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6th ICHNO

International conference on innovative approaches in head and neck oncology

16-18 March 2017
Barcelona, Spain

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6TH ICHNO CONTENT

Keynote lecture

SP-001 Immunotherapy for head and neck cancer: integrating the fourth modality

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Abstract text

The immune system plays a key role in the development, establishment and progression of head and neck cancer. A greater understanding of the dysregulation and evasion of the immune system in the evolution and progression of head and neck cancers provides the basis for improved therapies and outcomes for patients. Head and neck cancer evades the host`s immune system on different levels: 1. Manipulation of its own immunogenicity, 2. Production of immunosuppressive molecules, and 3. Promotion of immunomodulatory cell types. Through the tumor`s influence on the microenvironment, the immune system can be exploited to promote metastasis, angiogenesis and growth. In this chapter, we review basic immunology as it relates to head and neck cancer and discuss the theory of cancer immunosurveillance and immune escape. A brief overview to key components in the tumor microenvironment is provided. Current research on cytokines as biomarkers, cancer stem cells, tumor antigens and immunotherapeutic strategies are presented.

Keynote lecture

SP-002 State of the art in robotic surgery

E. Moore[1]
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Abstract text

Transoral robotic surgery (TORS) has evolved from an esoteric means of accessing tumors of the palate tonsil and tongue base to an essential tool and modality in the armamentarium of both oncologic and functional head and neck surgeons all over the world. This evolution has occurred in a relatively short time frame considering the usual slow and methodical course of surgical change. TORS is now utilized to access not only tumors of the tonsil and base of tongue, but also tumors of the nasopharynx, hypopharynx, supraglottis, and even glottis. TORS is utilized heavily in the treatment of obstructive sleep apnea.

The next phase of transoral robotic surgery will utilize instrument modifications that allow greater flexibility of the camera, smaller working arms, and new modalities of tissue interaction. Utilization of other lighting sources will allow improved recognition of tumors, lymphatics, and vascular structures. Combination of the visual interface with imaging will allow incorporations of image guidance to the surgical technique.

This talk will discuss what is happening with robotic surgery currently, the current limitations, and the evolutions that will hopefully expand the capabilities of transoral robotic surgery in the future. The audience will hopefully find inspiration to utilize new technology, and also to add innovation to the rapidly expanding field of transoral robotic surgery.

Symposium: Prognostic modelling

SP-003 Radiomics: the poor man molecular imaging?

P. Lambin
The Netherlands

Abstract not received

SP-004 Novel insights into head and neck cancer by transcriptome approaches

L. De Cecco[1]
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Abstract text

Head and neck squamous cell carcinoma (HNSCC) is the sixth leading cancer by incidence worldwide and its pathogenesis is multifactorial, being related to alcohol and tobacco exposure and to Human Papillomavirus infection. Despite the improvements in the therapeutic modalities, the long-term survival rate remained unchanged over the past decade. For this reason, there is a great need to find better ways to foresee outcome, to improve treatment choices, and to enable a more personalized approach. The development of high-throughput gene-expression assays in the last two decades has provided the invaluable opportunity to improve our knowledge on cancer biology and to identify signatures related to outcome in many malignancies. More than 100 studies reporting gene-expression profiling studies in HNSCC from clinical samples have been published since 2000; however, several limits are present including i) inadequate sample size; ii) heterogeneous anatomical districts under analysis; iii) unknown tumor-to-stroma ratio; iv) technical (microarray platforms) and analytical (bioinformatics tools) differences. Overall, these studies have improved our knowledge of the biology of the disease. In recent years in the attempt to reach adequate statistical power for identifying clinically relevant signatures, a number of studies reporting meta-analysis has been published. Eventually, the integration of gene expression profiles with other "omics" data including miRNome, methylome, copy number variation, and mutational status by whole-exome sequencing, and with new emerging tools, no strictly genetics/genomics-related, such as functional (e.g. Positron Emission Tomography) or morphological (Magnetic Resonance Imaging) imaging modalities may encourage the development of new diagnostic or therapeutic approaches. The key objective of the present talk is to provide an overview of the main achievements of transcriptome analyses in HNSCC including: i) identification of subgroups of tumors with different biology and associated prognosis; ii) prediction of outcome; iii) prediction of response to therapy.

SP-005 The TRIPOD guideline

K.G.M. Moons
The Netherlands

Abstract not received

Proffered papers 1

OC-006 Outcomes of head and neck cancer with N3 nodal disease: a review of the National Cancer Data Base

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Purpose or Objective
There is a paucity of level one evidence and a limited number of institutional series guiding management of patients with head and neck squamous cell carcinoma and N3 nodal disease (N3 HNSCC). Thus, larger data sets are essential to generate robust data appropriate for directing patient care.
The current study utilized the National Cancer Data Base (NCDB) to evaluate patterns of care and clinical outcomes for patients with N3 HNSCC.
Material and Methods
We performed a retrospective analysis of patients with N3 HNSCC identified in the NCDB treated with either primary surgery followed by adjuvant therapy or primary chemoradiotherapy (CRT). Factors associated with treatment were analyzed with binary logistic and multivariate regression. Multivariate (MVA) Cox proportional hazards analysis was utilized to determine factors correlated with overall survival. Kaplan-Meier curves with inverse probability of treatment-weighting were used for survival analysis.
Results
We identified 1,464 (30%) and 3,403 (70%) patients with N3 HNSCC treated with either primary surgery or CRT, respectively. Increasing age, non-private/unknown insurance, oropharyngeal or hypopharyngeal primaries, increasing tumor size, and higher T-stage were associated with CRT, whereas high-volume center, lower T-stage, oral cavity primary, and being diagnosed in more contemporary years were associated with surgery. On Cox proportional MVA, increasing age, non-white race, non-private/unknown insurance, increasing tumor size, T4 stage, and CRT were associated with lower overall survival. Propensity-adjusted median survival was 54.2 and 44.8 months for surgery and CRT, respectively ($p = 0.0589$). In subgroup analysis, oropharyngeal primary subsite gained a survival advantage with surgery versus CRT with median survivals of 86.0 and 61.9 months, respectively ($p = 0.0153$).
Conclusion
The majority of N3 HNSCC patients receive primary CRT. After adjustment for factors influencing treatment approach, patients treated with surgery and CRT exhibit similar survival outcomes with 5-year overall survival approaching 30-50% depending on the primary tumor subsite. Patients with oropharynx primaries benefit from primary surgical approach in terms of overall survival. Those with oropharynx HPV-positive tumors represent a favorable subset of N3 HNSCC patients. These data represent the most comprehensive analysis of N3 HNSCC outcomes and serve as a foundation to guide clinical management, as well as future research endeavors.

OC-007 Sentinel node biopsy for early stage oral cancer; experience of 2 Dutch head and neck centers
I. Den Toom[1,2], L. Janssen[1], R. Van Es[1], O. Hoekstra[3], H. Karagozoglu[4], B. De Keizer[5], A. Van Schie[3], S. Willems[6], S. Van Weert[2], R. Leemans[2], E. Bloemena[4,7], R. De Bree[1,2]
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[2]*VU University Medical Center, Otolaryngology-Head and Neck Surgery, Amsterdam, The Netherlands*
[3]*VU University Medical Center, Radiology and Nuclear Medicine, Amsterdam, The Netherlands*
[4]*VU University Medical Center/Academic Centre for Dentistry, Oral and Maxillofacial Surgery / Oral Pathology, Amsterdam, The Netherlands*
[5]*University Medical Center Utrecht, Radiology and Nuclear Medicine, Utrecht, The Netherlands*
[6]*University Medical Center Utrecht, Pathology, Utrecht, The Netherlands*
[7]*VU University Medical Center, Pathology, Amsterdam, The Netherlands*

Purpose or Objective
To evaluate the results of sentinel lymph node biopsy (SLNB) in patients diagnosed with a T1-T2 oral squamous cell carcinoma and clinically negative (N0) neck in two Dutch Head and Neck centers.
Material and Methods
Retrospective analysis of 226 previously untreated patients, who underwent SLNB between 2007 and 2016. The SLNB procedure consisted of preoperatively performed lymphoscintigraphy, intraoperative detection using blue dye and/or gamma probe guidance and histopathological examination including step-serial sectioning and immunohistochemical stainings. A positive SLNB was followed by a neck dissection, while regular follow-up with ultrasound guided fine-needle aspiration cytology was followed in case of a negative SLNB.
Results
The identification rate was 97% (220/226). At least one histopathologically positive SLN was found in 52 of 220 patients (24%). Sensitivity of SLNB was 83% and the negative predictive value was 93%. Patients with a floor of mouth tumor showed a lower sensitivity (67% vs. 88%, P=0.11) and negative predictive value (90% vs. 95%, P=0.31) compared with patients with other tumor locations. Median follow-up was 22 months (1-104). Overall survival, disease-specific survival and disease-free survival for SLN negative and SLN positive patients were 77%, 90% and 99% vs. 73%, 86% and 87%.
Conclusion
SLNB is a safe and reliable diagnostic staging technique for detection of occult lymph node metastasis in patients with early stage (T1-T2, cN0) oral cavity squamous cell carcinoma, but needs improvement in patient with floor of mouth tumors.

OC-008 Incidence of malignant disease outside the head and neck region in head and neck cancer
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Purpose or Objective
Due to lifestyle factors head and neck cancer patients have a high risk of having metastatic disease or a synchronous cancer at the time of diagnosis. Malignancy diagnosed outside the head and neck region can have a profound effect on the clinical approach. At our institution patients referred for curative radiotherapy have been routinely planned with whole-body PET-CT. To determine the incidence of malignant disease outside the head and neck region we examined the planning PET-CT scans of patients with squamous cell carcinoma of the head and neck (SCCHN).

Material and Methods
All patients with SCCHN planned for radiotherapy with curative intent who underwent a whole-body planning PET/CT scan from 2006 – 2012 were eligible. A radiologist and a nuclear medicine physician prospectively evaluated all scans. Any suspicious lesions outside the head and neck region were noted. Using patient files, pathology registers and other clinical systems all eligible patients were retrospectively investigated and evaluated for malignant disease. Confirmation of malignancy, either disseminated SCCHN or a synchronous secondary cancer was done by histological verification or by follow-up imaging.
Results
A total of 1110 patients with primary SCCHN were eligible. Pathological lesions outside of the head and neck region were described in 326 (29%) patients, with 158 patients having lesions suspicious of malignancy, whereas lesions on 168 patients were deemed benign. In total, malignancy was diagnosed in 92 (8.2%) patients of which 56 (61%) was confirmed histological. The malignant lesions comprised 48 patients (4.3%) with metastatic SCCHN, 38 (3.4%) patients with a synchronous cancer, and 6 (0.5%) patients with malignancy of unknown origin. Lung cancer (n=24) was the predominant synchronous cancer. Forty-two patients with pathological lesions outside the head and neck were unresolved due to death within 6 months of diagnosis (n=27), lost to follow-up (n=11) or refused further diagnostic evaluation (n=4). Of the 158 patients with lesions suspicious of malignancy, 76 (48%) patients had a malignant lesion confirmed, whereas it was rejected in 61 (39%) patients. In the 168 patients with lesions deemed benign by PET/CT a malignant lesion was later confirmed in 16 (10%) patients.
Conclusion
Patients with primary SCCHN have a substantial risk of malignant disease outside the head and neck region, which may influence the overall treatment strategy. A PET/CT scan before onset of radiotherapy is clinically useful in identifying these patients. However, a significant proportion of lesions described as suspicious of malignancy were in fact benign.

OC-009 Validation of a prognostic model in 600 patients with squamous cell carcinoma
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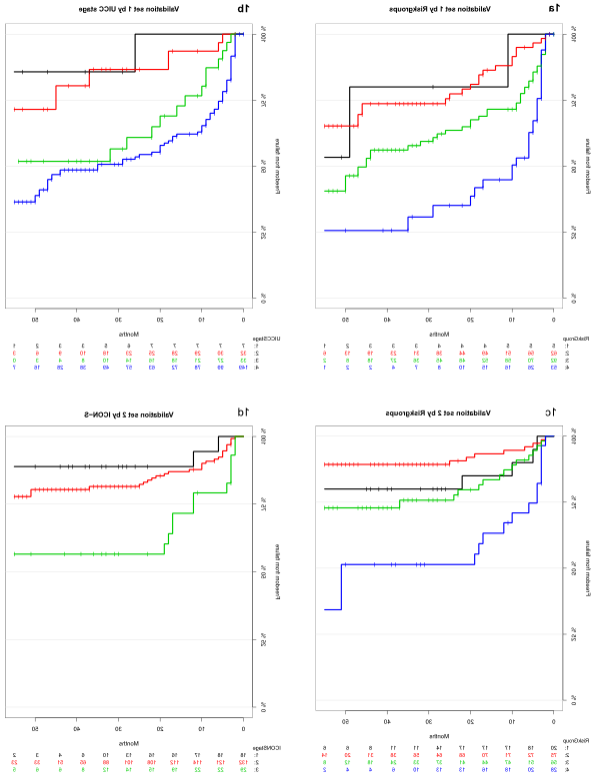
Purpose or Objective
Disease recurrence is an important clinical endpoint in head and neck cancer and we therefore validated a prognostic model on this endpoint with p16 negative (p16-) and p16 positive (p16+) neck squamous cell carcinoma (HNSCC). In addition, we compared the performance of the validated model with the proposed ICON-S staging for patients with p16+ oropharyngeal SCC (OPSCC)[1] and with UICC staging for other HNSCC.
[1] O'Sullivan B et al. Lancet Oncol 2016
Material and Methods
Consecutive patients with HNSCC (excluding nasopharyngeal carcinomas) and a pre-treatment FDG PET/CT treated with curative intent IMRT at a single institution from 2005 – 2012 were included. The cohort was divided into 3 groups: Training set (p16- OPSCC and non-OPSCC patients treated from 2005 – October 2009), Validation set 1 (p16- OPSCC and non-OPSCC patients treated from October 2009 – 2012) and Validation set 2 (p16+ OPSCC patients treated from October 2005-2012). We have previously developed and published a prognostic model including four significant variables (treatment with Cisplatin, smoking status, FDG uptake and tumor size; the latter two as continuous variables) in the training set. The prognostic model was used to generate four risk groups based on the predicted risk of disease recurrence after 2 years (Intervals 0-10%; 10-30%; 30-60% and >60%). Here, we test the prognostic model on the two validation sets. The performance of the original model was compared with the UICC staging for validation set 1 and with ICON-S staging for validation set 2. The performance was assessed with concordance index (CI) where a CI=1 corresponds to ideal prognostication and CI=0.5 corresponds to a coin toss.
Results
A total of 600 patients were included. The training set included 168 patients, validation set 1 included 224 patients and validation set 2 included 183 patients (p16 status could not be performed in 25 patients).Figures 1a and 1b depict the Kaplan-Meier (KM) curves of freedom from failure (FFF) in validation set 1 using the prognostic model developed from the training set (1a) and the UICC staging (1b).The prognostic model provides better distinction of patients than the UICC stating system in validation set 1. The CI for UICC staging is 0.63 compared to 0.74 for our validation (p=0.03; table 1). Figures 1c and 1d depict the KM curves of FFF for patients in validation set 2 using the prognostic model developed from the training set (1c) and ICON-S (1d). The distinction between patients is not obviously better with the prognostic model. The CI is slightly better with our prognostication (table 1), but only of borderline significance (p=0.05).



Conclusion
This is a validation of a previously suggested prognostic model. The validated model provides a better prognostication of risk of disease recurrence than UICC

stage in non-OPSCC and p16- OPSCC patients, and it seems to be equivalent to the staging proposed by ICON-S in p16+ OPSCC patients.

	Training set (non-OPSCC and p16- OPSCC patients)	Validation set 1 (non-OPSCC and p16- OPSCC patients)	Validation set (p16+ OPSCC patients)
Patients No.	168	224	183
CI for UICC (confidence interval)	0.82 (0.75 – 0.89)	0.63 (0.57 – 0.70)	NA
CI for prognostic model (confidence interval))	0.59 (0.52 – 0.66)	0.74 (0.66 – 0.81)	0.72 (0.62 – 0.82)
CI for ICON-S (confidence interval))	NA	NA	0.62 (0.54 – 0.71)

Table 1

Randomised trials: New data from randomised trials

SP-010 Update of the meta-analysis of chemotherapy in head and neck cancer (MACH-NC)

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Introduction
Our previous meta-analysis showed that concomitant chemotherapy (CT) improved overall survival (OS) in patients with non-metastatic head and neck squamous cell carcinoma (HNSCC). The study purpose was to update patient follow up, gather data on toxicity and include randomized trials conducted up to 2010, and to perform a network meta-analysis using data from MACH-NC and MARCH (meta-analysis on altered fractionation radiotherapy, updated data presented at ECCO 2013).
Methods
A fixed effect model was used for the standard meta-analysis. The log-rank test, stratified by trial, was used to compare treatments. OS was the primary endpoint. Progression free survival (PFS), locoregional control and distant control were the secondary endpoints. The network meta-analysis was performed under a frequentist approach using random effects due to significant heterogeneity. P-score (P-s), the percent of certainty to be the best treatment, was used to rank treatments.
Results
15 new trials (2,574 patients) were included. Updated data were obtained for 11 additional trials. For the comparison of LRT vs. LRT + CT, 94 trials (18,394 patients) with median follow-up of 6.7 years were analyzed and 8 trials (1,214 patients) for the comparison of induction CT to concomitant CT. The addition of CT improved OS with a hazard ratio (HR) [95% confidence interval] of 0.89 [0.86; 0.92], p<0.0001. There was a significant interaction between treatment effect and the timing of CT, the benefit being limited to concomitant CT (p<0.0001), with a HR of 0.83 [0.79-0.87], translating into a 5-(10-)year absolute survival benefit of 6.5 (3.4)%. The addition of induction CT did not increase OS, with a HR of HR=0.97 [0.91-1.03]. Analyses performed in recent concomitant trials revealed a trend toward decreased efficacy with increasing age (p for trend=0.06; HR of 1.00 [0.81-1.23] for age≥70) or performance status (p for trend=0.07, HR of 0.93 [0.73-1.19] for PS≥2). The network includes data from 117 RCTs, corresponding to 150 comparisons (28,804 patients; 19,131 deaths and 20,586 PFS events). 16 treatment modalities were compared pairwise. Hyperfractionated radiotherapy with concomitant chemotherapy (HFCRT) was ranked as the best treatment in all analyses. HR of HFCRT compared to platinum-based CRT was 0.80 [0.65-0.99] for OS (P-s 0.97) and 0.77 [0.62-0.96] for PFS (P-s 0.98). The table summarizes the comparison of the best treatments with platinum-based CRT and loco-regional treatment (LRT) alone for overall survival. The superiority of HFCRT was robust to sensitivity analyses.
Three other modalities of treatment had a better P-score than platinum-based CRT (P-s 0.78) but their HR for OS were not significantly different: induction chemotherapy (TaxPF) followed by LRT (IC-LRT, (P-s 0.89)), accelerated radiotherapy with concomitant chemotherapy (ACRT, (P-s 0.82)) and induction chemotherapy (TaxPF) followed by CRT IC-CRT, (P-s 0.79)).
Conclusion
This update of the MACH-NC meta-analysis confirms the superiority of concomitant CT for locally advanced HNSCC with longer follow-up, when compared to induction treatment. The network meta-analysis suggests the superiority of HFCRT. Although toxicity is not addressed, these results, which ideally need to be confirmed by RCTs, could be clinically useful in advanced diseases with a high risk of locoregional failure (such as HPV negative disease), as represented by the patients in these meta-analyses. Additional analyses on other endpoints will be presented at the meeting.

Treatment comparison	Rank	Network meta-analysis		Number of trials per comparison
		HR	CI 95%	
Compared to platinum-based CRT				
HFCRT	1	0.80	[0.65-0.99]	2
IC (TaxPF) followed by LRT	2	0.90	[0.73-1.12]	0
ACRT	3	0.97	[0.86-1.10]	4
IC (TaxPF) followed by CRT	4	0.98	[0.80-1.21]	3
Compared to LRT				
HFCRT	1	0.62	[0.51-0.76]	2
IC (TaxPF) followed by LRT	2	0.70	[0.57-0.86]	1
ACRT	3	0.75	[0.67-0.85]	1
IC (TaxPF) followed by CRT	4	0.76	[0.62-0.94]	0
Platinum-based CRT	5	0.77	[0.72-0.83]	23

Tax-PF= Taxane, Platin and 5-Fluorouracil.

Supported by INCa (PHRC, PAIR-VADS) and LNCC

SP-011 Update of the PET NECK trial

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Abstract text
The PET Neck trial examined the efficacy of a PET CT guided active surveillance policy compared to planned neck dissection for the management of advanced nodal disease in patients receiving radical chemoradiotherapy for advanced head and neck squamous cell carcinoma. It randomised 564 patients into PET CT guided active surveillance or planned neck dissection. The study found that there was no difference in overall survival or locoregional control between the two arms. There were also no differences in overall quality of life between the two arms. We will present new data on the detailed quality of life and functional status of patients who have

received neck dissection and those who did not receive neck dissection. We will also analyse the determinants of overall quality of life and of swallowing including factors such as neck dissection and HPV status. In addition we will also report on the functional and survival outcomes of different types of neck dissection in the context of definitive chemoradiotherapy.

SP-012 Update of neck dissection trial

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Abstract text

BACKGROUND: Appropriate management of the neck in clinically node negative early oral cancer has been a matter of debate for decades. A prospective phase III randomized controlled trial (RCT) was designed to address the issues of: 1. The superiority of elective neck dissection (END) over the wait and watch (WW) policy followed by therapeutic neck dissection (TND) when needed 2. The addition of ultrasonography to routine physical examination on follow up would help in earlier detection of neck metastasis influencing salvage and survival. METHODS: Patients with lateralized T1 or T2 squamous carcinoma of oral cavity, amenable to peroral excision were included in the trial. At initial surgery all patients underwent a wide local excision of the primary with appropriate margins. They were randomized to either END or WW policy for the neck management. Patients were randomized a second time to follow up with physical examination plus neck ultrasound (PE+USG) versus physical examination (PE) alone. Stratification was based on size, site, gender and preoperative neck ultrasound. The primary end point was overall survival (OS) and secondary end point was disease-free survival (DFS). The trial was planned to demonstrate a 10% superiority (α = 0.05 and ß = 0.2) in OS for END vs. TND, assuming 60% 5-year OS in TND arm, with a planned sample size of 710. RESULTS: This study was terminated after 596 patients were randomized between January 2004 and June 2014. An interim intent-to-treat analysis of initial 500 patients (255 in TND, 245 END) was performed as mandated by Data and Safety Monitoring Committee based on the number of observed deaths in each arm. Both arms were balanced for site and stage. There were 427 tongue, 68 buccal mucosa and 5 floor of mouth tumours; 221 were TI and 279 T2. At a median follow-up of 39 months 146 recurred in TND and 81 in END arms. The 3-year OS was significantly higher in END compared to TND arm (80.0% vs. 67.5%, HR = 0.64; 95% CI, 0.45 to 0.92; P=0.01) as was 3-year DFS (69.5% vs. 45.9%, HR = 0.45; 95% CI, 0.34 to 0.59; P<0.001). After adjusting for stratification factors in Cox regression, END continued to be significantly superior to TND for both OS and DFS.
In the follow up randomization 252 patients were allocated to PE+USG and 244 to PE. In addition to the stratification factors both arms were balanced for the surgical procedure (END vs. TND) as well. There were 118 recurrences with 67 deaths in PE+USG and 109 recurrences with 62 deaths in PE, respectively. There was no OS difference between PE+USG and PE in unadjusted analysis (3-year OS 73.3% and 73.8%, respectively, HR = 1.02, 95%CI 0.73-1.45, p = 0.89) and after adjustment (HR = 0.81, 95%CI 0.51-1.29, p = 0.37) for stratification factors, prognostic factors, surgical treatment (END vs. TND) and an interaction term between two study questions, in a Cox model. END vs. TND continued to be highly significant for OS in this model (HR = 0.54, 95%CI 0.32 - 0.92, p = 0.02). Within TND (wait and watch) arm there was no significant difference between PE+USG and PE (3-year OS 67.3% and 67.6% respectively, HR = 0.96, 95%CI 0.62–1.5, p = 0.86). CONCLUSIONS: There were 8 excess deaths for every 15 excess recurrences in the TND arm. Elective neck dissection in patients with early oral SCC results in 36% reduction in mortality and should be considered the standard of care. Neck ultrasound confers no survival advantage over physical examination in postoperative follow-up of clinically node negative early stage oral cancer patients.

N Engl J Med 2015;373:521-9

SP-013 Update on the ARCON study

J. Kaanders[1], W. Bots[1], C. Terhaard[2], M. Vergeer[3], P. Doornaert[2], H. Bijl[4], P. Van den Ende[5], M. De Jong[6], G. Janssens[2], P. Span[1]
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Abstract text

Purpose: "ARCON" combines accelerated radiotherapy to counteract tumor repopulation with carbogen breathing and nicotinamide to reduce chronic and acute hypoxia. We report the long-term results from a randomized phase III trial comparing accelerated radiotherapy (AR) with accelerated radiotherapy plus carbogen and nicotinamide (ARCON) in laryngeal cancer.
Methods and Materials: From April 2001 to February 2008, 345 patients with clinical stage T2-4 squamous cell laryngeal cancer were randomized to AR (N=174) and ARCON (N=171). AR was given to a total dose of 68 Gy in 2 Gy fractions within 36-38 days on the primary tumor and the pathological lymph nodes. In the experimental arm, a dose reduction to 64 Gy on the laryngeal cartilage was required and radiotherapy was combined with carbogen breathing during irradiation and administration of nicotinamide (60 mg/kg) 1-1.5 h before the first fraction of every day.
Results: After a median follow-up of 72 months, local control rate at 5 years was 78% with no difference between the study arms. The 5-year regional control was significantly better with ARCON (93% for ARCON versus 86% for AR, p=0.04). Analysis of late radiation morbidity did not reveal significant differences between the AR and ARCON treatment arms with respect to skin and subcutaneous tissues (severe telangiectasia, 8% *v* 8%; *P* = .56; severe subcutaneous fibrosis, 7% *v* 9%; *P* = .26; severe subcutaneous edema, 8% *v* 4%; *P* = .09) and mucous membranes (mucosal ulceration, 8% *v* 6%; *P* = .36; nasogastric tube feeding, 6% *v* 6%; *P* = .61, respectively). Twelve patients in the AR group and six patients in the ARCON group required a tracheostomy for severe edema with dyspnea and/or stridor. All patients who developed a cartilage necrosis could be managed conservatively. Four of the patients received a tracheostomy (n = 1 for AR, n = 3 for ARCON), and there was no need for laryngectomy. One year after diagnosis, 3% of patients in both groups needed nasogastric tube feeding (*P* = .88). At ≥2 years from baseline, the percentage of patients reporting moderate to severe complaints of dry mouth, sticky saliva, or changes in taste/smell was 30%, 22% and 18%, respectively, while the majority of patients had no or few complaints of swallowing (79%) or speech (64%).
Conclusion: Long-term morbidity was mild and quality of life was high with no difference between the study arms.

A significant gain in regional control rate was observed in favor of ARCON. Both AR and ARCON are excellent strategies for larynx preservation in (moderately) advanced larynx carcinoma with good functional outcome.

Symposium: Reductions of radiation induced toxicities

SP-014 Target volume reduction

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Abstract text

Radio(chemo)therapy (RCT) with curative intent for head and neck cancer (HNC) results in significant toxicity which is related to dose-volume parameters of target and surrounding normal tissues. Data on target-volume reduction as a strategy to reduce toxicity are scarce. Volumes for elective nodal irradiation are often manifold larger than volumes for gross tumour irradiation. A multicentre prospective randomised phase II trial investigated whether a 3-phase adaptive IMRT-scheme using reduced volumes of elective neck could reduce toxicity without compromising disease control compared to standard non-adaptive IMRT. In the experimental arm, elective sub-volumes were omitted if the population-based probability of subclinical disease was lower than ~7%. There were no significant differences in disease control, survival, acute or late toxicity and QOL between the experimental and the control arms. One patient in the experimental arm had regional recurrence in a region of the elective neck that would have been irradiated in the control arm. Volume de-escalation based on population-statistics are small, probably too small to yield relevant benefit regarding toxicity. Patient-individual volume de-escalation using sentinel lymph node mapping seems more promising. This could lead to a large volume de-escalation, as shown by Daisne et al. [1]. In this study, a significant reduction by factor of 2 of elective neck volume was achieved. Initial results of the ongoing phase II study of the same research group are promising, with the absence of any regional relapse in 22 patients at median follow-up of 14 months [2]. The utility of PTV-margins > 0 mm around elective neck volumes is debatable.

Clinical target volumes around GTV or tumour bed are based on educated guess rather than on scientific evidence. Surveys demonstrate large variations in GTV-delineation with no reports that smaller delineations change the rates or locations of recurrences. Reducing the high-dose CTV in nasopharyngeal cancer did not negatively affect survival rates but did reduce the late xerostomia events [3]. The use of reduced (5 mm ->3 mm) CTV-to-PTV margins in HNSCC was associated with reduced late toxicity while maintaining loco-regional control [4]. In oropharyngeal cancer, a planning study showed significant NTCP-reduction for ipsilateral parotid and contralateral submandibular glands by omitting the PTV-margin [5]. GTV is the union of volumes of malignancy demonstrable by imaging and clinical examination. 18FDG-PET translated to smaller GTV sub-volumes for the primary tumour than CT. PET-based planning demonstrated an improvement on dosimetry by lowering dose to organs at risk [6]. This information has been clinically investigated to dose-escalate volumes smaller than the multimodality GTV but not yet to reduce dose to low-avidity parts of the multimodality GTV aiming at reducing toxicity. Clinical data exist on the use of tumour regression in adaptive radiotherapy (ART) to treat smaller GTVs, CTVs and PTVs. ART increased minimum and decreased maximum doses in target volumes and improved dose/volume metrics of organs-at-risk [7]. The results revealed considerable heterogeneity in patient-specific benefit from ART which was underestimated by reporting population-average. ART has been explored to investigate the limits of dose-escalation [8]. Quantitative clinical data of ART regarding toxicity reduction are scarce, if not inexistent. Conclusions: ICRU recommends generous inclusion of (presumably) diseased and normal tissue volumes in GTV, CTV and PTV. Evidence exists that more restricted PTV, CTV and GTV volume definition may translate to less toxicity without increasing recurrence rates.

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SP-015 Prophylactic swallowing exercises in head and neck radiotherapy

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Abstract text

While treatment of head and neck cancer has improved the survival rates over the past years, long-term morbidity plays an increasing role. One of the significant morbidities is long term radiotherapy-related dysphagia. Dysphagia is a symptom that covers many different problems often leading to serious consequences and greatly affecting patient's quality of life. Different approaches have been taken towards reducing radiotherapy-related dysphagia including swallowing exercises implemented either as prophylactic exercises or reactive exercises.

Publications on prophylactic swallowing exercises have emerged during the past few years but evidence is still scarce. Studies are heterogeneous according to study design, interventions, evaluation times, outcomes and how they are measured making a comparison complicated. A review of the literature shows, that the current studies mostly include few participants, only a few small randomized controlled trials, high risk of bias and not all exercises used have sufficient evidence for long-term improvement in swallowing. Endpoints include objective endpoints, observed-rated endpoints, patient-reported endpoints and clinical endpoints like tube feeding. Evaluation times ranged from a few weeks to several months.

In general, most studies reports some positive results of swallowing therapy but the benefit is not consistent and not related to specific measures. Work is ongoing to elaborate on these differences. High rates of dropouts are a major concern when interpreting the studies and compliance to the exercises is generally poor.

In conclusion, the evidence for prophylactic swallowing exercises for all patients being superior to therapeutic intervention in symptomatic patients is still scarce. To address the question properly larger studies are needed with minimal risk of bias, strong methodologies and an agreement on primary outcome, evaluation method and time.

SP-016 the value of proton therapy for head and neck malignancies: reducing side effects and improving outcomes

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Abstract text

Due to the close vicinity between target volumes and several critical organ structures, head and neck cancer radiotherapy is associated with multiple severe acute and late toxicities. The improved survival in contemporary patients has shed light over the potentially devastating chronic complications that affect increasing numbers of patients. Intensity modulated external-beam photon radiation therapy (IMRT) allowed to spare some critical structures, thereby reducing xerostomia and improving patient reported outcomes (PRO) compared to traditional 2D/3D radiotherapy. However dose reduction to specified structures during IMRT was associated with an increased beam path dose to alternate non-target structures, resulting in clinical toxicities that were uncommon with previous approaches.

The physical advantage of proton beam therapy is its sharp increase in dose deposited at the end of the particle range, i.e. the Bragg peak, avoiding any exit dose beyond the target and reducing the integral dose delivered. Dosimetric comparisons between intensity-modulated proton therapy (IMPT) and IMRT have consistently shown that IMPT allowed a better sparing of normal tissues while maintaining dose to target volumes. Clinical reports have suggested improved swallowing and taste function, reduced need for acute and long-term feeding tube requirements, decreased rates of severe weight loss and malnutrition or reduced rates of osteoradionecrosis, for example. Some studies have even suggested that the physical and biological properties of proton therapy could result in improved survival in selected tumor types, such as sinonasal malignancies. The magnitude of the expected reduction in toxicity has been estimated using normal tissue complication probability models (NTCP) and the use of these models has been advocated to select the patients that will benefit the most from proton therapy compared to IMRT.

The aim of this presentation is to demonstrate how proton therapy could increase the therapeutic ratio in head and neck cancer. We will 1) introduce basic physics and dosimetry data; 2) discuss the clinical data published so far; 3) address the issue of patient selection for IMPT; 4) discuss the current limitations of proton therapy regarding physical and biological uncertainties, as well as cost effectiveness; and 5) discuss how to objectively evaluate the value of proton therapy in the treatment of head and neck cancers.

Keynote lecture

SP-017 New imaging techniques

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Abstract text

As chemo-radiation therapy is increasingly applied to head and neck cancer, there is a growing need to develop non-invasive surrogate-biomarkers to predict and assess the response to a non-surgical treatment. Therefore, imaging techniques exploring tumor properties other from CT density, T2-T1 weighting or the single-phase "static" enhancement pattern - have been devised. These "functional techniques" aim at targeting tumor micro-architecture (DWI), perfusion (DCE-MR) and heterogeneity (texture analysis). Researches on DWI showed that a high degree of restriction of water diffusion (low ADC) correlates with increased cellular density and extracellular space, a typical feature of neoplasms. DWI researches points to high pre-treatment mean ADC and a low increment in ADC early intra-treatment being indicators of poor outcome. CT and MR perfusion techniques have been developed to investigate the changes induced by neo-angiogenesis in the microcirculation of tumor. This has been accomplished by analysis of the kinetics of the passage through the tissues of a bolus of contrast agent (DCE-CT, DCE-MR) or of an endogenous bolus (blood, ASL-MR perfusion). Presently, most of the medical literature on perfusion analysis encompasses pilot studies only. Nevertheless, one emerging finding is that neoplasms showing great heterogeneity of a parameter like Ktrans are associated to a poorer prognosis. Probably related to the presence of areas capable of surviving in conditions of hypoxia. Overall, the availability of these imaging techniques has resulted in the growth of multi-modality and multi-parametric imaging. In addition, the analysis of the quantitative data acquired by both standard and functional imaging techniques has inspired the development of novel approaches of analysis leading to the extrapolation of textural, morphologic features with the potential of providing metrics that can be used to optimize the treatment.

Keynote lecture

SP-018 HNC Biomarkers - how do we translate biology into useful assays for clinical care?

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Abstract text

With the advent of powerful new profiling technologies (i.e. next generation sequencing, RNA profiling/nanostring, liquid biopsy, multiplex immune stains) our ability to query tumor biology and answer clinically relevant questions in patient samples has increased exponentially. However, understanding clinical usefulness, technical limitations, and logistics of implementing biomarker testing in clinical practice will take significant, collaborative effort of the HNC community. In this talk we will examine three examples pertinent to HNC: 1) Emerging biomarkers for Immunotherapy, 2) the usefulness and technical limitations of liquid biopsy in curative intent and palliative care, and 3) the hidden complexities of HPV testing, and heterogeneity of HPV biology.

Proffered papers 2

OC-019 The phase III study INTERCEPTOR: preliminary results

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Purpose/Objective
On January 2010 We started a randomized multicenter phase III study comparing chemoradiation (Aldestein RTOG regimen) (CRT) versus induction chemotherapy followed by bioradiation (RT +Cetuximab). The main objective of the trial is Overall Survival and secondary end points are Response Rate (RR), Progression Free survival (PFS) role of Biomolecular prognostic factors (EGFR,HPV) and Toxicities
Material/Methods
Naïve patients with locally advanced head and neck squamous cell carcinoma (HNSCC), histological proven, of the oral cavity larynx hypopharynx oropharynx stage III or IV are eligible. Additional requirement for enrolment included adequate bone marrow function, renal function, hepatic function and age higher than 18 yr old. Treatment consisted of: Arm A Taxotere 75 mg/mq and Cisplatin 75 mg/mq day 1, 5FU c.i. 750mg/mq 96h, every 3 weeks for 3 times and Cetuximab loading dose 400 mg/mq followed by weekly 250mg/mq with a standard Radiotherapy program equivalent daily dose 2Gy up to 70 Gy; Arm B Cisplatin 100 mg/mq day 1,22,43 concurrent with the same RT scheduling. Statistic: 278 pts twill be accrued. Primary end-point is OS; secondary end-points include PFS, LRC, Complete response rate, toxicity and metastasis free survival.
Results
276/278 pts were enrolled up to now. Accrual will be stopped on December 2016 and the final analyses will be provided by April 2018. Preliminary toxicity data on 170 pts previously presented (ESMO 2015) were as follows: (85 and 85 on Arm A and B). M/F were 70/15 and 66/19 in Arm A and B respectively. Toxicities are reported as the worst grade observed during the treatment. Haematological toxicities G3 + G4 in Arm A and B were: leukopenia 8 and 6; neutropenia: 18 and 7; anaemia: 2 and 3 ; thrombocytopenia were 0 and 1 respectively in arm A and arm B. Stomatitis G3/4 were 28/4 and 23/1. Weight loss G1/2/3 weight loss was 25/10/2 and 25/ 12/2 in arm A and in Arm B respectively. Radio-dermatitis G 3/4 was 14/1 and 3/0 in Arm A and B. Dysphagia G2/3 was reported in 16/11 and 10/15 patients at first post treatment clinical evaluation. 2 patients (1 in Arm A and 1 in Arm B) developed Renal toxicity. Final results on patients' population and toxicity will be presented at the ICHNO meeting.
Conclusion
The study will finish accrual in few weeks. Data from comparison of these two arms will be presented.

OC-020 Sarcopenia predicts chemotherapy dose-limiting toxicity in patients with head and neck cancer

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Purpose or Objective
Low skeletal muscle mass or sarcopenia is emerging as an adverse prognostic factor for chemotherapy dose limiting toxicity (CLDT) and overall survival (OS) in cancer patients. In contrast to other cancers, sarcopenia has not yet been researched as a prognostic factor in head and neck cancer. We recently published a novel method for accurate and easy measurement of skeletal muscle mass in head and neck cancer patients. Using this method, we aimed to determine the prognostic impact of sarcopenia on CDLT and OS in patients with locally advanced head and neck squamous cell carcinoma (LA-HNSCC) treated with primary radiochemotherapy (RCT).
Material and Methods
All patients diagnosed with LA-HNSCC and treated with primary RCT between January 2007 and December 2011 in the University Medical Center Utrecht, the Netherlands, were included in this study. Clinical variables were retrospectively retrieved. Skeletal muscle mass was measured at the level of the third cervical vertebra (C3) using pre-therapy CT scans and controlled for height (cm^2/m^2). A cut-off point for sarcopenia was determined using optimum stratification. We performed multivariate analysis to determine prognostic factors for CDLT and OS.

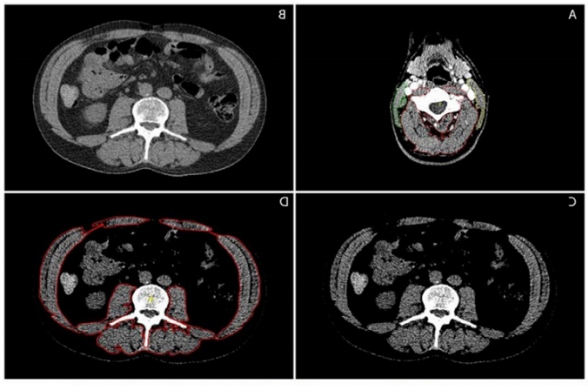

Figure 1: novel measurement of skeletal muscle mass at the level of the third cervical vertebra (image A) and regular method at the level of the third lumbar vertebra (images B, C, D)

Results
112 patients were included in this study. 34 (30.4%) experienced CDLT. The optimal cut-off value for defining sarcopenia as a predictor of CDLT was ≤43.2 cm2/m2. Using this cut-off, 61 patients were sarcopenic (54.5%). Sarcopenic patients experienced significantly more CDLT than non-sarcopenic patients (44.3% versus 13.7%, $p < 0.000$). In multivariate analysis, an increase in skeletal muscle mass was associated with lower odds of CDLT (OR 0.93, 95% CI: 0.88–0.98). OS did not differ significantly between sarcopenic and non-sarcopenic (45.1 versus 49.0 months, $p = 0.189$). Patients who experienced CDLT had a significantly lower OS than patients who did not (36.6 versus 54.2 months, $p = 0.038$).
Conclusion
Sarcopenia is an independent predictor of CDLT in LA-HNSCC patients treated with primary RCT. OS did not differ significantly between sarcopenic and non-sarcopenic patients, but patients with CDLT had a significantly lower OS. Pre-therapeutic assessment of skeletal muscle mass can help identifying patients at risk of CDLT. In the future, routine skeletal muscle mass assessment may allow for personalized cancer care regarding optimal chemotherapy dose and early supportive care interventions.

OC-021 Biomarker results from BERIL-1: buparlisib and paclitaxel in patients with platinum-pretreated SCCHN

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Purpose or Objective

BERIL-1 (NCT01852292) is a Phase 2, randomized, placebo-controlled study of the pan-phosphatidylinositol 3-kinase (PI3K) inhibitor buparlisib (BKM120) and paclitaxel in patients with recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN) who progressed on a prior platinum-based chemotherapy regimen. At the primary analysis date (cut-off Aug 31, 2015), the study met its primary endpoint, demonstrating improved median progression-free survival (PFS) with buparlisib + paclitaxel (buparlisib arm) vs placebo + paclitaxel (placebo arm) in the full population (4.6 vs 3.5 months; hazard ratio [HR] 0.65 [95% confidence interval (CI): 0.45–0.95]). Overall response rate (ORR: complete or partial response; locally assessed) was 39% vs 14% (buparlisib vs placebo arm). At the time of overall survival (OS) analysis (cut-off Mar 30, 2016), median OS was 10.4 vs 6.5 months (HR 0.72 [95% CI: 0.49–1.04]; buparlisib vs placebo arm). Here, we report the results of exploratory analyses conducted to identify predictive biomarkers.

Material and Methods

In total, 158 patients received buparlisib (100 mg/day) + paclitaxel (80 mg/m^2/week) or placebo + paclitaxel (n=79 in each arm). Genomic DNA from 84 archival tissue samples and circulating tumor DNA (ctDNA) from 112 plasma samples collected at baseline were analyzed by next-generation sequencing evaluating panels of 44 and 542 cancer-related genes (including *TP53*), respectively. The 542-gene panel used for ctDNA analysis included human papillomavirus (HPV) probes; HPV status was also assessed in 143 archival tissue samples by immunohistochemistry or fluorescence *in situ* hybridization. Mutational load was defined as the number of non-synonymous alterations detected in ctDNA samples for each patient. The correlation between OS and ORR with HPV and *TP53* status was assessed in archival and ctDNA samples.

