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THURSDAY 12 FEBRUARY 2015

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Keynote lecture:

SP-001
The evolving role of surgery and the surgeon in the treatment of head and neck cancer
R. Weber1
1University of Texas MD Anderson Cancer Center, Department of Head and Neck Surgery Division of Surgery, Houston, USA

Head and neck cancer is a rare and complex disease due to the heterogeneity of sites, stage, histologies, and treatment required to achieve, cure, and preserve or restore form and function. The surgeon’s role in the treatment of head and neck cancer is evolving in parallel to the emergence of non-surgical organ preservation strategies. The head and neck surgeon remains the leader of the multidisciplinary team of providers who are charged with providing coordinated, interdisciplinary care to these patients. The surgical clinic is usually the intake point for the newly diagnosed head and neck cancer patient. The surgeon is responsible for diagnosis, staging and coordination of care. A surgeon also frequently leads the Multidisciplinary Tumor Conferences where final treatment decisions are made. Although non-surgical modalities have become more prevalent for the treatment of upper aerodigestive tract cancer, long term toxicities are creating the need for re-examination of the role of surgery for these patients as perhaps a strategy to “de-intensify” therapy and reduce long term morbidity. Coupled with new image guidance and robotic technology, surgery has become more precise and potentially less functionally debilitating. When coupled with radiation, upfront surgery may allow radiation dose reduction or obviate the need for concurrent chemo-radiation particularly for HPV related oropharyngeal cancer patients. This presentation will focus on the current and re-emerging role of surgery for the treatment of head and neck cancer and how this modality is integrated into evolving treatment paradigms.

Keynote lecture: Novel opportunities in cancer immunotherapy

SP-002
Novel opportunities in cancer immunotherapy
G. Coukos1
1University Hospital Lausanne (CHUV), Department of Oncology, Lausanne, Switzerland

Immunotherapy of cancer is presently one of the areas where major medical breakthroughs are witnessed, with dazzling results reported by several groups recently. Two approaches stand out: On one hand, neutralizing antibodies that disable key inhibitory receptors regulating T lymphocyte function, such as CTLA-4 and PD-1, enable the potent activation of effector T cells against tumors. On the other hand, the adoptive transfer of autologous tumor-infiltrating lymphocytes (TILs) has been successful in melanoma, but could find applications in other tumor types as well. A major breakthrough in T cell engineering relates to the development of autologous engineered T cells generated ex vivo through the insertion of exogenous receptors that recognize cancer cells, such as cloned T cell receptors (TCRs) or chimeric antigen receptors (CARs). Although successful in many patients, these powerful therapies do not work in others. There is an acute need therefore to understand the factors affecting response to immunotherapy. The microenvironment of tumors with pre-existing TILs is conducive to T cell homing. Thus, in these tumors, a main barrier to successful immunotherapy is T cell function rather than homing. Checkpoint blockade therapy seems a rational approach in this patient subset, and combinatorial approaches aimed at correcting multifactorial T cell suppression are expected to enhance the efficacy of checkpoint blockade. Lack of TILs denotes a tumor microenvironment that is prohibitive to T cell homing, which may be due to the establishment of a vascular endothelial barrier, deregulation of chemokine expression etc. Pharmacologic intervention to reverse these mechanisms will be necessary to allow successful engraftment of T cells in these tumors.

Proffered papers: New data from randomised trials

OC-003
What is the best treatment in nasopharyngeal carcinoma?
An individual patient data network meta-analysis
1Institut Gustave Roussy, Radiation Oncology, Villejuif, France
2Pamela Youde Nethersole Eastern Hospital, Radiation Oncology, Hong-Kong, China
3Institut Gustave Roussy, Biostatistics, Villejuif, France
4Sun Yat Sen University Cancer Center, Radiation Oncology, Guangzhou, China
5Sir YK Pao Centre for Cancer The Chinese University of Hong Kong, Medical Oncology, Hong-Kong, China
6Sun Yat-sen University Cancer Center, Radiation Oncology, Guangzhou, China
7Fudan University, Radiation Oncology, Shanghai, China
8CHUV, Radiation Oncology, Lausanne, Switzerland

Purpose/Objective: The individual patient data (IPD) meta-analysis (MA) from the MAC-NPC collaborative group (Meta-Analysis of Chemotherapy [CT] in NasoPharynx Carcinoma) has been recently updated and presented (ASCO 2014 Abstract #6012). There was a significant benefit in favor of CT regarding overall survival (OS) (hazard ratio (HR) [95% confidence interval]: 0.79 [0.72; 0.86], p <0.0001; absolute benefit at 5 years=6.4%), with a median follow-up of 7.1 years. However it was not possible to evaluate which treatment was the best due to the use of standard MA methods. Network meta-analyses (NMA) allow one to perform simultaneous inference regarding all treatments and select the best among them. The aim of this work is to present the results of the NMA planned in the MAC-NPC protocol.

Materials and Methods: Trials of radiotherapy (RT) with or without CT in patients with non-metastatic NPC were identified and updated IPD obtained. Overall 19 trials and 4,806 patients were included. We applied NMA models to the MAC-NPC database. Fixed- and random-effect models were applied, and network inconsistency was evaluated. No inconsistency was observed. Adding random-effects did not improve fixed effect model. Therefore only fixed effect model analyses are presented here. Treatment were grouped in the following categories: RT alone (RT), induction chemotherapy followed by RT (IC-RT), induction chemotherapy followed by concomitant chemoradiotherapy (IC-CRT), concomitant chemoradiotherapy (CRT), concomitant chemoradiotherapy followed by adjuvant
chemotherapy (CRT-AC) and RT followed by adjuvant chemotherapy (RT-AC). The trial network is represented below. The size of the connector is proportional to the number of trials/patients in the comparison.

Results: For the entire network, CRT-AC ranked the best treatment regarding OS with a probability of 94%. Hazard ratio [95% Credible Interval] of OS for CRT-AC was 0.64 [0.55; 0.74] compared to RT alone and 0.82 [0.66; 1.01] compared to CRT. The probability of CRT-AC being the best treatment regarding the other endpoints was 72%, 75% and 16% for progression-free survival (PFS), locoregional failure-free survival (LRFFS) and distant metastases-free survival (DMFS) respectively. The probability that either CRT-AC or IC-CRT (i.e. CRT + CT given at another timing) is the best treatment was 97%, 96%, 81% and 93% for OS, PFS, LRFFS and DMFS respectively. When the network is restricted to cisplatin-based trials as a sensitivity analysis, CRT-AC and IC-CRT remain the two best treatments regarding OS and PFS (with respective probabilities of 53% and 44% for OS and 35% and 61% for PFS, compared to less than 3% for all other treatments).

Conclusions: This network meta-analysis of the treatment of nasopharyngeal carcinoma suggests that the addition of AC or IC to CRT may improve further the tumor control probability and patient survival over CRT alone. These exploratory results should be confirmed by large power randomized trials and interpreted with respect to clinical relevance for a given patient.

OC-004
A randomized trial of concomitant cisplatin-RT +/- induction TPF in locally advanced nasopharyngeal carcinomas
J. Daoud, A. Aupérin, Y.G. Tao, P. Lang, X.S. Sun, S. Racadot, J. Thariat, M. Alfonsi, C. Tuchais, A. Moussai, A. Cornely, J. Bourhis
1University Hospital, Radiation Oncology, Sfax, Tunisia
2Institut Gustave Roussy, Radiation Oncology, Villejuif, France
3Hôpital Pitié Salpêtrière, Radiation Oncology, Paris, France
4CHU Besançon, Radiation Oncology, Besançon, France
5Centre Léon Berard, Radiation Oncology, Lyon, France
6CAL, Radiation Oncology, Nice, France
7Clinique St Catherine, Radiation Oncology, Avignon, France
8Loire Hospital, Radiation Oncology, Angers, France
9Lausanne University Hospital (CHUV), Radiation Oncology, Lausanne, Switzerland

Background: Concomitant radio-chemotherapy CT/RT is a standard treatment in locally advanced nasopharyngeal carcinomas (NPC). The potential added value of induction chemotherapy before CT/RT remains to be studied and was tested in the current randomized trial.

Methods: Patients with locally advanced stage II-IVA NPC were randomized to induction taxotere-cisplatin-5FU (TPF) 2 cycles and a third cycle in case of tumor response followed by concomitant CT/RT (40 mg/m2 of cisplatin weekly) versus the same CT/RT without induction TPF. Radiotherapy delivered 70 Gy in 7 weeks with conventional fractionation in both arms. The primary endpoint was Progression Free Survival (PFS). The study was designed to detect a HR of 0.53, corresponding to a 17% absolute difference in 3-year PFS rate between the 2 arms, from 58% to 75%, with 85% power and alpha two-sided error rate of 0.05. The inclusion of 260 patients was required (88 events required). The secondary endpoints were overall survival (OS), time to loco-regional progression, time to distant metastasis, tumor response (RECIST), acute and late toxicity (NCI-CTC V3 and RTOG classification). The randomization was performed by minimization on center, N stage (N0-1 vs N2-3), RT type (IMRT vs not IMRT). The follow-up period duration must be of at least 3 years.

Results: Due to poor accrual, an early stopping of the trial was done after the inclusion 83 patients. 42 patients and 41 patients were randomized respectively in the induction-CT/RT and in the CT/RT arm, between January 2009 and July 2012 by 8 centers. Full results will be presented at the meeting, including side effects along with the PFS, loco-regional and distant progression rates, and overall survival and tumor response rates by treatment arms. The tumor response rate after induction CT will be given for the induction-CT/RT arm.

Conclusions: Despite the early stopping, this randomized trial is one of the very few trials evaluating the effect of induction chemotherapy before concomitant CT/RT in locally advanced NPC. This will provide important EBM level 2 results that could be later potentially integrated in future meta-analysis of randomized trials.
Concomitant treatment (CRT or cetuximab/RT) with or without induction TPF in Locally Advanced head and neck Cancer M.G. Ghil1, A. Paccagnella2, D. Ferrari3, P. Foa4, M. Cossu Rocca5, E. Verri5, F. Morelli6, G. Azzarello7, C. D’Ambrosio8, C. Casanova9, M. Guaraldi9, E. Massa9, C. Rossetto10, A. Bonetti11, S. Siena12, A. Frattegiani13, H. Koussis14, G. Pieri15, A. Gava16, I. Floriani17, For the GSTTC Italian Study Group 1Ospedale SS Giovanni e Paolo, Medical Oncology, Venezia, Italy 2San Paolo Hospital, Medical Oncology Unit, Milano, Italy 3Medical Oncology Unit of Urogential and Head and Neck Tumors, European Institute of Oncology, Milano, Italy 4IRCCS Casa Sollievo della Sofferenza, Medical Oncology, San Giovanni Rotondo, Italy 5Azienda ULSS 13, Internal Medical Sciences, Mirano, Italy 6University Hospital, Oncology, Modena, Italy 7Azienda USL, Medical Oncology, Ravenna, Italy 8Policlinico Sant’Orsola-Malpighi, Medical Oncology, Bologna, Italy 9Azienda Ospedaliero Universitaria, Internal Medical Science, Cagliari, Italy 10University Hospital, Oncology, Udine, Italy 11Mater Salutis Hospital-AULSS 21 della Regione Veneto, Legnago, Italy 12Niguarda Ca’ Granda Hospital, Milano, Italy 13Azienda Ospedaliera, Radiation Therapy, Perugia, Italy 14Istituto Oncologico Veneto - IRCCS, Padova, Italy 15Ospedali Riuniti di Trieste, Oncology, Trieste, Italy 16Ospedale Cà Foscari, Radiation Therapy Department, Treviso, Italy 17Laboratorio Trials Clinici, Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy

Background: Platinum-based CRT is the standard treatment of Locally Advanced Head and Neck Squamous Cell Carcinoma (LASCCHN). Cetuximab/RT (CET/RT) is superior to RT alone
and it is an alternative treatment to CRT as no phase III studies comparing these 2 strategies are available so far. Induction TPF resulted to be superior to cisplatin/5fluorouracil but its efficacy when added to concomitant treatment is to be demonstrated. This open-label multicenter 2×2 factorial study (NCT01086826) was designed to assess two primary endpoints: the overall survival (OS) of induction vs. no induction and the Grade 3-4 in-field mucosal toxicity of CRT vs. CET/RT.

Methods: 421 patients with LASCCHN of the oral cavity, oropharynx, hypopharynx, stage III-IV, ECOG PS 0-1 were randomized to one of four treatment options: Arm A1: CRT (2 cycles of cisplatin/5fluorouracil concomitant to standard RT fractionation); Arm A2: CET/RT; Arm B1: 3 cycles of TPF followed by the same CRT; Arm B2: 3 cycles of TPF followed by CET/RT. The superiority hypothesis of OS comparison of TPF induction vs. no induction (Arms B1+B2 vs. A1+A2), requires 204 deaths to detect a relative reduction of 33% with 2-sided 5% significance level for the log-rank test and a power of 80%.

Results: 414 out of 421 patients were finally analyzed: 206 in induction and 208 in concomitant arm. At a median follow-up of 45 months 240 events for PFS and 204 deaths were observed.

Median PFS was 30.5 mos in induction vs 19 mos in concomitant arm with a 3-year PFS of 47.2% vs 38.8% (HR: 0.74; 95%CI 0.58-0.96; p=0.024), respectively. Median OS was 54.7 mos in induction vs 31.7 mos in concomitant arm with a 3-year OS of 57.5% vs 46.4% (HR: 0.74; 95%CI 0.56-0.97; p=0.031) respectively. Compliance to concomitant treatments was not affected by induction TPF.

Conclusions: Induction TPF followed by CRT or CET/RT significantly improved PFS and OS (independently from the type of concomitant strategy) in LASCCHN patients without compromising compliance to the concomitant treatments.

OC-007
Is accelerated radiotherapy alone equivalent to chemoradiation in patients with moderate advanced HNSCC?

K. Skladowski1, A. Wygoda1, M. Snetura2, T. Rutkowski1, L. Michealecki1, A. Heyda1, A. Hajduk1, M. Kentnowski1, B. Lukaszczyk-Widel1, B. Maciejewski1
1Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology I Dept, Radiation Oncology and Chemotherapy, Gliwice, Poland
2Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology I Dept, Cancer Pathology, Gliwice, Poland

Purpose/Objective: The current indication for radiation therapy alone with altered fractionation regimens in patients with head and neck squamous cell cancer is not known. On the one hand - an indirect comparison with concurrent chemoradiation (CCR), based on existed meta-analyses, suggests that CCR has yielded a larger survival benefit than that achieved with AF, on the other - this benefit is seen predominantly in locally more advanced HNSCC (T3-4, N2-3), thus AF is believed as a reasonable treatment for patients with less advanced disease, or patients who are not suitable for chemotherapy. To study that problem we have conducted the randomized trial directly comparing CCR with accelerated radiotherapy alone (ARA).

Materials and Methods: Over 5 years (2008-13) consecutive 101 pts with oropharynx (46), hypopharynx (19) and larynx (36) cancer in moderate clinical stage, i.e. T2N2 (29), T3N2 (56) and T4N2 (16), with N+ limited to less or equal 3 cm in diameter, have been randomizing and treating by ARA (53) or CCR (48). ARA was delivered by 7 fractions of 1.8 Gy per week to 72 Gy in 40 fractions over 49 days was combined with 3 courses of cisplatin (100 mg/m²/d on day 1, 22 and 43). All OPC pts had examined HPV status. Radiation was delivered to all pts as an IMRT/IGRT.

Results: Median follow-up is 40 months. In CCR the number of administered cisplatin courses was as follows: 1 in 5 pts. (10%), 2 in 30 pts. (62%) and 3 in 13 pts. (28%). HPV status was evaluated as positive (+ve) in 11 (29%) and negative (-ve) in 35 (71%) OPC pts. The actuarial rates of 3-year OS and DFS are respectively, 58% and 56% for ARA compare to 79% and 73% for CCR (p=0.02 and p=0.05, respectively). Both OS and DFS were worse in ARA arm as a consequence of higher rates in: primary and neck failures, distant metastases and comorbidity deaths (25%, 9%, 9% and 9%, respectively), compare to CCR arm (14%, 6%, 4% and 4%, respectively). In CCR arm DFS rate was 77% for pts who received 2 or 3 courses of cisplatin and 50% for those who received 1 course only. Sub-site analysis revealed that benefit of CCR was disappeared only in pts with T1 and HPV+ve tumors - all HPV+ve OPC pts remain alive with no cancer failure, whereas OS for HPV+ve pts was 55% in ARA and 78% in CCR. There are no significant differences between the trial arms in acute and late toxicity, as well as, in quality of life, except of better social functioning in CCR pts.

Conclusions: 3-year results of the trial have proven that CCR takes an advantage over ARA in pts with MAHNSCC - CCR with conventional 7 weeks fractionation and, at least, 2 courses of cisplatin is more effective than ARA with 6 weeks. The only treatment target for ARA could be now the population of HNSCC pts with: stage T1, moderate stage HPV+ve OPC and contraindication to cisplatin.
Material and methods: Patients with HNSCC treated with curative surgery and with high risk factors for locoregional recurrence (i.e., positive surgical margins and/or extranodal spread) were randomly assigned to receive either standard postoperative radiotherapy (SPORT) at 2 Gy/fraction/day, 5 days/week to 66 Gy/33 fractions/7 weeks or postoperative accelerated radiotherapy (POPART) with 2 Gy/fraction/day, 5 days per week, to 20 Gy followed by 1.8 Gy/fraction/day and 1.3 Gy/fraction per day to a boost field as a second daily treatment to 66.5 Gy/40 fractions/5 weeks. The primary endpoint was locoregional tumor control (LRC). Secondary endpoints were overall survival (OS), progression-free survival (PFS), acute and late toxicity and quality of life.

Results: From November 2004 to August 2009, 148 patients were enrolled in the study (74 pts for SPORT and 74 pts for POPART). The median follow up time was 6.2 years. The two study-arms were well balanced with regard to the most important prognostic factors. No significant differences were noted with regard to acute and late toxicity, although there was a trend towards more use of pain medication among patients treated with POPART. At 3 years, the LRC rate was 76.5% (95% CI: 67.8-87.4) after POPART compared to 74.2% (95% CI: 64.6-85.0) with SPORT (HR: 0.75, CI 0.40-1.43; p=0.39). No difference was found with regard to PFS (p=0.16) with a HR of 0.95 (95% CI: 0.49 - 1.83). The medians were 42.6 (95%CI: 31-78.3) months for SPORT and 60.5 (95%CI: 34.6-NA) for POPART. The DFS probability at 8 years was 43.8% for SPORT (95% CI: 33.8-53.0) and 51% for POPART (95% CI: 40.7-63.8). No statistical difference was noted in the long term between the two arms. The 8-year overall survival rate was 46.0% with POPART compared to 33.1% with SPORT (HR:0.82, CI 0.53-1.28; p=0.39).

Conclusion: A reduction in the OTT of postoperative radiotherapy in patients with HNSCC with adverse factors for locoregional failure does not improve outcome in terms of LRC, PFS and OS.

OC-009
Update of the randomised phase III trial DAHANCA 19: Primary C-RT or RT and zalutumumab for squamous cell carcinomas of head and neck

1Odense University Hospital, Department of Oncology, Odense, Denmark
2Herlev Hospital, Department of Oncology, Herlev, Denmark
3Aarhus University Hospital, Department of Oncology, Aarhus, Denmark
4The Norwegian Radium Hospital Oslo University Hospital, Department of Oncology, Oslo, Norway
5Copenhagen University Hospital, Department of Oncology, Copenhagen, Denmark
6Aalborg University Hospital, Department of Oncology, Aalborg, Denmark
7Aarhus University Hospital, Department of Experimental Clinical Oncology, Aarhus, Denmark

Background: Monoclonal antibodies against the Epidermal Growth Factor receptor (EGFR-I) have been reported to increase tumor control and survival of patients with Head and Neck Squamous Cell Carcinomas (HNSCC) when combined with radiotherapy (RT). This study was conducted by the Danish Head and Neck Cancer group (DAHANCA) and aimed to evaluate if concurrent treatment with the EGFR-I zalutumumab during chemo-RT (C-RT) or RT improved outcome in patients with HNSCC.

Material and methods: 619 pts with biopsy-verified HNSCC entered the study from November 2007 to June 2012. The majority of tumors were of oropharyngeal origin (69%) whereas other sites were less represented: oral cavity (12%) and larynx (14%). Stratification was done by tumor-site, stage (554 (89%) patients were stage 3-4), p16-status (75% of oropharyngeal carcinomas were positive) and use of concurrent cisplatinum (71%). Patients were randomized to control-arm or zalutumumab-arm. The control-arm was primary accelerated RT; predominantly 66-68Gy, 2Gy/fx, 6fx/wk and concomitant daily hypoxic radiosensitisation with nimorazole. Stage 3-4 carcinomas received weekly cisplatinum 40 mg/m2 during RT. Elective neck-dissection was not performed. The zalutumumab-arm was identical with the control-arm plus zalutumab 8 mg/kg. First dose was given the week before start of RT and continued weekly during irradiation. Analyses were performed as intention-to-treat. Primary endpoint was Loco-Regional Control (LRC). Secondary endpoints were Disease-Specific Survival (DSS) and Overall Survival (OS).

Results: Median observation time was 48 month. 309 pts were in the control-arm and 310 in the zalutumumab-arm. Patient and tumor parameters were well balanced. The 4-year LRC rate was 71% in the zalutumumab-arm vs. 73% in the control-arm, HR: 1.16 [95% CI: 0.83-1.61]. This outcome was reflected in DSS: HR 1.12 [0.75-1.69] and in OS: HR 1.22 [0.88-1.67]. There was no benefit of adding zalutumumab to C-RT (HR: 1.08 [0.72-1.62]) nor RT alone (1.36 [0.88-2.44]). Treatment was generally well tolerated, but 94% of the pts in the zalutumumab-arm experienced a skin rash (29% had grade 3-4 rash). The degree of rash did not influence LRC (HR: 1.5 [0.9-2.7]) or the other outcome parameters. Finally, the effect of zalutumumab was not influenced by p-16 positivity (HR 1.0 [0.6-1.8]) nor p-16 negativity (HR 0.8 [0.5-1.4]).

Conclusion: Treatment with zalutumumab was generally well tolerated, but the addition of concomitant zalutumumab to primary C-RT or RT and nimorazole for HNSCC did not increase locoregional control nor disease-specific or overall survival at 4 years.

Symposium: Emerging treatment paradigms in head and neck cancer

SP-010
Effect of tumour heterogeneity on treatment selection and failure
R. Haddad

1Dana Farber Cancer Institute, Medical Oncology, Boston, USA

Patients with locally advanced head and neck cancer are often treated with a combined modality approach with surgery, radiation therapy and chemotherapy. Those with recurrent and metastatic disease are treated with palliative therapy that often includes chemotherapy and/or targeted therapy. Numerous advances have been made in understanding the genetic alterations present in these tumors and increasingly those alterations are used to select treatment options. The most important and relevant marker in the past decade has been the recognition that most oropharynx cancer is related to infection with the HPV16 virus and those patients have an excellent prognosis. Current research studies are looking at the concept of chemotherapy, radiation or surgical de-intensification for these patients with HPV related cancers and treatment INTENSIFICATION for those with HPV unrelated tumors. Recent research presented by the ECOG group showed promising results with de-intensification and further studies are being planned. HPV testing has become an important -and many consider standard-part of treating head and neck cancer patients. Other markers have also been identified in the recently presented TCGA project identifying various genomic alterations in patients with head and neck cancer. Those include PI3K, EGFR, MET, NOTCH, HRAS, FGFR and others.
Many of these alteration are "druggable" and ongoing clinical trials are studying their efficacy in treating patients with locally advanced disease. More work is needed to identify the best group of patients likely to benefit from these approaches.

One example has been the identification of EGFR as a major target in patients with head and neck cancer and numerous EGFR inhibitors are currently available. Monoclonal antibodies targeting EGFR have been shown to improve survival when combined with radiation therapy in previously untreated patients. In patients with recurrent and metastatic disease, chemotherapy with EGFR inhibition is superior to chemotherapy alone. EGFR expression though does not seem to predict response to these agents and more work is needed to identify who are the best patients for this approach. Anti-Angiogenic agents are also of interest in head and neck cancer, both monoclonal antibodies and tyrosine kinase inhibitors are being investigated and results are expected soon.

Finally, major advances in the field of immunotherapy have occurred in the past 5 years with the identification and subsequent development of anti-PD1 and PD-L1 therapeutics. These agents are already available for patients with melanoma and their role in patients with head and neck cancer is currently an area of active investigation. Recent studies presented in the ASCO meeting showed promising results with an anti-PD1 monoclonal antibody given to a patient population heavily pretreated with chemotherapy. In Summary, the era of genomic and precision medicine is here and growing rapidly. Many patients are currently undergoing genomic "profiling" of their tumors and this information in increasingly being used to decide on the best treatment strategies. Understanding these genomic alteration will hopefully lead to a more effective and less toxic treatment strategy for our patients.

**SP-011 What's new with sentinel nodes?**

M. McGurk

1Guy’s and St. Thomas’ Hospital NHS Foundation Trust, Oral and Maxillofacial Surgery, London, United Kingdom

Sentinel node biopsy (SNB) is a well-established technique for detecting occult metastasis with the proven track record in the management of breast cancer and melanoma. It is now being used in head and neck cancer (H&N) to address the question of the N0 neck. Squamous cell cancer spreads exclusively by way of lymphatic system in early disease and is ideally suited to SNB.

A recent prospective observational study - European Sentinel Node Trial (SENT) recruited 420 patients and is reporting interim results. A total of 27% (112/420) patients had occult metastases and SNB detected 87% with a false negative rate of 13%. Half of these patients were subsequently rescued by therapeutic neck dissection. As a by-product of the test, aberrant drainage to the contralateral neck was observed in 49 patients, 7 of which had a positive SNB and had an early neck dissection. The disease-free and the disease specific survival at a mean follow-up of 57 months were 93% and 94% respectively. The SNB technique did not impact on survival.

