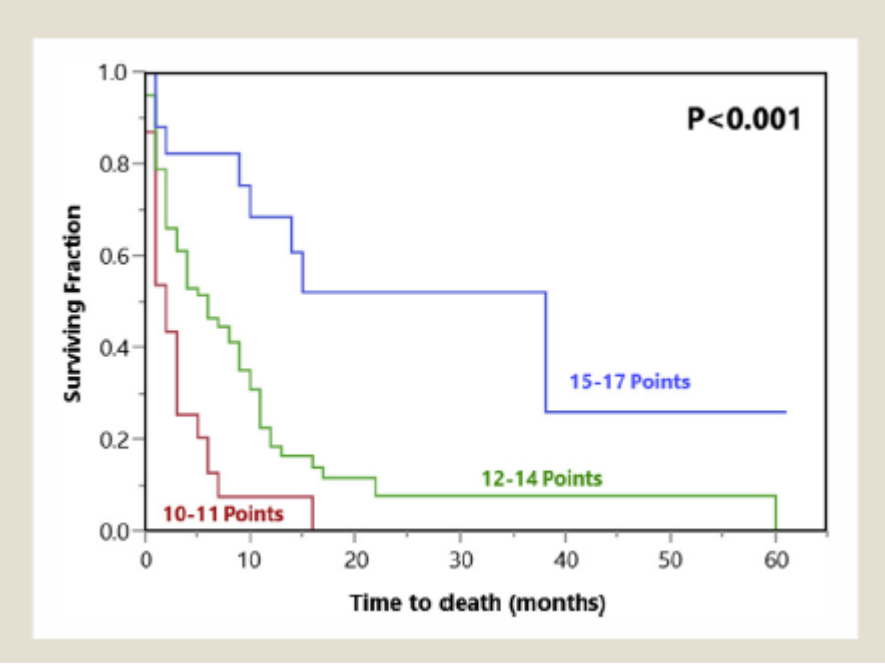
A Survival Score for Patients Receiving Palliative Irradiation for Locally Advanced Lung Cancer

Dirk Rades,[1] Lukas Käsmann,[1] Steven E. Schild,[2] Stefan Janssen[1,3]

Clinical Lung Cancer, doi.org/10.1016/j.cllc.2016.05.010

125 consecutive patients undergoing pall RT for NSCLC

Prognostic Factor	Survival at 6 mo (%)	Score
Karnofsky performance score		
≤60	47	5
≥70	31	3
N stage		
N0-N1	70	7
N2-N3	33	3
M stage		
M0	50	5
M1	38	4



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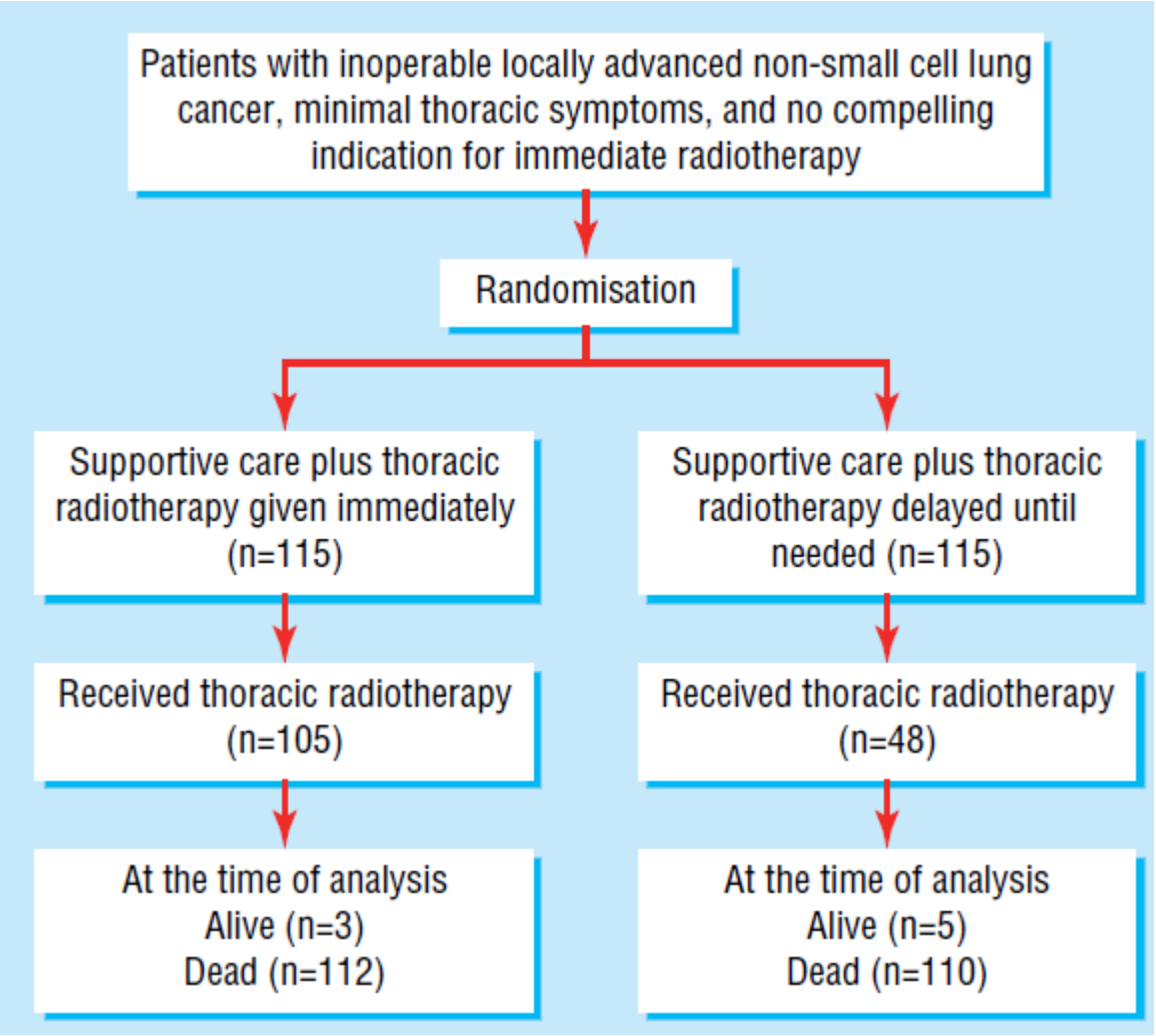
Immediate vs delayed palliative thoraic radiotherapy in patients with unresectable locally advanced non-small cell lung cancer and minimal thoracic symptoms

[Falk et al 2002]



bmj.com 2002;325:465

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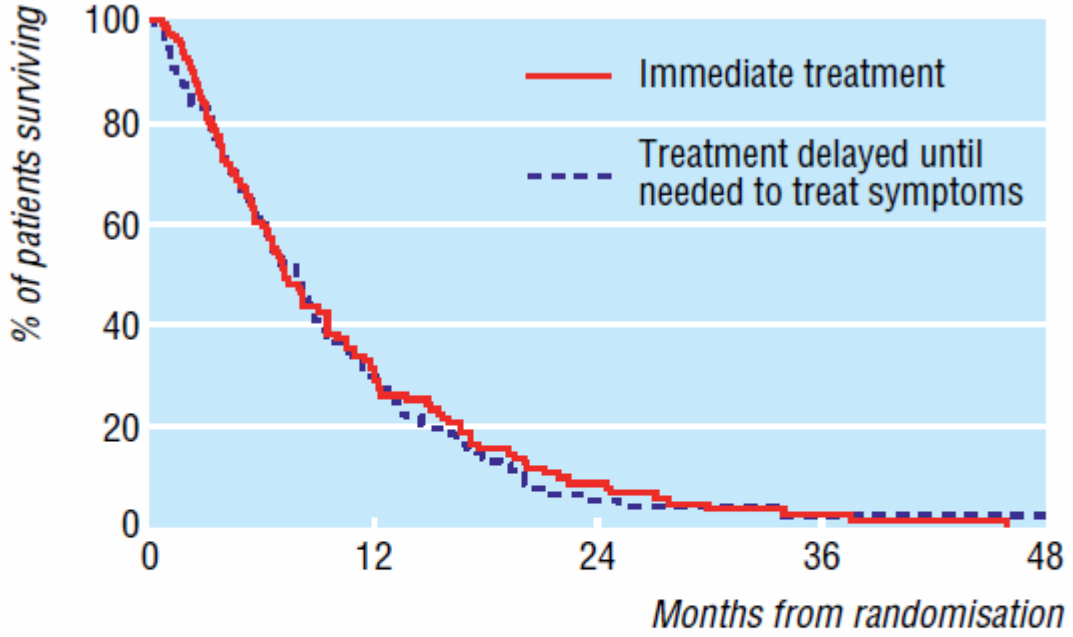


No of patients at risk					
Immediate treatment	115	35	9	2	0
Delayed treatment	115	33	5	1	1

p=0.71

Immediate vs delayed palliative thoracic radiotherapy in patients with unresectable locally advanced non-small cell lung cancer and minimal thoracic symptoms

[Falk et al 2002]

Rotterdam symptom check list

Month	No of evaluable patients		Median score (range)	
	Immediate treatment	Delayed treatment	Immediate treatment	Delayed treatment
0	109	110	9 (7-22)	9 (7-27)
1	59	81	11 (7-23)	9 (7-27)
2	61	51	9 (7-24)	10 (7-27)
4	59	58	10 (7-28)	10 (7-28)
6	45	49	10 (7-28)	12 (7-26)

HAD scores

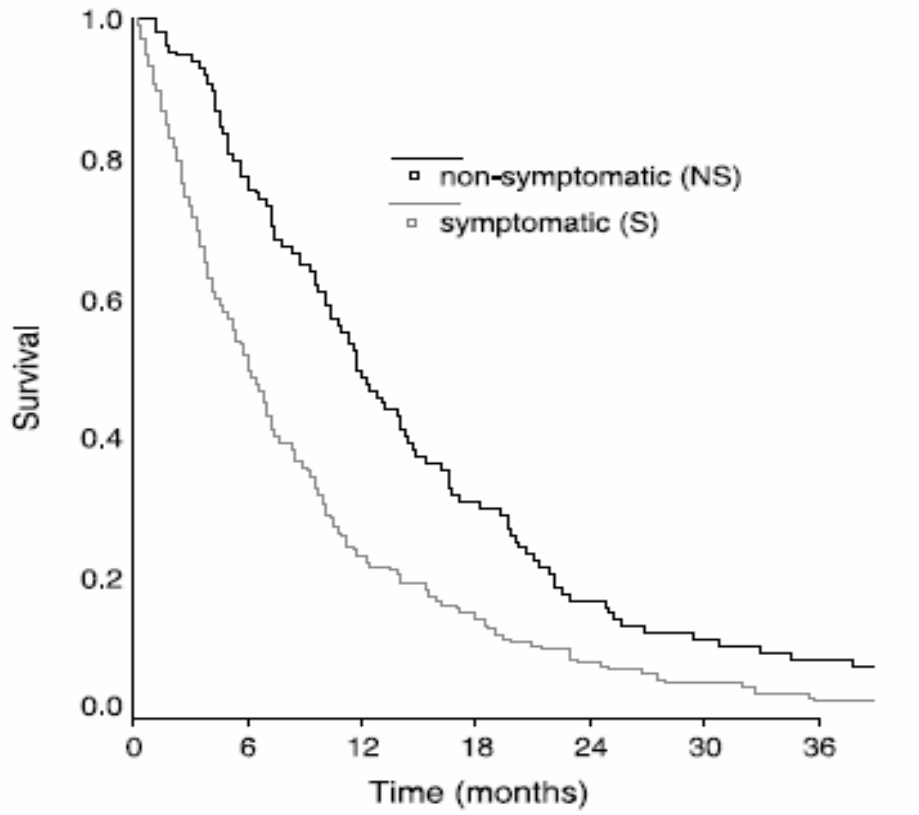
Month	No assessed		Normal		Borderline		Case	
	Immediate treatment	Delayed treatment	Immediate treatment	Delayed treatment	Immediate treatment	Delayed treatment	Immediate treatment	Delayed treatment
Anxiety:								
0	109	112	70 (64)	82 (73)	26 (24)	18 (16)	13 (12)	12 (11)
1	60	82	45 (75)	60 (73)	9 (15)	17 (21)	6 (10)	5 (6)
2	60	53	44 (73)	40 (75)	12 (20)	12 (23)	4 (7)	1 (2)
4	59	60	40 (68)	41 (68)	13 (22)	11 (18)	6 (10)	8 (13)
6	48	50	34 (71)	32 (64)	11 (23)	10 (20)	3 (6)	8 (16)
Depression:								
0	109	113	86 (79)	90 (80)	19 (17)	14 (12)	4 (4)	9 (8)
1	60	82	47 (78)	66 (80)	7 (12)	8 (10)	6 (10)	8 (10)
2	60	53	49 (82)	40 (75)	6 (10)	8 (15)	5 (8)	5 (9)
4	59	60	44 (75)	46 (77)	7 (12)	6 (10)	8 (14)	8 (13)
6	48	50	36 (75)	36 (72)	5 (10)	6 (12)	7 (15)	8 (16)

bmj.com 2002;325:465

Immediate or delayed radiotherapy in advanced non-small cell lung cancer (NSCLC)? Data from a prospective randomised study

Stein Sundstrøm[a,b,*], Roy Bremnes[c,d], Paal Brunsvig[e], Ulf Aasebø[c,f], Olbjørn Klepp[a,b], Peter M. Fayers[b,g], Stein Kaasa[a,b], For the Norwegian Lung Cancer Study Group

407 patients: fractionation study



Radiotherapy and Oncology 75 (2005) 141-148

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Symptom responses in prospective RCTs

Study (year)	Patients included (n)	Response rate (%)			
		Hemoptysis	*Cough*	*Chest pain*	*Dyspnea*
MRC (1991)	369	81–86	56–65	75–80	57–66
MRC (1992)	233	72–75	48–56	59–72	41–43
MRC (1996)	509	89–95	36–48	50–58	37–46
Nestle *et al.* (2000)	152	80–82	69–80	74–76	NR
Sundstrom *et al.* (2004)	421	80–90	20	NR	40
Erridge *et al.* (2005)	149	87–97	51–58	84	NR
Senkus-Konefka *et al.* (2005)	100	86	51	83	60

Expert Rev. Anticancer Ther. 10(4), 559–569 (2010)

ESTRO School

Palliative radiotherapy regimens for patients with thoracic symptoms from non-small cell lung cancer (Review)

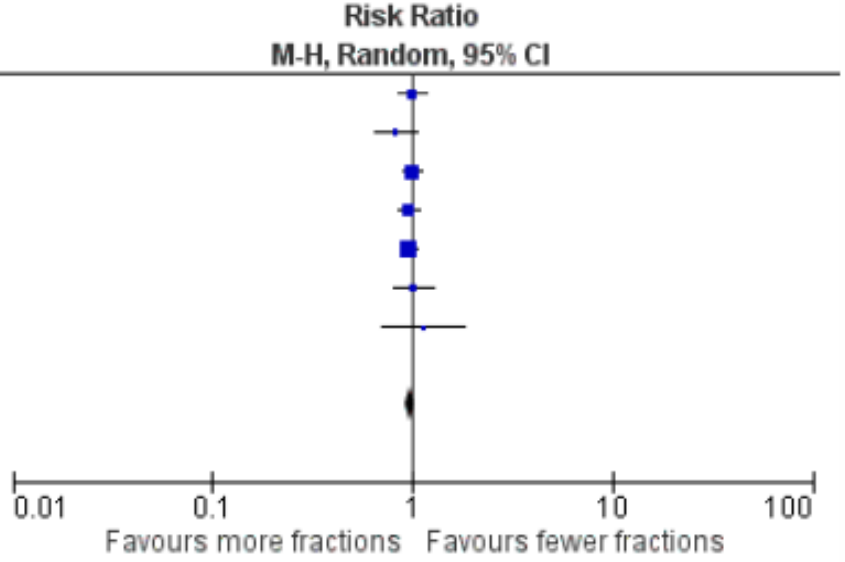
Stevens R, Macbeth F, Toy E, Coles B, Lester JF

One year survival in patients with PS 2-4

Study or Subgroup	More fractions Events	Total	Fewer fractions Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bezjak 2002	42	49	44	51	11.9%	0.99 [0.85, 1.16]
Erridge 2005	25	35	33	38	5.0%	0.82 [0.64, 1.05]
Kramer 2005	81	94	83	96	23.2%	1.00 [0.89, 1.12]
MRC 1991	72	87	81	93	19.4%	0.95 [0.84, 1.08]
MRC 1992	99	115	105	116	33.5%	0.95 [0.87, 1.04]
MRC 1996	43	60	43	61	5.7%	1.02 [0.81, 1.28]
Senkus-Konefka 2005	10	11	4	5	1.3%	1.14 [0.71, 1.83]
Total (95% CI)		**451**		**460**	**100.0%**	**0.97 [0.91, 1.02]**
Total events	372		393			

Heterogeneity: Tau² = 0.00; Chi² = 2.90, df = 6 (P = 0.82); I² = 0%

Test for overall effect: Z = 1.27 (P = 0.20)



http://www.thecochranelibrary.com

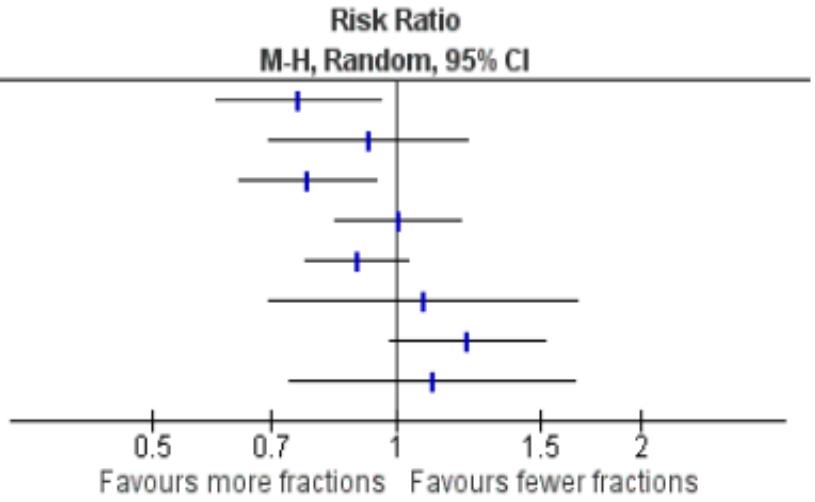
ESTRO School

Palliative radiotherapy regimens for patients with thoracic symptoms from non-small cell lung cancer (Review)

Stevens R, Macbeth F, Toy E, Coles B, Lester JF

One year survival in patients with PS 0-1

Study or Subgroup	More fractions Events	Total	Fewer fractions Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bezjak 2002	33	51	42	49		0.75 [0.60, 0.95]
Erridge 2005	27	39	27	36		0.92 [0.70, 1.22]
Kramer 2005	38	54	48	53		0.78 [0.64, 0.94]
MRC 1991	70	97	67	93		1.00 [0.84, 1.20]
MRC 1996	118	191	131	189		0.89 [0.77, 1.03]
Nestle 2000	21	39	18	36		1.08 [0.70, 1.67]
Senkus-Konefka 2005	39	44	29	40		1.22 [0.98, 1.52]
Sundstrom 2004	21	35	19	35		1.11 [0.74, 1.66]



Palliative radiotherapy regimens for patients with thoracic symptoms from non-small cell lung cancer (Review)

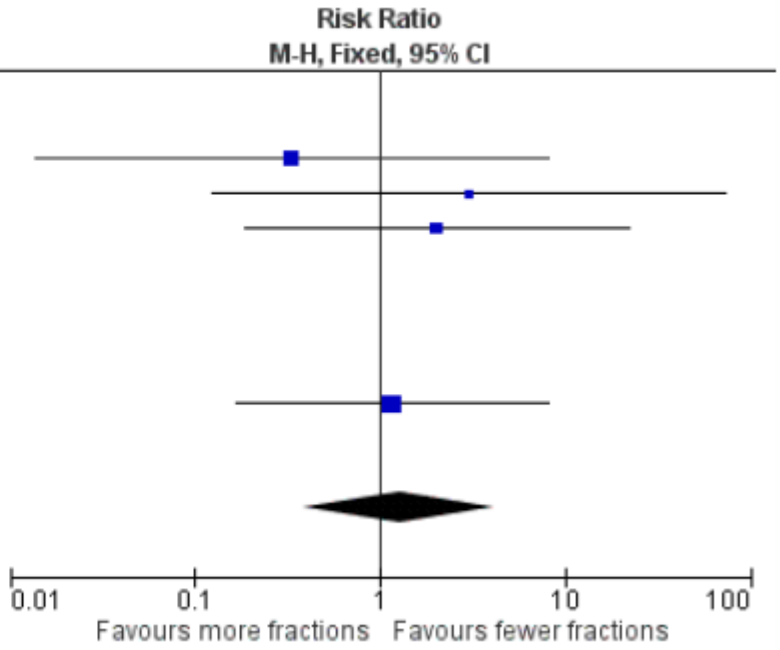
Stevens R, Macbeth F, Toy E, Coles B, Lester JF

Toxicity: myelopathy

Study or Subgroup	More fractions Events	Total	Fewer fractions Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bezjak 2002	0	114	0	116		Not estimable
Erridge 2005	0	74	0	74		Not estimable
MRC 1991	0	185	1	184	31.0%	0.33 [0.01, 8.09]
MRC 1992	1	116	0	117	10.2%	3.03 [0.12, 73.52]
MRC 1996	2	254	1	255	20.5%	2.01 [0.18, 22.00]
Nestle 2000	0	79	0	74		Not estimable
Rees 1997	0	81	0	83		Not estimable
Senkus-Konefka 2005	0	45	0	55		Not estimable
Simpson 1985	0	105	0	112		Not estimable
Sundstrom 2004	2	124	2	143	38.2%	1.15 [0.16, 8.07]
Teo 1988	0	128	0	145		Not estimable
Total (95% CI)		**1305**		**1358**	**100.0%**	**1.27 [0.39, 4.13]**
Total events	5		4			

Heterogeneity: Chi² = 1.11, df = 3 (P = 0.77); I² = 0%

Test for overall effect: Z = 0.39 (P = 0.70)



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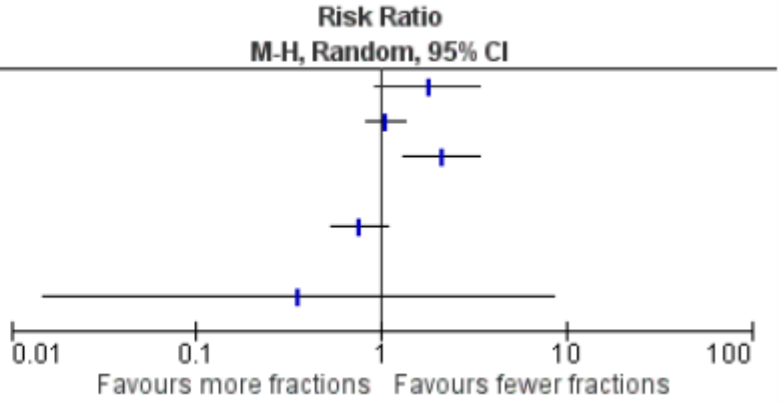
Palliative radiotherapy regimens for patients with thoracic symptoms from non-small cell lung cancer (Review)

Stevens R, Macbeth F, Toy E, Coles B, Lester JF

Toxicity: oesophagitis

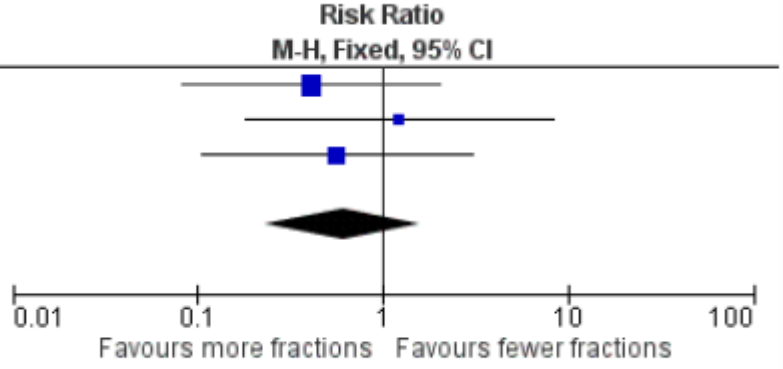
Study or Subgroup	More fractions Events	Total	Fewer fractions Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abratt 1995	17	41	10	43		1.78 [0.93, 3.43]
MRC 1991	80	185	75	184		1.06 [0.83, 1.35]
MRC 1992	38	77	18	77		2.11 [1.33, 3.36]
Nestle 2000	0	79	0	74		Not estimable
Rees 1997	31	81	42	83		0.76 [0.53, 1.07]
Reinfuss 1999	0	79	0	81		Not estimable
Simpson 1985	0	105	1	112		0.36 [0.01, 8.63]



Toxicity: pneumonitis

Study or Subgroup	More fractions Events	Total	Fewer fractions Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Reinfuss 1999	2	79	5	81	47.1%	0.41 [0.08, 2.05]
Senkus-Konefka 2005	2	45	2	55	17.2%	1.22 [0.18, 8.34]
Teo 1988	2	128	4	145	35.8%	0.57 [0.11, 3.04]
Total (95% CI)		**252**		**281**	**100.0%**	**0.61 [0.23, 1.60]**
Total events	6		11			