Results

HPV-negative status and *TP53* alterations in archival tissue and ctDNA were associated with trends for improved OS and ORR (locally assessed by investigators) in the buparlisib arm compared to the placebo arm (Table).

	HPV-negative status		*TP53* alterations	
	Archival tissue (n=115/143)	ctDNA (n=89/112)	Archival tissue (n=52/84)	ctDNA (n=43/112)
Median OS, months (buparlisib vs placebo arm)	10.1 vs 5.9	11.6 vs 6.5	10.9 vs 5.9	10.1 vs 5.8
HR for OS (95% CI)	0.61 (0.40-0.92)	0.51 (0.31-0.84)	0.52 (0.28-0.99)	0.55 (0.27-1.12)
ORR (buparlisib vs placebo arm)	40% vs 11%	44% vs 19%	39% vs 8%	33% vs 8%

In addition, 86/112 (77%) patients with a low mutational load in ctDNA (<13 variants; based on the 75th percentile of patients), showed a trend for improved median OS of 12.6 vs 6.5 months (HR 0.57 [95% CI: 0.34–0.97]; buparlisib vs placebo arm) and ORRs of 44% vs 19%, respectively.

Conclusion

Addition of buparlisib to paclitaxel is an effective treatment option for platinum-pretreated patients with recurrent/metastatic SCCHN, and may be particularly beneficial in patients with *TP53*-altered, HPV-negative tumors, or those with low mutational load. Further studies are warranted to confirm the observed benefit.

OC-022 Association of patient derived xenograft formation with oral cavity squamous cell cancer outcomes

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Purpose or Objective

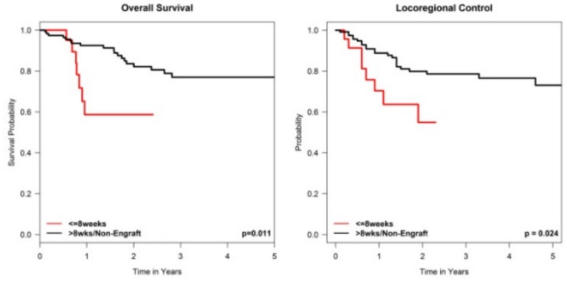
To assess correlation between patient derived xenograft formation (PDXF) and clinical outcomes following curative treatment of oral cavity squamous cell carcinoma (OCSCC).

Material and Methods

Patients undergoing curative surgery for OCSCC had tumor samples extracted and implanted into NSG (Jackson) mice to assess PDXF. Ten tumor samples per patient were implanted in murine flank and time to PDXF from any of the ten samples was recorded. Clinical outcomes for patients were collected prospectively and charts reviewed to confirm patient factors, pathologic details of surgery, adjuvant therapies, patient survival, and tumor outcomes. Univariable and multivariable analyses were performed to determine correlations between PDXF and cancer outcomes and overall survival.

Results

Between 2007-2015, 243 OCSCC patients had tumor samples explanted to attempt PDXF. Of these, 161 samples demonstrated PDXF, with a median time to PDXF of 50 days. Patients demonstrating PDXF had a high frequency of advanced nodal stage ($p<0.01$), close margins ($p<0.03$), and were more likely to receive adjuvant therapy ($p<0.02$). PDXF+ patients had significantly reduced 5-year overall survival (OS) (47% vs. 65%), higher rate of distant metastases (DM) (22% vs. 6%), and a trend to lower locoregional control (64% vs. 76%). OS was lower for PDXF+ patients in groups treated with surgery alone (64% vs. 88%) or with surgery and adjuvant radiation or radiochemotherapy (52% vs 72%). Patients who demonstrated PDXF within 8 weeks of surgery had lower survival (60% vs 92%, HR: 3.0, p=0.01) and lower locoregional control (70% vs. 90%, HR: 2.43, p=0.02) (see Figure). DM rates were similar for all PDXF patients regardless of time to PDXF, but was significantly higher than for patients who never demonstrated PDXF. Multivariable models of overall survival showed PDXF and nodal status (N0 vs N+) as independently significant ($p<0.01$).



Conclusion

PDXF in patients with OCSCC correlates with poor oncologic outcomes and lower overall survival. PDXF may provide a rapid (<8 week) biomarker to help select patients for the most appropriate adjuvant therapy following definitive surgery. PDXF in patients with OCSCC should be assessed prospectively to determine if this approach is feasible in a multi-institutional setting.

Symposium: New developments in surgery

SP-023 New developments in sentinel node biopsy of head and neck cancer

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Abstract text

Sentinel Node Biopsy (SNB) was introduced in the field of head and neck surgical oncology more than fifteen years ago. Meanwhile, the technique has been adopted for the treatment of early oral squamous cell carcinomas in the NCCN and several national guidelines. The feasibility, safety and efficacy has been proven in many published reports and meta-analyses. Several technological developments have considerably improved the process of lymphatic mapping, which consists of reliable detection and safe excision of the lymph nodes at risk and their thorough histopathologic work-up. The lecture reviews the current available evidence on SNB, reflects the most recent large scale studies, and gives an overview on current challenges and future developments. In particular, the role of new tracers, technological tools for tracer detection and possibilities of intraoperative real-time assessment of the seninel nodes are assessed.

SP-024 Integrated 3D virtual visualization of pathology and reconstructive planning in head & neck cancer

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Abstract text

Introduction: 3D surgical planning software does not allow tumor margin visualization which makes it difficult where to plan the cutting planes for the mandibulectomy or maxillectomy. 3D surgical planning is typically based on CT imaging which does not allow adequate tumor delineation. MRI allows for more precise tumor delineation, but is not easily integrated in 3D surgical planning due to limited bone segmentation options. We therefore studied a new strategy based on fusion of CT and MRI imaging in which MRI is used for tumor delineation and CT for planning of the bone cutting planes.

Methods: MRI images were projected onto the CT images for data fusion, which is typically supported by radiotherapeutic planning software (Mirada, Mirada Medical). Delineation of the gross tumour volume (GTV) on MRI was performed using a semi-automated brush tool in the software. The CT dataset, supplemented with the MRI-based tumor delineation data, was exported as a DICOM file and a radiotherapeutic structure set (RTSS) file. Converting this data towards the surgical planning software (Proplan, Materialise) required a conversion. A compatibility algorithm was written using Matlab (Mathworks). In the surgical software the cutting planes were planned, utilizing the 3D visualized tumor. Cutting guides were designed, 3D printed and sterilized for use in the OR.

Results: Twenty patients were included after being treated with either maxillectomy or mandibulectomy. On

average the GTV was 18.7cm^3 (range 6.4-66.7 cm^3). All patients had histological proven free bone tumor margins. Analysis of the accuracy of the cutting planes showed that the average deviation of the planned cutting plane was 2.1mm. Appr half of the cutting planes were closer placed to the tumor than planned with an average shift of 1.98 and 2.5 mm measured on the most cranial resp. caudal point of the buccal bone surface.
Conclusions: This study reports a method for image fusion and 3D surgical planning using the hospitals existing software architecture. Tumor visualization by fusion of CT and MRI for integration of tumor margins seems a safe method in 3D virtual planning of surgical removal of oral squamous cell carcinoma. This approach allows us to visualize not only tumors but also other useful information for surgical planning such as radiotherapy isodose lines

SP-025 Oropharyngeal surgery

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Abstract text

Over recent decades the incidence of oropharynx cancer (OPSCC) has doubled in many countries of the Developed World. Whilst much of this increase has been attributed to infection with Human papillomavirus (HPV+), recent UK data confirm a parallel rise in HPV negative OPSCC. HPV+ OPSCC affects patients who are younger, fitter, drink less alcohol and smoke less than patients presenting with HPV- head and neck cancer. Whilst they typically present with clinico-pathological features (multiple cervical lymph nodes with a high prevalence of extracapsular spread) traditionally associated with aggressive behaviour and poor treatment outcome, they, paradoxically, respond better to treatment. Current treatments based on cisplatin based chemoradiotherapy (CRT), however, result in marked early and late toxicity, particularly with respect to swallowing function. Whilst most patients with HPV+ disease will experience a favourable survival outcome, a significant minority, together with patients presenting with HPV- disease, will do less well.
This talk will highlight the contribution of contemporary surgery in the quest to develop novel
1. De-intensified treatment strategies for patients with favourable disease, in order to maintain current survival outcomes whilst reducing detrimental treatment-related effects on swallowing
2. More effective strategies for patients likely to experience a poorer outcome.

Poster discussion

PD-026 Correlation and prognostic impact of HPV and p16 on RT-outcome in larynx and hypopharynx cancer

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Purpose or Objective

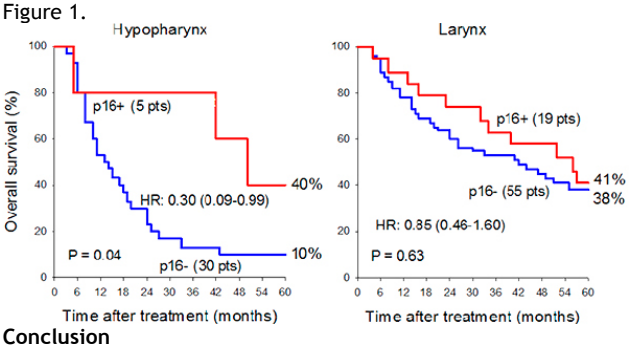
HPV has been found in head and neck cancer from all sites with a significantly higher prevalence in oropharyngeal carcinoma (OPC) compared to non-OPC. In previous randomised trials HPV-associated p16-expression has been shown to be the strongest independent factor for radiotherapy (RT) outcome in OPC. Outside OPC the correlation between HPV and p16 is less robust and the prognostic significance of p16/HPV less obvious. Previous analysis on DAHANCA patients found no prognostic impact of p16 outside OPC, but others have reported conflicting findings. With this study we wanted to investigate the correlation between HPV and p16 in advanced larynx and hypopharynx cancer and furthermore to analyse the potential prognostic impact of both markers on overall survival after primary, curatively intended RT.

Material and Methods

One-hundred-nine patients with stage III-IV larynx and hypopharynx carcinoma were identified in the DAHANCA database. All patients were treated with curatively intended primary RT according to DAHANCA guidelines from 1986-2006. The patient cohort was enriched for p16-positive tumors and as such not representative for unselected patients. Pre-treatment tumour blocks were evaluated by immunohistochemistry for p16-expression and classified as positive in case of strong cytoplasmatic and nuclear staining in >70% of tumor cells and in consideration of the typical microscopic appearance of an HPV-related tumor. HPV DNA and RNA was analysed by qPCR using specific primer sets for HPV16 E6 and E7 and HPV18 E6 and E7. Internal reference genes were *ERV3-1* and *HBB* for DNA and *ACTR3*, *NDFIP1*, and *RPL37A* for RNA.

Results

Twenty-six percent (19/74) of larynx cancers and 14% of hypopharynx cancers (5/35) were p16-positive. All p16-positive hypopharynx cancers were also positive for both HPV DNA and RNA. Of the 19 p16-positive larynx cancers only 1 was HPV DNA and RNA positive and 1 was HPV DNA positive but RNA negative. Only HPV subtype 16 was detected in case of HPV positivity. All p16-negative tumors were HPV-negative, regardless of tumor site. In univariate analysis overall survival was significantly associated with HPV/p16-status in hypophaynx: HR: 0.30 [95% CI: 0.09-0.99], whereas in tumors of laryngeal origin no prognostic impact of p16-status was found: HR 0.85 [0.46-1.60]. See Figure 1.



Conclusion

Our findings indicate a strong correlation between HPV and p16-status in hypopharynx cancer where there also seem to be a significant impact of the markers on overall survival after primary RT comparable to what is seen in OPC. Although no firm conclusions can be drawn due to the limited sample size, we find that there is a need for more investigation in the subject in order to enable proper definition of the group of patients with HPV-associated tumors and favourable prognosis, both in OPC and hypopharynx.

PD-027 cfHPV DNA as a marker of treatment results in patients with HPV-related head and neck cancer.

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Purpose or Objective
Circulating free HPV DNA (cfHPV DNA) could be found in patients with HPV-related HNSCC. Amount of cfHPV DNA may be related to treatment respond. If the response to treatment is reflected in cfHPV DNA detection, it may become a marker of treatment results. cfHPV DNA estimation after radiotherapy (RT) or radiochemotherapy in the relation to treatment results has been presented.
Material and Methods
Between 2012 and 2016 blood from 540 consecutive patients with HNSCC before definitive RT/CHRT was collected. If HPV-positive sample was identified, serial blood collections were taken after treatment and during follow-up. cfHPV DNA assessment was correlated with treatment results. cfHPV DNA complete remission (cfHPVrem) was defined as not detectable cfHPV DNA after RT/CHRT. cfHPV DNA recurrence (cfHPVrec) was defined as a detection of cfHPV DNA in previously cured patients during follow-up.
Results
In 71/540 (13%) of patients cfHPV DNA was found. At the end of treatment in all 70(98%) cured patients cfHPVrem was found. In 1 uncured patient cfDNA was still detectable. During follow up cfHPVrec was found in 9(13%) patients. Despite of no evidence of locoregional recurrence of disease on physical examination nor on imaging diagnostic (TK or MRI) PET scanning was additionally performed in these patients. PET revealed locoregional recurrence and metastatic disease in 5(7%) and 4(6%) patients respectively.
Conclusion
In patients with HPV-related HNSCC the presence of cfHPV DNA in blood reflect active cancer. Serial estimation of cfHPV DNA in cured patients may help to diagnose early treatment failure because cfHPVrec strongly suggest disease recurrence.

PD-028 Prognostic and predictive impact of HPV status in oropharyngeal cancer: the MARCH-HPV project

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Purpose or Objective
HPV-induced oropharyngeal cancers (OPC) have a better prognosis compared to classical squamous cell carcinoma of the head and neck (HNSCC). Whether HPV status is associated with a higher sensitivity to treatment modifications such as altered fractionation radiotherapy remains controversial.
Material and Methods The MARCH-HPV project is based on the first update of the Meta-Analysis of Radiotherapy in HNSCC (MARCH), which included 33 trials and 11833 patients (Blanchard et al. Rad Oncol; 111 (Suppl 1): 32). HPV status was determined according to p16 immunohistochemistry. The HPV analysis was restricted to patients with OPC and performed using a Cox model stratified by trial and adjusted on gender, age, T-stage, N-stage, radiotherapy fractionation schedule (standard, altered), p16 (positive, negative) and smoking status (never/former, current). Both prognostic and predictive effects were estimated for progression-free survival (PFS, primary endpoint) and overall survival (OS). Only prognostic effect was estimated for locoregional control and OS after first failure.
Results Data and tumor tissue from 815 patients enrolled in 4 trials (DAHANCA 6-7, RTOG 9003, ARTSCAN, RTOG 0129) was available for analysis: 350 (43%) p16 negative and 465 (57%) p16 positive. Patients with p16-pos tumors were significantly more likely to be younger (mean: 56 vs. 59 years, p=0.0002), have better performance (PS=0: 74% vs. 50%, p<0.0001), smaller tumors (T1-2: 46% versus 33%, p<0.0001), more advanced N-stage (N+: 87% versus 76%, p<0.0001) and were more often never or former smokers (77% versus 36%, p<0.0001) compared with the p16-neg subgroup. p16-status had a significant prognostic effect, with better PFS and OS in p16 positive patients: Hazard Ratio (HR)=0.42 [95% Confidence Interval (CI): 0.34;0.51] with a 37% absolute increase at 5 years for PFS, 0.40 [0.32;0.49] with a 39% absolute increase at 5 years for OS. Locoregional control and OS after first failure were also significantly better in p16 positive patients with HR of 0.31 [0.22;0.44] and 0.64 [0.47;0.87], respectively. Smoking also independently influenced outcome and never/former smokers had better prognosis than current smokers with HR of 0.61 [0.50;0.75] and 0.58 [0.47;0.72] for PFS and OS, respectively. Heterogeneity between trials was observed for PFS (p=0.03), and OS (p=0.02). Use of random effect model did not change conclusions. There was no statistical significant interaction between HPV status and fractionation schedule (p=0.45 for PFS and p=0.58, for OS) and as such no predictive impact of HPV could be demonstrated.
Conclusion The significant prognostic effect of HPV in OPC was confirmed in this pooled analysis based on individual patient data, but HPV status was not found to be predictive of outcome after altered fractionated radiotherapy.
Supported by PAIR-VADS.

PD-029 Causes-of-death underestimate the burden of head and neck cancers in France (EPICORL study)

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Purpose or Objective: Patients with head and neck (H&N) cancer carry the highest risk of secondary primary cancers. Determining the underlying cause of death is conflicting in presence of multiple primary cancer sites, and the burden of H&N cancers may be underestimated by causes-of-death statistics.
Material and Methods: Using the French National Hospital Discharge (PMSI) database, we identified all adult patients residing in metropolitan France and diagnosed with squamous cell carcinoma at hospital (ICD-10: C00-C06; C09-C14; C30.0; C31; C32) in 2008-2012. Among patients who died at hospital, we considered advanced H&N cancer (stage III/IV at diagnosis or disease progression) as a cause of death. We recorded competing causes of death from

other primary cancer sites and Charlson comorbidities. Death records from PMSI were compared to National causes-of-death statistics (CEPIDC) using the same ICD-10 definitions. The mortality gap (PMSI minus CEPIDC) was described overall and by sex, age category, region, H&N cancer site, and year. We further explored the role of primary cancer other than H&N cancer and Charlson comorbidities other than cancer on misclassification bias (i.e., a positive mortality gap) in multivariate Poisson regression.

Results

Of 94,672 French patients identified with H&N cancer in 2008-2012, 41,503 patients with advanced H&N cancer died at hospital. In comparison, 25,647 (61.8%) deaths were attributed to H&N cancers in National causes-of-death statistics during the same period. Misclassification bias increased from 2008 to 2012 (+8% by year). In multivariate Poisson regression, misclassification bias was maximum in patients with oral cavity or oropharynx cancer (except tongue), and misclassification bias was higher in patients with hypopharynx cancer as compared to laryngeal cancer. Misclassification bias significantly increased in presence of another primary cancer recorded before or at diagnosis of H&N cancer or distant metastasis. Misclassification bias was not associated with severe comorbidities other than cancer, but significantly increased in patients receiving palliative care. Correcting for mortality outside hospital would worsen the mortality gap from 38.2% to 49.8%.

Conclusion

The study results suggest that the actual burden of H&N cancer is underestimated by at least a third by French National causes-of-death statistics.

Misclassification bias of the number of deaths attributable to H&N cancer increased in the recent years.

PD-030 Survival of patients with head and neck cancers in France (EPICORL study)

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Purpose or Objective

The aim of this study was to have an exhaustive description of the recent epidemiology of head and neck squamous cell carcinoma (H&N SCC) patients in France.

Material and Methods

We completed a retrospective cohort study using the French National Hospital Discharge (PMSI) database. We identified all adult patients residing in Metropolitan France and diagnosed with H&N SCC (ICD-10: C00-C06; C09-C14; C30.0; C31; C32) in 2008-2012. Cancer location and stage (early I/II; locally advanced III/IVb; distant metastatic IVc) were determined at diagnosis. Time to relapse, secondary primary H&N cancer, other primary cancers, Charlson comorbidities were recorded until last hospital stay in 2013.

Hazard ratios (HR) for in-hospital death were estimated in a multivariate Cox model with use of time-dependent variables.

Results

131,965 French adults were identified with H&N SCC at hospital in 2008-2012: 79.4% were male with median (IQR) age of 61 (54-71) at diagnosis. Survival at 5 years was 34.0% (95% CI, 33.5%-34.4%) over a follow-up of 196,000 person-years. As compared to 23.2% patients with laryngeal cancer, survival was significantly lower for 29.3% patients with oral cavity cancer (HR=1.24), 19.5% patients with oropharynx cancer (HR=1.22), or 12.8% patients with hypopharynx cancer (HR=1.26). As compared to 30.7% patients with early cancer at diagnosis, survival was significantly lower for 57.2% patients with advanced cancer (HR=1.65) and 12.1% patients with distant metastasis (HR=6.19). Relapse rate at 3 years was 31.9% in patients with early cancer and 51.8% in patients with advanced cancer, with significantly lower survival (HR=5.92). Secondary primary H&N cancers were detected in 6.1% patients at diagnosis (HR=1.15) and 3.2% patients at 3 years (HR=1.70). During the study period, about 31% patients had another primary cancer (including 10.1% lung) and about 52% patients had severe comorbidities other than cancer incurring significantly lower survival.

Conclusion

This is the first national study on the epidemiology and survival of patients with H&N SCC in France. Distant metastasis at diagnosis and relapse in patients with early or locally advanced cancer had the strongest impact on prognosis. In addition, about two-third patients had another primary cancer or severe comorbidities other than cancer worsening prognosis over time.

PD-031 Quality of life, health status and work in head and neck cancer survivors treated with radiotherapy

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Purpose or Objective

Head and neck cancer (HNC) survivors are an increasing population, due to the improvement in diagnosis and treatment. The aim of this study is to analyse the quality of life, health status, psychological status and work activity in HNC survivors.

Material and Methods

The population was composed of a series of 50 HNC patients (>3 years post-diagnosis) treated in our institution from 2006 to 2013, having no signs of cancer recurrence to date. Quality of life was measured with EORTC QLQ-C30 and HN35. The health status items measured were: nutritional assessment using the Malnutrition Universal Screening Tool (MUST), cardiovascular risk (with the HeartScore® tool), toxic habits (tobacco and alcohol by the Alcohol Use Disorders Identification Test (AUDIT)) and physical activity (with the Global Physical Activity Questionnaire(GPAQ)). Psychological evaluation was performed by the State-Trait Anxiety Inventory (STAI) and the State-Trait Depression Inventory (STDI). Patients were asked about their work status before and after cancer treatment.

Results

The mean age was 64 years (range, 43-84 years) and 46 patients (92%) were male. The most frequent site of the primary tumour was larynx (48%) and the main histology squamous cell carcinoma (76%). 72% of patients had advanced cancers (stages III and IV), whereas 26% had

stages I and II. All patients received radiotherapy, of which 62% were given 3DRT technique and 38% IMRT technique. Surgery was performed 34%, and 40% underwent neck dissection. Most relevant results are described in Table 1. There were differences in cognitive functioning according stage and neck dissection. Physical functioning was related with age and primary tumour surgery. Emotional scale was also related with surgery. Global quality of life and fatigue were worst in >65 years' patients. Senses problems were linked to stage and surgery. There were more teeth problems regarding location. Dry mouth was related to stage and location of the tumour. Problems in opening mouth were also related to stage. Teeth problems were linked to location. Sticky saliva is found in active smokers. Regarding health status, we found larger sedentary hours in non-smokers. There were no differences between groups in MUST score, although 14% of patients were at high risk of malnutrition. Cardiovascular risk was high or very high in 62% of the patients. AUDIT score showed no problems with alcohol in the 88% of the patients. We found high prevalence of psychological symptoms (56% for anxiety and 46% for depression), with no differences between groups. There were also more not working patients related to surgery and location of the tumour.

Main relevant results in Head and Neck cancer survivors			
EORTC QLQ-C30 questionnaire*			
	≤ 65 years	**> 65 years**	***p value***
Physical functioning	100	86.7	0.057
Global quality of life	79.2	77.1	0.092
Fatigue	0	22.2	0.006
	Stage I-II	**Stage III-IV**	
Cognitive functioning	100	83.3	0.020
	Non Surgery	**Surgery**	
Physical functioning	100	86.7	0.058
Emotional functioning	100	91.7	0.080
	Neck dissection	**No neck dissection**	
Cognitive functioning	100	83.3	0.099
EORTC HN35 questionnaire*			
	Stage I-II	**Stage III-IV**	***p value***
Senses problems	0	62.5	0.016
Opening mouth	33.3	100	0.094
Dry mouth	0	100	0.043
	Non smoker	**Smoker**	
Sticky saliva	0	50	0.053
	Non Surgery	**Surgery**	
Senses problems	16.7	66.7	0.001
	Larynx-Hipolarynx	**Other locations**	
Teeth	0	33.3	0.027
Dry mouth	33.3	66.7	0.007
GPAQ questionnaire			
	Non Smokers	**Smokers**	***p value***
Mean sedentary hours	5.5	2.8	0.042
Work activity			
	Larynx-Hipolarynx	**Other locations**	***p value***
Not working	66.7%	33.3%	0.063
	Non Surgery	**Surgery**	
Not working	47.6%	52.4%	0.016

Table 1.

*EORTC questionnaires: In functional scales, higher scores indicate better functioning, and in symptoms scales, higher scores indicate a higher level of problem

Conclusion

Our study indicates that clinical and therapeutic characteristics impact on the quality of life of HNC survivors. We have found non covered needs in physical, emotional and cognitive spheres, and in clinical issues regarding local symptoms.

PD-032 Pharyngeal constrictor muscle dose correlated with dysphagia after radiotherapy in head and neck

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Purpose or Objective

Dysphagia is one of the main sequellae of radiotherapy for head and neck cancers. The aim of this prospective study was to to identify predictive factors of dysphagia in patients treated with intensity modulated radiotherapy (IMRT).

Material and Methods

Between 2011 and 2015, 226 patients (90 oropharynx, 48 oral cavities and 70 pharyngo-larynx, 11 nasopharynx and 7 unknown primary) were treated with IMRT with bilateral neck irradiation. Hundred had postoperative IMRT and 133 patients received concurrent chemotherapy. Prognostic factors studied were: the pharyngeal constrictor muscle mean dose, the larynx mean dose, age, location, tumor stage, xerostomia, mucositis, surgery, and concurrent chemotherapy.

Results

The median follow up was 17 months. The one year loco regional control and overall survival were 81 and 77% respectively.

At 3 monts and one year, grade ≥ 3 dysphagia were 34 and 13% respectively. The average duration of enteral feeding was 209 days and was correlated with the pharyngeal constrictor muscle mean dose (p = 0.012). Acute dysphagia grade ≥ 3 was influenced by the concurent chemotherapy (p <0.001), pharyngeal constrictor muscle mean dose (> 55Gy, p = 0.014), mucositis (p <0.001), xerostomia (p = 0.0013), age <55 years (p = 0.016) and a location other than pharyngo-larynx (p <0.001). In multivariate analysis, only mucositis (grade 3-4; OR: 7.85), the concurent chemotherapy (OR: 5.75) and location other than pharyngo-larynx (OR: 0.19) were independent prognostic factors. At 1 year, in univariate and multivariate analysis, only the pharyngeal constrictor muscle mean dose was an independent prognostic factor with a threshold at 55Gy (19% vs 4%, P = 0.037, OR: 4.73).

Conclusion

The acute dysphagia is related to concurent chemotherapy.Pharyngeal constrictor muscle mean dose > 55 Gy is associated with the risk of long-term dysphagia grade ≥ 3 .

PD-033 Cetuximab + RT shows an excellent long term OS in patients with both high ADCC and high EGFR

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Purpose or Objective

Cetuximab induces ADCC, but the clinical relevance of this additional mechanism of action is unknown.

In a multi-step proof of concept project we investigate the impact of individual ADCC activity in pts treated with cetuximab and radiotherapy (BRT) on the following outcome, by itself or in function of the cetuximab target EGFR.

In the present up-date, we investigated the role of ADCC perturbation during therapy, the relationship between

ADCC activity and the total number of circulating NK cells, and the interaction between iNKT and ADCC.

Material and Methods

In a multi-step proof of concept project we investigate the impact of individual ADCC activity in pts treated with cetuximab and radiotherapy (BRT) on the following outcome by itself or in function of EGFR expression. Additional analyses are also considered. A population of pts treated with chemo-radiotherapy (CRT) is considered as no formal control.

ADCC was measured in vitro by LDH release, using purified NK cells from fresh peripheral blood of pts.

The following analyses were performed: ADCC basal value and during treatment. EGFR status by IHC NK count in peripheral blood iNKT count in peripheral blood CD3+ count in peripheral blood

Results

A total of 58 pts treated with cetuximab + RT (43) or with CDDP + RT are evaluated.

In a previous paper we reported that complete responses did not correlate with either ADCC or EGFR expression. However, using a mixed score considering both ADCC and EGFR expression, they correlate with CR (p=0.04) in BRT treated pts. Additionally, pts showing both high basal ADCC and EGFR+++ achieved a 4-year OS of 100% compared with the others (p=0.02). No differences were observed in CRT treated patients.

Additional analyses here reported show that changes of ADCC induced by treatment do not correlate with outcome and basal ADCC remains the only prognosticator in patients treated with BRT.

We also observed that the basal value of ADCC is more important than the basal number of NK. This observation, made at baseline, suggests the presence of an impaired NK cell population in HNC pts, and that impairment is not treatment related.

We evaluate the combined role of iNKT and high basal ADCC activity since we observed a significant impact on outcome in colon cancer pts harbouring both high iNKT and high ADCC compared to other (p=0.0075). Analysis is under progress and results will be presented at the conference.

Conclusion

Our data show that ADCC plays an important role in cetuximab activity and, if confirmed in prospectic analysis, suggest that patients with high basal ADCC and EGFR+++ should be treated with cetuximab and RT

PD-034 Subsite-dependent prognostic impact of age in patients with nasopharyngeal and oropharyngeal cancer

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Purpose or Objective

Outcome results in elderly head and neck cancer (HNC) patients (pts) treated with concurrent chemoradiation are controversial. Comparative effectiveness analyses showed a lack of benefit in multimodal treatment; however, retrospective highly selected series reported older patients to have similar outcome compared to younger ones albeit with high burden of toxicities. No subsite-related differences were specifically investigated ever.

Material and Methods

Consecutive locally advanced oropharyngeal (OPC) and nasopharyngeal cancer (NPC) pts treated at our institution with concurrent platinum based chemotherapy (CHT) and intensity modulated radiation therapy (IMRT) techniques from 2004 to 2015 were retrospectively evaluated. Overall survival (OS) and Relapse Free Survival (RFS) Kaplan-Meier curves were estimated and compared with the log-rank test; acute toxicity rate > G3 according to Common Toxicity Criteria Adverse Event v4.0 was also analyzed, distinguishing between patients >65 years old (elderly) and ≤65 old. HPV status was recorded in all OPC patients.

Results

Globally, 375 pts received IMRT-CHT, 215 in OPC and 160 in NPC cohort. Elderly pts represented 26% and 11% of OPC and NPC pts, respectively. OPC HPV positive cases were similarly represented in older (73% of the cases) and younger pts (66%); HPV positivity maintained a significant prognostic role independently of age and also across different age group. On the contrary, age did not significantly impact on survival in OPC. Five-years RFS was 68% in older versus 76% in younger patients (p=0.391); the corresponding figures for OS were 93% versus 87% (p=0.541). There was no significant difference in cumulative acute toxicity rate ≥ G3 (39% in elderly vs 36% in younger, Fisher test p =0.778). When analyzed separately, no difference was shown for what concerns dysphagia and mucositis. NPC pts showed a different outcome according to age both in terms of RFS (5-years probabilities 41% in elderly vs 80% in younger pts, p <0.001) and OS (48% vs 90%, p <0.001), which turned out to be a negative prognostic factor in this disease. Also for NPC pts, the two age subgroups did not significantly differ in acute toxicity rate ≥ G3 (56% vs 61%, p = 0.800).

Conclusion

We observed a subsite-specific impact of age on treatment outcome: older NPC pts showed markedly worse survival than the younger counterparts, while in OPC pts such an effect was inconsistent. HPV status was confirmed to be a positive prognostic factor independently of age.

Symposium: New developments in systemic treatment

SP-035 Is there still a role for targeted signaling agents in head and neck cancer?

C. Le Tourneau[1]

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Abstract text

Head and neck cancers are essentially being treated with conventional treatments including surgery, radiotherapy and chemotherapy. EGFR is the only target that underwent clinical translation with the use of cetuximab, a monoclonal antibody targeting EGFR, either in combination with radiotherapy in the locally advanced setting or in combination with chemotherapy in first-line metastatic and/or recurrent setting. More recently, immune check point inhibitors targeting PD1 have been demonstrated to improve survival in second line metastatic and/or recurrent setting with a more favorable safety profile. Many clinical trials are now ongoing with these agents in first-line metastatic and/or recurrent setting and in the locally advanced setting. The question is whether there is still a role for targeted thérapies in head and neck cancer treatments beyond EGFR. Several targets have been identified in head and neck cancers. We aim to to review in this talk the results of the trials that have evaluated these targeted thérapies, as

well as to discuss their perspectives in the future.

SP-036 Immunity and immune toxicity: clinical management of immune checkpoint inhibition

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Abstract text

Immunotherapy with immune checkpoint inhibitors is rapidly developing as the fifth treatment modality in concert with surgery, radiotherapy, chemotherapy, and targeted therapy. Relevant clinical activity and especially pong-tem responses have been observed in a variety of histologies, mainly in cancers with high mutational load. However, novel toxicities have also been observed, some of them requiring tight clinical and pharmacological management. In general, these toxicities are immune-mediated and resemble a minor form of graft-versus-host disease after allogeneic stem cell transplantation. Following tightly the established management guidelines, toxicities can be detected early on and usually be confined to low grade with minor impact on patient's quality of life. The most important general principle is derived from the observation that more severe autoimmune toxicities require immunosuppressive medications, and that treatment of autoimmunity does not negatively impact on immune-mediated control of the neoplastic disease. Actually, many patients in whom severe autoimmune toxicities were observed and adequately managed belong to the group of patients with prolonged complete resolution of metastases. Organ systems most often affected by autoimmune toxicities include skin, liver, colon, lungs, kidneys and endocrine glands. While early recognition of toxicities to liver, kidney and endocrine glands can be achieved by monitoring liver enzymes, creatinine, TSH and cortisol, early recognition of colitis and pneumonitis require close clinical attention. In patients with diarrhea colonoscopy is indicated in case of pain or bloody stool. In patients with unexplained cough or shortness of breath, slight end-inspitatory rales may be the only clinical sign pointing towards extensive pneumonitis with profound infiltates on CT scan. Immediate and prolonged intervention with glucocorticoids, and sometimes immunosuppressive drugs is necessary to control these transient autoimmune reactions, only the endocrine toxicities may be permanent.

SP-037 Immunotherapy beyond anti PD1 inhibitors

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Abstract text

Immunostimulatory antibodies blocking the PD-1 co-inhibitory pathway have potent antitumor activity in a sizeable proportion of patients with various types of cancer. We will discuss the likely mechanism of action of these treatments, the proposed predictive biomarkers and the potential reasons for treatment failure. The latter include low tumor antigenicity, which in advanced cancer might result from previous immunoselections by antitumor T cells, poor immunogenicity of the tumor i.e. the absence of potent spontaneous antitumor T cell responses, and various mechanisms of local immunosuppression. Several of these mechanisms of tumor resistance to cancer immunotherapy with PD-1-blocking antibodies can be circumvented by drugs that are or will be tested soon in combination therapies.

Keynote lecture

SP-038 Clinical implementation of adaptive radiotherapy: challenges ahead

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Abstract text

Intensity modulated radiotherapy is the standard of care in organ preserving treatment of head and neck cancer. Highly conformal dose distributions are optimized based on the anatomy of the pre-treatment planning CT. However, during treatment, accurate delivery of the planned dose can be influenced by anatomical changes which occur, especially by non-rigid anatomical changes for which set up protocols cannot correct. Anatomical changes during treatment may be related to change in tumor volume, weight, edema, muscle mass or fat distribution. Several studies have described changes of gross tumor volume (GTV) and organs at risk (OAR) in size, shape and position during a course of radiotherapy. In the presence of these anatomical changes, the actual delivered dose may differ significantly from the planned dose. Anatomical changes during treatment can be accounted for with adaptive radiotherapy (ART) where the radiation plan is adjusted during the course of treatment. In recent years, considerable efforts have been made to develop ART to compensate for under-dosage of the target volumes or over-dosage of OAR. Ideally, the treatment plan is adapted on a daily basis. At the moment however, the effort of re-imaging, re-contouring and re-planning does not outweigh the advantage and ART is not routinely used for all patients. Selection of the appropriate patients for ART remains a challenge, as well as the timing of re-scanning. Moreover, re-definition of target volumes raises the question whether the clinical target volume (CTV) can safely be adjusted to spare OAR. For instance, field size reduction following visible tumor regression assumes that microscopic disease in the CTV behaves congruent with changes in the visible GTV. These challenges for the clinical implementation of ART in head and neck cancer patients will be discussed in this presentation.

Symposium: Adenoid cystic carcinoma

SP-039 Adenoid cystic carcinoma: considerations in surgical approach and factors modifying expected outcome following treatment

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Primary surgery

In AdCCs that are deemed resectable, the gold standard is free-margin resection with postoperative radiotherapy (RT). Clear margins are hard to achieve, given the

propensity for infiltrating adjacent tissues, mostly by perineural invasion. Combined with frequent origin in anatomical sites with difficult access, the surgeon is frequently disappointed following the attempted clear margin resection. A University of Michigan study reported 80% of skull base AdCC resection specimens with positive surgical margins, despite the preoperative impression that resection with clear margins would be possible (Naficy,1999). The latest trend is thus against super-radical surgery that still frequently fails to achieve negative margins. In this line, for parotid AdCC, there is consensus to preserve a normally functioning facial nerve, relying on RT to deal with residual microscopic disease (Vander Poorten,2012).Historically, a low prevalence of occult nodal metastasis in AdCC is assumed. Neck dissection is classically only performed for cN+ disease, which is infrequently encountered. For specific MiSG subsites (oral cavity-oropharynx), recent scrutinized literature appraisal of "elective neck dissection (END) specimens" suggests a higher rate of occult metastasis, ranging from 15 to 44%, (Suarez, 2016) and especially in AdCC with high-grade transformation, lymph node metastasis may occur in 43–57% of patients (Hellquist,2016), suggesting to reconsider the role of END in these patients. It remains unclear, however, whether regional control, let alone survival, is improved by performing END as compared to primary RT to the neck nodes.

Salvage surgery

Local salvage surgery is rarely feasible and indicated(Spiro 2013). When local recurrence occurs, frequently distant metastasis (DM) is imminent. In the MSKCC database of 191 patients with recurrent SGC only 2 of 22 patients with locally resectable disease were effectively salvaged. Generous radical surgery should be considered and almost invariably patients will need flap reconstruction (free flaps, but frequently pedicled flaps like the MPM are a sound option in extensively operated and radiated necks). There are retrospective data that re-resection followed by chemo-reirradiation gives better DFS in those selected for surgical salvage(Pederson,2010; Erovic,2010).

Prognostic factors

In general, prognosis of AdCC is poor and the experience of many authors is that ''cure is never achieved'' in this''clinically high grade'' neoplasm. Disease-related deaths occur for as long as patients are followed. One series reports an overall survival of 24.5% and a recurrence-free survival of 22.6% at 15 years. (Huang,1997). In the posttreatment setting, the appearance of DM determines long term prognosis. In one study, on average, death occurred at 32 months following the occurrence of lung metastases and at 21 months following metastases elsewhere (van der Wal,2002). The most important clinical factor is TNM stage at presentation, which is closely linked to the site of origin (Spiro and Huvos,1992;Vander Poorten,2000). Remarkably early stage disease can do well, with T1N0 tumors being reported with 10, 15 and 20 years DSS of 94%, 81% and 73% respectively, and T2N0 already doing significantly worse (DSS 50%, 40% and 33% at 10, 15 and 20 years, respectively). As stated above, nodal metastases can be histopathologically detected when the primary tumor is surgically removed together with a neck dissection. Metastases are often small, which may explain why clinical examination or imaging may fail to detect them. Histological prognostic factors are tumor grade and perineural/intraneural invasion. Tumors showing a predominantly "solid" growth pattern have been repeatedly associated with worse prognosis, advanced stage and development of DM. Perineural invasion has been inconsistently associated with DM and adverse final outcome. In this respect, recently, a prognostically relevant distinction has been made between perineural (P2: no impact on survival) and intraneural invasion (P1: independent predictor of poor prognosis).(Teymoortasch,2014;Amit,2015)

Among molecular biological factors with prognostic relevance are (1) cell cycle-based proliferation markers (high Ki-67, PCNA, MCM and AgNOR expression), and specific genetic and epigenetic changes in (2) growth factor receptor proteins and ligands(c-KIT, VEGF-C/VEGFR-3, Eph2a, EGFR, NGF), (3) cell cycle oncogenes (cyclin D1, SOX-4, SOX-10, NFκB, PI3K, STAT3 and mTOR), (4) DNA damage repair proteins (p53), (5) cell adhesion proteins (loss of E-cadherin expression, ICAM-A, increased expression of Ezrin and ILK), (6) estrogen receptors, (7) lymphangiogenesis markers (podoplanin) and (8) transcription factors. Most notably the reciprocal translocation t(6;9) (6q22–23; 9p23–24), fusing the MYB gene on chromosome 6q22–q23 and the transcription factor NFIB on chromosome 9p23–p24, has recently been associated with prognosis in AdCC.

SP-040 Radiotherapy in adenoid cystic carcinoma (ACC) of the head and neck

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Abstract text

Adenoid cystic carcinoma (ACCs) is a rare disease with an incidence of 1.3/100,000 per year. Many patients are diagnosed with advanced tumours, especially when these are located in the paranasal sinus, hence both surgical and radiotherapy treatments remain a challenge. Standard treatment consists of complete resection followed by adjuvant radiotherapy in the presence of risk factors. Due to their aggressive local growth patterns, high radiation doses are needed to achieve long-term local control. In standard photon radiotherapy though, this can be difficult to achieve faced with close proximity of critical structures at the base of skull. Neutron radiotherapy for salivary gland malignancies was explored in the early 1980s due to its increased biological effectiveness and did indeed demonstrate superior local control rates. Long-term toxicities however, were substantial. Due to their physical properties, charged particle beams can achieve highly conformal dose distributions through sharp dose gradients thereby leading to improved normal tissue sparing especially at complex anatomical sites. In consequence, the use of particle therapy and especially carbon ion therapy (C12) for adenoid cystic carcinoma has been intensively investigated by both Japanese and European groups. Recent analyses showed significantly improved control and survival rates in patients treated with a combination regimen of C12 plus IMRT. Results were confirmed by the prospective COSMIC trial and validated in a larger patient cohort. Moreover, control rates did not differ according to resection status in patients with T4 tumours treated C12. Therefore, debulking surgery with sometimes substantial morbidity may have to be reconsidered. Management of local recurrence following full course radiotherapy also presents a problem in ACC. When surgery is not feasible, the most active chemotherapeutic regimen can achieve response rates of between 40-50%. Due to the physical beam properties, re-irradiation with charged particles and comparatively high re-irradiation doses can be feasible and achieves response rates of >50% with moderate toxicity. However, further dose escalation needs to be considered carefully as the risk of higher-grade late toxicity increases. Particle therapy is also a good option to treat patients with locally recurrent disease, when surgery may not be feasible. In summary, particle therapy is a good treatment option

with promising local control rates especially in advanced ACC. The use of tumour debulking in advanced ACC may have to be reconsidered. In cases of local tumour relapse, C12 may be a good option when surgery is not feasible but has to be used with caution.