Analysis show that the false negative rate was partly due to operator factors that were remedial in nature. As in breast the presence of micrometastasis did not impact on survival. The potential of SNB has not been fully explored. It can be used in H&N to deescalate both surgical and radiotherapy treatment of the N0 neck. It retains fidelity after RT, chemotherapy and surgery as it simply tracks lymphatic flow and can identify new SN areas with recurrent or second primary cancers. The present limitation of this technology is that dynamic and CT SPECT imaging has to be undertaken in the nuclear medicine department with the effect that only superficial tumours that can be injected easily with tracer are candidates for SNB. This is changing with new 3D navigation systems that allow intraoperative freehand SPECT imaging of the SN. Surgeons treating all solid tumours can now avail themselves of this intraoperative system. In addition the radioactive tracer molecule can bind a fluorescent tag (ICG) which makes the sentinel node both "hot and glow". This dual tracer will help reduce the false/negative rate of the technique. With these new developments we are able to extend the role of SNB to other areas of the head and neck notably larynx, thyroid and the salivary glands.

**SP-012 Image guided minimally invasive and robotic techniques for sinus and base of skull malignancies**

P. Nicolai, A. Bolzoni Villaret, A. Schreiber, A. Carobbio

1University of Brescia, Otorhinolaryngology, Brescia, Italy

Malignancies of the sinonasal tract are rare, accounting for 3% of all cancers of the head and neck and present several unique features. Notably, in spite of the widespread use of endoscopy in routine daily practice and progress in imaging techniques, diagnosis is established at an advanced stage in view of the nonspecific symptoms associated with the early phase of growth. Consequently, involvement of the skull base is frequently observed in malignant tumours of these anatomic sites. A second hallmark is the extreme histologic heterogeneity, which impacts biological behavior and prognosis. The introduction of the anterior craniofacial resection should be considered the major advance in their management. In the last decades there has been growing interest in the use of transnasal endoscopic surgery in the management of malignant tumors of the sinonasal tract and adjacent skull base, as a result of a rapidly growing expertise in the field, refinements in imaging diagnosis, and impressive technological advances in surgical instruments. One of the main advantages of using an endoscope is the optimal illumination of the surgical field that allows a close-up view of the lesion and the surrounding neurovascular structures, and also, by rotation ofangled scopes, different perspectives of the surgical field. However, the highly complex anatomy of the skull base makes surgery in this area challenging: neurovascular structures are located within a small area with multiple anatomic variant. Landmarks are also frequently displaced by the tumors and orientation becomes more difficult, requiring meticulous analysis of the images. Modern imaging techniques with high-resolution computer tomography scans, magnetic resonance imaging and image guidance systems provide the skull base surgeons with valuable details of the anatomy during surgery. Although the standard surgical setting usually involves at least two surgeons operating through the two nostrils with the so-called "four hands technique", only two hands are really used because the other two hands need to hold the endoscope and to aspirate the surgical field or wash the tip of the scope. A possible solution for these limitations could be a robotic holder controlled by the surgeon himself with tele-manipulation/voice-control/co-manipulation systems, recently explored with different technical solutions. Moreover, intraoperative image guidance systems could be used in order to monitor the position and the movement of the holder into the surgical corridor. This device could avoid fine tremors, risk of accidental injuries to vital structures with the endoscope, and time-wasting for cleaning the lens. Nowadays, the Da Vinci Robotic System provides adequate endoscopic access to the skull base, although it is extremely invasive for the patients requiring a bilateral sublabial approach other than very prohibitive costs and dimension. For this reason the Units of Otorhinolaryngology, Robotics Engineering, and Software Engineering of the University of Brescia are working together on a dedicated robotic holder prototype with the intent to develop an innovative “hybrid
robot-assisted endoscopic surgery”
A complete review of the
literature and the state of the art on this topic will be
discussed.

SP-013
Beyond parotid sparing with IMRT
M. Oszahin
Switzerland

Abstract not received

Proffered papers: Highlights of proffered papers

OC-014
Molecular screening for cancer treatment optimization in head and neck cancer (MOSCATO 01)
C. Even1, I. Breuskin1, E. Ileana2, C. Massard3, L. Lacroix3, N. Lezghed4, J. Guigay1, F. Janot1, J.C. Soria1, C. Ferté2
1Institut Gustave Roussy, Head and Neck Department, Villejuif, France
2Institut Gustave Roussy, Drug Development Department, Villejuif, France
3Institut Gustave Roussy, Medical Biology and Pathology Department, Villejuif, France

Purpose/Objective: Patients with recurrent or metastatic head and neck cancers (HNC) have a poor prognosis. After first line chemotherapy, therapeutics are limited. The widespread use of high-throughput molecular techniques has allowed the identification of recurrent and actionable molecular traits across various tumor types. Translating these approaches to bedside may guide the decision-making for cancer patient candidates to early clinical trials.

Materials and Methods: Patients with advanced HNC, referred to our early drug development department, were enrolled in a prospective molecular screening program. Surgical or CT-Scan biopsies were performed in metastatic or primary tumor sites to carry out a comprehensive molecular characterization. DNA was extracted from fresh tumor samples and analyzed by comparative genomic hybridization (CGH) (> 30% tumor cells required), and by Next Generation Sequencing (NGS) for up to 74 target genes (> 10% tumor cells required). A weekly molecular tumor board reviewed all the profiles to identify actionable traits for which the most relevant targeted therapy may be available through early clinical trials or marketed drugs. Treatment efficacy was evaluated by RECIST 1.1 or PERCIST criteria.

Results: From July 2011 to August 2014, 78 heavily pretreated patients were included in the MOSCATO 01 trial. CGH and NGS profiles were assessed in 64 (82%) and 68 (87%) of biopsied patients, respectively. The median time for delivering results was 20 days. Actionable molecular aberrations were found in 30 patients (38%). Among these patients, 10 patients (33%) were treated with a targeted therapy according to the molecular profile. The most frequent actionable molecular aberrations were observed in the following pathways: FGFs/FGFRs (35%), PI3K/AKT/mTOR (26%), MYC (24%), CDKs/Cyclins (13%), EGFR (9%), HER2 (7%), NOTCH (4%), KIT (2%). Out of the 10 patients treated according to the genomic profile, we observed at first tumor evaluation: 3 partial responses (PR), 3 stable disease (SD) and 1 clinical progressive disease (PD), while 2 patients were not evaluable. Out of the 20 patients not treated according to the molecular triage whereas actionable traits were detected, we observed: 7 patients with exclusion criteria for clinical trial, 6 patients being dead during the process, 4 patients with feeding tube impairing oral treatment intake, and 3 patients treated by other antineoplastic therapy. Conclusions: High throughput genomic analysis is feasible in daily practice and allows the biological-orientation of up to 38% of recurrent or metastatic HNC patients.

OC-015
Therapeutic HPV vaccine increases sensitivity of poorly immunogenic tumor to anti-PD-1 monotherapy
S. Pai1, D. Smith2, S. Peng3, E. Ishida1, B. Akpeng1, C.F. Hung2, T.C. Wu2
1Massachusetts General Hospital Harvard Medical school, Otolaryngology, Boston, USA
2Johns Hopkins Hospital, Otolaryngology, Baltimore, USA

Purpose/Objective: The safety and efficacy of blocking antibodies to Programmed cell death-1 (PD-1) and its ligand (PD-L1) are actively being evaluated in the clinical arena for various cancers, including head and neck cancers. Identifying predictive biomarkers of clinical response to these immunomodulatory therapies is of great interest in the field. Since these agents aim to restore T cell function within the tumor microenvironment, one possible explanation for failed responses to immune checkpoint blockade may be attributed to a paucity or lack of immune responses to the host tumor. We found that our HPV tumor model is poorly immunogenic and, consequently, resistant to anti-PD-1 monotherapy. Thus, we aimed to evaluate whether an HPV vaccine can improve response rates to anti-PD-1 therapy by eliciting CD8+ anti-tumor immune responses.

Materials and Methods: C57BL/6 mice were subcutaneously inoculated in the right flank with 1x105 TC-1 tumor cells on Day 0. The mice were then treated with either anti-PD-1 blocking antibody, CRT/E7(detox) DNA vaccine, or a combination of anti-PD-1 and CRT/E7(detox) DNA vaccine. The mice were treated 3 days after tumor inoculation and received treatment every 4 days for a total of three treatments. Mice were monitored for survival and tumor growth by measuring tumor diameter with calipers twice a week. We also characterized the HPV-specific T cells in the various treatment groups. Therefore, one week after the last vaccination, TC-1 tumors were surgically excised and HPV16 E7-specific CD8+ T cells stained for PD-1 expression. The cells were acquired with a LSRII flow cytometer and analyzed with FACSDiva software.

Results: The administration of an HPV vaccine increased the frequency of vaccine-induced CD8+ T cells which express the PD-1 receptor. Interestingly, vaccination also upregulated PD-L1 expression within the tumors and rendered the tumor cells resistant to vaccine-induced cytotoxic T cell killing. With the combination of HPV vaccine and anti-PD-1, we observed a synergistic anti-tumor effect which resulted in improved overall survival. Functional studies demonstrated that vaccine-induced T cell killing could be restored with anti-PD-1 treatment.

Conclusions: We provide a rationale for combining vaccines with anti-PD-1 therapy as a strategy to further enhance clinical responses and/or overcome resistance to immune checkpoint blockade, particularly in poorly immunogenic tumors.

OC-016
Patient reported outcomes (PRO) of RTOG 9003
A. Konski1, Z. Qiang2, K.K. Ang3, K.K. Fu4, A. TrottiA, S. Spencer5, B. Gunn6, G. Shenouda7, Q. Le8
1University of Pennsylvania, Radiation Oncology Department, West Chester, USA
2NRG Oncology Group, Statistics, Philadelphia, USA
3MD Anderson Cancer Center, Radiation Oncology, Houston, USA
4UCSF, Radiation Oncology, San Francisco, USA
5Moffitt Cancer Center, Radiation Oncology, Tampa, USA
6UIAB, Radiation Oncology, Birmingham, USA
7McGill University, Radiation Oncology, Montreal, Canada
8Stanford, Radiation Oncology, Stanford, USA
Purpose/Objective: The final report of RTOG 9003 showed no difference in any grade ≥ 3, 4, or 5 toxicities, feeding tube use after 180 days and at 1 year when comparing any experimental altered fractionation arm to the standard fractionation (SFX) arm. The purpose of this study is to report the Patient Reported Outcomes (PRO) of patients treated on RTOG 9003.

Materials and Methods: RTOG 9003, a phase III trial, compared altered fractionation (hyperfractionation [HFX], accelerated fractionation continuous [AFX-C], or accelerated fractionation split [AFX-S]) to SFX. Quality of life (QOL) was added 6 months after trial activation. FACT questionnaires were completed at baseline (before treatment), at 3, 6, 9, and 12 months from start of treatment, and then every 6 months through year 5. At follow-up only patients with baseline FACT and applicable follow-up FACT were included in the analysis. Scores for each follow-up time point (raw values and change from baseline) were compared between each experimental arm and the SFX arm using t-test. Longitudinal trends were evaluated using the general linear model. An unplanned analysis comparing FACT by p16-status (limited to patients with oropharynx cancer) was performed.

Results: RTOG 9003 opened to patient accrual on September 30, 1991 and closed on August 1, 1997 after enrolling 1113 patients. Thirty-seven patients did not meet inclusion/exclusion criteria or withdrew consent, 80 were enrolled prior to FACT being added to the study, and 286 did not complete baseline FACT, yielding 710 analyzable patients. Demographic differences were seen between those patients with and without baseline FACT scores (age, race, KPS, p16 status, N and AJCC stage) but both groups had similar local-regional failure and overall survival. No significant difference in FACT scores were seen between treatment groups at baseline but HFX and AFX-C had significantly lower FACT scores compared to SFX (means 97.5 vs. 104, p=0.01, and 96.7 vs. 104, p=0.006, respectively) at 3 months while only AFX-C change from baseline was significantly lower than SFX (means -10.4 vs. -5.4, p=0.05). A difference in FACT scores was noted at 48 months for all experimental arms compared to the SFX arm but changes from baseline were not significantly different. When compared by P16 status, FACT scores change from baseline were significantly lower for p16 positive patients compared with p16 negative patients, (mean 6.8, p=0.04), at 3 months with no difference noted in later measurement points.

Conclusions: PRO are becoming an important endpoint in clinical trials. This is the first report of PRO in patients treated on RTOG 9003 showing a similarity to the toxicity results reported earlier. The unplanned analysis comparing p16 positive and negative status of patients with oropharyngeal cancer is interesting and hypothesis generating; however, it needs to be confirmed.
Purpose/Objective: Concomitant use of cetuximab and radiotherapy (RT) induces radiodermatitis in head and neck cancer (HNC) that can be severe. The OTD70DERM® is one of the Regenerating Agents (RGTA) which is a structural and functional analogue of glycosaminoglycans. Pre-clinical studies showed that RGTA reduced radiation-induced mucosal and cutaneous toxicities without tumor protection. This study was to evaluate RGTA effect on radiodermatitis in patients with newly diagnosed HNC receiving radiotherapy and cetuximab. The primary endpoint was the incidence of grade 2 or higher radiodermatitis.

Materials and Methods: A multicenter, randomized, double-blind, placebo-controlled trial was performed on HNC patients receiving conventionally fractionated RT (70 Gy/35F over 7 weeks, 2 Gy daily) and cetuximab: 400 mg/m² one week before RT, then 250 mg/m²/week, 8 cycles of cetuximab. The primary endpoint was the incidence of grade 2 or higher radiodermatitis.

Results: 270 consecutive patients were treated in our study, 243 male (89%) and 30 female (11%) with a mean age of 58 (30-81). We included patients with squamous cell carcinoma of the oral cavity (8.7%), oropharynx (42.7%), hypopharynx (23.3%) and larynx (25.3%) treated with bioradiotherapy with curative intention.

The Kaplan-Meier analysis showed a 5 year overall survival of 48.4%, with a local recurrence of 31.1%, locoregional recurrence of 39.7%. In the local recurrence population we observed a median overall survival of 11.8 months, 15.8 months in the salvage surgery cohort and 7.8 months in the other no surgical treatments cohort (log Rank test: p=0.148).

Salvage surgery after local recurrence was feasible in 19 patients (33.9%). Salvage surgeries included 9 total laryngectomy, 5 circular pharyngolaryngectomy (one with total glossectomy), 5 buccopharyngectomies (with 1 total glossectomy) and 1 total glossectomy.

A total of 15 patients required a flap reconstruction (4 pedicled flaps and 11 free flaps) with a 50% of success. The number of patients with complications after salvage surgery procedures were 16 (84.2%). We considered severe complications those which need a surgical intervention or blood concentrate transfusion. According to this definition we found 10 patients (52.6%) with severe complications: 6 pharyngocutaneous fistula (31.6%) and 5 bleeding or hematoma (26.3%).

A total of 10 secondary surgeries were required due to complications (5 pedicled flaps and 5 free flaps). Second surgery solved the complication in 80% of patients. One patient died in the postoperative period due to a massive bleeding.

Conclusions: To our knowledge, this is the largest analysis of salvage surgery after bioradiotherapy. According to our results, salvage surgery after bioradiotherapy is associated with a high rate of complications. Nevertheless, those complications have been solved with a second surgery with only 2 patients with persistent pharyngocutaneous fistula.

OC-020

Computer-guided surgery simulation for mandibular reconstruction with fibula free flap

Q. Dassonneville 1, G. Poissonnet 1, A. Iannessi 1, A. Bozec 1, D. Cuvic 1, J.C. Riss 1, R. Berguiga 1

1 Institut Universitaire de la Face et du Cou, Head and Neck Surgery, Nice, France
2 Centre Antoine Laccassagne, Imaging Department, Nice, France
3 Institut Universitaire de la Face et du Cou, Head and Neck Surgery, Nice, France

Purpose/Objective: The two main goals are to study the saving surgical and ischemic flap times and to evaluate the improvement of flap shaping in the light of our preliminary experience of computer-guided surgery simulation for mandibular reconstruction.

Materials and Methods: Since January 2014, we use routinely this technique which provides us surgical guides and preformatted osteosynthesis mini plates. Sixteen patients have benefited from this technique for a mandibular reconstruction in a tumoral context. We reported surgical times and ischemic flap times and compared them to patients who underwent the same procedures in 2013 without this technique (9 patients).

The three surgeons are the same in 2013 and 2014 and types of mandibular loss are classified in postero lateral and anterior defects.
Results: For the nine 2013 patients, ischemic average time was 155.6 min (90 to 200) and operative average time 532.8 min (430 to 565).

For the sixteen 2014 patients, ischemic average time was 83.3 min (50 to 120) and operative average time 474.6 min (255 to 565).

Regarding the type of reconstruction, for anterior defects, ischemic average time was in 2013, 163.3 and operative average time was 565 min. In 2014, respective average times were 80.7 min and 521.6 min. For posterior lateral defects, ischemic average time was in 2013, 151 min and operative average time was 516.7 min. In 2014, respective average times were 84.1 min and 472.6 min.

Conclusions: We found an important decreasing of the ischemic flap time estimated to 46.8% for all defects by using this new technology. There is also a decreasing of overall time of procedure estimated to 11%.

These findings are very important because we can hope a decreasing of flap loss rates and a decreasing in terms of time of use of the operating room, balancing the cost of this technology

OC-021 Development of a multivariable Normal Tissue Complication Probability (NTCP) model for tube feeding dependence
K. Wopken1, H.P. Bijl1, A. Van der Schaaf1, P. Doornaert2, S.F. Gosting1, B.P.A.M. Van der Laan1, J.L.N. Roodenburg1, C.R. Leemans6, I.M. Verdonck-de Leeuw6, J.A. Langendijk1
1University of Groningen University Medical Center Groningen, Department of Radiation Oncology, Groningen, The Netherlands
2VU University Medical Center, Department of Radiation Oncology, Amsterdam, The Netherlands
3University of Groningen University Medical Center Groningen, Department of Medical Oncology, Groningen, The Netherlands
4University of Groningen University Medical Center Groningen, Department of Otolaryngology/Head and Neck Surgery, Groningen, The Netherlands
5University of Groningen University Medical Center Groningen, Department of Otolaryngology-Head and Neck Surgery, Groningen, The Netherlands
6VU University Medical Center, Department of Otolaryngology-Head and Neck Surgery, Amsterdam, The Netherlands

Purpose/Objective: Curative (chemo-) radiation for head and neck cancer (HNC) may result in severe acute and late side effects, including tube feeding dependence. The purpose of this multicenter prospective cohort study was to develop a multivariable prediction model for tube feeding dependence at 6 months (TUBE6) after curative primary radiotherapy, radiotherapy with cetuximab (bioradiation) or chemoradiotherapy for head and neck cancer based on pretreatment and treatment characteristics (including dose volume parameters). This model can be used to select patients for radiotherapy treatment plan optimization.

Materials and Methods: The study included 355 patients with HNC. In all patients, TUBE6 was scored prospectively in a standardized follow-up program. To design the prediction model, the penalized learning method LASSO was used, with TUBE6 as the endpoint.

Results: The prevalence of TUBE6 was 10.7% (38 out of 355 patients). The multifactorial model with the best performance consisted of the variables: advanced T-stage, moderate to severe weight loss at baseline, accelerated radiotherapy, chemoradiation, radiotherapy plus cetuximab, the mean dose (Dmean) to the superior and inferior pharyngeal constrictor muscle (PCM), to the contralateral parotid gland and to the cricopharyngeal muscle (CM). Table: Model performance at internal validation in terms of area under the curve was 0.88 in double cross validation, while the prediction model scored excellent using other performance measures. Of the four dose-volume parameters, the mean dose to the PCM superior was most important.

In the graph (see: Figure) an example of the predicted NTCP value for TUBE6 as a function of the mean dose to the PCM superior for a patient with a T3-T4 tumor, with severe weight loss prior to the start of chemoradiotherapy with a dose of 70 Gy on the PCM inferior, the CM and the contralateral parotid gland.

Table Variables in the model and their regression coefficients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
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</thead>
<tbody>
<tr>
<td>Intercept</td>
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<td>T-stage</td>
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</tr>
<tr>
<td>T3 - T4</td>
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<tr>
<td>Baseline weight loss</td>
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<tr>
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</tr>
<tr>
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<tr>
<td>Severe (&gt;10%)</td>
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<tr>
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<tr>
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<tr>
<td>Dmean PCM inferior</td>
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<tr>
<td>Dmean contralateral parotid gland</td>
<td>0.006</td>
</tr>
<tr>
<td>Dmean CM</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Conclusions: We developed a multivariable NTCP model for TUBE6 after definitive (chemo-) radiation to identify patients at risk for tube feeding dependence. The dosimetric variables can be used to optimize radiotherapy treatment planning aiming at prevention of tube feeding dependence and to estimate the benefit of new radiation technologies.

OC-022 The results of second head and neck pathology screening campaign
I. Reshetov1, V. Starinskii2, M. Kazantseva3, O. Kit4, M. Yengibarian1, V. Shcherbina1
1I.M. Sechenov First Moscow State Medical University, Plastic Surgery, Moscow, Russian Federation
2PA Hertzen Moscow Cancer Research Center, Scientific, Moscow, Russian Federation
3Clinical Oncological Dispensary #1 Ministry of Health of
SP-024
Biomarker driven clinical trials
J.P. Machiels
UCL Cliniques Univ. St.Luc, Oncology, Brussels, Belgium

Despite progress in the therapeutic management of patients with squamous cell carcinoma of the head and neck (SCCHN), the mortality rate of patients presenting with advanced disease remains high. One approach to improve treatment efficacy is to add novel molecular targeted agents to the classical treatment regimens. Monoclonal antibodies targeting the epidermal growth factor receptor (EGFR) have shown clinical benefits in palliative and curative settings. However, only a minority of patients presenting with recurrent or metastatic SCCHN have meaningful tumor regression with these agents and virtually all who do develop acquired tumor resistance after a few months of treatment. For these reasons, other inhibitors of EGFR or molecules that interfere with known molecular pathways activated in squamous cell carcinoma of the head and neck are of considerable interest, either as single agents or in combination with other treatment modalities. Recently, deep sequencing technology has allowed a better characterization of the implicated genes. Somatic mutations in TP53 (47–72%), NOTCH1 (14–19%), CDKN2A (9–22%), PIK3CA (6–21%), FBXW7 (5%), HRAS (4–8%), FAT1 (23%) and CASP8 (8%) have been reported. Beside these mutations, some genes or their related proteins have been found to be altered by other mechanisms (amplification, deletion, epigenetic). Altogether, activating mutations in classical oncogenes seem relatively rare in SCCHN and most of the genetic alterations occur in tumor suppressor genes. These findings are important for the further development of novel therapies for SCCHN although developing new compounds to restore the activity of altered tumor suppressor genes is extremely challenging. In this review, we will discuss the different molecular therapeutic approaches explored in SCCHN. We will also outline new trial designs that could be used to accelerate the investigation of emerging therapeutic agents in this disease.

SP-025
Model based approach for testing new radiation technologies, including particle therapies
H. Langendijk
University Medical Center Groningen, Radiation Oncology, Groningen, The Netherlands

Introduction: Randomized controlled trials (RCT’s) are considered the holy grail of evidence-based medicine. However, most technology innovations and medical devices in health care have not been introduced based on the results of RCT’s. In general, setting up traditional RCT’s testing new technologies is considered complicated and sometimes even impossible, e.g. because of user-dependency, speedy technological developments, high and nonreimbursable costs, limited availability or because the clinical benefit is so large that testing in an RCT is regarded unethical. So far, new radiation technologies have been introduced without any testing in RCT’s and is mainly based on the assumption that lower dose to healthy tissues will result in less side effects. However, in order to justify high investments, such as in the case of proton therapy, the demand for alternative evidence-based methodologies is rising. The model-based approach such a alternative evidence-based method for selection of patients that will benefit most from new radiation technologies that are primarily aim at reduction of radiation-induced side effects (RISE) and to validate these technologies.

The model-based approach: The model-based approach consists of 4 steps. The first step is the development of validated Normal Tissue Complication Probability (NTCP) models, which are multivariable prediction models describing

SP-023
Lessons learned from running surgical clinical trials
H. Mehanna
University of Birmingham, Institute of Head and Neck Studies and Education, Birmingham, United Kingdom

Surgical clinical trials are uncommon, and often considered to be the most challenging clinical trials to run. In this talk we will discuss some of the challenges faced in running surgical clinical trials. We will give some real-life examples of these challenges, and some solutions that we have found successful. We will also then enumerate the top ten lessons learnt from running multicentre surgical trials.
the relationship between radiation dose metrics and the risk on RISE. NTCP-modeling studies provide information on which dose metrics are most relevant for the development of RISE (e.g., the mean dose or the maximum dose). This information is crucial for optimizing radiotherapy dose distributions aiming at less RISE. The second step is to test if the most relevant dose metrics can actually be reduced by new radiation techniques using in-silico planning comparative studies. The third step is to assess whether the dose reductions obtained with the new technology will translate into a clinical benefit in terms of less RISE (also referred to as ΔNTCP). This can be achieved by integrating the results of the in-silico planning comparative studies into the NTCP-models. These three steps can also be used to select patients for more complex and more expensive radiation technologies such as protons. Finally, the model-based approach can be used to validate the new technology, by validating the NTCP-model among patients treated with the new technology.

Conclusion: The model-based approach is a good alternative evidence based method to validate new radiation technologies that are primarily aiming at reduction of radiation-induced side effects.