Heterogeneity: Chi² = 0.75, df = 2 (P = 0.69); I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)



Meta-analysis comparing higher and lower dose radiotherapy for palliation in locally advanced lung cancer

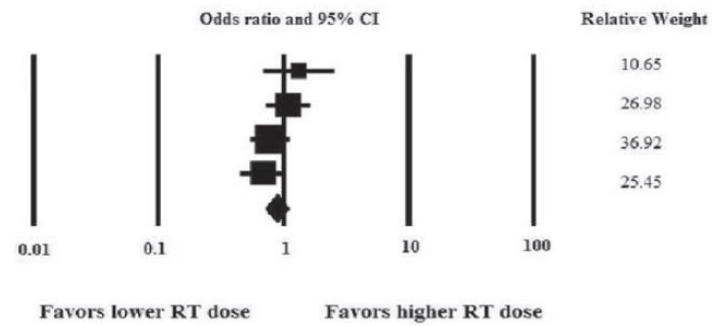
Cancer Sci **105** (2014) 1015–1022

Jie-Tao Ma,[1] Jia-He Zheng,[2] Cheng-Bo Han[1] and Qi-Yong Guo[2]

Cough

Study name	Comparison	Odds ratio	Lower limit	Upper limit	Z-Value	*P*-Value	Relative Weight
Erridge SC (2005)	≥30 Gy vs. < 30 Gy	1.33	0.69	2.54	0.85	0.393	10.65
Sundstrøm S (2004)	≥30 Gy vs. < 30 Gy	1.08	0.72	1.63	0.39	0.700	26.98
Macbeth FR (1996)	≥30 Gy vs. < 30 Gy	0.79	0.55	1.11	−1.35	0.176	36.92
MRC (1991)	≥30 Gy vs. < 30 Gy	0.69	0.45	1.04	−1.77	0.078	25.45
combined		0.88	0.71	1.08	−1.23	0.217	

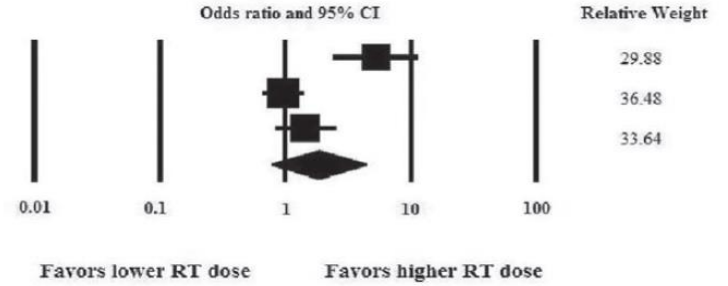
Heterogeneity test: Q = 4.30, df = 3, *P* = 0.230, I-square = 30.30%



Chest pain

Study name	Comparison	Odds ratio	Lower limit	Upper limit	Z-Value	*P*-Value	Relative Weight
Erridge SC (2005)	≥30 Gy vs. < 30 Gy	5.25	2.43	11.35	4.22	0.000	29.88
Macbeth FR (1996)	≥30 Gy vs. < 30 Gy	0.96	0.67	1.38	−0.24	0.814	36.48
MRC (1991)	≥30 Gy vs. < 30 Gy	1.44	0.83	2.51	1.29	0.197	33.64
combined		1.83	0.76	4.38	1.35	0.176	

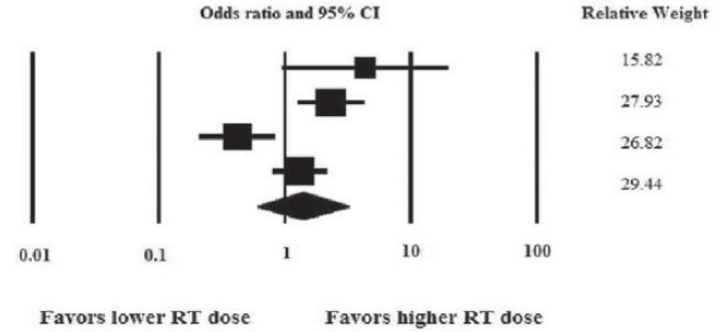
Heterogeneity test: Q = 15.42, df = 2, *P* < 0.001, I-square = 87.03%



Haemoptysis

Study name	Comparison	Odds ratio	Lower limit	Upper limit	Z-Value	*P*-Value	Relative Weight
Erridge SC (2005)	≥30 Gy vs. < 30 Gy	4.41	0.98	19.93	1.93	0.054	15.82
Sundstrøm S (2004)	≥30 Gy vs. < 30 Gy	2.36	1.29	4.34	2.77	0.006	27.93
Macbeth FR (1996)	≥30 Gy vs. < 30 Gy	0.43	0.21	0.85	−2.44	0.015	26.82
MRC (1991)	≥30 Gy vs. < 30 Gy	1.33	0.82	2.18	1.15	0.251	29.44
combined		1.39	0.60	3.20	0.78	0.437	

Heterogeneity test: Q = 16.39, df = 3, *P* = 0.001, I-square = 81.69%



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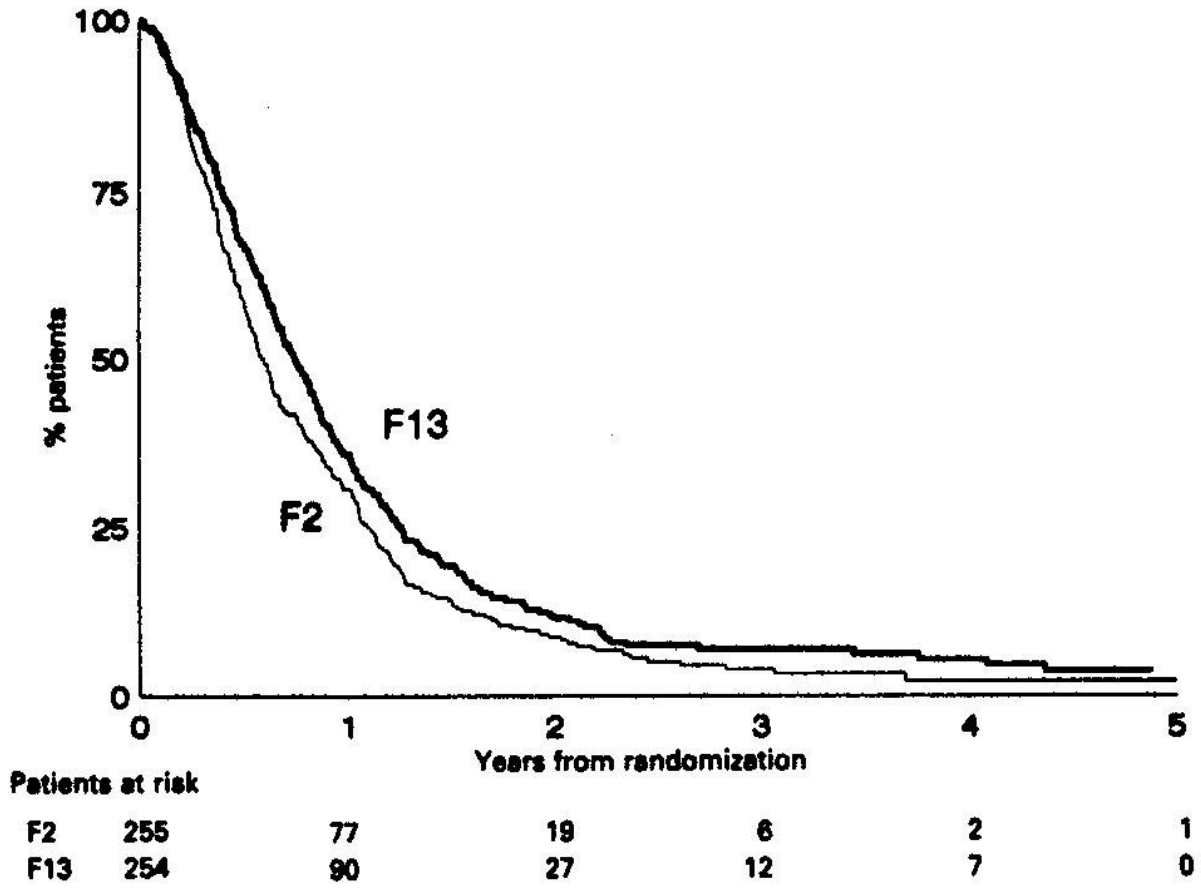
Randomised trial of palliative two-fraction versus more intensive 13-fraction radiotherapy for patients with inoperable non-small cell lung cancer and good performance status

[MRC 1996]

HR = 0.82 [0.69-0.99]

p=0.03



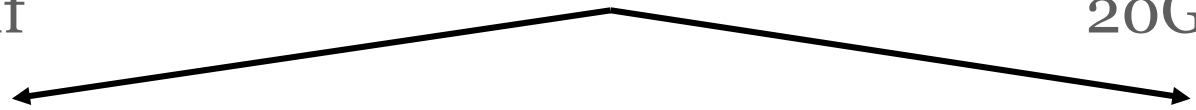
Randomized study of single versus fractionated radiotherapy in the palliation of non-small cell lung cancer;

NCIC CTG SC.15 [Bezjak et al 2002]

230 patients

PS 2 or 3: 52%

10Gy / 1f



20Gy / 5f

Patient diary cards at 1 month: No difference

Randomized study of single versus fractionated radiotherapy in the palliation of non-small cell lung cancer; NCIC CTG SC.15 [Bezjak et al 2002]

- EORTC QLQC30:
  - Dyspnoea better with 20Gy (p=0.027)
- Lung Cancer Symptom Scale:
  - 20Gy better for:
    - overall cancer-related symptoms (p=0.037)
    - pain (p=0.017)
    - daily activity (p=0.047)
- Survival
    - !0Gy: 4.mo 20Gy: 6.0mo p=0.014

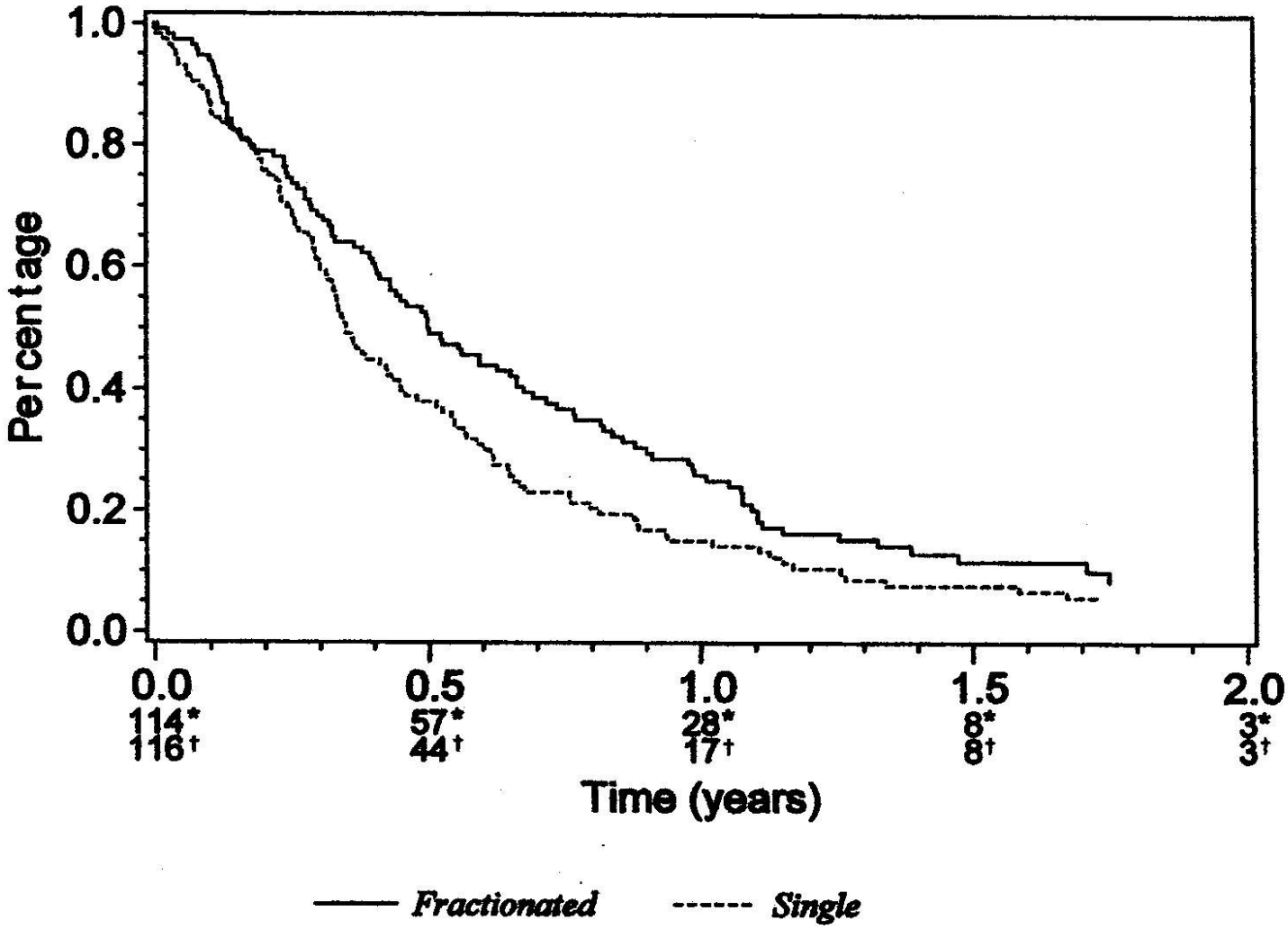


Fig. 4. Patient survival. *Number of patients at risk (fractionated arm). †Number of patients at risk (single arm).

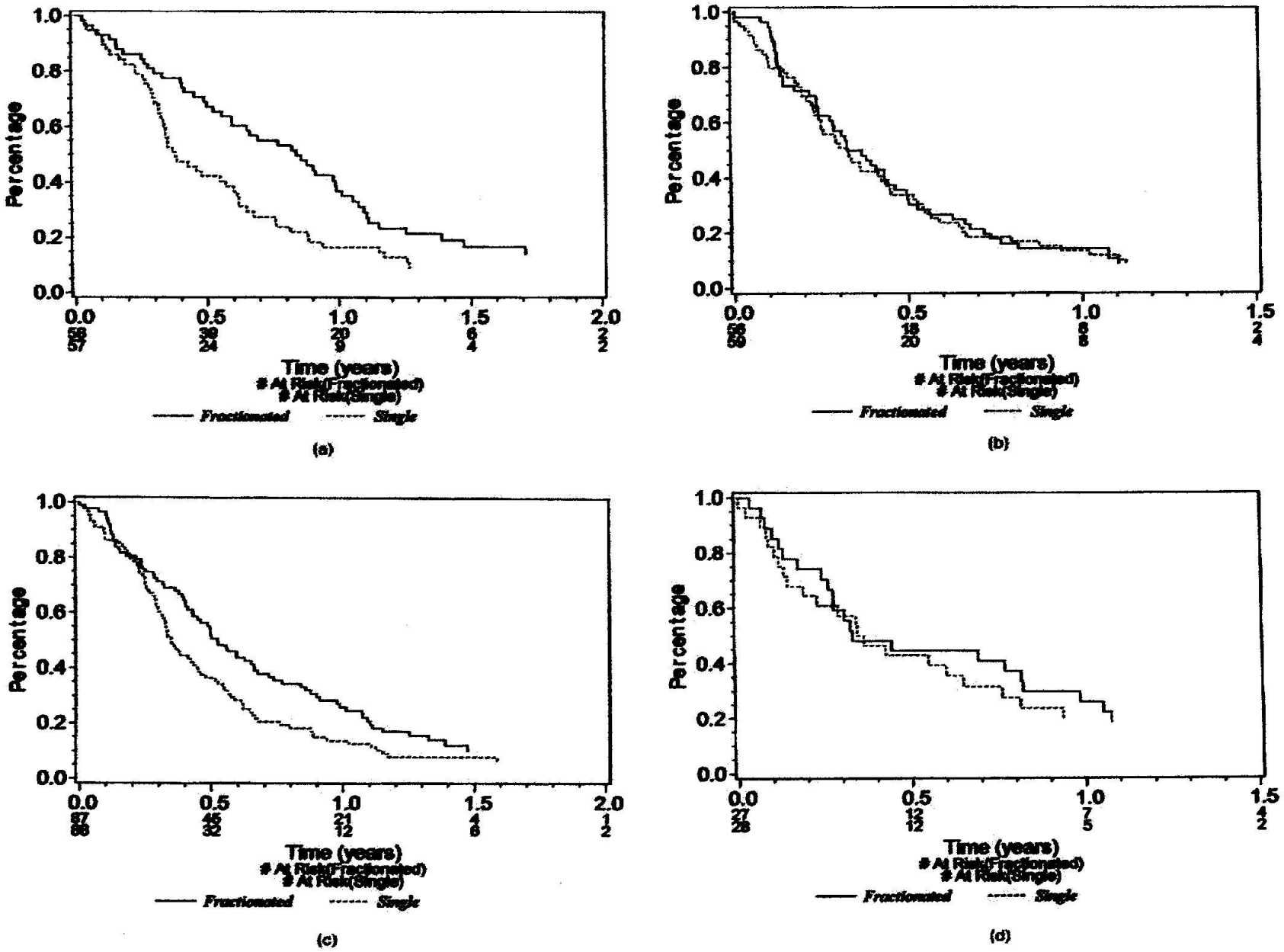
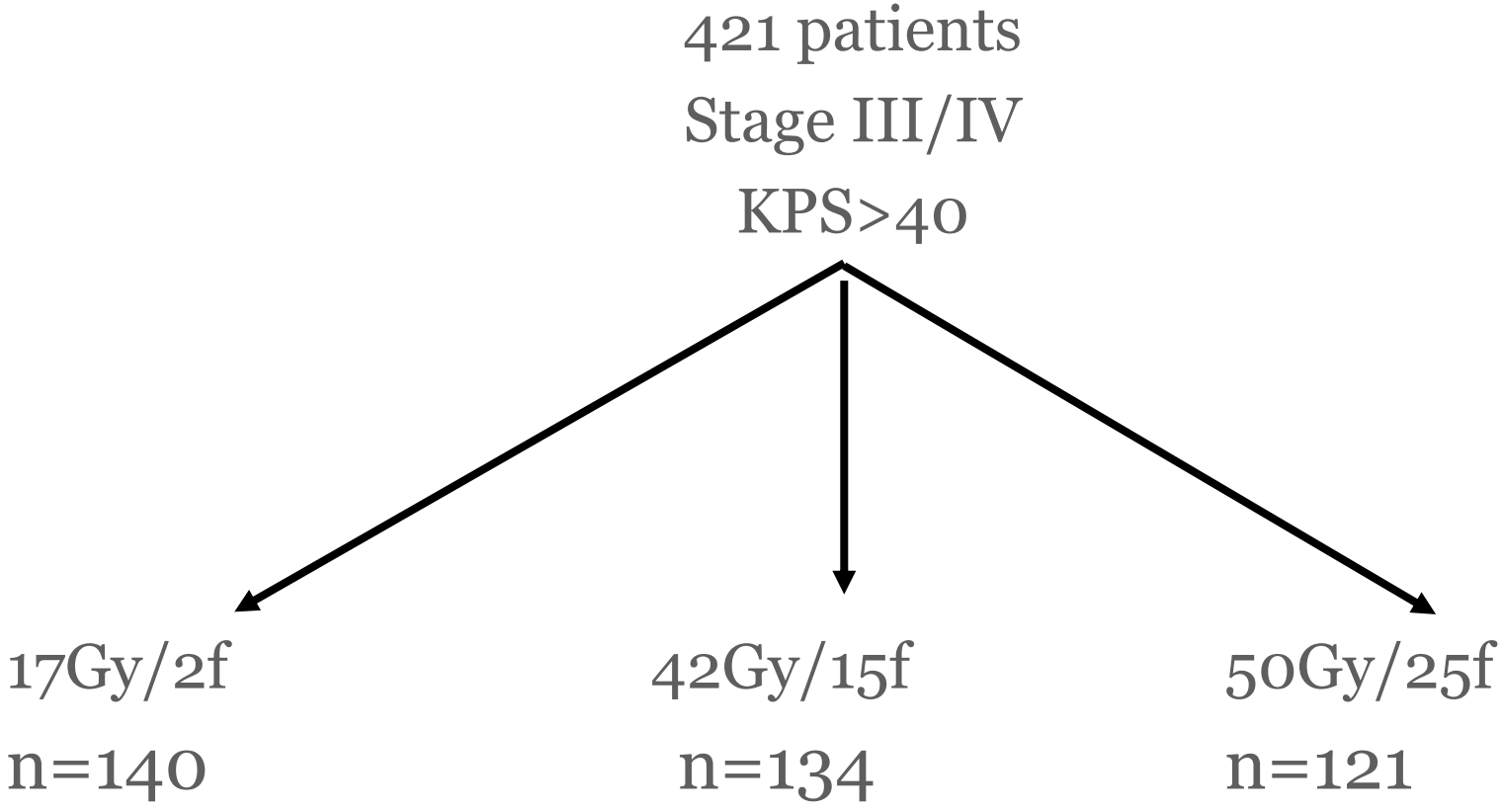


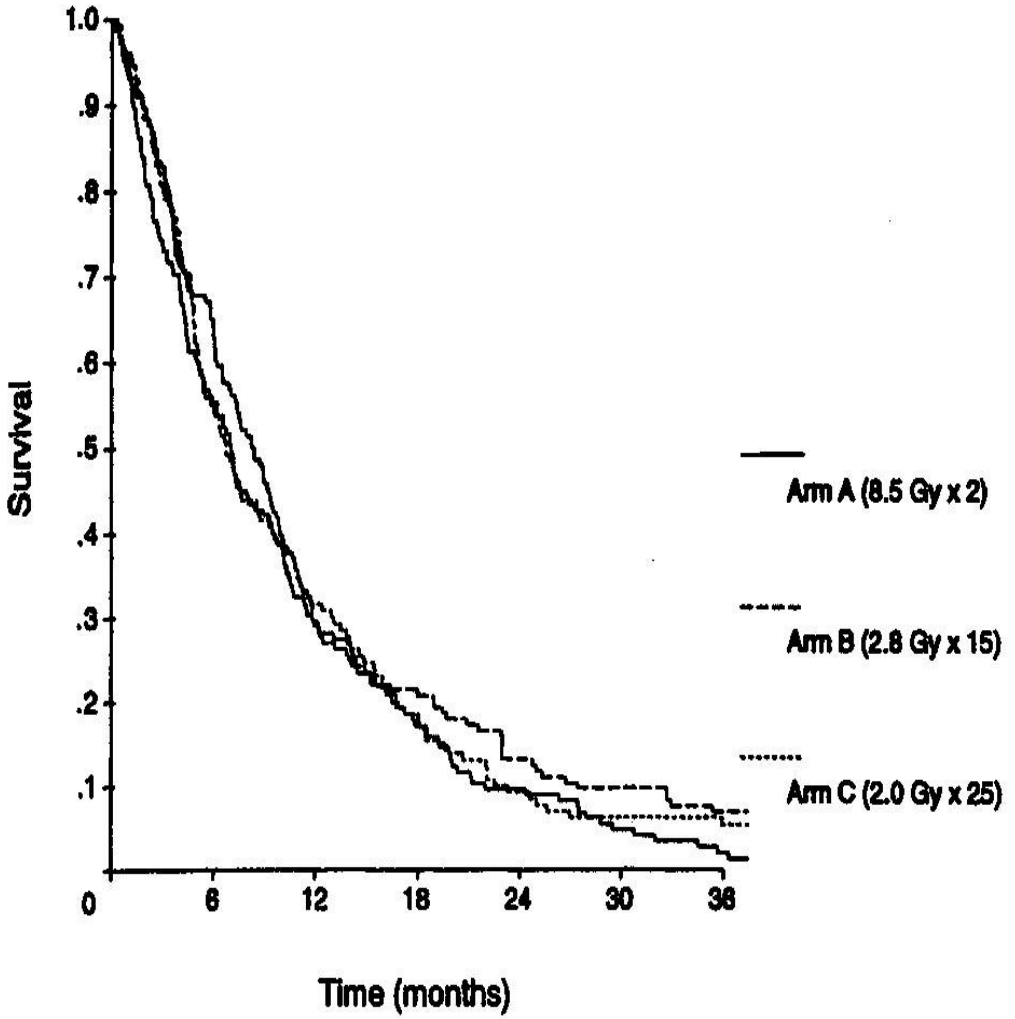
Fig. 5. Subgroup survival analysis for patients with (a) performance status 0 or 1; (b) performance status 2 or 3; (c) locally advanced disease; and (d) metastatic disease.