Proffered papers 3

OC-042 Re-irradiation with curative intent of squamous cell carcinomas of the head and neck in Denmark

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Purpose or Objective
To review outcomes of patients with recurrent squamous cell carcinoma of the head and neck (SCCHN) treated in five Danish institutions with definitive re-irradiation (RRT).
Material and Methods
We retrospectively reviewed the medical records and data from the Danish Head and Neck Cancer Database (DAHANCA) of patients with unresectable loco-regional recurrent or new primary SCCHN treated with definitive RRT with or without chemotherapy from January 1, 2007 through December 31, 2014 at five oncology centers in Denmark. The primary aim was to analyze disease-specific survival (DSS) and overall survival (OS) in a defined cohort and to report patient characteristics, cumulative radiation doses and systemic treatment.
Results
We identified 73 patients that received IMRT-based RRT. The predominant symptoms were dysphagia (22%) and pain (46%). 75% were recurrent stage IV. 74% were either pharyngeal cancer or a localized neck recurrence. RRT of 42-68 Gy resulted in cumulative radiation doses between 70 to 142 Gy (median 120 Gy). The majority was treated with hyperfractionated RRT; 41% received concomitant chemotherapy (median 5 cycles) and 35 patients (48%) had surgery at some point. Only one patient terminated treatment prematurely, all others completed the full treatment course.
The most prevalent side effects were difficulty swallowing (37%), grade 3 mucositis (29%), and 24 patients had a nasogastric feeding tube, which was permanent at last follow-up in 10.
Survival data were available for 70 patients. With a median follow-up for death of 15.8 months (range 1.4-100.7), the 5-year DSS was 35% and the 5-year OS 27%. Twenty-four patients (34%) were still alive at the end of the study.
Conclusion
This nation-wide study confirms that IMRT-based RRT can achieve long-term disease-control in a about one third of patients with recurrent SCCHN. Compliance to definitive multimodality treatment was high and the data support the use of RRT for SCCHN patients as a salvage treatment approach.

OC-043 Re-irradiation in head and neck cancers: A single institution prospective cohort study

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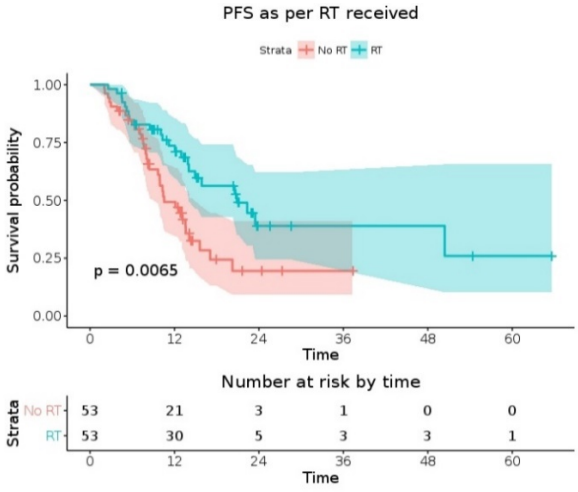
Purpose or Objective
To report the patterns of care and outcomes of patients of recurrent head neck cancer receiving re-irradiation (reRT) in a prospective cohort treated at a tertiary cancer care center in India.
Material and Methods
Since January 2014, 180 (male-150 , female- 30) patients were screened and prospectively accrued on this IEC approved study, after obtaining informed consent. Treatment decisions were taken in a multidisciplinary clinic. Analysis was conducted on 164 patients in whom treatment details after diagnosis of recurrence were available. Descriptive analyses conducted included frequencies for categorical variables and median (range) for continuous variables. Survival was estimated using the Kaplan Meier method. Propensity score matching using nearest neighbour matching was used to match patients who received and did not receive reRT with respect to variables of age, gender, site and stage of recurrence, disease free interval, nature of recurrence (second primary / true recurrence) and if the patient underwent surgery. Outcomes data was also calculated for the matched group.
Results
The median age was 56 yrs (17-95yrs). Oral cavity was the commonest site of the recurrence (n = 90, 55%). The median follow-up of the entire cohort was 12 months. 110 patients were treated with Surgery with / without adjuvant reRT, while definitive re-irradiation was offered to 37 patients (33%). 17 patients (10%) received chemotherapy or best supportive care only.
Most common cause of not considering reRT (n=53, 32%) were high grade of late toxicities (n=24, 45%) and extensive nature of recurrence (n= 12, 23%). All patients received re-RT with EBRT and the median dose delivered was 60Gy. Conformal techniques were used in 91 patients (88%) mainly in the form of IMRT (94%) and 3DCRT (6%) Concurrent chemotherapy was given in 16 patients(10%). Median overall survival (OS) was not reached, while the median progression free survival (PFS) was 14.9 months (95% CI: 13.6 - 20.9 months). PFS was significantly better in patients receiving reRT (20.0 vs 10.5 months, p = 0.003). This benefit was maintained in the 106 patients in the propensity score matched group (median PFS 34.4 vs 23.6 months, p = 0.01). Grade III - IV late toxicities were seen in 11 patients (10.2%), mostly in the form of subcutaneous fibrosis.



Conclusion
With proper case selection reRT can be delivered with acceptable toxicities and is associated with improved outcomes.

OC-044 ART DECO (CRUK/10/018): dose escalated vs standard dose IMRT in locally advanced head and neck cancer

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Purpose or Objective
Radical (chemo)radiotherapy offers curative treatment for patients with locally advanced laryngeal or hypopharyngeal cancer. IMRT permits safe dose-escalation and hence potential improved locoregional control given reduction in volume of normal tissue receiving high dose radiation.
Material and Methods
Patients with histologically squamous cell laryngeal or hypopharyngeal cancer (AJCC III-IVa/b) were randomised to dose-escalated (DE-IMRT) (primary tumour: 67.2Gray(Gy)/28 fractions(f), at risk nodes: 56Gy/28f) or standard dose (ST-IMRT) (primary tumour: 65Gy/30f, at risk nodes: 54Gy/30f) IMRT. Patients received 2 cycles concomitant cisplatin, and up to 3 cycles platinum-based induction chemotherapy. Treatment allocation (1:1) used minimisation, balancing for centre, tumour site, nodal status and planned chemotherapy. Primary endpoint was locoregional failure- free rate (LRFFR) i.e. time to locoregional relapse or completion of radiotherapy in patients with persistent disease 3 months after treatment (clinical assessment). Target recruitment was 354 patients; 100 events required to detect improvement in 2-year LRFFR from 60% to 77.5% (two-sided α=0.05, 90% power). LRFFR was analysed using competing risks methodology (with death as competing event), compared between groups by Gray's test. Secondary endpoints (α=0.01) included toxicity (CTCAEv4.0, LENT SOMA), patient-reported quality of life and overall survival.
Results
276 patients (138 ST-IMRT; 138 DE-IMRT) were randomised (2011-2015) from 32 UK centres. 84% were male, 66% had laryngeal tumours, 98% were N0-2, mean age was 62 years. Planned chemotherapy was 40% induction and concomitant, 48% concomitant only, 13% none. Recruitment stopped early due to planned interim futility analysis (subhazard ratio (SHR)>1 after 50% required events). 32/138 (23%) ST-IMRT and 37/138 (27%) DE-IMRT patients reported LRFFR events, SHR for DE-IMRT 1.22 (95%CI 0.76–1.94), p=0.42. Grade≥2 acute pharyngeal mucositis and 3 month post-RT pharyngeal dysphagia was higher with DE-IMRT (p=0.008, p=0.01 respectively).
Conclusion
There was no evidence for a statistically significant improvement in locoregional control with DE-IMRT compared with ST-IMRT. DE-IMRT was associated with a worse toxicity profile.

OC-045 Recurrence patterns after 40 Gy to the elective treated neck in head and neck cancer.

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Purpose or Objective
To investigate the patterns of regional recurrences with emphasis on recurrences in the electively irradiated lymph node regions after dose de-escalation to 40 Gy (EQD2Gy) in head and neck cancer.
Material and Methods
Two hundred thirty-three patients treated with radio(chemo)therapy using **40 Gy (EQD2Gy) to the** elective lymph node regions were included. All regional recurrences were reconstructed and projected on the

initial radiotherapy planning Computed Tomography studies to identify the localization of recurrence. Furthermore, patient and treatment characteristics were correlated with the regional recurrences to identify risk factors.

Results

The median follow-up in our study was 26 months. Overall- and disease-specific survival at 2 years were 71.2% (95% CI 65.3-77.1) and 64.2 % (95% CI 59.2-69.3), respectively. Local, regional and distant control at 2 years was 84.1% (95% CI 79.1-89.2), 89.2% (95% CI 84.3-94.1) and 83.2% (95% CI 76.3-90.1), respectively.

The actuarial rate of recurrence in the electively irradiated lymph node regions was 3.9% (95% CI 1.8-6.0) at 2 years. No significant associations could be observed between recurrence in electively irradiated lymph node regions and age, gender, tumor site, stage, or the presence of human papillomavirus in oropharyngeal cancers (table 1).

Patient characteristics			Number of events (regional recurrences in elective lymph nodes)	
Age	In years (range)	61 (38-86)	≤60 4 60-70 3 ≥70 2	p= 0.41
Gender	Male Female	190 43	7 2	P=0.84
Site	Oral cavity Oropharynx Hypopharynx Larynx CUP	16 115 51 47 4	2 5 2 0 0	P=0.63
HPV-status oropharynx	Positive Negative Unknown	21 85 9	0 4 1	p=0.16
Stage grouping	I II III IV	4 20 47 162	0 1 1 7	P=0.09
T-staging	T1 T2 T3 T4 x	11 74 78 66 4	0 3 4 2 0	P=0.62
N-staging	N0 N1 N2a N2b N2c N3	53 30 7 74 59 6	1 1 0 5 2 0	P=0.47
Pre-IMRT neck dissection	Yes No	34 199	2 7	P=0.32
Concomitant systemic therapy	Cisplatin-based Cetuximab Other No	133 8 1 91	4 1 0 4	p=0.29
Neo adjuvant chemotherapy	Yes No	5 228	0 9	p=0.30

Table 1. Cox regression analysis of patient characteristics for recurrence in electively irradiated nodal regions.

Conclusion

The actuarial rate of recurrence in the electively irradiated lymph node regions was 3.9% (95% CI 1.8-6.0) at 2 years. This incidence is comparable to recurrence rates after standard dose of 50 Gy, suggesting that lower doses to the elective neck do not result in higher regional recurrences.

Debate: Early stage HPV related oropharyngeal cancer should not be treated with radiotherapy anymore

SP-046 Early stage HPV related oropharyngeal cancer should not be treated with radiotherapy anymore: for the motion

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Abstract text

Early stage oropharyngeal cancer is a rare disease with a very favorable prognosis. Current treatment guidelines recommend either radiation therapy-only or surgery-only as treatment options and the analysis of the literature fails to demonstrate any difference in terms of oncological outcome for the two modalities. Given that patients with this disease will likely be cured, it seems critical to choose a treatment, which provides excellent short- and long-term functional recovery and quality-of-life. Whilst no level 1 evidence yet exists as to which treatment will perform better in this regard, concerns over radiation therapy-based treatments have been raised as a consequence of reported late toxicities. Within this debate the pros and cons of surgery-based treatment for early stage oropharyngeal cancer will discussed and arguments presented, favoring surgery as the primary modality of treatment for this disease.

SP-047 Early stage HPV related oropharyngeal cancer should not be treated with radiotherapy anymore against the motion

V.Budach
Germany

Abstract not received

SP-048 Early stage HPV related oropharyngeal cancer should not be treated with radiotherapy anymore: for the motion

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Abstract text

The use of one modality in the treatment of early stage head and neck cancer represents an advantage for the patient regarding the toxicity and the possible use of other modalities in case of recurrence or second primary. Despite of the lack of direct comparative studies primary radiotherapy and surgery are considered to provide comparable survival in early stage oropharyngeal tumors both in the group of HPV positive and negative tumors. Up to date HPV status should not influence the choice of treatment modality. Ongoing clinical trials are supposed to answer the question of possible de - escalation of treatment in HPV positive tumors. There is a general agreement that HPV status is the most important prognostic factor in oropharyngeal cancer. Patients with HPV positive tumors are usually younger and have better survival hence the quality of life after treatment becomes more important in this group of patients. Radiotherapy particularly when combined with chemotherapy has a known acute and late toxicity and leads in considerable part of patients to xerostomia, deterioration of teeth and dysphagia. The newly developed surgical techniques are able to treat radically the early stage oropharyngeal cancer without the need of adjuvant therapy. Transoral laser surgery, ultrasonic surgery or robotic surgery even in combination with some external approaches like neck dissection result in better quality of life and should be therefore preferred.

SP-049 Early stage HPV related oropharyngeal cancer should not be treated with radiotherapy anymore against the motion

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Abstract text

Human papillomavirus-related (HPV+) oropharyngeal cancer is a rapidly emerging disease in many countries that differs from tobacco-related and alcohol-related (HPV-) oropharyngeal cancer. HPV+ oropharyngeal carcinoma is now established as a distinct biological entity, being prognosis significantly superior than HPV negative tumor.
Some studies suggest that Trans Oral Radical Surgery (TORS) achieves excellents outcomes with less toxicity.
Published clinical trials and published clinical data comparing TORS and RT will be presented and discussed as well as the most important ongoing trials.

Poster: Multidisciplinary management

PO-050 The interplay between all-trans-retinoic acid and radiotherapy in inducing cancer stem cell arrest

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Purpose or Objective
Head and neck cancer stem cells (CSC) display a number of properties that lead to treatment failure. Conventional treatment techniques are unsuccessful in long-term tumour control due to radioresistance of CSCs and their ability to regrow the tumour. Therefore, more targeted therapies are needed. A CSC targeting agent is all-trans-retinoic acid (ATRA) that was shown to induce CSC differentiation, cell cycle arrest and apoptosis in head and neck cancer cell lines. However, the limited data available in the literature indicates that the effect of ATRA is cell line dependent, as it can induce cell arrest in either G_1 or G_2 phase. The aim of this work was to investigate the interplay between ATRA and radiotherapy and to assess the phase-specific treatment outcome.
Material and Methods
A hierarchical in silico head and neck cancer model has been developed using Monte Carlo techniques. The tumour contains cancer stem cells, differentiated cells and quiescent cells with varying radioresistance. The pre-treatment CSC population given by the model is 5.9%, which changes during treatment. The tumour was treated with hyperfractionated radiotherapy (1.2 Gy twice daily, 5 days a week, 7 weeks) given the higher locoregional control obtained as compared to conventional fractionation. Radiotherapy (RT) was simulated using the Linear Quadratic model and the properties of ATRA were implemented based on literature data.
Results
The model showed that with cell arrest in G_2, the effect of ATRA combined with radiotherapy leads to a dose reduction of 28% for the same killing effect as radiotherapy as a sole agent. However, with G_1 arrest cellular response is substandard, requiring an increase in dose of 11.7% as compared to radiation treatment. With larger ATRA doses, when the dual effect of cell arrest and apoptosis was simulated, both G_1 and G_2 arrests led to a significant decrease of total dose required to control the CSC population (see table 1).

Table 1. The cell cycle phase-dependent effect of ATRA + RT on tumour kill

Cell arrest by ATRA			
	ATRA G_2 arrest +RT	**ATRA G_1 arrest + RT**	**RT-only**
No of fractions	43	67	60
Total dose (Gy)	51.6	80.4	72
RT dose reduction by ATRA (%)	28.33	-11.67	-
Cell arrest and apoptosis by ATRA			
No of fractions	32	43	60
Total dose (Gy)	38.4	51.6	72
RT dose reduction by ATRA (%)	46.67	28.33	-

Conclusion
CSC-targeting agents play a critical role in the future of head and neck cancer treatment. While ATRA shows promising early results, it needs more investigations in determining the cell cycle phase-specific arrest for each histopathological tumour type, as well as more quantitative studies to establish the threshold values required for its full potential. While both G_1 and G_2 phase arrests can lead to improved results when combined with radiotherapy, the model showed that the overall outcome is phase-dependent.

PO-051 A 7-year overview on advanced nasopharynx's cancer: features influencing survival outcomes

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Purpose or Objective
Our aim was to assess population characteristics, treatment safety and efficacy, PFS, OS and prognostic value of population and treatment's features.
Material and Methods
Retrospectively, we analyzed patients treated for advanced nasopharynx's cancer (stage III, IVA and IVB) from January 2009 to December 2015, in one institute. Clinical files enquiry were revised and SPSS analysis (Kaplan Meier's method) used for survival analysis.
Results
All 33 patients, 33.3% females and 66.7% males, had a median diagnosis age of 47 years (15-74 years) and a good performance status (ECOG 0 or 1). History of tobacco and alcohol use was present in 51.5% and 36.4%, respectively, and 39.4% had history of occupational exposure. Epstein Barr DNA test was positive in 21% of them.
Histological study revealed undifferentiated carcinoma in 81.8% of cases. Tumors were classified as stage III (45.4%), IVA (27.3%) and IVB (27.3%).
In this population, 84.8% underwent concomitant chemoradiotherapy with cisplatin 100 mg/m^2 3/3 weeks. Of those, 32.1% received the 3 planed cycles. Radiotherapy dose was 70.2 Gy/33Fractions/6.5 weeks.
69.7% of patients underwent adjuvant chemotherapy with 5-FU and cisplatin with a median of 2 cycles, mostly with dose reduction. Major acute toxicities were grade 3/4 neutropenia (26%), grade 3 mucositis (13%), nausea and vomiting (8.7% and 4.3%, respectively) and anemia (8.7%). There were major infectious complications in 33.3%.
We observed a complete response in 48.3% of patients, partial response in 44.8%, stable diseases in 3.4% and progression in 3.4%.
1 year and 5 year PFS was 72.2% and 46.4% respectively. Infectious complications had a negative correlation with PFS ($p<0.0001$) and adjuvant chemotherapy had a positive correlation ($p = 0.019$).
1 year and 5 year OS was 84.3% and 42.6% respectively. Infectious complications and weight loss had a negative correlation with OS ($p<0.0001$ and $p=0.004$, respectively)

and the use of gastrostomy and adjuvant chemotherapy had a positive correlation (p=0.045 and p = 0.047, respectively).

Conclusion

Both OS and PFS in our population were similar to current literature. We found a significant correlation between treatment features (use of gastrostomy, adjuvant chemotherapy, infectious complications) and patients features (weight loss) with survival outcomes.

PO-052 N2 node metastasis in squamous cancers of head and neck: failure patterns and future management

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Purpose or Objective

To evaluate outcomes of patients with N2 Neck nodes from Squamous Cell Head and Neck Cancers.

Material and Methods

Between 2009-2014, 172 patients were treated at our center; 71 white, 98 African American (AA) and 3 other races, with a median age of 55 yrs. The T stages were: Tx 5 (3%), T1 13 (7%), T2 45 (26%), T3 34 (20%), T4 75 (44%). The N2 neck stages were: N2A 13(8%), N2B 67 (39%) and N2C 92 (53%). The primary sites included: oropharynx 73 (42%), Larynx 39 (23%), Hypopharynx 17 (10%), Oral cavity 20 (12%), Nasopharynx 9 (5%), other 14 (8%). Treatment consisted of Surgery followed by Radiation therapy (SRT) for 41 (24%). The median radiation dose was 60 Gy in 30 fractions of 2 Gy once daily. All radiation therapy was given by Intensity Modulated Radiation Therapy (IMRT). Another 131 (76%) patients were treated by concurrent chemotherapy and IMRT (CRT). The chemotherapy consisted of either Cisplatin or Cetuximab. The radiation dose was 70 Gy in 35 fractions of 2 Gy each. The minimum follow up was 24 months.

Results

The overall local control (LC) in the neck for the entire group is 147/171 (85%). The LC was 38/41 (93%) in those who were treated with SRT and 107/131 (81.6%) in the CRT group, which was not statistically significant. There were no statistical differences between location of primary and subsequent neck disease control.

32/172 (25%) developed distant metastasis (DM). In the SRT group it was 6/41 (14%) and CRT 26/131 (19.8%), which was statistically insignificant. There were no differences between the various N2 groups. There was also no correlation with failure at the primary site. The DM rate was significantly worse in African Americans (AA) versus white patients (p = 0.01). Patients who developed metastatic disease did so within 18 months.

The disease free survival (DFS) and overall survival (OS) at 3 years were calculated by Grays test and Log Rank Test, respectively. The DFS for the entire group was 49% (95% CI 0.39-0.58). There were no differences between the various N2 stages. The DFS was significantly worse in AA (40%) versus white patients (62%) (p = 0.007). The OS was 71% for the entire group with no difference in OS by N2 stages. Similarly, there was no difference in OS between AA and white patients (p=0.6).**Conclusion**

We report on 172 patients with advanced squamous cell cancer of the head and neck who underwent combined modality treatment, which was tolerated well.

Patients with N2 neck disease have an excellent LC rate with combined modality treatment; either surgery followed by CRT or CRT alone.

AA patients have a significantly worse DFS compared to the white patients. They also have a significantly increased risk of developing DM.

Nearly a quarter develop DM with the majority having loco regional control. These patients should be considered for neoadjuvant chemotherapy trials.

PO-053 Impact of PTV coverage on local recurrences and overall survival after IMRT for head and neck cancers

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Purpose or Objective

Intensity modulated Radiotherapy (IMRT) is the standard radiotherapy technique for head and neck cancer irradiation. The International Commission on Radiation Units (ICRU) recommends covering 95% of the target volume with 95% isodose. However, this objective is not always achievable due to organs at risk constraints. **Objective:** To assess the impact on local recurrences and overall survival of high risk PTV (HRPTV) coverage by 95% isodose among patients treated for a head and neck squamous cell carcinoma, with simultaneous-integrated boost-IMRT (SIB-IMRT) and bilateral lymph node irradiation.

Material and Methods

From May 2011 to January 2014, 119 patients who underwent RapidArc® SIB-IMRT were included in this prospective evaluation (22 oral cavities, 58 oropharynx, 25 hypopharynx, 14 larynx). Sex ratio was 6.4, median age was 61.5 years. Doses, delivered in 33 fractions, were: post-operative HRPTV (38 patients): 66Gy; non-operative HRPTV (81 patients): 70Gy; intermediate risk PTV: 59.4Gy; low risk PTV: 54Gy. Age, sex, clinical stage, tumour location, chemotherapy, overall treatment time and HRPTV coverage (V95HRPTV) at 90 or 95% were studied.

Results

Among postoperative patients, local control after 2 years of follow-up was 70% vs 100%, p = 0.0083 (V95HRPTV+/-95%) and 40% vs. 90.7%, p = 0.0000052 (V95HRPTV+/-90%). Two-year overall survival was 75% vs. 88.9%, p = 0.046 (V95HRPTV+/-95%) and 40% vs. 87.9%, p = 0.0030 (V95HRPTV+/-90%). Among non-operative patients, two-year local control was 66.4% vs. 75.9%, p = 0.47 (V95HRPTV+/-95%) and 54.4% vs.74.6%, p = 0.15 (V95HRPTV+/-90%). Two-year overall survival was 57.1% vs. 79.5%, p = 0.015 (V95HRPTV+/-95%) and 40% vs. 74.2%, p =0.0040 (V95HRPTV+/-90%). With multivariate analysis, V95HRPTV ≥ 95% was a prognostic factor of overall survival, V95HRPTV ≥ 90% was a prognostic factor of overall survival and local control.

Conclusion

High risk PTV coverage by 95% isodose affects local control and overall survival. ICRU guidelines must be followed as often as possible. When impossible, coverage must remain above 90% of the high risk PTV so as not to compromise local control and overall survival.

PO-054 Cisplatin use in UK head and neck cancer management: a clinician survey of current practice

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Purpose or Objective
In patients with locally advanced squamous cell carcinoma of the head and neck (LASCCHN), concurrent chemo-radiation therapy (CRT) is the current standard of care. Based on published evidence, International and European guidelines for the management of LASCCHN recommend single-agent cisplatin given 3-weekly at a dose of 100mg/m^2 as the preferred regimen. We conducted a survey of H&N cancer clinicians from oncology departments in the UK and Ireland to explore the current clinical management of LASCCHN, with a particular focus on the use of cisplatin.
Material and Methods
During March 2016, 55 H&N cancer clinicians from centres across the UK and Ireland were invited to complete an e-mail survey about their use of cisplatin in the management of patients with LASCCHN receiving concurrent CRT. We present here the responses of 50 oncologists (47 consultant clinical or medical oncologists [n=44 and n=3, respectively]) and 3 specialist oncology registrars/clinical fellows).
Results
39% of respondents (19/49 who answered the question) stated that they use the guideline-recommended cisplatin dosing schedule (3-weekly high dose cisplatin [100mg/m^2]) for patients with LASCCHN receiving concurrent CRT whereas 61% (30/49) use weekly cisplatin at a dose of 35-45mg/m^2. The estimated percentage of patients with LASCCHN who are unsuitable for platinum-based therapy ranged between respondents from 5-60%, with a median of 30%. Poor performance status (n=33), age (n=6) and platinum side effects (n=5) were the main reasons given for patients being unsuitable.
Conclusion
Despite strong clinical trial evidence and International guidelines recommending high dose 3-weekly cisplatin, over half of the clinicians surveyed use weekly cisplatin for patients with LASCCHN who are receiving concurrent CRT. This may reflect current pressures within the NHS to reduce inpatient stays, and the burden of inpatient admission required to administer the 3-weekly regimen due to the greater need for supportive care than with the weekly regimen, which can be administered on an outpatient basis. Also, many clinicians perceive weekly cisplatin to be a "gentler" way of giving concomitant chemoradiotherapy. However, further research is required to confirm the efficacy and reasons for this widespread non-compliance with International guidelines.

PO-055 Subglottic squamous cell carcinoma in Denmark from 1971-2016 -a report from the DAHANCA-group
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Purpose or Objective
The aim of this study was to describe the pattern of failure in a national consecutive cohort of patients diagnosed with subglottic squamous cell carcinoma (SCC) over a 45 years period.
Material and Methods
All patients diagnosed with a subglottic SCC in Denmark between 1971 and 2016 were included and followed from the first contact with the oncology center to death or May 1 2016. Patients were identified in the Danish Head and Neck Cancer Database (DAHANCA database) after combining with the Danish Cancer Registry. Information regarding patient and tumor characteristics, treatment and outcome was prospectively registered in the DAHANCA database. National patient charts were used to identify missing information.
Results
169 patients were identified of whom 139 (82%) were male. The stage distribution was I=13 (8%), II=60 (36%), III=47 (28%), and IV=47 (28%). Two patients had unknown tumor stage due to death (n=1) and emigration (n=1) prior to the final staging. The tumor differentiation was well or moderate in 84 (50%) patients, poor in 36 (21%), and unknown in 49 (29%). The primary treatment intent was curative for 145 (86%) patients and palliative for 8 (5%). 143 received primary radiotherapy and six received primary surgery. Information regarding primary treatment was missing in four patients. 16 patients (9%) did not receive any primary treatment at all. The median follow-up was 5.1 years/1.9 years (patients alive/patients who died). Only one patient was lost to follow-up. 82 failures were observed among the 145 patients treated with curative intent; of these 70%, 18%, and 5% included T site, N site, and M site, respectively. 18 patients did not achieve disease control at any time despite definitive treatment. 85% of failures observed after curatively intended treatment were observed within the first two years. Salvage treatment cured 22 of the 82 patients with failure.
The five-year cumulative incidences of treatment failure for patients treated with curative intent was 61%. The five-year cumulative incidence of ultimate treatment failure (failure despite salvage attempt) was 46%. For all patients, the five-year disease-specific survival (DSS) and overall survival (OS) were 50% and 37%, respectively. For patients treated with curative intent the five-year DSS was 54% and OS was 41%.
Conclusion
This study describes a complete national cohort of patients diagnosed with a subglottic SCC in Denmark over a 45 year period. Subglottic SCC is a rare disease with male predominance and typically diagnosed in advanced stage. The disease has a poor prognosis and more than half of patients treated with curative intent experienced treatment failure. Only few of whom were saved by salvage.

PO-056 Tolerance and outcomes of radical hypofractionated radiotherapy for glottic cancer in the elderly
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Purpose or Objective
There is limited data to guide the management of elderly patients with head and neck cancer with regard to treatment outcomes and tolerability. The aim of this study is to review the tolerance and disease outcomes of patients aged over 70 years treated with definitive

hypofractionated radiotherapy 55 Gy in 20 fractions over 4 weeks for glottis carcinoma.

Material and Methods

Patients aged over 70 years and treated for glottic cancers with definitive radiotherapy, between 2007 and 2014, were retrospectively identified. Characteristics reflective of fitness (smoking status, performance status and ACE 27 score) as well as tolerance (compliance with radiotherapy, need for acute hospitalisation during treatment, need for enteral feeding, 30-day mortality) were collected. The probabilities of local control, disease free and overall survival were calculated using Kaplan-Meier statistics. Univariate Cox Regression investigated factors potentially important in outcome.

Results

53 patients were identified. Median age was 76 years (71 – 91). Median follow up was 40.1 months (range 1.1 -103.3 months). 24 (45%), 26 (49%) and 3 (6%) had T1, T2 and T3 disease respectively. Two and three year local control, DFS and OS rates were 85%, 80% and 76% and 83%, 77% and 71% respectively. On univariate analysis, there was no significant difference in outcomes for T1 and T2 disease: 2-year local control and DFS were 85%, 84% for T1 and 89% and 89% for T2 respectively. No other factors (e.g. age, gender, T-stage or histological grade) significantly influenced local control, DFS or OS, with the exception of ACE 27 Score (0-1 versus 2-3), which significantly influenced overall survival (ACE 27 score 2/3 vs 0/1: hazard ratio: 2.65, 95% confidence interval 1.22-5.77, p=0.014). All patients were able to complete their course of treatment with 6/53 patients experiencing a treatment delay of >3 days (median 28 days (26-34)). A total of 11/53 (21%) patients required hospital admission during treatment; 9 (17%) for enteral tube feeding and 2(4%) for symptom management. 30 day mortality was 0%. All 8 patients with a local recurrence were offered salvage options. Of these 5 patients underwent salvage surgery with 2 recurrences (1 local, 1 distal)and 3 patients disease free on follow up; 3 refused salvage surgery.

Conclusion

Patients aged over 70 years tolerate definitive hypofractionated radiotherapy with high rates of local control. Comorbidity scoring with the ACE 27 scale is an independent prognostic factor for overall survival.

PO-057 Radiation induced skin reaction in head neck malignancies and assessment of quality of life

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Purpose or Objective

To evaluate the skin reactions in patients receiving head and neck radiation and assessing the outcomes of the same in respect to the modality of the treatment. Head and Neck malignancies for the bulk of cancer cases in India and Radiation therapy forms a part of management of the same. With Radiation fractionations delivered either with IMRT or 3DCRT, there is a risk of development of skin reactions during the treatment period and can lead to varying degree of complications i.e. infection, ulcerations or even necrosis. The assessment of skin reactions needs to be looked in to as it can be easily avoided with proper prophylaxis and the progression can be managed at an earlier stage. We present our institutional experience in the treatment of the head and neck cancer case treatment.

Material and Methods

In a prospective, non-randomized study of 100 histo-pathologically proven head and neck cancer cases of various subsites, planned for adjuvant radiation therapy, were enrolled in our study. The patients were treated with IMRT or 3DCRT plan for External beam radiation therapy to standard dose of 60Gy in 30 fractions with 200cGy dose 5 times a week over 6 weeks. Of the 50 cases, 26 received adjuvant chemotherapy. The patients were given EORTC Qol 30 and QoL HN 35 at start of treatment, at completion of radiation therapy and subsequently at 1 month and 3 months of follow up. The skin reactions were assessed using EORTC and CTCAE 3.0 toxicity grading scales. The scores were analyzed and subsequently the toxicity grades were looked in to and compared and outcome was assessed.

Results

Out of the 100 patients, 76 developed skin toxicity as per the scales; of which 56 developed grade I toxicity and 20 developed grade II toxicities. The questionnaires were assessed with suitable statistical analysis and no statistical significant was found in the 3DCRT or IMRT arms. However, with increasing grade of tumor, the Qol showed a significant difference in the physical and functional symptoms. The skin toxicity too showed a statistically significant outcome with varying grades of the tumor assessed. The evaluation of toxicities and subsequent management reveleaed better outcomes in the QoL at the end of 3 months wherein the acute form of the toxicities subsided. None of them developed grade 3 or 4 skin toxicities

Conclusion

The morbidity associated with skin reactions related to radiation therapy in head and neck malignancies were high in 2D era and now with advent of conformal therapy there is a reduction in the cases of the same. However, the incidence can still be reduced further with proper review of patients during treatment and assessment of quality of life. The acute reactions can be prevented to develop in to chronic complications which increase further the morbidity of such patients. Appropriate management of such cases at the right time helps in improving the quality and make the treatment an even better option.

PO-058 Nasopharingeal carcinoma treated with intensity modulated radiotherapy in an non-endemic area.

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Purpose or Objective

NFC is frequent in some areas but not in Europe. There is a few information in non-endemic population.
The aim of this study is to describe and analyze the results in treating all-stages NPC with IMRT-simultaneous integrated boost (SIB), in a non-endemic area.

Material and Methods

A retrospective review of 62 consecutive patients with NPC treated with curative intention with IMRT-SIB between 2007-14 in a single institution.
RT scheme: 33 daily fractions,1.64 Gy to intermediate-risk volume, 2.12 Gy to high-risk volume. Total dose 54.12 Gy and 69.96 Gy respectively.
Overall survival (OS), loco-regional relapse-free survival (LRRFS), and progression free survival

(PFS) and toxicity have been evaluated . Kaplan-Meier method has been used.

Results

Median follow-up: 29.7 months. Median age 51 years (range, 15-78).

Mainly men (69%), Caucasian (77.4%) locally advanced disease (93.5%) and undifferentiated (WHO III) (71%). Epstein Bar Virus (EBV) positive in 40 p. (64.5%).Only 6 patients (10%) were treated exclusivel y with RT, while the rest received chemotherapy (CT), mainly concurrent (85%). Inducctio n CT was delivered to 71.% patients and/or adjuvant CT to 36% patients received neoadjuvant and adjuvant CT.

The 2 and 5 year OS was 84.0%- 61,3% , LRRFS: 97% and 93,7% and PFS were 81.5% and 60.4% respectively.

Main chronic toxicity was xerostomia G1 in 51% and G2 in 10%.

Conclusion

The treatment of NPC (predominantly locally advanced) using IMRT-SIB offer a result comparable to results described in endemic population with minimal chronic toxicity.

PO-059 Efficacy and safety of modified-increased FEP regimen and chemo-radiation for locally advanced HNSCC

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Purpose or Objective

The optimal sequencing of chemotherapy (CT), radiation, and surgery in the management of locally advanced HNSCC remains a subject of debate. To improve RR and functional outcomes, CT has been added into various approaches. These approaches have been applied for both patients with unresectable cancers and those with resectable disease who prefer organ preservation. Moreover, in the large Meta-Analysis of CT on Head and Neck Cancer, induction CT improved the rate of distant metastases and the CCRT improved the locoregional and distant control. Phase II and III trials using more intensive CT with three-drug regimens demonstrated a better RR than two drugs. To figure out if this promising three-drugs induction CT followed by CCRT in locally advanced HNSCC is active and safe, we evaluated induction CT using modified increased doses of FEP regimen (Fluorouracil, Leucovorin, Epirubicin, Cisplatin) followed by CCRT for locally advanced HNSCC.

Material and Methods

Between January 2008 and January 2015, 13 patients with histologically confirmed non mestastatic HNSCC were treated with induction CT using 5-Fluorouracil 500 mg/m2 d1-4, Leucovorin 200mg/m2 d1-4, Epirubicin 35mg/m2 d1-2, Cisplatin 25mg/m2 d1-4 associated to G-CSF, every three weeks followed by CCRT at Alazhar Oncology Center group in Rabat, Morocco. We performed retrospective analysis for efficacy in terms of response rate and toxicity profiles. Survival data were not mature enough to be presented. Medical records were also reviewed for clinicopathologic characteristics. 9 patients were locally advanced (IIB-IVB) and 4 were recurrent HNSCC. Patients were first treated with 3 cycles of induction chemotherapy with increased doses FEP regimen (mid FEP). After induction chemotherapy, weekly cisplatin was administered concurrent with radiation. Radiation consisted of 65-70 Gy to the planning target volumes of the primary tumor and 45 -60 Gy to any positive nodal disease using 1,8 Gy per fraction.

Results

The median age was 62 years and 86% were male. The majority were diagnosed with locally advanced HNSCC with performance status of 0 to 1. All patients received 2 to 3 cycles of induction chemotherapy based on 5-FU 500 mg/m2 d1-4, Leucovorin 200mg/m2 d1-4, Epirubicin 35mg/m2 d1-2, Cisplatin 25mg/m2 d1-4 with G-CSF every 3 weeks. Concerning response rates (RR), 46% achieved a PR, 38% had a CR and 15% SD, whereas 1% could not be evaluated due to loss of follow-up. The most common adverse events were neutropenia, thrombocytopenia and anemia. One patient developed renal failure. The adverse events that occurred during treatment were predictable and manageable. After completion of the whole treatment, small residual tumors were noted either at the primary site and / or neck.

Conclusion

Through this retrospective study, we were able to analyze RR and safety of modified-increased FEP regimen followed by chemo-radiation for locally advanced HNSCC in Moroccan patients. Our results showed that this regimen is feasible and

PO-060 Dose received by the pituitary gland during irradiation of nasopharyngeal carcinoma

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Purpose or Objective

Hypopituitarism is a commonly reported consequence of external radiotherapy during the treatment of nasopharyngeal carcinoma (NPC).The aim of this work was to evaluate the dose received by the pituitary gland during irradiation of NPC.

Material and Methods

This is a retrospective study including 91 patients treated for nasopharyngeal carcinoma between 2011 and 2016 at the department of radiotherapy; Habib Bourguiba hospital at Sfax Tunisia. Radiation therapy was performed according to a conformational technique. The prescribed dose was 68-70Gy to the nasopharynx and the initially involved nodes. A dose of 50Gy was deliverated to the rest of cervical lymph nodes. We delineated all of the pituitary gland and we studied the dose received: the minimum dose (Dmin), the maximum dose (Dmax) and the mean dose (Dmean). Then, we compared the different parameters according to the tumor stage (TNM 2009).

Results

The average Dmin was 37,9Gy vs. 49,4Gy respectively for T1-T2 and T3-T4 (p = 0.04).The average Dmean was 46,8Gy vs. 55,5Gy respectively for T1-T2 and T3-T4 (p = 0.007).The average Dmax was 53,8Gy vs 59,7Gy respectively for T1-T2 and T3-T4 (p = 0.02).

Conclusion

The occurrence of pituitary disorders depends on the dose received by the pituitary gland. Until now, there is no consensus about the dose tolerance of this gland. However, all published data agree that the maximum delivered dose should not exceed 50Gy. Those doses are generally outdated as was the case in our study. This is because of the proximity of the target volume to the pituitary gland. In fact, in our study, the dose received was significantly higher for the T3-T4 group.

PO-061 Stomal underdose in post-laryngectomy radiotherapy via VMAT: phantom study and clinical case analysis

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Purpose or Objective
Post-laryngectomy stomal recurrence of head & neck cancer may result from underdosage due to the well-known skin-sparing effect of photon irradiation, even via modern Volumetric Modulated Arc Therapy (VMAT) technique. We aim to verify the VMAT dose coverage and evaluate the dose-compensatory effect of bolus placement by (1) using a physics phantom study and (2) comparing the dose distributions of conventional anterior-to-posterior (AP) and VMAT plans in real-case clinical application.
Material and Methods
(1) Radiation dose distribution for post-laryngectomy stoma was planned using a physics phantom made of tissue-equivalent solid with a cylindrical hole opening emulating the tracheal stoma. A tracheostomy tube obturator was inserted and 5-mm thick bolus material was used as tissue compensator. Small pieces of bolus cuts were custom-made to reduce the air gaps between the mechanical device and skin surface. Thermoluminescent dosimetry (TLD) was used to verify the dose predicted by a commercial treatment planning system (TPS) on the stoma lumen and the peri-stoma skin. Three VMAT plans were generated using 6MV photon beams: no bolus, bolus with and without air gap compensation.
(2) A set of CT-simulation images for post-laryngectomy case was used for meticulous contouring of the catheter cuff, stoma lumen, peri-stoma skin and subclinical tumor bed around the primary site. The resulting dosimetry plans were analyzed with or without bolus placement. Wet gauze was used to minimize the effect of any air gap. Four plans were generated: AP superclavicular (SCV) plan with or without bolus, and VMAT plan with or without bolus. A dose of 60Gy in 30 fractions was prescribed at 3 cm depth for AP SCV plan, and to 95% of the PTV volume for VMAT plan.
Results
(1) The phantom study shows the dose difference between TPS calculations and TLD measurements for VMAT to be within 5%. The TLD result inside the stoma lumen differs by <1% with vs. without bolus placement. The TLD under the bolus on the peri-stoma skin receives full prescription dose, while it is 20% less without bolus.
(2) The peri-stoma skin dose is sensitive to bolus placement for the AP SCV plans (V95% of 20.7%, 33.0% and 94.8% for no bolus, bolus without and with air gap compensation, respectively). The dose drops off rapidly in depth for the stoma lumen. The dose distributions of the two VMAT plans are moderately different for peri-stoma skin (V95% of 95.0% with bolus and air gap compensation, and 82.3% without bolus), but nearly identical for stoma lumen (V95% of 91.5% and 92.0%, respectively).
Conclusion
The TPS dosimetric results are verified to be in agreement with TLD measurements by the physics phantom study. The clinical case analysis shows that the dose coverage around the stoma in the VMAT plan is better than the conventional AP SCV plan. For VMAT, it is still recommended to place physical bolus and reduce the air gaps in order to achieve optimal dose distribution.

PO-062 Retrospective analysis of 72 patients treated with FEP regimen and CCRT for locally advanced NPC.
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Purpose or Objective
The role of neoadjuvant chemotherapy (CT) followed by concurrent chemo-radiotherapy is a matter of interest in nasopharyngeal carcinoma. Several clinical phase III trials have proved that induction chemotherapy based on three-drugs, may significantly improve treatment outcomes in patients with squamous cell carcinoma of the head and neck. We conducted this study to evaluate the experience of induction chemotherapy using modified increased doses FEP regimen (mid FEP) (Epirubicin, Cisplatin, 5-FU, and Leucovorin) followed by concurrent chemoradiation for nasopharyngeal carcinoma (NPC).
Material and Methods
Between August 1994 and December 2009, 72 patients with pathological proven nonmetastatic NPC were enrolled. Ninty five percent of patients were locally advanced (IIB – IVB). Patients were first treated with 3 cycles of induction chemotherapy with increased doses FEP regimen (mid FEP) based on 5-FU 500 mg/m2 d1-4, Leucovorin 200mg/m2 d1-4, Epirubicin 35mg/m2 d1-2, Cisplatin 25mg/m2 d1-4 every 3 weeks, associated to Granulocyte colony-stimulating factor (G-CSF). After induction chemotherapy, weekly cisplatin was administered concurrently with radiation. Radiation consisted of 65-70 Gy to the planning target volumes of the primary tumor and 45 -60 Gy to any positive nodal disease using 1,8 Gy per fraction.
Results
Median follow-up of 96 months. After completion of induction CT, 46 evaluable patients (35%) achieved complete clinical response in regional nodes and nasopharynx. After completion of the whole treatment, small residual tumors were noted either at the primary site and / or neck in 26 % of patients. The complete response rate of the nodal area and primary location was 72 %. Residual tumors all showed complete regression upon follow-up after 3 months. The estimated 5-year PFS was 78%. The 5-year OS was 80 % and the estimated 8-year PFS was 67%. The 8-year OS was 73 %. The main grade 3 to 4 (G3/G4) adverse events during neoadjuvant chemotherapy were hematological but manageable.
Conclusion
Induction chemotherapy using modified increased doses FEP regimen (mid FEP) (Epirubicin, Cisplatin, 5-FU, and Leucovorin) followed by concurrent chemoradiation for locoregionally advanced NPC is feasible and effective in regard to locoregional control and distant metastasis with high compliance. A long-term follow-up study is needed to confirm these preliminary findings.

PO-063 Waiting time and fast track model for head and neck cancer patients in Finland
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Purpose or Objective
Waiting time from referral to treatment has an effect on cancer patients' prognoses and in addition waiting can be

mentally stressing. The total waiting time consists of delay before the referral to the specialist, delay from the referral to the diagnosis, and then the delay before the treatment.