SP-026 Integrating functional imaging in clinical trials
V. Gregoire
Belgium

Abstract not received

SP-027 Response evaluation in a clinical trial
A. Dietz1, G. Wichmann1, A. Boehm1, C. Mozet1
1University of Leipzig, ENT Head and Neck Surgery, Leipzig, Germany

Since the two landmark-phase-III studies from France and the USA demonstrated convincingly that there is a real alternative treatment for advanced laryngeal and hypopharyngeal cancer, the discussion about definitive non-surgical treatment in head and neck cancer started all over the world. The scientific community which is concerned with head and neck cancer had to face alternative multimodality treatment of squamous cell carcinomas of the head and neck (HNSCC). On the other hand, they have to manage difficulties such as early and late toxicities, reduced functional outcome, and treatment failure leading to high risk surgery with severe complications in too many cases. Furthermore, chemo and radio resistance of tumor cells in general can be provoked by mutations in oncogenes (e.g., K-ras), loss of tumor suppressors (e.g., p53, p16INK4a) or dysregulation of genes involved in cell cycle control, cell proliferation, signal transduction, angiogenesis or apoptosis. Unfortunately in HNSCC, all these biomarkers showed vague correlation with better outcome after chemo radiation, but suffer from strongly discriminating results, many technical peculiarities, and in particular from investigations being addressed only in highly selected artificial surrogates for real tumors, namely cell lines; thus the clinical relevance is still limited (except regarding p16INK4a and HPV-16 in oropharyngeal cancer).

On the other hand, research in specific genetic profiles associated with radio or chemoresponse is a highly encouraging and promising field for many tumor entities. However, today’s main guidelines for treatment in HNSCC are still based on phase III-trials and comprehensive meta-analyses, with excess of radiation or chemo radiation studies at the expense of surgical trials. Cancers are just as individual as their hosts, and arguably more so, as acquired genetic alterations are influenced by the genotypic and phenotypic differences between patients. Despite widespread recognition of this heterogeneity, oncology remains a largely empirical discipline, on the basis of randomized clinical trials that treat all patients with one cancer type as though they were identical.

There is an increasing body of literature focusing on assay-based chemoresponse evaluation in individual tumors but for HNSCC such assays are not yet in clinical use. Unfortunately, implementation of chemosensitivity testing into clinical practice has failed, despite growing knowledge and the availability of advanced and stable methods in this field. Although chemosensitivity testing in vitro at first glance is a very attractive concept, it might not necessarily properly predict in-vivo responses due to a number of different factors: Subpopulations of tumor cells may expand clonally in cell culture and the possible absence of immune cells and - in particular important - the absence of a functional tumor microenvironment (i.e., extracellular matrix, blood vessels, nerves, and soluble factors produced by leukocytes or the tumor itself) may influence the outcome and cause highly relevant differences to the clinical response to a given chemotherapy.

There are interesting clinical observations showing that response on induction chemotherapy may predict the outcome after radiotherapy. Some trials use this empirical phenomenon to pre-select non-responders for primary surgical treatment avoiding severe salvage complications after failure of complete chemo radiation treatment. Going one step further, recent literature and our own investigations implicate that response evaluation of the individual patient’s HNSCC in a suitable ex-vivo assay just before starting the treatment is mature for clinical research (FLAVINO Assay).

Poster discussion session

PD-028 FDG based dose painting in head and neck cancer: preliminary results of a phase I trial
J.H. Rasmussen1, I.R. Vogelius1, B.M. Fischer2, M.C. Aznar1, A.B. Gothelf1, J. Friborg1, C.A. Kristensen1, S.M. Bentzen3, L. Specht1
1Rigshospitalet University of Copenhagen, Department of Oncology Section of Radiotherapy, Copenhagen, Denmark
2Rigshospitalet University of Copenhagen, Department of Clin.Phys. Nucl.Med. & PET PET & Cyclotron Unit, Copenhagen, Denmark
3University of Maryland School of Medicine, Division of Biostatistics and Bioinformatics University of Maryland Greenebaum Cancer Center and Department of Epidemiology and Public Health, Baltimore, USA

Purpose/Objective: The aim of this phase I trial is to test the safety of FDG PET guided dose redistribution in patients receiving accelerated chemo-radiation therapy for locally advanced head and neck squamous cell carcinoma (HNSCC). An escalated dose is prescribed to the FDG positive target volume (GTV-PET), where the probability of recurrence is high, and a reduced dose is prescribed to the elective target volume.

Materials and Methods: The prospective trial is designed with two dose-escalation steps to GTV-PET. The primary end point is any early grade 4 or greater toxicity (grade 4+ toxicity) according to CTC. In step 1 the dose to the GTV-PET is escalated to 82 Gy eqiueffective dose in 2 Gy fractions (EQD2). Sixteen patients were included. One, however, had to be excluded because GTV-PET was not delineated according to protocol, leaving 15 patients for further analysis. Inclusion criteria were primary SCC of oral cavity, oro- or hypo-pharynx, or laynx, candidates for concomitant chemo-radiotherapy, p16 negative tumors or a smoking history of > 10 pack years, and written informed consent. Patients were FDG-PET/CT scanned while immobilized in treatment position. GTV-PET was defined by a specialist in...
nuclear medicine and a radiologist together, while the anatomic GTV was defined in collaboration between an oncologist and a radiologist. The treatment was given in 34 fractions, 6 fractions per week, and weekly administered concomitant cisplatin for all patients.

Results: Table 1 shows patient characteristics. Median follow up time from treatment start is 4 months (range 2-9). All 15 patients completed the concomitant chemo-radiotherapy and no incidents of grade 4+ toxicity were observed. In the 14 cases who have passed the 3-month follow-up, the upper limit on the 95% confidence interval for the incidence of G4+ early toxicity is 21.5%. Twelve patients were hospitalized during treatment which is not unexpected in our patient population and 7/12(58%) were planned due to weight loss and need for tube feeding (figure 1). However, 2 patients were hospitalized because of febrile leucopenia. Overall eleven patients required nasogastric tube feeding before (1 patient) or during treatment (10 patients). Four patients had nasogastric tube at the evaluation two months after end of treatment, only one patient required feeding tube more than three months after treatment and received a PEG tube. This patient was the only one with ulceration at the former tumor site three months after treatment which healed within 6 months after treatment. All patients had remission at the two months evaluation and currently only 1 patient has experienced treatment failure at N- and M-site 6 months after treatment start.

Conclusions: With 14 of the 15 cases having passed 3 months follow up required by the trial protocol FDG-PET based dose escalation to 82 Gy seems safe. When the last patient passes 3-month follow-up the dose will be escalated to 85 Gy.

PD-029
Temporal stability and reproducibility of FDG-PET-based dose painting targets in head and neck cancer
I. Vogelius1, J.H. Rasmussen1, B.M. Fischer1, M.C. Aznar2, A. Loft3, C.B. Christensen4, J. Friborg5, C.A. Kristensen1, L. Specht1
1Rigshospitalet University of Copenhagen, Department of Oncology Section of Radiotherapy, Copenhagen, Denmark
2Rigshospitalet University of Copenhagen, Department of Clin.Phys. Nucl.Med. & PET PET & Cyclotron Unit, Copenhagen, Denmark

Purpose/Objective: The FDG avid sub-volume of the gross tumor volume, assessed on PET scans is hypothesized to be a clinically relevant target in painting strategies. Stability of the FDG positive tumor volume (GTVPET) is important for clinical implementation of dose painting. The purposes of this study are (1) to assess the stability of FDG PET/CT target volumes in a cohort of patients with squamous cell carcinoma of the head and neck (HNSCC) and (2) to assess the impact of a potential variability on radiation dose distributions in a dose painting trial.

Materials and Methods: Thirty patients with pharyngeal HNSCC were included in this prospective study. All patients were scanned prior to treatment with exactly three days interval between the two scans. Patients were scanned on the same PET/CT scanner according to same protocol and the patients were immobilized with an individually molded thermoplastic mask in supine position on a flat scanner couch as during radiotherapy treatment. The PET positive tumor (GTVPET) was defined and delineated visually and the same specialist in nuclear medicine who had delineated on the first scan did delineation on the second scan to reduce intra-observer variability. The delineation on the second scan was done with at least one month's delay and during this delineation they did not have access to the first scan. This yielded two GTVPET, one from the first scan (GTVPET1) and one from the second scan (GTVPET2). The images were co-registered systematically for each patient rigidly on bone (corpus of C2-C5 and the mandible) and mismatch between GTVPET1 and GTVPET2 was assessed. Dose plans with dose escalation (82 Gy) to GTVPET1 were simulated and all plans were approved as in clinical evaluations for an in-house phase I dose painting protocol. PTVPET were constructed from GTVPET with a 4 mm margin yielding PTVPET1 and PTVPET2 respectively. Mean dose and the percentage volume receiving 95% of prescribed dose (V95) were assessed to evaluate to which extend the variability impacted dose distribution. Results: Three patients were only scanned once and another three patients did not have pathological FDG uptake on neither of the two PET/CT scans, leaving 24 patients for further analysis. In average 17% of GTVPET1 was not in GTVPET2 (range 0.4-59.0) and in average 9.6% of GTVPET1 was not in GTVPET2 (range 0.0-41.0). Figure 1 shows a CT slice from the patient with the largest mismatch (59%) with DVH. Table 1 shows the mean dose and V95 for all 24 patients from the dose painting plans with dose escalation (82 Gy) to GTVPET1.
Conclusions: The use of a delineation guideline and fused MR-CT images evidently improved consistency and accuracy in delineation of OAR. The standardised delineation avoids a falsely anterior-caudal displacement of the optic chiasm, which often results in a dose overestimation in the chiasm and might lead to unnecessary underdosage of the tumour. This is a factual problem, especially when there is a steep dose gradient such as in proton therapy.

PD-031
Video-assisted minimally invasive surgery in patients with thyroid tumors
A. Polyakov1, F. Sevrakov1, M. Ratushnyy1, O. Matorin1, M. Filushin1, V. Vasylev1, I. Rebrikova1, A. Panaseikin1, N. Babaskina1

1P.A.Hertzen Moscow Cancer Research Institute, Microsurgery, Moscow, Russian Federation

Purpose/Objective: To assess the safety of video-assisted minimally invasive thyroid surgery in patients with benign or well-differentiated malignant thyroid tumors by the use of video-assisted minimally invasive surgery.

Materials and Methods: In the microsurgery department of P.A. Hertzen Cancer Research Institute, 325 patients with thyroid adenoma or differentiated thyroid carcinoma (T1-T2N0M0) were treated with video-assisted surgery since 2000.

In 321 patients we used lateral neck mini-incision, in 10 patients - axillary incision. Before surgery patients underwent multifocal fine-needle aspiration thyroid biopsy (ultrasound-guided) from the nodules and visually intact thyroid tissue. Biopsy was made from three sites in each of the thyroid lobes and from one site in the isthmus. The extent of surgery: hemithyroidectomy (the removal of one lobe with the isthmus) or subtotal thyroidectomy.

Results: Mean video-assisted surgery duration was 45 minutes with lateral neck incision and 180 minutes with axillary incision. There were no intraoperative complications. Patients were discharged from hospital at the 2nd-3rd day after surgery.

Conclusions: Video-assisted hemithyroidectomy or subtotal thyroidectomy from lateral-neck mini-incision or axillary incision is safe and adequate treatment method with good cosmetic outcome in patients with benign or well-differentiated malignant thyroid tumors.

PD-032
Sk(C)ip into the mouth
Y. He1, Z. Zhang1, C. Zhang1

1Shanghai 9th People’s Hospital Shanghai Jiao Tong University School of Medicine, Oral and Maxillofacial-Head & Neck Oncology, Shanghai, China

Purpose/Objective: Radical treatment of neoplasms may leads to complex oral and maxillofacial defects that pose a formidable challenge for reconstructive surgeons as this region is important both functionally and aesthetically. The main goal of a complex soft-tissue reconstruction is to replace ‘like with like’ tissues at minimal donor site ‘cost’ and
with maximal efficacy. Perforator flaps represent an important step forward and allow surgeons to accomplish these goals better. In this presentation, we would like to introduce the SCIP (superficial circumflex iliac perforator flap) in oral and maxillofacial defect reconstruction.

Materials and Methods: The anatomy and methods of preoperatively locating perforating vessels for the use of SCIP flaps are described. Color ultrasound, CTA were used in preoperative imagine of the perforators and operative design. 12 cases of oral cancer defects were repaired with the SCIPs from Nov 2013 to Oct 2014 in our department with the 100% survival rate of the flaps. The donor site research of pedicle length, vessel caliber, perforator study, flap thickness, flap complications was recorded as well. The recipient vessel was strictly selected in the head and neck region according to the donor site vessel caliber, position and length. The contour and function of the reconstructive site was compared and recorded. The advantages and disadvantages of this technique are discussed and are compared with that of non-perforator flaps, particularly the Radial Forearm Flap.

Results: In these 12 cases of microsurgery or supermicrosurgery, all the flaps are successful alive with no partial necrosis complication and flaps crisis. From the preoperative ultrasound, CTA and operative approval, 10/12 cases have one perforator and 2/12 have two perforators. 1 case out of these 12 cases has no SCIA in the imaging technique and approved in the operation. The mean caliber of SCIA is 0.7 mm, which leaded to strictly selection of recipient vessels taken the branches of superior thyroid artery as the first choice and branch of common facial vein as well. Post-operative outcomes of contours and functions are excellent and acceptable by the surgeons and patients compared with the conventional methods like RFF and ALTFT. Conclusions: SCIP flap have been shown unique advantages including being reliable, offering versatility in design and diverse tissues for composition, sparing major vessels, as well as improved donor site morbidity. It can often be raised using a two-team approach, without change of the patient’s position. The variability in the position and size of the perforator vessels, unpredictable pedicle length and the feasibility for microvascular anastomosis in the perforator level have to be considered as the main disadvantages of this technique. Advances in technology and continue to make preoperative planning of surgical flaps easier. With adequate training and supramicrosurgical techniques, SCIP flap also can be raised safely. We believe this perforator flaps will become more and more versatile options in oral and maxillofacial reconstruction.

PD-033
Value of lymphatic mapping SPECT/CT for sentinel node biopsy in 37 patients with T1-T2N0 oral cancer
G. Poissonnet1, E. Berta1, M.J. Ouvrier2, A. Sudaka3, O. Dassonville3, A. Bozec4, D. Culié4
1Institut Universitaire de la Face et du Cou, Head and Neck Surgery, Nice, France
2Centre Antoine Lacassagne, Nuclear Medicine Department, Nice, France
3Centre Antoine Lacassagne, Anatomopathology, Nice, France

Purpose/Objective: Correlation between lymphatic preoperative mapping, using SPECT/CT and surgical outcomes after Sentinel Lymph Node Biopsy (SLNB) for early N0 oral squamous cell carcinomas. Technical points

Materials and Methods: Thirty seven patients with primitive early stage of N0 oral squamous cell carcinoma were retrospectively studied after combination of surgical tumor resection and SLNB. Nuclear medicine procedures were performed preoperatively and included 2 planar acquisitions (antero-posterior and lateral views) and a SPECT/CT. 99mTc-Nanocolloid (15 MBq x 4) was injected peritumorally. Planar lymphoscintigraphies were acquired on a Siemens Symbia T2 immediately after injection, systematically followed by a SPECT/CT. SPECT images were reconstructed using CT for attenuation correction and using iterative reconstruction. Planar lymphoscintigraphy and SPECT/CT were analyzed by an experienced nuclear physician. A skinmark was done to help the surgeon localize the hot lymph nodes. Gammaprobe® detection was used for every patient during surgery. Correlation between preoperative lymph nodes mapping, surgical results such as levels or cervical side and histologic examination have been studied. When frozen section of the sentinel node was negative, patients were simply followed and when it was positive, patients were treated by elective neck dissection. When sentinel node was positive on definitive histologic examination, prophylactic neck dissection was secondarily performed.

Results: On SPECT/CT, 27 patients showed ipsilateral SLN and 9 patients contralateral SLN (24.3%). Of the 9 patients who have presented controlateral SLN, two had a median tumor. On surgery, positive SLNB on frozen section examination were found in 4 patients (10.8%), completed by selective neck dissection in the same operation. On definitive examination, positive SLN were found in 5 others patients (13.5%) and a prophylactic neck dissection was performed secondarily. No other positive lymph nodes have been found in all neck dissection for the 9 positive SLN. Macrometastases were found in 5 cases, micrometastases in 3 cases and isolated tumour cells in 1 case. Median follow-up was 21.1 months. As of today, none of the 29 negative SLNB patients have developed a regional neck recurrence, 1 patient have relapsed in primitive site tumor at 37.2 months and 1 patient had an earlier metastatic visceral evolution at 2 months. Neck control rate was 100 % in negative SLNB patients and 100 % in positive SLNB patients. In our specific experience, sensitivity of SPECT/CT was 100 % and negative predictive value was 100 %.

Conclusions: SPECT/CT combined with SLNB is able to detect with an excellent reliability occult node metastases. According to the surgeon and the nuclear physician, SPECT/CT was more informative than planar scintigraphy. It allows targeting of the level and the neck side for T1-T2N0 oral cancer and enables carcinologic control of the neck.

PD-034
Data from Pet Neck and GSK trials: Regional and geographic variability in HPV-associated oropharyngeal cancer
H. Mehanna1, M. Robinson2, N. Powell3, V. Paleri4, A. Hartley5, L. Fresco6, H. Al-Booz7, E. Junor8, S. Roberts9, K. Harrington10
1University of Birmingham, Institute of Head and Neck Studies and Education School of Cancer Sciences, Birmingham, United Kingdom
2Newcastle University, Centre for Oral Health Research, Newcastle, United Kingdom
3Cardiff University, Institute of Cancer and Genetics School of Medicine, Cardiff, United Kingdom
4Newcastle University, Dept. of Otolaryngology-Head and Neck Surgery, Newcastle, United Kingdom
5Old Queen Elizabeth Hospital, Hall-Edwards Radiotherapy Research Group, Birmingham, United Kingdom
6University Hospitals Coventry and Warwickshire, Department of Oncology, Coventry, United Kingdom
7Bristol Haematology and Oncology Centre, Haematology, Bristol, United Kingdom
8Western General Hospital, Edinburgh Cancer Centre, Edinburgh, United Kingdom
9University of Birmingham, School of Cancer Sciences, Birmingham, United Kingdom
10The Institute of Cancer Research, Radiation Oncology, London, United Kingdom
Background: There are variations in the reported proportions of head and neck cancers (HNC) caused by the Human Papillomavirus (HPV) between different countries and regions. It is unclear if these are true variations or only a result of different study designs and assays.

Materials and Methods: We performed post-hoc testing of formalin-fixed paraffin-embedded diagnostic biopsies for p16 immunohistochemistry and HPV-DNA (by polymerase chain reaction and in-situ hybridization) using validated protocols in 2 centralized, quality-assured laboratories on samples from 801 patients with HNC recruited prospectively between 2006-2011 in 4 multinational randomised trials.

Results: 21% (170/801) showed both HPV-DNA and p16 positivity, detected almost exclusively in oropharyngeal cancer (OPC) (55%); only 1% non-OPC were positive. HPV-OPC positivity differed significantly between Western Europe and Eastern Europe (37% vs 6%, p<0.0001) and between Western Europe and Asia (37% vs 2%, p<0.0001). Multivariate analysis showed geographic location (Western Europe OR 7.47, 95% CI: 3.07-18.17, p<0.0001; Asia OR 0.56, 95% CI: 0.13-2.53, p=0.4537 relative to Eastern Europe) was significantly associated with HPV-positivity, along with primary tumor site and smoking status.

Conclusions: This is the first study to firmly establish geographic variability as an independent risk factor in the prevalence of HPV-positive OPC, which appears to be prevalent in Western Europe, and is much less prevalent in Eastern Europe and Asia. Therefore, for most regions, the main burden of HNC caused by HPV-negative-HNC, with implications for planning of local healthcare provision, preventative public health policies, and design of global trials.

Acknowledgements: We would like to thank all the clinicians and patients who participated in the Pet Neck and GSK head and neck trials. We would also like to thank Mrs Gemma Jones for her help with preparing the manuscript. All authors have read and approved the most recent version of the manuscript. They have completed author disclosure and contribution forms.

PD-035
Outcomes following unilateral neck irradiation for oropharyngeal cancer stratified by HPV status
J. Waldron 1, S. Huang 1, J. Kim 1, A. Bayley 1, J. Ringash 1, A. Hope 1, M. Giuliani 1, J. Cho 1, L. Tong 1, B. O'Sullivan 1
1Princess Margaret Cancer Center, Radiation Oncology, Toronto, Canada

Purpose/Objective: To describe the outcomes and pattern of failure in oropharyngeal cancer (OPC) patients treated with unilateral radiotherapy (RT) to primary tumor and neck stratified by HPV status.

Materials and Methods: OPC patients treated with unilateral RT between 1999 and 2012 were identified from a prospective anthology of outcomes database. Tumor HPV status was ascertained by p16 staining for all available tissue blocks. Actuarial rates of overall survival (OS), local (LC), regional (RC), distant control (DC), and grade 3-4 late toxicity (LT) were estimated for the entire cohort and compared between p16-positive (p16+) and p16-negative (p16-) cases. Patterns of failure were described.

Results: A total of 96 eligible OPC patients were identified (87 tonsil, 7 soft palate, 2 base of tongue). Tumor p16 staining was ascertainment in 70 cases revealing 40 p16+ and 36 p16- cases. All patients were staged according to clinical/endoscopic and CT/MRI findings, including T1-2N0 (52), T1-2N1 (28), T1-2N2a (11), T3N0 (1), T3N1 (1), T1N2b (2), and T1N3 (1). Nodal burden was higher in p16+ cases (53% vs 27%, N+ p<0.01) and primary burden higher in p16+ cases (80% vs 58% T2, p=0.01). The primary tumors were all lateralized (>1 cm from midline) and with minimal (0-1 cm) tongue base or soft palate involvement. PET CT was not used for the staging workup. Median age was 58 years for all patients (range: 42-93), and 70 (73%) were male. p16+ patients were significantly younger than p16-, (median age 57 vs 68 years, p=0.001) and had less smoking history (48% vs 93% >10 pack year, p=0.001). RT was delivered with an ipsilateral wedged pair of beams (53) or IMRT (43) to include the primary site and ipsilateral neck. RT dose to gross tumor was: 51 Gy in 20 fractions over 4 weeks (51 Gy/20f/4w) (21), 60 Gy/25f/5w (56), or 70 Gy/35f/6-7w (12), and other (3). No patients received chemotherapy. Median follow-up was 5.8 years. 5-year OS, LC, RC, DC, and LT for the entire cohort were 74% (65-84), 92% (86-98), 95% (91-100), 99% (97-100), and 14% (5-22), respectively. Compared to the p16- cohort, p16+ OPC patients had much higher 5-year OS [91% (82-100) vs 56% (34-77), p<0.001] but similar LC [95% (82-100) vs 84% (68-99), p=0.33], RC [97% (91-100) vs 93% (83-100), p=0.75], DC [100% vs 96% (89-100), p=0.83], and LT [21% (7-34) vs 11% (0-27), p=0.25]. Treatment failure was identified in 9 cases: local 4, locoregional 2, regional 2, and local/distant 1. The two isolated regional failures occurred in contralateral level 2 in patients presenting with T2 N1 tonsil primaries (p16+:1; p16-: 1) and both were salvaged successfully with neck dissection.

Conclusions: Unilateral RT without chemotherapy for well-lateralized primary OPC with minimal nodal disease based on CT/MRI without PET results in high rates of disease control in both p16+ and p16- cases. Improved OS observed in the p16+ cases was likely influenced by their younger age and less smoking history. Contralateral neck failures were rare and successfully salvaged.

PD-036
Association of HPV/p16 status with efficacy and safety in pts with OPC in the phase 3 RT/cetuximab registration trial J.A. Bonner 1, P.M. Harari 2, J. Giralt 3, D. Bell 4, D. Raben 5, J. Liu 6, J. Schulten 7, K.K. Ang 8, D.I. Rosenthal 8
1University of Alabama at Birmingham, Comprehensive Cancer Center Department of Radiation Oncology, Birmingham, USA
2University of Wisconsin, Department of Human Oncology, Madison, USA
3Hospital Vall d’Hebron, Department of Radiation Oncology, Barcelona, Spain
4MD Anderson Cancer Center, Department of Pathology, Houston, TX, USA
5University of Colorado School of Medicine, Department of Radiation Oncology, Aurora, USA
6Merck Serono, Biostatistics Department, Beijing, China
7Merck KGaA, Medical Affairs, Darmstadt, Germany
8MD Anderson Cancer Center, Department of Radiation Oncology, Houston, TX, USA

Purpose/Objective: This retrospective analysis of the phase 3 IMCL-9815 trial assessed the role of human papillomavirus (HPV) in patients (pts) with locally advanced squamous cell carcinoma of the head and neck. Prior subgroup analyses suggested that pts with p16+ or p16- oropharyngeal carcinoma (OPC) had improved overall survival (OS) and locoregional control (LRC) when cetuximab was added to radiotherapy (RT) (Rosenthal et al, ASCO 2014). The objectives of the current analysis were to (1) expand upon prior efficacy analyses of p16 subgroups and assess the association of HPV status with LRC and OS in pts with p16+ OPC receiving RT + cetuximab compared with those receiving RT alone and (2) evaluate the effect of adding cetuximab to RT on mucositis and dysphagia in pts with p16+ and p16- OPC.

Materials and Methods: Pts received RT + weekly doses of cetuximab or RT alone. Efficacy subgroup analyses were conducted on pts with p16+, HPV-evaluable OPC (n = 63) and safety subgroup analyses were conducted on pts with p16- (n = 75) or p16- (n = 106) OPC. HPV and p16 status were determined by in situ hybridization and...
immunohistochemistry, respectively. Rates of LRC and OS by treatment arm and HPV status, as well as onset and duration of mucositis and dysphagia by treatment arm and p16 status, were estimated by the Kaplan-Meier method and log-rank statistics. P values for the incidence of mucositis and dysphagia were calculated using the Fisher exact test and χ² test, respectively.

Results: Baseline characteristics in the p16-evaluable OPC population were broadly similar, with the exceptions of lower tumor and nodal stages, a higher performance status, and a predominantly US origin in pts with p16+ OPC. LRC and OS analysis of pts with p16+/HPV+ (n = 49) or p16+/HPV- (n = 14) OPC yielded results similar to those of prior p16 subgroup analyses. In pts with p16-evaluable OPC, the addition of cetuximab to RT was not associated with a higher incidence of all grades of mucositis (P = .688) or dysphagia (P = .887) than RT alone. In pts with p16+ or p16- OPC, RT + cetuximab was not associated with significant changes in time to onset or duration of resolution of all grades of mucositis or dysphagia vs RT alone (Table).