Hypofractionated palliative radiothearpy in advanced non-small-cell lung carcinoma …..a national phase III study (Norway) [Sundstrom et al 2004]



Hypofractionated palliative radiotherapy in advanced non-small-cell lung carcinoma …..a national phase III study (Norway) [Sundstrom et al 2004]

All patients
N=421

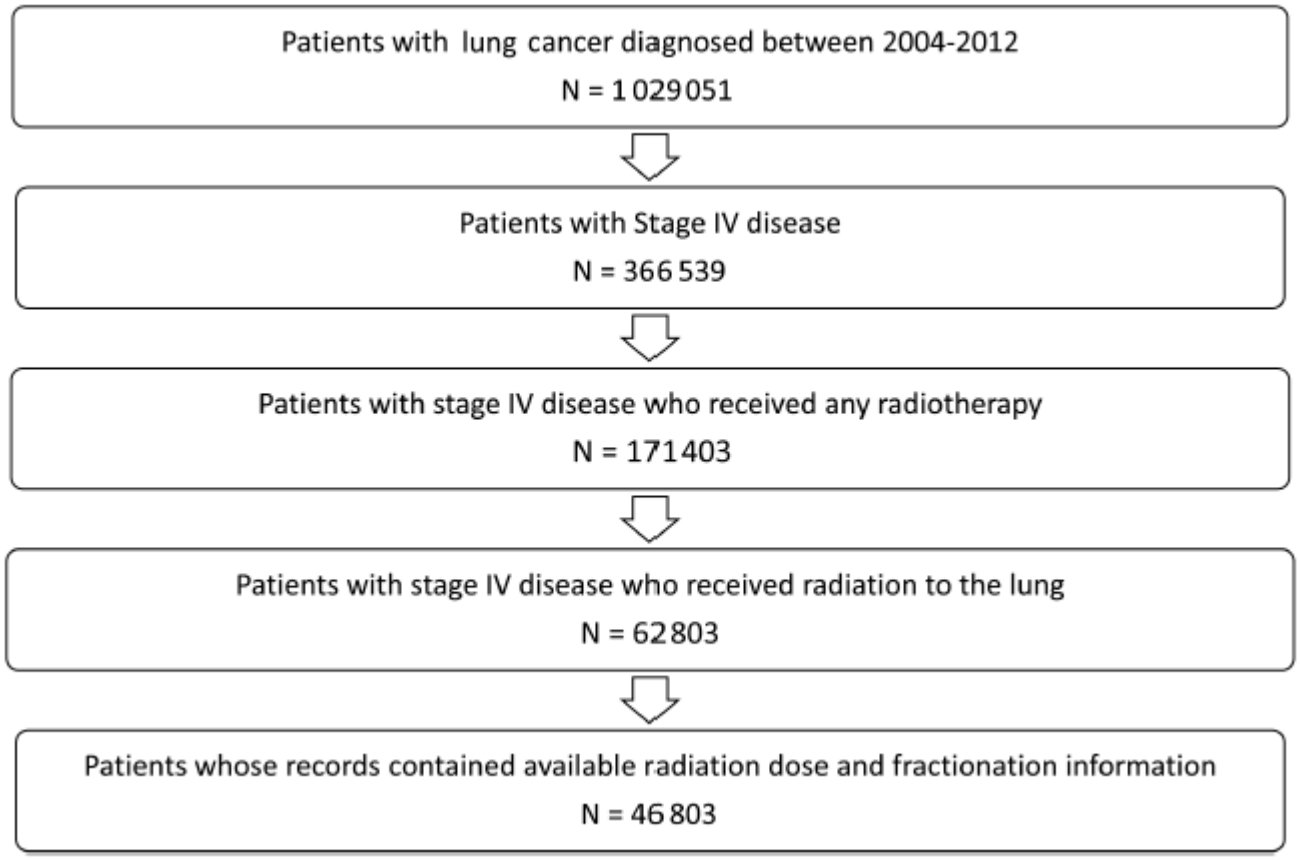


Prevalence and Predictors of Inappropriate Delivery of Palliative Thoracic Radiotherapy for Metastatic Lung Cancer

JNCI J Natl Cancer Inst (2015) 107(12): djv278

Matthew Koshy, Renuka Malik, Usama Mahmood, Zain Husain, Ralph R. Weichselbaum, David J. Sher

NCDB



Median duration 26d(IQR 15-45d)
70% > 10 fractions
29% > 15 fractions
28% > 20 fractions

Median dose 39Gy (IQR 30-58d)

ChemoRT 19%

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Prevalence and Predictors of Inappropriate Delivery of Palliative Thoracic Radiotherapy for Metastatic Lung Cancer

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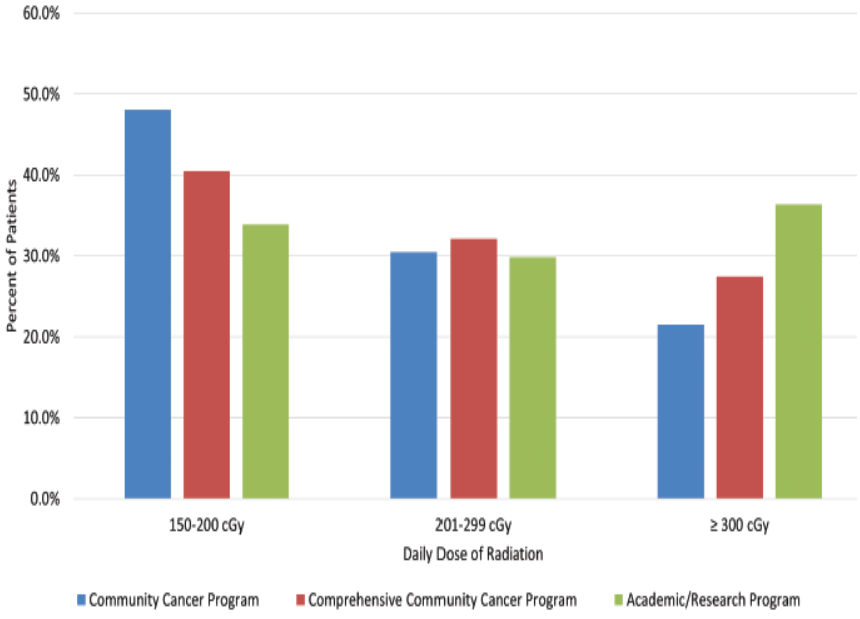

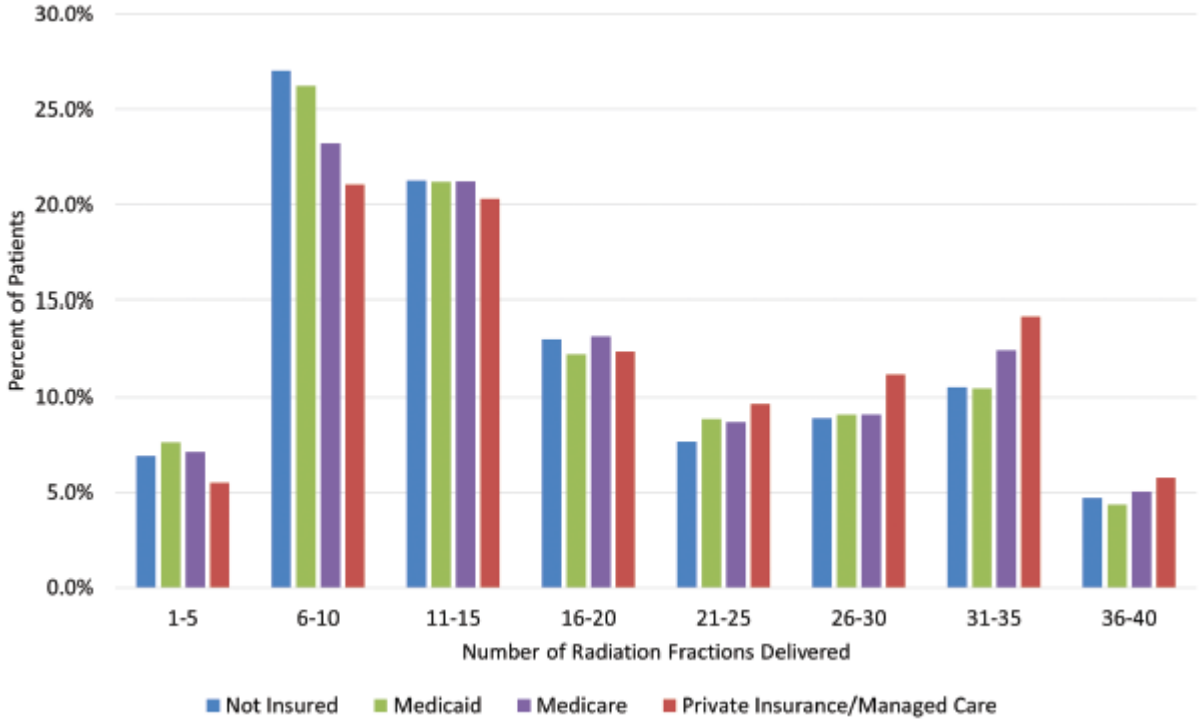

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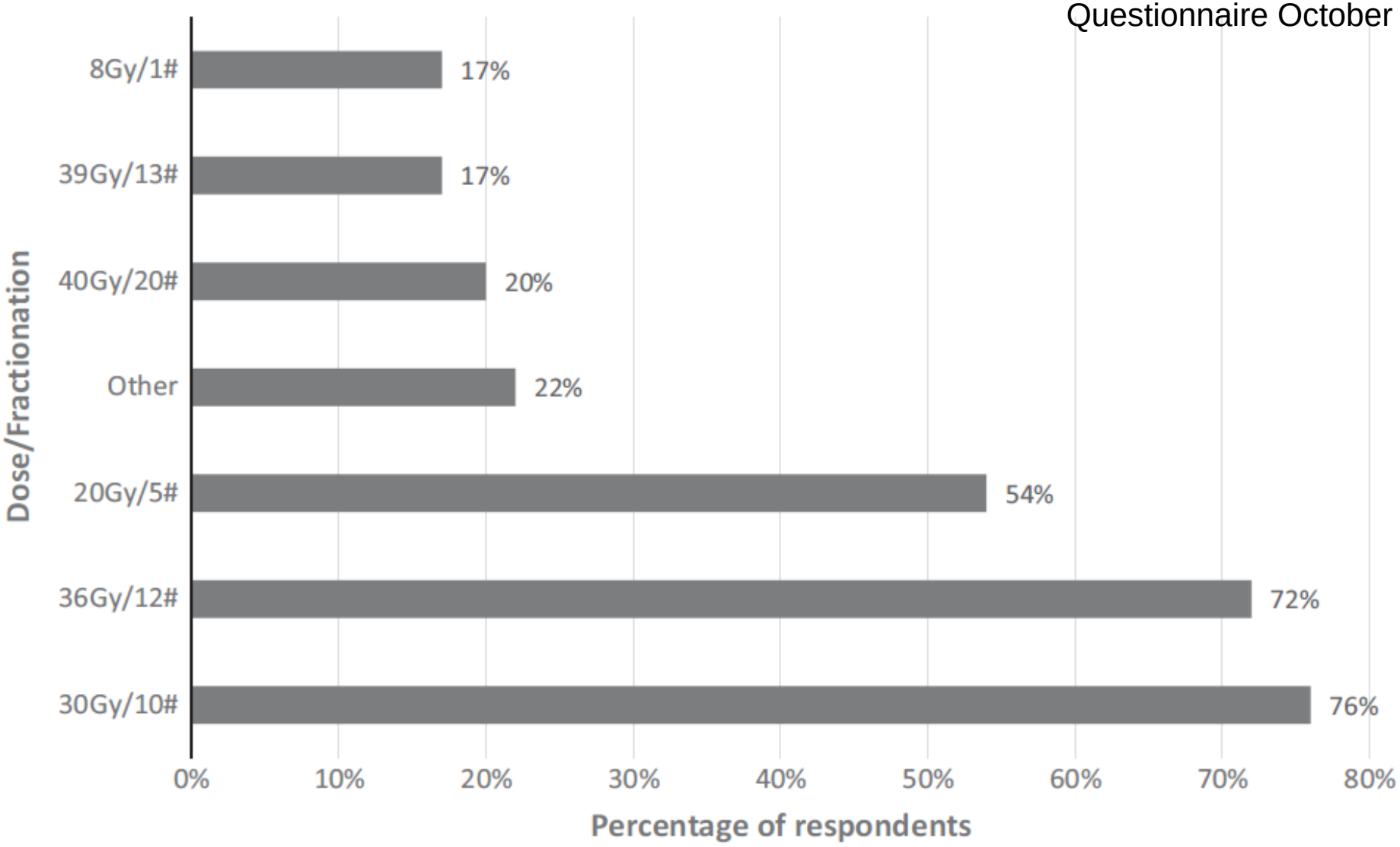
Lung cancer radiation therapy in Australia and New Zealand: Patterns of practice

Journal of Medical Imaging and Radiation Oncology **60** (2016) 677–685

Syed Muntasser Islam,[1] Shalini K Vinod,[2] Margot Lehman,[3] Shankar Siva,[4] Tomas Kron,[5] Patrick M Dwyer,[6] Lois Holloway,[7,8,9] Louis Lao,[10,11,12] Mei Ling Yap[9,13,14] and Jeremy D Ruben[1,15]

Questionnaire October 2014



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Endobronchial brachytherapy: palliative single treatment

Christie series [Gollins et al 1994]:

406 patients
65 previous XRT
17 previous brachy

15Gy @ 1cm (18% 20Gy)

Response (n=324)

Stridor	92%
Haemoptysis	88%
Cough	62%
Dyspnoea	60%
Pain	50%
Collapse	46%

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UK RCT: endobronchial brachytherapy vs external beam [Stout et al 2000]

106 patients 15Gy brachy vs 32Gy/8f ext beam

Symptom scores by physician and patient
No difference in survival: median 250 vs 287 days

No difference in scores at 8 weeks for:

cough
haemoptysis
SOB
hoarseness

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UK RCT: endobronchial brachytherapy vs external beam [Stout et al 2000]

	Brachy	XRT
Physician scores for improvement		
Dysphagia	85%	45%
Patient scores for improvement		
Chest pain	43%	77%
Anorexia	43%	77%
Tiredness	30%	65%
Nausea	58%	81%

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Opportunity cost in palliation of NSCLC

Currency is

- Toxicity
- Time

Purchase is

- Symptom control
- Quality of life
- Survival

Opportunity cost in palliation of NSCLC

- Median survival with inoperable NSCLC
  - PS 2 - 3 or mets: 120 days
  - PS 0 - 1, no mets: 240 days

Opportunity cost in palliation of NSCLC

- Median survival with inoperable NSCLC
  - PS 0 - 1, no mets: 240 days

	Proportion of survival
• 17Gy / 2f:	0.08% (3.3% = 8 days)
• 20Gy / 5f:	2.1%
• 30Gy / 10f	5%
• 39Gy / 13f	7.1%

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Opportunity cost in palliation of NSCLC

- Median survival with inoperable NSCLC
  - PS 2 - 3 or mets: 120 days

	Proportion of survival
• 10Gy / 1f:	0.08%
• 17Gy / 2f:	1.6% (6.7% = 8 days)
• 20Gy / 5f:	4.2%
• 30Gy / 10f	10%
• 39Gy / 13f	14.2%

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Opportunity cost in palliation of NSCLC

- Median survival with inoperable NSCLC
  - PS 2 - 3 or mets: 120 days
  - Asymptomatic
    - No treatment; no toxicity; no loss of survival
  - Symptomatic
    - 1 treatment for equivalent symptom control and toxicity to longer treatment
    - BUT…will any patients live longer with 20Gy/39Gy

Opportunity cost in palliation of NSCLC

- Median survival with inoperable NSCLC
  - PS 0 - 1, no mets: 240 days
    - MRC 13#: 17days treatment to gain 54 days
    - NCIC 5#: 5 days to gain 60 days
    - Equivalent toxicity and symptom control

Palliative management of lung cancer

- Chemotherapy for good PS patients and advanced disease
  - Improves survival by around 2 months
  - In NSCLC improves QoL
  - ? Role of second and third line tretament

- Palliative radiotherapy for specific symptoms
  - Cough, haemoptysis, chest pain, SOB
  - Hypofractionation
  - ?more prolonged RT for good PS patients

- PS 2-3: consider BSC alone

Re-irradiation for palliation

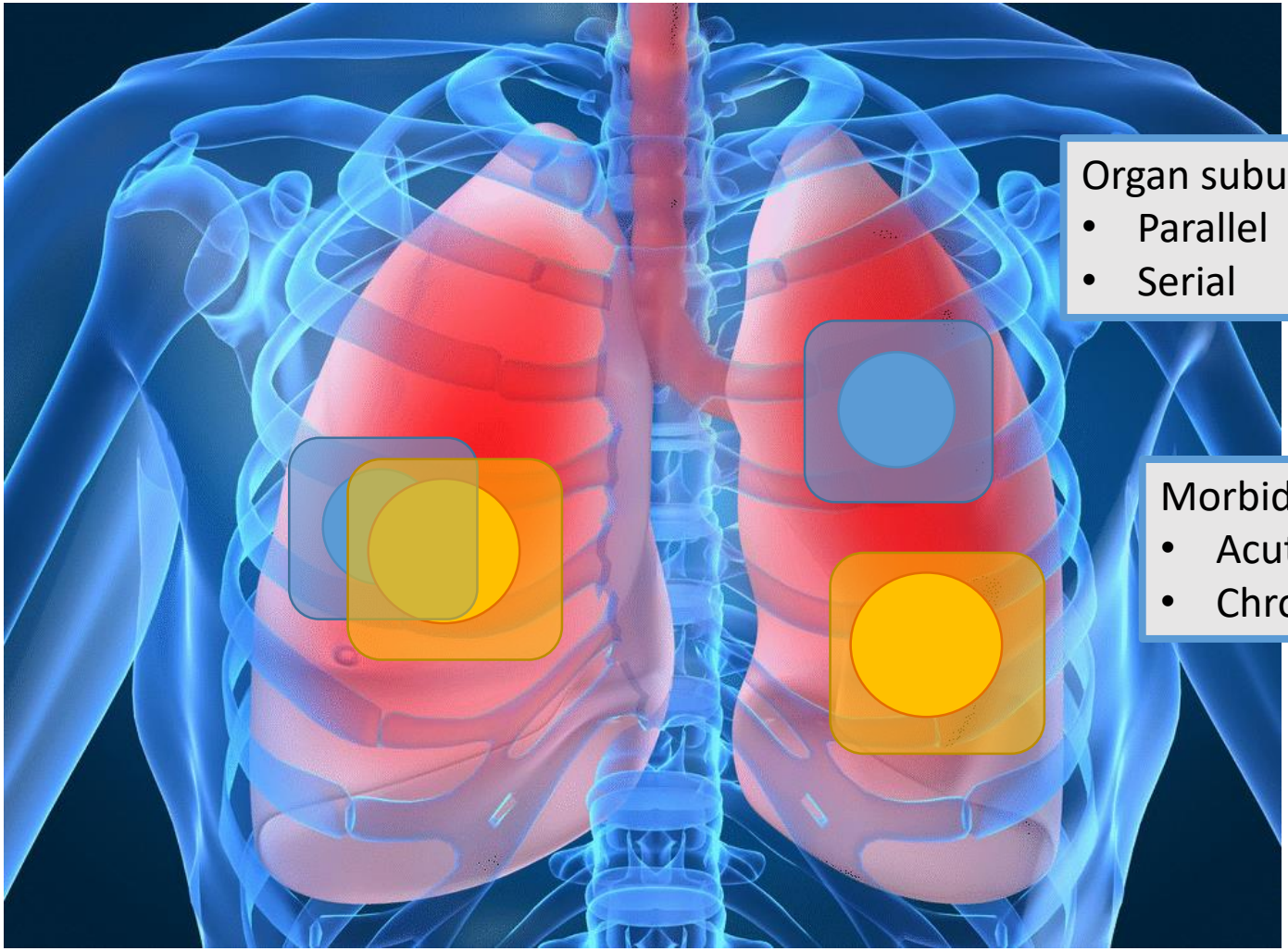
Morten Høyer
Danish Center for Particle therapy
Aarhus University Hospital
Denmark

Why is re-irradiation so underused?

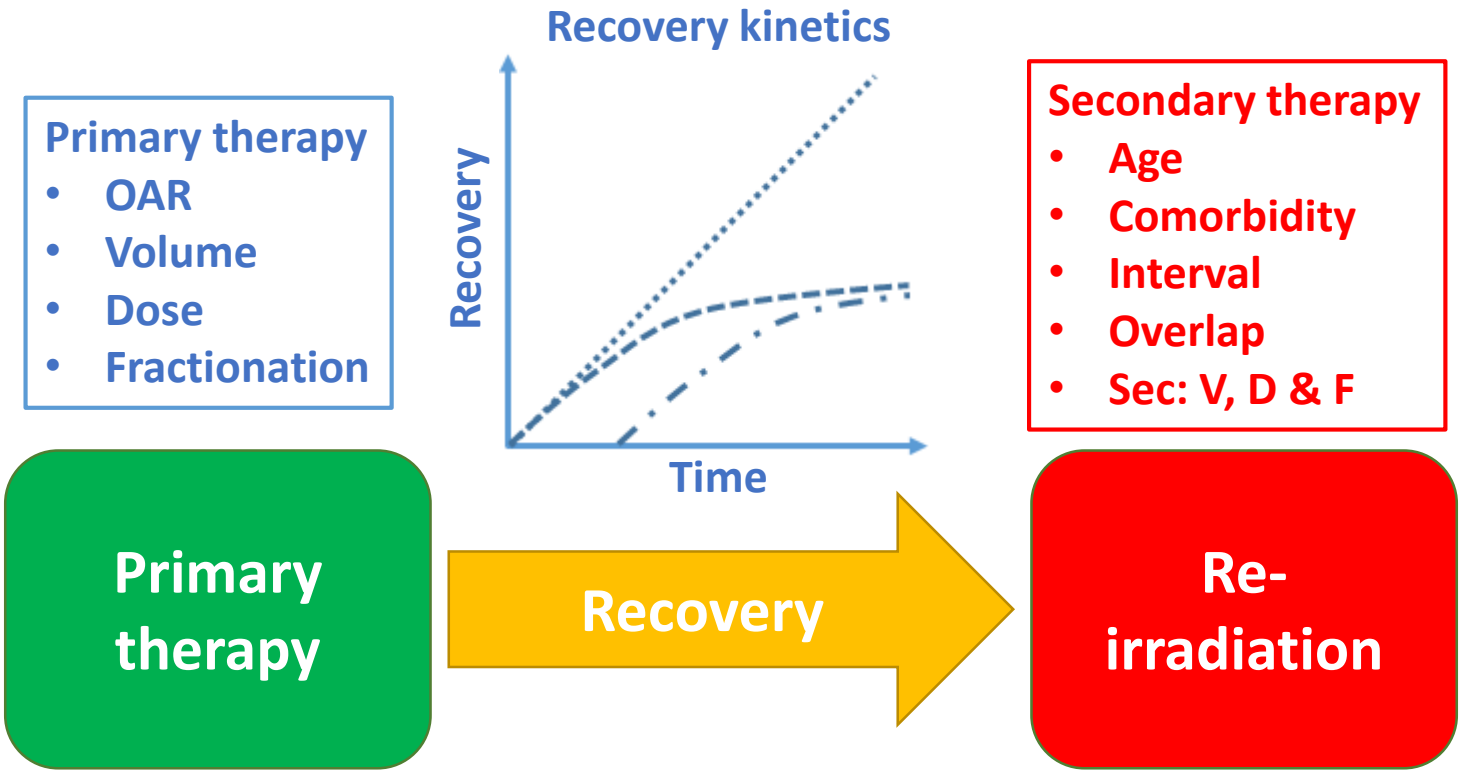
More reirradiation

- Patients live longer
- Technique allow normal tissue sparing (and higher doses)
- Patient’s and physician’s preferences

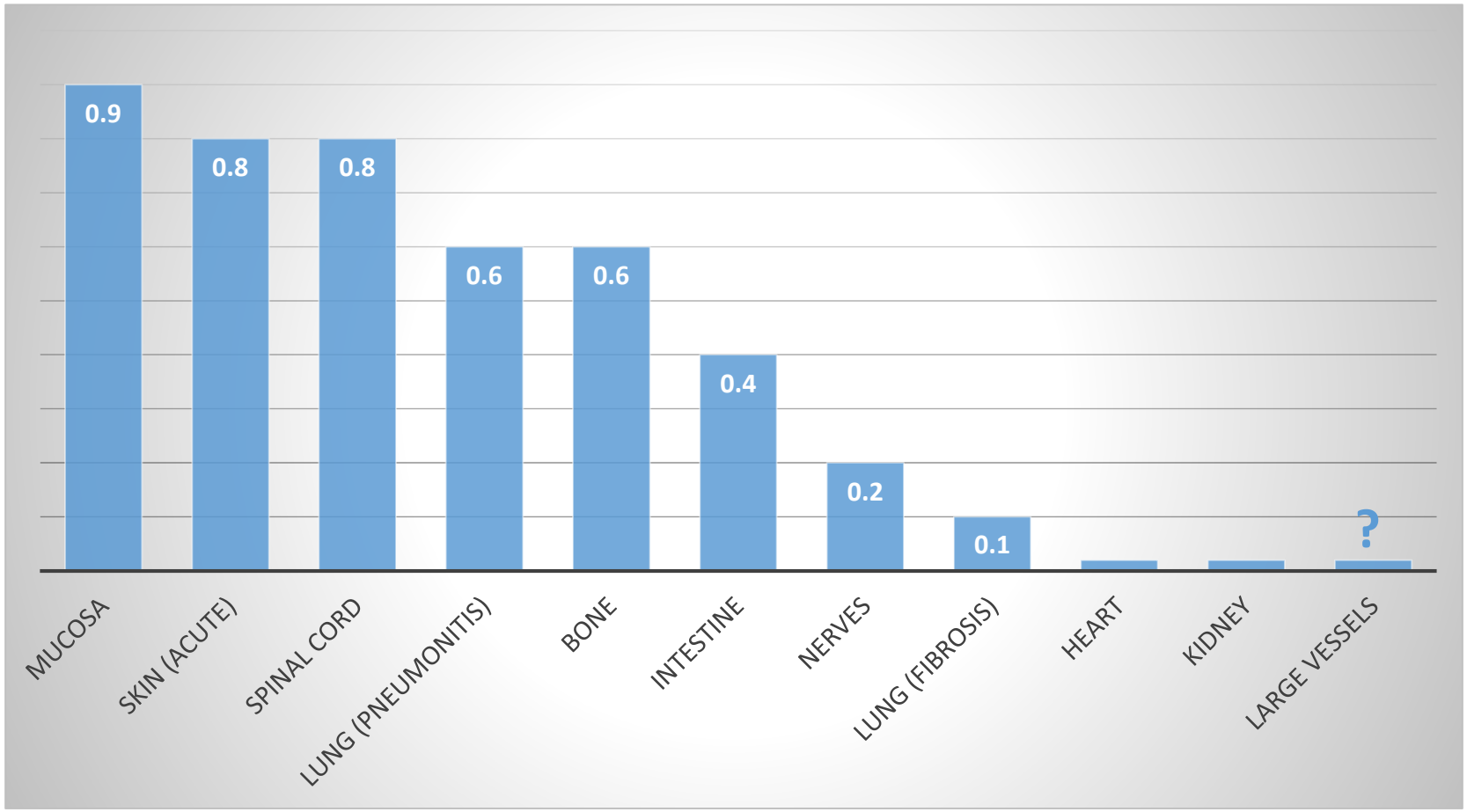
Re-irradiation for local- or distant relapse