Material and Methods

The Finnish national Head and Neck Oncology working group has evaluated the waiting time of head and neck cancer patients at the university hospital level bi-annually starting 2012 and taking a two-month period annually. At Turku University Hospital the waiting times were analysed in more detail starting from the year 2013 by analysing all the new patients referred to the tumour board meeting in October and November each year.

Results

At national level the waiting time from the first referral to the beginning of the treatment varied depending on the treatment modality and also depending on the hospital. In the latest analysed time period the waiting time varied from 15 to 45 days for patients receiving surgical treatment and from 31 to 83 days for those having definitive oncological therapy. In general the waiting time has slightly decreased from 2012 with a couple of exceptions. During this period Turku University Hospital has introduced a diagnostic package for head and neck cancer patients and the waiting time has decreased especially for the patients whose diagnosis was known at the time of referral.

Conclusion

The data from the national follow-up study will be presented. The presentation includes more detailed data from Turku University Hospital including the system of diagnostic package.

PO-064 Normal tissue complication probability model for tube feeding dependence 6 months after radiotherapy

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Purpose or Objective

A multivariable normal tissue complication probability (NTCP) model for tube feeding dependence 6 months after radiotherapy (TUBEM6) was published in "Radiotherapy and Oncology" 2014. The purpose of this study is to externally validate the published NTCP model for TUBEM6 and to develop NTCP model for TUBEM6 of our institute.

Material and Methods

This study included 122 patients of pharyngeal or laryngeal cancer treated by definitive intensity modulated radiotherapy (IMRT). The median total dose was 69.96 Gy/33 fr and the median dose to elective area was 45 Gy/25 fr. One hundred and one (83%) patients received chemoradiotherapy. We omitted level Ib, except in case of deep invasion to the oral cavity or highly suspicious lymph node for metastasis on level Ib. The organs at risk relating to swallowing dysfunction (pharyngeal constrictor muscle, cricopharyngeal inlet, supraglottic larynx, glottis area, oral tongue and anterior oropharynx) were contoured according to the consensus guideline published in 2015. The external validity was assessed by the calibration curve using the Hosmer-Lemeshow test. The discriminative ability of the model was calculated using the area under the curve (AUC) and the (pseudo) explained variance was measured with the Nagelkerke's R^2. A backward approach was used to select the most predictive variables in the multivariable logistic regression analysis, out of variables which were significant in the univariable analysis.

Results

The prevalence of TUBEM6 was 5.7% in the cohort of our institute. When we calculate by the published NTCP model, the mean predicted value of TUBEM6 was 12.2% (95% CI: 8.3%-16.0%). Using the published NTCP model, Nagelkerke's R^2 was 0.06. The AUC was 0.79 and the Hosmer-Lemeshow chi^2 was 9.3 (p = 0.320). One hundred and six (87 %) patients had bilateral level Ib omitted from elective nodal area. The group where bilateral level Ib was omitted (omitting level Ib group) had lower TUBEM6 compared with the group where level Ib was included in the elective nodal area (including level Ib group; 3.8% vs. 18.8%, p = 0.043). In omitting level Ib group, there was significant reduction in the mean dose to the oral tongue compared with including level Ib group (35.3 Gy vs. 48.8 Gy, p < 0.001). In multivariable analysis, the most predictive factors for TUBEM6 in our institute were the mean dose to the supraglottic larynx, the contralateral parotid, and the oral tongue. In the NTCP model of our institute, Nagelkerke's R^2 was 0.36. The AUC was 0.89 and the Hosmer-Lemeshow chi^2 was 4.64 (p = 0.795). 95% CI of the predicted value of TUBEM6 was 3.7%-7.7%.

Results of multivariable analysis of tube feeding dependence at 6 months after radiotherapy (TUBEM6)

	OR	(95% CI)	p value
Supraglottic larynx mean dose (Gy)	1.105	(1.023-1.222)	$p = 0.009$
Contralateral PG mean dose (Gy)	1.132	(1.027-1.262)	$p = 0.015$
Oral tongue mean dose (Gy)	1.094	(1.004-1.208)	$p = 0.040$

Abbreviations: OR = odds ratio, CI = confidence interval, PG = parotid gland
For dose variables OR, increase per 1 Gy.

The risk of TUBEM6 can be estimated using following equation:
$NTCP = (1+e^{-s})^{-1}$
Where, s = -15.729 + (mean dose to the supraglottic larynx*0.100) + (mean dose to the contralateral parotid* 0.1 (mean dose to the oral tongue* 0.090)
For dosimetric variables in equation, the dose in Gy can be filled in.

Conclusion

The prevalence of TUBEM6 was lower than expected in the published NTCP model. However, the discriminative ability and calibration was good. The mean dose to the supraglottic larynx, the contralateral parotid and the oral tongue play important role in TUBEM6. Neck irradiation to the elective nodal area without level Ib contributes to lower TUBEM6.

PO-065 Survival outcomes in Unknown Primary with nodal metastases and role of Radiation therapy

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Purpose or Objective

Unknown primary with neck nodal metastases forms a grey area in oncology wherein the treatment options are limited and the outcomes vary with the modality chosen for the same. Unknown primaries especially in head and neck carcinoma require thorough evaluation and radiation therapy to the neck nodal metastases forms an important treatment in the armamentarium available for better survival outcomes. In our retrospective study at our center, we evaluated and present the survival outcomes

and associated acute and late toxicities with the disease associated with radiation therapy

Material and Methods

Retrospective medical data presented 25 patients and were followed up for the survival outcomes. The patients were assessed for local and regional failures and the median follow up duration was assessed along with the survival and local control rates and disease free survival. The patients were also assessed for the acute and late toxicities and the outcomes were evaluated with appropriate statistical tests. The Radiation therapy were uniformly delivered using either 3DCRT or IMRT with standard dose of 60Gy in 30 fractions (2Gy per fraction) and multivariate analysis done for factors such as sex, age, site and extent, grade of tumor and staging of disease and the treatment modality used.

Results

The median follow up of the patients were found to 25 months and overall survival was found to be 80%. The disease free survival was found to 70 % and progression free survival was 65 %. The toxicities were analyzed using EORTC Toxicity scales and analyzed using appropriate statistical analysis. The outcomes were more in the form of dermatitis, dysphagia and decreased salivation which were found to be statistically significant in these cases.

Conclusion

Radiation therapy forms an important role in the treatment armamentarium for the unknown primaries with nodal metastases in the cervical region. The treatment modality is associated with better survival outcomes and also better tolerance to acute and late toxicities.

PO-066 Early-stage tonsil cancer submitted to primary surgery and adjuvant therapy: retrospective study

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Purpose or Objective

To review the outcomes of early-stage squamous cell carcinoma of the tonsil submitted to primary surgery and adjuvant treatment.

Material and Methods

We did a retrospective study of patients diagnosed with squamous cell carcinoma of the tonsil between January 2009 and December 2014, who underwent primary surgery followed by adjuvant therapy and were staged pT1 to T2 pN0. We analyzed patient charts, imaging and clinical data regarding primary therapy, adjuvant treatment and side effects. Toxicity was graded according to Common Terminology Criteria for Adverse Events (CTCAE v4.0). Survival was estimated with Kaplan-Meier survival analysis.

Results

Between January 2009 and December 2014, 15 patients with pT1 to T2 pN0 squamous cell carcinoma of the tonsil were treated with primary surgery and adjuvant therapy. Most patients were male (n=13), with a median age of 58 years, current moderate to heavy-smokers (more than 10 pack-years, n=11) and/or moderate to heavy-drinkers (more than 14 units of alcohol per week, n=11). All of them underwent surgical resection with ipsilateral (n=13) or bilateral neck dissection, followed by radiotherapy with (n=3) or without (n=12) systemic therapy (high-dose cisplatin), due to positive (n=4), close (less than 5 mm, n=9) or non-evaluable (n=2) surgical margins. The disease was stage I in 5 patients and stage II in 10. They were all treated with intensity modulated radiotherapy (IMRT) using simultaneously integrated boost (SIB-IMRT). The prescribed dose was 60 to 70 Gy (2 Gy/fraction) to the high-risk planning target volume (PTV) and 50 to 54 Gy (1,64 to 2 Gy/fraction) to the low to intermediate-risk PTV. There was no contralateral nodal irradiation.

After a median follow-up of 3 years, one patient had local failure and no one developed distant metastasis. Both the median overall and progression-free survival were approximately 3 years. The 3-year and 5-year overall survival were 86% and 71%, and the 3-year and 5-year progression-free survival were 100% and 80%, respectively. Three patients died due to complications related to mandibular osteonecrosis, pulmonary infection and second tumor (lung cancer). Only three patients reported acute grade 3 toxicity (mucositis, dysphagia and/or dermatitis). All other patients had acute grade 1 or 2 dysphagia, xerostomia and dysgeusia. One patient required nasogastric tube insertion before the beginning of radiotherapy and another needed one placed during the treatment. One year after the end of radiotherapy, 2 patients still had grade 1 xerostomia and one patient had osteoradionecrosis of the mandible.

Conclusion

In our study, close margins were the main reason to indicate adjuvant therapy in early-stage tonsil carcinoma. Despite good progression-free survival, the toxicity profile of combined modality requires caution. Further margin analysis may identify subgroups in which adjuvant radiotherapy could be avoided.

PO-067 Mucosal Melanoma of the head and neck: single institution experience

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Purpose or Objective

Report our clinical results of treatment for Mucosal Melanoma of the Head and Neck (MMHN).

Material and Methods

Retrospective study of patients with pathologic proven MMHN treated with curative intent between April/05 and Jun/15. Demographic data, tumor characteristics, imaging, and treatment factors were recorded. Survival and disease-control outcomes were analyzed with Kaplan-Meier. Toxicity was scored with the CTCAE v4.0.

Results

34 patients with a median age of 71 years were included; 62% female; 38% male. Tumor was located at the nasal cavity (62%), 24% in oral cavity; 9% in oropharynx; 3% in maxillary sinus; 62% were Stage III and 38% Stage IVA; 6% had c-KIT mutation. Only 21% of cases were evaluated regarding BRAF expression, none was positive. 94% were treated with surgery in which 25% involved lymphadenectomy. Pathologically 63% had R2 margins, 16% R1 margins and 16% R0 margins. 65% did adjuvant radiation therapy (RT) while only 6% definitive RT. 54% were treated with IMRT and 25% with 3DCRT. 38% did elective node irradiation. Overall treatment time of RT was below to 49 days in 63% of cases. A total of 10 patients did systemic therapy. Most of the patients had anorexia and nausea and 1 patient had platelet count decreased grade I. No grade 3 toxicity was reported. After a median follow up of 20 months, median overall survival was 13

months; 1-year locoregional control was 35% and freedom from distant metastases was 30%. Surgery was statistically significant to locoregional control. None of the remaining analysed variables had influence on survival and locoregional control.

Conclusion

Our results have a lower than expected local control. Despite the small number of patients, surgery was the only factor with positive impact on locoregional control. New strategies are warranted to improve the outcome of this disease.

PO-068 Head and neck cancer of unknown primary origin: a single institution experience

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Purpose or Objective

To analyse the outcomes, patterns of failure and toxicity in patients with head and neck cancer of unknown primary origin (HNCUP).

Material and Methods

A retrospective database was used to identify patients with HNCUP for which they received curative-intent radiotherapy in our institution between 2009 and 2014. The patient characteristics, treatment plans and late toxicity profiles were reviewed, and the survival rates were calculated using the Kaplan-Meier method.

Results

We found 28 patients, 23 men and 5 women, with a median age of 57.5 years (range 41-82), and a KPS of 70 or higher in 64% of these patients. All patients were staged as T0 after comprehensive workup evaluation. Two (7%) presented with stage N2a, 10 (36%) with stage N2b, 3 (7%) with stage N2c, and 13 (46%) with stage N3 disease. A total of 15 (54%) patients underwent up-front neck dissection. 23 (82%) patients received systemic chemotherapy in a combined-modality setting. All patients underwent RT, 6 3D-CRT and 22 IMRT. Generally, patients were treated with comprehensive nodal irradiation to the bilateral neck and mucosal axis (nasopharynx, oropharynx, hypopharynx and larynx). No patient received oral cavity mucosal irradiation. Median doses to gross disease were 69.96 Gy, 66 Gy to high-risk or postoperative areas, 60 Gy to the mucosal axis and 50-54 Gy to the lower risk node levels. With a median follow-up of 3.6 years for the surviving patients, the overall survival, disease-free survival, distant metastasis-free survival and locoregional control rates were 64%, 47%, 69% and 54% at 3 years, respectively. Only 3 patients developed distant metastasis with locoregional control. Nine (32%) patients had persistent neck disease from which two were N2b and seven, N3. Only two nodal recurrences occurred within the RT volume: one in a 54 Gy level and the other in a 60 Gy level. There was one probable mucosal failure (larynx) in the 8 patients in which the larynx was spared from radiation. 8 (29%) patients reported Grade 1 late xerostomia, 7 (25%) Grade 2, with no Grade 3 late xerostomia reported.

Conclusion

Our study showed lower than expected locoregional control and survival rates. The large proportion of patients presenting with N3 disease may explain the suboptimal results. There were no failures in the spared oral mucosa. RT with or without chemotherapy for HNCUP produced reasonable toxicity profile.

PO-069 Radiation Dose and Distribution Following Transoral Robotic Surgery of the Palatine Tonsil

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Purpose or Objective

The improved survival of HPV-associated oropharynx cancer has stimulated an interest in new approaches which de-escalate radiotherapy and in turn decrease treatment-related morbidity while maintaining a high rate of disease control. New technologies for transoral surgery of the oropharynx have emerged as an opportunity for reducing traditional radiotherapy dose applied to the mucosal site. Unilateral radiotherapy has been described as a unique opportunity for decreasing radiotherapy dose delivered to the contralateral neck in early palatine tonsil cancer.

Material and Methods

Since 2010, our Tumor Board has embraced transoral surgery with selective neck dissection for tonsil cancer with the objective of decreasing radiotherapy dose and distribution. Herein we present our experience with twenty-seven consecutive tonsil cancer patients undergoing transoral robotic surgery, including demographics, TNM stage, p16 status, margin control, extracapsular spread, perineural and lymphovascular invasion, locoregional control and disease-free survival. Radiation dose and distribution are reported in light of changes in the treatment plan that result from successful surgical treatment of the tonsil and neck. Patients recommended for unilateral post-operative radiotherapy included those with 1.) Pathologic T1-2 staging 2.) No extension beyond the glossotonsillar sulcus or within 1 centimeter of the uvula 3.) Clear pathologic margins and 4.) Pathologic neck stage ≤ N2b.

Results

In this series, there was 100% disease-free survival with a median follow up of 30 months. The radiation records of 12 patients were available through a questionnaire to the radiation oncologists and review of radiotherapy treatment records. In two patients, no radiotherapy was given due to early stage disease with clear margins (T1-2, N0). De-escalation of 10Gy to the tonsil primary site was observed in 10/12 patients. 7/12 patients received unilateral radiotherapy to the cervical nodes. 3/12 patients received therapeutic-dose radiation to both sides of the neck.

Conclusion

The role of transoral surgery and neck dissection in the de-escalation of adjuvant therapy is highlighted. Transoral surgery may also help guide which patients are candidates for unilateral radiotherapy by providing pathologic staging of the neck and histologically-confirmed tumor mapping in the oropharynx. Our series, in aggregate with others, strongly supports a treatment paradigm which distinguishes early stage tonsil cancer from other cancers of the oropharynx and endorses unilateral radiotherapy in selected cases.

PO-070 Conventional vs bifractionated radiotherapy innasopharyngeal cancer 10years followup of phase3 trial

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Purpose or Objective
Standard treatment of nasopharyngeal carcinoma (NPC) is radiotherapy frequently associated with chemotherapy in advanced disease. However, after conventional radiotherapy results remain poor with a high rate of both local relapse and distant metastasis. The aim of our study was to evaluate the impact of a split course bifractionated radiotherapy regimen. Here, we present the 10-year follow-up results.
Material and Methods
From January 1997 to September 2003, 154 patients with M0 histologically proven NPC were treated in the Habib Bourguiba hospital, Sfax Tunisia. Patients with locally advanced nodal disease (N2–N3) received induction chemotherapy. All patients were randomized to receive either conventional radiotherapy at 2 Gy/fraction/day, 5 days/week to 70 Gy/7 weeks or split course bifractionated radiotherapy at 1.6 Gy/fraction, twice daily, 5 days/week to 70.4 Gy/ 6 weeks.
Results
Update of survival data was done in 2016. With a median follow-up of 13, 6 years, 10-year overall survival (OS) did not differ between the two treatment arms: 52% for the conventional radiotherapy versus 49, 7% for the split course regimen (p= 0, 3). Loco regional and distant free survival rates were, respectively (55% and 55, 4%), in conventional arm and (51, 1% and 51, 5%) in bifractionated arm, the difference was not statistically significant. There was more grade II–III skin fibrosis (68, 9% vs. 64, 9%) and more grade II-III xerostomia (49, 3% vs. 48%) in experimental arm, but the difference being statistically non significant.
Conclusion
Compared with conventional radiotherapy, split course bifractionated radiation therapy failed to demonstrate significant improvement in locoregional control or overall survival even after 10-year follow-up.

PO-071 Dose to the thyroid gland during irradiation of nasopharyngeal carcinoma
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Purpose or Objective
The thyroid dysfunction is a frequent late toxicity observed after radiotherapy of nasopharyngeal carcinoma (NPC).The aim of this study is to evaluate the dose received by the thyroid gland during irradiation of NPC.
Material and Methods
This is a retrospective study including 87 patients treated for nasopharyngeal carcinoma between 2011 and 2016 at the department of radiotherapy; Habib Bourguiba hospital at Sfax Tunisia. Radiation therapy was performed according to a conformational technique. The prescribed dose was 68-70Gy to the nasopharynx and the initially involved nodes. A dose of 50Gy was deliverated to the rest of cervical lymph nodes. We delineated the thyroid gland and we studied the dose received: the minimum dose (Dmin), the maximum dose (Dmax), the mean dose (Dmean) and the dose to 50% of the thyroid (D50%). Then, we compared the different parameters according to the node stage (TNM 2009).
Results
The average Dmin was 6Gy vs. 7,9Gy respectively for N0-N1 and N2-N3 (p = 0.3). The average Dmean was 41,2Gy vs. 43,5Gy respectively for N0-N1 and N2-N3 (p = 0.3). The average Dmax was 59,6Gy vs. 65,4Gy respectively for N0-N1 and N2-N3 (p = 0.07). The average D50% was 48Gy vs. 48,7Gy respectively for N0-N1 and N2-N3 (p = 0.7).
Conclusion
The Irradiation of the thyroid gland cannot be avoided during radiotherapy for nasopharyngeal carcinoma. There is no consensus about the dose constraints. It seems preferable to not irradiate more than 50% of thyroid volume with a dose superior to 50Gy. These constraints were sometimes exceeded in our study especially for patients with N2-N3 nodal involvement.

PO-072 Compliance and acute toxicity of chemoradiotherapy for undifferentiated nasopharyngeal cancer
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Purpose or Objective
To evaluate treatment compliance and acute toxicity for patients with locally advanced undifferentiated nasopharyngeal cancer treated with induction Cisplatin-based chemotherapy followed with concurrent chemo radiation and adjuvant chemotherapy.
Material and Methods
A total of 73 patients with locally advanced, non metastaticundifferentiated nasopharyngeal cancer were included. 42 patients (57.5%) were diagnosed in clinical stage IV and 31 (42,11%) stage III. Two cycles of chemotherapy with Epirubicin (dose of 90 mg /m2) and Cisplatin (60mg/m2) were administrated in induction and adjuvant approaches, and two cycles Epirubicin and Cisplatin with dose 60mg/m2, were given concurrently with radiotherapy on day 1 and 21 . Three dimensional radiotherapy was delivered with total dose 70Gy , using conventional regimen of fractionation.
Results
All patients received induction chemotherapy. Three patients developed progression of disease after induction chemotherapy 69 patients (94%) were treated with 3D conformal radiotherapy and received total dose of 70Gy using conventional regimen of fractionation . 67 patients received II cycles chemotherapy concurrently with radiation. After concurrent chemo radiation , 57 patients were treated with adjuvant chemotherapy. 56 patients (77%)completed treatment according to protocol and protocol modifications were observed in 23% (17 patients).
Most common acute toxicities were mucositis, dysphagia and skin toxicity. Severe mucositis grade 3/4 was observed in 47patients (64, 4 %) Most common hematological toxicities grade 3/4 was neutropenia , seen in 17 patients (23, 3%) . Two patients developed febrile neutropenia in concomitant chemoradiation and two in adjuvant treatment. No treatment related death was observed.
After 5years, there were no relapses of disease in 65, 3% patients.

Conclusion
Induction chemotherapy followed with concurrent chemo radiotherapy and adjuvant chemotherapy is feasible treatment, but with high rate of severe acute toxicity grade 3/4.

PO-073 Viable tumour in salvage neck dissections: relation with initial treatment, lymph node size and HPV
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Purpose or Objective
The objective of this study was to identify predictive factors for the presence of viable tumor and outcome in therapeutic salvage neck dissections in head and neck squamous cell cancer.
Material and Methods
Retrospective analysis of 87 salvage neck dissections after radiotherapy alone (n=30), radiotherapy in combination with carboplatin/5-FU (n=43) or with cetuximab (n= 14).
Results
Viable tumor was detected in 47% of all neck dissections and was associated with poor survival. Univariate analysis revealed initial treatment with radiotherapy alone (OR 7.12, $p < .001$), clinical suspicion of recurrence during follow-up (OR 7.10, $p = .015$), increased lymph node size (OR 28.16, $p = .002$), more extensive neck dissections (OR 8.70, $p < .001$), and human papillomavirus (HPV) negative cancer (OR 7.76, $p = .010$) as predictors of viable tumor. Decreased or unchanged but still enlarged lymph nodes after chemoradiation was a predictor of a negative neck dissection (OR: 0.11, $p < .001$).
Conclusion
Viable tumor in salvage neck dissections is associated with reduced survival. Increased lymph node size especially after radiotherapy alone for HPV negative cancers, is associated with viable tumor in salvage neck dissections. In case of decreased or unchanged lymph node size after chemoradiation, watchful waiting could be considered.

PO-074 Concomitant chemoradiotherapy alone or with induction chemotherapy in advanced head and neck cancer.
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Purpose or Objective
The purpose is to compare the treatment outcomes of patients with locally advanced head and neck cancer treated with Concomitant Chemoradiotherapy (CRT) alone versus induction chemotherapy (IC) followed by CRT in a retrospective study.
Material and Methods
From February 2009 to December 2015 patients with nonmetastatic stage III-IV were evaluated in a multidisciplinary board and assigned to CRT or IC followed by CRT. IC consisted of TPF (cisplatin, docetaxel, and fluorouracil), PF (cisplatin, fluorouracil), TCF (carboplatin, Docetaxel, and fluorouracil) and TP (cisplatin, docetaxel). The chemotherapy administered concurrently to most patients was cisplatin, given days 1, 22 and 43. Adverse events were assessed according to the common toxicity criteria of adverse events (CTCAE v. 4.0) and survivals were estimated using Kaplan-Meier method.
Results
The median follow-up was 29 months. A total of 138 patients were treated, 78 (56,5%) with CRT and 60 (43,5%) with IC followed by CRT.
At 3 years the overall survival for CRT versus IC followed by CRT was 50, 4% *vs* 34, 3%, respectively (p = 0,006). The Local control at 3 years was also higher for CRT compared to IC followed by CRT, 61% *vs* 42,4% (p= 0,02). The most common grade 4 toxicity during IC was leukopenia and during QRT the hematologic and non-hematologic toxicities were similar in both treatment modalities.
Conclusion
Results suggest that CRT was associated with higher overall survival and local control and that IC did not improve the distant control.

PO-075 Treatment of nasopharyngeal cancer: a Serbian institututinal experience
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Purpose or Objective
Since 2005.-2012. we have treated patients with advanced nasopharyngeal cancer (NPC) with neoadjuvant chemotherapy, concomitant chemoradiotherapy (CHRT) adjuvant chemotherapy. We herein report the results of our experience.
Material and Methods
There were 73 patients with previously untreated stage III (41,1%), IVa (19,3%) and IVb (38,6%) NPC. The median age was 52 years. Two cycles of neoadjuvant chemotherapy consisting of Epirubicin and Cisplatin, 90mg/m2 of each, were administered followed by CHRT with two same cycles but at the dose of 60mg/m2 of each drug and once-daily RT 2Gy/ day (median RTdose was 70GY). Finally, patients received adjuvant chemotherapy at the same dose as neoadjuvant approach.
Results
Response to neoadjuvant therapy was 72,6%: complite response (CR)1,4% and partial responce (PR)71.2%. After that, 15,5% patiemts had neck dissection. 69 patients completed CHRT. Response to CHRT was 92%: CR 37,7% and PR 53,6%, 57 patients received adjuvant treatment.Therewere 98,2% response, CR 84,2% and PR 14%. The progression' free' survival (PFS) at 3 and 5 years was 76,5% and 65,3%, respectivaly. Overall survival (OS) at3 and 5 years was 79% and 67,1%, respectivaly. Median od PFS and OS not achieved.
Conclusion
Treatment og locoregioally advanced NPC with induction chemotherapy, CHRT andadjuvant chemotherapy resulted in very good OS. These results are encouraging. A phase III study to definitively test this treatment strategy is warranted.

PO-076 Predictive and prognostic value of pretreatment fdg-pet suv parameters in head-and-neck

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Purpose or Objective
To evaluate the predictive significance of different descriptive parameters in head-and-neck cancer patients undergoing pretreatment [F18] FDG-PET imaging**Material and Methods**
Thirty-eight head-and-neck cancer patients who underwent FDG-PET before a course of curative intent radiotherapy were retrospectively analyzed. FDG-PET imaging parameters included maximum (SUVmax), and mean (SUVmean) standard uptake values, metabolic tumor volume (MTV), and total lesion glycolysis (TLG). We studied three threshold methods: the threshold of the 40% of the maximum uptake value (SUV40%), the threshold of the 50% of the maximum uptake value (SUV50%) and the adaptive threshold algorithm (ATA) implemented on the iTaRT workstation (Tecnologie Avanzate, Italy), this algorithm used specific calibration curves that depended on the lesion-to-background ratio (LB ratio) and on the amplitude of reconstruction smoothing filter (FWH). The correlation of SUV parameters with tumour characteristics, treatment response, and survival were analysed.
Results
Higher SUVmeanATA was associated to higher primary tumour staging (p= 0.04). SUV parameters resulted not predictive of tumour response. The TLG_{ATA} was predictive of local recurrence (p = 0.04) and MTV_{ATA} of overall survival (OS) (p= 0.04). SUVmax (ROC 0.8, p= 0.01) was predictive of 2-year DFS.
Conclusion
This study suggests that the baseline [18F]FDG-PET/CT parameters could predict recurrence risk and overall survival in head and neck cancer patients treated with chemoradiotherapy

Abstract submission: 6th ICHNO withdrawn

PO-077 Cisplatin or Carboplatin in locally advanced head and neck squamous cell carcinoma
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Purpose or Objective
This single center open labelled randomized controlled trial comparing concurrent chemoradiotherapy with weekly cisplatin versus weekly carboplatin in patients with locally advanced head and neck squamous cell carcinoma
Material and Methods
From march 2013 to december 2015 62 patients with locally advanced head and neck squamous cell carcinoma were randomized with 31 to cisplatin arm and 31 to carboplatin arm planned radiotherapy was the same in both groups all patients were evaluated for efficacy and toxicity according to the as treated principle
Results
With a median follow up of 6 months the acute non hematological toxicity in the form of renal toxicity was significant in cisplatin ARM (p=0.03)and hematological toxicity in the form of neutropenia was significant in carboplatin arm (p=0.001) xerostomia as late toxicity was significant in carboplatin ARM (p=0.004)
the 2 years pfs was 10 months in cisplatin ARM and 6 months in carboplatin arm (p=o.048)
Conclusion
We concluded that efficacy of weekly cisplatin is superior to weekly carboplatin as part of CCRT moreover the tolerability of weekly cisplatin regimen was acceptable

Poster: Innovative treatments

PO-078 The evaluation of the set-up differences between radiation therapists for head and neck patients
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Purpose or Objective
The set-up accuracy is important in intensity modulated radiation therapy (IMRT) to avoid the geographical misses increasing the risk of recurrence. In radiation therapy the set-up errors in the therapeutic fields are determined by using portal imaging and cone beam computed tomography (CBCT). The images obtained during treatment are compared with the planning images to verify the treatment fields. In this study, we try to figure out the electronic portal images' (EPI) evaluation differences between the therapists in the reference of CBCT.
Material and Methods
In this study, 62 EPI images belonging to 13 head & neck patients treated in our department were evaluated separately by 4 therapists as offline and the amount of shift in the center of fields were determined. CBCT taken at the same time with the EPI images were accepted as reference and the amount of shift in the center of fields were compared separately for each therapist with the results of EPI.
Results
According to our results, the amount of shift in the center of fields have changed between therapists with 0 mm to 9,4 mm in the reference of CBCT. The probability of shifting center of fields to be greater than 3 mm were %60 for the first therapist, %35 for second therapist , %63 third therapist and %50 fourth therapist. The probability of shifting center of fields to be greater than 5 mm were 24%, 8%, 27% and 14.5%, respectively. ANOVA (analysis of variance for repeated measures) test was applied to center shift values by using SPSS program and there was significant difference in the groups (sig. <0.05) and a significant difference between the groups (sig. <0.05). The degree of impact of the difference between the groups is defined as statistically large.
Conclusion
This study that we have performed on 13 patients and 62 fractions due to figure out the evaluation differences of EPI images between therapists have revealed the importance of CBCT imaging in IMRT plannings having high dose gradient. The usage of CBCT for the verification of treatment fields eliminates the differences in interpersonal evaluation. CBCT improve the set-up accuracy such that PTV expansion margin can be safely dropped. Therefore, CBCT should be the preferred imaging modality in IMRT planning. Our results suggest

that PTV margins can be safely reduced if daily CBCT is possible.

PO-079 Hypofractionated versus prolonged chemo-IMRT schedules in oropharyngeal carcinoma

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Purpose or Objective
Hypofractionated radical radiotherapy is gaining acceptance with proven non-inferiority demonstrated in breast and prostate cancer. Rotational IMRT with daily image guidance has increased confidence in the safe delivery of hypofractionated treatment. The purpose of this study was to compare efficacy outcomes at a minimum follow up of 2 years in two historic cohorts of locally advanced oropharyngeal carcinoma patients treated with 4-week (20#) or 5-7 week (25-35#) schedule in a single institution.
Material and Methods
Between June 2009 and May 2012 (4 week cohort), patients undergoing chemoIMRT were treated with 55Gy/20# over 25 days, with synchronous carboplatin. From June 2012 to April 2014 (>4 week cohort), similar patients were treated with either (a) 64Gy/25# over 32 days, (b) 65Gy/30# over 39 days, or (c) 70Gy/35# over 46 days, with synchronous cisplatin or carboplatin. Patients treated with synchronous cetuximab were excluded from this study. Overall survival, local control, distant control, and freedom from recurrence at 2 years were calculated for these cohorts. The effect of the following variables on outcome was analysed: age, T-stage, N-stage, p16 status, smoking status, chemotherapy agent (cisplatin/carboplatin), use of neoadjuvant chemotherapy, and radiotherapy schedule (4-week vs. >4 week).
Results
131 patients with non-metastatic oropharyngeal carcinoma received radical IMRT with concurrent platinum (4-week, n=70; >4 week, n=61). There were significantly more smokers with >10 pack year history ($p<0.001$) and less patients who received neoadjuvant chemotherapy in the >4 week cohort ($p=0.001$). Conversely more patients received cisplatin synchronously in this cohort ($p<0.001$). There were no other significant differences in baseline characteristics. T stage was found to have a statistically significant effect on overall survival ($p=0.02$) and local control ($p=0.04$). p16 status was statistically significantly associated with overall survival ($p=0.002$). None of the other variables evaluated had a statistically significant impact on the endpoints considered. At 2 years, local control ($p=0.256$), freedom from recurrence ($p=0.192$), and overall survival ($p=0.511$) were not statistically different between the 4-week and >4 week cohorts.
Conclusion
Survival and disease control were comparable in oropharyngeal carcinoma patients treated with 4-week or >4 week hypofractionation schedules. However, due to obvious confounding factors in this retrospective study; accelerated hypofractionated schedules for radical chemoIMRT in oropharyngeal carcinoma need prospective evaluation to determine whether such potentially resource sparing regimes truly offer equivalence in efficacy and quality of life.

PO-080 Challenges and opportunities in head and neck cancer research in the UK: a survey of oncologists

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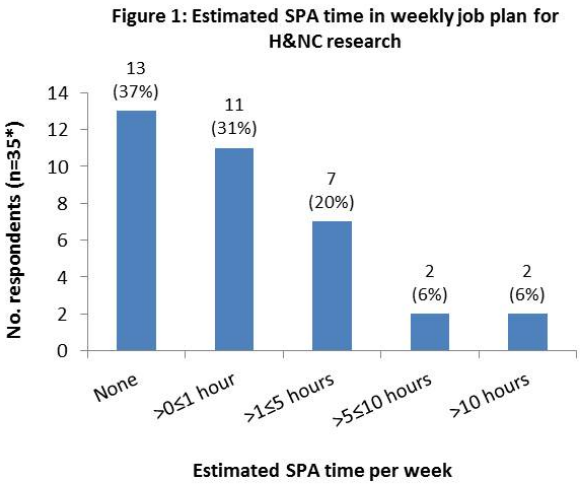
Purpose or Objective
Research into head and neck cancer (H&NC) management is vital for the development of new treatment options and improving patient outcomes; recent evidence (Wuthrick et al, 2015) suggests that outcomes are better when patients are treated at centres with high levels of participation in H&NC clinical trials. We conducted a survey of H&N cancer clinicians from oncology departments in the UK and Ireland to gain insights into their experiences of H&NC research.
Material and Methods
During March 2016, 55 H&N cancer clinicians from centres across the UK and Ireland were invited to complete an e-mail survey about their level of participation in H&NC research, the current challenges and priorities for future research. Here we present the responses of 45 consultants (43 clinical oncologists and 2 surgeons) from National Health Service centres in the UK (excluding Ireland).
Results
When asked to estimate the amount of Supporting Professional Activities (SPA) time in their weekly job plan for H&NC research, 37% of respondents (13/35 for whom the question was relevant) answered that they had no allocated time. Among the remaining 22 respondents, the median estimated SPA time was 1.25 hours per week (range 0.25-15) (**figure 1**). 16% of respondents (7/45) are not currently recruiting to a major national clinical trial (De-ESCALaTE, PATHOS, NIMRAD, CompARE, HOPON or DAHANCA 21), 52% (23/44) are not recruiting to any local/non-portfolio trials and 58% (25/43) are not aware of the trials that are open in other centres. The most frequently identified constraints in H&NC research were lack of clinician time and service pressures (80%, 36/45); lack of resources, staff or infrastructure to support and run trials (71%, 32/45); lack of interest (16%, 7/45); patient factors including the relative rarity of H&NC, co-morbidities and poor performance status (13%, 6/45); lack of funding/budget (13%, 6/45) and a lack of H&NC trials (13%, 6/45). A wide variety of priorities and potential questions for future H&NC research were identified.



** 10 'not relevant' or missing*

Conclusion
The results of this survey demonstrate that despite the recognised fundamental importance of H&NC research to care quality, many UK oncologists have limited or no time specifically allocated to this in their job plan. Many are not actively recruiting to national or local/non-portfolio trials, although there is willingness for greater involvement. The results provide useful insights into the constraints in H&NC research currently faced by clinicians within the NHS, which will need to be addressed in order to facilitate H&NC research in the future.

PO-081 Recurrence analysis in head and neck squamous cell carcinoma treated with adjuvant EUD-based IMRT
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Purpose or Objective
Resected high-risk patients with squamous cell carcinomas of the head and neck (HNSCC) experience local recurrences in about 20% despite adjuvant radio- or radiochemotherapy. There is a paucity of data concerning the recurrence rates and sites in patients treated with IMRT, especially when planned with a Monte-Carlo algorithm based on an equivalent uniform dose (EUD) approach. We analyzed our data in this respect.
Material and Methods
We included all HNSCC (oral cavity, oropharynx and hypopharynx) patients from 2008 to 2012 who received a resection and completed an adjuvant IMRT of 60 to 66 Gy with or without a cisplatinum based chemotherapy. Follow up visits were scheduled at least every 3 months including CT scans. Recurrences were categorized as in-field, marginal or ex-field.
Results
128 patients were included. Median follow-up was 24 months. 54% received adjuvant radiotherapy only, 46% had radiochemotherapy. Locoregional control was 94% with 2% only local, 2% local and nodal and 2% locoregional and distant recurrence. Of the 8 local recurrences, 3 were in-field, 4 were marginal and one was ex-field. Two-year overall survival was 79%, disease-free survival was 86%. Grade 1-2 acute toxicity occurred in 67% of the patients, grade toxicity 3-4 in 30%.
Conclusion
Adjuvant radio- or radiochemotherapy using IMRT with an EUD based prescription is safe. Recurrences occur mainly in or close to the tumor bed.

PO-082 Correlation between HI, GI, CI and Size of Metastases for Linac-Based High Dose SRT / SRS
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Purpose or Objective
To evaluate correlation between Heterogeneity Index (HI), Gradient Index (GI), Conformity Index (CI) and size of metastases for high dose Stereotactic Radiotherapy/Radiosurgery (SRT/SRS) using Elekta Versa HD® lineer accelerator with Agility® collimator system.
Material and Methods
Twelve patients with single metastases were used in this study. For each of the patients, the target was defined on CT-MR fused images. Agility® Multi Leaf Collimator system's features were used for patients treatment planning. Minimum segment width adjusted 0.5cm, grid spacing adjusted 0.2cm and statistical uncertainty adjusted 1%. Patient's treatment planning were performed using Monaco5.1® treatment planning system (TPS) with three or four non-coplanars 6 MV Flattening Filter Free (FFF) beams by partial Volumetric Modulated Arc Therapy (VMAT) tecnique for each patient. We determined four different size of metasteses catagory which are less than 0.5cc volume, between 0.5cc and 1cc volume, between 1cc and 5cc volume and between 5cc and 10cc volume. Also, five different plans were performed for getting different HI for each patients and maximum HI was restiricted 1.50.
Results
Correlations were determined between HI, GI, CI and size of metastases. Also, new Plan Quality Index (pQI) suggested for plan quality level of high dose Stereotactic Radiotherapy/Radiosurgery (SRT/SRS) plans. The mean lowest pQI was determined 6.60±0.3 for less than 0.5cc metastases volume, 5.28±0.7 for between 0.5cc and 1cc metastases volume, 4.57±0.2 for between 1cc and 5cc metastases volume and 3.29±0.2 for between 5cc and 10cc metastases volume.
Conclusion
Ideal one is the lowest GI and CI for good quality plan but GI and CI are not giving plan quality level exactly one by one. Therefore, we could determine plan quality level of treatment with pQI. Also, pQI depends on significantly size and HI of metastases especially for less than 1cc volume. When the metastases size is larger than 5cc, size of metastases and HI is losing its importance for pQI. Based on the correlation between HI, GI, CI and size of metastases we have decided that pQI should be ≤ 7.0 for less than 0.5cc metastases volume, pQI should be ≤ 6.0 for between 0.5cc and 1cc metastases volume, pQI should be ≤ 5.0 for between 1cc and 5cc metastases volume and pQI should be ≤ 4.0 for between 5cc and 10cc metastases volume for linac-based high dose Stereotactic Radiotherapy / Radiosurgery (SRT/SRT).

PO-083 Adaptative radiotherapy for nasopharyngeal carcinoma
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Purpose or Objective
Adaptative radiotherapy is a modification of the initial radiotherapy plan during the radiation course to re-optimize the treatment to take into account the anatomic variation such as the tumor response and weight loss.

Material and Methods
The study concerned three patients with nasopharyngeal carcinoma stage N2-3. A first CT dosimetry was performed for treatment planning using a 3D conformal radiotherapy. A second CT scan was acquired at 38-40 Gy.
After merging the two scans, we quantified the anatomic variations in target volumes and organs at risk, and then we faithfully reproduce the original planned parameters on the new CT to assess the dosimetric changes and check constraints to organs at risk.
A new treatment plan was generated based on the new target volumes and organs at risk. The new dose distribution and new dose-volume histograms were calculated and compared to the reference plane.
Results
The average reduction in lymph node and tumor macroscopic volumes (GTV) after 38-40 Gy was 53% and 40% respectively. Dosimetric coverage of planned target volume (PTV) and lymph node tumor remained satisfactory. To organs at risk, we found an increase of the maximum dose to the spinal cord for the three patients (1.4 Gy on average) and brainstem (1.5 Gy for a patient).
After adaptation of the treatment plan, The coverage of PTVs remained satisfactory. For organs at risk, maximum doses to the spinal cord and brainstem decreased. On average, the decrease was about 1.15 Gy to the spinal cord and 6.85 Gy to the brain stem
Conclusion
Ours results demonstrated a dosimetric benefit with the use of adaptative radiotherapy in nasopharyngeal patients.
This study should be continued with a greater number of patients to define a clear procedure especially that the application of this concept in clinical practice is limited due to the dependence on human resources.

PO-084 HDR Interstitial Brachytherapy for head and neck malignancies with Iridium 192 implants
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Purpose or Objective
To evaluate the treatment outcomes with HDR Interstitial Brachytherapy in Head and Neck Cancers at our Institute with use of Angiocatheters as carrier source of Iridium – 192 wire implants.
Material and Methods
58 Patients with Head and Neck malignancies of varying TNM staging as per AJCC staging criteria were analyzed retrospectively between 2008 and 2015. 42 patients (72.41%) received EBRT with HDR – BRT and 26 patients (27.59%) received BRT alone. The age group ranged from 27 to 81 years (Median age 56 years) with 41 patients (70.69%) males and 17 patients (29.31%) females. HDR – BRT was delivered with Iridium – 192 wire implants using plastic bead techniques with varying dose rates. The Biological equivalent doses (BED) were calculated for both BRT and EBRT keeping α/β =10 for tumor and α/β =3 for normal tissue and subsequently median BED doses were calculated and similarly 2 Gy equivalent dose (EQD2) were calculated and loco-regional control and disease free survival was assessed.
Results
After completion of HDR – BRT, Patients for followed up one month later and subsequently every 3 months for first 2 years and thereafter every 6 months with median follow up period of 25 months (Range 2-84 months). The DFS probability at year 1 was 82.76% and 68.05% at year 7. The overall survival probability was 91.37% at year 1 and 85.89% at year 5. The local control rate was 67.27% and the control rates according to the stage of disease and T size classification are mentioned in **Table 1.** The rate of local recurrence was 8.62%, Regional Recurrence was 1.72%, Loco-Regional Failure was 3.44% and Distant metastases following local or regional failure was 17.23%. The Median BED for α/β =10 was 86.775Gy and DFS was 74.07% in patients receiving more than 86.775Gy and DFS was 64.82% in patients receiving less than 86.775Gy and Median BED for α/β =3 was 128.76Gy and DFS was 74.07 in patients receiving more than 128.76Gy as compared to 64.82% in patients receiving less than 128.76Gy. The median EQD2 for α/β =10 was 71.6Gy and for α/β =3 was 75.85Gy. The DFS was 75.86% in patients receiving more than median dose of 71.6Gy compared to 61.53% in those receiving less than the median dose. The DFS was 78.57% in patients receiving median dose of 75.85Gy as compared to 59.26% in those receiving less than the median dose.
Conclusion
The overall outcome in the Patients with oral cavity and oropharyngeal malignancies was good with implementing of HDR – Interstitial Brachytherapy and use of Angiocatheters as carriers of Iridium – 192 wire. The BED10 value of 86.775Gy and BED3 of 128.76Gy showed that the dose received more than the median showed better outcomes in the form of DFS. The EQD2 calculated values suggested the dose received more than 71.6Gy (α/β =10) and 75.85Gy (α/β =3) showed better outcomes .The role of HDR Interstitial Brachytherapy in Head and Neck cancers is a proven, effective and safe treatment method with excellent long term outcome.