Conclusions: Prior subgroup analyses of the IMCL-9815 trial suggested that pts with p16+ OPC and p16- OPC had improved OS and LRC when cetuximab was added to RT (Rosenthal et al, ASCO 2014). LRC and OS results for pts with p16+HPV+ OPC and p16+HPV- OPC reported here resemble these prior results. Furthermore, the addition of cetuximab to RT did not alter the time to onset or duration of resolution of mucositis or dysphagia in pts with OPC, irrespective of p16 status. While small sample size is a limitation of these subgroup analyses, the current findings should be regarded as hypothesis generating and should provide an impetus for future studies with larger sample sizes.

Results

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Conclusions: Prior subgroup analyses of the IMCL-9815 trial suggested that pts with p16+ OPC and p16- OPC had improved OS and LRC when cetuximab was added to RT (Rosenthal et al, ASCO 2014). LRC and OS results for pts with p16+HPV+ OPC and p16+HPV- OPC reported here resemble these prior results. Furthermore, the addition of cetuximab to RT did not alter the time to onset or duration of resolution of mucositis or dysphagia in pts with OPC, irrespective of p16 status. While small sample size is a limitation of these subgroup analyses, the current findings should be regarded as hypothesis generating and should provide an impetus for future studies with larger sample sizes.

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During treatment, no grade 4 acute toxicity was observed. Grade 3 dysphagia was seen in 58% in the AD-arm and 50% in the C-arm ($p = 0.43$). Grade 3 dermatitis was seen in 14% in the AD-arm and 12% in the C-arm ($p = 0.77$). Grade 3 mucositis was seen in 28% in the AD-arm and 40% in the C-arm ($p = 0.21$). Grade 3 pain was seen in 20% in the AD-arm and 12% in the C-arm ($p = 0.28$).

At 3 months of follow-up, 24% of patients in the AD-arm and 23% in the C-arm were PEG-dependent; grade $\geq 2$ dysphagia was seen in 15% in the AD-arm and 16% in the C-arm; grade $\geq 2$ mucositis was seen in 11% in the AD-arm and 10% in the C-arm; and grade $\geq 2$ xerostomia was seen in 40% in the AD-arm and 41% in the C-arm.

Conclusions: At 3 months of follow-up, no significant differences were observed in local, regional or distant control between both arms. Neither were there differences in acute or subacute toxicity. Long-term follow-up is needed to evaluate late control and toxicity.

PD-038
Risk factors for recurrence after carbon ion therapy for adenoid cystic carcinoma: impact of the histologic subtypes
H. Ikawa¹, M. Koto¹, A. Hasegawa¹, R. Takagi¹, K. Naganawa¹, T. Takenouchi¹, H. Tsuji¹, T. Kamada¹
¹National Institute of Radiological Sciences, Research Center for Charged Particle Therapy Hospital, Chiba, Japan

Purpose/Objective: Carbon ion beams provide a more beneficial dose distribution and a larger relative biological effectiveness compared to photons. Therefore, carbon ion radiotherapy (CIRT) may represent an effective treatment for adenoid cystic carcinomas (ACCs), which are known to be radio-resistant. ACC of the head and neck (H&N) is characterized by frequent development of local recurrences. Several reports have shown that the histologic subtype is one of the main risk factors for local recurrence after surgical treatment. However, the risk factors for local recurrence after CIRT are currently unclear. Thus, the aim of this study was to evaluate the risk factors, including histologic subtypes, for local recurrence after CIRT for H&N ACC.

Materials and Methods: Between December 2006 and July 2013, CIRT at a total dose of 57.6 or 64.0 Gy equivalent (GyE) was administered in 16 fractions to 114 patients with ACC of the H&N. Of these, 100 patients with identified histologic subtypes according to the World Health Organization classification were enrolled in this study. We divided the tumors into two grades as follows: low-grade tumors were defined as tumors with mostly tubular and cribriform areas (no stipulations on minor solid components), whereas high-grade tumors were defined as tumors with solid areas. The following factors were analyzed to identify the risk factors for local recurrence: age, gender, history of operation, prescribed radiation dose, tumor site, gross tumor volume, and the histologic grade of the tumor. The cumulative incidences of local recurrence were evaluated using the Kaplan-Meier method and compared by the log-rank test as a univariate analysis among the different subgroups. Furthermore, the significant factors ($p < 0.05$) in the univariate analyses were applied to the multivariate Cox's proportional hazard analysis. Local recurrence was defined as recurrence within the area treated by CIRT.

Table 1.
Patient and tumor characteristics
- Gender
  - Male: 35
  - Female: 65
- Age (y)
  - Median: 57
  - Range: 19-79
- History of operation
  - No: 85
  - Yes: 15
- Prescribed dose
  - 57.6 GyE/16fr: 33
  - 64 GyE/16fr: 67
- GTV, (cm³)
  - Median (Range): 38.6 (0.64 – 235.3)
- Tumor site
  - Nasal cavity and paranasal sinus: 50
  - Oral cavity and pharynx: 32
  - Others: 18
- Histologic grade
  - High grade: 17
  - Low grade: 83

Results: The 5-year local control rate of all patients was 68.6%, with a median follow-up period of 36.0 months. In the univariate analyses, the prescribed dose (57.6 GyE), gross tumor volume (> 38.6 cm³), and tumor grade (high-grade) were found to be risk factors for local recurrence ($p = 0.00001$, 0.012, and 0.001, respectively). In the multivariate analysis, the prescribed dose (hazard ratio [HR] = 6.923, 95% confidence intervals [CI] = 2.296–20.878, $p = 0.001$) and tumor grade (HR = 3.224, 95% CI = 1.199–8.669, $p = 0.02$) were demonstrated to be significant independent risk factors for local recurrence. The 5-year local control rates of the tumors receiving 57.6 GyE and 64.0 GyE were 32.1% and 84.5%, respectively. The 5-year local control rates of low- and high-grade tumors were 77.3% and 29.5%, respectively (Fig. 1).
Conclusions: A lower prescribed dose (57.6 GyE) and high tumor grade were found to be significant independent risk factors for local recurrence after CIRT for H&N ACC.

Conclusions: Patterns of long-term swallowing dysfunction after definitive radiotherapy or chemoradiation

Purpose/Objective: To identify patterns of long-term, radiation-induced swallowing dysfunction after definitive radiotherapy with or without chemotherapy (RT or CHRT) and to determine which factors may explain these patterns over time.

Materials and Methods: The study population consisted of 238 consecutive head and neck cancer patients treated with RT or CHRT. The primary endpoint was grade 2 swallowing dysfunction at 6, 12, 18 and 24 months after treatment. Cluster analysis was used to identify different patterns over time. The degree of swallowing dysfunction at baseline and at all subsequent time points (at 6, 12, 18 and 24 months) were considered for cluster modeling on the basis of their contribution to characterizing the patterns of late radiation-induced swallowing dysfunction. The differences between the dose-volume histograms (DHVs) of the swallowing organs at risk for each pattern were determined by using dose maps.

Results: The cluster analysis revealed five patterns of swallowing dysfunction: low persistent, moderate persistent, severe persistent, transient and progressive (Figure 1). Patients with high dose to the upper pharyngeal, laryngeal and lower pharyngeal region had the highest risk of severe persistent swallowing dysfunction. Transient problems mainly occurred after high dose to the laryngeal and lower pharyngeal regions, combined with moderate dose to the upper pharyngeal region. The progressive pattern was mainly seen after moderate dose to the upper pharyngeal region.

Conclusions: After definitive RT or CHRT, five different patterns of swallowing dysfunction can be identified over time. This could reflect different underlying biological processes. These results may improve identifying patients who are at the highest risk for developing severe persistent swallowing problems and who may benefit most from different preventive measures.

Proffered papers: Session 2:

OC-040
Hypopharynx carcinoma - the influence of IMRT and concurrent chemotherapy

T. Hermanrud1, M. Farhadi1, C. Boje2, C.D. Madsen2, K. Nowicka-Matus1, J. Johansen1, E. Andersen3, H. Primdahl1, M. Andersen1, J. Friberg1
1Rigshospitalet Copenhagen University, Department of Clinical Oncology, Copenhagen, Denmark
2Herlev Hospital Copenhagen University, Department of Clinical Oncology, Copenhagen, Denmark
3Aarhus University Hospital, Department of Clinical Oncology, Aarhus, Denmark
4Odense University Hospital, Department of Clinical Oncology, Odense, Denmark
5Aalborg University Hospital, Department of Clinical Oncology, Aalborg, Denmark
6Herlev University Hospital, Department of Clinical Oncology, Copenhagen, Denmark

Purpose/Objective: Carcinoma of the hypopharynx is a rare disease with a poor prognosis. As the majority of patients have localized disease at diagnosis, recent developments in radiation treatment techniques together with the introduction of concurrent chemo-radiation are likely to increase tumor control and survival rates. To investigate this at a population level, we used the Danish Head and Neck Cancer Group (DAHANCA) database.

Materials and Methods: All patients diagnosed with primary carcinoma of the hypopharynx in Denmark 2001-2010 were retrieved from the DAHANCA database. Missing information was obtained by review of hospital files. Incidence rates were calculated using the Danish population as denominator. Patients were followed until August 31, 2013, and univariate and multivariate survival analyses were performed using a Cox proportional hazards model, with overall survival and loco-regional control as end-points. Patients treated with curative intent were included in the survival analysis, and the final model included age, year of diagnosis, gender, stage, performance status, smoking history and concurrent chemotherapy.

Results: A total of 642 patients were identified, corresponding to an overall incidence rate of 1.2 per 100000 person-years (men 1.8 / women 0.4), and an age-standardized rate of 1.4 (WSP). Of these 642 patients, 507 (79.0%) received primary radiotherapy with curative intent with 27.0% receiving intensity-modulated radiotherapy (IMRT) and 20.3% concurrent chemotherapy. Comparing 2001-2005 to 2006-2010, loco-regional control, HR 0.67 (0.51-0.88) and overall survival, HR 0.79 (0.65-0.97) increased, corresponding to an increase in 2-year loco-regional control from 48.4 to 63.5% and overall survival from 41.9 to 50.2%. In univariate analysis, IMRT and concurrent chemotherapy were both associated with increases in survival and loco-regional control. However, in multivariate analysis, only concurrent chemotherapy significantly increased overall survival, HR 0.54 (0.40-0.73) and loco-regional control, HR 0.40 (0.26-0.61).

Conclusions: Overall survival and loco-regional control after primary radiotherapy with curative intent for carcinoma of the hypopharynx increased in Denmark during 2001-2010. Concurrent chemotherapy improved loco-regional control and survival, while these outcomes seemed unaffected by radiation treatment technique (IMRT/non-IMRT).
Pivotal trial results and EU comparison of 99mTc-Tilmannocept in sentinel node biopsy in head and neck cancer patients

R. De Bree1, J. Buscombe2, S.Y. Lai3, A. Agrawal4, C. Reininger2, F. Civantos6
1VU University Medical Center, Dept of Otolaryngology - Head and Neck Surgery, Amsterdam, The Netherlands
2Addenbrooke’s Hospital, Nuclear Medicine, Cambridge, United Kingdom
3MD Anderson Cancer Center, Dept. of Head and Neck Surgery, Houston, USA
4The Ohio State University, Dept. of Otolaryngology, Columbus, USA
5Navidea Biopharmaceuticals, Clinical, Columbus, USA
6University of Miami Hospitals and Clinics, Dept of Otolaryngology, Miami, USA

This abstract forms part of the media programme and will be available online on the day of its presentation to the conference.

Definitive chemoradiotherapy: An alternative to surgery in stage III/IV squamous cell carcinoma of the oral cavity?

M.H. Bertke1, N.E. Dunlap1, M.J. Amsbaugh1, C.L. Silverman1, J.M. Bumpous2, K.L. Potts2, R.A. Redman1, J.N. Shaughnessy1
1University of Louisville Brown Cancer Center, Radiation Oncology, Louisville, USA
2University of Louisville Brown Cancer Center, Otolaryngology, Louisville, USA
3University of Louisville Brown Cancer Center, Medical Oncology, Louisville, USA

Purpose/Objective: Locally advanced squamous cell carcinoma (SCC) of the oral cavity is most commonly treated with surgical resection followed by adjuvant radiation (RT) or chemoradiation (CRT). Complete resection of these tumors often requires extensive surgery and possible reconstruction. Definitive CRT is a preferred treatment strategy for advanced SCC in other head and neck subsites. Our objective was to compare functional and oncologic outcomes in patients treated with primary surgery followed by RT/CRT to those treated with definitive RT/CRT.

Materials and Methods: We retrospectively evaluated a cohort of 191 patients assessed in our institution’s multidisciplinary head and neck clinic between 2009 and 2014 for SCC of the oral cavity. Of these, 51 were found to be non-metastatic with stage III or IV disease treated with definitive RT/CRT (n=15) or upfront surgery (n=36). Following primary surgery, 25 (69.4%) received adjuvant CRT and 11 (30.6%) received adjuvant RT. Primary site was oral tongue in 30 patients (58.8%), floor of mouth in 9 (17.6%), gingiva in 9 (17.6%), and retromolar trigone in 3 (5.9%). Cox proportional hazard models were used to analyze risk of death or treatment failure and potential prognostic factors.

Results: The median follow-up period was 11.7 months (range 0.3 - 60.0). Of the 15 patients treated with definitive RT/CRT, upfront surgery was not employed due to patient refusal in 9 patients (60%), multidisciplinary consensus due to surgical morbidity in 5 patients (33.3%), and medical comorbidities in 1 patient (6.7%). Median radiation dose was 7,160 cGy in patients receiving definitive RT/CRT and 6,170 cGy in patients receiving upfront surgery. One patient in the upfront surgery group received a brachytherapy implant as a component of their treatment. In the RT/CRT group 14 patients (93.3%) received concurrent chemotherapy, and 8 (53.3%) were treated using IMRT with the remainder treated with 3D-CRT. The groups were well matched by gender, age, HPV status, smoking history, and nodal stage. There was a significantly higher rate of advanced T stage in the RT/CRT arm (p=0.008), with 6 (40%) and 9 (60%) RT/CRT patients staged T3 and T4 respectively versus 6 (17%) and 17 (47%) of upfront surgery patients. No difference was seen between the RT/CRT and upfront surgery groups in terms of overall survival (HR 0.644, p=0.434), local recurrence free survival (HR 0.672, p=0.547), local regional recurrence free survival (HR 0.374, p=0.195), or distant metastasis free survival (HR 1.031, p=0.971). Patients receiving upfront surgery were more likely to require a feeding tube for more than 3 months (p=0.049), but there was a trend toward increased radionecrosis in the RT/CRT group (p=0.258).

Conclusions: Definitive RT/CRT may be a viable alternative to upfront surgery in selected patients with locally advanced SCC of the oral cavity to avoid surgical morbidity without adversely affecting survival. Further prospective analysis is warranted.
Purpose/Objective: European Laryngological Society (ELS) classified transoral supraglottic resections (TSR) according to different types (Type I, limited to one supraglottic subsite; Type II, epiglottectomy without pre-epiglottic space removal; Type III, complete supraglottic resection including pre-epiglottic space; Type IV, resection of the 3-folds area and medial wall of the pyriform sinus). Aim of this paper is to seek a correlation between these types of resections with postoperative morbidity/complications and functional outcomes.

Materials and Methods: A retrospective chart review was performed on 96 patients affected by T1-T3 supraglottic SCC. TSR were classified according to ELS classification. Kaplan-Meier curves were used to evaluate 5-year overall (OS), disease-specific survivals (DSS), local control with laser alone (LCL), and organ preservation rates (OP). A cohort of 36 (38%) patients was submitted to functional evaluation by M.D. Anderson Dysphagia Inventory (MDADI), video-endoscopy of swallow (VEES) and videofluoroscopy (VFS) scored according to the Donzelli’s scale. Hospitalization time, tracheotomy, nasogastric-feeding tube (NGFT), and complications rate were compared among Type I-II vs. III-IV resections. The VEEs/VFS score was related to type of resection, age, radiotherapy (RT), and neck dissection (ND).

Results: Staging resulted 28 pT1, 46 pT2, and 22 pT3. The 5-year OS, DSS, LCL, and organ OP were 69.5%, 97.4%, 86.9%, and 94.6%, respectively. Types of resection were: 29 Type I, 14 Type II, 35 Type III, and 18 Type IV. Mean hospitalization time for the entire cohort was 9 days, temporary tracheotomy was performed in 7 (7%) patients (mean 4 days, range 1-14), NGFT was applied in 32 (33%) (mean 7 days, range 2-30). Ten (11%) patients experienced major complications: 3 bleeding at T site, 1 bleeding after ND, 2 subcutaneous emphysema, 2 aspiration pneumonia, 1 myocardial infarction, and 1 tracheal dehiscence after tracheotomy. Comparing Types I-II vs. Types III-IV TSR, the latter required an increased hospitalization time (11 vs. 5 days), more tracheotomies (9% vs. 5%), and NGFT (47% vs. 16%). Ninety percent of complications occurred in Types III-IV. MDADI mean value was 93.86, 93.65 and 94.13 in Type I-II and III-IV, respectively. According to Donzelli’s scale, at VEEs 27 (75%) patients were in Level 1 (normal), 8 (22%) in Level 2 (vestibule penetration), and 1 (3%) in Level 3 (tracheal aspiration), and at VFS 17 (47%) patients were in Level 1, 11 (31%) in Level 2, and 8 (22%) in Level 3. Level 3 was seen in 11% of Type I-II, and 33% of Type III-IV (p=not significant). RT, neck ND, and age didn’t impact on tracheal aspiration.

Conclusions: Type III-IV TSR are associated to longer hospitalization time, more frequent tracheotomy and NGFT, and higher complications rate compared to Type I-II. Even if not statistically significant, swallowing is more frequently impaired in more extended TSRs.

OC-044
‘Cure’ is a realistic goal in HPV-related oropharyngeal cancer with oligometastasis
S. Huang1, J. Waldron1, W. Xu1, J. Ringash1, A. Bayley1, A. Hope1, J. Kim1, J. Cho1, M. Giuliani1, B. O’Sullivan1
1Princess Margaret Cancer Centre / University of Toronto, Radiation Oncology, Toronto, Canada

This abstract forms part of the media programme and will be available on line on the day of its presentation to the conference.

OC-045
Best practices for supportive care during chemoradiotherapy in head and neck cancer patients
P. Bossi6, E. Russi1, G. Numico2, J.B. Veromken1, B. Murphy4, J. Raber-Durlacher3, J.A. Langendijk6, C. Rognoni7, S. Quaglini7, L. Licitra8
1Azienda Sanitaria Ospedaliera S.Croce e Carle, Radiation Oncology, Cuneo, Italy
2Hospital of Aosta, Medical Oncology, Aosta, Italy
3U.Z.A. University Hospital Antwerp, Department of Oncology, Edegem, Belgium
4Vanderbilt School of Medicine, Department of Oncology, Nashville TN, USA
5Academisch Centrum Tandheelkunde, Department of Periodontology, Amsterdam, The Netherlands
6University Hospital Groningen (UMCG), Radiation Oncology, Groningen, The Netherlands
7University of Pavia, Department of Biomedical Engineering, Pavia, Italy
8Fondazione IRCCS Istituto Nazionale dei Tumori, Medical Oncology, Milan, Italy
Purpose/Objective: Acute toxicity induced by concurrent chemoradiation (CRT) in locally advanced head and neck cancer (HNC) affects patients’ quality of life and their compliance with timing and dose intensity, possibly reflecting also into the burden of late effects. No guidelines exist for comprehensive best practices of supportive care (BPSC) during CRT.

Materials and Methods: Due to the lack of evidence from randomized controlled trials on most aspects of BPSC during CRT, an alternative approach to provide guidance was adopted. A formal consensus methodology was employed according to the model proposed by ASCO (Loblaw DA, Journal of Clin Oncol 2012), through a modified Delphi strategy. Briefly, a consensus group of 40 experts including medical oncologists, radiation oncologists, surgeons, nutritionists, speech language pathologists, infectious disease specialists, dentists and nurses was constituted.

A panel of facilitators for each topic performed a systematic review of the literature and a series of statements were defined. These were differentiated according to the timing of intervention (pre-treatment, during and after the treatment) and included an indication of the person in charge of the management of each BPSC aspect (e.g., physician, nurse, patient, and caregiver).

All experts rated these statements through a two-round process. A 4-point scale was adopted (1 = high consensus, 2 = low consensus, 3 = no consensus and 4 = unable to express an opinion).

Consensus was defined as agreement by ≥ 75% of voters. The statements were then finalized according to the suggestions of external reviewers. A computer-based guideline editor was employed to represent the recommendations within a decision algorithm, in order to facilitate their adoption.

Results: The following topics were included: mucositis, dysphagia, hematological toxicity, infections, nutrition and hydration, pain, skin toxicity and dental problems.

Recommendations were delivered for each topic.

Eventually, a proposal for algorithms with a comprehensive care of patients was defined, including timing of intervention and the expertise requested to manage the specific symptom.

Conclusions: Practice guidelines for BPSC during CRT for HNC and specific algorithms have been defined with a recognized methodology, in an area where high-quality evidence is lacking. The results of consensus, the algorithm of comprehensive BPSC and the areas where further studies are requested will be presented. Future developments will regard the analysis of compliance to the proposed BPSC, the impact on treatment efficacy and cost-effectiveness and the periodic update according to new published data.

Presented on behalf of Consensus Group on Supportive care during head and neck cancer chemoradiation

Debate: This house believes that radiotherapy should be combined with cetuximab but not with chemotherapy in patients with locally advanced HPV positive oropharyngeal cancer

For the motion
K. Harrington
The Institute of Cancer Research, Radiation Oncology, London, United Kingdom

Against the motion
J. Overgaard
Aarhus University Hospital, Department Experimental Clinical Oncology, Aarhus C, Denmark

SP-046
For the motion
B. Burtness
Yale Cancer Center, Yale University School of Medicine, Department of Internal Medicine, New Haven, USA

The study of organ preservation for locally advanced oropharyngeal cancer began at a time when tobacco-associated cancer predominated, and before the recognition that a subset of oropharynx cancers due to HPV infection existed, associated with significantly more favorable prognosis. Interpretation of older studies in light of the emergence of this second disease at the oropharynx subsite thus relies on the ability to test for HPV association and reexamine data in the HPV-associated and non-associated cohorts. There can be no question that chemotherapy with radiation is an effective and organ-preserving treatment for locally advanced HPV-associated oropharynx cancer: E2399 demonstrated 2 year progression-free survival of 86% in HPV-ISH positive oropharynx cancer treated with paclitaxel and carboplatin induction followed by paclitaxel/radiation; R0129 demonstrated 8 year survival of 81% for the best prognosis HPV-associated oropharynx cancer patients. However, chemotherapy may be associated with greater acute and late toxicity, and the long-term results of the 91-11 larynx preservation trial raise the possibility that concurrent cisplatin and radiation increases late non-cancer mortality. Thus, the availability of a non-nephrotoxic radiosensitizer such as cetuximab is of interest in this population. Concern has been expressed that cetuximab may be a suboptimal drug in HPV-associated oropharynx cancer because EGFR expression is somewhat lower (although still quite abundant) in HPV-associated than in HPV-negative cancers. However, cetuximab response has not been linked to EGFR expression intensity and density (ES397) or copy number (EXTREME); since EGFR ligand-binding exhibits negative cooperativity, this is not surprising. Cetuximab resistance has now been linked to downstream molecular abnormalities, such as the cluster of PTEN loss, AKT mutation, or PIK3Ca mutation, and this signature is less common in HPV-associated cancer. The ASCO presentation of outcome by p16 subsets in the Bonner trial of radiation vs. cetuximab/radiation is highly informative. This study demonstrated a HR for locoregional recurrence of 0.31 and for survival of 0.38, favoring cetuximab/radiation over radiation alone in p16+ oropharynx cancer patients. It also demonstrated 3 year locoregional control of only 65% for p16+ cancers treated with radiation alone, emphasizing the continued need for a radiosensitizer even in the p16+ population. For patients with chemotherapy-responsive disease, studied in E1308, the use of cetuximab with only 54Gy of radiation led to a 96% progression-free and overall survival in best prognosis patients, with very low rates of feeding tube use and low rates of grade ¾ toxicity in the 54Gy arm of the study. Thus, acute and late toxicity can be minimized, and very excellent cure rates maintained, with the use of cetuximab and radiation.

SP-047
Against the motion
U. Keilholz
Charité Comprehensive Cancer Center, Department Medical Oncology, Berlin, Germany

What is the basic result we currently achieve with radiotherapy-based treatment of locally advanced head and neck cancer patients? An overall cure rate of about 50%. But this cure rate varies considerably according to tumor site (with inferior outcomes for non-oropharyngeal and for HPV negative disease) and covariate. For oropharyngeal HPV positive tumors, the overall cure rate with radiochemotherapy varies among trials, but generally is in
the order of 80% in European as well as US patient populations. What do we know for oropharyngeal HPV positive cancer patients treated with radiation alone? Not much. What do we know for oropharyngeal HPV positive cancer patients treated with radiation plus cetuximab? We only have US data from the single randomized trial ever performed. This trial population has been retrospectively analyzed for HPV, and for a total of 75 patients there are outcome data, with 41 treated with radiotherapy plus cetuximab and 34 with radiotherapy only. The results for the cetuximab group look strikingly good with very few (4) recurrence events only and an overall survival of 88% at three years, compared to 72% with radiotherapy alone (HR 0.38, CI 0.15-0.94). And overall, the radiotherapy cetuximab combination was not associated with significantly more long-term toxicity as compared to radiotherapy alone. But there are remaining questions. The first obvious one is, whether we can base decisions on general treatment strategies on such a small subgroup of a single trial. But let us accept this one. However, my main question is whether these trial results are applicable to oropharyngeal HPV positive cancer patients in Europe. Why this question? Because the high incidence of smoking in Europe renders the majority of oropharyngeal HPV positive cancer patients from the good risk to an intermediate risk group, as shown by several studies. The molecular biology of this intermediate risk group still has to be deciphered, but it is difficult to apply the current data of the US population with low smoking prevalence to our patient cohorts in Europe. What is the goal of current treatment trial strategies in oropharyngeal HPV positive cancer patients? An overarching goal is to reduce long-term toxicity from radiochemotherapy, but there is a high degree of uncertainty, how to achieve this, and strategies vary considerably. Several trials are under way comparing radiochemotherapy to radiotherapy plus cetuximab, but robust results will not be available for a long time. But toxicity is not the only limitation, there is also need for improvement of cure rates, especially in the intermediate risk patient group of smokers with HPV positive oropharyngeal cancer. The goal to improve cure rates is addressed in another set of current trials with induction chemotherapy followed either by radiochemotherapy or radiotherapy plus cetuximab. However, only a meta-analysis of those trials will be able to answer the question on the best treatment regimen for patients with HPV positive oropharyngeal cancer patients, and may allow some conclusions for smokers. What should we do tomorrow? As we have no data on radiotherapy plus cetuximab for oropharyngeal HPV positive cancer in smokers and very limited data in non-smokers, we should develop science-driven novel treatment protocols, for which radiochemotherapy has to remain the reference treatment.