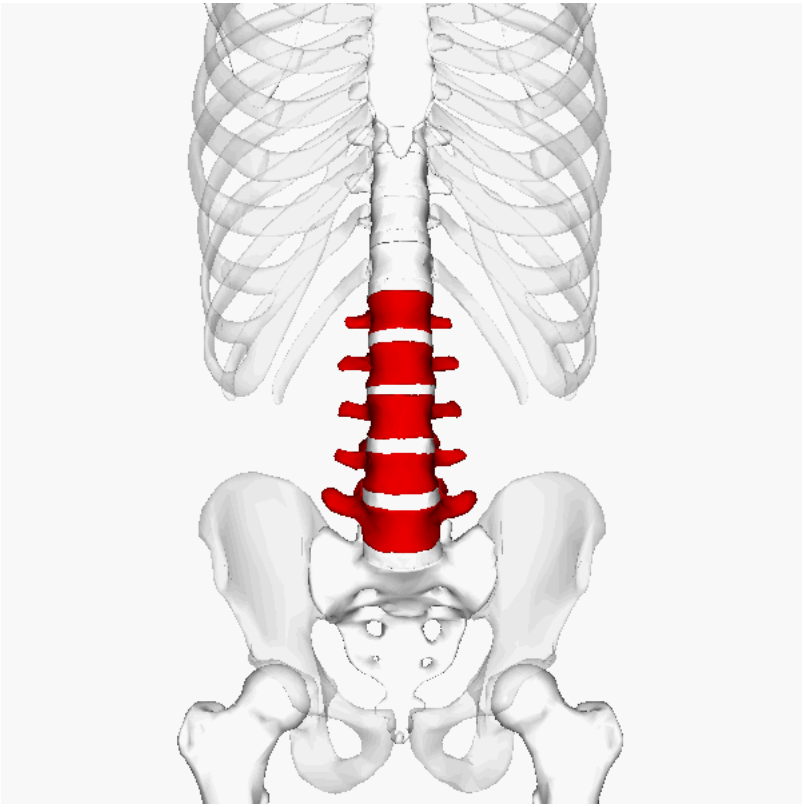
Considerations in reirradiation



Re-irradiation tolerance (recovery)
Feeling based…… (little evidence)



The equation



Total BED = BED (1) + BED (2) – Dose (recovered)

$$BED = n \times d \left(1 + d/[\alpha/\beta]\right)$$

SRT for re-irradiation in

This lecture

- Bone
- Spine
- Lung
- Liver

Additional sites

- Brain
- Head & neck
- Lymph nodes
- Pancreas
- Rectum
- Cervix
- Prostate

Bone metastases

Dogma

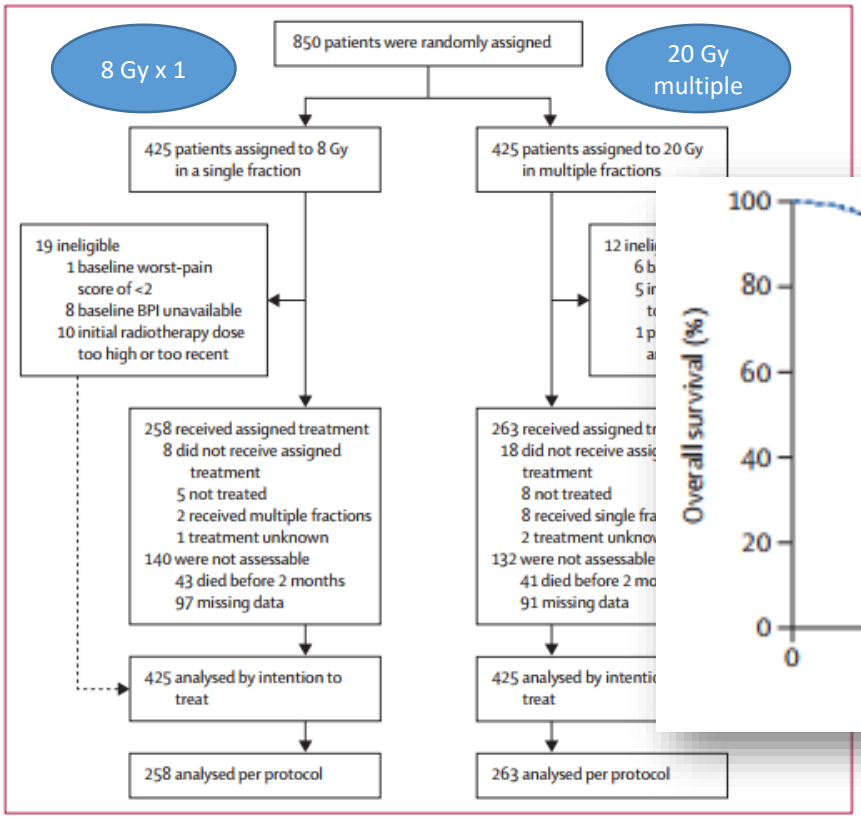
- Reirradiation more frequent if the patients received single frx in initial course

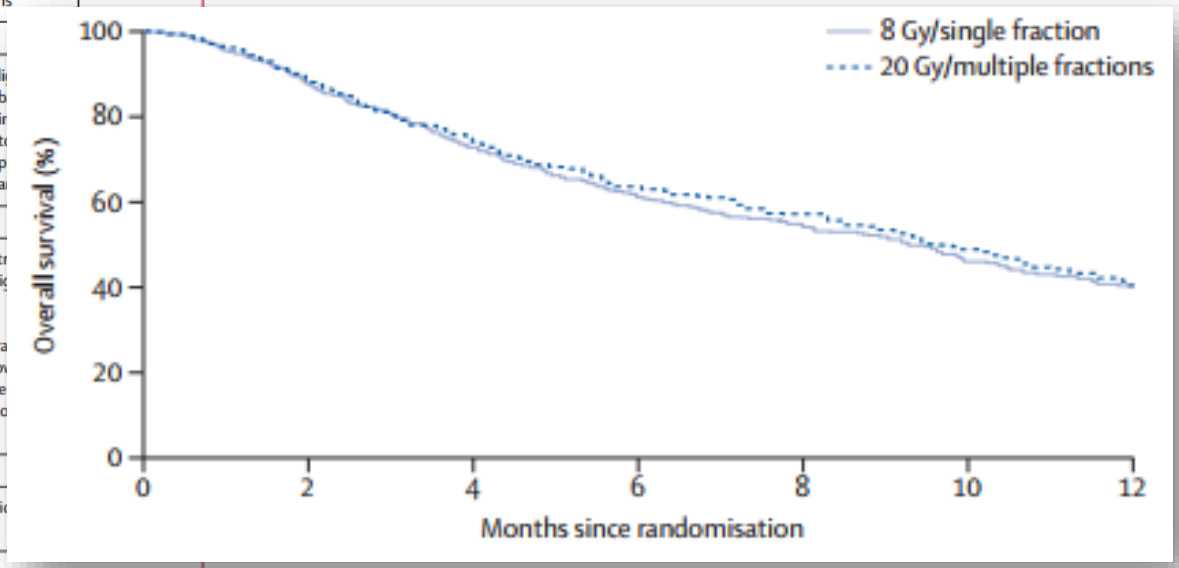
Table 1 — Re-irradiation rates reported in randomised trials of dose-fractionation schedules

Randomised study	Re-irradiation rate (%)	
	Low-dose fraction	High-dose fraction
Trials comparing single-fraction against multifraction radiotherapy		
Bone Pain Trial Working Party [1]	23	10
Steenland *et al.* [8]	25	7
Nielsen *et al.* [4]	20	12
Cole [10]	25	0
Price *et al.* [6]	11	3
Hartsell *et al.* [15]	18	9
Roos *et al.* [16]	29	24
Trials comparing single fractions at different doses (4 vs 8 Gy)		
Jeremic *et al.* [3]	42	38
Hoskin *et al.* [18]	20	9
Trials comparing different multifraction regimens		
Niewald *et al.* [5]	2	2
Tong *et al.* [9,19] (RTOG 7402)		
Solitary met	24	11
Multiple mets	23	12

Chow et al
Clinical Oncology (2006) 18: 125

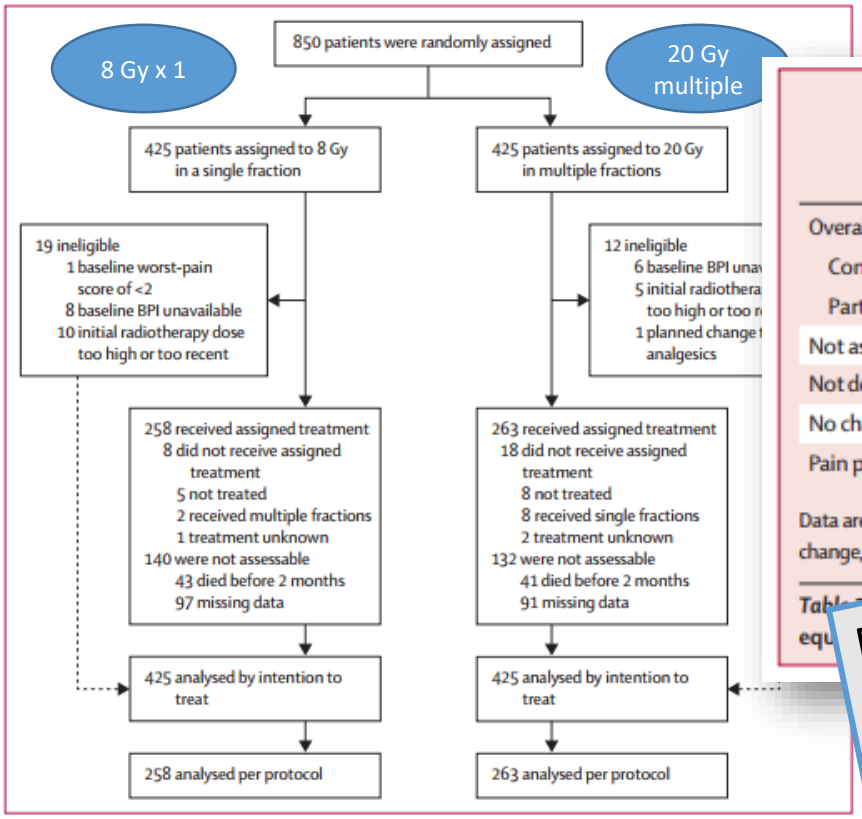
Randomized trial: single versus multiple fraction re-irradiation of painful bone mets.





Chow et al. Lancet Oncol 2014; 15: 164

Randomized trial: single versus multiple fraction re-irradiation of painful bone mets.



	Intention-to-treat analysis		Per-protocol analysis	
	8 Gy/single fraction (N=425)	20 Gy/multiple fractions (N =425)	8 Gy/single fraction (N=258)	20 Gy/multiple fractions (N=263)
Overall response	118 (28%)	135 (32%)	116 (45%)	134 (51%)
Complete response	36 (8%)	30 (7%)	35 (14%)	29 (11%)
Partial response	82 (19%)	105 (25%)	81 (31%)	105 (40%)
Not assessable	162 (38%)	160 (38%)	0	0
Not defined*	92 (22%)	91 (21%)	91 (35%)	91 (35%)
No change	7 (2%)	7 (2%)	7 (3%)	7 (2%)
Pain progression	46 (11%)	32 (8%)	44 (17%)	%)

Data are number (%). *Response assessments that could … change, or pain progression. … no

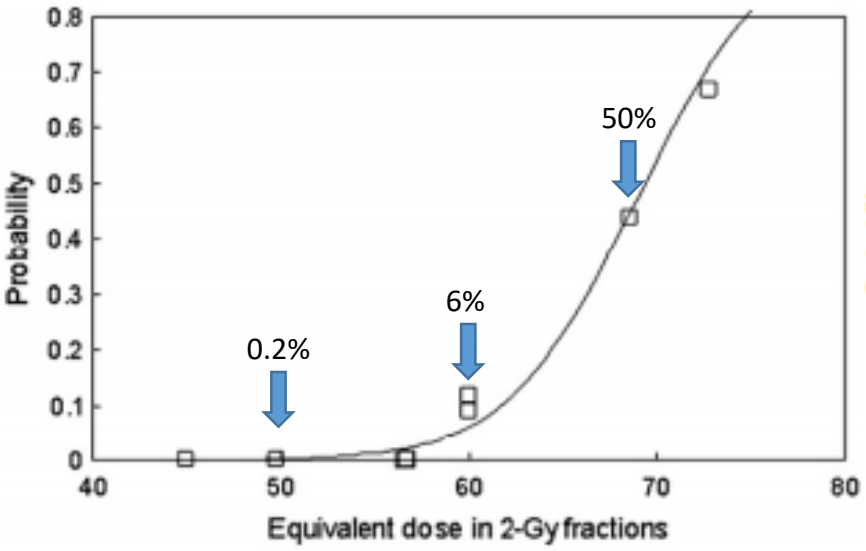
Morbidities	Single	Multiple	p
Loos of appetite	56%	66%	0.01
Diarrhoea	23%	31%	0.02
Pat. fracture	7%	5%	0.15
mSCCS	2%	<1%	0.09

Chow et al. Lancet Oncol 2014; 15: 164

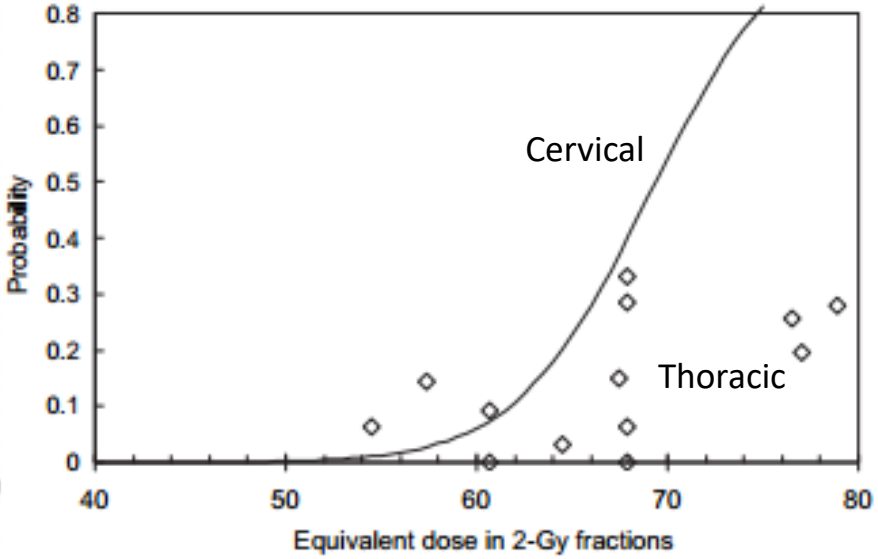
Spinal cord

Spinal cord radiation tolerance – primary RT

Cervical spine

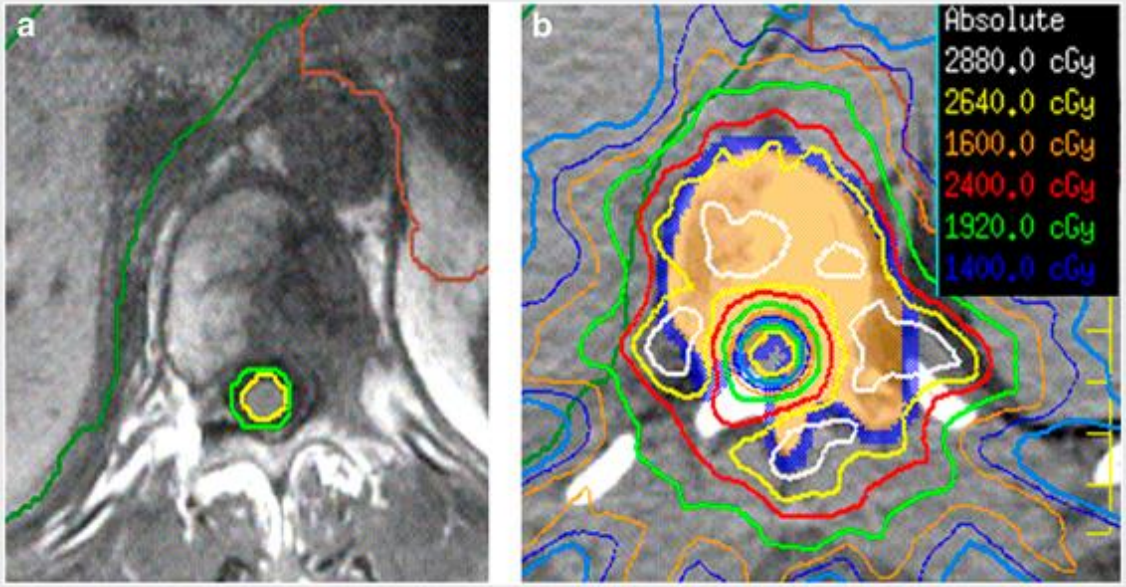


Cervical and thoracic spine



QUANTEC
Kirkpatrick IJOBP 2005;76(3 Suppl):S42

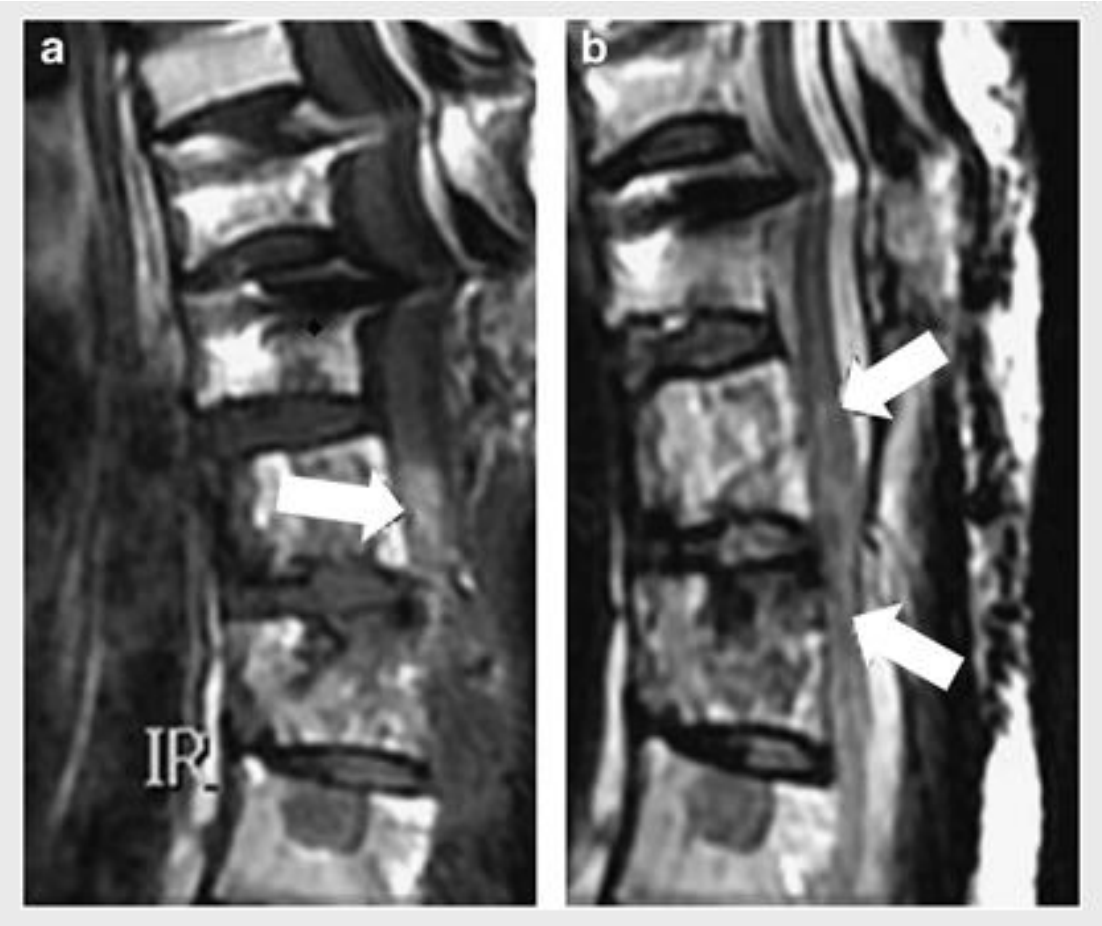
Radiation myelopathy



On the left (**a**) represents a spinal metastasis as imaged on a T1-weighted axial MRI. The planning organ-at-risk volume is the thecal sac (green) outlined with a 1.5 mm margin applied beyond the true cord (yellow). The disease involves the vertebral body, ipsilateral pedicle and lamina. The right panel (**b**) is the spine stereotactic radiation dose distribution targeting the entire vertebral body and ipsilateral posterior elements and demonstrates the dose wrapping around the spinal cord and the steep dose gradient. The prescription was 24Gy in two fractions and the spinal cord spared to a point maximum of 17Gy.

Wong et al. *Spinal Cord* (2015) **53,** 574

Radiation myelopathy

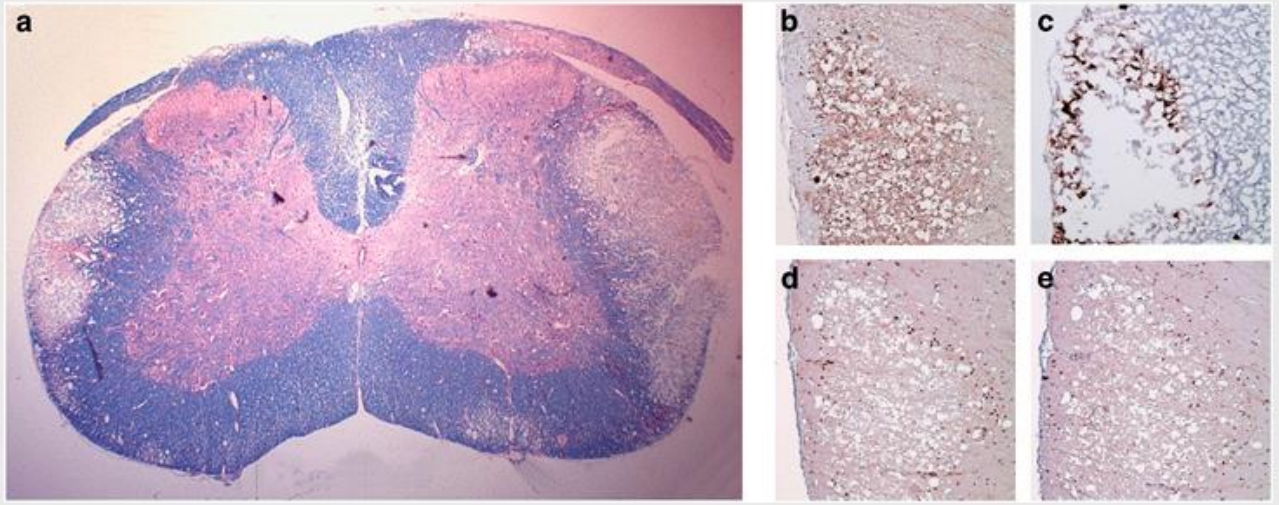


Spinal Cord (2015)
53, 574

MRI changes of radiation myelopathy. On the left (**a**) is a sagittal T1 postgadolinium MRI showing the area of enhancement within the cord (arrow) and on the right (**b**) is the T2-weighted image showing edema in the cord above and below the lesion (arrows). This patient developed a Brown–Séquard syndrome following spine stereotactic radiation treatment and represents a case of radiation myelopathy. A full color version of this figure is available at the *Spinal Cord* journal online.