PO-085 Role of L Glutamine in reducing severity of chemoradiation induced mucositis and improve QoL in HNC
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Purpose or Objective
The incidence of mucositis in the oral cavity, pharynx and larynx is high among patients with head and neck cancer (HNC) receiving chemo-radiotherapy (CRT), resulting in significant pain and impairment of quality of life. The present study investigated whether L-glutamine (glutamine) decreases the severity of mucositis in the oral cavity, pharynx and larynx induced by CRT
Material and Methods
Patients were randomized to orally receive either glutamine or placebo at a dose of 10 g 3 times a day throughout the CRT course. Mucositis was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. The primary end point was mucositis severity. Seventy biopsy proven patients with head and neck cancer receiving primary or adjuvant radiation therapy were randomized to receive either oral glutamine suspension daily 2h before radiation in the study arm (10 g in 1000 ml of water) (n = 35) or placebo before radiation; control arm (n = 35)
Results
Total 30 patients in the glutamine arm and total 33 patients in placebo developed mucositis. Grade 3 mucositis and grade 4 mucositis in the study arm (who received oral glutamine) were significantly less in the glutamine arm. The mean duration of grade 3 or worse mucositis (grade 3 and grade 4) was significantly less in study arm with $P < 0.001$. Mean time of onset of mucositis was significantly delayed in patients who took glutamine in comparison to control arm with $P < 0.001$. Overall, glutamine was associated with a significant reduction of mucositis, WL, and enteral nutrition.
Conclusion

Glutamine delays oral mucositis in the head neck cancer patients. Moreover, it reduces the frequency and duration of grade 3 and grade 4 mucositis. More of the patients not receiving glutamine developed severe malnutrition when compared with those receiving this supplement, but there were no differences in other outcomes such as interruption of RT, hospitalization, use of opioid analgesics, or death during RT. Glutamine may have a protective effect during RT, reducing the risk and severity of OM, preventing weight loss, and reducing the need for nutritional support.

PO-086 Brachial plexus position reproducibility for head and neck radiotherapy and it's dosimetric impact

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Purpose or Objective

Radiation-induced brachial plexopathy is a rare late complication of radiotherapy(RT) that can cause significant morbidity [1]. The Radiation Therapy Oncology Group recommends limiting the brachial plexus (BP) maximum dose to 60 to 66 Gray(2) Delineation of the BP and any dose constraints are defined at the point of radiotherapy planning. However, lack of reproducibility of patient position during RT treatment for example due to weight loss may lead to dosimetric uncertainties. The purpose of this retrospective study was to determine any change in position of the BP during head and neck RT treatment in relation to it's original planned position and the dosimetric consequences of this.

Material and Methods

The study population consisted of 10 patients with oropharyngeal squamous cell carcinoma (OPSCC) treated with volumetric arc radiotherapy (VMAT) to a dose of 65Gy in 30 fractions over 6 weeks. Prior to commencing VMAT, patients underwent CT planning scan in a supine position in a 9-point thermoplastic mask. The treatment volumes and organs at risk (OAR) were delineated and a plan created using Eclipse Planning System. Treatment verification was achieved using weekly Cone Beam CT (CBCT) and daily KV imaging. For this retrospective study the brachial plexus position was delineated on each weekly CBCT. The position of the brachial plexus and the dose received was compared and re-calculated against the original planning scan. This resulted in 6 CBCT scans or data points for each of the 10 patients.

Results

The position of the BP varied on each weekly CBCT throughout treatment compared to the original planning scan. It's most stable point was at the level of C5/C6 while most variation in position was observed around the T1 level. The results demonstrate an average dose increase of 4% to the minimum and mean brachial plexus dose over the course of the treatment equivalent to 2.6Gy.

Conclusion

VMAT allows us to plan and deliver high dose RT to achieve maximum Planning Target Volume (PTV) coverage whilst OAR dose constraints. The extent of OPSCC at both the primary site and nodal levels treated with radiotherapy impacts the maximum dose to the brachial plexus. However, any loss of reproducibility of patient position during RT may lead to uncertainty of dose delivered to both PTV and OAR. Therefore, a dose constraint to the BP may be exceeded. A recent study by Chen *et al.* [3] suggested a dose-response relationship for the development of brachial plexopathies with a 1.39 times greater odds ratio of developing symptoms with each 1Gy increase in the maximum BP dose. Our small study suggests that the actual dose received by the BP may be higher than planned due to it's variation in position throughout treatment. This may lead to increased risk of brachial plexopathy in this patient population. In order to avoid this risk there are a number of solutions that can be considered including; lower dose constraints on the brachial plexus, a margin on the BP volume to account for any positional change or adaptive planning again to account for any positional change.

PO-087 Adaptive 18F-FDG-PET-guided reirradiation for recurrent and second primary head and neck cancer

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Purpose or Objective

To evaluate feasibility, disease control, survival and toxicity after adaptive ^{18}F-FDG-positron emission tomography (PET) guided radiotherapy in patients with recurrent and second primary head and neck squamous cell carcinoma (HNSCC).

Material and Methods

A non-randomized prospective trial investigated the feasibility of adaptive radiotherapy ± concomitant cetuximab in 10 patients with recurrent (n=5) and second primary (n=5) HNSCC. A primary endpoint of the study was to achieve a 2-year survival free of grade ≥3 late toxicity in ≥30% of patients. Three treatment plans based on 3 pre- and pertreatment PET/CT scans were consecutively delivered in 6 weeks. The range of dose painting was 66.0-85.0 Gy in the dose-painted tumoral volumes in 30 fractions with fraction doses delivered to the tumor and/or positive lymph nodes of 2.2-3.5 Gy, 2.2-2.5 Gy and 2.2-2.5 Gy during fractions 1-10, 11-20 and 21-30, respectively. Patients were treated with static beam IMRT (n=6) or helical tomotherapy (n=4). If multidisciplinary decision for concomitant systemic therapy was taken, patients received a cetuximab loading dose (400 mg/m^2) one week before start of radiotherapy (RT), followed by weekly doses of 250 mg/m^2 up to 6 times concomitant to RT. Twenty patients were planned to be recruited.

Results

Due to a slow accrual the study was terminated after the tenth patient. One patient did not complete the prescribed treatment course because of arterial bleeding during radiochemotherapy.

Median dose of the initial RT was 67.6 Gy. Median time interval from initial RT to reirradiation was 6.3 years. Median follow-up time was only 5.2 months, reflecting the poor overall survival. One-year locoregional and distant control were 38% and 76%, respectively. Overall and disease-free survival at 1 year were 30% and 20%, respectively (Figure 1).

No grade 4 or 5 acute toxicity was observed in any of the patients, except for arterial mucosal bleeding in one patient. Three months after radiotherapy, grade 4 dysphagia and mucosal wound healing problems were observed in 1/7 and 1/6 of the patients, respectively. Grade 5 toxicity (fatal bleeding) was seen in 2 patients, respectively at 3.8 and 4.1 months of follow-up. Late toxicity until 1 year of follow-up could only be assessed in 2 patients (Table 1). Data on 2-year grade ≥3 toxicity-free survival is not yet available; however, since only 20% of

patients are still alive, a 30% 2-year survival free of grade ≥3 toxicity will not be achieved.

Figure 1. Disease control and survival.

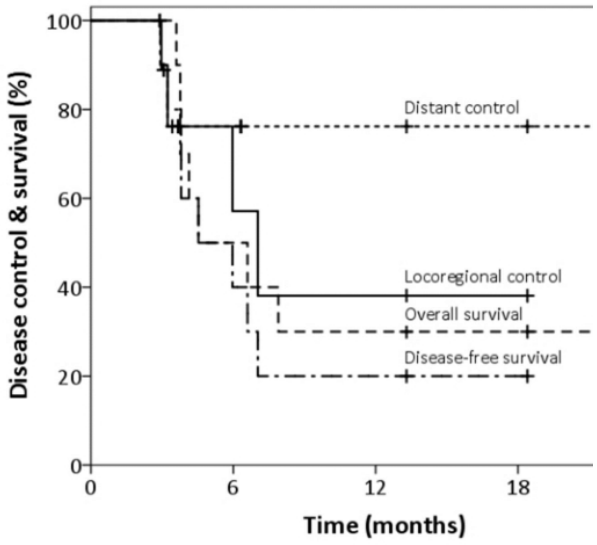

Table 1. Acute, subacute and late toxicity.

	Grade 0	Grade 1-2	Grade 3	Grade 4	Grade 5
Acute toxicity (during therapy)					
Dysphagia	-	8/9	1/9	-	-
Mucositis	1/9	6/9	2/9	-	-
Pain	-	9/9	-	-	-
Dermatitis	1/10	8/10	1/10	-	-
Subacute toxicity (up to 3 months after therapy)					
Dysphagia	3/7	2/7	1/7	1/7	-
Xerostomia	3/7	4/7	-	-	-
Mucosal integrity	1/6	3/6	1/6	1/6	-
Ulcer necrosis	4/4	-	-	-	-
Fibrosis	2/5	3/5	-	-	-
Bleeding	-	-	-	-	2/10
Late toxicity (up to 12 months after therapy)					
Dysphagia	1/2	1/2	-	-	-
Xerostomia	-	2/2	-	-	-
Mucosal integrity	1/2	-	-	1/2	-
Ulcer necrosis	2/2	-	-	-	-
Fibrosis	-	2/2	-	-	-

Conclusion

Adaptive PET-guided reirradiation is feasible. However, due to slow accrual, the trial was stopped early. We weren't able to evaluate the grade ≥3 toxicity rate at 2 years since poor survival was observed.

PO-088 The study of constant dose rate and gantry speed arc therapy for glottic carcinoma on Varian 23EX

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Purpose or Objective

Volumetric-modulated arc therapy, the novel techniques during the rotating irradiation a variable dose-rate(VDR) and gantry speed is required, allowing the aperture weights to vary at different beam angles,which can only be achieved in the new accelerator and prevents most existing linacs from delivering VMAT, we propose an alternative planning approach for VMAT using constant dose-rate and gantry speed arc therapy(CDR-CAS-IMAT) implementation on conventional Linac . Planning study was performed to evaluate the performance of CDR-CAS-IMAT on glottic carcinoma patients. Conventional fixed field IMRT was used as a benchmark, comparisons between CDR-CAS-IMAT and IMRT are made in the review within the areas of planning, delivery and quality assurance.

Material and Methods

Six patients with glottic carcinoma planning target volumes (PTVs)who were previously treated with IMRT on Varian 23EX were retrospectively planned for half arc （C. W. from 265°to 95°）CDR-CAS-IMAT plans, see Figure 1 and Figure 2. All plans dose prescription was set to 60 Gy to PTVs and 66 Gy to CTVs in 30 fractions. The planning objectives for PTVs and CTVs were corresponding with the IMRT plans at least 95% planning target volume reached the prescription dose and V110 no more than 10%, maximum dose to spinal cord was limited to 42 Gy. Calculated dose to the PTVs and organs at risk (OAR) were compared to standard IMRT with respect to plan quality, total plan monitor units(MU), and treatment time. And delivery accuracy were analysed by delivered plan to a Delta4 phantom. Using SPSS 19.0 software paired T-test analysis two sets of data.

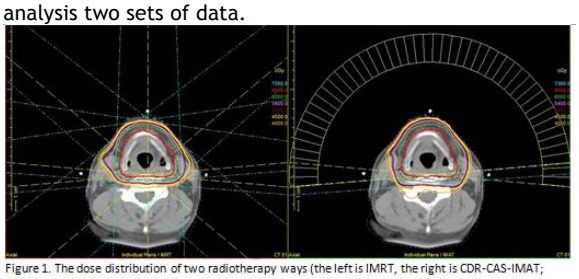

Figure 1. The dose distribution of two radiotherapy ways (the left is IMRT, the right is CDR-CAS-IMAT; IMRT was used as a benchmark)

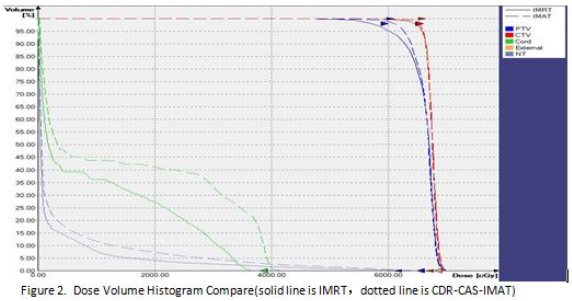

Figure 2. Dose Volume Histogram Compare(solid line is IMRT，dotted line is CDR-CAS-IMAT)

Results

Table 1. and Table 2.shows for glottic carcinoma half arc CDR-CAS-IMAT plans have equivalent or superior plan quality as compared to IMRT. Not only can incresed the Ptv d98, ptvv95, ptvv100, and minimum dose for PTV, but also can improve homogeneity Index (HI) of PTV. The mean HI are 0.17 and 0.35 for CDR-CAS-IMAT and IMRT plans, respectively. Volumes in the cord receiving 40Gy were increased from 0.4% with IMRT to 1.4% with CDR-CAS-IMAT. And compared with IMRT plans increased the E-P low dose area. Table 3. shows treatment times were reduced significantly with CDR-CAS-IMAT(mean 69.5s vs. 223.8s, $p < .05$), and total plan monitor units(MU), however, increased by a factor of 1.9. There was no significant difference in γ-test and Delta4 measurements results between both planning techniques($p > 0.05$).

Table 1 CDR-CAS-IMAT and IMRT in target volume, and organ at risk volume dosimetric parameters comparison（$\bar{x} \pm s$）

	Ptv d98	ptvv95	ptvv100	PTV CI	PTV min	PTV HI	CordV40(%)
CDR-CAS-IMAT	5993.7±100.2	99.3±0.25	97.8±1.1	0.75±0.02	5264.5±182.3	0.17±0.03	1.4±0.2
IMRT	5529.4±165.5	97.4±0.46	94.9±0.4	0.79±0.05	4813.0±254.8	0.25±0.05	0.4±0.4
T Value	7.315	12.423	4.737	-2.655	3.432	-11.667	5.295
P Value	.005	.001	.018	.077	.041	.001	.013

Comments：PTV D98 is 98% planning target volume accepted dose；PTV V95 is 95% planning target dose accepted irradiated volume；the other the same as.

Table2 Volumes in the healthy tissues receiving comparison（$\bar{x} \pm s$）

	E-P V5(%)	E-P V10(%)	E-P V15(%)	E-P V20(%)	E-P V30(%)
CDR-CAS-IMAT	15.4±2.2	10.4±2.0	7.7±1.9	5.8±1.7	3.6±1.2
IMRT	11.7±2.2	6.4±1.8	4.5±1.5	3.4±1.1	2.3±0.7
T Value	6.110	7.304	7.068	6.031	5.042
P Value	.009	.005	.006	.009	.015

Comments: E-P is CT scan body volume subtraction the volume of PTV

Table 3 CDR-CAS-IMAT and IMRT comparison in MU , delivery time and delivery accuracy of DTA and γ pass rate（$\bar{x} \pm s$）

	γ（±3mm、±3%）	DTA（±3mm、±3%）	Treatment time (s)	MU
CDR-CAS-IMAT	91.5±1.1	94.8±2.4	69.5± 9.5	611.8± 139.3
IMRT	94.9±3.4	94.5±1.3	223.8± 35.9	321± 46
T Value	-2.8	.43	-8.6	5.1
P Value	.070	.699	.003	.015

Comments： DTA :Distance to Agreement

Conclusion

Conventional Varian 23EX Linac CDR-CAS-IMAT Plans for glottic carcinoma can be implemented smoothly and quickly into a large, busy cancer center. CDR-CAS-IMAT planning can meet the clinical demand, gives comparable OAR and improved PTV CI, give a reduction in treatment time but increased the MU and low dose irradiated area. An evaluation of weight loss must be performed during treatment for CDR-CAS-IMAT patients, and should be selected according to the actual situation of the patient treatment.

PO-089 Melatonin enhances the toxicity of radio- and chemotherapy in head and neck cancer cells

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Purpose or Objective

After reported a melatonin's gel that protects normal cells from oral mucositis induced by radio- or chemotherapy, we wondered about how melatonin affects tumoral cells. It is well known that both radio- and chemotherapy act at different intracellular levels such as nucleus, membranes and mitochondria. On the other hand, mitochondrion is the main melatonin target. So we evaluated here whether melatonin can synergize with radio- or cisplatin- therapies to enhance the cytotoxic effects of these treatments.

Material and Methods

The dose-dependent effects of melatonin were analyzed in irradiated or cisplatin-treated Cal-27 and SCC-9 tongue cell lines. Cells were maintained in DMEM medium, supplemented with 10% fetal bovine serum at 37 °C in a humidified atmosphere of 5% CO2 and 95% air. Cells were treated with melatonin (100 μM, 500 μM , and 1500 μM) alone or in combination with 8 Gy irradiation or 10 μM CDDP. The clonogenicity capacity of the cells, proliferative potential (MTT), apoptosis, cell cycle, mitochondrial mass, mitochondrial respiration, ROS production, nitrites and GSH/GSSG levels, as well as antioxidant enzymes activity and western blot, were assessed. We also studied the potential synergistic effects of melatonin with the different treatments in vivo. Moreover, we induced tumour xenografts in nude mice using Cal-27 cells. Mice with tumour were treated with radio-or chemotherapy. Hematoxylin/Eosin staining, immunohistochemical analyses such as Ki-67 (proliferation) and TUNEL assay (apoptosis) were performed to evaluate the tumoral progress.

Results

The in vitro results showed a rise in the treatment toxicity in a melatonin dose-dependent manner, potentiating the cytotoxic effects of the radio- and the chemotherapy. Melatonin also acts inhibiting the tumor growth in vivo.

Conclusion

High melatonin concentrations enhance the cytotoxicity of radiotherapy and the chemotherapeutics in head and neck human cancer.

Ortiz F, et al. J Pineal Res 2015; 58: 34-49

Escames G, et al. Hum Genetics 2012; 131:161-173

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PO-090 Oncostatic effect of melatonin in head and neck cancer: role of mitochondrial function

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Purpose or Objective

Cancer cells have some special features that give them the ability to change and to resist different types of treatments. These changes are produced by modifications in the mitochondrial bioenergetics, that is, a switch in the metabolism. These advantages consist in the so-called Warburg effect. Cancer cells depend on glycolysis instead of oxidative phosphorylation to get the energy necessary to proliferate and to survive. Thus, a treatment against this mechanism would control cancer spread. In normal cells melatonin boosts the mitochondrial function and scavenges oxygen radicals, protects them from oxidative damage and increasing cell's survival. As mitochondrion is a therapeutic target in cancer cells, we wanted to know how melatonin affects the mitochondria of these cells.

Material and Methods

The effects of high concentrations of melatonin (100 μM, 500 μM, and 1500 μM) were evaluated in Cal-27 cell lines. Cells were cultured in DMEM supplemented with 10% fetal bovine serum at 37 °C in a humidified atmosphere. Cells were treated with melatonin for 1, 3 and 5 days. The following parameters were analyzed: proliferation, mitochondrial mass, mtDNA content, mitochondrial respiratory capacity, glycolytic capacity (Seahorse), ROS production, activity of antioxidant enzymes, glutathione levels, and metabolomic study. Moreover, the *in vivo* oncostatic effect of melatonin was assessed in mice with Cal-27 xenografts. Tumour-carrying mice were treated with 300 mg/kg melatonin for 21 days when immunohistochemical, TUNEL assay and MRI studies were performed. Toxicity study of melatonin was performed using C57BL/6J with a chronic treatment of oral melatonin at high concentration for 3 and 6 months measuring biochemical and histological markers.

Results

The results showed that melatonin induced a switch to aerobic mitochondrial metabolism in cancer cells that increased ROS production, reducing cell proliferation. Melatonin also showed an oncostatic effect *in vivo*, with a reduction in the tumor cell proliferation, and increasing the apoptotic rate, with histological changes compaytble with these changes. Concerning toxicity studies, melatonin did not show any side effects in healthy mice.

Conclusion

Mitochondrial changes induced by melatonin lead to a metabolic switch in cancer cells inducing cellular dead but doesn't affect normal tissues.
Ortiz F, et al. J Pineal Res 2015; 58: 34-49
Escames G, et al. Hum Genetics 2012; 131:161-173
Supported in part by grant nº SAF2013-49019-P

PO-091 Intensity modulated radiotherapy (IMRT) in nasopharyngeal cancer - a dosimetric and QoL analysis

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Purpose or Objective
Intensity modulated radiation therapy (IMRT) as a treatment technique has become the standard of care in treatment of nasopharyngeal carcinoma. The dosimetry of the modality with respect to parotid and other normal organ sparing and other clinical outcomes are presented in our study.
Material and Methods
The medical records of 32 patients with histologically proven primary nasopharygeal carcinoma treated with IMRT were retrospectively reviewed. The majority of patients showed advanced clinical staging. IMRT was performed in step-and-shoot technique using an integrated boost concept. The boost volume covered the primary tumor and involved nodes with doses of 66–70.4 Gy (single dose 2.2 Gy) and uninvolved regional nodal areas were covered with doses of 54–59.4 Gy (median single dose 1.8 Gy). The dose constratints were optimized and normal organs at risk (OARs) spared. Dosimetric analysis was done and quality of life was assessed at initial stage and later during follow up at 3 and 6 months. The survival analysis was evaluated.
Results
The median follow-up for the entire cohort was 24 months. Radiation therapy was completed without interruption in all patients. Four local recurrences have been observed, transferring into 1-, 3-, and 5-year Local Control (LC) rates of 95%, 90% and 90%. Two patients developed regional nodal recurrence, resulting in 1-, 3-, and 5-year Regional Control (RC) rates of 95%. All locoregional failures were located inside the radiation fields. Distant metastases were found in three patients, transferring into 1-, 3, and 5-year Distant Control (DC) rates of 90%, 84% and 82%. Progression free survival (PFS) rates after 1, 3 and 5 years were 85%, 72% and 65% and 1-, 3- and 5-year Overall Survival (OS) rates were 90%, 85% and 80%. Acute and chronic toxicities were assessed as per EORTC grading scale and found to be better with IMRT and under acceptable tolerance levels.
Conclusion
IMRT with an integrated boost concept yielded good disease control, good OARs sparing, better quality of life outcomes and overall survival in patients suffering from primary nasopharyngeal cancer with acceptable acute side effects and limited rates of late toxicity.

PO-092 Dosimetric comparaison of conformal and intensity modulated radiotherapy for locally recurrent NPC

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Purpose or Objective
Locally recurent nasopharyngeal carcinoma (NPC) can be salvaged by reirradiation with a substantial degree of radiation related complications.
The aim of this study was to evaluate the dosimetric advantage of intensity modulated radiotherapy (IMRT) in treating locally recurrent NPC.
Material and Methods
Between January 2014 and september 2016, six patients with no metastatic locally recurrent NPC were re-irradiated with concomitant chemotherapy. The median prescrepted dose was 60 Gy with 2 Gy per fraction. Treatment planning of each patient was performed for tow techniques : Three dimentional Conformal radiotherapy (3D CRT) and Intensity modulated radiotherapy (IMRT). The minimum dose (Dmin), the maximuim dose (Dmax) and the volume that received 95% of the dose prescrepted (D95%) of the planning target volume (PTV) and doses to the organs at risk (Spinal cord and brainstem) were calculated and compared for the tow techniques.
Results
All two techniques delivered adequate doses to the PTV. The average Dmin was 48Gy for the two techniques, the average Dmax was 67,5 Gy vs 64,2 Gy respectively for IMRT and 3D CRT (p=0,41) and D95% was 96%. Concerning the organs at risk, the Dmax for the brainstem was significantly higher for 3D CRT (22 Gy vs 14 Gy, p= 0,003). This finding were similar for the spinal cord (20Gy vs 7,8 Gy). But, the difference was not statically significant (p=0,12).
Conclusion
Based on the dosimetric comparaison, IMRT was optimal by delivering a conformal and homogenous dose to the PTV with significant better sparing of critical organs than 3D CRT.
In this regard, re-irradiation using IMRT may be a very attractive technique for locally recurrent NPC.

PO-093 COSTAR trial results: 3-D Conformal Radiotherapy vs Cochlea-Sparing IMRT in parotid cancer patients

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Purpose or Objective

30-50% of patients receiving post-operative radiotherapy (RT) for parotid cancer experience ipsilateral hearing loss. IMRT can reduce radiation dose to the cochlea. COSTAR (CRUK/08/004) investigated the role of IMRT in reducing hearing loss in these patients.

Material and Methods

Patients with histologically confirmed carcinoma of the parotid gland (pT1-4, pN0-3, M0) were randomized 1:1 to receive CT-planned 3-D Conformal RT (3DCRT) or Cochlea Sparing-IMRT (CS-IMRT). 60Gy (R0 resection) or 65Gy (R1-2) in 30 fractions were delivered over 6 weeks. Treatment allocation used minimisation, balancing for centre and planned RT dose. The primary endpoint was proportion of patients with hearing loss in the ipsilateral cochlea of ≥10dB measured by bone conduction at 4000Hz 12 months (m) after RT; compared between randomized groups by an exact test (α=0.05). Secondary endpoints (α=0.01) included hearing loss at 6 and 24m, vestibular function, acute and late toxicity, patient reported quality of life (including Glasgow Hearing Aid Benefit Profile (GHABP), time to tumour recurrence and survival.

Results

110 patients (54 3DCRT; 56 CS-IMRT) were randomised between 2008 and 2013 from 22 UK centres. 99 (90%) patients were R1-2 (47 3DCRT; 52 CS-IMRT). Mean dose to the ipsilateral cochlea was 56.2Gy for 3DCRT and 35.7Gy for CS-IMRT, (p<0.001). 66/110 (60%) patients were evaluable for the primary endpoint; the main reasons for non-evaluability were non-attendance at follow-up audiology and bone conduction assessment not performed. At 12m, a loss of ≥10dB in ipsilateral bone conduction was observed in 14/35 (40%) 3DCRT and 11/31 (36%) CS-IMRT patients (p=0.80). No statistically significant differences in bone or air conduction were observed at 6m or 24m after RT nor for any GHABP initial disability or handicap subscales, vestibular function, acute or late toxicity, overall quality of life, time to tumour recurrence or survival.

Conclusion

IMRT reduced the radiation dose below the accepted tolerance of the cochlea, but this did not lead to a statistically significant reduction in the proportion of patients with hearing loss in the ipsilateral ear at 12 months after RT.

PO-094 Radiation induced volume changes in Salivary glands in head and neck cancer patients receiving IMRT

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Purpose or Objective

To evaluate radiation induced volume changes in the parotid glands and submandibular glands in patients with head and neck cancer receiving Intensity Modulated Radiotherapy (IMRT) and correlation with the mean doses received by the glands and assessment of timings of the volume changes during fractionated RT.

Material and Methods

Fourty five patients of Head and Neck Cancers, satisfying the inclusion criteria were included from May 2015 to Dec 2015 and were treated with radical or post-operative Radiotherapy using IMRT with or without Chemotherapy. Radiotherapy planning CT scans were done at pre RT, after 40 Gy and on completion of treatment for each patient. Parotid and submandibular gland volumes were re contoured on each study scan and rechecked with same observer. The volumes (V0 - Volume on initial CT scan) and mean doses to the parotid and submandibular glands were calculated from the Dose-volume histograms (DVHs) of the IMRT plan, done on pre RT scan. The re contoured volumes of parotid and submandibular glands on the CT after 40 Gy (V1) and on completion (V2) were noted. Volume changes of the glands were assessed and statistical analysis was done to see any correlation between the mean dose and volume changes of the glands.

Results

The total mean dose to the parotid glands in IMRT patients was 24.47 Gy (for the ipsilateral and contralateral parotid glands they were 41.61 Gy and 26.13 Gy, respectively). For IMRT patients, the total mean doses to spared and irradiated submandibular glands were 7.39 Gy and 58.04 Gy, respectively. The average volume loss after 4 weeks of RT, upon completing RT versus before RT were 22.12%, 31.12%, and between 4 th week to completion of RT 11.56% for the parotid glands and 25.26%, 32.93% and between 4 th week to completion of RT 10.28% for the submandibular glands, respectively. The average mean volumes of both parotid glands and submandibular glands after 4 weeks of RT and upon completing RT were significantly smaller than before RT (P value <.001). We observed volume loss during RT in the parotid and the submandibular glands. The average rates of volume loss during the first 4 weeks of RT (22.12% and 25.26% respectively) were larger than in the last 2/3 weeks of RT (11.56% and 10.28% respectively). Volume loss at higher doses (>30 Gy) to the glands was significantly larger than at low doses (<30 Gy; P < .001).

Conclusion

The parotid and submandibular glands shrunk during RT. These gland volume reductions correlated significantly with the mean dose to the irradiated glands; the spared glands showed few changes.

PO-095 Electrochemotherapy for mucosal head and neck tumours: results from a phase II clinical trial.

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Purpose or Objective

Electrochemotherapy is a local tumour treatment currently used for cutaneous tumours and metastases in a palliative setting. Electric pulses are applied to the exterior of the cells creating a temporary permeability of the cell membrane. During this phase chemotherapy can gain access to the interior of the cell and cause apoptosis. Electrochemotherapy applied on mucosal tumours has only been tested in a few trials. The purpose of this trial was to evaluate electrochemotherapy on recurrent head and neck tumours in a palliative setting.

Material and Methods

ClinicalTrials.gov Identifier: NCT02549742. The study was designed as a phase II, clinical trial, with planned decision to discuss continuation after the first twelve evaluable patients. Patients included had recurrence of carcinoma in the oral cavity, rhino-, oro- or hypopharynx and no further curative treatment options left as determined by multidisciplinary conference (MDT). Electrochemotherapy

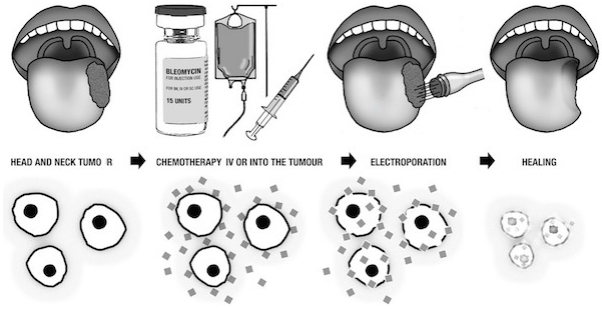
was performed in general anaesthesia using systemic bleomycin (15.000 IU/m^2) prior to electroporation with sequences of 8 pulses of 100µs and 1000 V/cm applied voltage to electrode distance ratio. Evaluation of tumour response was assessed from PET/CT-, MRI- scans and biopsies. Primary objective was tumour response measured using RECIST criteria. Secondary objectives included tumour response in the treatment area from MRI and multiple time point FDG PET scans as well as patient evaluation of treatment using pain score and quality-of-life questionnaires (EORTC QLQ-C30 and QLQ-H&N35).

Results

Nineteen patients were included in this ongoing trial and treated for a recurrent carcinoma in the head and neck area. Due to large tumours, treatment could in most cases only be applied to parts of the tumour thereby leading to a debulking. Thirteen patients were evaluable according to RECIST criteria at evaluation 8 weeks after treatment. One patient died before evaluation. Five patients had cystic tumours at evaluation and therefore not evaluable according to RECIST criteria. Overall response in the 13 patients evaluable by REICST was 62% (8 of 13 pts): of these 2 (15%) had complete remission (CR), 6 (46%) had partial remission (PR), while progression (PD) was observed in 5 (39%). The MRI and PET results from the treatment area are currently being assessed. There was no change in pain score from baseline to evaluation. Quality-of-life questionnaires only demonstrated a change in dysphagia.

Conclusion

Electrochemotherapy was feasible in patients with recurrent head and neck cancer without further standard treatment options. Overall response rate was 62% with limited side effects, warranting continuation of the study.



PO-096 Dosimetric evalutation of volumetric modulated arc therapy (VMAT) in sinonasal cancer raiotherapy

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Purpose or Objective

To assess dosimetric parameters of volumetric modulated arc therapy (VMAT) for nasosinusal malignancies with regard to the coverage of planning target volume (PTV) and the sparing of organs at risk (OAR).

Material and Methods

Nine patients with naso sinusal malignancies were treated with postoperative radiotherapy (VMAT, 2-3 non coplanar arcs) between 2015 and 2016. Seven patients were treated on primary target volume only (tumor bed), two patients required also nodal irradiation. Planning goals were the following: PTV: > 98% volume covered by >95% of prescribed dose; >107% of prescribed dose to < 2% PTV volume; for organs at risk (OARs): maximum doses (D(max)) < 60 Gy to the brainstem, < 54 to the optic chiasm, < 50 to the optic nerves, <40 Gy to the eyes and < 5 Gy to the lenses. Dose was prescribed to the median dose according to ICRU 83. Dose-volume histogram, the maximum, minimum, and mean doses to the target volumes and organs at risk, and monitor units (MUs) were evaluated.

Results

VMAT offered a good tumor volume coverage and provided a good sparing of OARs (mean Dmax ipsilateral optic nerve:45,8 Gy, mean Dmax contralateral optic nerve: 43,3; mean Dmax optic chiasm: 46,4 Gy; mean Dmax brainstem: 37,9 Gy; mean Dmax ipsilateral eye: 47,6 Gy; mean Dmax contralateral eye: 33,3 Gy). VMAT showed low MUs (mean MUtot: 583,7) and low treatment delivery.

Conclusion

VMAT's plans further reduce doses to critical structures that are in close proximity to the target volume, and reducing treatment delivery time, decrease the effects of intrafractional uncertainties that can occur because of patient movement during treatment delivery.

Poster: Biology, HPV and molecular targeting

PO-097 Droplet Digital PCR for detection of circulating tumour DNA in blood of head and neck cancer patients

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Purpose or Objective

During posttreatment surveillance of head and neck cancer patients, imaging is insufficiently accurate for the early detection of relapsing disease. Free circulating tumor DNA (ctDNA) may serve as a novel biomarker for monitoring tumor burden during posttreatment surveillance of these patients. In this exploratory study, we investigated whether low level ctDNA in plasma of head and neck cancer patients can be detected using droplet digital PCR (ddPCR).

Material and Methods

TP53 Mutations were determined in surgically resected primary tumor samples from 6 patients with high stage (II-IV), moderate to poorly differentiated head and neck squamous cell carcinoma (HNSCC). Subsequently, mutation specific ddPCR assays were designed. Pretreatment plasma samples from these patients were examined on the presence of ctDNA by ddPCR using the mutation-specific assays. The ddPCR results were evaluated alongside clinicopathological data.

Results

In all cases, plasma samples were found positive for targeted *TP53* mutations in varying degrees (absolute quantification of 4.2 – 422 mutational copies/ml). Mutations were detected in wild-type *TP53* background templates of 7,667 – 156,667 copies/ml, yielding fractional abundances of down to 0.03%.

Conclusion

Our results show that detection of tumor specific *TP53* mutations in low level ctDNA from HNSCC patients using ddPCR is technically feasible and provide ground for future research on ctDNA quantification for the use of diagnostic biomarkers in the posttreatment surveillance of HNSCC patients.

PO-098 Searching for therapeutic targets from whole transcriptome of oral cancer

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Purpose or Objective
Gingivo-buccal squamous cell carcinoma (GBSCC) is one of the most common oral cavity cancers in India. Even after decades of intense research, 5-year survival is less than 50%. So, it is necessary to discover therapeutic targets for better treatment of oral cancer patient. To search for therapeutic targets; expression and somatic mutations in whole transcriptomes of GBSCC from tobacco smokers and smokeless tobacco users/chewers were examined.
Material and Methods
Whole transcriptome data from 12 pairs of GBSCC and adjacent normal tissues were generated by next generation sequencing method in Illumina platform. Data were analyzed to find out expression deregulation and somatic mutations of the transcripts.
Results
Expression of 1582 genes was significantly deregulated in cancer tissues. Data analysis indicated that cell-cell adhesion and ECM-receptor processes were most aberrant pathways. Other altered pathways include AMPK, PPAR and arachidonic acid metabolism which may highlight their importance in primary GBSCC. Interestingly, smokeless tobacco users/chewers were clustered together when expression deregulation of genes involved in cell adhesion, proteoglycans, AMPK and PPAR pathways were considered for cluster analysis. We also generated proliferation score using expression of cell cycle progression marker genes and found that smokeless tobacco users tend to show higher proliferation score. Tumors from smokers and smokeless tobacco users have distinct CD47 & SIRPA and PD-1 & PDL-1 expression, respectively, and a range of variation in infiltrating immune cell signature to infer differential immune evasion strategy. Integrative analysis of miRNA and mRNA expression helped us to identify several important miRNAs which are playing important roles in shaping expression profiles of several cell adhesion, tissue architecture maintenance and energy metabolism pathways.
Conclusion
Transcriptome analysis highlighted few potential targetable nodes and neo-antigens which could be effective precision therapeutic or immunotherapeutic targets. Further, this study also suggests that therapeutic targets might be different for oral cancer patients who used smoking or smokeless tobacco. Data of deleterious somatic and germline variants along with expression profile could be useful in treatment plan.

PO-099 Human papillomavirus in head and neck cancer in the UK: a clinician survey of current practice

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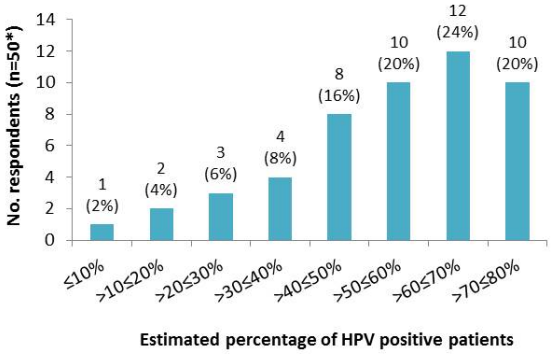
Purpose or Objective
An increasing number of head and neck (H&N) cancers are associated with human papillomavirus (HPV) infection. Compared with HPV negative H&N cancers, HPV positive tumours tend to affect younger patients and non-smokers. The prognosis on the whole is very high, with cure rates published in excess of 90%; this presents unique challenges for patient management in view of the late consequences of H&N cancer treatment. Additionally, because HPV is a sexually transmitted infection, the diagnosis may have an impact on patients' emotional and psychological wellbeing. We conducted a survey of H&N cancer clinicians from oncology departments in the UK and Ireland, to increase understanding about the current management of patients with HPV positive H&N cancers.
Material and Methods
During March 2016, 55 H&N clinicians from centres across the UK and Ireland were invited to complete an e-mail survey about their current practices in relation to HPV screening, counselling on the implications of HPV positivity and approaches to treatment.
Results
The majority of respondents (85%, 47/55) were consultant clinical or medical oncologists (n=44 and n=3, respectively), with the remaining 8 comprising H&N cancer specialist nurses (n=3), specialist oncology registrars/clinical fellows (n=3) and surgeons (n=2). 36% of respondents (20/55) said that they routinely test all H&N cancer patients for HPV, 60% (33/55) test only specific subgroups (oropharyngeal [n=28], unknown primary [n=6], oral cavity [n=3], basaloid [n=1]) and 4% (2/55) don't test routinely. The estimated percentage of patients with oropharyngeal cancer who are HPV positive ranged between respondents from 5-80%, with a median of 60% (**figure 1**). The number of respondents from each UK region was low, but median HPV prevalence estimates ranged from 25% in Ireland (n=5) to 75% in the South of England (n=8) and Wales (n=3). 33% of respondents (18/55) routinely counsel patients about the implications of HPV positivity, 47% (26/55) provide counselling only when asked and 20% (11/55) don't provide routine counselling. 33% (18/55) have literature available in clinic about HPV positive tumours. Outside of clinical trials, 91% (50/55) don't treat HPV positive patients differently to HPV negative patients.

Figure 1: Estimated percentage of patients with oropharyngeal cancer who are HPV positive



** 5 respondents did not provide an estimate*

Conclusion
The wide range in the estimated percentage of patients with oropharyngeal cancer who are HPV positive suggests that there may be geographical variations in the prevalence of HPV in different areas of the UK. This would correlate with known national variation in cigarette smoking. Differences in HPV screening practice were also identified, with some clinicians routinely testing all patients and others testing only specific subgroups. There is a need for more literature about HPV positive tumours, to facilitate healthcare professional discussions with

patients about the important implications of HPV positivity.

PO-100 Oral cancer microenvironment - PI3K/AKT/mTOR and ERK/MAPK pathways dependent targets

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Purpose or Objective
Oral cancer represents 30% of all head and neck cancer and over 95 % are squamous cell carcinomas (OSCC). The anatomy of the oral cavity is particularly challenging due to different microenvironments identified in this relatively small area. Thus, the interplay between tumor cells and stromal structure has been receiving growing attention as it can contribute for malignant transformation. The PI3K/AKT/mTOR and the ERK/MAPK pathways regulate cell survival, proliferation, and motility and can converge to regulate each other.
The aim of our study is to understand the role of PI3K/AKT/mTOR and ERK/MAPK in oral cancer microenvironment, namely in the reciprocal interplay between malignant cells and stromal structure, in order to identify new diagnosis and therapeutic targets for OSCC.
Material and Methods
For this purpose, the human OSCC cell line, HSC-3, was cultured. Then, approximately 3, 15 or 30 million were inoculated in *Balb/c nu/nu* mice (4/location) on tongue, on jugal submucosa and on dorsal side subcutaneously (back), respectively (Of. 3-CE-2011 FMUC, Portugal). During 3-7 weeks, the mice were supervised. After, they were killed by anesthetic overdose and tumor nodules and involving tissue were excised for *ex vivo* studies. The histology was assessed by the hematoxylin-eosin staining. The immunophenotype was evaluated by immunohistochemistry (IHC) using AE1AE3 cytokeratin cocktail, Vimentin, phospho(p)mTOR and Ki67. For genetic studies the samples were Purezol® processed and the obtained RNA was converted to cDNA and a 48 RT-PCR array for PI3K/AKT/mTOR pathway specific for human was applied.
Results
Our results showed that depending on the inoculation/implantation site HSC-3 cells exhibit different gene expression and immunophenotype profile as well as different amount of keratinizing cells, large cells and basal/intermediate cells. Tongue location showed increased IHC expression of AE1/AE3, Vimentin and pmTOR comparing with the other models. The Ki67 index was higher in large and basal cells in all models. The gene expression profile showed that the PI3K/AKT/mTOR pathway has a different transcription regulation according to the tumor implantation site. The jugal submucosa location showed increased expression of *AKT3, PDK1, PDK2, PRKCA, IGF1R, MAPK3/ERK1, CTNNB1* (1.5x higher), and decreased expression of *FASL* and *NFKB1A* (0.5x higher). These results with IHC unstaining of pmTOR indicate that in jugal submucosa MAPK/ERK pathway has a critical role in carcinogenesis.
Conclusion
Our preliminary results suggest that tumor microenvironment determines different gene expression and immunophenotypic profile in OSCC. In tongue the PI3K/AKT/mTOR pathway appears to have a determinant role whereas in jugal submucosa the ERK/MAPK pathway maybe a preferential target.