Symposium: New Treatments for tomorrow

SP-048
Tissue Engineering and in-vivo-regeneration of salivary glands
N. Rotter1, S. Schwarz1
1Universitätsklinikum Ulm, ENT Department, Ulm, Germany

Radiation therapy is a standard therapeutic modality in the treatment of patients with head and neck cancer. Despite the latest technological developments including intensity modulated radiation therapy (IMRT), irradiation still leads to severe and irreversible salivary gland damage in a large number of patients treated. As a consequence, loss of acinar cells and fibrosis of salivary gland tissue occurs and in turn leads to xerostomia, rampant caries, and recurrent infections. Because there is neither an effective nor a causative treatment available up to now, in recent years several groups worldwide started to focus their research on strategies for salivary gland regeneration. These strategies comprise in vitro engineering of salivary gland structures, gene-therapeutic therapies as well as stem cell based strategies for in-vivo-regeneration. Tissue engineering strategies range from the cultivation of differentiated acinar cell on various biomaterials to the recently reported transplantation of a bioengineered organ germ. In stem cell based approaches various different types of stem cells, such as mesenchymal stem cells from the bone marrow, adipose derived stem cells as well as salivary gland derived stem cells, have been applied with significant success in different animal models. However, the exact mechanisms of increased saliva flow in these models have not been elucidated yet. This discussion will give an overview of the different cell based techniques and will cover the most promising studies in more detail to give a definite answer to the question where we are currently positioned in salivary gland repair after radiation therapy.

SP-049
A stem cell therapy for xerostomia
R.P. Coppes1
1University Medical Center Groningen, Departments of Radiation Oncology and cell Biology, Groningen, The Netherlands

Radiation therapy for head and neck cancers commonly causes hyposalivation and its consequence xerostomia due to functional ablation of the salivary glands (SG). even after IMRT still 40% of the patients treated for head and neck cancer suffer from oral dryness leading to impaired speech, chewing, taste and swallowing, higher susceptibility for infections, and caries. These sequela severely affect the patients’ wellbeing and quality of life. A lack of viable stem cells able to maintain glandular homeostasis underlies radiotherapy induced SG dysfunction. Therefore, stem cell therapy could ameliorate xerostomia. Indeed, recently we showed that transplantation of mouse stem cells can rescue murine SG from radiation damage. Currently, we are translating our findings in mice to the human situation. Using human submandibular and parotid biopsies material we are able to culture human primary salispheres (hS) from which single cells could be obtained that were able to self-renew for ≥ 5 passages In vitro. Moreover, single hS cell derived salispheres could be stimulated to develop into an organoid with cells differentiating in ductal and acinar lineages as indicated by the expression of cytokeratins (Cyt+) and aquaporin-5 (AQPS51), respectively. These results indicate that in vitro we can obtain cells that are able to self-renew and differentiate into salivary gland lineages, two prerequisites of tissue stem cells. When xeno-transplanted into a mouse model of radiation-induced hyposalivation, hS cells proliferate extensively and were found to differentiate into human salivary gland structures within the mouse. Transplanted cells restored saliva production and improved regenerative potential of irradiated SGs. Tissue regeneration was elicited through different mechanisms, which will be discussed during the presentation. In conclusion, from human salivary glands a population of cells can be obtained that contain stem cell capable of self-renewal and differentiation and rescuing saliva production. Therefore, stem cell therapy may be a viable therapeutic option in the near future for the treatment of radiation-induced xerostomia.

N. Rotter1, S. Schwarz1
1Universitätsklinikum Ulm, ENT Department, Ulm, Germany

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SP-050
Promising targets beyond EGFR
M. Merlano, N. Denaro
Azienda Ospedaliera S. Croce e Carle, Medical Oncology, Cuneo, Italy

HNC represent a heterogeneous disease with regard to primary site, histology, molecular signature carcinogenesis and prognosis. EGFR represent a critical target for treatment approach both in tobacco/alcohol and HPV-induced HNC. A monoclonal antibody against EGFR (Cetuximab) has gained EMA and FDA approval to treat locally advanced HNC in combination with RT and in recurrent/metastatic setting in combination with platinum based CT. However cure rate and survival remain dismal. Therefore further drugs targeting molecular pathways associated with HNC are under evaluation. The specific targeting of new pathways (such as PI3K-akt-mTOR pathway; JAK-STAT pathway; tumor suppressive miRNAs; Notch1 and 2; epithelial to mesenchymal transformation and immunitary check points) is needed to improve survival outcomes in HN SCC. Moreover second and third generation EGFR inhibitors have the ability to overcome Cetuximab resistance for example targeting the tumor-specific EGFR deletion mutant EGFR VIII. A promising approach is also to combine several target therapy to abrogate the cross-talk between various receptor TK cascades. Phase III are currently on going using combinations of PI3K inhibitors or mTOR inhibitors and chemotherapy in platinum resistant R/M HNC (6-8% of HNCs present PIK3CA mutations). Recently studies on JAK inhibitors showed their antitumor activity in combination with EGFR inhibitors. An emerging field of treatment is to act on immune system. HNC elicits T cell anergy in both peripheral and tumor infiltrating lymphocytes (TILs). In the tumor microenvironment a low level of antimuor cytokines and co-stimulatory mediators has been reported. On the other hand co-inhibitor signals are increased (cytotoxic T lymphocyte associated antigen 4 (CTLA4) and programmed death 1 (PD-1))
Successful response depends on prevalence of co-stimulator and/or block of co-inhibitory signaling on immune system
A new therapeutic paradigm is to use mAb against co-inhibitory receptors CTLA4 and PD1. In particular objective responses with mAbs against PDL1 correlates with PDL1 expression on tumour. Moreover as in the melanoma setting the use of antiPDL1 AB (BMS936559) there is also growing enthusiasm for therapeutic vaccines against HPV16-18 and pneumonitis related to immunologic reaction may occur. Pre-treatment PDL-1 IHC expression (positivity above 5%) seems to be correlated with activity, but threshold of positivity needs to be defined.

SP-051
SBRT for oligometastatic disease
J. Eriksen
Odense University Hospital, Department of Oncology, Odense, Denmark

Stereotactic Body Radiotherapy (SBRT) is a well established treatment option for some cancer types like lung cancer but is also increasingly used in other sites like head and neck tumours.
SBRT requires a high level of accuracy for all phases of the treatment planning and delivery: Immobilization, target location, dosimetry, image guided treatment verification and a careful consideration of organ motion. Due to the hypofractionated nature of the treatment, attention must also be given to new dosimetric constraints for OAR’s. The optimal fractionation, total dose and patient selection still need to be defined.

SBRT can be used in the primary curative setting as boost for dose escalation or for distant single metastases in combination with curative radiotherapy for primary locoregional disease. SBRT might be especially interesting for selected groups like the elderly cancer patient or the patient with several co-morbidities due to the short overall treatment time and low acute morbidity. In fact, emerging data suggests locoregional control rates for >80 year old head and neck cancer patients that almost equal curative results for younger head and neck patients.
SBRT might also be indicated in the irradiation setting or as palliative treatment. As most of the recurrences occur in the previously irradiated field, it is often impossible with traditional radiotherapy to deliver an adequate dose to control the disease. SBRT enables to consider reirradiation in these inoperable localized recurrent cases. One year locoregional control rates of around 50% have been reported. In most cases, fractionated SBRT are preferred. Although encouraging data on toxicity are published with especially promising data on recurrent or oligometastatic lesions, the late morbidity might be high depending on site and previous radiotherapy. Risk of fatal carotid blow-out as an example is reported in around 8% of the cases.

The presentation will discuss the available data for using SBRT for head and neck oligometastatic disease in the primary situation and for irradiation as well as the indications in selected patient groups. Outcome results will be discussed considering the available data on acute and late morbidity.

SP-052
The role of PD-L1/PD1 pathway in SCCHN
J. Guigay, F. Peyrade, E. Saada
Antoine Lacassagne Cancer Center, Medical oncology, Nice, France

Recent progress has been made in oncology with new drug targeting immune system.
Ipilimumab which targets CTLA-4 has been the first one approved in melanoma.
Another way to block the deleterious cascade of T-lymphocyte inhibition is to block an extracellular target, namely Programmed Death Receptor-1 (PD-1). PD-1 is a cell surface receptor expressed by T cells, B cells, and myeloid cells, and member of the CD28 family involved in T cell regulation. PD-1 pathway is activated by receptor binding to ligands (PD-L1 or PD-L2) and its physiological role is to prevent uncontrolled immune activation during chronic infection or inflammation. In cancer, activation of PD-1 pathway can suppress antitumor immunity. Expression of PD-L1 on tumor cells is reported in renal cell carcinoma, melanoma, non-small cell lung cancer, and more recently in SCCHN. In mouse models, antibodies blocking PD-1/PD-L1 interaction lead to tumor rejection.

In clinical trials, targeting PD-1 pathway using human monoclonal antibody such as nivolumab, which blocks binding of PD-1 to PD-L1, showed promising results in metastatic solid tumors with durability of objective responses, and sustained overall survival (Topalian and al, NEJM 2012). Phase I studies showed a potential better safety profile of anti-PD1/PD-L1 agents in comparison with ipilimumab. Flare-up reaction with increase of tumor volume and pneumonitis related to immunologic reaction may occur. Pre-treatment PDL-1 IHC expression (positivity above 5%) seems to be correlated with activity, but threshold of positivity needs to be defined.
Results of phase I studies testing anti-PD1/PD-L1 agents in SCCHN patients have been recently reported with promising results in terms of efficacy with prolonged responses. During ASCO 2014 meeting, Seiwert et al. presented results of a phase Ib study of pembrolizumab in patients with HPV-negative and HPV-positive head and neck cancer. Pembrolizumab is a high-affinity monoclonal anti-PD-1 antibody with dual PD-1 ligand blockade: PD-L1 and PD-L2. Patients with recurrent/metastatic (R/M) SCCHN who were either HPV-positive or HPV-negative, with ≥1% PD-L1 immunohistochemistry expression in tumor cells or stroma
were enrolled in the study. The majority of patients received two or more prior chemotherapies. 78% of the screened patients were PD-L1-positive. 20% of patients treated every 2 weeks (q2w) at a dose of 10 mg/kg showed an objective response, and PD-L1 expression correlated with response. The anti-tumor effect was observed both in patients with HPV-positive and HPV-negative tumors. The duration of these responses was impressive, some already lasting over one year (Seiwert TY et al., ASCO 2014, CS5 6011). Updated data have been presented at ESMO 2014, showing that tolerance of pembrolizumab delivered in 56 patients seems good, with 1-2% of grade 3/4 fatigue, diarrhea, and rash (Chow L. et al., LB3A1, ESMO 2014).

First results of a phase I study evaluating the safety and efficacy of another anti-PD1 agent, MEDI4736, have been presented at ESMO 2014 congress (M. Fury M et al., abstr 988PD, ESMO 2014). MEDI4736 is a human IgG1 mAb, engineered to prevent ADCC activity, that blocks PD-L1 binding to PD-1 and CD-80. 50 pts with SCCCHN, with median 3 prior treatments received median 3 doses of MEDI4736 10 mg/kg q2w. Toxicity on the most apparent treatment was in 39% of pts; most frequently nausea (6%), diarrhea, dizziness, and rash (4% each). Dyspnea, syncope, raised GGT and sepsis (each 5%) were the most common grade ≥3 AEs. Among 29 evaluable SCCHN pts for efficacy, 4 pts had a partial response.

At now, randomized trials with anti-PD-L1/PD1 agents are ongoing in R/M SCCCHN patients in second line after platinum-cetuximab based first line therapy. Beside evaluation of efficacy, these studies should help to define the best population (HPV status, prior therapies) and useful biomarkers (threshold of PDL-1) to select patients who can benefit from these new agents.

New approaches combining anti-PD-L1/PD1 agents and other immunotherapy, chemotherapy and radiotherapy are currently explored.

Debate: This house believes that fit elderly patients with locally advanced disease should not be treated differently from younger patients

SP-053
For the motion
V. Budach
Germany

SP-054
Against the motion
P. Blanchard1
1Gustave Roussy, Radiation Oncology, Villejuif, France

Elderly patients, defined as patients older than 70 years old, account for 20-25% of all head and neck cancer patients. There is no consensus on the most appropriate treatment of this subpopulation. Although it is tempting to say that fit elderly patients should be treated similarly to younger patients, this sentence might cause harm to many patients. Indeed when looking at the available evidence, there is no demonstration that intensified treatment (e.g. concomitant chemoradiation, altered fractionation radiotherapy) provides any benefit to elderly patients compared to single modality treatment. And surgery is also associated with more complications in elderly patients. Most reports state that the presence of comorbidities rather than chronological age is associated with the occurrence of acute and late treatment side effects as well as treatment related deaths. But the frequency of comorbidities increases with increasing age of the patients and age remains the easiest thing to assess. The best practice for such patients is the inclusion in clinical trials evaluating the safety and efficacy of intensified treatments. When this is not possible, a comprehensive geriatric assessment should be performed. If the patient is deemed fit for aggressive treatment then extra-care should be given during and early after treatment, to closely monitor and treat acute toxicity and prevent treatment discontinuation. If possible a unimodal treatment should be preferred over complex multimodal treatments. As a conclusion although fit elderly patients could be treated like younger patients, they should receive an adapted clinical evaluation (namely comprehensive geriatric assessment) and be treated and monitored with extra-care to avoid undue treatment related toxicity. Whenever possible clinical trials directed to the geriatric population should be favored.

SP-055
For the motion
J. Vermorken
Belgium

SP-056
Why are elderly patients with locally advanced disease treated differently from younger patients?
J. Klozar1
1Charles University Hospital, Department of Otorhinolaryngology Head and Neck Surgery First Medical Faculty, Prague, Czech Republic

The survival is poorer in older patients treated for head and neck cancer than in younger patients. This is partially due to mortality connected with comorbidities but can also be a result of suboptimal treatment provided for this age group. Several reasons can lead to the less successful treatment in elderly patients: It may be the tendency not to use expensive diagnostic tools, to avoid extensive surgery and limit heavy multimodality treatment due to concern about toxicity. Also the participation in the decision making process regarding treatment plan is sometimes problematic in the older age group which can lead to the refusal of standard therapy. Even when the general point of view is that the age itself should not influence the choice of treatment modality, in reality the treatment of elderly patients often differs from the treatment of younger patients. This is partially due to higher rate of chronic diseases in the older age group. In general head and neck cancer patients are not a healthy population, between 46% and 65% of them suffers of other diseases. The frequency of comorbidities increases with age but interestingly diminishes after the age of 70. This is probably because part of the polymorbid patients already has died before this age and only patients with a healthier life style survive. Other problem in the elderly population may be the poor functional physical performance status, which can increase the postoperative morbidity and the rate of complication. Also the psychological status of elderly cancer patient can be modified in the sense of more significant depression and anxiety. Finally also the cognitive status is frequently modified in the elderly population and can be further deteriorated due to treatment. In spite of these differences, there is no doubt that part of the geriatric cancer patient population could benefit of the more aggressive tactic in the diagnostic and treatment approach. The question is how to sort out this patient group. It is clear that a simple assessment of comorbidity would omit other important parameters which should be taken into account in the decision making process. The most complex diagnostic tool is probably Comprehensive geriatric assessment (CGA) which has been well defined as a “multidimensional—usually interdisciplinary—diagnostic process designed to quantify an elderly individual’s medical, psychosocial, and functional capabilities and problems with the intention of arriving at a comprehensive plan for therapy and long-term follow-up.” This approach could probably help in the better choice of
diagnostic and therapeutic approach also in patients with head and neck cancer, but it requires the inclusion of a geriatrician in the team and is time consuming, costly and most likely not suitable for daily clinical practice. Currently there is one ongoing randomized study investigating the impact of CGA on survival, function and nutritional status in elderly patients treated for head and neck cancer. There are other diagnostic tools assessing the single different domains mentioned. Recently frailty questionnaires were developed. The term frailty is defined as a clinically recognizable state of increased vulnerability resulting from aging-associated decline in reserve and function across multiple physiologic systems. It should express the easiness with which a minor stressor can have a major impact on the physical state of a vulnerable patient. The assessment includes somatic, functional and psychosocial domains and seems suitable to help in the decision making process. However there are no results currently available confirming the beneficial role of frailty evaluation in the head and neck cancer patient.
1St James Institute of Oncology, Clinical Oncology, Leeds, United Kingdom

Purpose/Objective: To evaluate clinical outcomes in patients with nasal cavity or paranasal sinus tumours treated with surgery and adjuvant radiotherapy or with primary (chemo)radiotherapy

Materials and Methods: 52 patients with a nasal cavity or paranasal sinus tumour who had received either radical or adjuvant radiotherapy between 2007 and 2012 were retrospectively identified. Outcome measures were 2 year locoregional disease free survival (LRDFS), distant metastases free survival (DMFS), progression free survival (PFS), cause specific survival (CSS) and overall survival (OS).

Results: Median follow up was 32 (range 4-102) months. Median age was 65 years (range 22-87). 31 (60%) were male. The primary tumour location was maxillary sinus (22 (42%)), ethmoid sinus 2 (4%), nasal cavity 28 (53%). Breakdown of T staging was: T1 6 (12%), T2 15 (30%), T3 3 (6%), T4a 24 (46%), T4b 1 (2%). N staging was: N0 45 (87%), N1 2 (4%), N2a 0 (0%), N2b 0 (0%), N2c 3 (6%), N3 0 (0%). The tumour histological type was: squamous cell carcinoma 43 (83%), adenocarcinoma 5 (10%), olfactory neuroblastoma 2 (4%), malignant melanoma 1 (2%), neuroendocrine carcinoma 1 (2%). Infracranial, orbital and skin invasion was documented in 4 (8%), 5 (10%) and 7 (13%) of patients respectively.

31 (60%) of patients underwent surgery, 27 open and 4 endoscopically; neck dissections were performed in 13/31 (42%) patients (12 unilateral and 1 bilateral). Reported margins of excision were positive (<1mm) in 17/31 (55%) and close in 6/31 (19%) of patients. Radiotherapy was delivered with a 3D-conformal technique, electrons and IMRT in 43 (83%), 3 (6%) and 6 (12%) of patients respectively. Commonly prescribed radical radiotherapy doses were 70Gy in 35 fractions (n=6), 55Gy in 20 fractions (n=10). Commonly prescribed adjuvant radiotherapy doses were 66Gy in 33 fractions (n=9) and 60Gy in 30 fractions (n=10), 55Gy in 20 fractions (n=6). Radiotherapy was delivered to the primary site alone in 47 (90%), primary site and ipsilateral neck in 2 (4%) and primary site and bilateral neck in 2 (4%) of patients.

4 (8%) patients received induction chemotheraphy and 5 (10%) of patients received concurrent chemotherapy. 2 year LRDFS, DMFS, PFS, CSS and OS were 79%, 84%, 64%, 80%, and 75% respectively. Local, regional, local and regional and distant failure occurred in 8 (14%), 3 (6%), 1 (2%) and 6 (12%) of patients. There was no significant difference comparing outcomes of patients who underwent radical radiotherapy (n=21) and surgery and adjuvant radiotherapy (n=31): 2 year LRDFS was 73.8% and 76.6% (NS), and 2 year CSS was 81.3% versus 79.5% (NS).

Conclusions: Local and distant sites are the predominant patterns of treatment failure; regional failure is uncommon. In this series, disease outcomes appear similar regardless of whether treatment is with surgery and post-operative radiotherapy or radical radiotherapy.

PO-058 Primary chemotherapy followed by Transoral Laser Microsurgery and early laryngeal squamous cell carcinoma M. Cossu Rocca, F. Maffini, L. Santoro, S. Chiocca, M.A. Massaro, E. Preda, A. Cattaneo, E. Verri, D. Alterio, M. Ansarin
1European Institute of Oncology, Division of Medical Oncology, Milan, Italy

Purpose/Objective: Treatment of laryngeal cancer is particularly challenging because of the need to combine cure with preservation of laryngeal functions. We conducted a randomized phase II study based on a multimodal treatment with platinum induction chemotherapy followed by Transoral Laser Microsurgery (TLM) in patients with intermediate laryngeal cancer. Primary endpoints were disease free survival (DFS), overall survival (OS), and organ preservation (OP) at 2 years. The second endpoint was to look for predictive markers.

Materials and Methods: 161 patients with laryngeal cancer were evaluated at European Institute of Oncology from 2006 to 2008. Thirty-two of them were eligible for the study and 22 were finally enrolled. All patients had histologically proven diagnosis of squamous cell carcinoma of the glottis in stage T2 N0 M0 (tumor extended to supraglottis and/or subglottis, and/or with impaired vocal cord mobility) or T3 N0 M0 (only tumors limited to the larynx, with invasion of the paraglottic space or with minor thyroid cartilage erosion and without arytenoid fixation). 11 patients were randomized to a standard treatment with cisplatinum+5FU in 5 days continuous infusion (CDDP + SFU) and 11 patients to an experimental treatment with CDDP + vinorelbine + SFU in 21days continuous infusion. 2-3 cycles were administered before surgery and TLM was performed within the fourth week from the beginning of the last course of chemotherapy. All resections corresponded to type IV and V cordectomy and in case of positive resection margins after the first intervention, laser surgery was repeated within 6 weeks from the first operation. Finally, on every collected specimen we evaluated the expression of p53 (tumor suppressor protein), p27 (cell cycle inhibitor), Skp2 (phase kinase-associate protein), TS (thymidylate synthase enzyme), ERCC1 (repair S enzyme), and PI3K (phosphoinositide 3-kinase) activating mutations, which have all been described as actively involved in the pathogenesis of head and neck cancer.

Results: At 2 years DFS, OS and OP were respectively 70%, 100% and 100%. Laryngeal function was near normal in all patients and none of them underwent gastrostomy or tracheostomy. We didn't find any predictive factor between those examined but we noted that levels of Thymidylate Synthetase (TS) were statistically significant lower in those examined but we noted that levels of Thymidylate Synthetase (TS) were statistically significant lower in responder patients.

Conclusions: We did not achieve one of the primary endpoints of the study (DFS > 90% at two years), but our strategy did not worsen DFS and OS compared to the results of standard treatments reported in the Literature. About biological findings, our results may be a good omen for future studies aimed at identifying possible predictive factors that can direct the course of laryngeal cancer treatment.
**PO-060**

Long term results with intensified intensity modulated radiotherapy for nasopharyngeal cancer treatment

A. Bacigalupo, L. Belgioio, S. Vecchio, M. Marcenaro, S. Vagge, D. Agnese, S. Agostinelli, R. Corvò

1IRCCS San Martino IST, Radiation Oncology, Genova, Italy
2IRCCS San Martino IST, Medical Oncology, Genova, Italy
3IRCCS San Martino IST, Medical Physics, Genova, Italy

**Purpose/Objective:** We present our experience to assess the feasibility and efficacy outcomes of an intensified IMRT with simultaneous integrated boost (SIB) delivered in patients with nasopharyngeal carcinoma (NPC).

**Materials and Methods:** Between March 2009 and September 2013 34 patients affected by NPC including 30 males and 4 females with median age of 53 (range 11-77) were treated with definitive RT. Patients with stage T2 or greater or with positive nodes received concomitant chemotherapy (CT). Induction chemotherapy (ICT) was given to 20/34 patients with bulky local/regional disease, two of them have bone clearance of disease. At a median follow-up of 36 months (range 5 to 63), local regional control at 2 and 4 years were 66 Gy to macroscopic disease, 60 Gy to high risk subclinical disease, 54 Gy to low risk disease in 30 fractions. The daily SIB dose was 2.2 Gy on macroscopic disease.

**Results:** Thirty-two (96.9%) patients obtained a complete clearance of disease. At a median follow-up of 36 months (range 5 to 63), local regional control at 2 and 4 years were respectively 94% and 78.3% and the overall survival at 4 years was 93.2%. The most significant acute toxicities were grade 2 and grade 3 mucositis (41%). No grade 3 and 4 late toxicities have been observed; grade 2 xerostomia after six months from the end of treatment was reported in 11 patients; xerostomia toxicity decreased to grade 1 in 6 /11 within twelve months.

**Conclusions:** These results show intensified IMRT with SIB as an excellent strategy offering mild acute and late toxicity and high local control rates for patients with nasopharynx cancer.

**PO-061**

Primary Chemo-Radiotherapy outcomes for locally advanced head and neck cancers

R. Dandamudi, C. Fong, L. Fresco

1University Hospitals Coventry & Warwickshire NHS Trust, Clinical Oncology, Coventry, United Kingdom

**Purpose/Objective:** To evaluate the 5-year cause-specific and overall survival (OS), loco-regional control rates and late toxicities of locally advanced Head and Neck cancer patients treated with Primary Chemo-radiotherapy (CRT) over a two year period. We have also compared our results against the international standards published in the literature.