Pathobiology of radiation myelopathy and strategies to mitigate injury
C S Wong, M G Fehlings and A Sahgal

Radiation myelopathy

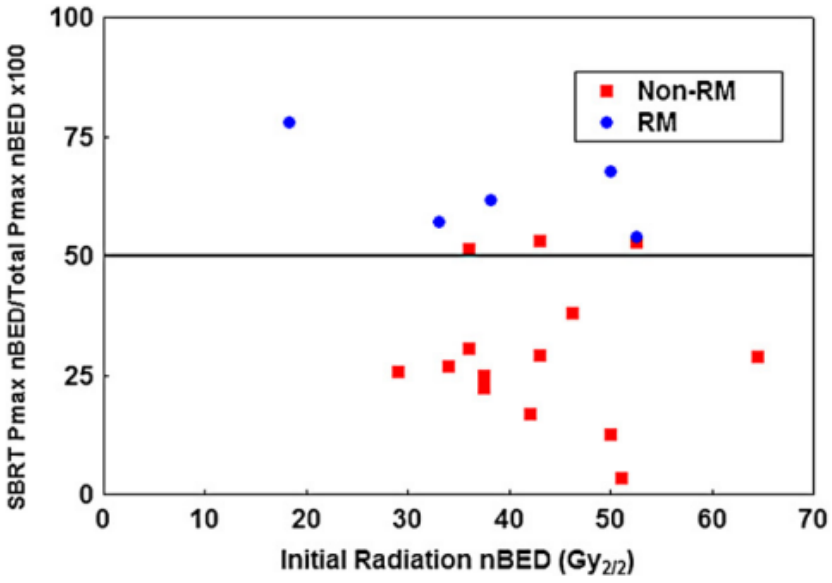


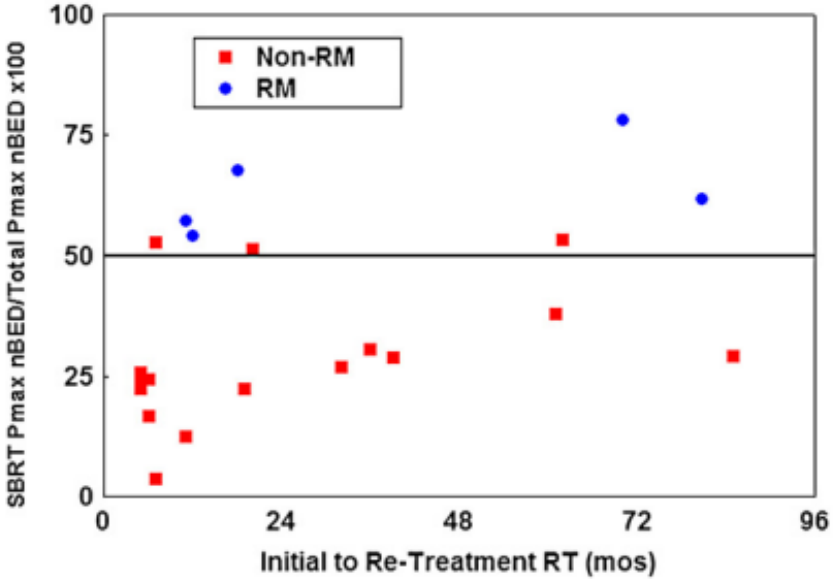
Molecular pathology of radiation myelopathy. Demyelination and focal to confluent necrosis represent the hallmark of radiation myelopathy, as demonstrated by the absence of Luxol blue staining in rat spinal cord white matter at 20 weeks after 22Gy (**a**, blue). White matter lesions are associated with disruption of the blood–spinal cord barrier shown by albumin leakage (**b**, albumin immunohistochemistry), tissue hypoxia (**c**, nitroimidazole EF5 immunohistochemistry) and upregulation of HIFα and VEGF, as demonstrated by an increase in reactive glia immunopositive for HIFα (**d**) and VEGF (**e**).

Wong et al. *Spinal Cord* (2015) **53,** 574

Spinal cord tolerance: re-irradiation

Min 6 months apart

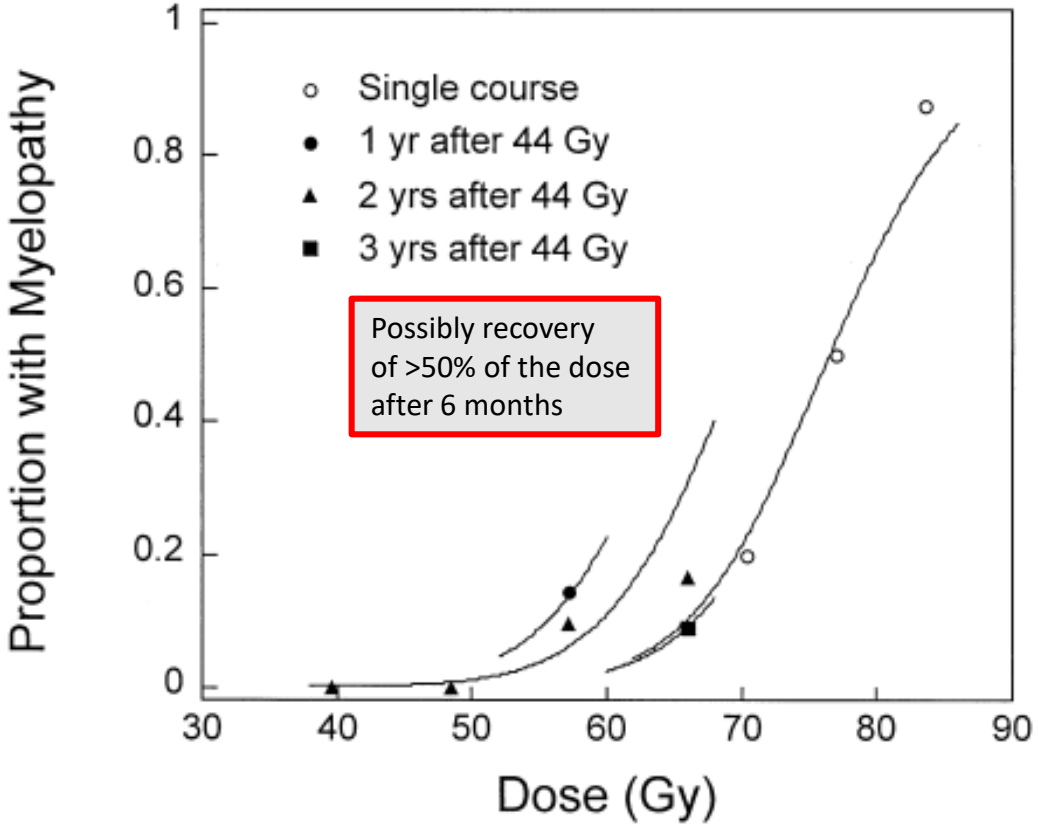




Sahgal et al. IJROBP 2012; 82(1): 107

Spinal cord re-irradiation tolerance

Repair kinetics in monkey
after 44 Gy (2.2 Gy/frx)



Ang et al IJROBP 2001 50(4):1013

Spinal cord tolerance

Review of radiation myelopathy

Table 1 SBRT point maximum dose limits to thecal sac

Prior radiation	*1 fx SBRT* P_{max} *limit*	*2 fx SBRT* P_{max} *limit*	*3 fx SBRT* P_{max} *limit*	*4 fx SBRT* P_{max} *limit*	*5 fx SBRT* P_{max} *limit*
None	12.4 Gy	17 Gy	20.3 Gy	23 Gy	25.3 Gy
20 Gy in 5 fx to 45 Gy in 25 fx	9 Gy	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
50 Gy in 25 fx	N/A	11 Gy	12.5 Gy	14 Gy	15.5 Gy
>50 Gy in 25 fx	N/A	N/A	N/A	N/A	N/A

Abbreviations: fx, fractions; N/A, not applicable, insufficient data to make SBRT dose limit recommendations; P_{max}, point maximum volume.

Wong et al. Spinal Cord (2015) 53, 574

SBRT re-irradiation of spinal cord

Safe SBRT re-irradiation

- Re-irradiation SBRT Pmax $EQD_{2/2}$ < 25 Gy
- Interval between courses > 5 mts.
- Initial RT dose < 50 Gy ($EQD_{2/2}$)
- Total $tEQD_{2/2max}$< 70Gy

Magnitude of risk of radiation myelitis in a patients reirradiated for painful spine metastases?

Course I: 30 Gy/10 frx.; course II: 30 Gy/10 frx; 6 months interval

$$D2 = \frac{d1 + (\frac{\alpha}{\beta})}{d2 + (\frac{\alpha}{\beta})} * D1$$

$$EQD2 = \frac{3+2}{2+2} * 30Gy = 37.5\ Gy$$

A) 20%

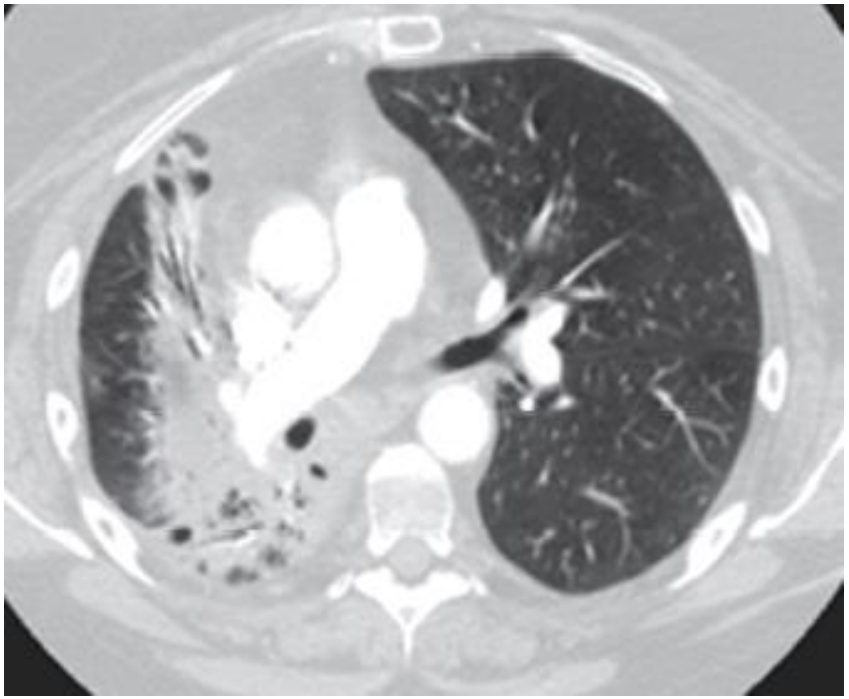
B) 5%

C) 2%

D) <1%

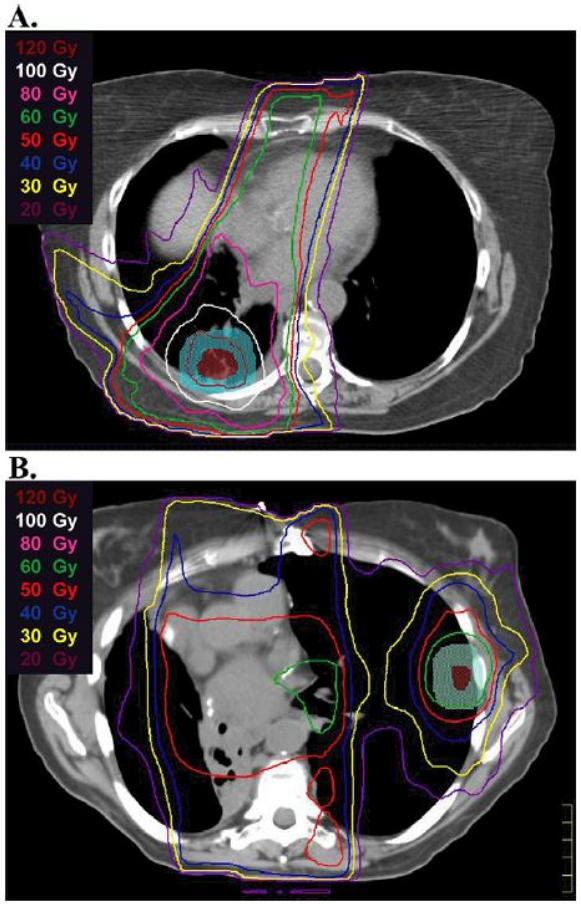
Repeat the vote on next slide!

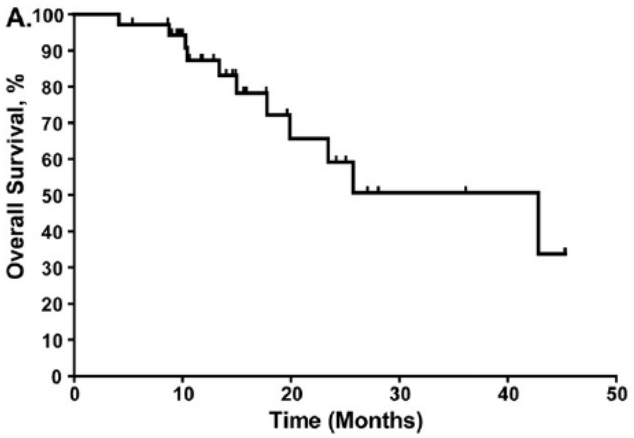
Lung

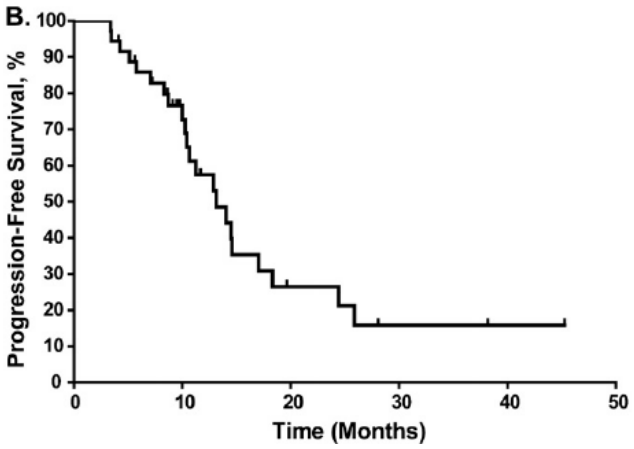


SBRT salvage after chemo-RT of lung cancer

In-field/out of field recurrences or second primary

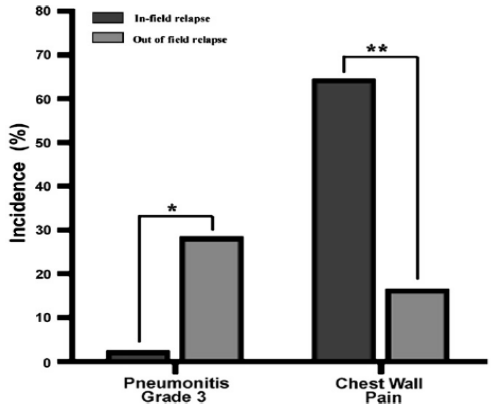






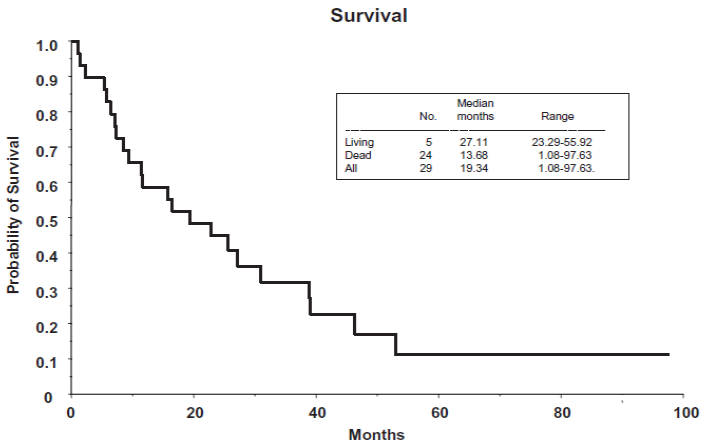
36 pts NSCLC
67% initial definitive RT
SBRT: 50 Gy/4 f.
Time interval 22 (0-90) mts.
Central/peripheral?

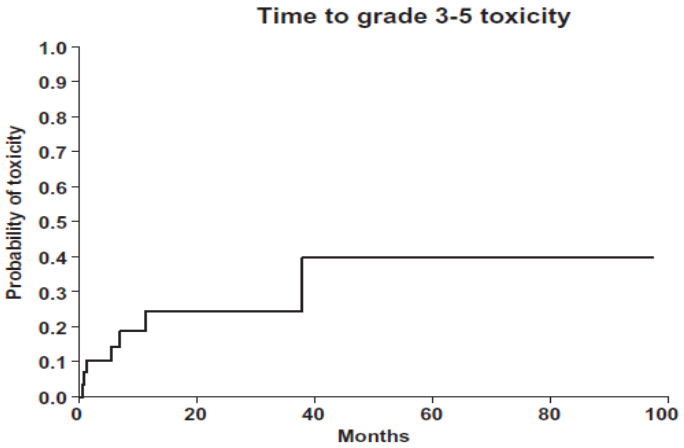
50% worsening of dyspnea
19% requiring oxygen
30% chest wall pain
3% esophageal scrinture



Kelly et al. IJROBP 2010;78(5):1387

SBRT salvage of central and peripheral lung cancer





29 patients
Interval 12 (1-97) mts.
Some with large volumes
3 pts 3 times
1 pt 4 times

Central $n = 11$						Peripheral $n = 18$				
Grade 1	Grade 2	Grade 3	Grade 4	Grade 5		Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
2	2	–	–	–	Atelectasis	1	3	–	–	–
1	1	3	–	–	Cough	2	6	–	–	–
1	1	1	–	–	Dyspnoea	–	5	3	–	–
–	1	1	–	–	Pneumonitis	–	2	–	–	–
–	–	1	–	–	Stenosis of airway	–	–	–	–	–
–	–	–	–	3	Bleeding	–	–	–	–	–
–	2	–	–	–	Pleural effusion	1	3	1	–	–
2	2	–	–	–	Pulmonary fibrosis	2	5	–	–	–
–	–	–	–	–	Fracture	1	–	–	–	–
–	1	–	–	–	Dermatitis	–	–	1	–	–
1	–	x	x	x	Hyperpigmentation	–	1	x	x	x
–	–	1	–	–	Pain	2	4	–	–	–
–	1	–	2	–	Other	–	1	–	–	–

Peulen et al. Radiother Oncol 2011;101:260

SBRT re-irradiation of lung

Safe SBRT re-irradiation

- Peripheral tumors
- Small volumes
- *OBS!*
  - COPD
  - Central (close to hilus, esophagus, large vessels)
  - Large volume
  - Chest wall
  - Same volume

Liver

Huang et al. Radiation Oncology (2016) 11:89
DOI 10.1186/s13014-016-0663-1

Radiation Oncology

RESEARCH Open Access

Clinical parameters for predicting radiation-induced liver disease after intrahepatic reirradiation for hepatocellular carcinoma

Yaoru Huang[1,3], Shang-Wen Chen[2,3], Ching-Chao Fan[4], Lai-Lei Ting[1,3], Chia-Chun Kuo[1,3] and Jeng-Fong Chiou[1,3*]

Conventional (2 Gy) frx.: 13/36 patients with HCC developed liver failure

Table 1 Characteristics of all patients

Variables	Patients with RILD $N = 13$	Patients without RILD $N = 23$
Interval between 2 courses (months) abutting score for two PTV	8.1 ± 8.1	12.6 ± 12.2
0	4	5
1	2	9
2	7	9
1st RT parameters		
Mean prescribed dose (EQD_2, Gy)	49.5 ± 8.2	52.5 ± 5.7
Mean CTV (cm3)	392.9 ± 407.0	345.2 ± 565.0
Mean PTV (cm3)	257.9 ± 207.8	314.4 ± 480.7
Mean normal liver dose (EQD_2, Gy)	20.8 ± 11.3	20.1 ± 8.2
Mean normal liver volume (cm3)	1255.5 ± 569.4	926.5 ± 242.4
2nd RT parameters		
Mean prescribed dose (EQD_2, Gy)	32.9 ± 14.5	40.6 ± 12.8
Mean CTV (cm3)	139.1 ± 150.2	211.3 ± 343.1
Mean PTV (cm3)	257.9 ± 207.8	314.4 ± 480.7
Mean normal liver dose (EQD_2, Gy)	12.3 ± 6.6	10.2 ± 5.5
Mean normal liver volume (cm3)	1173.4 ± 622.2	992.5 ± 196.1
Mean cumulative prescribed dose (EQD_2, Gy)	80.9 ± 17.8	94.4 ± 13.9
Mean cumulative normal liver dose (EQD_2, Gy)	32.5 ± 15.1	30.5 ± 9.6

Huang et al Radiat Oncol 2016; e-pub

Table 2 Risk factors associated with RILD after reirradiation

Variables	RILD (+)	RILD (–)	Univariate	Multivariate		
			p value	*p* value	OR	95 % CI
Total number	13	23				
Liver function before 2nd RT						
Total bilirubin ≧2.0 mg/dL	4	0	0.016			
Albumin ≦3.5 g/dL	8	4	0.007			
Presence of ascites	3	1	0.086			
INR ≧1.71	0	0				
CTP score ≧6	10	4	<0.0001	0.001	15.833	2.947 ~ 85.075
Presence of PVTT	8	5	0.017			
AST/ALT ≧3x of upper normal limit	5	1	0.088			
Hepatitis						
Hepatitis B infection	6	10	0.877			
Hepatitis C infection	2	6	0.458			
RT parameters of 2nd RT						
Mean CTV (cm^3)	158.8 ± 157.9	204.2 ± 348.7	0.740			
Mean PTV (cm^3)	257.9 ± 207.8	314.4 ± 480.7	0.260			
Mean normal liver dose (EQD_2, Gy_8)	12.0 ± 6.8	10.2 ± 4.8	0.726			
Mean normal liver volume (cm^3)	1173.4 ± 622.2	992.5 ± 196.1	0.332			
Interval between 2 courses (month)	8.1 ± 8.1	12.6 ± 12.3	0.247			
Mean cumulative normal liver dose (EQD_2, Gy_8)	32.0 ± 15.0	30.6 ± 9.7	0.233			
Mean cumulative prescribed dose (EQD_2, Gy_{15})	82.8 ± 15.9	90.6 ± 15.4	0.065			
Abutting score for two PTV	1.3 ± 0.9	1.1 ± 0.7	0.548			

Abbreviation: RILD radiation-induced liver disease, *OR* odds ratio, *CI* confidence interval, *CTP* Child-Turcotte-Pugh, *PVTT* portal vein tumor thrombosis, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CTV* clinical tumor volume, *NS* no significance, *EQD2* biologically equivalent doses calculated in 2Gy

Original Article
Radiat Oncol J 2015;33(4):276-283
http://dx.doi.org/10.3857/roj.2015.33.4.276
pISSN 2234-1900 · eISSN 2234-3156

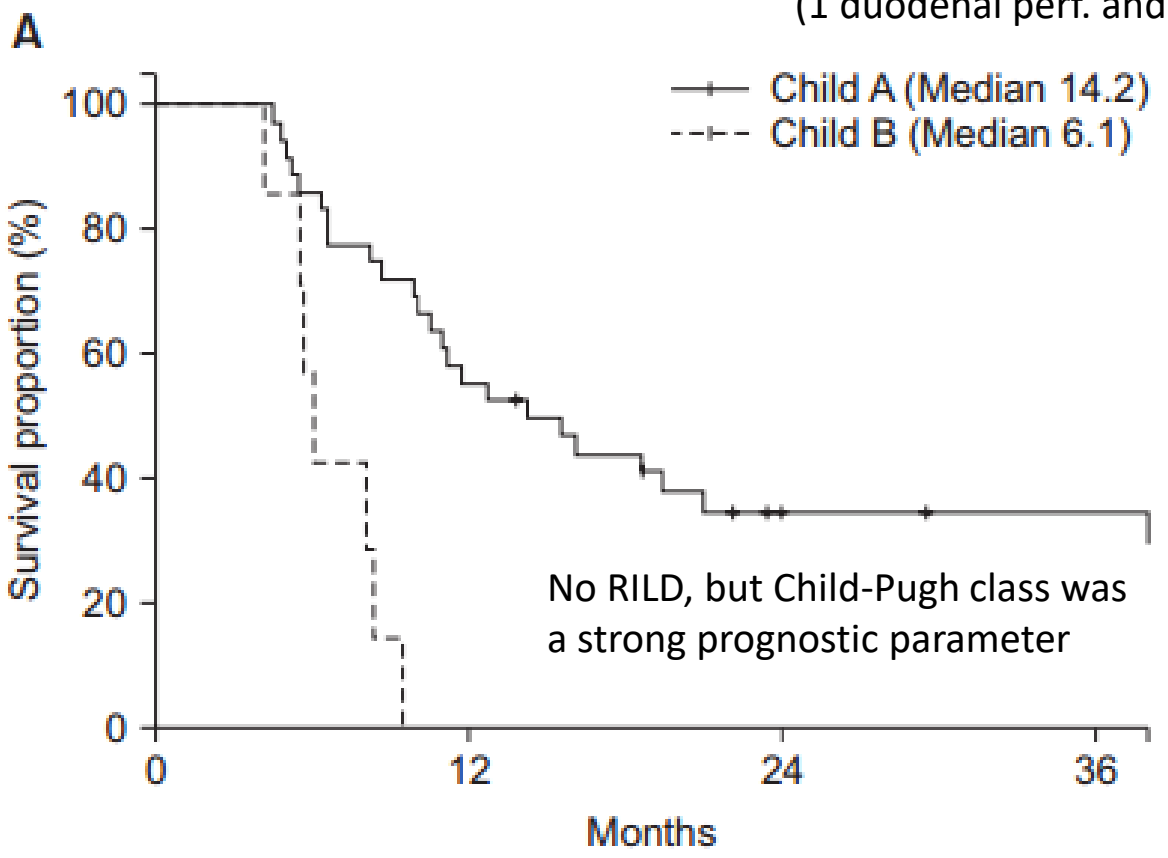
ROJ Radiation Oncology Journal

Treatment outcome of hepatic re-irradiation in patients with hepatocellular carcinoma