PO-101 Osteopontin (OPN) as an instant, predictive marker of tumour hypoxia in head and neck cancer patients

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Purpose or Objective
Despite of well known prognostic factors like locoregional stage of disease, there is still lack of markers describing individual feature of the tumor. Some of proinflammatory cytokines are supposed to predict the nature of the tumor what may help to optimize the therapy. Plasma osteopontin (OPN) is a putative marker of tumor hypoxia in patients with head and neck squamous cell carcinomas (HNSCC). Additionally, OPN has been recognized as important in the processes of tumorigenicity and metastasis. The aim of the study was to assess clinical utility of OPN as the biomarker of treatment outcome of radiotherapy (RT) or radiochemotherapy (CHRT) in HNSCC.
Material and Methods
Between 01/2009 and 08/2013 251 patients in the mean age of 59 years with squamous cell carcinoma of oropharynx (39%), hypopharynx (13%), larynx (44%) or oral cavity (4%) were treated with RT alone (48%) or combined with chemotherapy (52%). The median duration of symptoms prior the treatment was 33 months (range: 1 – 70). The stage of disease was determined due to a TNM scale. There were 15 (6%), 112 (45%), 74 (29%), and 50 (20%) patients with T1, T2, T3 and T4 tumor stage, respectively, and 99 (40%), 26 (10%), 105 (42%), and 21 (8%) patients with N0, N1, N2 and N3 nodal stage of disease, respectively (no patients with distant metastases were included). OPN was indicated in plasma before treatment and immediately after treatment completion. In statistic overview of the results STATISTICA 9.1 (StatSoft) program was used. While interpreting the results median value was used. U Mann-Whitney test was used for analysis of correlation between protein concentration and the stage of the disease. Multivariate Cox analysis of factors related to OS was carried on. Log-rank test was used to compare OPN as categorized value acc. to median respectively.
Results

Pretreatment OPN levels were higher in patients with advanced T stage compared with early stage (p=0.024). There was no correlation between N stage and OPN (p=0.58). Median plasma levels of OPN measured before (67.9 ng/ml) and after (97.8 ng/ml) treatment differed (p=0.0001). OPN levels before treatment were significantly related to overall survival (OS) ratio in both, univariate (p=0.019) and multivariate analysis (0.001). Posttreatment OPN levels (97.8 ng/ml) were also associated with survival time in univariate analysis (p=0.04). Additionally, OPN after treatment was significantly higher in patients with distant metastasis (p=0.015).

Conclusion

High levels of OPN before therapy have been associated with advanced stage and adverse prognosis. OPN after therapy may play important role in the process of tumor development and metastasis. OPN concentrations increase during treatment may reflect acute mucosal reaction after radiotherapy. Pretreatment OPN is an independent prognostic determinant of survival.

PO-102 EGFR detection in saliva as an easy diagnostic and prognostic tool in oral squamous cell cancer

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Purpose or Objective

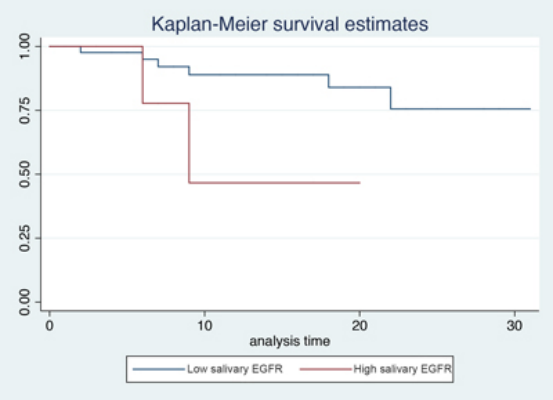
Epidermal growth factor receptor (EGFR) is a type I transmembrane glycoprotein widely expressed on epithelial cells and required for their development and proliferation. The extracellular domain of EGFR can be released by proteolytic cleavage and shed from tumor cells surface, thus representing a potential tumor marker. EGFRs have been frequently found to be overexpressed in a wide variety of malignancies, including oral squamous cell carcinoma (OSCC). Our objective was to assess the EGFR diagnostic and prognostic values in OSCC, investigating its expression in serum and saliva of a homogeneous group of patients in comparison with that of healthy subjects.

Material and Methods

Serum and saliva samples were collected from a cohort of OSCC patients before surgery and a matched group of healthy subjects. A written consent was obtained in all cases. Serum EGFR concentration was determined by an enzyme-linked immunosorbent assay (ELISA), according to manufacturer's instructions. Saliva EGFR concentration was determined with a modified protocol of the same immunoassay. Sixty-three naïve patients affected by OSCC (cases) and 60 healthy individuals (controls) were included in the study.

Results

Regarding serum EGFR levels, OSCC patients (mean, 47.6 ng/ml; range, 29.9-82.5) evidenced significantly lower values (p<0.001) when compared with controls (mean, 53.7 ng/ml; range, 38.6-70.7). Conversely, salivary EGFR concentrations were significantly higher (p=0.001) in OSCC patients (mean, 8.2 ng/ml; range, 0.9-37.8) than in controls (mean, 4.4 ng/ml; range, 0.6-20.6). Salivary EGFR levels were also significantly related with tumor pT classification (p=0.02). Considering 9.0 ng/ml (75° percentile) as the cut-off, patients with higher values of salivary EGFR had a worse prognosis in terms of disease specific survival (p=0.017) (Fig. 1), even when limiting the evaluation to pT4 tumors only (p=0.05).



Conclusion

Salivary EGFR can be considered a potential tumor marker for OSCC detection, with both diagnostic and prognostic values. Serum EGFR, on the other hand, was significantly lower in patients but did not show any prognostic impact. Determination of these markers requires a non-invasive sampling procedure and is based on a low-cost technique.

PO-103 Oropharyngeal cancer patient-derived xenografts: Characterization and radiosensitivity.

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Purpose or Objective

Oropharyngeal squamous cell carcinoma (OPSCC) is now the most common type of head and neck cancer. HPV, tobacco smoking or a combination of the two are the major etiologic factors.

After radiotherapy-based treatment, prognosis is superior for patients with purely HPV-associated OPSCC compared to patients with tobacco-associated HPV-negative disease. As an explanation, it has been hypothesized that HPV-associated tumors are more radiosensitive. Patients with overlapping etiologies (i.e., both HPV and tobacco smoking) appear to have an intermediate prognosis, something that is currently unexplained.

Since OPSCC is heterogeneous in disease biology and treatment sensitivity, further personalization of treatment is needed, which is the focus of ongoing clinical trials. However, adequate pre-clinical models and biomarkers reflecting treatment sensitivity are lacking.

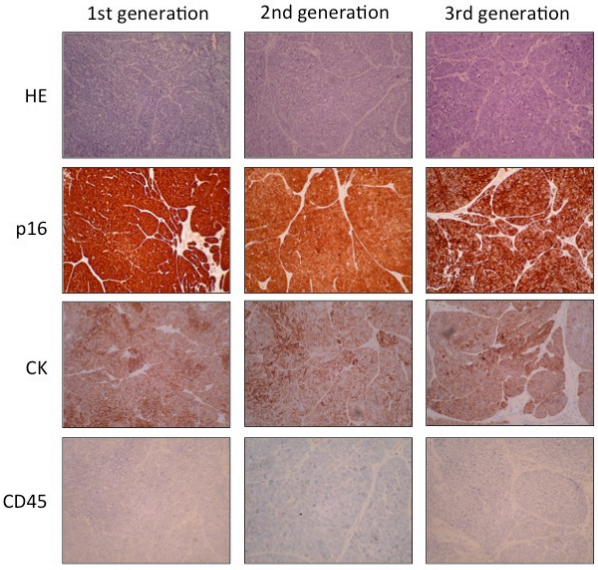
Purpose of this study was to create a number of patient-derived xenografts (PDX) reflecting the heterogeneity of OPSCC and compare the models with the corresponding original human tumors. Also, we wished to determine if the PDX model is suitable for radiotherapy research.

Material and Methods

Fresh tumor biopsies from patients with primary, untreated OPSCC were implanted subcutaneously in immunodeficient mice. PDX tumors were serially transplanted and expanded, producing generations of PDX tumors with identical origin.

Xenograft tumors and human originals were compared using histology and immunohistochemistry for p16, cytokeratin AE1/AE3 and CD45. To characterize radiosensitivity, PDX tumors were subjected to low-dose irradiation in a growth delay assay (4 - 8 Gy, single fraction).

Results
To date, tumor biopsies from 24 OPSCC patients have been xenografted resulting in xenograft tumor growth in 15 cases (63 %). PDX models were established from OPSCC patients with HPV-positive and HPV-negative disease as well as a wide range of tobacco exposure. Most PDX tumors retained the histological appearance of squamous cell carcinoma and immunoprofile of the original tumor. Other tumors adopted a lymphoproliferative appearance. Low-dose irradiation of PDX tumors resulted in a reproducible growth delay.
Conclusion
It is possible to generate PDX models that represent the clinical heterogeneity of disease with a satisfactory success rate. Most PDX models retain the characteristics of the original tumor. The PDX model is suitable for radiotherapy research.



Sample AUHSCC-10. PDX derived from a patient with a poorly differentiated tonsillar squamous cell carcinoma. *HE:* Hematoxylin and eosin stain. *CK:* Cytokeratin AE1/AE3.

PO-104 Everolimus in oral cancer: a potential therapeutic approach dependent on cell type?
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Purpose or Objective
Oral squamous cell carcinoma (OSCC) is the most common cancer of oral cavity with poor prognosis and survival rates. The PI3K/AKT/mTOR signaling pathway plays a central role in cell proliferation, migration, survival and angiogenesis regulation. Recently, the aberrant activation of mTOR has been connected with poor prognosis in various cancers including OSCC, becoming a promising anti-cancer target therapy.
The main objective of this study was to evaluate, *in vitro*, the therapeutic efficacy of a mTOR inhibitor, everolimus (EVE), in OSCC and the related underlying mechanisms.
Material and Methods
Two OSCC cell lines were maintained in culture, BICR-10 (*in situ*) and the HSC-3 (high metastatic potential) cells, in absence and in presence of increasing concentrations of EVE, 10-50 μM. Cell viability was assessed by the rezasurin metabolic assay and cell death by optical microscopy (May-Grünwald-Giemsa staining) and flow cytometry (Annexin V-Propidium Iodide staining). Cell cycle was assessed by flow cytometry using PIRNase kit. The Caspases, BAX, BCL-2, Cyclin D1 and E-cadherin expression levels were also evaluated by flow cytometry. Western blot was used to evaluate the expression of total and phosphorylated AKT and P70S6K as well as the total expression of Integrin Beta 1 and Beta 1 Catenin. Cell migration was evaluated by the wound healing assay. Enzymatic activity of metalloproteinase (MMP)-2 and -9 was evatuated by zymography. Results were statistical analyzed.
Results
Our results showed that EVE induces antiproliferative and cytotoxic effects in a dose, time and cell type dependent manner. The HSC-3 cells were the more sensitive to EVE, with IC50 at 48h around 35μM. In HSC-3 cells EVE induced cell death mainly by later apoptosis/necrosis associated to the increase in BAX/BCL-2 ratio and Caspases levels. Furthermore, EVE induced cell cycle arrest in S phase with the increase in Cyclin D1 expression. EVE also reduced migration and invasion in HSC-3 cells dependent on the following: increase of E-Cadherian expression and decrease of both Integrin beta 1 expression and MMP-2 enzymatic activity.
Conclusion
In this work, we did not observe significant statistical alterations in the OSCC *in situ* cells treated with EVE. However, in OSCC cells with high metastatic potential we observed that EVE induced a significant statistical decrease in cell proliferation, migration, invasion and an increase in cell death. These results suggest that EVE constitutes a promising therapeutic approach in OSCC with high metastatic potential.

PO-105 Is there justification for age bias in HPV p16 testing for Oropharyngeal Squamous Cell Carcinoma?
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Purpose or Objective
Human Papilloma Virus (HPV) p16 is a causative agent in a biologically distinct subset of Oropharyng
eal Squamous Cell Carcinoma (OPSCC), with a highly favourable prognosis[1]. Updated guidelines pertaining to OPSCC now require universal HPV p16 immunohistochemistry testing[2]. Using this as our standard, we undertook a retrospective audit of all OPSCC treated in our centre during 2015, identifying the prevalence of OPSCC in our population, p16 status, the proportion of p16 positivity, and their age-gender demographics. We

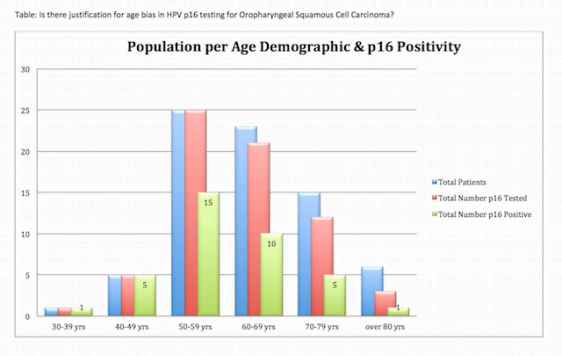
hypothesised an element of age bias in relation to determining p16 status, and questioned its justification.
Despite Public Health efforts reducing tobacco consumption, a well-recognised causal agent of OPSCC, the expected decrease in OPSCC incidence was only brief, before resurging dramatically. In the United States alone, the percentage of OPSCC p16 positive cases has risen from 16% in 1989 to over 70% in 2004[3], whilst studies in Scandinavia have suggested HPV becoming the sole progenitor of OPSCC, foreboding a virus-induced carcinoma epidemic[4].

Material and Methods

75 cases of OPSCC admitted to our Centre in 2015, were identified using CaPPs (Cancer Patient Pathway System). Using Electronic Care Records, 67 (89%) of these cases had p16 status confirmed either on initial or secondary testing.

Results

Of the 67 cases tested, 37 (55%) were p16 positive. Of these 37 p16 positive cases, 78% were male, with 65% being males aged 40-69, compared with 16% females aged 40-69. This is comparable with evidence that p16 positive OPSCC is a disease of the middle-aged male[5]. All cases were ethnically white.
There was evidence of age bias in our Centre in relation to determining p16 status from age 60 onwards. Per decade there was a step-wise percentage reduction of OPSCC cases being stratified by p16 status. Of the total OPSCC cohort tested: 100% aged 30-59 were tested; 91% aged 60-69; 80% of ages 70-79; and only 50% of those over 80 were tested. However, this was followed by a comparable step-wise decrease in p16 positive incidence per decade also, from 100% in cases aged 40-49, 60% aged 50-59, to 33% aged over 80. Incidentally, the youngest case of p16 positivity was a 32-yr-old female, the eldest an 85-yr-old male. The youngest p16 negative case was a 50-yr-old male.



Conclusion

Despite a decreasing incidence of HPV p16 positivity with older age, there were nonetheless cases of such identified in our cohort. We know that p16 status is associated with a better prognosis, especially when other risk factors such as tobacco and alcohol are less. As tobacco consumption decreases, the increasing primacy of OPSCC p16 positivity will endure. With trials underway on therapy de-intensification, there is a duty to assess all OPSCC for p16 status to offer the opportunity for prognostic discussion and the possibility of older patients to be represented in these trials. We feel there is justification to test all OPSCC for p16 status.

PO-106 Prognostic significance of cyclin D1 and pRb expression in oropharyngeal carcinoma

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Purpose or Objective

In oropharyngeal squamous cell carcinoma (OPSCC), high-risk human papilloma virus (HR-HPV) infection is associated with deregulated expression of cell cycle associated proteins, including cyclin D1 and pRb. Based on studies analysing patient cohorts with predominantly advanced tumour stages and heterogeneous treatment modalities, Cyclin D1 and pRb overexpression has been linked to poor prognosis in OPSCC.The objective of our study was to evaluate the prognostic significance of cyclin D1 and pRb expression in surgically treated OPSCC patients.

Material and Methods

Retrospective analysis of clinicopathological characteristics of surgically treated OPSCC patients was performed. Tumour tissue samples were tested for HR-HPV DNA using PCR. Cyclin D1, pRb and p16 immunohistochemistry were performed using OPSCC tissue microarrays and were scored positive if more than 25% (Cyclin D1, pRb) and 70% (p16) of tumour cells stained positive, respectively. Overall survival (OS) and disease-specific survival (DSS) were analysed by Kaplan-Meier curves and log-rank test. The prognostic significance of cyclin D1 and pRb expression was assessed by uni- and multivariate cox regression analysis, adjusted for established prognostic factors.

Results

322 OPSCC patients treated with surgery alone (n=110) or surgery with adjuvant radio-(chemo) therapy (n=212) were included in the analysis. Cyclin D1 and pRb expression was found in 42% and 49% of tumours, respectively. 48% of OPSCC had a positive HR-HPV status defined as the combined positivity for HR-HPV DNA and p16 expression. Cyclin D1and pRb was inversely correlated with tumoral HR-HPV status ($p<0.001$). Cyclin D1 expression of tumour cells was associated with reduced 5-year OS (81.2% versus 66.7%, $p=0.01$) and DSS (87.8% versus 80.6%, $p=0.03$). This result was even more pronounced with pRb expression5-year OS (85% versus 67%, $p=0.0001$) and DSS (92% versus 77%, $p=0.0001$) In multivariate analysis, including tumour stage, HR-HPV status and smoking history, cyclin D1 and pRb expression lost its prognostic Impact whereas only tumoral HR-HPV status positively influenced survival.

Conclusion

Cyclin D1 protein and pRb expression is inversely correlated with tumour HR-HPV positivity and may serve as a diagnostic and prognostic marker in OPSCC patients in addition to the HR-HPV status.

Acknowledgement: This study was supported by the Swiss Cancer League. The authors appreciate the contribution of the other investigators of the Swiss Cohort of Oropharyngeal Cancer Patients (SCOC).

PO-107 Clinical outcomes of HPV-positive non-oropharyngeal squamous cell carcinoma: analysis of the NCDB

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Purpose or Objective

The favorable prognosis of patients with HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) is well established. Conversely, the clinical significance of HPV-positive non-OPSCC is controversial. We sought to describe patient characteristics and clinical outcomes for HPV-positive non-OPSCC using the National Cancer Database (NCDB).

Material and Methods
We performed a retrospective analysis of patients with non-nasopharyngeal, non-OPSCC and known HPV status identified in the NCDB. Patient characteristics and survival data were analyzed by univariate and multivariate analyses using Cox proportional hazards regression and the log-rank test within Kaplan-Meier analysis.
Results
A total of 27,160 patients with known HPV status were identified of which 8,672 (32%) were HPV-positive. Patients with HPV-positive disease were more likely to be male, younger, and present with an oral cavity primary, greater nodal burden and higher overall clinical stage than HPV-negative patients ($p < 0.01$). On multivariate analysis, factors predictive of worse overall survival included age ≥ 65 years (HR: 1.45; 95% C.I. 1.34-1.57; $p < 0.001$), Charlson/deyo comorbidity score of 1 (HR: 1.10; 95% C.I. 1.01-1.20; $p < 0.05$) and ≥ 2 (HR: 1.78; 95% C.I. 1.57-2.02; $p < 0.001$), non-private/unknown insurance (HR: 1.41; 95% C.I. 1.30-1.54; $p < 0.001$), hypopharynx subsite (HR: 1.23; 95% C.I. 1.09-1.38; $p < 0.01$), tumor size (HR: 1.19; 95% C.I. 1.16-1.22; $p < 0.001$), increasing nodal stage (N1 = HR: 1.19; 95% C.I. 1.06-1.33; $p < 0.01$), (N2 = HR: 1.16; 95% C.I. 1.05-1.29; $p < 0.01$), (N3 = HR: 1.66; 95% C.I. 1.20-2.28; $p < 0.01$), and HPV-negative status (HR: 2.01; 95% C.I. 1.83-2.21; $p < 0.001$). Unadjusted 2-year overall survival for patients with HPV-positive and HPV-negative disease according to stage was: Stage I 92% vs. 88%, Stage II 86% vs. 75%, Stage III 88% vs. 68%, Stage IVA 85% vs 60%, and Stage IVB 68% vs 46%.
Conclusion
Patients with HPV-positive non-OPSCC exhibit similar patient and disease characteristics as those previously described for patients with HPV-positive OPSCC. Overall survival was significantly influenced by HPV status. As such patients with HPV-positive non-OPSCC disease represent are favorable cohort that warrant further investigation.

PO-108 TLR induced PDL-1 expression in HNSCC as a potential tool of immunomodulation
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Purpose or Objective
Head and neck squamous cell carcinoma (HNSCC) is one of the most common solid neoplasms worldwide. Its occurrence is being associated with exposure to smoking and alcohol consumption. Even though enormous progress concerning the treatment of HNSCC has been made, the mortality rates are still high due to local tumor invasion, development of metastases and failure of chemo- and radiation therapies.
In Neuroblastoma it has been shown that specific antibody targeting of PD-L1 leads to increased anti-tumor functions of T-lymphocytes, whereas triggering with the TLR3 ligand Poly I:C leads to a strong up regulation of PD-L1. We therefore asked whether Toll-like receptors act as PD/PD-L1 regulators in HNSCC and which consequence this finally has for the immuno-activity of natural killer (NK-) cells.
Material and Methods
Different established HNSCC cell lines were treated with the TLR3 ligand Polyinosinic:polycytidylic acid (PolyI:C) and TLR4 ligand LPS through both extracellular and intracellular ways. PD-L1 expression was analyzed on the mRNA- as well as on the protein level using RT-PCR and Western hybridization experiments. NK cells were analyzed for cytolytic activity using the CytoTox-96 Non-Radioactive Cytotoxicity Assay (Promega). This colorimetric assay quantitatively measures lactate dehydrogenase (LDH), a stable cytosolic enzyme that is released upon cell lysis. Released LDH in culture supernatants were measured using a coupled enzymatic assay, which resulted in the conversion of a tetrazolium salt (INT) into a red formazan product.
Results
We observed that TLR3 as well as TLR4 agonists resulted in significantly increased expression levels of PD-L1 in permanent HNSCC cell lines. These data could be corroborated by immunohistochemical analyzes of the sub-cellular PD-L1 expression in response to TLR stimulation. Increased expression of PD-L1 correlated with modulated NK-cell activities and strongly affected cytolysis of the analyzed target cells.
Conclusion
When considering innovative antibody-based immunotherapy approaches, check-point regulators such as the PD-1/PD-L1 pathway have recently shown very promising results. Our data underline the requirement of combined therapeutic strategies, namely to inhibit the PD1 function on the immune cell side as well as to block the TLR dependent up-regulation of check point inhibitors on the tumor side.

Poster: Imaging and radiomics

PO-109 The added value of SPECT-CT for identification of sentinel lymph nodes in early stage oral cancer
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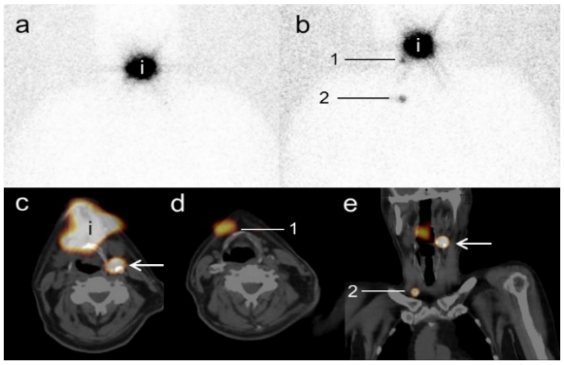
Purpose or Objective
To assess the role of Single Photon Emission Computed Tomography with Computed Tomography (SPECT-CT) for the identification of sentinel lymph nodes (SLNs) in patients with early stage (T1-T2) oral cancer and a clinically negative neck (cN0).
Material and Methods
In addition to planar lymphoscintigraphy SPECT-CT was performed in 66 consecutive patients with early stage oral cancer and a clinically negative neck. The addition of SPECT-CT to planar images was retrospectively analysed for the number of additional SLNs, more precise localisation of SLNs and importance of anatomical information by a team consisting of a nuclear physician, surgeon and investigator.
Results
Identification rate for both imaging modalities combined was 98% (65/66). SPECT-CT identified 15 additional SLNs in 14 patients (22%). In 2/15 (13%) of these additional SLNs the only metastasis was found, resulting in an upstaging rate of 3% (2/65). Figure 1 shows an example of an additional SLN level II on the left side (arrow) on SPECT-CT. In 20% of the patients with at least one positive SLN the only positive SLN was detected due to the addition of SPECT-CT. SPECT-CT was considered to add important anatomical information in 2 patients (3%). In 5/65 (8%) of the patients initially scored SLNs on planar

lymphoscintigrams were scored as non-SLNs when SPECT-CT was added. There were 4 false negative SLN biopsy procedures in this cohort.



Conclusion
The addition of SPECT-CT to planar lymphoscintigraphy is recommended for the identification of more (positive) SLNs and better topographical orientation for surgery in sentinel lymph node biopsy for early stage oral cancer.

PO-110 Analysis of loco-regional failures after IMRT for HNSCC using deformable image registration
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Purpose or Objective
Most failures after curative radiotherapy for head and neck squamous cell carcinoma (HNSCC) appear loco-regionally. Moreover, IMRT may increase the risk of marginal failures due to the high conformity. Identification and analysis of possible points of loco-regional recurrence (LRR) in relation to treatment volume may pave the way for improved treatment planning and outcomes. The aim of this project was to analyze loco-regional recurrence pattern after curative IMRT.
Material and Methods
457 patients with larynx, pharynx and oral cavity HNSCC were consecutively treated with primary IMRT from 2006-2012 in one institution. The majority of patients had loco-regionally advanced disease. Most patients were treated with curatively intended primary IMRT with 66-68 Gy in 6 fractions weekly with concomitant Nimorazol and Cisplatin according to DAHANCA guidelines. Elective therapeutic levels were treated to 50 Gy. All CT or PET/CT-confirmed loco-regional recurrences were identified, and the diagnostic CTs were deformable registered with planning CTs. Four different approaches to define possible points of LRR origin (PO) were identified: two by independent observers, mass mid-point (MMP), and a point with maximal surface distance (MSD). Points were further analyzed in relation to clinical high-risk treatment volume (CTV1) and planned treatment volume (95% isodose of high-risk volume).
Results
Median follow-up was 41 months (range 2-107). 290 patients (63%) remained recurrence-free and 167 developed some sort of failure. The three-year loco-regional control rate was 68%. 70 patients with 105 CT verified LRR were further analysed. 35, 19 and 16 pts had recurrences in T, N or both T and N sites, respectively. Median distances between the four different ways to estimate POs in the x. y and z axis were 3.0. 3.0 and 8.2 mm, respectively. The distances between all four POs to CTV1 and the 95% isodose curve were consistent. 41% of POs were within CTV1 (Figure 1.) and 58% were covered by the 95% isodose curve. In 13 cases, LRRs were outside the treatment volume. LRR identified 5 mm outside the CTV1 accounted for 13.3% of all LRR and may represent marginal recurrences in the present study.
Conclusion
We confirmed that the majority of loco-regional recurrences appear in the high dose volume. This is consistent using four different recurrence identification approaches. The current data may differ between centres using larger treatment margins and this is currently under investigation.

PO-111 Dermal backflow: NIRFLI pattern associated multimodality therapy in patients with oropharynx cancer
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Purpose or Objective
Lymphedema is a ubiquitous side effect of oropharynx cancer treatment and is characterized by swelling and fibrosis which leads to a deterioration in quality of life. Currently there is limited understanding about how to properly diagnose and treat head and neck lymphedema. Our team has previously described a novel imaging system for the identification of aberrant lymph vessel flow of the cervical region in patients with Head and Neck Cancer.
Material and Methods
Following intraoral and intradermal injections of indocyanine green, lymphatic anatomy was visualized using near-infrared fluorescence lymphatic imaging (NIRFLI). Six oropharynx cancer patients were imaged prior to treatment, and then followed up for thirty weeks. One subject received neither neck surgery nor radiation, one patient had bilateral therapeutic-range neck radiation without neck dissection, two patients had unilateral neck dissection with post-operative radiation to the operated neck alone, one patient had unilateral neck dissection but post-operative radiation applied to both sides of the neck, and one patient had bilateral neck dissections and bilateral post-operative neck irradiation.
Results
Lymphatic vessels were readily visualized in all six subjects (12 necks). All five necks that received both neck dissection and post-operative therapeutic-dose radiation (>56Gy) exhibited dermal backflow (5/5). In the necks that received neither surgery nor radiation, dermal backflow was not observed (4/4). One of three necks that received radiation alone without neck dissection also developed dermal backflow.
Conclusion
Post-operative radiotherapy is strongly associated with the development of dermal backflow. Likewise, treatment de-escalation in early stage oropharynx cancer which spares a therapeutic dose of radiation to the contralateral neck also preserves the native lymphatic function. It is our contention that NIRFLI is an emerging imaging modality for the identification of aberrant lymphatic backflow following treatment of oropharynx cancer and specifically

identifies the side and site of lymphedema for the purposes of intervention.

PO-112 Role for interim PET in patient selection for dose escalation and boost volume definition in HNSCC?

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Purpose or Objective
The aim of this prospective pilot study was to look at the feasibility and clinical value of performing an interim ^{18}F-FDG-PET-CT (iPET) in patients with head and neck squamous cell carcinoma (HNSCC). The spatial stability of the most FDG avid area of the tumour during treatment and the correlation of the data provided by pre-treatment, interim and post treatment scans with known prognostic factors and early survival was assessed.
Material and Methods
Eligible patients included those undergoing primary concomitant chemoradiotherapy (65Gy/30F) with weekly Cisplatin for Stage III/IV SCC of the Oropharynx. HPV status and smoking history was determined on enrolment. Each patient underwent a contrast enhanced planning CT and PET scan immobilised in the treatment position on consecutive days prior to the start of treatment and then again after 8 fractions of radiotherapy. A primary boost volume was defined according to 50% of the SUVmax of the tumour using the autocontouring function in the treatment planning system. A margin of 3mm was applied to this to provide a PTVboost.
Results
Eighteen patients (14M, 4F) fitting the above criteria were recruited. Mean follow up is 20 months.
All patients completed their scans on schedule with the exception of one patient due to machine breakdown. A boost volume was successfully delineated on both pre- and interim scans using the above method in all except 3 patients where the SUVmax was not sufficiently higher than background on one or both scans to define an accurate volume.
The SUVmax of the primary tumour on the initial scan was higher in the p16 -ve and patients with a smoking history of >10 years (Table 1). The results did not reach statistical significance, however when the patients who were p16 +ve with a smoking history of >10years were excluded from the p16 analysis then the difference between the positive and negative patients was greater (p=0.052).
All except 3 patients showed a drop in SUVmax between the pre- and interim scans. The volume of the PTVboost reduced by an average of 49% between the two scans (29 – 100%). Two patients showed only very marginal increase which did not subsequently lead to an increase in the size of the PTVboost.
One patient showed a big rise in their SUVmax (9.7 to 19.6). The volume of their PTVboost therefore increased by 99%. Their 12 week PET scan was deemed to show complete response but the patient subsequently had a local relapse 7 months after completion of treatment.
Conclusion
In comparison to other studies that have looked at the value of an iPET in patients with HNSCC this was a more tightly controlled study with a more homogenous group of patients. The results suggest the PET characteristics do correlate with known prognostic factors which has not been documented previously. The dual role of the iPET for identifying patients who may benefit from dose escalation and defining a volume for a radiotherapy boost merits further investigation.

PO-113 Dynamics of biological imaging parameters in PW-MRI and FMISO-PET/CT during chemoradiation of SCCHN

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Purpose or Objective
Tumor hypoxia in squamous cell carcinoma of the head and neck (SCCHN) is related to poor prognosis. Reoxygenation during treatment leads to improved radiosensitivity. Adaptation of radiotherapy planning may allow for a more individualized treatment. The following study seeks to detected the dynamics of hypoxia during chemoradiation (RCTx) with FMISO PET/CT and correlated to perfusion MRI (PWI) parameters.PWI parameters can be correlated with tumor hypoxia and thereby have the potential to serve as predictors of treatment failure. In particular, the volume transfer constant between plasma and interstitial space Ktrans is an indirect measure of the capillary permeability and blood flow. High skewness of Ktrans is shown to be associated with improved treatment response, while tumors with low Ktrans have a poor prognosis (Shukla-Dave et al., 2012). A rise of Ktrans during RCTx is associated with a good response to treatment.
Material and Methods
We conducted a prospective imaging study in patients undergoing definitive RCTx (70 Gy, concomitant cisplatin) for HNSCC: in weeks 0, 2 and 5, 3-Tesla-MRI and FMISO PET were acquired. Tumor hypoxia was assessed in FMISO PET 2.5 h p.i. Gross tumor volume in MRI (GTVMRI) was defined as the area of high signal on T2-weighted images using the T1-weighted images for anatomic cross reference. Perfusion parameters Ktrans was calculated from dynamic T1-weighted MRI after contrast agent injection. MRI and PET scans were matched using iPlan contouring tool (v. 3.0.0, BrainLAB AG). Hypoxic subvolume (HSV) of GTVMRI was defined after normalization to the FMISO background in the contralateral sternocleidomastoid muscle, multiplied by 1.4. Volumetric parameters between weeks 0, 2 and 5 were compared and related to treatment response in terms of local recurrence (LR) and stable disease (SD). Statistical analysis was done with Spearman correlation. Before t-test analysis, normal sample distribution was confirmed with Shapiro–Wilk test.
Results
Between 2014 and 2015 10 male patients, treated for SCCHN with RCTx, were included. All received a total dose of 70 Gy. In total, 30 FMISO-PET/CT data sets and 27 MRI data sets were obtained. Mean follow up (FU) was 14.6 months (4 - 28 months). In weeks 0-5, patients with LR showed a mean Ktrans-decrease of 19%, whereas in weeks 0-2 an increase of SUVmax (57 %) was shown. Patients with SD showed Ktrans-increase (36 %) and SUVmax-decrease (-61 %). HSV diminished in all patients. The correlation was significant between Δ GTVMRI and Δ Ktrans in week 0-2 (p=0.037) and between Δ SUVmax (week 0-5) and Δ Ktrans (week 0-2), p=0.045.
Conclusion
As was previously shown we conclude that changes in SUVmax are crucial in week 2. In our limited patient cohort and the short FU, we found that an increase in Ktrans might be related to improved outcome. Finding

markers in bioimaging may allow individualization of treatment by dose painting and adaptive radiotherapy.

PO-114 Alterations in tumour hypoxia in serial F-MISO/PET-CT during chemoradiation in HNSCC

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Purpose or Objective
Tumor hypoxia, a common feature of locally advanced head and neck cancer (HNSCC), is associated with higher malignancy and increased radioresistance. The decrease of tumor hypoxia during fractionated radiation treatment is assumed to be decisive for treatment success. [18F]-Fluoro-Misonidazole PET (F-MISO-PET) allows noninvasive assessment of hypoxia during treatment. The purpose of the present study was to noninvasively assess the time course of tumor hypoxia.
Material and Methods
A prospective serial imaging study was conducted in patients undergoing definitive chemoradiation (dRCTx, total dose 70Gy) for locally advanced HNSCC, accompanied by cisplatin in weeks 1, 4 and 7. Tumor hypoxia was assessed by F-MISO-PET by static scans acquired 2.5 h p.i. Tumor volumes were determined for FDG PET/CT scans and the coregistered F-MISO/CT scans. At baseline MRI, FDG-PET/CT and F-MISO-PET were acquired (week 0). Additional F-MISO-PET/CT scans were acquired in treatment weeks 2 and 5. Normal sample distribution was confirmed with Shapiro-Wilk test. Unpaired t-test analysis of the mean SUVmax(tumor)/SUVmean(muscle) ratios of F-MISO-PET in weeks 0, 2 and 5 were performed. Significance-level was defined as $p<0.005$.
Results
Between 2012 and 2014 18 patients (16 men, two women, mean age 60 years), treated for HNSCC with dRCTx were included. All received a total dose of 70 Gy in 35 fractions. Concomitant cisplatin chemotherapy was administered in weeks 1, 4 and 7. 14 patients had all F-MISO-PET scans, while 4 had two F-MISO-PET scans (week 0, 5). The mean follow-up time was 14.6 months (range: 4 - 28 months). Mean SUVmax(tumor)/SUVmean(muscle) in weeks 0, 2 and 5 were 1.9 (n=18, SD ± 0.1), 1.5 (n=14, SD ± 0.1) and 1.2 (n=18, SD ± 0.1), respectively. Unpaired t-test for SUVmax(tumor)/SUVmean(muscle) between week 0 and 5 was performed, showing a singnificant decrease ($p<0.0001$). Between weeks 0 and 2 ($p=0.0346$) and between weeks 2 and 5 the decrease again was highly significant ($p=0.0113$). In two patients no residual hypoxia was measured in week two, resulting in SUVmax(tumor)/SUVmean(muscle) =1.0. In week 5 this was found in seven patients. In two patients hypoxia had increased in week 2 but decreased in week 5 compared to pre-treatment measurements. In one patient hypoxia had increased by the end of treatment.
Conclusion
Differences in hypoxia between weeks 0-2, 2-5 and 0- 5, respectively, show statistical significance. This is crucial in the process of re-oxygenation. As concluded in previous works, change of treatment strategy, e.g. by means of dose escalation might be most efficient early during treatment. However further analysis, with more patients and correlation to disease-free and overall-survival are needed.

PO-115 A [18F] FDG-PET adaptive thresholding algorithm delineation of RT tumour volumes of head and neck cancer

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Purpose or Objective
The aim of this study was to evaluate a [18F] FDG-PET adaptive thresholding algorithm (ATA) for the delineation of the biological tumour volume for the radiotherapy (RT) treatment planning of head and neck cancer patients.
Material and Methods
Thirty-eight patients, who underwent exclusive intensity modulated RT with simultaneous integrated boost (IMRT-SIB) for head-and-neck squamous cell carcinoma (3 oral cavity, 9 nasopharynx, 19 oropharynx, 6 hypopharynx, and 1 larynx cancer) were included in the present study. Thirty-five/38 patients presented a locally advanced disease, and 33/38 received a concomitant chemoradiotherapy treatment. For all patients [18F] FDG-PET/CT was performed in treatment position with the customized thermoplastic mask. Two radiation oncologists defined the primary gross tumour volumes (GTV) using the ATA implemented on the iTaRT workstation (Tecnologie Avanzate, Italy). The algorithm used specific calibration curves that depended on the lesion-to-background ratio (LB ratio) and on the amplitude of reconstruction smoothing filter (FWH). The reproducibility of ATA in volume estimation was determined evaluating the volume overlap of multiple segmentation of the same lesions by different operators. Each primary tumour volume segmented by the ATA (GTV_{ATA}) was compared to the GTVs contoured on two different sets. In the first, the two radiation oncologist manually draw the standard GTV (GTV_{ST}) based on clinical information, CT simulation, and magnetic resonance imaging (MRI); in the second, a fixed image intensity threshold method (40% of maximum intensity) of [18F] FDG-PET standardized uptake value was used to define the $GTV_{40\%SUV}$.
Results
The ATA previously performed only in a phantom study generate a GTV in all head and neck patients. The mean value of volumes based on the three different methods are reported in Table 1.
The GTV_{ATA} was smaller than the GTV_{ST} (17 vs 21 cc); the similarity coefficient (DICE) was 0.7 (Sensibility 66%, specificity 85%). GTV_{ATA} is a part of the GTV_{ST}.
The GTV_{ATA} was bigger than the $GTV_{40\%SUV}$ (17 vs 15 cc), the DICE was 0.2.
Conclusion
The proposed ATA resulted robust and reproducible in a clinical context. The ATA used in the present study allows the delineation of a BTV for dose escalation. A IMRT-SIB with a boost based on GTV_{ATA} is feasible.

PO-116 Potential applications of spectral CT imaging in patients with head and neck squamous cell carcinoma

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Purpose or Objective
Several clinical questions have been shown to be difficult to answer with conventional imaging in patients with head and neck squamous cell carcinoma (HNSCC). This presentation focuses on three of these questions.
1. The differentiation between malign and benign lymph nodes.
2. The detection of cartilage and bone invasion
3. The differentiation between post-radiation effects and tumor recurrence.
Due to improvements in scanning equipment spectral CT imaging has recently become commercially available in daily clinical practice. Spectral CT utilizes different x-ray energies in order to obtain tissue characteristics. This additional information might be able to answer some of the above questions.
Purpose: To investigate the potential of spectral CT in the detection of lymph node metastases, cartilage and bone invasion and tumor recurrence in patients with HNSCC.
Material and Methods
In this analysis we describe the basic principles of spectral CT including concepts such as iodine and calcium density and effective atomic number (effective Z). Furthermore the role of spectral CT in answering the above mentioned questions will be discussed using clinical cases.
Results
Preliminary data of spectral CT for the detection of lymph node metastases, cartilage and bone invasion and tumor recurrence from patients scanned and treated in our head and neck center.
Conclusion
Spectral CT is a new technique potentially able to answer clinical questions in patients with HNSCC which currently are inadequately able to be assessed by conventional imaging.

Poster: Supportive care, quality of life, rehabilitation

PO-117 Swallowing exercises: Will it really help head and neck cancer patients?

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Purpose or Objective
Dysphagia has been reported in 30-50% of head & neck cancer patients (HNCPs). It is defined as the difficulty or impossibility to swallow liquids, food, or medication; which can occur during the oropharyngeal or esophageal phase. Factors that predict dysphagia include: T & N stage, primary site, type of treatment, extension of treated region, patient characteristics (baseline swallowing function, PS, smoking & alcohol abuse, age, lean mass, gender). All treatment options, including surgery & CRT result in swallowing problems along with aspiration. The work was a comparative study, the aim of which is to evaluate the impact of swallowing exercises on swallowing problems among HNCPs after CRT.
Material and Methods
A sample of 60 HNCPs was equally divided into 2 groups, control and study groups. The investigators met all patients 3 times (before, during & after CRT); swallowing ability was assessed using Sydney Swallowing Questionnaire (SSQ). The University of Texas, MD Anderson Cancer Center Swallowing Exercise Protocol was explained and demonstrated by the investigators to the study group. Patients in the study group were encouraged to adhere to the swallowing exercises regularly. All tools used were translated into Arabic language. Data analyses were carried out using statistical package for social sciences (SPSS), program version 20.
Results
Most of the patients from both groups experienced mild dysphagia during the 1st visit. By the 3rd visit, severe dysphagia (to thin & thick liquids, and soft & hard food) was higher in the control group (73.3%) compared to the study group (26.7%). During the 1st visit, there was no statistical significant difference between control and study groups regarding cough or choking during swallowing hard food (p =1.00) and swallowing thin liquids (p = 0.42); yet the difference reached a significant level by the 3rd visit. By the third visit there was statistically significant difference between both groups in swallowing thin liquids (p = 0.00), as well as thick liquids (p = 0.00). At the 1st visit, there was no significant difference regarding swallowing soft food (p = 0.24), hard food (p = 0.12), dry food (p = 0.89) and swallowing Saliva (p = 0.28). While by the 3rd visit, there was significant difference between control & study groups in all parameters.
Conclusion
Dysphagia has been under-estimated & improperly treated in HNCPs. Adequate prevention & treatment of dysphagia is essential to plan a complete therapeutic programme, by reducing the side effects that may have negative impact on QoL and might affect the overall survival.