**Materials and Methods:** Between June 2006 and May 2008, sixty three patients with locally advanced Head & Neck cancer who had not undergone previous surgery were consented for primary CRT with curative intent. Three patients died prior to commencement of treatment due to disease-related problems, leaving 60 patients available for analysis. All were Squamous cell carcinomas, involving Oropharynx (63.3%), Nasopharynx (8.3%), Supraglottis (11.6%), Glottis (6.6%) and Hypopharynx (10%). Overall, 17 patients (28.33%) were Stage 3, 39 patients (65%) were Stage 4A, 4 patients (6.66%) were Stage 4B. Primary CRT was delivered using concurrent 3 weekly Cisplatin (75-80 (mg/m²)) and radiotherapy dose of 66-70 Gy in 33-35 fractions, treated daily in three phases by conformal 3-dimensional CT-planning. Treatment response was assessed radiologically 3 months post primary CRT. Survival was calculated from the start date of CRT and Time to Treatment Failure (TTF) from the completion of treatment. Radiation related toxicities were classified according to Radiation Therapy Oncology Group (RTOG) criteria. 2-year cause-specific survival was calculated using Kaplan-Meier curves.

**Results:** The median age was 57 years (range 18-79) with a Male: Female ratio of 3:1. Out of 60 patients who have completed intended treatment, the 5-year OS was 61.66 % and loco- regional control rate was 83.33 %. The primary treatment failure rate was 16.66 % (10/60 patients) of which 3 patients had residual disease at 3 months imaging and rest of the 7 had loco-regional recurrence. The median TTF was 16 months (range 3 to 44 months). Twenty three patients (38.3%) died with in 5 years of treatment of which ten patients (16.3 %) died of loco-regional disease progression and six patients (10 %) died of distant recurrence. Remaining seven died of other causes including four (6.6%) from second primary (lung and oesophageal) cancers. The incidence of persistent oral mucositis was 8.3 % (RTOG grade 3) and none had grade 3/4 skin toxicity. The incidence of late toxicities was 8.3 % for Osteoradionecrosis (ORN) of the mandible, 6.6 % for severe trismus and 1.6 % had sinus formation. The incidence of severe oropharyngeal stenosis/ total dysphagia was 6.6 % and 3 patients (5 %) were on long term (15-32 months) gastrostomy feeding tube for nutrition. None of the patients had treatment related death.

**Conclusions:** The 5 year survival and loco-regional control rates for locally advanced head & neck cancers treated with primary CRT (conventionally) from this single institute in UK were on par with international standards published in the literature. The incidence of late toxicities was below 9%. This data will be followed up for long term outcomes and can be used as a bench mark for comparison with current modern planning techniques like Intensity Modulated Radiotherapy (IMRT).

**PO-062**

Dose-painting IMRT with chemotherapy for nasopharyngeal carcinoma: single institution retrospective study


1NOVA Medical School U.N.L, Radiation Oncology, Lisboa, Portugal

**Purpose/Objective:** At the crossroads of medicine and dentistry, Oral Surgery, a recognized dental specialty by the European Union, is a key actor in the multidisciplinary management of head and neck cancer patients. The goal of our study is to evaluate the state of Oral Surgery in Europe in 2013 from its teaching to its practice, the hypothesis being that a notable diversity persists despite European Union harmonization process.

**Materials and Methods:** To understand the impact of this diversity applied to European Union freedom of movement and its ethical implications for the practice of oral surgery, we submitted a questionnaire to universities and organisms delivering authorization to practice in France, Germany, Spain, Sweden and United Kingdom chosen based upon inclusion and exclusion criteria.

**Results:** The profile of practicing Oral Surgeons is different dependent on the country. The university and hospital training conform to European recommendations and span 3 to 4 years. European Board certification is not required. Continuing education is mandatory only in France, United Kingdom and Germany. As for curricula and scope of practice, no consensus can be derived. A main ethical dilemma stands out. There is potential for a notable diversity persists despite European Union mobility of practice, no consensus can be derived. A main ethical dilemma stands out. There is potential for a notable diversity persists despite European Union mobility.
Materials and Methods: The clinical results of combined modality treatment for nasopharyngeal carcinoma with dose-painting intensity modulated radiation therapy (DP-IMRT) and chemotherapy in a European cohort of patients.

Results: The patients' characteristics are: median age 53 years; 97% Caucasian; 74% male; 71% WHO grade III; 43% T1; 14% T2; 18% T3; 25% T4; 17% N0; 17% N1; 39% N2; 27% N3. After a median follow-up of 22 months, 2-year local control was 95.9%, regional control was 98%, freedom from distant metastases was 88% and overall survival was 79.8%. Six patients underwent surgery for suspicious residual neck disease, no tumor was found. Grade 3 toxicities were: 37% mucositis; 5% dermatitis; 26% dysphagia; 3% xerostomia. With a mean cochlear dose of 496Gy, 8 patients required hearing prosthesis. Eight patients had grade 2 peripheral neuropathy and other three had grade 3-4 vacular toxicity. No patient developed brain necrosis.

Conclusion: Despite our short median follow-up, DP-IMRT with or without chemotherapy provided excellent local control and a major improvement from our previous 3D conformal published series. There have been no recurrences on the lower dose level. Caution is required regarding surgery for suspicious residual lymph nodes. Ultimately, further improvements must be achieved on toxicity profile and distant metastases control.

Purpose/Objective: To review outcomes and analyse the pattern of disease recurrence in patients with oral cavity squamous cell carcinoma (OCSCC) treated with surgery and post-operative adjuvant (chemo)radiotherapy (RT).

Materials and Methods: Patients treated with surgery followed by adjuvant (chemo)RT between 2007-2012 for OCSCC were retrospectively identified. A 3D conformal RT technique was used until 2010 and subsequently patients were treated with IMRT. Outcome measures were 2 year local control, regional control, disease free survival (DFS), distant metastases FS, and overall survival. Multivariate Cox regression analysis was performed for survival outcomes. Locoregional recurrences were reconstructed on the planning CT scan and were analysed in relation to target volumes and dosimetry.

Results: A total of 106 consecutive patients were identified. Median follow up was 27 (range 4-92) months. Median age was 60 years (range 28-82). 70/106 (67%) were male and 82/106 (77%) were current or ex-smokers. The primary tumour location was floor of mouth 34 (32%), anterior tongue 57 (54%), retromolar trigone 7 (7%); other 8 (8%). Breakdown of pathological TNM stage were: pT1 12 (11%), pT2 48 (45%), pT3 15 (14%), pT4 31 (29%), pN0 29 (27%), pN1 19 (18%), pN2a 0 (0%), pN2b 50 (47%), pN2c 8 (8%). 21 (20%), 48 (45%) and 37 (35%) tumours were well, moderately and poorly differentiated respectively. Pathologically 25 (24%) had positive (<1mm) margins, 25 (24%) margins <5mm and 56 (53%) had negative (≥5mm) margins. Perineural and lymphovascular invasion was present in 48 (45%) and 40 (38%) patients. Extracapsular spread was present in 40 (38%) patients.

Surgery involved resection of the primary with a unilateral neck dissection (ND) in 75 (71%) patients, and bilateral ND in 31 (29%) patients. RT was delivered with a 3D conformal technique and IMRT in 61 (57%) and 45 (43%) patients respectively. Prescribed RT dose was 66Gy in 33 fractions in 47 (44%), 60Gy in 30 fractions in 45 (43%), and other schedule in 14 (13%) of patients. Concurrent platinum chemotherapy was delivered to 30 (28%) of patients. 2 year local control, regional control, disease free survival, distant metastasis free survival, and overall survival were 93%, 91%, 82%, 94%, and 86% respectively. Factors which remained significant in multivariate analysis are summarised in Table 1. 14 (13%) patients experienced locoregional failure. Analysis of these recurrences revealed 6 in-field and 4 marginal to the high dose CTV, and 4 to be out-of-field. Overall the marginal/out-of-field recurrence rate was 8 out of 106 (7.5%) patients.

PO-064 Nodal failures of nasopharyngeal cancer: a Tunisian experience L. Ghobar1, O. Jmour1, F. Elloumi1, W. Siala1, N. Tourni2, A. Ghorbel1, M. Frikha1, J. Daoud1

1Hopital Habib Bourguiba, Département de Radiothérapie Cancériologique, Sfax, Tunisia
2Hopital Habib Bourguiba, Département de Cancinologie Medicale, Sfax, Tunisia

Purpose/Objective: To report our experience in the treatment of nodal failures of nasopharyngeal carcinoma (NPC).
Materials and Methods: 530 patients presenting with non-metastatic NPC were treated between 1993 and 2012 within the ORL committee in the University Hospital of Sfax. Treatment consisted of radiotherapy which was associated to chemotherapy in locally advanced stages. During follow-up, 8 of them experienced nodal failures. Treatment included cervical adenectomy, external irradiation, chemotherapy or a combination of these modalities.

Results: Median age at initial diagnosis was 42.3 years (31–49) and 50% had locally advanced disease. Nodal relapse was detected after a median follow-up of 41.4 months (14–71). Two patients had N2/N3 failure. Four patients had cervical surgery followed by radiotherapy or chemo-radiotherapy. Two patients had chemo-radiotherapy and the 2 others had chemotherapy. After a median follow-up of 8 months (2–15), only 3 patients accomplished complete remission, however, 2 of them presented metastatic failure later. The others died of progressive disease. Late toxicities include cervical sclerosis and xerostomia.

Conclusions: Radiotherapy (RT) is the mainstay of treatment of nasopharyngeal carcinoma (NPC). Innovation in radiation modalities and adjunction of chemotherapy had improved therapeutic ratio. However, nodal failures represent a scarce experience even for patient and physician and their treatment remains controversial. Multimodal treatment is often required. Many institutions recommend cervical dissection, others indicate re-irradiation. Therapeutic results remain scarce and are worse than those with local failures. We will compare our results to our previous experience in the treatment of local treatment in the poster. Caution is necessary to morbidity related to cumulative radiation induced late effects.

Complete response to treatment was achieved in 70%. Of these, 28.6% relapsed (7 locally and 3 regionally) and 71.4% have not recurred to date. Median follow-up was 3.4 years (range: 2–20 years). Second neoplasm appeared in 10% of cases and 26% presented distant metastases.

Conclusions: Nasopharyngeal carcinoma occurs in young people. It is diagnosed in advanced stages, with a clear predominance of undifferentiated carcinomas and patients achieve good overall response rates to treatment. Our results correlate with those described in the literature.

Purpose/Objective: Describe the epidemiology and treatment of our series and compare our results with those published to date.

Materials and Methods: A retrospective study of 50 patients diagnosed with nasopharyngeal carcinoma. The following variables were studied: age, sex, first symptoms, histology, stage, recurrences, metastases, treatment performed, response to therapy and survival.

Results: The mean age at diagnosis was 55 years; male/female ratio was 4/1. Cervical tumour was the first sign at diagnosis in 56% of cases, with a mean clinical evolution of 5 months. Undifferentiated nasopharyngeal carcinoma was the most common histology (72%); 76% were diagnosed at advanced stages, 76% with regional lymphadenopathy and 6% with metastases at diagnosis.

PO-065
A 23 year retrospective review of patients with nasopharyngeal carcinoma
T. Bonfill Abella, Y. Escamilla Carpintero, A. Aguilà Artal, E. Mur Restoy, J. Diaz Arguello, E. Garcia Perez, M.A. Seguí Palmer, E. Saigí Grau
1Parc Taulí Sabadell. Hospital Universitari. Universitat Autònoma Barcelona, Medical Oncology, Sabadell, Spain
2Parc Taulí Sabadell. Hospital Universitari. Universitat Autònoma de Barcelona, Otorhinolaryngology, Sabadell, Spain
3Institut Oncològic del Vallés (CST-CSPT-HGC), Radiation Oncology, Sabadell, Spain
4Parc Taulí Sabadell. Hospital Universitari. Universitat Autònoma de Barcelona, Medical Oncology, Sabadell, Spain

Purpose/Objective: Describe the epidemiology and treatment of our series and compare our results with those published to date.

Materials and Methods: A retrospective study of 50 patients diagnosed with nasopharyngeal carcinoma. The following variables were studied: age, sex, first symptoms, histology, stage, recurrences, metastases, treatment performed, response to therapy and survival.

Results: The mean age at diagnosis was 55 years; male/female ratio was 4/1. Cervical tumour was the first sign at diagnosis in 56% of cases, with a mean clinical evolution of 5 months. Undifferentiated nasopharyngeal carcinoma was the most common histology (72%); 76% were diagnosed at advanced stages, 76% with regional lymphadenopathy and 6% with metastases at diagnosis.

PO-066
Impact of intensity-modulated radiotherapy in the treatment of nasopharyngeal cancer: single center experience
1Azienda Ospedaliero-Universitaria Careggi, Radiation Oncology, Florence, Italy
2Azienda Ospedaliero-Universitaria Careggi, Human Pathology, Florence, Italy
3Azienda Ospedaliero-Universitaria Careggi, Otolaryngology - Head and Neck Surgery, Florence, Italy

Purpose/Objective: to report the clinical outcome and toxicity of patients affected by nasopharyngeal cancer treated with different radiotherapy (RT) techniques, namely 3-dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT).

Materials and Methods: between January 2000 and December 2013, 82 patients underwent concomitant chemoradiation with curative intent. By January 2007, IMRT was clinically available at our department and became preferentially adopted in place of 3DCRT. Progression-free survival (PFS) was defined as the time from first day of treatment to progressive disease or death from any cause; overall survival (OS) was defined as the time from first day of...
treatment to death from any cause. Acute and late toxicities were retrospectively evaluated according to NCI Common Terminology Criteria for Adverse Events (CTCAE version 4.0) and LENT SOMA scale, respectively.

Results: Fifty-one patients (62.2%) were treated with 3DCRT while 31 with IMRT (37.8%). The median age of patients was 52.4 years. The majority of patients (54; 65.8%) were diagnosed with loco-regional advanced disease: 35 (42.6%) were in stage IVA/IVB disease and 19 (23.1%) in stage III, respectively. Sixty-four patients (78%) were treated with a conventionally-fractionated, 7 weeks RT regimen delivered in a sequential approach: 50 Gy were delivered to sites deemed at low risk of microscopic infiltration, 60 Gy to macroscopic uninvolved sites but deemed at high risk of disease presence or relapse, 70 Gy to tumor and involved nodal clinical target volumes (CTV’s). In 18 patients (22%) the IMRT technique allowed the simultaneous delivery of different doses per fraction, namely 1.8 Gy, 2 Gy and 2.2 Gy aimed at the same volumes described above within a shorter overall treatment time (30 fractions delivered in 6 weeks). The majority of patients (62; 75.6%) received cisplatin-based, concomitant chemotherapy: a 100 mg/m² three-weekly schedule was administered to 34 of them (56%) while the rest (28; 44%) received a 40 mg/m² weekly schedule. Twenty patients (24.3%) of the whole cohort diagnosed with very advanced tumors infiltrating neurological structures were given induction chemotherapy (cisplatin-5 fluorouracil or cisplatin-5 fluorouracil-docetaxel regimen) before concomitant chemoradiation. Twenty-five patients (24.3%) mostly affected by stage II and II N0 disease, or unfit to receive chemotherapy, were treated with radiotherapy alone. In terms of clinical outcome, the 30-month PFS was 69.6%; progressive disease was diagnosed in 25 patients (30.4%), among them 18 treated with 3DCRT and 7 with IMRT. The first site of failure was distant in 12 (48%) cases and loco-regional in 13 (52%). In terms of OS, at a median follow-up of 51 months, 47 patients (57.3%) were alive. Regarding acute toxicity, the most frequent adverse event was severe (G3-G4) mucositis which was diagnosed in 17 patients in the 3DCRT group (33.3%) and in 8 in the IMRT group (25.8%). The 12-month xerostomia of moderate-severe intensity (G2-G3) was also more frequently found in the 3DCRT cohort than in the IMRT one (31.3% and 10% of patients, respectively).

Conclusions: our retrospective, single-center experience supports the positive impact of technology evolution of RT techniques from 3DCRT to IMRT in the treatment of nasopharyngeal cancer in terms of reduced toxicity and, potentially, improved quality of life.

PO-067
The impact of different radiotherapy techniques on treatment outcome of hypopharyngeal carcinomas
B. Aydin¹, E. Dogan¹, H. Cetinayak¹, O. Ozdemir¹, S. Sarioglu¹, E. Ada¹, F. Akman¹
¹Dokuz Eylul Univ. School of Medicine, Radiation Oncology Department, Izmir, Turkey
²Dokuz Eylul Univ. School of Medicine, Department of Otorhinolaryngology - Head and Neck Surgery, Izmir, Turkey

Purpose/Objective: To evaluate the outcomes of two dimension conventional radiotherapy (2D-RT) versus three dimensional conformal radiotherapy (3D-CRT) for hypopharyngeal cancer.

Materials and Methods: We compared 2D-RT and 3D-CRT techniques in patients with hypopharyngeal squamous cell carcinoma (SCC) treated with curative radiotherapy (RT) or chemoradiotherapy between January 1992 and August 2011 according to the DEHNTG protocol for head and neck carcinoma in our department. Fifty-six patients with hypopharyngeal cancer were analyzed retrospectively. Thirty-three patient (Group 1) were planned using 2D-RT and 23 patients (Group 2) with 3D-CRT plans. Median age at diagnosis was 55 (13-79). The distribution of clinical stages of patients according to the seventh edition of the American Joint Committee on Cancer (AJCC) staging system were Group 1 patients: 1 (3.0%) Stage II-III, 32 (97.0%) Stage IV; Group 2: 7 (30.4%) Stage II-III and 16 (70%) Stage IV, respectively. The standard approach was conventionally fractionated RT (66-70 Gy/33-35 fractions/6-7 weeks) with concurrent chemotherapy (cisplatin 75-100 mg/m² on days 1, 22 and 43). Group 1 patients were irradiated through bilateral, opposing and 1 anterior cervical field or two oblique fields and Group 2 non-coplanar 3-7 beams were used to a dose of 66-70 Gy in 33-35 fractions. The acute and late side effects were graded according to Radiotherapy and Oncology Group criteria (RTOG).

Results: The median follow-up time was 14 (2-214) months. While complete response rate in Group 2 patients was higher than Group 1, the difference was not statistically significant (p=0.09). The 2, 5, 10-year overall survival (OS) rates for Group 1 and Group 2 were 25.8%, 19.3%, 19.3% and 61.9%, 55.0%, 55.0%, respectively. The 2, 5, 10-year disease specific survival (DSS) and disease free survival (DFS) rates for Group 1 were 33.6%, 25.2%, 25.2% and 29.9%, 22.4%, 22.4%; for Group 2; %69.6, %64.6, 64.6 and 60.3%, 53.6%, 53.6%. Early side effects in patients in Group 1 were statistically significantly more frequent than in Group 2 patients (p=0.04). Late side effects in Group 2 were lower than Group 1, however it was not statistically significant (P=0.09).

Conclusions: Chemoradiotherapy is an effective treatment modality in organ-sparing treatment, inoperable advanced stages of hypopharyngeal carcinoma. With a relatively small number of patients in this study 3D-CRT group compared to conventional RT group showed an advantage in DSS and early side effects. Overall survival, DFS, late side effects and treatment response rates were higher in the group treated with conformal RT, but it was not statistically significant. In the treatment of hypopharyngeal cancer morbidity will affect the quality of life therefore it is appropriate to treat with modern radiotherapy techniques.

PO-068
Soft tissue necrosis in head and neck cancer patients treated with radiation therapy after transoral robotic surgery
Y.H. Lee¹, Y.S. Kim¹, H.S. Jang¹, B.O. Choi¹, J.H. Chang¹, M.S. Kim², D.I. Sun², J.H. Kang³, S.H. Hong³, S.L. Jung⁴
¹Seoul St.Mary’s Hospital The Catholic University of Korea, Department of Radiation Oncology, Seoul, Korea Republic of
²Seoul St.Mary’s Hospital The Catholic University of Korea, Department of Otorhinolaryngology, Seoul, Korea Republic of
³Seoul St.Mary’s Hospital The Catholic University of Korea, Department of Surgery, Seoul, Korea Republic of
⁴Seoul St.Mary’s Hospital The Catholic University of Korea, Department of Radiology, Seoul, Korea Republic of

Purpose/Objective: We investigated the frequency and risk factors for surgical bed soft tissue necrosis (STN) of head and neck cancer patients treated with post operative radiation therapy (PORT) after transoral robotic surgery (TORS) or wide excision (WE) with primary closure.

Materials and Methods: A total of 67 patients treated with TORS or WE and PORT between 2008 and 2014 were retrospectively analyzed for STN. Radiation was prescribed to primary tumor bed with median 63.3 Gy (range, 45-67.2 Gy) with 2 Gy/fraction. STN was defined as ulceration and necrosis of surgical bed, persistant unhealing high grade acute mucositis with pain or surgical bed necrosis in the imaging study after completion of PORT.

Results: A total of 12 of 67 patients (17.9%) was diagnosed of STN. Oropharyngeal site (21.6%) was most susceptible to STN. For patients with STN, median tumor size was 2.9 cm.
Conclusions: The patients treated with TORS or WE with primary closure and PORT had risk of surgical bed STN than free flap reconstructed patients. Risk factors of STN was DOI and grade 3 acute mucositis in multivariate analysis. STN patients showed no local recurrence but significant lower distant metastasis free survival. Radiation therapy plan after TORS has to be carefully designed to prevent STN. Longer follow-up and a larger number of patients are needed to determine the risk factors of STN.

PO-069 The role of neoadjuvant chemotherapy in the treatment of nasopharyngeal carcinoma

1The Catholic University of Korea, Radiation Oncology, Seoul, Korea Republic of
2Seoul National University College of Medicine, Radiation Oncology, Seoul, Korea Republic of
3Samsung Medical Center Sungkyunkwan University School of Medicine, Radiation Oncology, Seoul, Korea Republic of
4Yonsei University College of Medicine, Radiation Oncology, Seoul, Korea Republic of
5Research Institute and Hospital National Cancer Center, Radiation Oncology, Il-San, Korea Republic of
6Chonnam National University Medical School, Radiation Oncology, Kwang-Ju, Korea Republic of
7Ajou University School of Medicine, Radiation Oncology, Su-Won, Korea Republic of

Purpose/Objective: The purpose of this study was to compare treatment results and toxicity in nasopharyngeal carcinoma (NPC) patients treated by concurrent chemotherapy (CCRT) alone (the CRT arm) or neoadjuvant chemotherapy followed by CCRT (the NCT arm). Materials and Methods: To review NPC patterns of care and treatment outcome in South Korea, a multi-institutional retrospective study was performed (KROG 11-06). The data of 1474 primary NPC patients were collected from 15 institutions. Of these patients, 568 patients treated by CRT alone or by neoadjuvant chemotherapy followed by CCRT were selected. Response rates, survivals, compliances, and toxicities were analyzed. Results: At baseline, more patients with a WHO type I histology were included in the CRT arm (20.3% vs. 9.0%, \( p < 0.0001 \)), and more patients were treated by IMRT in the NCT arm (39.2% vs. 66.5%, \( p < 0.0001 \)). Three-year overall survival rates were 88% and 85% in the CRT and NCT arms, respectively, which was not a significant difference (\( p = 0.066 \)). Three-year failure-free survival (66% vs. 63%, \( p = 0.025 \)) and grade 3 acute mucositis were similar in both arms. This study did not show the superiority of NCT followed by CCRT over CCRT alone compared with other promising results performed in endemic area. The role of NCT in addition to CCRT remains to be defined and should not be viewed as the standard of care.

PO-070 Experience of induction chemotherapy in head and neck tumors ECIVb in Mexico City

M. Villavicencio-Queijeiro4, A.E.V.S. Aura Erazo Valdies-Solis1, A.J.R. Alejandro Juarez Ramiro1, H.G.M. Hector Gurrola Machuca1, J.P.M. Josue Perez Mora1
1ISSSTE 20 de Nov. (Govermement), Departamento de Radio-Oncology, DF, Mexico
2ISSSTE 20 de Nov. (Govermement), Departamento de Oncology, DF, Mexico

Purpose/Objective: In Mexico, the incidence of head and neck cancer is low and does not appear among the top 10 causes of death. The age of presentation is 50-60 años, with an incidence of 3.74 per 100,000 population, Induction chemotherapy is considered an option for first-line treatment followed by radiotherapy impact on progression-free survival, locoregional control and preservation of body. Objectives: To describe the clinical responses in patients with head and neck cancer locally advanced, treated with induction chemotherapy during the period January 1, 2011 to August 31, 2014. Materials and Methods: Retrospective research in 44 patients with head and neck squamous cell carcinoma who were treated with induction chemotherapy (3 cycles of chemotherapy with Docetaxel, Cisplatin, 5FU) in the Department of Medical Oncology Service in Hospital National Medical Center November 20 from January 1st 2011 to August 31st 2014. Patients were divided into three groups non-homogeneous (complete response, stable disease, progression of the disease). In the table 1 are the results of the different localizations and the answers should be mentioned that after induction chemotherapy, received concomitant chemotherapy and radiotherapy at the end of it, imaging studies, and biopsy nasofibrolaryngoscopy were made. Results: The incidence of head and neck tumors were analyzed for the period January 1, 2011 to August 31, 2014, finding a total of 356 cases, of which 44 patients received induction chemotherapy, 80 men, aged average of 60 years, with 63% of EC IVb, 16% EC, 11% nasopharynx, maxillary antrum 8%, paranasal sinuses, 11% amygda, 5% other site (gingiva and lips), with complete responses in 58% of cases, 23% with disease progression, 3% of deaths, 16% stable disease, anatomical site analysis showed that the site is more complete answers larynx subsequently amygda. Conclusions Induction chemotherapy is a treatment option in patients with laryngeal tumors and amygda ECIVb in Mexican population.
PO-071
ELAN Program: Personalized treatment according to geriatric assessment in elderly patients with head & neck cancer

C. Ortholoin, H. Le Caer, C. Mertens, A. Leysalle, C. Even, S. Renard-Oldrin, M. Alfonsi, Y. Pointreau, A. Auperin, J. Guigay, on behalf of GERICO and GORTEC.