Seung Won Seol, MD, MS[1], Jeong Il Yu, MD[1], Hee Chul Park, MD, PhD[1], Do Hoon Lim, MD, PhD[1], Dongryul Oh, MD[1], Jae Myoung Noh, MD[1], Won Kyung Cho, MD[1], Seung Woon Paik, MD, PhD[2]

Departments of [1]Radiation Oncology and [2]Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

1st: 33-94 Gy_{10} (median 49 Gy_{10})
2nd: 31-94 Gy_{10} (median 44 Gy_{10})
Only 2 patient developed $\geq$ 3 tox
(1 duodenal perf. and 1 pneumonitis)



Re-irradiation for liver metastases

- 28 patients re-irradiated with SBRT for liver metastasis 3-30 months after primary SBRT
- No patients developed RILD

Høyer et al Aarhus University Hospital 2016

SBRT re-irradiation of liver cancer

Safe SBRT re-irradiation of **HCC**

- Child-Pugh A $\leq$ 6
- Limited volumes
- No recommendation on dose, volume and interval

Notice

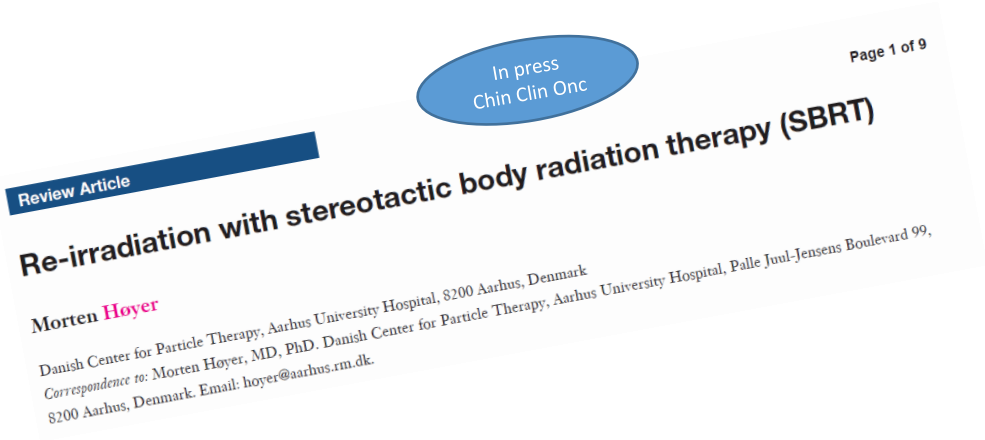
- Patients with portal hypertension have a high risk of peptic ulcer

Safe SBRT re-irradiation of liver **metastases**

- Limited volume
- Re-irradiation time interval >3 months
- No recommendation on dose and volume

Final conclusions

- Consider selection of the patients
  - Type and structure of the tissue (parallel/serial)
  - Volume
  - Previous dose
  - Overlap
  - Time interval
  - Summarize the plans
- Conservative dose
- Conservative fractionation


In press
Chin Clin Onc

Page 1 of 9

Review Article

Re-irradiation with stereotactic body radiation therapy (SBRT)

Morten Høyer

Danish Center for Particle Therapy, Aarhus University Hospital, 8200 Aarhus, Denmark

Correspondence to: Morten Høyer, MD, PhD. Danish Center for Particle Therapy, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus, Denmark. Email: hoyer@aarhus.rm.dk.

Terminal care

Johan Menten

Radiation Oncology & Palliative Care

University Hospital Gasthuisberg

Leuven (Belgium)

How / Do we recognize the terminal patient ?

WIKIPEDIA:

"terminal illness is a disease that cannot be cured or adequately treated and that is reasonably expected to result in the death of the patient within a short period of time "

UK Social Security legislation

terminal illness is defined as: "a progressive disease where death as a consequence of that disease can reasonably be expected within 6 months".

Mosby's Medical Dictionary, 9th edition. © 2009, Elsevier.

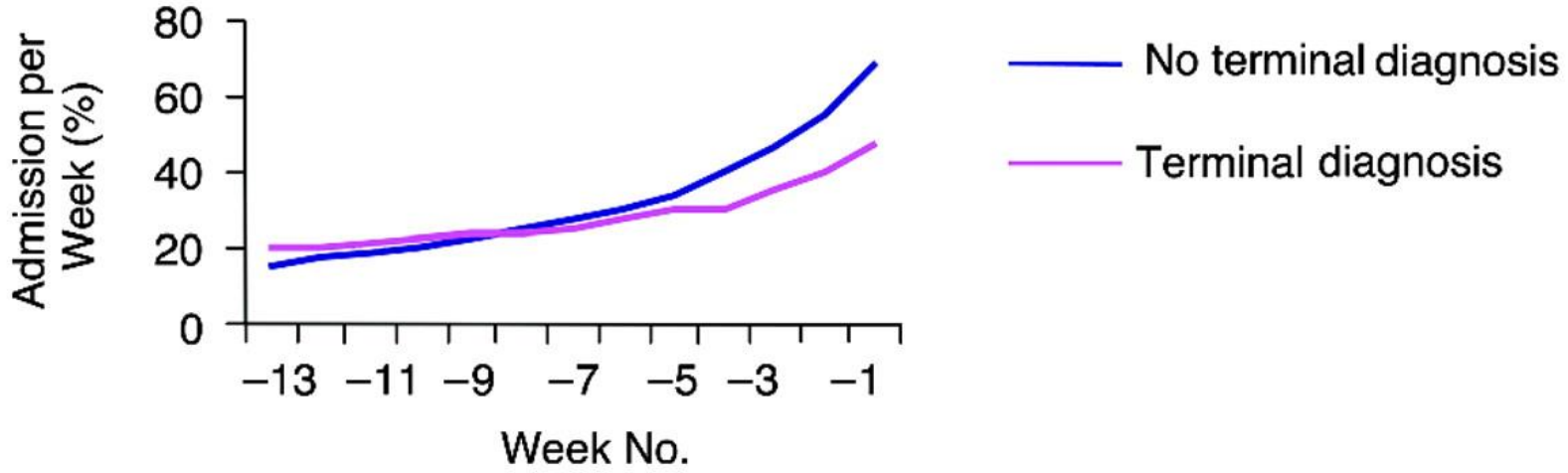
"Terminal illness is a malignancy which is expected to cause the patient's death in a short period of time—i.e., weeks to several months"

Defining Cancer Patients As Being in the Terminal Phase: Who Receives a Formal Diagnosis, and What Are the Effects?

The Danish “terminal declaration” issued by a physician for a formal terminal diagnosis (prognosis of death within 6 months) gives right to economic benefits and increased care for the dying

Aabom et al. JCO 2005;23:7411-7416

Effect of terminal diagnosis on admissions per week.



Conclusion:

1 Women and the elderly were less likely to receive a formal terminal diagnosis.

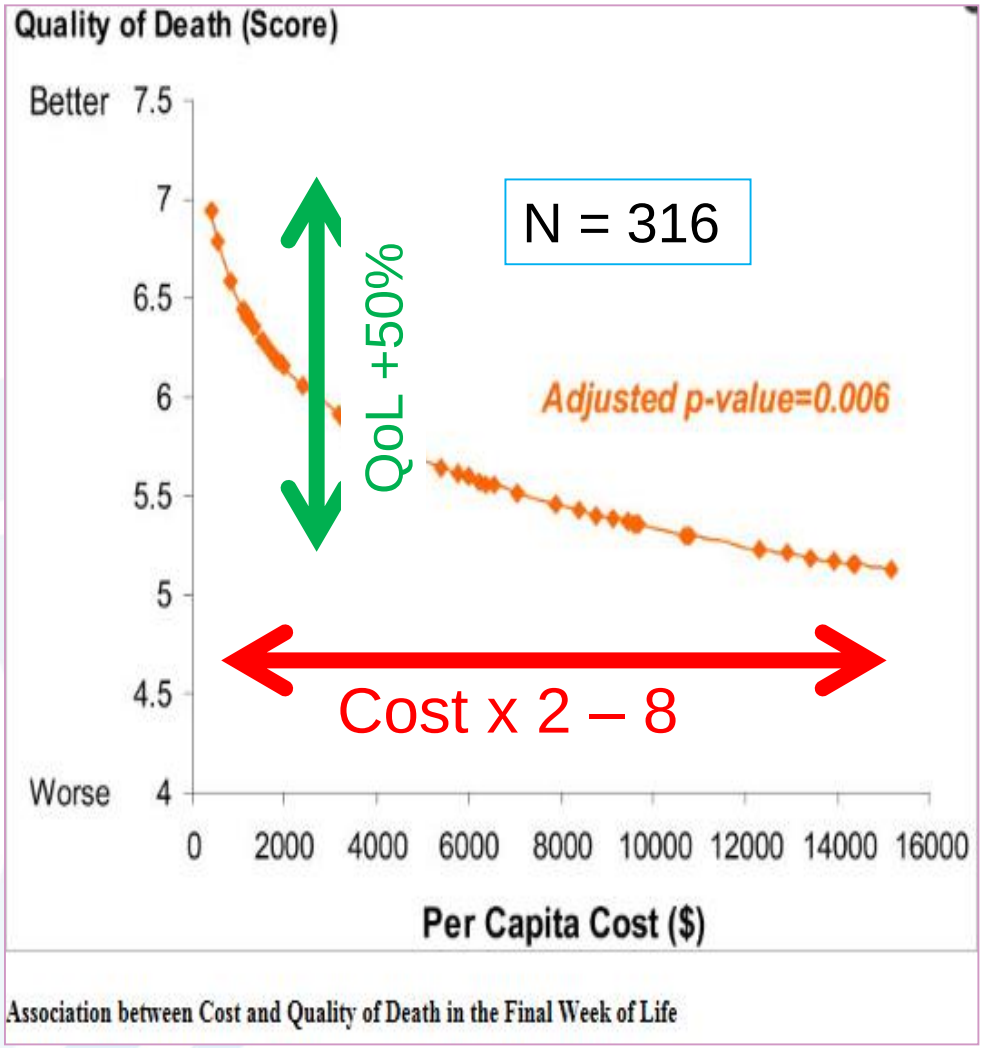
2 The formal terminal diagnosis reduced hospital admissions and increased the possibilities of dying at home.

B. Aabom et al. JCO 2005;23:7411-7416

Arch Intern Med. 2009 Mar 9;169(5):480-8

Health care costs in the last week of life: associations with end-of-life conversations

Zhang B1, Wright AA, Huskamp HA, Nilsson ME, Maciejewski ML, Earle CC, Block SD, Maciejewski PK, Prigerson HG



Association between Cost and Quality of Death in the Final Week of Life

Socio-demographic characteristics of
-age,
-race,
-gender,
-education,
-survival time,
-and source of report,
were controlled for in the adjusted analyses per capita cost predicting quality of death in the deceased cohort.

Funded by the National Institute of Mental Health
and the National Cancer Institute - USA

Systematic Review of Cancer Presentations with a Median Survival of Six Months or Less

Shelley R. Salpeter, M.D., Dawn S. Malter, M.D., Ph.D., Esther J. Luo, M.D.,Albert Y. Lin, M.D., and Brad Stuart, M.D.

Despite different cancer characteristics,
a fairly universal picture of terminal disease included :

1- decreasing performance status,
2- advancing age,
3- weight loss,
4- metastatic disease,
5- disease recurrence,
6- laboratory abnormalities indicating extensive disease.

Most of these **prognostic indicators** found were continuous, independent risk factors for mortality.

We found little evidence that treatment improved survival at these terminal stages, with increased risk for toxicity.

JOURNAL OF PALLIATIVE MEDICINE Vol, 15, No 2, 2012

Systematic Review of Cancer Presentations with a Median Survival of Six Months or Less

Shelley R. Salpeter, M.D., Dawn S. Malter, M.D., Ph.D., Esther J. Luo, M.D.,Albert Y. Lin, M.D., and Brad Stuart, M.D.

with relatively good prognosis and treatment options,

such as breast cancer, become terminal

-when the patient manifests KPS less than 60%

or

-at least three prognostic factors

while cancers with poor prognosis, such as biliary cancers, become terminal

-with KPS less than 90%

or

-1 prognostic factor

Our review of studies from 1980 to 1998 showed that survival for these presentations has not changed significantly over the past 30 years, despite many treatment advances.

JOURNAL OF PALLIATIVE MEDICINE Vol, 15, No 2, 2012

ESTRO School

Palliative Prognostic Index: PPI

The PPI is quick and easy to use,
can be applied to patients with cancer,
in hospital, in hospice and at home.

It may be used by general physicians
to achieve prognostic accuracy comparable,
if not superior,
to that of physicians experienced in oncology

Palliative Prognostic Index: PPI

Performance status/Symptoms	Partial score
Palliative Performance Scale	
10–20	4
30–50	2.5
≥60	0
Oral Intake	
Mouthfuls or less	2.5
Reduced but more than mouthfuls	1
Normal	0
Edema	
Present	1
Absent	0
Dyspnea at rest	
Present	3.5
Absent	0
Delirium	
Present	4
Absent	0

Scoring

PPI score
> 6 : survival < 3 weeks
> 4 : survival < 6 weeks
≤ 4 : survival > 6weeks

Prospective Validation of the Palliative Prognostic Index in Patients with Cancer.
Stone, C ,Tierman, E., & Dooley, B., Journal of Pain and Symptom Management, 2008,Vol. 35, No. 6, 617–622

Systematic Review of Cancer Presentations with a Median Survival of Six Months or Less

Shelley R. Salpeter, M.D., Dawn S. Malter, M.D., Ph.D., Esther J. Luo, M.D.,Albert Y. Lin, M.D., and Brad Stuart, M.D.

TABLE 4. PERFORMANCE STATUS SCORE[a]

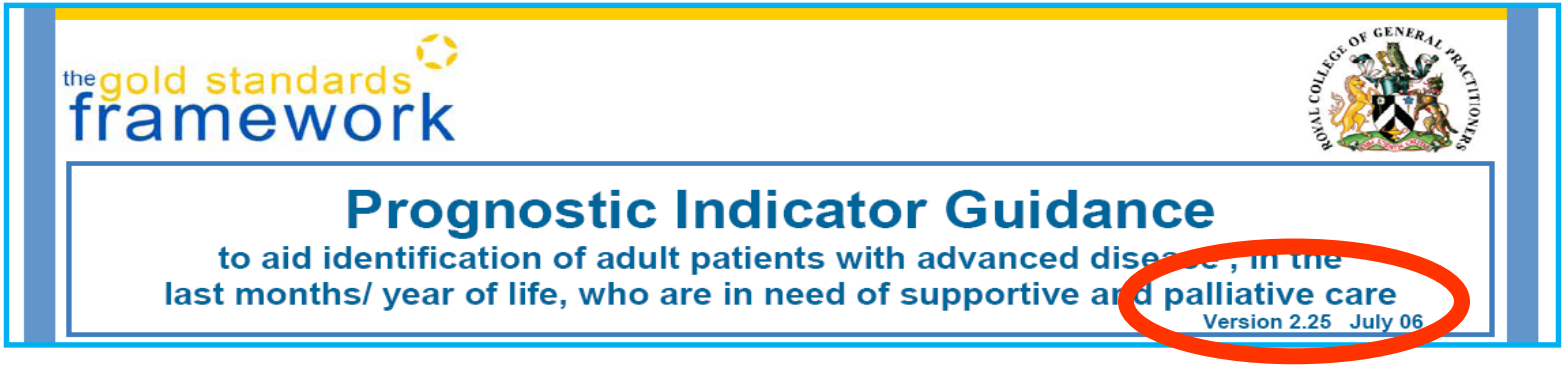
ECOG	*Level of functional capacity*	*Karnofsky*	*Level of functional capacity*
0	Fully active, able to carry on all predisease performance without restriction	100	Normal, no complaints, no evidence of disease
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.	90	Able to carry on normal activity, minor signs or symptoms of disease
		80	Normal activity with effort, some signs or symptoms of disease
2	Ambulatory and capable of all self-care but unable to carry out any work activity. Up and about more than 50% of waking hours	70	Cares for self, unable to carry on normal activity or to do active work
		60	Requires occasional assistance, but is able to care for most needs
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	50	Requires considerable assistance and frequent medical care
		40	Disabled, requires special care and assistance
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair	30	Severely disables, hospitalization is indicated although death is not imminent
		20	Hospitalization is necessary, very sick, active supportive treatment necessary
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

[a]Karnofsky Performance Status[10,12,13] and Eastern Cooperative Oncology Group (ECOG) performance status scale.[14]

JOURNAL OF PALLIATIVE MEDICINE Vol, 15, No 2, 2012

ESTRO School

How to identify the palliative care patient ?



Indications to start palliative care :

1-Surprise question:

"Would You be surprised if this patient is dying within 6-12m?"

or

2-What are the wishes and needs of this patient?

or

3- Are there clinical indicators of progressing disease:

cancer – organ failure - frailty (±dementia)

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Co-morbidities or other General Predictors of End Stage illness[1,2]

Co-morbidity is increasingly the biggest predictive indicator of mortality and morbidity. Also-

- Weight loss - Greater than 10% weight loss over 6 months
- General physical decline
- Serum Albumin < 25 g/l
- Reducing performance status / ECOG/Karnofsky score (KPS) < 50%. Dependence in most activities of daily living(ADLs)

1. Cancer Patients

Cancer[3]

Any patient whose cancer is metastatic or not amenable to treatment, with some exceptions – this may include some cancer patients from diagnosis e.g. lung cancer. 'The single most important predictive factor in cancer is performance status and functional ability' – if patients are spending more than 50% of their time in bed/lying down, prognosis is estimated to be about 3 months or less. More exact predictors for cancer patients are available elsewhere on the GSF website.

2. Organ Failure Patients

2.1 Heart Disease - CHF [4]

At least two of the indicators below :-

- CHF NYHA stage III or IV – shortness of breath at rest or minimal exertion
- Patient thought to be in the last year of life by the care team - the 'surprise' question
- Repeated hospital admissions with symptoms of heart failure
- Difficult physical or psychological symptoms despite optimal tolerated therapy

2.2 Chronic Obstructive Pulmonary Disease – COPD [5]

- Disease assessed to be severe e.g. (FEV1 <30%predicted – with caveats about quality of testing)
- Recurrent hospital admission (>3 admissions in 12 months for COPD exacerbations)
- Fulfils Long Term Oxygen Therapy Criteria
- MRC grade 4/5 – shortness of breath after 100 meters on the level or confined to house through breathlessness
- Signs and symptoms of right heart failure
- Combination of other factors e.g. anorexia, previous ITU/NIV/resistant organism, depression
- >6 weeks of systemic steriods for COPD in the preceding 12 months

2.3 Renal Disease [6]

- Patients with stage 5 kidney disease who are not seeking or are discontinuing renal replacement therapy. This may be from choice or because they are too frail or have too many co-morbid conditions.
- Patients with stage 5 chronic kidney disease whose condition is deteriorating and for whom the one year 'surprise question' is applicable ie overall you would not be surprised if they were to die in the next year?
- Clinical indicators:
  - CKD stage 5 (eGFR <15 ml/min)
  - Symptomatic renal failure - Nausea and vomiting, anorexia, pruritus, reduced functional status, intractable fluid overload)
- Increasingly severe symptoms from comorbid conditions requiring more complex management or difficult to treat

NB. many people with Stage 5 CKD have stable impaired renal function and do not progress or need RRT.

2.4 Neurological Disease - a) Motor Neurone Disease[7]

MND patients should be included from diagnosis, as it is a rapidly progressing condition

Indicators of rapid deterioration include:

- Evidence of disturbed sleep related to respiratory muscle weakness in addition to signs of dyspnoea at rest
- Barely intelligible speech
- Difficulty swallowing
- Poor nutritional status
- Needing assistance with ADL's
- Medical complications eg pneumonia, sepsis
- A short interval between onset of symptoms and diagnosis
- A low vital capacity (below 70% of predicted using standard spirometry)

http://www.gpscbc.ca/sites/default/files/Gold%20Standard%20Framework-Prognostic%20Indicator%20Guidance.pdf

Co-morbidities or other General Predictors of End Stage illness

Co-morbidity

is increasingly the biggest predictive indicator of mortality and morbidity.

Also-

- **Weight loss** - Greater than 10% weight loss over 6 months
- **General physical decline**
- **Serum Albumin** < 25 g/l
- **Reducing performance status** / ECOG/Karnofsky score (KPS) < 50%. Dependence in most activities of daily living(ADLs)

Disease specific predictors of end stage illness in cancer

Any patient whose cancer is metastatic and not amenable to treatment, with some exceptions – this may include some cancer patients from diagnosis e.g. lung cancer.

'The single most important predictive factor in cancer is performance status and functional ability' – if patients are spending more than 50% of their time in bed/lying down, prognosis is estimated to be about 3 months or less.

3. Patients with Frailty and Dementia

Frailty [10]

- Multiple comorbidities with signs of impairments in day to day functioning
- Deteriorating Karnofsky score
- Combination of at least 3 symptoms of: weakness, slow walking speed, low physical activity, weight loss, self reported exhaustion

Dementia [11]

- Unable to walk without assistance, and
- Urinary and fecal incontinence, and
- No consistently meaningful verbal communication, and
- Unable to dress without assistance
- Barthel score < 3
- Reduced ability to perform activities of daily living

Plus any one of the following:

10% weight loss in previous six months without other causes, Pyelonephritis or UTI, Serum albumin 25 g/l, Severe pressure scores eg stage III / IV, Recurrent fevers, Reduced oral intake / weight loss, Aspiration pneumonia

Stroke [12]

- Persistent vegetative or minimal conscious state / dense paralysis / incontinence
- Medical complications
- Lack of improvement within 3 months of onset
- Cognitive impairment / Post-stroke dementia

Palliative –Terminal care algorythme

Identification of the palliative patient

1. “Surprise question” 2. Wish/ need of the pt 3. clinical indicators

Cancer

Organ failure

1. Heart failure
2. COPD
3. Renal failure disease
4. Motor neuron
5. Z v Parkinson sclerosis
6. Multiple

Elderly & dementia

1. Frailty 2. Dementia 3. CVA

1 Childhood
2 Psychiatr. pt.

3 steps in GSF (+ optimal communication) :

1 Patient identification.

2 Assessment of needs/wishes

3 Planning of care ~ prognosis.

GSF : **5 goals to reach qualified care**

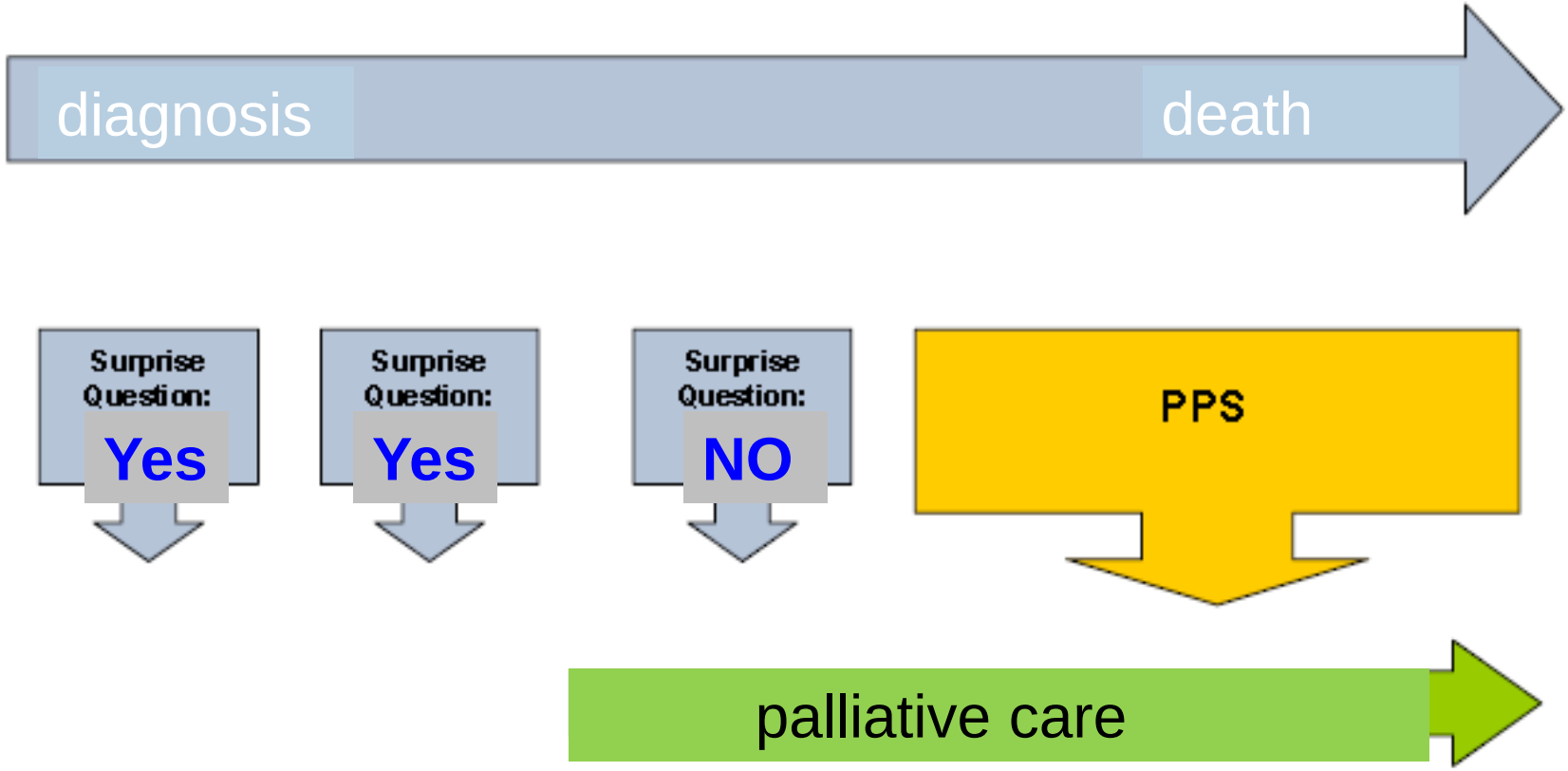
1 optimal symptom control.