PO-118 Acute and late toxicities in patients with oral cancer treated with intensity-modulated radiotherapy

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Purpose or Objective
to analyze acute and late toxicities in patients (pts) with oral cancer treated with IMRT.
Material and Methods
From January 2011 to January 2016, 58 pts (mean age 62.9 yrs; range 42-87) with oral cancer who underwent adjuvant RT or exclusive RT-CT were analyzed. RT was performed with IMRT technique and LINAC DHX (Varian Medical Systems). The prescribed dose was 66 Gy (2.2 Gy/ff) for PTVs high risk; 60 Gy (2.0 Gy/ff) for PTVs intermediate risk and 54 Gy (1.8 Gy/ff) for PTVs low risk. Acute and late toxicity was evaluated according to CTCAE scale vs. 4.0 by weekly examination during RT treatment and every 3 months after RT.
Results
At analysis 41 pts (70%) were male and 17 (30%) female. The median follow-up was 23.3 months (range 3-63months). Overall, 36 pts (62%) underwent surgically treatment and 22 (38%) exclusive RTCT treatment. RTCT or RT plus molecular-target therapy was prescribed in 27 pts (47%); in addition to RT, 22 pts (81%) received CDDP 40 mg/mq q7 and 5 pts (19%) received Cetuximab 250 mg/mq q7. Acute toxicity: G1/G2 mucositis occurred in 52 pts (89%) and G3 in 2 pts (3.5%); G1/G2 dysphagia in 35 pts (60%) and G3 in 3 (5%) pts; G1/G2 odynophagia was observed in 40 (69%) pts and G3 in 4 pts (8%); G1/G2 dysgeusia in 49 pts (84%) and G3 in 2 (3.5%) pts. Finally, G1/G2 weight loss was observed in 29 pts (50%) and G3 in 3 pts (5%). Patients with G3 dysphagia or weight loss underwent parenteral nutrition and those with G2 weight loss required nutritional support. Only 1 pts required the placement of PEG because of significant weight loss (10 kg). Late toxicity: G1/G2 mucositis occurred in 5 pts (9%); G1/G2 dysphagia in 24 pts (41%) and G3 in 3 (5%) pts; G1/G2 odynophagia in 26 pts (45%) and G3 in 1 (1.7%) pts; G1 dysgeusia occurred in 23 pts (40%) and G3 in 2 (3.5%); G1/G2 xerostomia was observed in 15 pts (26%) and G3 in

1 pts (1.7%). Finally, G1/G2 weight loss occurred in 6 pts (10%) and G3 in 1 (1.7%) pts. Overall G3 late toxicity was observed in 8 pts, of them 6 pts required nutritional support and 2 pts placement of PEG due to weight loss and dysphagia.

Conclusion

The IMRT technique has proven to be feasible for treatment of oral cancer with acceptable acute and late toxicities. Overall, G3 acute and late toxicities occurred in 26% and 13% respectively. Our study showed better results compared with the data in literature. Nevertheless, it is mandatory to identify the pts who are at high risk of severe toxicity to get a better clinical management of this subset of pts.

PO-119 Does mucosal appearance predict mucosal PRO in oropharyngeal carcinoma treated with chemoimrt?

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Purpose or Objective

The importance of patient reported outcomes (PRO) as opposed to physician scored toxicity grading has been increasingly recognised. However, historical response relationships exist between dose and mucosal appearance. The purpose of this study was to investigate the ability of mucosal appearance scored in differing ways to predict mucosal PRO.

Material and Methods

Patients undergoing chemoimrt for oropharyngeal cancer were examined during treatment and in the recovery phase. The presence of a patch of confluent mucositis > 1cm in area was scored as grade 3. On each examination a grade was reported for the whole visible oral and oropharyngeal mucosa and for this volume divided into quadrants and octants. Patients were also asked to respond to the PRO-CTCAE question: What was the severity of your mouth or throat symptoms at their worst? The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for each method of scoring the appearance of the mouth in predicting severe or very severe mucosal PRO was calculated.

Results

Data from 124 examinations was included in this analysis. The sensitivity, specificity, PPV and NPV respectively for the following scoring methods were: at least 1 area of grade 3 mucositis in the whole visible oral and oropharyngeal mucosa- 75%, 73%, 83%, 61% ; at least 2 quadrants with grade 3 mucositis 71%, 83%, 89%, 60%; at least 3 octants with grade 3 mucositis 66%, 86%, 89%, 58%.

Conclusion

A high positive predictive value of mucosal examination in predicting mucosal PRO can be achieved if grade 3 mucositis is scored by dividing the visible oral and oropharyngeal mucosa into quadrants or octants. Quadrants seem to offer the best compromise between sensitivity and specificity. The negative predictive value of all methods of scoring was disappointing. This underlines both the importance of recording PRO in routine practice and clinical trials and the need to consider concomitant factors including levels of provision of analgesia and psychological support.

PO-120 Head and neck cancers are associated with poor EQ-5D-related utility in France (EPICORL study)

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Purpose or Objective

Health-related quality-of-life generic instruments such as EQ-5D are recommended for use in cost-effectiveness analysis of new cancer treatments in most European countries. However, EQ-5D-related utility estimates are inexistent for head and neck (H&N) cancer patients. The study objective was to estimate EQ-5D-related utility from the Karnofsky index recorded at hospital for French patients with H&N cancer.

Material and Methods

We completed a retrospective cohort study using the French National Hospital Discharge (PMSI) database that contains all public and private claims for acute care (MCO) and post-acute care (SSR and HAD) in 2008-2013. Of all adult patients identified with squamous cell carcinoma (ICD-10: C00-C06; C09-C14; C30.0; C31; C32), we selected all 53,257 incident cases in 2010-2012 without a personal history of cancer. Patients' trajectory was defined according to 3 phases-of-care: 1) initial care (first 6 months after diagnosis), by cancer stage (early I/II; advanced III/IVb; distant metastatic IVc); 2) continuing care without relapse (6 months after diagnosis); and 3) relapse care in the follow-up of patients without distant metastasis at diagnosis.
EQ-5D utility estimates for all phases-of-care were derived from the Karnofsky index recorded in post-acute care (HAD) by a three-steps procedure:
1) in post-acute care (HAD), the Karnofsky index (0 to 100) was calibrated with the EQ-5D utility metric (-0.53 to 1) used in France (Chevalier Eur J Health Econ 2013);
2) in post-acute care (HAD and SSR), EQ-5D utility was estimated from the functional relationship between the Karnofsky index and 6 Activities of Daily Living recorded weekly;
3) in all patients (HAD, SSR, MCO), EQ-5D utility was averaged by phase-of-care and corrected for sample selection bias from acute care (MCO) to post-acute care (HAD, SSR) with the Heckman selection model.

Results

Patients were 78.2% male with a median (IQR) age of 61 (54-71) at diagnosis and 20,582 (38.6%) patients died in the follow-up.
In post-acute care (HAD and SSR), 15,096 patients were identified at any phase-of-care with a mean (std) EQ-5D utility of 0.148 (0.227) and 0.071 (0.107) after correcting for sample selection bias. Overall (HAD, SSR, MCO), 94,456 patients were identified at any phase-of-care with a mean (std) EQ-5D utility of 0.133 (0.114). Patients diagnosed at early or advanced stage had higher mean EQ-5D utility than patients diagnosed with distant metastasis at diagnosis or relapsing in the follow-up. Patients with laryngeal cancer had higher mean EQ-5D utility than others. Though, mean EQ-5D utility primarily decreased with an older age at diagnosis and the number of severe comorbidities other than H&N cancer.

Conclusion

EQ-5D-related utility was poor in a national sample of patients with H&N cancer and even worse in presence of frequent, severe comorbidities.

PO-121 Fentanyl Pectin Nasal Spray in head and neck cancer irradiation. First results of the PecDICO study

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Purpose or Objective
Previous pivotal clinical trials demonstrated efficacy and safety of Fentanyl Pectin Nasal Spray (FPNS) in breakthrough pain in cancer patients (BTPc). Considering the specific profile of patients with head and neck (H&N) cancer, this non-interventional study mainly aims to describe the real-life satisfaction with FPNS in patients treated with radiotherapy.
Material and Methods
PecDICO is an ongoing French non-interventional, prospective, and multicentre study conducted in patients receiving radiation therapy for H&N cancer and who started FPNS treatment for BTPc at inclusion. Data collection is mainly based on a patient BTPc diary and medical visits. We present here the results from inclusion data collected between November 2014 and June 2016.
Results
When introducing FPNS, the characteristics of the 93 patients enrolled in 7 centres were as follows: mean age 60±8 years, 80% male, 94% BMI ≥18.5 kg/m², 100% ECOG score ≤2 , 77% at least one concomitant disease/risk factor (past or current smoking 67%, past or current alcoholism 41%). The H&N cancer was located at oropharynx (44%), oral cavity (25%), hypopharynx (19%), larynx (14%), and/or other sites (3%); median time from initial diagnosis was 3.8 months (range: 1.8-30.9). At inclusion, disease stage was III/IV in 19%/56% of the cases. Cancer treatments included surgery (30%), chemotherapy (67%; chemoradiotherapy: 54%), and/or cetuximab (23%). Radiotherapy was started 4 weeks (median; range: 0.4-7.9) prior to FPNS start. Patients' nutritional assessment showed dysphagia in 97% of the cases (grade 1/2/3/4: 20%/61%/7%/9%), oral food supplements (65%), feeding tube (15%) or gastrostomy (15%). A weight loss >10% over the last month was observed in 22% of patients. As opioid therapy for chronic pain, 93% of patients received transdermal fentanyl and rescue treatment was added in 40% of cases (morphine sulfate 18%, oxycodone 17%). Other treatments with an analgesic effect were given in 94% of the patients (grade 1/2 analgesics 62%/26%, lidocaine gel 43% and/or corticosteroids 19%). The first BTPc episode occurred 4 days prior FPNS initiation (median; range: 0-78). BTPc were nociceptive (45%) or mixed pain (55%) and they were procedural, predictable or spontaneous in 8%, 90% and/or 30% of the patients. The duration of BTPc episodes was ≤20 minutes in 83% of the cases. At FPNS initiation, BTPc intensity was assessed ≥5 by 60% of patients (30/50) on the basis of a 0-10 numerical scale, with up to 4 daily episodes (86%; 37/43).
Conclusion
These first results provides detailed information about patient characteristics receiving radiotherapy for H&N cancer and starting FPNS for BTPc, as well as on cancer management, BTPc episodes, and pain treatments. Real-world data on patient satisfaction with FPNS (and then its perceived efficiency and tolerability) are expected in 2017.

PO-122 Psychological profile of patients with head and neck cancer during radiotherapy: preliminary data

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Purpose or Objective
Radiation treatment (RT) with radical intent for head and neck (H&N) cancer is usually complex and burdensome. The radiation course generally lasts 6 to 7 weeks and more than half patients can experience relevant acute toxicity. Toxic effects may be even more frequent in patients who also receive concurrent chemotherapy (CT). Therefore the experience of receiving RT can be both uncomfortable and anxiety provoking. Aim of this study is to evaluate the psychological profile of patients with H&N cancer during RT.
Material and Methods
Consecutive patients with H&N cancer who underwent RT with radical intent were included between January and September 2016. Psychological support was available for all patients and Distress Thermometer (DT) and Hospital Anxiety and Depression Scale (HADS) were administered to evaluate emotional distress and mood, respectively. These tests were administered at the beginning (T0), the middle (T1), and the end (T2) of the RT course.
Results
Fifty patients (36 male and 14 female, mean age 61, range 14-82 years) who underwent radical RT for H&N cancer were included. RT was post-operative in 22 patients (44.0%) and was delivered up to a medial total dose of 68 Gy (range 50-70 Gy). Twenty-five (50.0%) patients received concurrent CT.
All 50 patients underwent the T0 evaluation. The T1 and T2 evaluations were done in 40 (80.0%) and 34 (68.0%) patients, respectively.
At T0 evaluation, 32/50 patients (64.0%) were emotionally distressed (cut off value DT score≥4) and 12/50 patients (24%) showed anxiety/depression (cut off value HADS score≥14).
At T1, 27/40 (67.5%) patients had significant emotional distress and 9/40 (22.5%) patients had significant anxiety and depression.
At T2, 25/34 (73.5%) patients had significant emotional distress and 12/34 (35.3%) patients had significant anxiety and depression.
During RT, patients who were distressed (32/50) or anxious and depressed (12/50) at the beginning of treatment did not show any significant variation of their DT score, while HADS score significantly improved at T2 evaluation (median HADS score 19 and 15, at T0 and T2 respectively, p=0.03). Patients who were not distressed (18/50) or anxious and depressed (38/50) at baseline, showed a worsening of DT score at both T1 (p=0.02) and T2 (p=0.01) as compared to baseline; HADS score remained substantially stable at T1 while worsened at T2 (p=0.03).
Conclusion
In this small series of consecutive patients with H&N cancer treated with RT, a psychological support during treatment allowed to prevent any further deterioration in distressed patients. However, it did not completely prevent a worsening in patients who had initially normal scores. The occurrence of acute treatment related toxic effects could explain such deterioration and further analysis is ongoing to test this hypothesis.

PO-123 Hypothyroidism after radiotherapy of head and neck - incidence and risk factors.

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Purpose or Objective
To establish the incidence of hypothyroidism after irradiation of the neck, and to determine risk factors

Material and Methods
Prospective study of 47 patients who received radical radiotherapy to the neck between 2008 and 2010 ; TSH measurements were taken before the start of radiotherapy (TSH0), at the end (TSH end), 3 and 6 months after the treatment, and then every 6 months. Statistical method: Cox regression and the Kaplan-Meier analysis.

Results
Average dosimetric finding were collected in the table 1. Hypothyroidism after radiotherapy of head and neck was diagnosed in 25,5% of patients. In the univariate Cox regression analysis statistical significance was achieved by: female gender, initial TSH (TSH 0), TSH at the end of treatment (TSHend). Patients age, type of the treatment or thyroid volume did not have a statisticly significant impact on posttreatment thyroid function. None of the dosimetric parameters (V10-V60, Dmean, Dmodal, Dmed, Dmin, Dmean) showed significant correlation with thyroid function (among all of them, Dmed was closest to statistical significance).
In further analysis, a prognostic parameter that would include both initial thyroid function and influence of radiotherapy, was prospected. The factor which was a product of initial TSH (TSH 0) and the median dose absorbed by thyroid gland during radiotherapy was calculated for all of the patients (equation 1). This parameter showed a statistically significant impact in the univariate Cox regression analysis (p = 0,001).
In the multivariate Cox regression analysis only the calculated product (p 0,001)) and the TSHend (p 0,02) were statistically significant.
In the Kaplan-Meyer analysis (figure 1), the 3yrs-hypothyroidism -free-survival was 93% in the the group with the calculated parameter < 70. In the group with the parameter > 70 the 3yrs-hypothyroidism free survival was 0%(p=0.0004) - all of that patient developed hypothyroidism.

Dose absorbed by thyroid gland – dosimetric findings

		Average value [Gy]	Range [Gy]
Minimal dose	**D min**	26,4	1,1-53,9
Maximal dose	**D max**	58,8	46-74,6
Mean dose	**D mean**	43,6	11,8-64,1
Modal dose	**D mod**	45,1	1,3-73,5
Median dose	**D med**	43,9	2,7-68,8

		Average percentage of volume [%]	Range [%]
Percetage of thyroid volume irradiated to a given dose	**V10**	93,8	27,8-100
	V20	90,9	22,9-100
	V30	84,9	14,1-100
	V40	73,3	8,3 -100
	V50	33,1	0-100
	V60	8,9	0-71,4
Total thyroid volume	[ml]	17,2	5,4-42,8 ml

Conclusion
The risk of hypothyroidism after irradiation of head and neck is 25%. The initial thyroid function (based upon TSH level, even within its range of norm) is the strongest risk factor of developing a posttreatment hypothyroidism. The product of initial TSH and median dose absorbed by thyroid (TSH0*Dmed) seems to be a usefull tool predicting a posttreatment hypothyroidism. It can be used to select a group of patients who should have very carefull thyroid function monitoring during their follow-up.

PO-124 A melatonin gel protects the mitochondria from radiation damage preventing mucositis

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Purpose or Objective
Mucositis is a common and distressing side effect of chemotherapy or radiotherapy that has potentially severe consequences, and no treatment is currently available. On the other hand, radiotherapy-induced gut toxicity is among the most prevalent dose-limiting toxicities following radiotherapy. The purpose of this study was to analyze the molecular pathways involved in the development of oral mucositis, to investigate the changes induced in the rat small intestine after external irradiation of the tongue, and to explore the potential radio-protective effects of melatonin gel.

Material and Methods
Male Wistar rats were subjected to irradiation, and their tongue and duodenum were obtained for subsequent determinations. The radiation was administered using a Ray-X YXLON Y.Tu 320-D03 irradiator, and the rats received a dose of 7.5 Gy/day for 5 days in their oral cavity. Rats were treated with 45 mg/day melatonin gel or vehicle during 21 days post-irradiation, by application in their mouths. Mitochondrial oxidative stress, mitochondrial bioenergetic capacity, NF-κB/NLRP3 inflammasome signaling activation, histology and electron microscopy, were determined.

Results
Tongue irradiation induced oral mucositis and gut toxicity. Our results showed that mitochondrial oxidative stress, bioenergetic impairment, and subsequent NLRP3 inflammasome activation were involved in the development of oral mucositis and radiotherapy-induced gut toxicity. Oral treatment with melatonin gel had a protective effect in the oral mucosa and in small intestine, which was associated with mitochondrial protection and, consequently, with a reduced inflammatory response, blunting the NF-κB/NLRP3 inflammasome signaling activation.

Conclusion
Our findings suggest that oral treatment with melatonin gel may be a potential preventive therapy for oral mucositis and also for radiotherapy-induced gut toxicity in cancer patients. These results have led to a clinical trial (Nº EudraCT: 2015-001534-13)

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Ortiz F, et al. J Pineal Res 2015; 58: 34-49
Escames G, et al. Hum Genetics 2012; 131:161-173

PO-125 Effects of melatonin oral gel to prevent radiation-induced mucositis model in rat

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Purpose or Objective
Melatonin (N-acetyl-5-methoxytryptamine) is a potent free radical scavenger with anti-oxidative and anti-inflammatory properties. It reportedly maintains mitochondrial homeostasis under various pathophysiological conditions, including radiation injury. We recently found that a melatonin oral gel at 3% restored melatonin levels in the tongue and prevented mucosal disruption and ulcer formation caused by irradiation due to its anti-inflammatory properties. Melatonin oral gel protected the mitochondria from radiation damage and blunts inflammasome signal activation in the tongue. The objective of this study was to analyse several melatonin formulations to prevent oral mucositis and gastrointestinal damage in radiation-induced mucositis model in rat.
Material and Methods
Male Wistar rats were subjected to irradiation. The radiation was administered using a Ray-X YXLON Y.Tu 320-D03 irradiator, and the rats received a dose of 7.5 Gy/day for 5 days in their oral cavity. Irradiated rats were treated during 19 days T.I.D. with different melatonin formulations. During the study, local effects were controlled, tongue and duodenum were analysed and melatonin levels were also evaluated in tongue and plasma.
Results
We demonstrated that treatment with 3% melatonin selected gel protected rats from oral mucositis after irradiation, also protected duodenum against inflammation and necrosis, and restored endogenous local melatonin levels in irradiated animals.
Conclusion
The formulation of melatonin oral gel, chosen for preclinical and clinical development, showed the highest efficacy preventing oral mucositis and gut damage in irradiated rats. The selected melatonin gel formulation also showed the highest local absorption, restoring endogenous melatonin levels, and the lowest systemic absorption after repeated oral administration. These results have led to a clinical trial (N° EudraCT: 2015-001534-13)

PO-126 Consenting patients for late-effects of head and neck radiotherapy: an audit of UK oncology practice
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Purpose or Objective
Long-term morbidity after the curative treatment of head and neck cancer is well-recognised as a significant issue, but for many patients and clinical staff it can be seen as a 'secondary problem' to face only once they have got over the major hurdle of their cancer being cured. Because late complications of treatment may occur many years after curative cancer treatment, it can be a neglected area at the time of primary consent especially when patients are faced with the often over-whelming package of immediate cancer treatment that is facing them. It can then remain a neglected area during follow-up. This survey investigates the extent to which Radiotherapy Late Effects (RTLE) are routinely discussed during the consent process, prior to commencing curative treatment for Head and Neck cancer.

Material and Methods
During March 2016, clinical staff from radiotherapy centres across the UK and Ireland, involved in the consent process for Head and Neck Radiotherapy (HNRT), completed an e-mail survey about their current consent practice for HNRT. They were asked to tick, from a list of 14, which RTLE they would routinely discuss with a patient who had a T3N2bM0 squamous cell carcinoma of the oropharynx, and who was due to undergo curative radiotherapy. They were also asked to list any other RTLE for which they would routinely consent, which were not on the list. They were also asked about their process for monitoring and support of RTLE during follow-up.
Results
Responses were received from 53 clinical staff. The median number of RTLE discussed with patients was 9. The range was between 2 and 14.
Table 1 shows the RTLE and the frequency with which they are discussed at consent.
16.6% of clinical staff prospectively score RTLE in clinic during follow-up ; 61.1% only document if there is a RTLE-related problem mentioned in clinic. 81.5% of clinical staff measure thyroid function only if symptoms of hypothyroidism are mentioned. 42% of clinical staff did not know if their patients are still feeding tube dependent at one year. 18.2% of clinical staff have access to a dedicated RTLE clinic service.

Radiotherapy Late-effect (RTLE)	% discussed at consent
Xerostomia	96.2
Difficulty swallowing	94.3
Difficulty swallowing that might require a permanent feeding tube	81.1
Osteoradionecrosis	77.0
Skin fibrosis	73.6
Permanent beard/hair loss	73.6
Hoarse voice	64.2
Hearing loss	64.2
Permanent loss of taste	60.4
Telangiectasia	35.8
Neck pain or stiffness	32.1
Second malignancy related to radiotherapy	30.2
Hypothyroidism	28.3
Carotid stenosis	17.0
Others - Trismus	3.8
Others - Lymphoedema	1.9
Others - skin discolouration	1.9
Others - dental decay/infection	1.9
Fatigue	1.9

Conclusion
There is a wide variation across UK radiotherapy centres in what is discussed with patients concerning RTLE prior to curative treatment with radiotherapy. With increasing emphasis on survivorship, RTLE must have a higher priority not only in our pre-treatment discussions but more intentional follow-up processes are needed where RTLE are easily identified and support given.

PO-127 Melatonin oral gel for prevention oral mucositis head and neck cancer undergoing chemo/bio radiation (MUCOMEL)

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Purpose or Objective
Oral mucositis (OM) is the most significant adverse event (AE) in patients undergoing concurrent chemo/biotherapy plus radiotherapy for treating head and neck (H&N) cancer.
The objective of the ongoing Phase Ib-II trial is to evaluate the safety of melatonin (MLT) oral gel, its efficacy in the prevention of severe OM in H&N cancer patients (84) and to assess the pharmacokinetic profile of MLT in the subgroup of the first 24 patients.**Material and Methods**
Prospective, randomized, double blind and placebo-controlled study. Eligible patients are assigned at 1:1 ratio to receive 3% melatonin or matching placebo oral gels (mouthwashes followed by swallowing).
All patients receive concomitant standard symptomatic treatment for OM along the study, according to the clinical practice of the hospitals.
All patients take MLT oral-gel or placebo oral gel from two to three days before start of systemic treatment until one to four weeks after completion of radiotherapy. Eight additional weeks of observation are needed to rule out late-onset adverse events related to MLT.
The selected radiotherapy is VMAT-SIB once daily (5 days a week), 50.4 Gy (low risk area), 69.96 Gy (high risk area) and 66 Gy (post-operative oral cavity tumour). Radiotherapy plan was previously agreed between all the radiotherapists participating in the study in order to ensure homogeneity between centres. Concurrent systemic treatment is either cisplatin or cetuximab.
Primary endpoint: Num. of patients with severe OM (G3-G4 / RTOG).
Secondary endpoints:
Efficacy: Num. of patients with SOM (G3-G4 / NCI-CTCAE), Num. of days with OM (RTOG), Num. of days with G3-G4 OM (RTOG), Time to onset of G3-G4 OM (RTOG)
Quality of Life: Change from baseline in EORTC QLQ-C30 & EORTC QLQ-H&N35 scores ,Change from baseline in ECOG-PS
Safety: Num. of patients with G1-G4 NCI-CTCAE rel. to IMP , Num. of patients who develop cisplatin or cetuximab-associated G1-G4 AEs (NCI-CTCAE)., Num. of patients who develop RT-associated AEs different from OM (RTOG)
PK: C_{max}, $C_{min,}$ T_{max}, AUC, $T_{1/2}$, V_d, Clearance (Cl)
Results
The first patient was enrolled in November 2015 and, up to 10 October 2016, 40 patients were randomized to treatment with either MLT or placebo oral gel. Results are expected by mid of 2017.
Conclusion
This prospective, randomized, double-blind and placebo-controlled study will demonstrate if melatonin oral gel 3% is safe and has been able to prevent severe OM in H&N cancer patients undergoing QRT, and if has shown efficacy in the other evaluated endpoints.

PO-128 Follow up dysphagia in head and neck cancers is related to RT dose received by swallowing structures

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Purpose or Objective
To study relationship of radiation dose received by Dysphagia and Aspiration Related Structures (DARS) and degree of dysphagia in head and neck cancers post radical radiation therapy (IMRT) with or without Chemotherapy (CT). If positive correlation exists, then assess the dose to DARS in patients previously treated with Brachytherapy boost and suggest Brachytherapy as a good boost modality to further reduce dysphagia and aspiration.
Material and Methods
42 patients of head and neck cancers, satisfying the inclusion criteria were included from April 2014 to May 2015 and were treated with radical IMRT. DARS structures which included superior (SC), middle (MC) and inferior constrictors (IC), supraglottic (SGL) and glottic larynx (GL) and cervical esophagus (CE) were contoured on the planning CT scan along with other Organs at risk (OAR's). Dysphagia was evaluated at baseline and at 6 months post treatment using Subjective questionnaires M.D Anderson Dysphagia Inventory (MDADI) and Performance Status Scale for Head and Neck Cancers (PSSN) and using Modified Barium Swallow for Objective Scoring of dysphagia: Swallowing Performance Scale (SPS) and Penetration Aspiration Scale (PAS).
42 patients of cancer of the pharynx and larynx who were treated with EBRT followed by Brachytherapy boost from 2009 to 2016 were also evaluated (dosimetrically) retrospectively.
Results
On applying non-parametric correlation, there's correlation between V30 of SC and the PSSN Score at 6 months and Dmax of SC and PSSN score at 6 months. For MDADI scores, there's a positive relationship of Dmax of SC and 6 month MDADI score. There's correlation between V30, V50, V60, V66, V70, Mean doses of MC and the PSSN Score at 6 months; For MDADI scores, there's a positive relationship of V30, V50, V60, V66 and V70 of MC and 6 month MDADI score. There's correlation between V30, V50

and Dmax of IC and MDADI Score at 6 months; There's correlation between V30, V50, V60, V66, V70, Mean doses of SGL and the PSSN Score at 6 months. For MDADI scores, there's a positive relationship of V30, V50, V60, V66, V70 and Mean of SGL and 6 month MDADI score.There is no significant correlation between doses to GL and CE and Scores. There is a high rate of baseline aspiration on objective testing with Modified Barium Swallow. In the brachytherapy group, D mean and D max and various V d's of the DARS were significantly lower than in the EBRT alone group. This dosimetric analysis demonstrated that brachytherapy can significantly reduce dose to DARS. But more prospective trials are required to study swallowing outcomes post Brachytherapy.

Conclusion

The findings of this study motivate further efforts beyond IMRT to reduce the dose to the swallowing structures when planning chemoradiotherapy for locally advanced head-and-neck squamous cell carcinoma in cases where the planning target volume does not overlap with DARS. Use of Brachytherapy as a boost could spare significant dose to the pharyngeal constrictors in such cases post External Radiotherapy.

PO-129 managing the consequences of head and neck in radiotherapy a Radiotherapy Late Effects clinic

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Purpose or Objective

Due to the rising number of patients' now surviving head and neck cancer, there are increasing number of patients living with the long-term consequences of treatment. Since October 2014, our hospital has run a fully comprehensive Radiotherapy Late Effects (RTLE) programme for all patients who are disease free but suffering with the adverse late effects of their radiotherapy treatment. At the centre of the programme is an open access clinic, where patients can self-refer. From there, patients can be given information about managing their RTLE. For those with more severe symptoms we have developed clinical pathways now accessing a vast array of specialist interest clinical teams within the hospital. This study assesses the patients attending the RTLE clinic who have previously been treated for Head and Neck cancer

Material and Methods

The database was reviewed for all patients who have attending the RTLE clinic. Details of tumour location, treatment details, time since treatment were recorded alongside patient quality of life measures using a simple modified Holistic Needs Assessment (HNA) tool that identifies people's concerns and needs from a score of 1 – 10, where 1 represents the lowest level of concerns and 10, the highest.

Patients were seen in the clinic by therapy radiographers, their symptoms and difficulties discussed and HNA carried out. Depending on the symptoms and the severity of the presentation, patients were either given information sheets pertinent to their specific late-effects or would be advised to access one of the specialist pathways. HNA was carried out at presentation to the clinic and then at approximately 6 months later. Patients were required to have completed RT more than 6 months prior to referral.

Results

From October 2014 – Sept 2016, 153 patients have been seen the RTLE clinic. Of these, 45 patients had previously been treated for Head and Neck cancer with a radical dose. This group was larger than the prostate cancer patient group within the clinic. 35.7% had received treatment for oropharynx cancer, 28.6% for tongue cancer, 14.3% for hypopharyngeal/larynx cancer. 39 patients had follow-up data available. Median time from end of radiotherapy to clinic referral was (2.52 years). Range 5.6 months – 30 years. 16/39 (41.0%) patients were given general advice and information only. 23/39 (59.0%) needed referral to a specialist team as described in Table 1. A total of 28 specialist team referrals were made, some patients requiring more than one referral. Only 6 of the 28 referrals required going back into specialist medical clinics. The mean HNA score at initial presentation was 7.28 and at follow-up the mean score had reduced to 4.72.

Table 1 Outcomes of the Radiotherapy Late Effects clinic

Outcome of RTLE clinic	Numbers of patients
General advice/information sheets	16
Specialist referral:	23
Restorative dentistry team	2
Pain acceptance team	6
Facial Pain clinic	4
Orthotics clinic	2
Physiotherapy	11
Psychological therapies	3

Conclusion

A RTLE clinic can provide an excellent support for people suffering the consequences of the Head and Neck cancer treatment. Giving advice and signposting patients to the correct clinical pathways can reduce patients concerns and provide a cost-effective management strategy that does not necessarily involve medical appointments.

PO-130 Longitudinal assessment of enteral nutrition requirement in 1st line treatment of SCCHN

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Purpose or Objective

First line SCCHN patients can be treated by: surgery (S), radiotherapy (RT), chemotherapy (C), radiochemotherapy (RTCT), induction chemotherapy ± RTCT (IND), surgery + RT, surgery + RTCT.

There is a lack of prospective data regarding nutritional support necessity whatever treatment realized.

Material and Methods

This was a prospective study conducted in a single institution from December 2012 to December 2014. The aim was to evaluate enteral nutrition importance (rate, length and occurrence) and outcomes over the first 18 months of treatment.

Results

Hundred and thirty-five patients have been enrolled: 22 in the S group, 16 in the RT group, 3 in the CT group, 28 in the RTCT group, 31 in the IND group, 11 in the surgery + RT group, 23 in the surgery + RTCT group. EN was set up before treatment in 11.8% of patients and the mean EN length (SD) during this period was 20.4 (16.2) days.

From treatment start to 18 months after, 67.4% of patients beneficiated from EN. The mean time (SD) of first support set up was 73.3 (87.2) days. The total EN mean length (SD) during the period was 133.7 (137.5). During the post treatment period, EN was set up one time in 57 patients

(42.2%), 2 times in 28 patients (20.8%) and 3 times in 6 patients (4.4%).
Patients who received EN before treatment were respectively: 2 in the S group (mean length (SD): 2 (1.4) days), 1 in the RT group (mean length: 43 days), 1 in the CT group (mean length 47 days), 7 in the RTCT group (mean length (SD): 14.7 (12) days), 5 in the IND group (mean length (SD): 25.8 (14) days). Pretreatment EN was received by no patient in the surgery +RT and surgery +RTCT groups.
Regarding the post treatment period, the number of patients having received EN is: 20 in the S group (mean length (SD): 42.3 (59) days), 4 in the RT group (mean length (SD): 72 (14) days), 1 in the CT group (mean length 53 days), 22 in the RTCT group (mean length (SD): 102.7 (93) days), 15 in the IND group (mean length (SD): 103.4 (100) days), 8 in the surgery +RT group (mean length (SD): 32 (30) days) and 20 in the surgery +RTCT group (mean length (SD): 70.5 (110) days). Some patients always beneficiated from EN 18 months after treatment start.
Conclusion
Enteral nutrition seems necessary during the post treatment period in 66.7% of patients, whatever the type of treatment received.

Poster: Minimal invasive and reconstructive surgery

PO-131 Resecting the carotid artery for invasive head and neck cancer: Time to reconsider its feasibility

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Purpose or Objective
Head and cancer invading the carotid artery poses a difficult question for the clinician as the optimum management strategy is unclear. What is known is that carotid artery involvement is a poor prognostic indicator with survival rates ranging from 0% to 35% at 1 to 2 years. The surgical options include peeling the tumour from the carotid artery adventitia, performing en bloc resection and ligation of the carotid artery, or en bloc resection followed by reconstruction of the carotid artery. Aims: Does survival time improve with surgery compared with chemoradiotherapy (CRT)? If so, does the survival benefit outweigh the risks of surgery? When surgery has been decided upon, what is the most effective method of resection and should reconstruction of the carotid artery be attempted?
Material and Methods
This review reflected upon the major historical papers and provides an in-depth analysis of research over the last 10 years pertaining to the management of malignant carotid invasion.
Results
Survival outcomes are presented in Table 1. Okamoto et al reported 100% mortality at 8 months of patients who did not undergo surgical intervention and no patients survived longer than 15 months who underwent CRT within the series by Roh et al. The evidence suggests that with careful selection of patients, surgical management can improve survival outcomes and may be the only solution to achieve long term survival.
Following 401 surgical procedures involving the carotid artery, 14 patients suffered strokes (3.49%) and 22 patients (5.49%) suffered carotid blowouts. Zhengang et al do not provide peri-operative mortality data; as such their series is removed from the overall post-operative stroke or death rate calculation. Therefore, following 328 procedures, 5 patients (1.52%) died within the post-operative period and 15 patients (4.57%) suffered major stroke or death in the post-operative period.This is an improvement from outcomes described by the meta-analysis of Snyderman et al, who found carotid resections were complicated by major neurological deficit in 16.7% of patients.
Rates of post-operative stroke did not differ between patients that underwent tumour peel and those that underwent resection and reconstruction ($p = 0.76$). Whilst rates of carotid blowout syndrome were greater than twice as high within the tumour peel group, the results were not significant ($p = 0.11$).

The evidence pertaining to oncological outcomes weighs in favour of performing resection and reconstruction, as opposed to performing tumour peel.
Conclusion
When considering the available evidence, the best oncological outcomes are most likely achieved by centres performing carotid resection and reconstruction. It can also be seen that outcomes are further improved when surgery is performed as the primary treatment modality, in the absence of metastatic lesions. There is also evidence to suggest that performing resection and reconstruction may reduce the risk of carotid blowout syndrome compared with tumour peel.

PO-132 Risk of re-operation for bleeding in head and neck surgery.

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Purpose or Objective
Intraoperative bleeding complicates the identification of crucial structures in head and neck area and is potentially fatal. We conducted a retrospective study to assess head and neck cancer (HNC) operations which carry high risk factors for re-operation due to postoperative bleeding.
Material and Methods
Study included a total of 456 patients (591 operations) who underwent surgery for HNC between 1999-2008 in tertiary care center of Turku University Hospital. Need of re-operation for bleeding was evaluated.
Results
Data on intraoperative bleeding was available in 265 operations. Median estimated intraoperative bleeding was 700mL [IQR 800] and operations with ≥ 700ml bleeding were defined as high bleeding risk operations. High bleeding risk operations included surgery with microvascular reconstruction or reconstruction using pedicled regional flap, salivary gland operation with neck dissection and major sinonasal surgery. Moreover, high bleeding risk operations were associated with increased risk for re-operation due to postoperative bleeding ($p=0.001$). Other risk factors for re-operation because of postoperative bleeding were history of heavy alcohol consumption ($p=0.014$), preoperative oncologic treatment ($p=0.017$), higher tumor stage ($p=0.020$), higher T-classification ($p=0.034$) and over 4000ml fluid administration within the operation day (24h) ($p>0.001$). Re-operation for bleeding was an independent risk factor for 30-day mortality after operation ($p=0.014$).
Conclusion
High bleeding risk operation, heavy alcohol consumption, preoperative oncologic treatment, higher tumor stage and

classification and excessive fluid administration increase the risk of re-operation for bleeding in patients undergoing HNC surgery. Moreover, patients with re-operation due to bleeding have over 5-fold risk for mortality.

PO-133 Occult lymphnode metastasis in early stage OPC treated with TORS without neck lymphnodes dissection

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Purpose or Objective
Standard treatments for early stage (I and II) squamous cell oropharyngeal cancer (OPC) are both curative radiotherapy and surgery. Since the incidence of occult lymph node metastasis for early stage OPC is about 30%, an elective neck treatment is generally performed. We retrospectively evaluated consecutive patients (pts) with early stage (cT1-cT2 cN0) OPC treated with Transoral Oropharyngeal Robotic Surgery (TORS) without elective treatment on the neck lymph nodes. Aim of this analysis was to evaluate both locoregional control and impact on clinical outcomes of the deferred treatment of the neck lymph nodes.
Material and Methods
All consecutive pts treated with TORS without elective treatment on the neck (neither neck dissection, nor radiotherapy) were evaluated. Lymph node recurrences were classified as localized in the neck and/or in the retropharyngeal space ("retropharyngeal nodes"-RPN). Tumor recurrences of the "parapharyngeal space (PPS)" were considered separately.
Results
Twenty pts (7 female and 13 male, median age 61 years) met inclusion criteria. Median follow up was 28 months (mean 40 months, range 7-97months). Six and 14 pts had HPV positive HPV negative tumors, respectively. Ten (50%) pts experienced a locoregional tumor appearance after a median time of 10 months (mean time 11 months, range 4-17 months). As expected, 35% of patients experienced clinical appearance of occult lymph node metastasis (only in the neck lymph nodes in 5 patients, RPN 1 patient, neck lymph nodes and RPN 1 patient) after a median time of 10 months (mean 11 months, range 7-15 months). Of note, all three pts with PPS recurrences did not show any evidence of mucosal lesion in the oropharynx suggesting a submucosal localization of the tumor recurrence and authors suggested that this aspect could be probably related to a residual microscopic disease in the "T-N" tract (soft tissues and lymphatic network lied between the tumor and the neck lymph node chains). RPN metastasis appeared in 15% of pts. For the locoregional recurrences a second treatment was performed (Table 1). At last follow up 17 (85%) pts were alive without disease, two pts were alive with disease (one patient with distant metastasis and one patient with e second primary tumor in the supraglottic larynx) and one patient died for non-cancer related causes. Estimated 2-years overall survival and locoregional free-survival were 92.9% and 39.4%, respectively.
Conclusion
TORS without elective treatment of neck lymph nodes doesn't represent a standard of care in early stage OPC but our results suggested that pts treated with salvage treatments maintained good oncologic results. This study could provide useful information on both the occult lymph node metastasis (site and time of their clinical appearance) and the impact on clinical outcome of the deferred lymph node treatment in early stage OPC.

PO-134 Retrospective analysis of treatment outcomes of sinonasal malignancies. Our 22-year experience

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Purpose or Objective
1.We report our experience with surgical management of sinonasal malignancies
2.To assess the role of oncologic surgery alone or combined with radiotherapy and/or chemotherapy in sinonasal malignancies
Material and Methods
A total of 132 patients with the naso sinusal malignancies between 1994 and 2015 were analyzed retrospectively. There were 86 males and 46 females; the average age was 59.1 years. The median follow-up time was 57 months (range 1-216 months). According to the American Joint Committee on Cancer 7th staging, patients were: 2 (1,5%) St I, 27 (20,3%) St II, 42 (31,6%) St III, 27 (20,3%) St IVa, 24 (18,0%) St IVb, 10 (7,5%) St IVc. The most frequent histotypes encountered were: adenocarcinoma 44 (33,8%), adenoid cystic carcinoma 24 (18%), squamous cell carcinoma 19 (14%), mucosal melanoma 11 (8,3%), Esthesioneuroblastoma 8 (6%), neuroendocrine nasosinusal carcinoma 8 (6%). Before the treatment, magnetic resonance imaging (MRI) and computed tomography (CT) were performed. 90 (68,2%) patientes were treated with exclusive endoscopic approach (EEA) and 42 pts (31,8%) with combined approach. Postoperative treatment were performed in 57 patients (43,2%): 35 patients received postoperative radiotherapy alone, 18 pts radiotherapy concomitant with chemotherapy and 4 pts CT only.
Results
Analyzing the cases based on a surgical technique, EEA and combined approach, we have noted the lack of statistically significant difference of survival between the two approach (5 year disease-specific survival respectively: 72,4% ± 5,6% vs 68,8% ± 7,8%; p=0,67). Twelve (9,1%) complications were present in 132 patients postoperatively without statistical difference between the two different approaches (10% vs 7.1%).
Conclusion
The results seem to indicate that endoscopic surgery, when properly planned and in expert hands, may be a valid alternative to standard surgical approaches for the management of malignancies of the sinonasal tract; less aggressiveness do not means less radicality. Follow the oncologic roles the endoscopic oncologic surgery alone or combined with external approaches achieves the same results. Every choice of treatment should be discussed by a dedicated oncology group formed by neurosurgeons,

medical oncologists, otolaryngologists, pathologists, radiation therapists and radiologists.

Poster: Epidemiology and prevention

PO-135 Head and neck squamous cell carcinoma of unknown primary treated in the era of FDG-PET and IMRT

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Purpose or Objective
Head and neck carcinoma of unknown primary (HNCUP) is a diagnosis of exclusion after an extensive workup. Since the introduction of PET-CT in the diagnostic arsenal the area of true unknown primaries narrowed. Most literature available nowadays describes cohorts of patients before the era of PET-CT and IMRT. This cohort thus represents a more applicable patient selection for current medical practice.
Material and Methods
Retrospective analyses of 80 PET-staged patients that were curatively treated with intensity-modulated radiotherapy (IMRT) between 2006 and 2016. Patient, tumor and treatment demographics were recorded and oncologic outcomes were analyzed.
Results
Half of the patients underwent upfront neck dissection, mostly (super)selective. Of all, 97% received mucosal irradiation. Unilateral irradiation of the neck was done in 18% of the patients.
Overall survival at 5 year was 62% and disease specific survival 78%. Extracapsular extension (ECE), N3 neck, multiple levels of positive lymph nodes (PLN) and PLN in the lower neck were associated with worse prognosis. Local control was 100% in the mucosal irradiated patients. Neck control was 90%. In total 10 patients developed distant metastases, N3, ECE and lower neck PLN were associated with DM. Patients treated unilaterally had significantly less acute dysphagia grade III (0% vs. 33%).
Conclusion
This series gives a current overview of the HNCUP patients treated over the last 10 years in the Netherlands Cancer Institute by IMRT in the era of FDG-PET. Five-year disease specific survival is fairly good with 78%, however ECE, N3 and lower neck PLN are factors associated with a worse prognosis. These patients are prone for distant metastasis and future research need to focus on identification of these patients and development of new strategies to improve the outcome of this group of patients.