1Princess Grace Hospital, Radiotherapy - Oncology, Monaco, Monaco
2Hospital Center Draguignan, Oncology, Draguignan, France
3Centre Antoine Lacassagne, Radiotherapy - Oncology, Nice, France
4Centre Antoine Lacassagne, Radiotherapy - Oncology, Nice, France
5Gustave Roussy, Oncology, Villejuif, France
6Institut de Cancérologie de Lorraine, Radiotherapy - Oncology, Vandoeuvre-les-Nancy, France
7Institut Sainte Catherine, Radiotherapy - Oncology, Avignon, France
8Clinique Victor Hugo, Radiotherapy - Oncology, Le Mans, France
9Gustave Roussy, Biostatistics, Villejuif, France
10Centre Antoine Lacassagne, Oncology, Nice, France

Purpose/Objective: 30% of SCCHN occur in patients more than 70y; the main challenge in these patients is to balance the benefit/risk treatment ratio regarding tumor related symptoms. However, these patients are usually excluded from trials. We developed a large prospective clinical program planned to enroll 448 patients in 3 distinct trials to improve the multidisciplinary management of elderly SCCHN patients.

Materials and Methods: To be included among one of the three trials, elderly SCCHN patients, not suitable for surgery, must first be enrolled in ELAN-ONCOVAL study where they are classified as fit or unfit, using a geriatric evaluation applicable to the daily practice of oncologists. Comprehensive Geriatric Assessment is optional. Assessments of efficacy, toxicity, autonomy (Activities in Daily Living (ADL) Instrumental ADL (IADL) scales) and Health related quality of life (EORTC QLQ-C30 and QLQ-H&N35 questionnaires) are performed in clinical trials.

In curative situation, unfit patients are proposed to be enrolled in the randomized, non-inferiority, ELAN-RT trial, comparing standard radiotherapy (RT) (70 Gy, 35 fractions, 7 weeks) and hypofractionated split course schedule (30 Gy in 10 fractions, 2 weeks stop, 25 Gy in 10 fractions, total 6 weeks). Main endpoint is the rate of patients alive with local control 6 months after the end of RT. 202 patients are planned to be randomized.

In first line treatment of recurrent and/or metastatic (R/M) patients:

- Fit patients are proposed to be enrolled in the phase II ELAN-FIT trial, which evaluates the cetuximab-carboplatin-5FU (EXTREME) combination in terms of efficacy (objective response at 12 weeks) and safety assessed by lack of grade >= 3 toxicity and lack of loss of independence, according to a 2-stage Bryan and Day trial design. Enrollment of 82 patients is planned.

- Unfit patients are proposed to be enrolled in the efficacy, randomized phase III ELAN-UNFIT trial, that compares two monotherapies (cetuximab 500 mg/m² every 2 weeks versus weekly methotrexate 40 mg/m²) in terms of failure free survival (failures are progression, treatment stop, loss of local control 6 months after treatment). 164 patients are planned to be randomized.

Results: Inclusions started on June 2013. Currently, 35 centers are opened. 121 patients are registered in ELAN ONCOVAL study. 48 patients of them are included in the three trials: 25 in ELAN-RT, 9 in ELAN-FIT, 14 in ELAN-UNFIT.

Conclusions: The main objectives of this study are to demonstrate that a geriatric evaluation is feasible in daily practice for SCCHN patients and to set new standards of care in this population.

Grants: INCa, Ligue contre le Cancer, ARC, Cancéropole l’île de France (INCa PAIR). Cetuximab is provided by MERCK-SERONOB for ELAN-UNFIT.

Clinical trial identifiers: NCT01884623; NCT01864850; NCT01864772.

PO-072
7-year experience of 18FDG PET-CT, IMRT and IGRT in Nasopharyngeal carcinoma (NC)


1Hospital Universitario Madrid Sanchinarro - Grupo Hospital de Madrid, Radiation Oncology Department, Madrid, Spain

Purpose/Objective: IMRT, IGRT and 18FDG PET-CT planning have shown a contribution not only in the accuracy when outlining target volumes but also in the delivery of the radiation treatment in patients with nasopharyngeal carcinoma. The purpose of this study is to assess the impact of the use of these techniques in patients with NC.

Materials and Methods: All patients with NC treated with radiotherapy with IMRT technique, planned with 18FDG PET-CT and verified with IGRT at our institution have been included in this analysis.

Results: A total of 25 patients with NC have been treated between April 2008 and September 2013 with radical intention. The average age was 52 years (range 16-66). The 96% of the sample received concomitant Chemotherapy based on CDDP and the 88% used a gastrostomy feeding tube inserted prophylactically before the beginning the treatment. Planning simulation was performed with 18FDG PET-CT in the 100% of the sample and 12 (48%) with MRI. All the patients received radiation therapy with Steep and Shoot IMRT. The prescription dose was 66 Gy in 30 fractions with and integrated boost of 2,2Gy per fraction in areas with macroscopic involvement and 54 to 60 Gy in 30 fractions of 1,8-2 Gy per fraction in the regions at risk of microscopic spread.

IGRT (Cone Beam CT) was used for treatment verification in all the cases. DVH were assessed according to institutional constraints. The mean follow up was 24, 7 months (median: 22 months; range: 8,2-75,4 months).

Up to date, 24 out of 25 patients are in complete response. The patient who progressed died 2 years after treatment with local and systemic disease.

1-year Local Failure Free Survival (LFFS) is 100%. 2-year LFFS is 94,4% which is better than 2-year LFFS from historical studies (around 80%).

The 88% of patients completed treatment without interruptions.


Conclusions: IMRT, IGRT and 18FDG PET-CT are perfectly integrated in the clinical management of patients with NC allowing the improvement of historical clinical results.

PO-073
Increased acute mortality with chemoradiotherapy for locally advanced head and neck cancer in patients >70 years.

PO-074
Outcome of patients with T1-T2 laryngeal carcinoma treated with laser surgery vs radiotherapy
F. Holguín1, J. Marruecos2, C. Urbano1, M. Tobed1, A. Hernandez1, I. Diez2, J. Rubio1
1Hospital Josep Trueta-ICO, Medical Oncology, Gerona, Spain
2Hospital Josep Trueta-ICO, Radiation Oncology, Gerona, Spain

Purpose/Objective: Squamous cell carcinoma of the head and neck (SCCHN) is the sixth most common cancer worldwide, laryngeal tumors represents about 30% of this entity. Earlier stage disease is more likely treated by surgery or definitive irradiation with a curative intent. Transoral laser surgery is less invasive compared with the open procedures without prognostic detriment. Presently there are no randomized controlled trials comparing both treatments. Therefore treatments decisions are based in retrospective hospital series.

The aim of our study was to evaluate the clinical features of laryngeal carcinoma patients and to compare local control and survival rates among patients affected by early laryngeal carcinoma in whom received laser surgery treatment versus radical radiotherapy.

Materials and Methods: We retrospectively evaluated 51 cases of primary laryngeal carcinoma diagnosed between January first 2008 and May 31 2012 in our institution. We collected clinical and pathological features: age, gender, histology, laterality, tobacco and/or alcohol consumption, stage, laser surgery treatment or radiotherapy. Subsequently we compared overall survival and recurrence rate between the two treatment groups.

Results: Mean age was 65 years old. 92% of patients were male (47/51). Initial symptom was dysphonia in the 98% of cases and only one case started with foreign body sensation. The 49% of the carcinomas were located at the right vocal cord (25/51), 31% at the left vocal cord, 16% were bilateral and 4% at the anterior commissure laryngeal. Fifty percent of patients had history of alcohol consumption and the 90% of patients were current smokers. Almost two thirds of cases (69%; 35/51) were T1, 25% (13/51) T2 and 6% T3 (3/51). Sixty-nine percent (35/51) of patients underwent laser surgery treatment and 31% (16/51) were treated with radiotherapy. A total of 5 patients progressed after initial treatment, three in the lase CO2 group and two in the radiotherapy arm. There were three deaths among the patients studied, one that received laser surgery and two that underwent radiotherapy as initial treatment.

Conclusions: The laryngeal carcinoma affects mostly men around 65 years. Likewise in our series we found a direct relationship between tobacco and this pathology. The first symptom in most cases was dysphonia. And the main location affected was right vocal cord. The low number of deaths and recurrence events reported at this moment does not show differences between the treatment groups. Statistical results with overall survival and local control will be presented at the congress.
p = 0.002; ICT response > 50 %; p = 0.02) survival. At the end of the study (median follow-up of 41 months), 10 patients had undergone total pharyngo-laryngectomy. Among the 43 laryngectomy-free patients, 38 had a functional larynx. During the treatment period, 17 patients (32%) required enteral nutrition. Six months after therapy, 28 patients (53%) recovered a normal or near-normal oral diet but 4 patients (8%) were still dependent on enteral nutrition. Pretreatment patient performance status (PS ≥ 1, p = 0.02) and maximum weight loss during therapy (p = 0.03) were significant predictive factors of grade 3/4 radiotherapy-related acute toxicities. Larynx remobilization after ICT was a significant predictive factor of swallowing outcome after treatment (p = 0.01). Nutritional status (weight loss before or during therapy) had no significant impact on survival or post-therapy functional outcome.

Conclusions: TPF-ICT followed by (chemo-)radiotherapy in good responders to ICT produced satisfactory oncologic and functional outcomes in patients with locally advanced hypopharynx cancer. T4 tumor stage was associated with worse prognosis. Response to ICT was one of the main predictive factors of oncologic and functional outcomes.

PO-076
Is there a dose-response relationship in loco-regional control or survival outcomes in tonsil cancer?
H.J. Park1, J.H. Kim1, H.G. Wu2
1Seoul National University Hospital, Department of Radiation Oncology, Seoul, Korea Republic of

Purpose/Objective: To evaluate the correlation between radiation dose and loco-regional control or survival outcomes for patients with tonsil cancer treated with definitive or postoperative radiotherapy

Materials and Methods: We retrospectively analyzed 631 patients with tonsil cancer treated with radiotherapy between 1998 and 2010 at 16 hospitals in Korea (Korean Radiation Oncology Group 11-07). The number of patients in stage I, II, III, and IV were 14, 53, 87, and 477, respectively. Two hundred and thirty-five patients received definitive radiotherapy(RT), while 390 patients received surgery postoperative RT (PORT) after surgery. The median dose of definitive RT was 70 Gy, and 136 patients (57.9%) received more than 70 Gy. The median dose of PORT was 63 Gy, and 224 patients (56.6%) received more than 63 Gy. Compared with PORT group, definitive RT group had more patients who were old, more advanced stage, and received higher dose RT given by intensity modulation techniques. Loco-regional progression-free survival (LRPFS), disease-free survival (DFS), distant metastasis-free survival (DMFS), and overall survival (OS) were calculated in relation to radiation dose.

Results: With a median follow-up of 58 months (range, 2-224), loco-regional failure occurred in 12.8% in definitive RT group, and 8.3 % in PORT group. The 5-year LRPFS, DFS, DMFS, and OS rates were 86.9%, 80.1%, 92.8%, and 74.5% in definitive RT group, and 90.5%, 76.1%, 89.3%, and 80.6% in PORT group, respectively. High dose definitive RT ≥70 Gy was not correlate with superior outcomes; 5-year LRPFS (p=0.751), DFS(p=0.280), DMFS(p=0.218), and OS(p=0.724). Likewise, high dose PORT ≥63 Gy was not correlate with superior outcomes as well; 5-year LRPFS(p=0.555) and OS(p=0.133). However, 5-year DFS(p=0.039) and DMFS(p=0.032) were superior in low dose PORT group.

Conclusions: In our large-scale retrospective tonsil cancer cohort, higher radiation dose was not correlated with superior loco-regional control or other survival outcomes, in both definitive RT and PORT groups. Moreover, treatment outcomes were favorable considering that 75.6% of patients were stage IV. Therefore, this study suggests that less intensive radiotherapy could be achieved without oncologic outcomes in selected group of patients.

PO-077
Chemotherapy with cetuximab for head and neck squamous cell carcinoma: a retrospective study
L. Pinto1, M. Teixeira2, J. Casal3, L. Khouri4, R. Nobre5, I. Pires6, M. Costa7, B. Goncalves8, R. Silva9, H. Gervasio10
1Instituto Portugues de Oncologia - Coimbra, Oncology, Coimbra, Portugal
2Centro Hospitalar e Universitário de Coimbra, Radiology, Coimbra, Portugal
3Instituto Portugues de Oncologia - Coimbra, Oncology, Coimbra, Portugal
4Instituto Portugues de Oncologia - Coimbra, Otorhinolaryngology, Coimbra, Portugal
5Instituto Portugues de Oncologia - Coimbra, Imagiology, Coimbra, Portugal
6Instituto Portugues de Oncologia - Coimbra, Stomatology, Coimbra, Portugal

Purpose/Objective: Cetuximab in combination with platinum and fluorouracil (PF) chemotherapy is effective in untreated recurrent or metastatic squamous cell carcinoma of head and neck (SCCHN), however the available robust evidence pertains to only one prospective trial. The aim of our study was to evaluate effectiveness of this combination in our population.

Materials and Methods: Retrospective cohort study treated in a single clinical cancer center (2009-2014). Eligibility criteria included histology confirmed recurrent or metastatic SCCHN cancer. Patients received an infusion of fluorouracil (1000mg/m² continuous infusion D1-D4), cisplatin (100mg/m², D1) or carboplatin (AUC 5, D1) and cetuximab (loading dose 400mg/m² D1 followed by weekly doses of 250mg/m²) on a 3-weekly schedule up to 6 cycles or until progression / unacceptable toxicity. Primary endpoint: overall-survival (OS); secondary endpoints: progression-free-survival (PFS); disease control rate (DCR), defined as having had complete response, partial response or stable disease; treatment toxicity. Survival outcomes were estimated using Kaplan-Meier’s method.

Results: A total of 61 patients were included with median age 53 (28 to 72) years. Location of primary tumor: oropharynx 21 (34.4%), larynx 15 (24.6%). The majority (n=59) had metastatic disease with or without loco-regional recurrence. Median number of cycles: 5 (2 - 6), median follow-up: 11 months (1 to 60). OS - 10.0 months (95% confidence interval [95%CI] [9.8;12.2]), PFS - 8.0 months (95%CI [7.0 ; 9.0]) and DCR - 73.8%. Grade 3-4 toxicities included skin reactions (24.0%), neutropenia (13.3%) and infusion-related reactions (6.5%). There were no cetuximab-related deaths. OS was higher in the responders group (12.0 vs. 6.0 months, p<0.001).

Conclusions: Cetuximab in combination with PF was effective in our population with a considerable DCR. Response to treatment seems to be associated with longer survival, however powered prospective studies are needed in order to clarify which subgroup of responders might benefit the most of this approach.

PO-078
Concurrent Cisplatin-radiotherapy with or without induction chemotherapy in nasopharyngeal carcinoma
W. Mnejja1, N. Toumi2, R. Bouguenida2, W. Siala1, A. Khatmir2, M. Hgorbet1, M. Frikha2, J. Daoud1
1Hopital Habib Bourguiba, Radiotherapy, Sfax, Tunisia
2Hopital Habib Bourguiba, Oncology, Sfax, Tunisia
3Hopital Habib Bourguiba, ORL, Sfax, Tunisia

Purpose/Objective: Concurrent chemoradiotherapy (CCRT) is the standard of care of patients with locally advanced nasopharyngeal carcinoma (NPC). The effect of induction chemotherapy (CT) before CCRT is still controversial. The purpose of this study is to report safety and results of two
Materials and Methods: Between June 2004 and January 2009, 103 patients with locally advanced NPC were treated with CCRT in our institution. Thirty-two patients received induction chemotherapy with Docetaxel, Cisplatin and 5-FU (TPF Group) and forty-one with Cisplatin and 5-FU (PF Group). Chemoradiation alone was administered for 30 patients (CCRT Group). T stage was similar in the three groups. However, there was more N2N3 stage in the two neoadjuvant groups compared to the CCRT group (82.9% vs 53.3%, p=0.03). All patients were assessed for toxicity according to the World Health Organisation. Survival curves were calculated with Kaplan-Meier method.

Results: Neoadjuvant chemotherapy compliance was 96.6% in the PF group and 78.1% in the TPF group (p=0.008). Toxicity was dominated by grade 1-2 vomiting in the PF group, and grade 1-2 diarrhea and mucositis in the TPF group. High grade 3-4 neutropenia (18.2%) was observed during neoadjuvant TPF chemotherapy. During chemoradiation, there was no difference in acute toxicities between the three arms. Complete responses rates were 89.6%, 90% and 96.7% in the TPF group, PF group and CCRT group respectively. After a median follow up of 63 months, there were no significant differences in survival. The 5-year overall survival (OS) in the TPF, PF and CCRT groups were respectively 69%, 60% and 73.3% (p=0.72). The 5-year disease free survival were respectively 65.6%, 56.2% and 68.8% in the TPF, PF and CCRT groups (p=0.46).

Conclusions: Induction chemotherapy followed by CCRT was tolerated with a manageable toxicity profile. It will be an interesting approach for patients with poor prognosis (N2-N3 stage). A phase III trial should be conducted to evaluate the effect of neoadjuvant chemotherapy followed by CCRT for patients with locally advanced NPC.

PO-079 Base of tongue squamous cell carcinoma as potential nonsurgical pathology. Biological and clinical background

A. Gevorkov1, A. Boyko1, L. Zavalishina1, A. Chernichenko1, I. Reshetov1, R. Plavinik1, E. Nosova1, E. Khmelevsky1

1Moscow Research Gerzen Oncology Institut, Radiation Oncology, Moscow, Russian Federation

Purpose/Objective: The optimal treatment for patients with base of tongue (BOT) squamous cell carcinoma remains controversial and depends on various factors. These factors include the tumor characteristics, patient condition, potential outcomes and adverse effects. Nonsurgical therapy is of great interest because of the possible dysfunction of swallowing and speech associated with radical surgical resection. On the other hand, BOT historically has a better swallowing and speech associated with radical surgical resection. On the other hand, BOT historically has a better outcome than oral tongue. The aim of the study was to identify biological and clinical potential predictors of swallowing and speech functions in patients with tongue cancer.

Materials and Methods: We included 130 patients with histologically proven the base (39 pts, 30%) and the mobile part of the tongue (MOT) cancer (91 pts, 70%), diagnosed and treated between January 1, 2003, and December 31, 2012. Patients with BOT cancer had locally advanced process more often (92% vs 66%), especially stage IV (69% vs 20%). Nonresectable process was diagnosed in 38% patients with BOT cancer and in 23% cases of mobile part cancer primary tumor. All patients underwent photon external beam radiation in non-conventional fractionation to the dose of 50Gy in the preoperative mode treatment and to 70Gy as radical irradiation. Radiomodification with SFU/cisplatin or cisplatin/cetuximab was performed in 104 (80%) cases. Nonsurgical treatment was performed in 44 (34%) cases. Patients with BOT primary tumor underwent conservative therapy more often (62% vs 22%). Combined treatment with surgery was performed to 86 (66 %) patients, with the preservation of the organ in 59 (69 %) cases. Organ-sparing surgery was possible in 54 (76%) cases of mobile part cancer and only in 5 (33%) cases of base of tongue cancer.

Results: After irradiation we observed complete response in 21% cases of BOT cancer and 7% of MOT cancer, partial response in 79% and 82% respectively. Stabilization and progression was diagnosed in 8% and 3% of cases MOT cancer. Complete morphological response in surgically removed tissues was obtained in 48% of BOT cancers and 22% of MOT cancers. 5-year general and disease-free survival were 70 % and 58% respectively and there was not reliable difference between localizations. Surgical treatment for local relapse were performed 23 of 48 (48%) patients. Multivariate analysis revealed (p <0,05) a positive correlation of the treatment effectiveness with BOT tumor location, the female sex, the high expression of E-cadherin, p21, Bcl-2 proteins. Patients with BOT cancer have less chances for organ-sparing surgery. In conclusion, BOT cancer is an aggressive disease that is often diagnosed at a late stage, but may be effectively treated by nonsurgical modality with preservation of swallowing and speech functions.

PO-080 Trends in irradiating the mucosae in cervical adenopathies from unknown primaries

J. Thariat1, I. Troussier2, M. Kengli1, J. Mirroir4, X.S. Sun5, S. Shaked1, A. Coutte2, N. Blanchard6

1Centre Antoine Lacassagne, Department of Radiation Oncology, Nice, France
2CHU, Department of Radiation Oncology, Poitiers, France
3CHU, Department of Radiation Oncology, Pauve, Italy
4CHU, Department of Radiation Oncology, Clermond Ferrand, France
5CHU, Department of Radiation Oncology, Montbelloir, France
6CHU, Department of Radiation Oncology, St Denis, France

Purpose/Objective: Advances in radiation therapy techniques have dramatically changed the treatment paradigms in cervical adenopathies from unknown primaries. In particular, IMRT has enabled parotid and constrictors sparing while irradiating the whole mucosae and cervical nodes. In contrast, the deleterious impact of large volumes of irradiation on the mucosae and cervical nodes has led to strategies of unilateral selective nodal irradiation with highly selective or no mucosal irradiation.

Materials and Methods: An ambispective study has been initiated to address the current trends in irradiating the neck and mucosae in cervical adenopathies from unknown primaries.

Results: Among 53 patients, 10% were females, 92% had conventional squamous cell carcinoma. 77% underwent a neck dissection and nodal irradiation was performed in 94% of patients. Mucosal irradiation (doses 40-70 Gy) in 78%, using IMRT in 25% of cases. Chemotherapy was performed in 56% of cases. The nasopharynx, oropharynx, oral cavity, larynx and
hypopharynx were irradiated in 64%, 69%, 40%, 58% and 66%, respectively. Detailed data on target volumes are available.

**Conclusions:** There is no unanimous definition for mucosal target volumes. In the context of technical advances, a consensus approach would be most useful to update the recommendations with respect to quality of life / late sequelae and relapse rates (nodal relapse or emerging primary).

**PO-081**
A longitudinal study of follow-up activities after curative treatment for head and neck cancer

A.P. Pagh1, C.G. Cal Grau2, J.O. Jens Overgaard3
1Aarhus University Hospital, Department of Experimental Clinical Oncology, Aarhus C, Denmark
2Aarhus University Hospital, Department Radiotherapy, Aarhus C, Denmark
3Aarhus University Hospital, Department Experimental Clinical Oncology, Aarhus C, Denmark

**Purpose/Objective:** Danish head and neck cancer (HNC) patients are offered a five year follow-up (FU) program according to DAHANCA guidelines. This involves frequent visits in the first two years (every third and every fourth month, respectively), twice a year in the third and fourth year, and a final visit after five years. The aim of this study was to evaluate the FU activities performed in a cohort of patients followed longitudinally for 5 years.

**Materials and Methods:** The study was a retrospective study of a cohort of 141 consecutive patients, identified through the DAHANCA database. All patients had carcinoma of the head and neck and received treatment with curative intent in the period from Jan 1 to Dec 31, 2009 at Aarhus University Hospital. Primary treatment was distributed between radiotherapy (81), postoperative RT (22) and surgery (38). All patients (141) with complete response at the first FU visit five months after ended primary treatment were analyzed for FU activities. Data were collected through a medical chart review. Parameters recorded were: regular or extraordinary visit, alarm symptoms, late morbidity and the consequences of the visit (did the patient continue as planned or was further diagnostic work-up initiated on suspicion of recurrent disease or late morbidity).

**Results:** A total of 1343 FU visits among 141 HNC patients were analyzed. Only 21 patients (15%) had no visits at all with tumor or morbidity issues raised. Suspension of recurrent disease was present in 200 of the 1343 visits (15%), involving 101 of the 141 patients (72%) and a total of 361 diagnostic investigations; 170 (85%) visits with suspicion of recurrence occurred within the first 3½ years after treatment start. A recurrence was verified in 30 patients and a new primary cancer was verified in 20 patients, five of these in the head and neck region. Overall, the number of suspected cases per verified recurrence was 7. Late morbidity after primary treatment was recorded in a total 1106 visits (82%) involving 135 patients (96%). Seventy patients (50%) had actions taken related to morbidity, and 86% of them were within the 3½ years. Importantly, only very few new problems appeared after three years regarding both tumor problems and late morbidity.

**Conclusions:** Our data document the importance of specialized FU, as 85% of all HNC survivors have tumor or severe morbidity issues during FU. For the majority of patients it may be sufficient with a three year FU after ended therapy. The strategy with higher frequency of the visits in the first two years should be maintained, as the density of problems is highest. Resources should be allocated for individualized FU for those patients who continue to have severe problems after three years.

**Poster: Innovative treatments**

**PO-082**
To quantify dosimetric effects of adaptive radiotherapy for head and neck cancer

E. Kara1, B. Dirican2, A. Yazıcı1
1Onko Ankara Oncology Center, Oncology Department, Ankara, Turkey
2GATA, Radiation Oncology, Ankara, Turkey

**Purpose/Objective:** In routine clinical practice, radiotherapy treatment planning is performed based on the patient CT images. However, the actual delivered dose to the patient might be different from the planned dose because of various reasons such as weight loss and tumor shrinkage. Under such situations, it is desirable to modify the original treatment plan in order to partially remedy the dose delivery errors in the subsequent dose delivery process. Such modification can be implemented by modifying the original treatment plan using reimage and replan. Adaptive radiotherapy (ART) is an approach to correct for daily tumor and normal tissue variations through online or offline modification of original intensity modulated radiotherapy (IMRT) target volumes and plans. The aim of this study is to quantify dosimetric effects of ART on critical tissues and CTV for head and neck cancer patients.

**Materials and Methods:** In this study, immobilization and CT simulation were performed for 20 head & neck cancer patients, as is routine for head & neck cancer patients receiving IMRT in our department. The determination of the 20 head & neck cancer patient's target volume and critical structures are done by using CT images obtained from our clinic. After definition of the critical organs which were spinal cord, brainstem and parotid glands, IMRT plans were optimized for each of 20 patients using 7 fields setting by using Prowess Panther DAQ planning system. All patients were reimaged after fraction number 25 and recalculated with old plan in new CT to quantify dosimetric effects.