2 Place of care: desired ⟷ realistic

3 Safety and support: pro-active, information➔ less anxiety, less unwanted investigation/treatment, less hospitalisation.

4 Care and information for caregivers

5 Communication and collaboration becomes better


diagnosis
death
Surprise Question:
Yes
Surprise Question:
Yes
Surprise Question:
NO
PPS
palliative care

The **7 Key messages – or core tasks** (or quality standards),

7 C's, according to GSF:

C1 -Communication: ask for symptom control/wishes in every contact!!!

C2 -Coordination: who can be contacted for questions/problems?

C3 -Control of symptoms: evaluate treatment effect

C4 -Continuity (incl. 'out of hours' (≠ *voice mail*))

C5 -Continued learning: stay at the "state of the art"

C6 -Carer support: for your team and for yourself

C7 -Care in the dying phase: for patient (+family + carers+ bereavement)

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There is no strong
evidenced based medicine
about
medical decision making at the end of life.

Medical decision making in palliative care

There is a need for prospective randomised trials in palliative care and end of life issues!?

But:

-Trials measure only what is measurable
and not always what is meaningfull (QoL) !

-Moral and ethical issues are always coming up NOT to do clinical trials in this group of very frail patients!

Is it not immoral and unethical if no research
is done to solve the many difficult questions at the end of life?

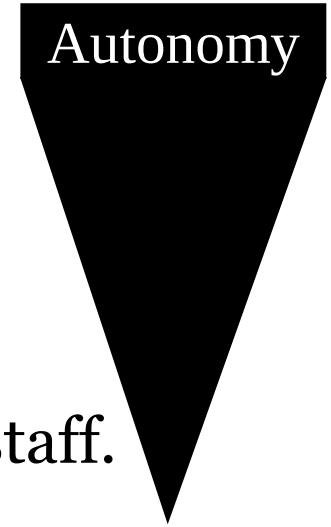
Medical decision making in palliative care

Some patients make decisions:

- only by themselves.

- with advice from medical and nursing staff.

- in collaboration with medical and nursing staff.



Others want

- that their doctors make the decisions for them.

Medical decision making in palliative care

How decide patients at the end of their life ?

9% decides self (= complete autonomy)

73% collaborate

younger, better educated, fitter patients

⇒ seraching for agreement between patients' preferences and physicians views

18% follow the decision of the physician

Oral presentation of a Study in London
Research congress EAPC dec 2000 Berlin

Medical decision making in palliative care

Patients at the end of life want :

to be treated as patients

-with dignity

-as they were (profession, social status, age,…)

-as an individual

to be known and respected

to be helped to avoid dehuminisation

Medical decision making in palliative care

Most patients want:

-not to be kept alive to all costs (not die in ICU)
-to die peacefully and with dignity
-to die at home (⇒ but, burden for family!?)
-to die pain free (⇒ or don't,
to avoid somnolence, confusion, …)

Medical decision making in palliative care

What does this patient want?

What does this patient NOT want?

“What is now troubling you?”

“What is most important at this moment of your life?”

“Look beyond stereotypes,
but to the individual patient !!”

Medical decision making in palliative care

-Help the patient / family to find their solution

-The physician / caregiver is katalysator,
not messanger / bringer of standard solutions.

-Avoid medicalisation of the dying process

Medical decision making in palliative care

Check what the patient wants,

not once

but at regular times

and give answers to their questions, not to ours.

End of life = a dynamic process !!

Medical decision making in palliative care

What patients want, is influenced by their:

- own history and experiences
- individual values
-wishes and dislikes

Medical decision making in palliative care

Who can give patients:

-information they want ? (Not all has to be told !)
-information they can understand ?
-repeated information ?
-time (or give at least the impression to have time) ?

public interest ?

Medical decision making in palliative care

The statement at the end of the ‘70 :

“We ‘ll kill cancer… !”

It was a wrong statement …

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Medical decision making in palliative care

The statement of the ‘80 :

> “If you can’t kill the tumour,
> kill the pain … !”

It was at least a partially wrong statement …

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Medical decision making in palliative care

The statement after 2000:

> "If you can't kill the tumour,
> and you can't kill the pain,
> kill patient … !"

Will this be the right statement … ?

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Objectively observable signs of imminently dying in palliative patients

A prospective cohort study in 8 palliative care units

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University Hospital Gasthuisberg, Leuven

[2]Center of hospital and nursing sciences,

Catholic University Leuven

[1]Flemisch Federation of Palliative Care

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Objectively observable signs of imminently dying in palliative patients

	Mon		Tues		Wen		Thur		Fri		Sat		Sun	
	M	E	M	E	M	E	M	E	M	E	**M**	E	**M**	E
cold +/or white nose														
cold extremities					x	x								
cyanotic lips			x	x	x	x								
livid spots														
death rattle					x	x								
apnoe (>15"/min)														
oliguria (<300 cc/24h)						x								
somnolence (>15h/24h)														

Death 02.45 am

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Objectively observable signs of imminently dying in palliative patients

Results of this pilote study (n = 80)

➔ **Research group**

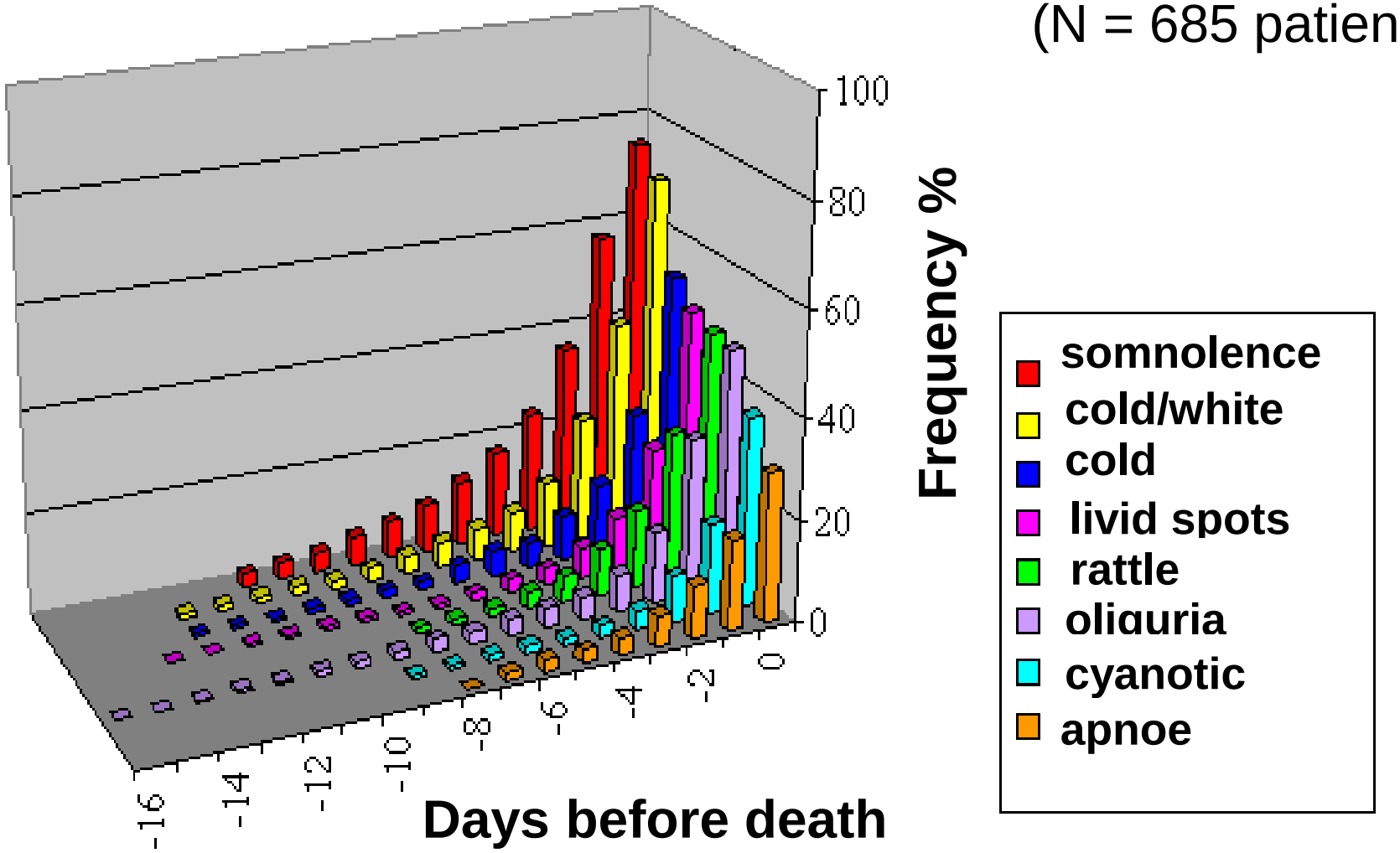
Flemisch Federation of Palliat. Care

Multicenter prospective study

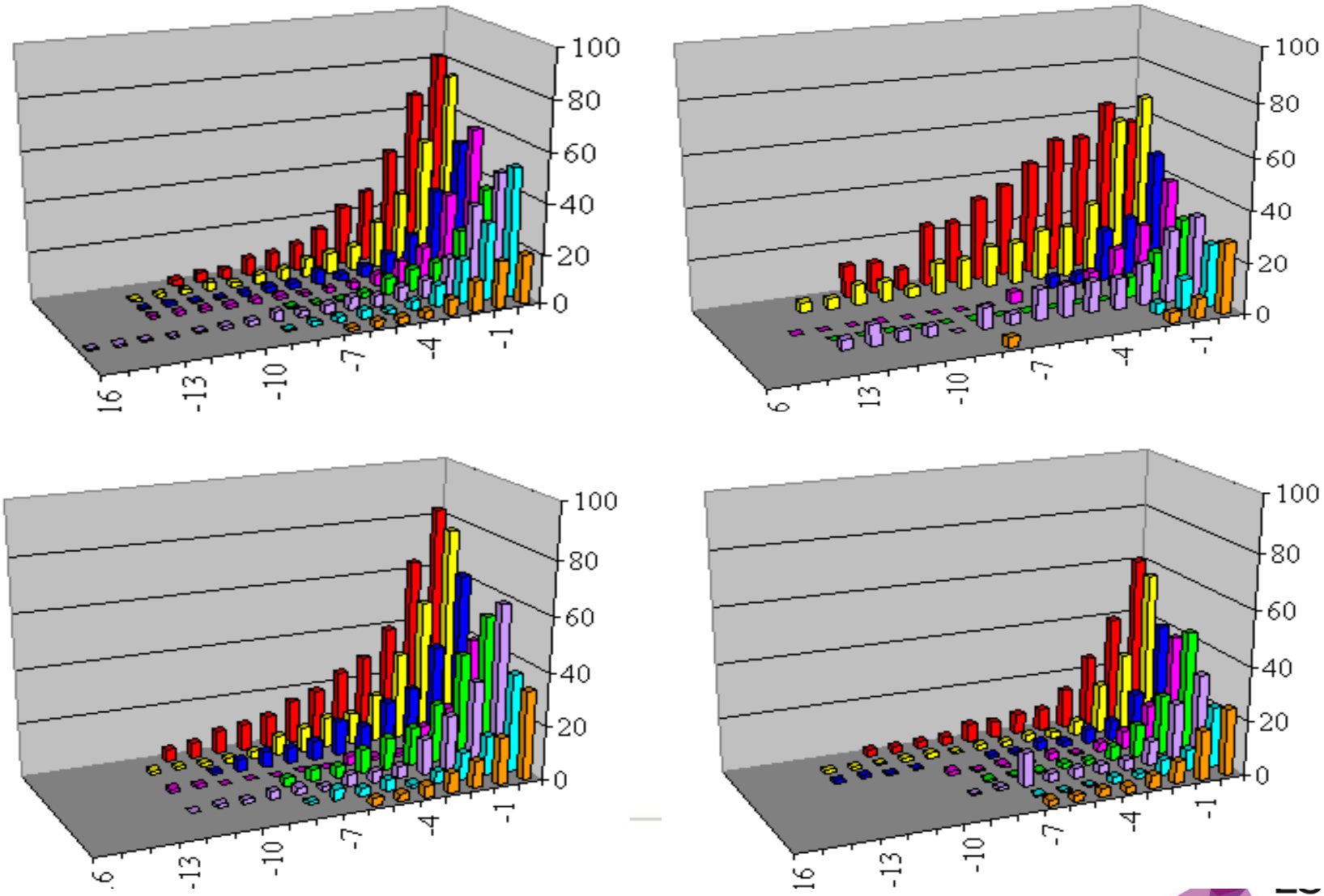
in 8 palliative care units (n = 685)

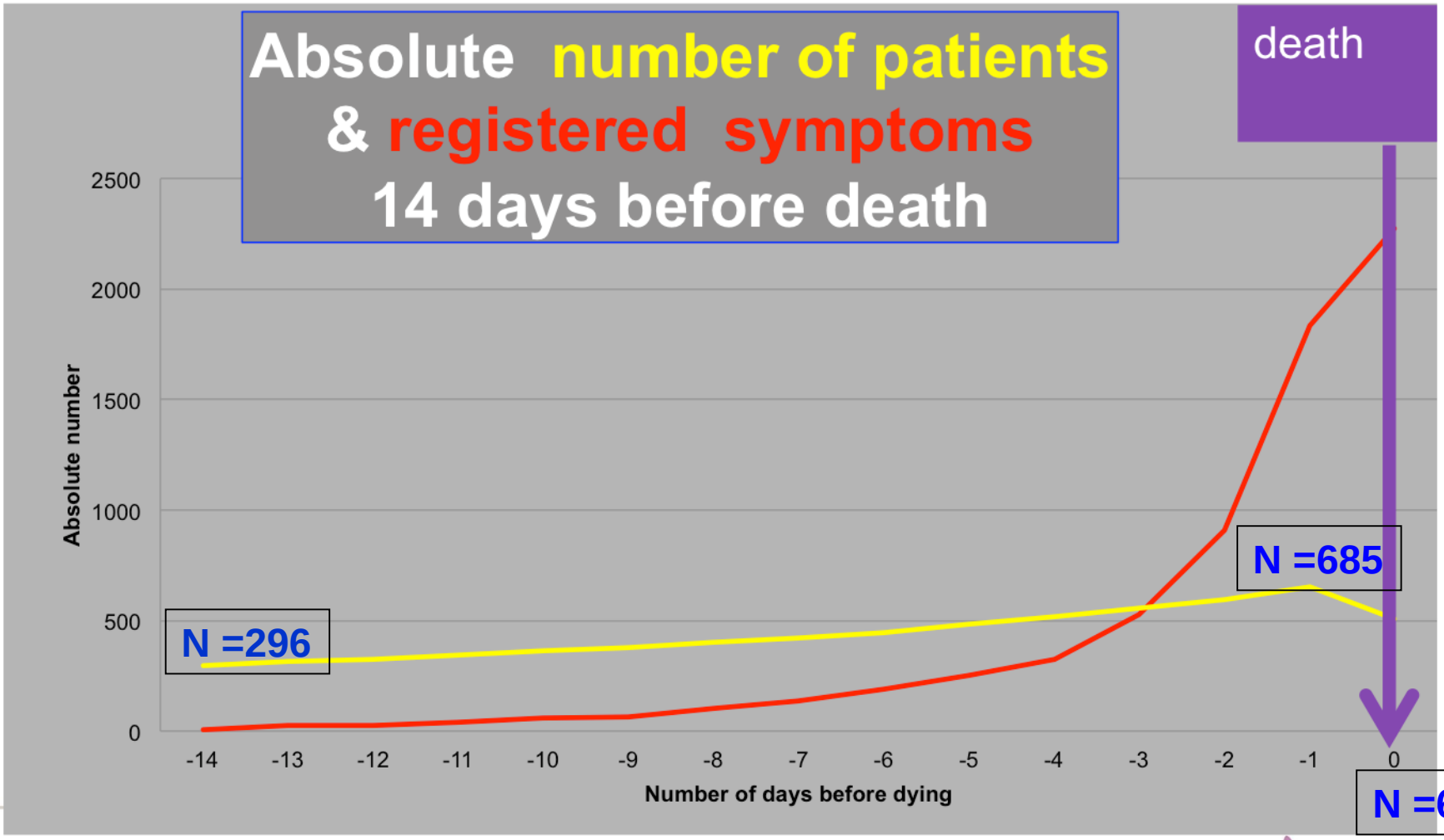
Objectively observable signs of imminently dying in palliative patients

(N = 685 patients)



Objectively observable signs of imminently dying in palliative patients





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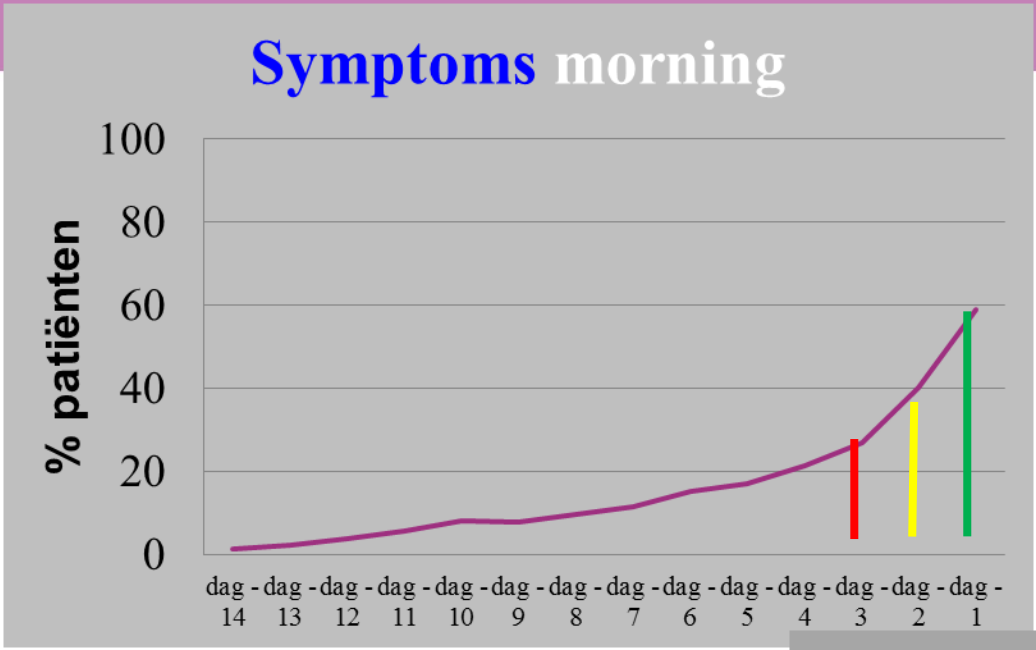
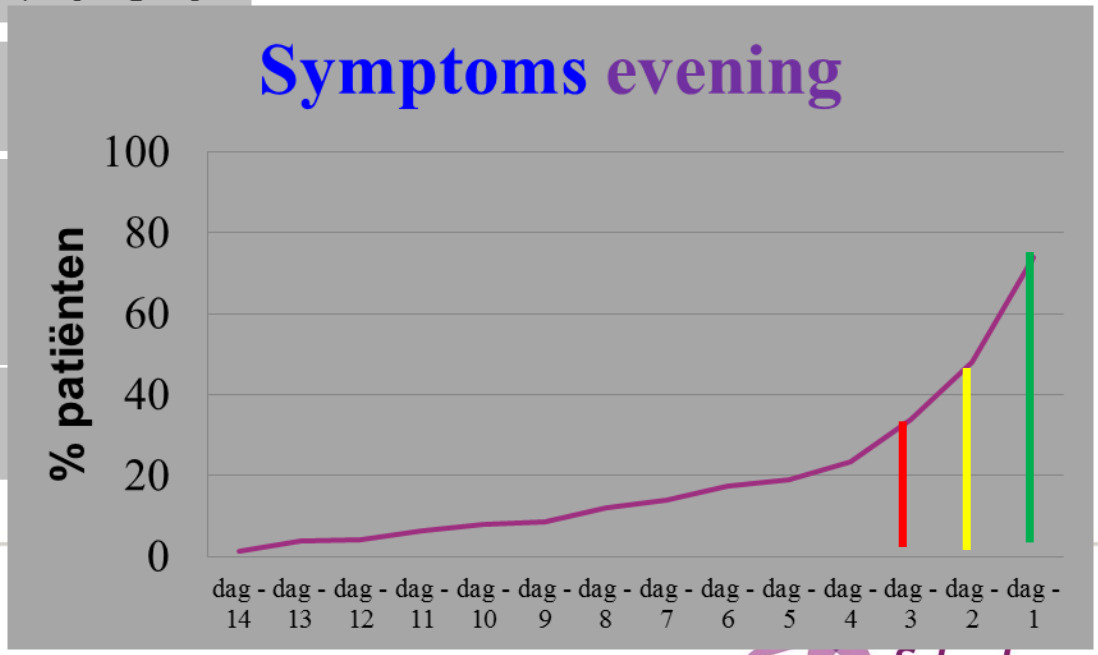


%	d-3	d-2	d-1	d0
Morning	27	40	59	92
Evening	33	47	74	



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Objectively observable signs of imminently dying in palliative patients

Results

-Somnolence is the most prevalent sign ➔ inform patients

-Oliguria and livid spots occurred the most early

-Death rattle and apnoea appeared most close to actual death

Objectively observable signs of imminently dying in palliative patients

Conclusion:

- Death ~ reproducible predictable within days

for terminal pal. pts by 8 obj. signs in standard nursing care.

-This study proved that clinical research is feasible in palliative care, necessary and useful.

Treatment terminal patient

Stop useless medication

It opens doors for communication.

Only medication that makes a difference today

Treatment terminal patient

Published studies indicate that
"within the context of adequate palliative care,
the refusal of food and fluids
does not contribute to suffering among the terminally ill",

and might actually contribute to a comfortable passage from life: "At least for some persons, starvation does correlate with reported euphoria."[11]

Patient Refusal of Nutrition and Hydration: Walking the Ever-Finer Line
American Journal Hospice & Palliative Care, pp. 8-13, March/April 1995

Pacemaker in terminal patients

Background

-Is it possible that a pacemaker postpones cardiac arrest in the dying patient,

➔ longer time to die for patients with a pacemaker

-If yes, do we have to switch of the pacemaker?