PO-136 Hospital costs associated with head and neck cancer by phase-of-care in France (EPICORL study)

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Purpose or Objective
Costing studies of head and neck (H&N) cancer care are scarce.
The study objective was to estimate monthly hospital costs associated with H&N cancer by phase-of-care in France.
Material and Methods
We completed a retrospective cohort study using the French National Hospital Discharge (PMSI) database that contains all public and private claims for acute care (MCO) and post-acute care (SSR and HAD) in 2008-2013. Of all adult patients identified with squamous cell carcinoma at hospital (ICD-10: C00-C06; C09-C14; C30.0; C31; C32), we selected all 53,257 incident cases in 2010-2012 without a personal history of cancer.
Hospital stays were valued from a societal perspective using national public tariffs and out-of-pocket expenses at hospital. Hospital stays attributable to cancer care were identified using French guidelines (INCA 2013) and summed over 3 phases-of-care:
1) initial care (first 6 months after diagnosis), by cancer stage (early I/II; locally advanced III/IVb; distant metastatic IVc);
2) continuing care without relapse (6 months after diagnosis);
3) relapse care in patients without distant metastasis at diagnosis.
Mean monthly costs were computed by phase-of-care with use of two-part models taking into account the probability of hospitalization during continuing care and a log-normal distribution of costs.
Results
Patients were 78.2% male with a median (IQR) age of 61 (54-71) at diagnosis and 20,582 (38.6%) patients died in the follow-up.
During initial care (first 6 months), mean (std) monthly hospital costs attributable to cancer care increased with a worse cancer stage at diagnosis: 1,878 (3,277) euros in 15,747 (29.6%) patients with early cancer; 5,199 (3,434) euros in 32,723 (61.4%) patients with locally advanced cancer; 6,999 (2,626) euros in 4,785 (9.0%) patients with distant metastasis. In the follow-up (6 months after diagnosis), continuing care was associated with hospital costs of 423 (1,259) euros per month, while relapse care increased monthly hospital costs to 5,069 (3,353) euros. In multivariate analyses by phase-of-care, mean monthly hospital costs significantly varied by cancer site (min: lip cancer ; max: laryngeal cancer). The presence of primary cancers other than H&N or Charlson comorbidities other than cancer almost all significantly increased monthly costs at all phases-of-care. Death at any phase-of-care doubled mean hospital costs per month.
Conclusion
Monthly hospital costs were maximum in patients diagnosed with distant metastasis, and still very high in patients with locally advanced stage at diagnosis or relapsing in he follow-up.
Less than one third patients with H&N cancer were diagnosed at early stage during the study period in France. Increasing early diagnosis would substantially decrease hospital costs associated with H&N cancer care.

PO-137 Multivariate oral rinse models predict Head and Neck squamous cell carcinoma (HNSCC)

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Purpose or Objective
Background: Head and neck squamous cell carcinoma (HNSCC) is the 6th most common cause of cancer mortality throughout the world affecting some 50,000 people in the US and 600,000 worldwide each year. The ability to detect the disease in a potentially malignant phase and earlier stage could have significant impact on overall outcome. Previous studies have demonstrated that a combined salivary CD44, a tumor-initiating marker, and total protein assay was able to aid in the diagnosis of HNSCC. We sought to better understand the cut-point performance characteristics of these biomarkers in an expanded training cohort.
Material and Methods
Methods: Oral rinse specimens from 310 patients (107 HNSCC cases; 203 controls) were obtained from biorepositories. A training cohort was generated, divided equally and demographically balanced. Levels of CD44 and total protein (TP), +/- clinical variables were evaluated using the AUC, sensitivity, specificity; support vector machine (SVM) multivariate models were also generated.
Results
Results: 95% HNSCC patients (cases) were >/=40 years of age, 72% male, 97% white and 65% smokers vs. 23%, 36%, 60% and 44% respectively, for controls. Predicted cut-points for CD44 and TP yielded an AUC of 0.72 for discriminating cancers. A logistic regression model which included continuous levels of CD44 and TP combined with sex, and race produced an of AUC 0.83; while an SVM model which incorporated age, sex, race, smoking history with continuous CD44 and TP yielded a sensitivity of 87% and a specificity of 94%.
Conclusion
Conclusions: Elevated and combined levels of both CD44 and TP continue to perform well for discriminating HNSCC from control patients. The incorporation of clinical factors including smoking status, sex and race appears to improve overall performance of the assay. Additional validation studies are underway to further confirm these results.

Poster: Salivary gland, skull base, skin and thyroid cancers

PO-138 IMRT of sino-nasal cancer: improved results compared to 3D radiotherapy.

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Purpose or Objective
Prospective evaluation of the results of intensity-modulated radiation therapy (IMRT) in sino-nasal cancer compared to a historical series of patients (pts) treated with three-dimensional conformal radiotherapy (RT3D).
Material and Methods
Between 2011 and 2015, 42 pts were treated with IMRT and integrated boost (Rapidarc®). Doses in low-risk, intermediate and high volumes were 54, 60 and 66-70 Gy respectively. They were retrospectively compared with a historical series of 30 pts treated with RT3D (50 to 66Gy), from 2007 to 2011. There were 28 ethmoid, 27 maxillary sinuses and 17 nasal cavities. There were 34 squamous cell carcinomas, 27 adenocarcinomas and 4 other histological types. There was no significant difference between the 2 groups (histology, location, stage and surgery). The efficacy and toxicity results were evaluated.
Results
Median follow-up was 30 months (range, 1.4-112 months). Two-year local control was 81% in IMRT vs 57% in RT3D (p=0,05). In multivariate analysis, the prescribed dose at high risk volume was predictive of local control regardless technique (p=0,05). Two-year overall survival was 92% in IMRT vs 55.5% in RT3D (p = 0.002). In IMRT, ocular acute toxicity rate of grades 1, 2 and 3 were 48%, 28% and 0% respectively. Mucosa, skin and salivary acute toxicity rate of grade ≥ 3 were 14%, 2% and 0% respectively. At one year, ocular toxicity rate of grades 1, 2 and 3 were 36%, 18% and 0%.
Conclusion
IMRT significantly improves local control and overall survival in sino-nasal cancer allowing to bring a higher dose to the target volume. Acute and late toxicities remain low.

PO-139 Hypofractionated accelerated chemo-Tomotherapy for nasopharyngeal cancer: 2-year treatment outcomes

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Purpose or Objective
To report outcomes for nasopharyngeal carcinoma (NPC) patients treated with selective neoadjuvant docetaxel, cisplatin and 5FU (TPF) chemotherapy and IMRT delivered by helical TomoTherapy® (HT) using a hypofractionated accelerated schedule plus concurrent platinum in a UK institution.
Material and Methods
Since December 2011, patients with NPC receiving chemoradiotherapy were treated using HT. Three dose levels were used: 65Gy/30 fractions to GTV; 60Gy/30 fractions to high-risk local site plus retropharyngeal nodes; 54Gy/30 fractions to uninvolved bilateral nodal levels Ib, II, III, IV, V, VIIb. All patients received concurrent platinum chemotherapy. Patients with T≥3 or N≥1 or M1 also received neoadjuvant TPF. Data collected included locoregional control, survival and late radiation toxicity using CTCAE v4.
Results
19 patients met the inclusion criteria (median age 46 years, range 19-68). WHO histology: keratinising squamous = 4; non-keratinising = 14 (undifferentiated = 11, differentiated= 3); basaloid squamous = 1. TNM-7 staging was: I =3; II =3; III =4; IVa =4; IVb =2; IVc =3. Fourteen patients received neoadjuvant TPF (median 3 cycles, range 1-5). All patients completed the prescribed radiation dose with median overall treatment time of 39 days (range 37-45). Concurrent chemotherapy used were cisplatin (n=15) or carboplatin (n=4).
At a median follow-up of 31 months (range 13–52) post-chemoHT, none of the 19 patients have developed locoregional relapse. 2 patients with stage IVc disease developed further distant metastases at 3 and 6 months

post-chemoHT, whilst 2 patients (stage IVa, IVb) developed distant metastases 20 and 32 months post-chemoHT. 3 deaths have occurred at 6 months (stage IVc), 21months (stage IVb), and 31 months (stage IVc) post-chemoHT. Locoregional control and overall survival at 2 years was 100% and 86% respectively.
At 2 years, reported late side-effects included hearing problems G2/3 (n=2), neck pain/stiffness G2 (n=2), vestibular disorder G2 (n=1), trismus G2 (n=1), depression G1 (n=2), diplopia G2 (n=1), watery painful eye G2 (n=1). No patients were feeding tube-dependent at 1 year.**Conclusion**
Image-guided chemoHT with moderately accelerated hypofractionation and selective neoadjuvant TPF is associated with acceptable efficacy and late radiation-induced toxicities.

PO-140 Long-term outcomes of surgery ± radiotherapy for salivary gland carcinoma at a single institution
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Purpose or Objective
Salivary gland carcinomas are a heterogeneous group of tumours. Surgery remains the primary treatment modality of choice, with or without adjuvant radiotherapy (RT) for high-risk patients. The purpose of this retrospective audit was to review outcomes of patients treated for salivary gland carcinomas (SGC) at a single institution based on prognostic factors, and treatment modality.
Material and Methods
An Ethics approved (HREC11/040) head and neck cancer database was audited between 1971-2014. Patient eligibility criteria were: histologically confirmed diagnosis of primary SGC (newly diagnosed or recurrent), age ≥18 years, definitive treatment with surgery ± RT, or RT-alone. Primary outcomes were local-control (LC), ultimate-local control (ULC), cancer-specific survival (CSS) and overall-survival (OS). Secondary outcomes were rates of distant metastases. Time to events were estimated using the Kaplan-Meier method and log rank test, with $P<0.05$ considered significant. All analyses were performed using IBM SPSS version 23.0.
Results
Of the 298 patients with SGC, 161 met the eligibility criteria (n=145 newly diagnosed, n=16 recurrent). Ninety patients were male (56%) and median age at presentation was 63 years (range 21-88). Parotid gland was the most common location of primary tumour (70%). Twenty-four patients (15%) were node positive at diagnosis, and 58% and 29% of tumours were staged T1-2 and T3-4, respectively, with the remainder not staged or unknown. Five-year LC, ULC, CSS and OS were 71%, 88%, 72% and 63%, respectively. LC was significantly higher in patients with T1-2 disease, and ULC was lower in node positive and high-grade disease ($p<0.05$). CSS and OS were higher in patients with T1-2 disease, node negative, low/intermediate tumour grade and no peri-neural invasion (PNI). Absence of lympho-vascular invasion (LVI) was associated with increased OS ($p<0.05$ for all variables). Thirty-one patients developed distant metastases, rates of which were significantly higher in patients with T3-4 disease, node positive, high tumour grade, and PNI or LVI ($p<0.05$ for all variables). Rates of LC were significantly higher in patients given adjuvant RT ($p<0.01$). No other differences by treatment in survival outcomes were found.
Conclusion
While the addition of RT increased LC, patients with advanced stage and infiltrative disease continue to have poor prognoses, with higher rates of local failure, distant metastases, as well as decreased survival.

PO-141 Adenoid cystic carcinoma of the head and neck: solid growth pattern as an adverse prognostic factor
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Purpose or Objective
To analyse and report the recent experience of our center in patients with adenoid cystic carcinoma of the head and neck (ACC) treated with surgery and radiation therapy (RT).
Material and Methods
Retrospective and unicentric study of patients diagnosed with ACC between 2009 and 2014 treated at our institution. Data were obtained from medical records, pathology and radiology reports. We evaluated overall survival (OS), disease free survival (DFS) and locoregional control (LRC) calculated by the Kaplan-Meier method. Log-rank test was used for univariate analysis. Toxicity was recorded according to Common Terminology Criteria for Adverse Events v4.0 (CTCAE).
Results
Thirty-six patients were identified (53% male; 47% female). Median age at diagnosis was 63 years (range 18-81 years). The subsite distribution was oral cavity, 42% (n=15); paranasal sinuses, 22% (n=8); major salivary glands, 19% (n=7); nasal cavity, 6% (n=2); other subsites, 11% (n=4). T Stage distribution was T1, 25% (n=9); T2, 22% (n=8); T3, 25% (n=9); T4a, 17% (n=6); T4b, 11% (n=4). Seventeen percent of the patients (n=6) had node positive disease and 6% (n=2) had distant metastases at diagnosis. The primary treatment was surgery in 33 patients (92%), while the remaining 3 patients received RT alone. Pathologically, 88% (n=29) of the patients had R1 margins (R0, 6%; R2, 6%), 70% (n=23) had perineural invasion (PNI) and 64% (n=21) had a non-solid growth pattern (solid growth pattern, 24%; not reported, 12%). Median time interval between surgery and radiotherapy was 56 days. Median radiation dose was 66Gy (range 60-72Gy) and it was delivered using either 3D-CRT (53%) or IMRT (47%). Nodal irradiation was performed in 8 patients (22%). Median overall RT treatment time was 48 days (range 39-61 days). Median follow-up time for surviving patients was 41.7 months (range 17.4-84 months). Fourteen patients (39%) had disease recurrence. First site of failure was locoregional in 8 patients, distant in 5 patients and one patient failed in both sites. Two-year and 3-year OS were 80% and 70%, respectively. Two-year and 3-year DFS were 74%/56% and LRC rates were 89/69%, respectively. On univariate analysis, solid growth pattern was associated with worse OS ($p<0.001$), DFS ($p=0.001$) and LRC ($p=0.008$). Overall RT treatment time superior to 49 days was associated with worse DFS ($p=0.01$) and LRC ($p=0.001$), whereas PNI showed a trend to significance in predicting worse DFS ($p=0.06$). Both patients with distant disease at diagnosis are alive and have stable M1 disease, one with local progression. Most frequent reported acute adverse events were dermatitis and oral mucositis (grades 1-3).

Conclusion
In our study, surgery and radiation therapy produced excellent locoregional control similar to the published literature. Solid growth pattern was associated with worse OS, DFS and LRC. Our study also shows the impact of overall treatment time in DFS and LRC. Longer follow-up is encouraged to better understand the natural history of this carcinoma.

PO-142 A 10-year review of primary major salivary glands carcinomas
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Purpose or Objective
Primary salivary gland malignancies, which comprise a diverse group of histological entities, represent less than 5% of all new head and neck cancers. Currently, surgical resection remains the standard of care, with adjuvant radiotherapy performed in selected cases. Chemotherapy can be used in metastatic or recurrent setting, but has limited effect.
Our objective was to review a 10-year experience of a single institution on major salivary glands carcinomas, aiming on demographics, treatment and outcomes.
Material and Methods
A pathology database of salivary glands tumours was reviewed for all cases of a single institution from January 1995 until July 2016. Then we selected all the patients with histopathological diagnose of primary major salivary gland carcinoma from March 2006 to July 2016.
Results
A total of 933 patients were identified, with 33% of them with malignant histology. After excluding patients with metastasis from other sites, we identified, in the last 10 years, 93 patients with primary major salivary gland carcinoma.
In this sample of patients, the median age at diagnosis was 63.1 years (age range 17-90 years), and 51% (n= 48) were male. The majority of the primary tumours were from the parotid gland, representing 76% of all cases. Salivary duct carcinoma was the most frequent histological type (21,5%), followed by adenoid cystic carcinoma (16,1%) and mucoepidermoid carcinoma (13,9%). About 25% of patients had recurrent disease, with 41,6% (n=10) of patients with salivary duct carcinoma; median time to recurrence was 21.52 months. The 5-year survival was 90.2% for stage I; 85.2% for stage II; 66.6% for stage III; and 6.4% for stage IV. Median overall survival for stage IV was 30 months (95% confidence interval 19.67- 40.32). Only 5 patients received palliative chemotherapy based on doxorubicin and platinum agent.
Conclusion
Our analysis of this retrospective cohort is in accordance with the literature in respect of median age at diagnosis, gender predominance and outcomes, with the exception in terms of most frequent histological type in our series, the salivary duct carcinoma (estimated to represent only 1-3% of the salivary tumours), probably because our institution is a high-specialized oncology center.
Patients with advanced disease have worse survival, and only few patients were treated with palliative chemotherapy, making it difficult to draw conclusions.

PO-143 Salivary gland tumours: preliminary results of the Trento Protontherapy Centre
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Purpose or Objective
To report the initial experience in treating salivary gland tumors with protontherapy (PT)
Material and Methods
Between October 2014 and October 2016, 20 patients (pts) (10 M, 10 F) have been treated with PT. Median age at PT was 58.5 years (range,23-90). Median KPS was 90 (80-100). Stage was II: 2; III: 3, IVa: 11; IVb: 2; IVc: 1 and 1 benign pleomorphic adenoma. Parotid gland was involved in 8 cases, submandibular in 3. Minor sites were: maxillary sinus 6; hard palate 1; nasopharynx1; skull base 1. Pathology was: 10 adenoid cystic carcinoma, 6 mucoepidermoid carcinoma, 1 SCC, 1 adenocarcinoma ex pleomorphic adenoma, 1 pleomorphic adenoma, 1 other. Eight pts received one surgical resection, 5 pts 2 resections, 4 pts 3 resections. Three pts had biopsy only. Eleven pts were treated at their initial disease course, 7 in adjuvant setting (1 R0; 4 R1; 2 R2), 3 with definitive intent, one palliative. Nine pts were treated for recurrent disease, 5 with adjuvant intent (1 R0, 4 R1), 3 with radical intent, 1 palliative. Re-irradiation (Re-RT) was performed in 4 cases. Acute and late toxicities have been reported according to CTCAE scale version 4.0.
Results
Median follow-up was 6.1 months (range, 0-12.4). All pts but one completed their treatment without any break due to acute toxicity. Withdrawal from PT was for patient's personal conviction. PT was delivered in all cases with single field optimization-active scanning technique. Median definitive total dose was 69.3 Gy(RBE) (range, 60-70 Gy(RBE), median adjuvant dose 66 Gy(RBE) (range, 60-70.4 Gy(RBE). Pts receiving Re-RT had been previously irradiated at a median dose of 60Gy (range, 60-70 Gy). PT Re-RT median dose was 66 Gy(RBE) (range 60-70 Gy(RBE). In one case PT was given as the third RT course, to a radical dose of 70 Gy(RBE). No acute toxicity > grade 3 was observed. Grade 3 acute cutaneous toxicity was seen in 4 pts. Oral and sinonasal mucositis of grade 3 occurred in 2 pts. Other acute toxicities < grade 3 are listed in the table below. One diabetic patient experienced surgical wound dehiscence one month after PT completion. Cutaneous G1 late toxicity was seen in 3 pts, grade 2 in one pt, 2 patients developed oedema and fibrosis of the subcutaneous tissues and 1 pt cutaneous telangiectasia G1. Two cases of trismus G1 and one case G2. Two pts had necrosis of irradiated mucosa but it was limited to a little area in both cases. At the time of the analysis, 13 pts are free of disease, 4 pts have stable disease, 2 pts in local control developed distant metastasis, one pt (treated with palliative intent) died for local recurrence and distant metastases.

Acute Toxicity	Tot. pts	G1	G2	G3
Cutaneous	16	1	11	4
Mucositis	12	6	4	2
Wound dehiscence	1			1
Xerostomia	3	3		
Fatigue	2	1	1	
Conjunctivitis	5	4	1	
Otitis	5	2	3	
Alopecia	4	4		
Dysgeusia	2	1	1	

Conclusion

PT to treat salivary gland tumors showed to be feasible and safe; initial outcomes are encouraging. Longer follow-up is required to better evaluate the durability of local control and the possible development of late toxicities.

Poster: Special requirements for elderly patients

PO-144 Chronic radiation-associated dysphagia after curative reirradiation. Does age affect?

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Purpose or Objective
Chronic radiation-associated dysphagia (RAD) is a complex toxicity. The Total Dysphagia Risk Score (TDRS) was developed to predict which patients are most at risk to develop grade ≥ 2 dysphagia at 6 months following radiotherapy (RT). The mylo/geniohyoid complex (MHM) V69 (the volume receiving ≥69 Gy), , and superior constrictor muscle (SPC V70), especially in older patients (>62-years), were associated with chronic-RAD.Acute during the course of RT are strong prognostic factors for late
dysphagia. There is no effective treatment to reverse chronic-RAD in longterm survivors; and intensive and costly therapies are required for incremental gains in functionality.
We have the objective to study the incidence of chronic RAD in these head and neck recurrent tumors, previously irradiated, including patients (p) over 70 years old (y).
Material and Methods
We evaluated 57 p with recurrent disease, between 2005 to 2014. 27 larynx, 6 nasopharynx,12 oropharynx, 6 hypopharynx and 6 oral cavity. The initial dose received 50- 70 Gy(2-2.2Gy/fraction), 25/57 received radical radiotherapy,17 /57 radical chemoradiation; other adjuvant radiotherapy, of which 8 / 57 was combined with chemotherapy. In 24 / 57 nodal recurrence (N1-N2), local 18/57 (T2-T4),6/57 local+nodal recurrence, 9/57 seconds tumor, median age 58 year (range 42–79) . Reirradiation with external 3D conformal/IMRT techniques/ and dose: 50-70 Gy.
Results
The acute grade 2–4 RTOG dysphagia in week 6 (RTOG G2-4) was 75.4% (G2: 26/57, G3: 17/57). Of 57 p, 17 (29.8%) had chronic-RAD at 12 months (G2: 14/57, G3: 2/57 G4: 1/57). All of these patients had acute toxicity G3. After calculation of the TDRS, 7 patients(2 p <62 years old/ 5p ≥ 62 y (2p ≥ 70 y)), were classified in low-risk group (TDRS 0–9); 12 patients (4 p <62 years old/ 8 p ≥ 62 y (4p ≥ 70 y)),in intermediate-risk group (TDRS10–18) and 38 patients (13 p <62 years old/ 25p ≥ 62 y (12p ≥ 70 y)),in high-risk group (TDRS > 18). MHM V69 was ≥ 79.5% in all patients with chronic-RAD at 12 months, with median age 58 y, 68% ≥ 62 years (31.5% ≥ 70 years).
Conclusion
Aggressive treatment of this disease , allowing long survival, even in extensive disease is superior to best supportive care.
We have not seen a high incidence of severe damage in healthy tissues. TDRS can be used to predict chronic-RAD at 12 months (Grade ≥2), but also other relevant endpoints such as acute dysphagia during RT and MHM V69. In our series patients older ≥ 70 y, did not suffer more chronic toxicity dysphagia type.

PO-145 Definitive sequential radiotherapy in elderly patients with locally advanced oropharyngeal cancer

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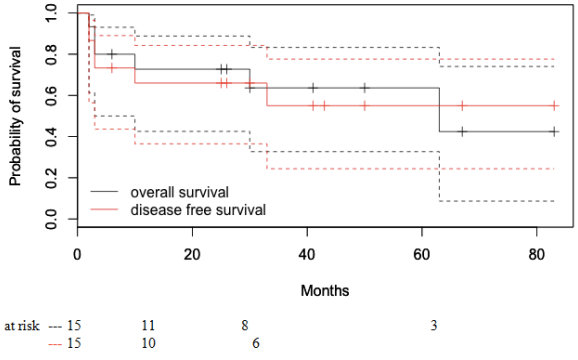
Purpose or Objective
To evaluate the treatment tolerance and long term follow-up data in patients aged 70 years and older with locally advanced oropharyngeal cancer treated by definitive sequential intensity modulated radiotherapy (IMRT).
Material and Methods
We retrospectively analysed 15 consecutive elderly patients, with histologically proven squamous cell carcinoma of the oropharynx, staged T3-4 with or without involved lymph nodes at diagnosis, who received definitive sequential IMRT (70 Gy; 2 Gy/fraction). Performance status (PS) and Adult Comorbidity Evaluation-27 (ACE-27) scores were calculated, and their influence on treatment tolerance and clinical outcomes was analysed. Overall survival (OS) and disease-free survival (DFS)were estimated according to Kaplan-Meier method and survival curves were compared using the log-rank test.
Results
A total of 15 patients were included with a median age of 77 years (range 70-88 years). At baseline, all patients had a PS score of 0, whereas 8 patients (53.3%) had an ACE-27 score of 1, and the remainders (n= 7, 46.7%) had a comorbidity index of 0.
All patients received the IMRT prescribed total dose. Two patients had a temporary RT interruption for a mean period of 5 days, due to severe toxicity. Globally, severe toxicity was recorded in 9 cases. Mucositis and oral pain were the most common acute side effects, classified as Grade 3 in 6 patients (40%) only. Xerostomia was reported in 13 patients (86.7%), without severe manifestation. There was no haematological toxicity. ACE-27 score was not related to higher severe acute toxicity. No patients experienced grade ≥ 3 late toxicity.
Two and 5-year OS were estimated at 72.7% (95% confidence interval [CI] 0.425 - 0.888) and 63.6% (95% CI 0.327 - 0.833), respectively. Two and 5-year DFS rates were66% (95% CI 0.365 - 0.843) and 55% (95% CI 0.244 - 0.776), respectively. Figure 1 showed Kaplan Meier curves of OS and DFS. Comorbidity score did not influence survival outcomes, both OS (p = 0.46) and DFS (p = 0.55).

Figure 1. Kaplan Meier curves of overall survival and disease free survival



Conclusion
Treatment tolerance, as well as survival outcomes were good in elderly oropharyngeal cancer patients treated with definitive sequential IMRT. Due to age and comorbidity, no dose or volume reduction for IMRT should be considered in this setting of patients. A prospective

randomized trial with a large sample size should be conducted to confirm our results.

PO-146 Radiotherapy in elderly patients aged ≥ 70 years with head and neck squamous cell carcinoma

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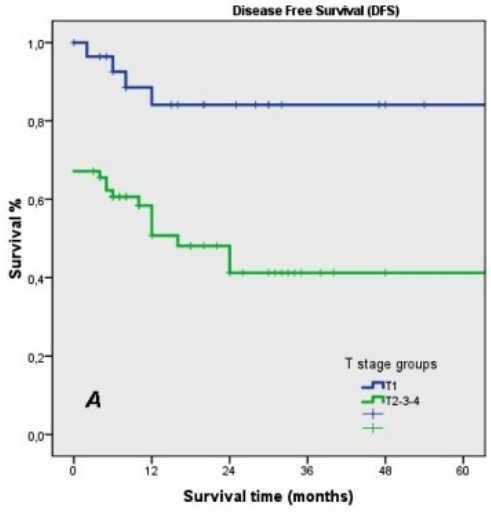
Purpose or Objective

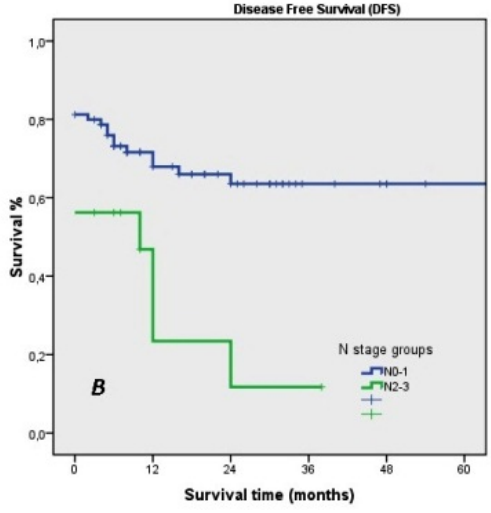
To review survival outcomes and analyse the treatment tolerance in elderly patients aged ≥ 70 years with head and neck squamous cell carcinoma (HNSCC) treated with radiotherapy (RT).

Material and Methods

Patients aged ≥ 70 years treated with radiotherapy between 2005-2016 for HNSCC were retrospectively identified. 2D conventional and 3D conformal radiotherapy technique was used until 2015, and subsequently patients were treated with IMRT. Outcome measures were 1 and 2 year disease free survival (DFS), and overall survival (OS). Univariate and multivariate analyses was performed for survival outcomes.

Results





A total of 96 consecutive ≥70 years and patients were identified. Median follow up was 26 (range 3-125) months. Median age was 78 years (range 70-97). 77/96 (80%) were male and 30/96 (31%) were ≥80 years old. The primary tumour location was larynx 63 (66%), pharynx 12 (13%), oral cavity 11 (12%), other 10 (9%). Breakdown of TNM stage were: T1 29 (30%), T2 15 (16%), T3 23 (24%), T4 29 (30%), N0 69 (72%), N1 11 (12%), N2 13 (14%), N3 3 (2%). Surgery involved in 25 (26%) patients followed by adjuvant RT. Curative RT was delivered to 61/96 (64%) patients with median 66 (range 62-70) Gy and palliative RT were to 10/96 (10%) patients with median and 30 (range 30-39) Gy. 2D conventional, 3D conformal technique and IMRT were used in 11 (12%), 60 (62%) and 25 (26%) patients respectively. Concurrent platinum chemotherapy was given to 6 (6%) of patients. Acute toxicity was seen in 86 (90%) patients (grade-1 75%, grade-2 10%, grade-3 5%). Median 3 (range 1-10) days off in the treatment in 61 (64%) patients. 82/96 (85%) patients completed their RT scheme without any interruption.

71 (74%) patients experienced complete response. 1 and 2 years DFS for the all cohort was 61% and 56%, and OS was 84% and 78%, respectively. Radiotherapy technique did not significantly affect the survival. In univariate analysis, gender (female, p=0.01), advanced T stage (T2-4, p=0.001) and N stage (N2-3, p=0.003) for DFS, and older age (≥80 years, p=0.008), and advanced N stage (N2-3, p=0,01) for OS had found the negative impact (Figure 1). Stage 2-4 disease was found a poor prognostic factor for DFS in multivariate analysis (p<0,05, Exp(B)=0,190, 95% CI for Exp(B)=0,065-0,556).**Conclusion**

Radiotherapy provides high rates of tumor control and survival with reasonable toxicity, although the very low concurrent chemotherapy usage in elderly patients aged ≥70 with HNSCC. Radiotherapy requires careful schedule selection and follow-up in elderly patients aged ≥ 80 years.

PO-147 The ELAN program: Customised treatment of SCCHN elderly patients according to geriatric assessment

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Purpose or Objective

Thirty percent of SCCHN occur in patients (pts) more than 70y; the main challenge in these pts is to balance the benefit/risk treatment ratio regarding tumor related symptoms. However, these pts are usually excluded from

trials. We developed a large prospective clinical program planned to enroll 448 pts not suitable for surgery in 3 distinct trials to improve the multidisciplinary management of elderly SCCHN pts. The main objectives of this study are to demonstrate that a geriatric evaluation is feasible in daily practice for SCCHN pts and to improve older adults' treatment by setting standards of care in this population.

Material and Methods

To be enrolled in one of the three trials, elderly SCCHN pts must first enter the ELAN-ONCOVAL study, which aims to classify pts as fit or unfit using an adapted geriatric evaluation usable in daily practice by oncologists. G8 score is also done, and Comprehensive Geriatric Assessment (CGA) is optional.

Fit pts with recurrent and/or metastatic (R/M) SCCHN may enroll onto a phase II trial evaluating the clinical benefit of cetuximab/carboplatin/5FU (EXTREME regimen) as first line treatment (ELAN FIT-NCT01884623). Eighty pts are planned to demonstrate efficacy (objective response at 12 weeks) and safety (absence of grade ≥ 4 toxicity and preservation of autonomy) of treatment. Unfit R/M pts may enroll onto a randomized phase III trial of cetuximab (500mg/m^2 every 2 weeks) or methotrexate (40 mg/m^2/week) monotherapy as first-line therapy (ELAN UNFIT-NCT01864772). The main endpoint is failure free survival (defined as death, progression, treatment stop or loss of at least 2 points in ADL scale). Hundred and sixty-four pts are planned.

In curative situation, unfit pts may enroll onto a randomized, non-inferiority trial comparing standard radiotherapy (70Gy, 35 fractions, 7 weeks) and hypofractionated split course schedule (30Gy in 10 fractions, 2 weeks stop, 25Gy in 10 fractions, total 6 weeks). Main endpoint is the rate of alive pts with local control 6 months after treatment. Two hundred and two pts are planned to be randomized (ELAN-RT-NCT01864850).

Assessments of efficacy, toxicity, autonomy (ADL, IADL scales) and health related quality of life (EORTC QLQ-C30 and HN35 questionnaires) are performed in clinical trials.

Results

Inclusions are underway since June 2013. Currently, 58 centers are opened in France. Four hundred and thirty-one pts are registered in ELAN ONCOVAL study. At now, 80% of geriatric evaluation has been done by physicians, and CGA performed for 52% of pts. Approximately 55% have been then enrolled in a clinical trial: ELAN-RT (125, 61.9%), ELAN-FIT (57, 70%), ELAN-UNFIT (57, 34.7%). Interim safety analysis of ELAN FIT study did not reveal safety issues.

Conclusion

Just over half of the program, we are already experiencing a strong support of the french medical community to geriatric assessment of elderly SCCHN pts. Based on ELAN consortium, pts may benefit from adapted care and innovation.

PO-148 Hypofractionated radiotherapy for head and neck cancer patients unfit for standard treatment

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Purpose or Objective

With prolongation of life expectancy the proportion of elderly HNSCC patients is also increasing with most cases occurring in the sixth or seventh decade of life. The purpose of our study was to report on the toxicity and response to moderately hypofractionated, "involved-field" radiotherapy (HIRT) in patients deemed unfit to receive standard curative treatment due to impaired, baseline performance status and/or high burden of comorbidity whit a palliative regimen that provide symptom control, minimal treatment-related toxicity and improve quality of life (QoL).

Material and Methods

A total of 34 patients affected by HNSCC treated with HIRT were included in or analysis. Patients treated at the Radiation Oncology Unit of the University of Florence between December 2011 and July 2016 was retrospectively analyzed. At clinical evaluation, HIRT was selected when patients were considered unsuitable for standard treatment with curative intent (concurrent CTRT or high-dose, conventionally fractionated radiotherapy). In 50% of cases the disease was localized in the oral cavity; in 15% at the level of the oropharynx and 20% larynx; in 15% in the nasopharynx, salivary glands, skin and soft tissues. The dose/fractionation prescribed in all cases was 40 Gy/2.5 Gy per fraction delivered to gross tumor and nodal disease without inclusion of elective target volumes. Acute toxicity was scored according to NCI – CTCAE v.4. Clinical assessment was performed at 25 days from the end of treament, while response to treatment was evaluated between 45 and 60 days with appropriate morphologic and/or metabolic imaging. Progression-free survival (PFS) was calculated from the end of treatment to the date of first event of disease progression

Results

All patients are evaluable for acute toxicity assessment while clinical outcome has been analyzed in 32/34 (94%) patients, with a median follow-up of 6 months (range 2-45). Median age of the cohort was 77,5 years (48-91). The majority of patients underwent 3-D conformal radiotherapy, namely 29/34 patients (85%), while in 4 cases (15%) IMRT was delivered. Only one patient didn't complete HIRT due to worsened clinical conditions at 32.5 Gy. In terms of acute toxicity, the rate of G2 mucositis and dysphagia were 29% and 23,5%, respectively; the G3 rate were 18% and 6%. No G4 toxicity was reported. Early efficacy assessment was favorable: absence of local progression was achieved in 26 patients (76%): complete response was attained in 3 case (9 %), partial response in 16 (47%) and stable disease in 3 (9%), respectively.Median PFS was 6 months (range 2 – 45). 20 of 34 patients (59%) were alive at last follow

Conclusion

In our experience, HIRT was associated with a favorable acute toxicity profile and proved to be effective in terms of local disease control. Longer follow-up is needed to confirm the long-term benefit and to evaluate the incidence of late toxicity in this frail cohort of patients

PO-149 Survival outcomes for very elderly patients after definitive radiotherapy for head and neck cancer

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Purpose or Objective

At our institution between 2011 and 2015, 25% and 6% of radically treated head and neck cancers were respectively in patients aged ≥70 and ≥80 years. There is lack of trial data describing clinical outcomes for these patient groups. This retrospective review describes our experience in patients aged ≥80 years.

Material and Methods

62 patients aged ≥80 years with oropharynx, larynx, hypopharynx and oral cavity squamous cell carcinoma treated with definitive radiotherapy between January 2011 and December 2015 were included. All patients were

staged using cross-sectional imaging. Early laryngeal cancers (T1N0) were excluded. A retrospective chart review determined patient demographics, tumour and treatment factors. Survival analysis was performed using the Kaplan-Meier method, and comparisons between groups used the log rank test.

Results

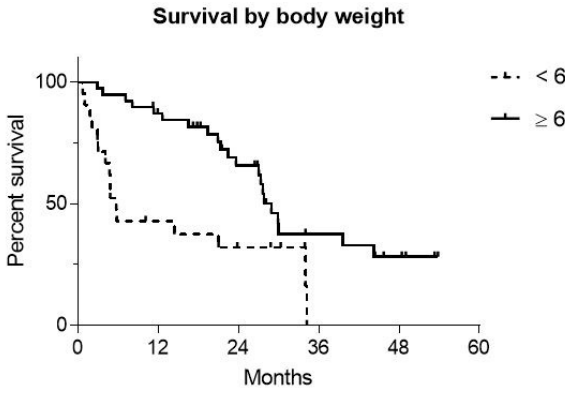
Median age was 82 years (range 80-92). Patient demographics are shown in Table 1. 42 (68%) had stage III-IVb disease. Radiotherapy was delivered using volumetric modulated arc therapy (VMAT), 5-7 field intensity modulated radiation therapy (IMRT), or conformal technique. Prescribed doses were: 52.5-55Gray in 20 fractions and 60-66Gray in 30 fractions. Two (3%) patients received synchronous cetuximab and two (3%) were treated in the NIMRAD trial (+/-synchronous nimorazole). Four (6%) had a neck dissection prior to radiotherapy.

Eight (13%) were electively treated as inpatients. Six (10%) did not complete radiotherapy: four (6%) due to co-morbidities and two (3%) due to poor tolerability. 43% patients required acute admissions for nutritional support and symptom control. Fourteen (44%) required tube feeding prior to treatment and an additional 17 (27.4%) commenced enteral feeding during radiotherapy. The median enteral tube feeding duration was 3 months.

Grade 2-3 mucositis occurred in 28 (60%), and Grade 2-3 skin reactions in 21 (57%) patients.

Median overall survival was 27.3 months (range 0.7-62.4m); and 2-year overall survival was 57%. There was a non-significant trend towards improved survival with performance status (PS) 0-1 compared to PS 2-3, (28.9m v 21.0m, p=0.1372). Patients who initially weighed <60kg at start of radiotherapy had significantly worse survival than those ≥60kg (5.7m v 28.9m, p=0.0033).

Table 1: Patient Demographics		Number	Percentage
Sex	Male	42	67.7
	Female	20	32.3
Performance Status (PS)	0	9	14.5%
	1	31	50%
	2	14	22.6%
	3	4	6.5%
	Unknown	4	6.5%
Comorbidity score (ACE27)	0	8	12.9%
	1	24	38.7%
	2	24	38.7%
	3	5	8.0%
	Unknown	1	1.6%
Smoking Status	Never smoker	13	21.0%
	Ex-smoker >1yr	33	53.2%
	Ex-smoker <1yr	3	4.8%
	Current smoker	7	11.3%
	Unknown	6	9.7%
Alcohol Intake	Never heavy	44	71.0%
	Previous heavy	3	4.8%
	Current heavy	1	1.6%
	Unknown	14	22.6%
Site	Larynx	25	40.3%
	Oropharynx	18	29.0%
	Hypopharynx	13	20.9%
	Oral cavity	6	9.7%
Stage	1	2	3.2
	2	18	29.0
	3	15	24.2
	4 a	24	38.7
	4 b	3	4.8



Conclusion

We show promising survival outcomes in very elderly patients treated mainly with radiotherapy alone for head and neck cancer. We note poor survival outcomes associated with low pre-treatment weight. Optimisation of nutritional status may be an important factor to improve outcomes for this patient group.

PO-150 Age ≥70 is not an adverse prognostic factor for accelerated radiotherapy in head and neck cancer

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Purpose or Objective

Based on meta-analysis it is stated that accelerated fractionation for patients with intermediate staged head and neck cancer above an age of 70 years has no benefit, with however an increased risk of complications, compared to patients younger than 70. In a large dataset we evaluated the prognostic significance for outcome of age in a group of patients with a WHO performance status of 0 to 1 .

Material and Methods

Since 1998 we treat advanced T2 glottis (based on volume and/or impaired mobility of the vocal cord), T2 supraglottis , T3 glottis/ supraglottis, T2/ T3 hypopharyngeal cancer, including nodes smaller than 3 cm, with accelerated fractionation. A dose of 47 Gy is given in 10 fractions of 2 Gy, followed by 15 fractions of 1.8 Gy, week 3-5, on the primary tumor and the elective neck levels. A boost dose of 22.5 Gy in 15 fractions of 1.5 Gy is given as a first daily fraction in week 3-5, at least 6 hours before the second fraction. Results have been published previously[1]. Until July 2014, 310 patients were treated with this schedule with a minimum follow-up of 2 years, median FU 5 years. Eighty-two patients were ≥ 70 years (O) (70-87, median 75), WHO performance 0-1, 228 < 70 years (Y) (32-69, median 59). Distribution of T-stage was for T2, T3 and T4, 59%, 30%, and 8%, respectively.; 35% was N+. Distribution of prognostic factors was equal for gender and Stage. Distribution of tumor location was larynx, hypopharynx, and oropharynx in 77% vs. 79%, 11% vs. 16%, and 12% vs. 5%, for group O and Y respectively. A smoking history was positive in 99% and 87 % for Y vs. O (p=sign.). Continuation of smoking occurred in 39% vs. 11% respectively (p=sign.)

Results

Five years local recurrence e free survival was 86% vs. 84% for Y vs. O (p=n.s.). Actuarial 5 years disease free survival

was 77% vs. 79%, for Y vs. O, respectively. Local control was significantly correlated with T stage (T2 89%, T3 80%, T4 56%), mobility of the vocal cord (87%, 90% and 71% for normal, impaired, and fixed cord, respectively). In multivariate analysis the only independent prognostic factor for local control was T-stage.
Tube feeding during treatment was given in 24%, equal for both age groups. Severe late toxicity (PEG tube and/or tracheotomy dependency) after 2 years was 10% and 12% for Y and O respectively. In multivariate analysis severe late toxicity was related to yes or no tube feeding dependency during treatment, need for tracheotomy or debulking before treatment, and field size.
Conclusion
In this large group of patients treated with accelerated fractionation for intermediate size head and neck tumor age ≥ 70 was not a negative prognostic factor for local control, disease free survival and risk of complications. For patients ≥ 70, with a WHO performance 0-1 with our fractionation schedule excellent outcome is shown.
1: Terhaard CH, Kal HB, Hordijk GJ. Int J Radiat Oncol Biol Phys. 2005 May 1;62(1):62

Poster: Immunodiagnosis and immunotherapy

PO-151 Immunotherapy for refractory brain metastasis in cases of oropharangeal squamous cell carcinoma
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Purpose or Objective
To investigate the efficacy and tolerability of checkpoint inhibition in cases of progressive CNS/brain metastasis from squamous cell carcinoma of the head and neck after optimal radiation therapy.
Brain metastasis from head and neck squamous cell carcinoma (HNSCC) is a unfortunately clinical entity and can occur in HPV positive as well as smoking associated, HPV negative HNSCC. Disease progression after optimal radiation therapy to the sites of brain metastasis is difficult to control and has almost no viable therapeutic options. These patients are often recommended hospice based supportive care only. Herein, we investigate and report the case series of the first 3 patients with disease progression post-optimal radiotherapy revealing disease control beyond median of 6 months utilizing systemic immunotherapy with pembrolizumab (Ketruda^{R}, Merck).
Material and Methods
Institution approved, compassionate access program guided therapy utilizing pembrozulimab (Ketruda) at 2mg/kg every 3 weeks until disease progression or intolerable toxicity.
Results
We report a case series of the first 3 patients treated with metastatic squamous cell carcinoma of oropharynx with brain metastasis in our institutional protocol. Patients were treated upon disease progression in CNS post optimal radiotherapy. Two patients had HPV negative, smoking associated primary HNSCC prior to development of systemic relapse and CNS metastasis and one patient had HPV positive primary HNSCC. One smoking associated HNSCC patient has stayed on continuous therapy beyond 1 year with no CNS or systemic disease progression and with radiographic evidence of CNS disease regression. Two other patients have stayed on therapy for 9 and 6 months respectively, with one experiencing disease progression at the 7th month of therapy. Overall disease control rate & data from further patients enrolling this study will be reported in this small case series. The first 3 patients have a median time to disease progression of over 8 months, which is unprecedented in these clinical settings. Responses are seen irrespective of PD-1 staining, but all three patients had a gene signature of high tumor mutation burden (TMB).
Conclusion
Checkpoint inhibitors may have a large role to play as salvage therapy or as maintenance post primary radiotherapy for CNS metastasis from HNSCC. Disease control is seen so far in smoking and HPV associated HNSCC brain metastasis. Tumor mutation burden has been found to predict clinical disease control, rather than IHC for PD-1 or PDL-1 in our single instruction case series. Further clinical trials of immunotherapy for CNS metastasis from HNSCC is warranted.

Author Index

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