Method

Patients that died in the PCU in UH Leuven

Database = **3011 patients (1999- 2015)**

Pacemaker patients **n = 83**

2 matched patients for each pm-patient **(n = 163)**

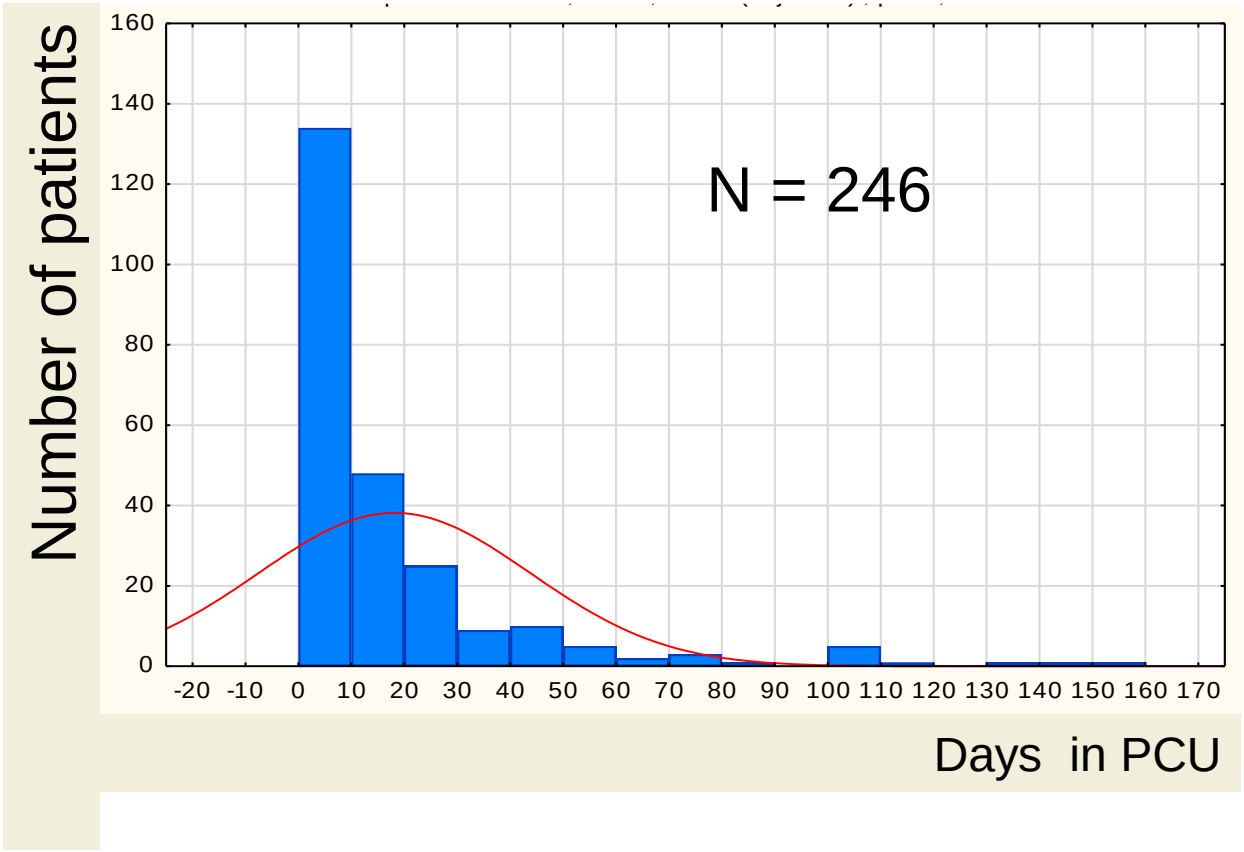
- 1 pt. died within 6 m before the pm patient
- 1 pt. died within 6 m after the pm-pt

Same age

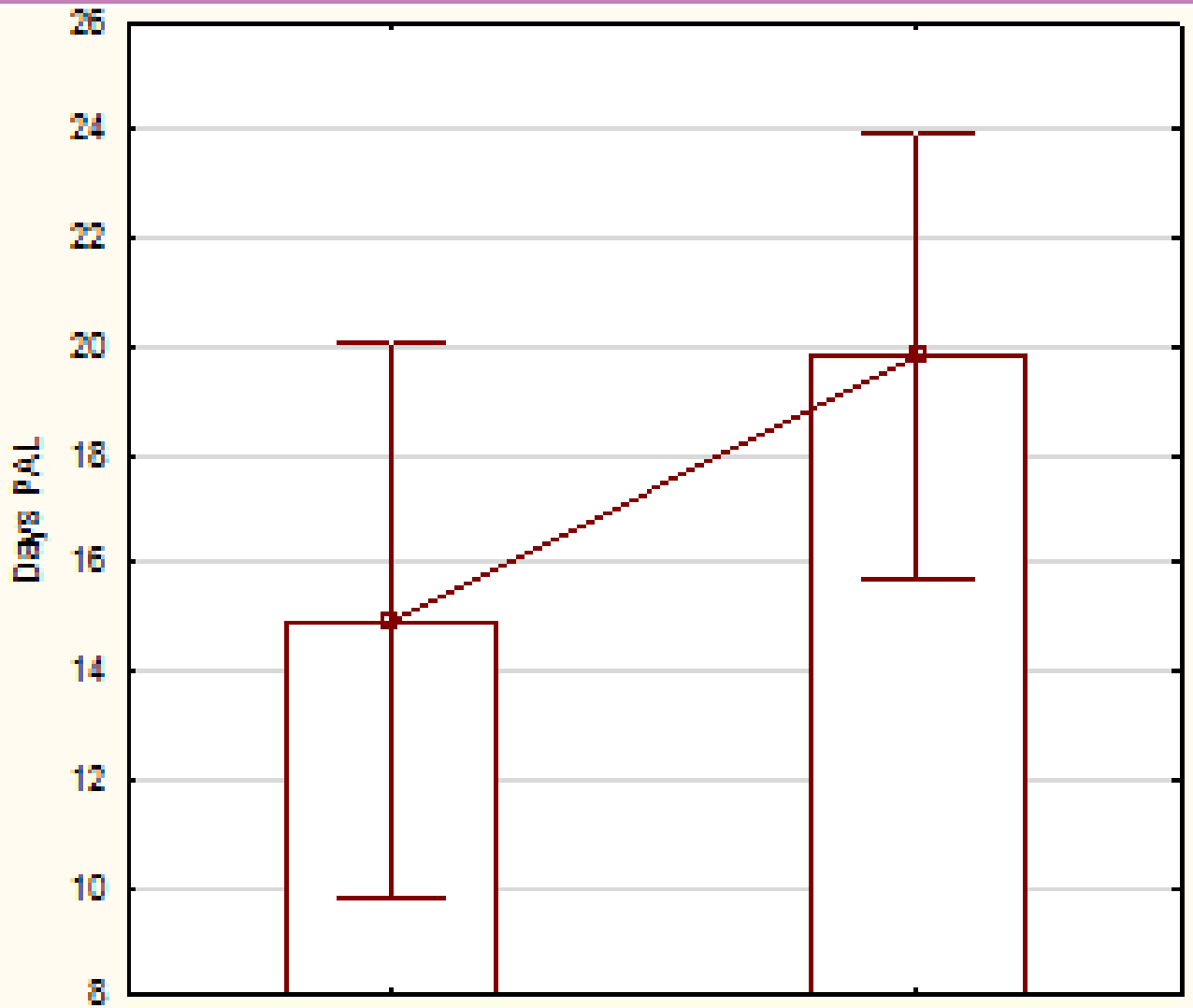
Same gender

Same pathology (non-onco or onco: breast/urol/digest/neuro…)

Duration of stay on the PCU till death



Duration of stay in the PCU till death



P = 0,0055

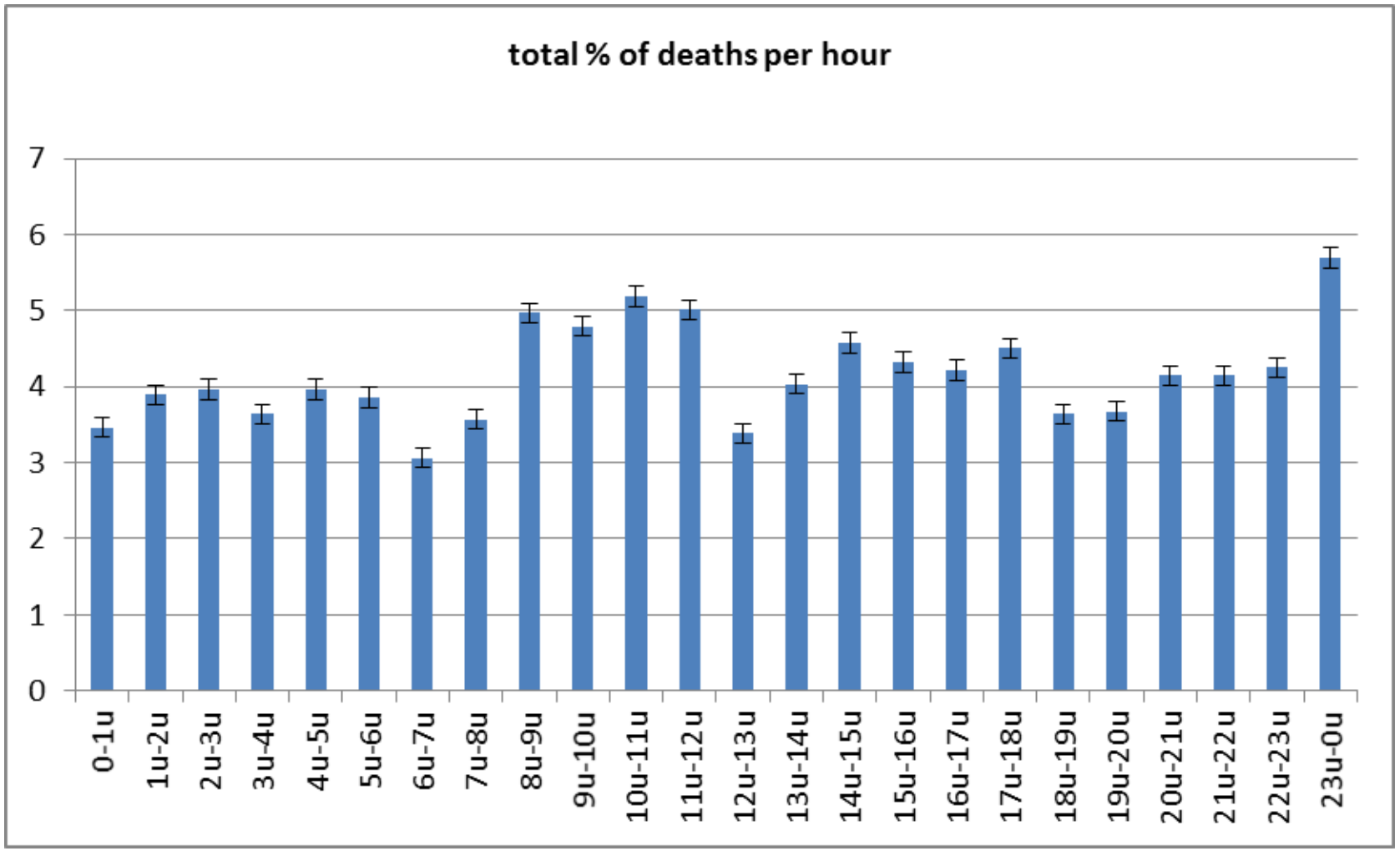
Duration of stay in the PCU till death

	Pacemaker pt		Control pt	
gender	N	Duration of stay mean(d)	N	Duration of stay mean(d)
Man	52	**14,0**	101	**21,1**
Women	31	**16,3**	62	**17,6**

Duration of stay in the PCU till death

	Pacemaker pt		Control pt	
age	N	Duration of stay mean(d)	N	Duration of stay mean(d)
<80j	49	**13,6**	96	**21,3**
>80	34	**16,8**	67	**17,7**

Patients are dying at random over all hours of the day



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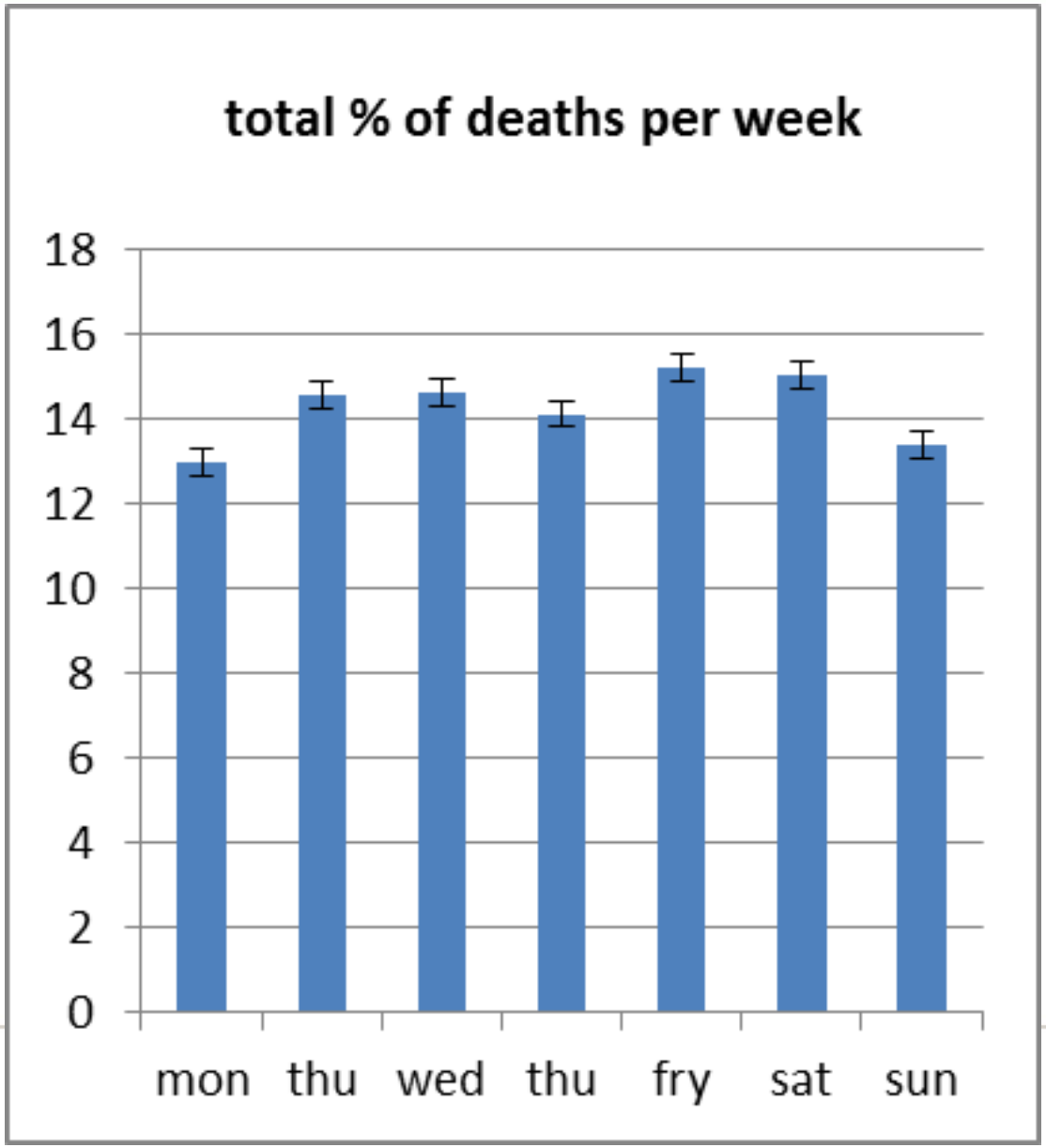
total % of deaths per week
18
16
14
12
10
8
6
4
2
0
mon
thu
wed
thu
fry
sat
sun

N = 3011

UNIVERSITAIRE ZIEKENHUIZEN LEUVEN

COMMISSIE MEDISCHE ETHIEK

CODE OMTRENT BEPERKING VAN THERAPIE

Nr. 1010

DOCUMENT IN VERPLEEGDOSSIER

CODE 1: NIET REANIMEREN **datum:____ uur:____**

- ❑ in geval van circulatiestilstand geen defibrillatie, thoraxmassage noch medicatie
- ❑ in geval van respiratoir falen geen intubatie of kunstmatige beademing
- ❑ in geval van respiratoir falen wel intubatie maar geen kunstmatige beademing

Naam voluit van het verantwoordelijk staflid
Supervisor ID.nr.:____
Dr. ____
Handtekening:

Besproken met patiënt ❑ ja ❑ neen
Besproken met familie ❑ ja ❑ neen
Besproken met huisarts ❑ ja ❑ neen

} **do not reanimate**

CODE 2 EN 3 ZIJN SLECHTS VAN TOEPASSING WANNEER OOK CODE 1 IS AANGEKRUIST

CODE 2: NIET STARTEN MET BEPAALDE BEHANDELINGEN **datum____ uur:____**

Niet starten met:

- ❑ Vasopressoren of inotropica
- ❑ Opdrijven vasopressoren
- ❑ Anti-aritmica
- ❑ Transfert naar intensieve zorgen
- ❑ Antibiotica
- ❑ Dialyse
- ❑ Andere:____
- ❑ Bloed en/of bloedproducten
- ❑ Parenterale nutritie
- ❑ Enterale nutritie
- ❑ Chemotherapie
- ❑ Heelkundige ingreep

Specifieer

Naam voluit van het verantwoordelijk staflid
Supervisor ID.nr.:____
Dr. ____
Handtekening:

Besproken met patiënt ❑ ja ❑ neen
Besproken met familie ❑ ja ❑ neen
Besproken met huisarts ❑ ja ❑ neen

} **not extend therapy**

CODE 3: STOPPEN MET BEHANDELEN **datum:____ uur:____**

Stop volgende behandeling(en)

- ❑ ____
- ❑ ____
- ❑ ____

De waardigheid en het comfort van de patiënt blijven de hoogste prioriteit

Naam voluit van het verantwoordelijk staflid
Supervisor ID.nr.:____
Dr. ____
Handtekening:

Besproken met patiënt ❑ ja ❑ neen
Besproken met familie ❑ ja ❑ neen
Besproken met huisarts ❑ ja ❑ neen

} **therapy withdrawing**

ANNULEER ONMIDDELLIJK BOVENSTAANDE RICHTLIJN(EN)

DATUM:____ UUR:____

Naam voluit van het verantwoordelijk staflid
Supervisor ID.nr.:____
Dr. ____
Handtekening:

Trek meteen ook een streep door het formulier.
Vul desgevallend een nieuw formulier in.
Het doorstreepte formulier blijft deel uitmaken van het medisch dossier.

Adressogram

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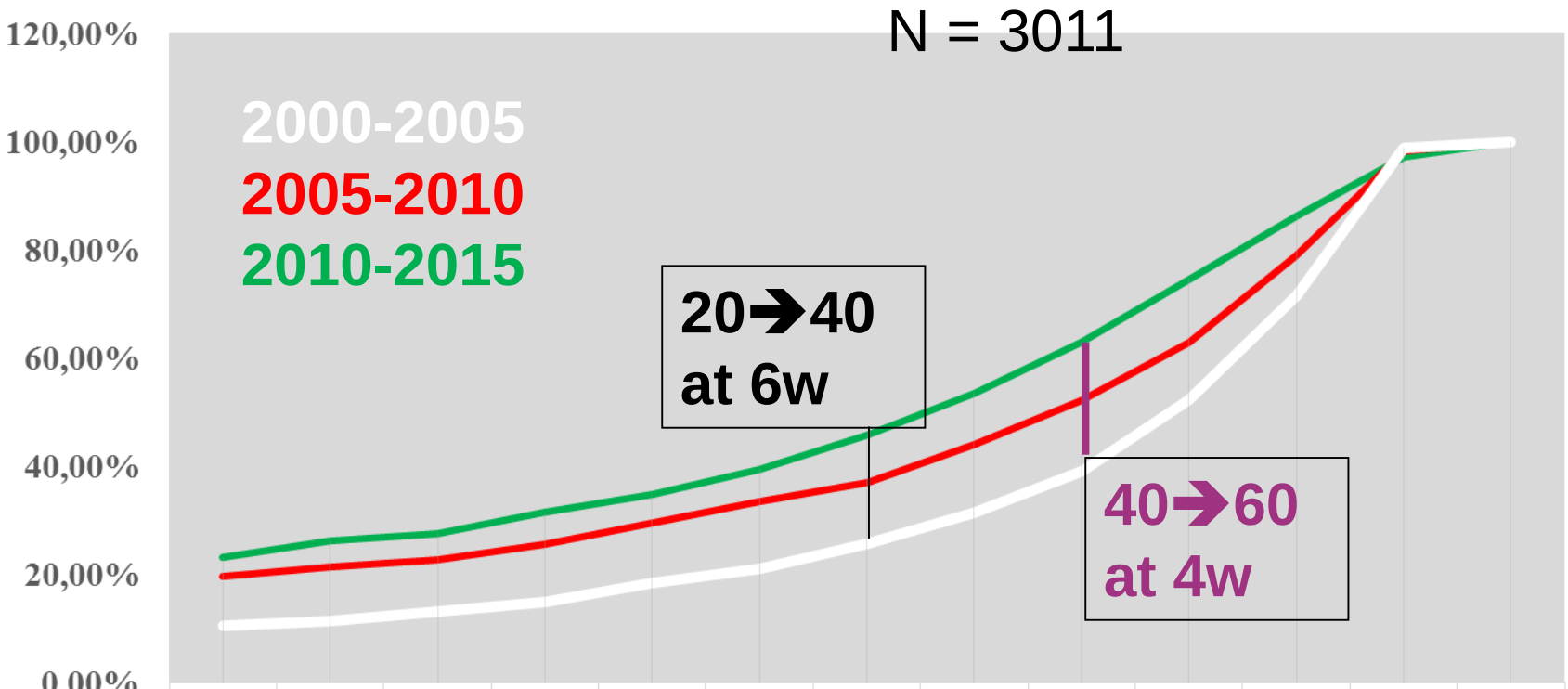
DNR labeling of patients in weeks before death



	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	Overlijden
Termijn 3	23,11%	26,13%	27,65%	31,43%	34,77%	39,42%	45,68%	53,56%	62,96%	74,62%	86,29%	97,19%	100,00%
Termijn 2	19,62%	21,51%	22,79%	25,67%	29,44%	33,40%	36,97%	44,10%	52,13%	62,93%	78,89%	98,22%	100,00%
Termijn 1	10,47%	11,37%	13,18%	14,99%	18,35%	21,06%	25,71%	31,40%	39,15%	52,33%	71,71%	98,84%	100,00%

TIJD TUSSEN 1STE DNR CODE EN OVERLIJDEN (WEKEN)

Termijn 3 Termijn 2 Termijn 1

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-be assertive in treatment of :

-Pain

-Dyspnoea

-Discuss ethical discussion concerning fluid en food

-Delirium, anxiety, uncertainty,

-……..

-make therapeutic agreements

-Take scientific team decisions and advice and motivate the patient and family…

Avoid that the family needs to decide ….

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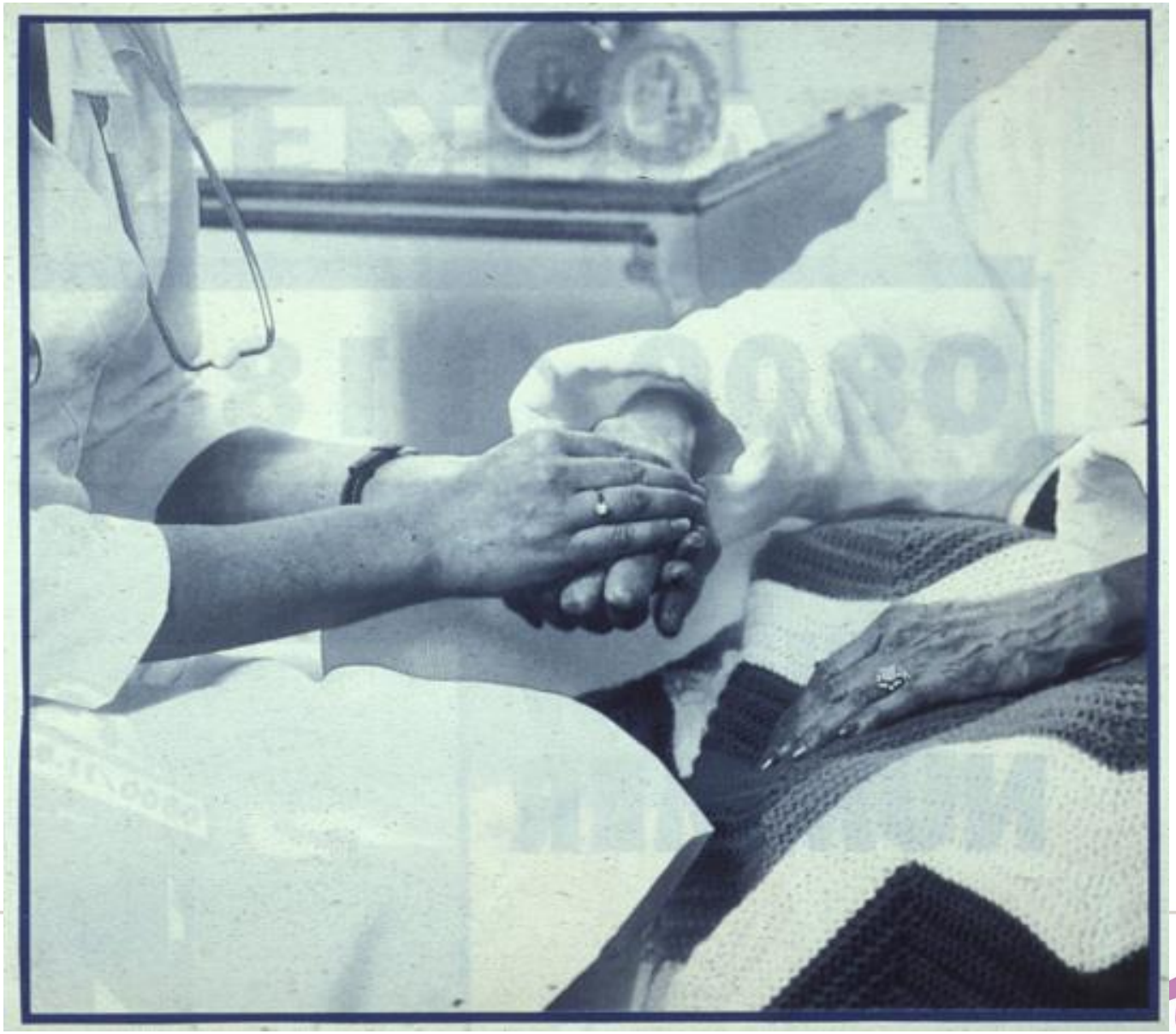
Terminal care is more than handholding,
We have to treat, to care, to inform, to guide the pt/fam, team.



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