**Results:** Because of weight loss and tumour shrinkage during treatment the dose distribution that was delivered to the patient significantly different from what was planned. The volume of the CTV and parotid glands significantly decreased after 5 weeks treatment. The CTV volume changed from 5% to 15% (p<0,001) and parotid glands changed from 1% to 27%, (p<0,001). The doses delivered to the spinal cord and brainstem was increased compared with the planned doses. The spinal cord max. dose changed from 1% to 10,3% (p<0,001) and brainstem doses changed from 0.5% to 5,5% (p<0,001).

**Conclusions:** Our study show that adaptive radiotherapy improve radiation treatment significantly. Due to weight loss and tumour shrinkage during treatment dose actually delivered was higher than the planed dose. Offline ART can be used to correct for daily tumor and critical tissue variations of IMRT for H&N patients.

**PO-083**
Freedom from regional failure of contralateral neck with ipsilateral neck radiotherapy for node and tonsil cancer

A. Raben1, T.U. Dan1, C. Schneider1, N. Hockstein1, R. Witt1
1Helen F. Graham Cancer Center, Radiation Oncology, Newark DE, USA

**Purpose/Objective:** To update the outcomes of a prospective management approach using ipsilateral neck radiotherapy in the treatment of node-positive squamous cell carcinoma of the tonsil with a well lateralized primary lesion.
Materials and Methods: Between August 2003 and April 2014, 61 consecutive patients with ipsilateral node-positive squamous cell carcinoma of the tonsil without involvement of the base of the tongue or midline soft palate were prospectively treated at a community hospital-based cancer center with radiotherapy to the primary site and ipsilateral neck. Overall survival, disease-free survival and freedom from contralateral failure were calculated. Acute and late toxicity were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Results: Of the 61 patients, 15 had Stage III and 45 had Stage IVA disease; 15 patients had Stage N1, 14 had Stage N2a, and 31 had Stage N2b disease. One patient had N3 disease. Median follow up was 37.2 months (range 4-121 months).

PO-085 Evaluation of the impact of the oral cavity contour on dose and constraint compliance in head-and-neck IMRT

I. Prieto1, S. Gomez-Tejedor1, J.P. Marin1, A.M. Perez1
1Capio-Fundación Jimenez Diaz, Radiation Oncology, Madrid, Spain

Purpose/Objective: Oral cavity includes different structures that are affected in advanced head and neck cancer irradiation. Dose to the oral mucosa and its contribution to acute mucositis is a dose/volume/outcome relationships recommended for investigation. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) report has not well-defined which structures should be included in the oral cavity (OC) as organ at risk (OAR) and has not determined the constraints to apply. The aim of this study is to demonstrate that different structures included in this OAR mean different dose constraints and outcomes.

Materials and Methods: We compared theoretically the dose delivered to the oral cavity as OAR designing three different contours in the same advanced head and neck cancer patient (Fig. 1). Treatment was calculated according to international recommendations utilising Intensity Modulated Radiotherapy (IMRT) technique with 7 fields and dynamic multileaf collimator, delivering 70 Gy to the Planning Treatment Volume (PTV). The Monaco treatment planning system with Monte Carlo algorithm was used. Each contour included different structures defined in Table 1. Anterior OC included painful mucosa that can have a significant negative impact on quality of life and swallowing. Extended OC included anterior OC and other structures that inevitably are close to the PTV. Inner OC was a middle volume that includes the structures inside the gingiva. Oral cavity Dmean, Dmax, V50Gy, V45Gy, V40Gy, V35Gy, V30Gy, V25Gy and V20Gy were recorded and compared with standard statistical analysis (Tab. 1).

Results: Each defined contour allowed different constraint compliance for the oral cavity and made easier or more difficult to achieve the prescribed dose to the PTV. Results obtained for anterior OC showed the lowest Dmean and Dmax in this OAR. Anterior OC does not receive more than 30-35 Gy, however inner and extended OC receive 45-50 Gy. These results allowed to apply a tighter constraint, decreasing the expected mucosa oral toxicity, and to achieve the prescribed doses to the PTV. Results for extended OC forced to apply a more relaxed constraint for the OAR to achieve the prescribed dose. Higher Dmean and Dmax would be supposed to produce more severe toxicity as such as other surveys have suggested. Inner OC showed worse results compared with extended OC due probably to the differences of volume.

PO-084 The pharmacokinetic characteristics of nimorazole in head and neck cancer patients treated in the DAHANCA-5 trial

M.A.H. Metwally1, J.A. Jansen1, J. Overgaard2
1Aarhus University Hospital, Department of Experimental Clinical Oncology, Aarhus C, Denmark

Purpose/Objective: To study the pharmacokinetic characteristics of the hypoxic radiosensitizer nimorazole in patients with head and neck squamous cell carcinoma (HNSCC).

Materials and Methods: The pharmacokinetics of the hypoxic radiosensitizer nimorazole was studied in 63 patients treated in the DAHANCA-5 trial. After the first day of treatment, serial venous blood samples were taken and plasma concentrations of nimorazole measured by high pressure liquid chromatography (HPLC). Plasma concentration profiles were subjected to non-compartmental pharmacokinetic analysis using validated PC-based software. The different pharmacokinetic parameters were calculated and correlated with the different patient- and treatment-related variables.

Results: HPLC measurements showed a linear relationship between peak plasma concentration and administered dose. Mean peak concentration adjusted for dose in g·m⁻² was 32.2±0.9 µg·ml⁻¹. The time of peak concentration ranged between 30 to 180 min (median 60 min). Plasma elimination occurred with a mean half-life of 3.35±0.09 h and was not significantly altered as a function of dose. There was a well-established linear-linear relationship between AUC (mean 191±6 µg·ml⁻¹·hr) and administered dose, especially when expressed as g·m⁻². The mean apparent volume of distribution was 0.77±0.02 l·kg⁻¹. A statistically significant longer elimination half-life in males relative to females (mean difference 0.40h; 95% CI 0.77-0.03; P 0.03), was detected. Nimorazole was well tolerated; with 67% of patients reporting no toxicity; nausea/vomiting was the most reported toxicity in the remaining patients.

Conclusions: The study supports the current clinical dose scheduling practice with nimorazole.
Conclusions: It is necessary to define the structures that should be included in the oral cavity as OAR to unify criteria in contour planning and limiting dose (constraint). Differences among observers’ criteria influence on OARs volume and furthermore, have an impact on constraint compliance for the oral cavity as OAR.

PO-086
IMRT in Nasopharyngeal carcinoma - Single institution - experience from a developing country
C. Kainickal1, B. Azariah1, R. Kumar1, M. Rafi1, A. Sudha1, R. Rajeev1, S. Bhasi1, R. Kunnambath1
1Regional Cancer Center, Radiation Oncology, Trivandrum, India
2Regional Cancer Center, Radiation Physics, Trivandrum, India

Purpose/Objective: To retrospectively review the outcomes of the patients with nasopharyngeal cancer (NPC) treated with whole field simultaneous integrated boost (WF-SIB) Intensity Modulated Radiotherapy (IMRT).

Materials and Methods: From Jan 2011 to Dec 2013, 55 NPC patients have been treated with WF-SIB IMRT. Median age was 42 years (range 13-77). 64% of the patients were males and 98% were WHO II b disease. Stage at presentation was I in 2%, II in 16%, III in 51%, IVa in 26% and IVb in 2% of the patients. The doses to the planning target volumes of primary tumor and involved lymph nodes (PTV66), high risk (PTV60), and low risk (PTV 54) regions were 66 Gy, 60 Gy and 54 Gy delivered simultaneously over 30 fractions. 56% of patients received Neoadjuvant chemotherapy with cisplatin and 5 fluorouracil, 95% received concurrent cisplatin and 5 fluorouracil, 95% received concurrent cisplatin and 5 fluorouracil, 95% received concurrent cisplatin and 5 fluorouracil, 95% received concurrent cisplatin and 5 fluorouracil, 95% received concurrent cisplatin and 5 fluorouracil.

Results: On average, the target coverage, defined as the percentage of target volume that received 98% of the prescribed dose, was 99% for the CTV and that received 95% of the prescribed dose was 97.5% for the PTV. 2.8% of PTV received <95% of prescribed dose, and 1.8% of PTV received >110% of the prescribed dose. The conformity index [TV/PTV] of PTV was 0.82.

The mean dose to the Parotids were 33.2 Gy, the average D max to Brain stem, Cochlea, Optic Chiasma and Spinal Cord were 52.9 Gy, 59.2 Gy, 46.9 Gy and 42.6Gy respectively. All patients achieved complete remission in the primary site and 96% achieved complete remission in the neck. After a median follow-up of 18 months (range, 5-40 months), 13 patients have relapsed. 3 had loco regional failure, 1 patient had both loco regional and systemic failure, and 9 patients had systemic failure. The actuarial 2 year Kaplan-Meier estimates of loco regional and distant disease free survival were 95.8% and 78.7% respectively.

Conclusions: This retrospective analysis implies that WF-SIB IMRT with or without chemotherapy in the treatment of NPC achieves good loco regional control. Distant metastasis represents the predominant mode of treatment failure.

PO-087
Long-term outcome of 18F-FDG-PET-guided dose painting for head-and-neck cancer: matched case-controlled study
1Universiteit Gent, Radiation Oncology/Nuclear Medicine, Gent, Belgium
2Universiteit Gent, Radiation Oncology, Gent, Belgium
3Universiteit Gent, Head Neck Surgery, Gent, Belgium

Purpose/Objective: To compare long-term outcome of 18F-FDG-PET-dose painting for head-and-neck cancer with conventional IMRT in a matched case-controlled study.

Materials and Methods: Seventy-two patients treated with dose painting between 2003 and 2011 were compared with 72 control patients matched on tumor site and stage. Either 18F-FDG-PET-guided or 18F-FDG-PET-voxel intensity based IMRT was used in dose painting; control patients underwent conventional IMRT. In all study patients and 66 control patients 18F-FDG-PET/CT was used in target volume delineation. A total median dose to the dose-painted target was between 70.2 and 85.9 Gy in 30-32 fractions vs. 69.1 Gy in 32 fractions with conventional IMRT. In 31 patients dose-painting was adapted to per-treatment changes in the tumor. Results: A median follow-up in living dose-painting and control patients was 31.2, range 14.8-47.5 and 25.7, range 11.5-40.0 months, respectively. Five-year local control in the study patients was 83.4% against 75.2% in the control (p = 0.28); there was no difference in regional (p = 0.78) or distant control (p = 0.75). Five-year overall and disease-specific survival was 32.6% vs. 38.8% (p = 0.41) and 51.9% vs. 45.3% (p = 0.67), respectively. Higher rates of acute mucositis (p = 0.02) and dysphagia (p = 0.003) in dose-painting patients were not translated in significantly higher rates of late toxicity. For late toxicity, there was significantly more trismus (p = 0.05), while pain, dysphagia, taste alteration, mucosal integrity, xerostomia and fibrosis did not differ significantly.

Conclusions: Dose painting in non-selected patients has the potential to improve loco-regional control and disease-specific survival, although it appeared to have no effect on overall survival as compared to conventional IMRT. Acute mucositis and dysphagia were significantly higher in patients treated with dose painting. More trismus was seen in the experimental group. Randomized clinical trials are needed to confirm our results.

PO-088
Chemoradiotherapy for poor/intermediate risk oropharyngeal carcinoma: First results of the ArchIMEDeS study
V. Harrop1, S. Meade1, L. Wagstaff2, J. Babrah1, P. Gaunt1, M. Robinson2, J. Cashmore1, H. Mehanna2, A. Hartley1, P. Sanghera1
1Hall-Edwards Radiotherapy Research Group Queen Elizabeth Hospital, Oncology, Birmingham, United Kingdom

Adenoid cystic carcinoma of the head and neck represents the predominant mode of treatment failure.
Purpose/Objective: HPV negative and smoking associated locally advanced oropharyngeal squamous cell carcinoma (OPSCC) is associated with a poor prognosis. Synchronous chemotherapy and altered fractionation independently improve survival of OPSCC. Radiobiological modeling can be used to predict an optimum schedule for maximizing tumour cell kill within limits of tolerability. The aim of this study was to investigate the tolerability of a dose intensified schedule in poor/intermediate prognosis OPSCC.

Materials and Methods: Patients with either p16/HPV negative OPSCC or p16 positive N2b OPSCC with a greater than 10 pack year smoking history were eligible for this prospective pilot study. Patients were planned to receive 64Gy in 25 fractions to the high dose PTV, and 50Gy in 25 fractions to at risk nodal levels with concomitant cisplatin 100mg per m² week 1 and week 5. Patients with a contraindication to cisplatin were given carboplatin AUC 4.5. Up to 3 cycles of induction TPF chemotherapy were permitted. All patients were treated with TomoTherapy®.

The primary end point was absence of grade 3 mucositis at 3 months using visible assessment as per CTCAE v3. Other acute toxicity was scored using CTCAE v4 and late toxicity measured using RTOG.

Results: Fifteen patients were entered between 20th December 2012 and 22nd January 2014. Median age was 63 years (range: 35-69). All patients completed the minimum 3 months follow up required for the primary end point. All 15 patients completed the full intended dose of radiotherapy within a median overall treatment time of 32 days (31-35). Grade 3 mucositis was absent in all patients at three months. Maximum acute toxicities (CTCAE v4) were grade 3 dysphagia (93%), grade 3 radiation dermatitis (60%) and grade 3 radiation-induced pain (100%). There were no grade 4 toxicities or deaths. Median duration of grade 3 mucositis was 4 weeks (range 1 to 8). Primary complete response rate at 3 months was 100% (15/15). Regional lymph node complete response was 93% (14/15). One patient developed distant metastases at the 3 month assessment. This was in the liver which one trade-off objective can only be improved by displays extracted from planning. The purpose of this study was to demonstrate automatic plan optimization directly minimizing several NTCPs. This was demonstrated by use of multivariable NTCP models for dysphagia (RTOG/EORTC grade II-IV at 6 months after treatment) and tube feeding dependence (TFD; at 6 months after treatment).

Materials and Methods: The study cohort of this in-silico comparative planning study consisted of 100 HNC patients, previously treated with a conventionally optimized IMRT plan. To determine the gain of NTCP-based MCO planning, two additional plans were automatically created, aiming at minimizing NTCP for dysphagia (SW-MCO) or TFD (TFD-MCO). Therefore, per patient and per technique, 200 IMRT plans were optimized (in total 40,000 optimizations). Of each 200 plans, the Pareto optimal plans with adequate target coverage and low as possible dose to the individual organs at risk (OARs). However, in HNC, several treatment related complications, expressed by normal tissue complication probabilities (NTCP), relate to multiple OARs. More recently, IMRT plans can be optimized by minimizing the NTCP directly during plan optimization, automatically balancing the dose among the OARs. This optimization method was implemented in a multicriteria optimization (MCO) planning framework. The purpose of this study was to demonstrate automatic plan optimization directly minimizing several NTCPs. This was demonstrated by use of multivariable NTCP models for dysphagia (RTOG/EORTC grade II-IV at 6 months after treatment) and tube feeding dependence (TFD; at 6 months after treatment).
parotid (SW-MCO: 5.2 Gy 95% CI 4.9 - 5.6 Gy; TFD-MCO: 4.8 Gy 95% CI 4.5 - 5.1 Gy), ipsilateral parotid (SW-MCO: 6.5 Gy 95% CI 6.2 - 6.7 Gy; TFD-MCO: 7.4 Gy 95% CI 7.2 - 7.7 Gy) and the oral cavity (SW-MCO: 2.2 Gy 95% CI 1.8 - 2.5 Gy; TFD- MCO: 2.0 Gy 95% CI 1.6 - 2.4 Gy).

The SW-MCO plans showed no differences in NTCP estimates for dysphagia and slightly higher NTCP estimates for tube feeding dependence (0.7% 95% CI 0.6% - 0.8%). The TFD-MCO plans resulted in slightly lower NTCP estimates for dysphagia (1.3% 95% CI 1.2% - 1.3%). In 3% of patients the TFD estimates reduced with >5%. Results per patient are shown in figure 1. Comparisons for the OARs are listed in table 1.

Conclusions: Automated treatment planning using NTCP-based MCO significantly reduced the dose to several OARs by more optimally distributing dose among multiple OARs. However, pushing dose in one region consequently led to increased dose in other regions. To further improve HNC radiotherapy, techniques such as adaptive radiotherapy and proton therapy are required.

PO-091

The TPExtreme randomized trial: Docetaxel-Platinum(P)-Cetuximab(C) versus FU-P-C in recurrent/metastatic HNSCC

J. Guigay, U. Kellholz, R. Mesia, N. Vintonenko, J. Bourhis, A. Auperin

1Centre Antoine Lacassagne - Head & Neck Unicancer Group, Cancer Research Center - Medical Oncology, Nice, France
2Charite Comprehensive Cancer Center - AIO Group, Medical Oncology, Berlin, Germany
3Institut Catala d’Oncologia - TITC Group, L’Hospitalet Llobregat - Medical Oncology, Barcelona, Spain
4GORTEC CORAD, Clinical Research, Tours, France
5GORTEC, Radio-Oncology, Lausanne, Switzerland
6Gustave Roussy, Biostatistics and Epidemiology, Villejuif, France

Purpose/Objective: The EXTREME regimen (6 cycles of FU-cisplatin-cetuximab followed by cetuximab maintenance) is currently the standard of care in first line recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). The GORTEC phase II trial evaluating the TPEx regimen (4 cycles of docetaxel-cisplatin-cetuximab followed by cetuximab maintenance) demonstrated good results (median overall survival (OS) 14 months, overall response rate 54%) with acceptable safety profile, excellent dose intensity, high rate of patients who started maintenance and easy implementation. The aim of the current trial is to compare TPEx and EXTREME regimens.

Materials and Methods: International, randomized, open-label trial. Main inclusion criteria are: histologically confirmed HNSCC with metastasis or recurrence not suitable for locoregional treatment, age 18-70 years, PS 0-1, prior total dose of cisplatin < 300 mg/m². The control arm EXTREME consists of 6 cycles, every 21 days, of cisplatin 100 mg/m² day1, 5FU 4000 mg/m² continuous infusion day1-4, and weekly cetuximab 250 mg/m² (after a loading dose of 400 mg/m²) followed by weekly cetuximab 250 mg/m² maintenance. The experimental arm TPEx consists of 4 cycles, every 21 days, of docetaxel 75 mg/m² day1, cisplatin 75 mg/m² day1, and weekly cetuximab 250 mg/m² (after a loading dose of 400 mg/m²), followed by maintenance cetuximab 500 mg/m² every 2 weeks. If cisplatin is not tolerated or when the total cumulative dose reaches 600 mg/m², it must be replaced by carboplatin AUC5. Prophylactic administration of G-CSF must be done systematically after each chemotherapy cycle in the TPEx arm. Cetuximab maintenance is given only in patients with at least disease stabilization and is continued until PD or unacceptable toxicity.

The primary endpoint is OS. Assuming a 2-sided type I error of 0.05, observing 295 deaths will provide a 80% power to detect a hazard ratio of 0.7. 295 deaths are expected out of a total of 416 patients.

Secondary endpoints are objective response rate, best response rate, PFS, time-to-progression, toxicity and quality of life. Tumor response assessments are planned every 6 weeks until week 18, then every 8 weeks until progression and will be reviewed by a blinded central image review committee. HPV central analysis and cost-effectiveness study are ancillary studies.

75 sites in France (GORTEC), Germany (AIO-Studien-gGmbH) and Spain (TTCC) will participate in the trial. Patients are randomized between the 2 arms (1:1) by minimization on PS, type of evolution, previous cetuximab treatment and country.

Results: The first patient has been enrolled in October 2014. Results are expected by the end of 2017.

Conclusions: This randomized trial will establish if TPEx regimen is a relevant substitute for EXTREME as 1st line treatment in fit patients with R/M HNSCC.

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PO-092

Phase II study of TPF and cetuximab+RT in locally advanced laryngeal/hypopharyngeal carcinoma


1Complejo Hospitalario de Navarra, Oncología, Pamplona, Spain
2Hospital Regional Universitario Carlos Haya, Oncología, Málaga, Spain
3Hospital Universitario Fundación Jiménez Díaz, Oncología, Madrid, Spain
4Hospital Universitario Parc Taulí, Oncología, Barcelona, Spain

Purpose: To evaluate the safety and efficacy of TPF, a 5-drug induction therapy regimen followed by definitive chemoradiotherapy with cetuximab maintenance, in patients with locally advanced laryngeal/hypopharyngeal carcinoma (LA/HPC). The primary endpoint was OS. The secondary endpoints included: local failure, distant metastasis, relapse-free survival (RFS), progression-free survival (PFS), overall response (OR), response rate (RR), time to progression (TTP), and toxicity.

Methods: The trial was a multicenter, single-arm, phase II study. Patients with biopsy-confirmed LA/HPC were enrolled between September 2009 and January 2012. The eligibility criteria included: age ≥ 18 years, Karnofsky performance status (KPS) ≥ 70%, histologically confirmed LA/HPC, with T3-4, N0-3, M0 disease, and no prior treatment.

Results: A total of 20 patients were enrolled from 6 centers in Spain. The median age was 61 years (range: 40-73 years), and 18 patients were male. The median KPS was 90% (range: 70-90%). The median follow-up time was 24 months (range: 6-48 months). The median OS was 26 months (range: 6-48 months). The 1-year OS rate was 75% (95% CI: 51-89%). The 1-year RFS rate was 65% (95% CI: 42-80%). The 1-year TTP rate was 57% (95% CI: 34-76%). No grade 5 toxicity was reported. The most common grade 3-4 toxicities were mucositis (35%), dermatitis (35%), and neutropenia (30%). The overall response rate was 90% (95% CI: 70-99%). The median duration of follow-up was 24 months (range: 6-48 months).

Conclusions: The TPF induction therapy regimen followed by definitive chemoradiotherapy with cetuximab maintenance was well tolerated and effective in patients with locally advanced laryngeal/hypopharyngeal carcinoma. Further studies are needed to confirm the efficacy and safety of this regimen.
Purpose/Objective: Neoadjuvant docetaxel, cisplatin, and 5-fluorouracil (TPF) may improve survival in same locally advanced head and neck cancer (LAHNC). Cetuximab improves the tumor response and survival in LAHNC and this effect seems to improve when boost concomitant scheme is used. In 2008 we began a Phase II Trial with TPF followed by RT (boost concomitant) plus cetuximab in LA laryngeal/hypopharyngeal carcinoma.

The primary endpoint was 2-year progression free survival (PFS) for those patients with complete response (CR) or partial response (PR) after receiving TPF. Secondary endpoints included: overall survival (OS), specific total laryngectomy-free survival, and quality of life (QoL). Adverse events were assessed for safety.

Materials and Methods: Phase II, open, multicenter study in patients with locally advanced laryngeal/hypopharyngeal carcinoma. All patients received 3 cycles of induction chemotherapy with TPF, followed by cetuximab + radiation therapy (RT) or surgery. Radiotherapy consisted of 72 Gy/6 weeks in boost concomitant regimen. IMRT was not allowed in this study. Survival data was analysed using Kaplan-Meier.

Patients that discontinued the study for any reason were censored.

Results: The study was prematurely closed because of low recruitment. A total of 25 patients started the treatment: 21 of them (84%) had CR/PR after TPF. Two-years PFS 47.9% (95% CI: 15.7, 74.6). For patients with CR/PR after TPF, median survival time was 21.1 months. For all patients, two-year PFS was 37.8% (95% CI: 12.4, 63.6), and median survival time was 21.1 months. Secondary end points were: overall survival, 42.1% (95% CI: 13.4, 68.8); specific survival free of laryngectomy, 54.2% (95% CI: 16.7, 81.1); the evaluation of quality of life increased with time. There were seven deaths during the study: three were related to disease progression, one sudden death, one due to hepatic insufficiency, one pancreatic adenocarcinoma, and one fulminant acute hepatitis. The most frequent serious adverse events (SAEs) were febrile neutropenia (20%, n=5) and mucositis (16%, n=4). Other SAEs observed were: headache, epiphelitis, hepatic insufficiency, febrile neutropenia, pancytopenia with septic shock, ORL bleeding and tracheotomy.

Conclusions: This study was prematurely terminated because of the difficulties in the recruitment of patients. Descriptive results are presented about efficacy and safety of the treatment with TPF and cetuximab+RT boost concomitant in locally advanced laryngeal/hypopharyngeal carcinoma. Our preliminary data, do not support this approach due to higher toxicity and similar results than other standard treatments.

PO-093
Influence on toxicity mucositis depending on contouring the oral cavity: our experience
J. Marin1, M.A. García1, I. Prieto1, A.M. Perez1
1Fundación Jimenez Diaz, Radiation Oncology Department, Madrid, Spain

Purpose/Objective: Acute mucositis in the oral cavity (OC) is an important adverse reaction in the locally advanced head and neck cancer patients treated with radiotherapy. The impact of the treatment in the quality of life in these patients can be negative, reducing the adherence and efficacy of the therapy.

Minor risk of severe mucositis can be achieved by lowering the D mean and D max constrains to the OC as an organ at risk (OAR) without compromise the prescribed dose to the PTV. There is no consensus of which is the best way of contouring the OC as OAR. The aim of this study is to assess whether the way we contour the OC reduces the mucositis without compromising the treatment plan.

Materials and Methods: Nineteen patients with locally advance head and neck cancer treated with radical IMRT were analysed for this study. Treatment was calculated according to international recommendations utilising Intensity Modulated Radiotherapy (IMRT) technique with 7 fields and dynamic multileaf collimator, delivering dose between 66 and 70 Gy to the PTV. The Monaco treatment planning system with Monte Carlo algorithm was used.

The same physician made the contouring of the PTV volume and the OC. The oral cavity included: hard palate mucosa, floor of the mouth, orbicular muscle and lips, upper and lower teeth and gingiva, oral vestibule and the ventral 2/3 portion of the tongue.

Patients were followed weekly by the physician recording and classifying the grade of mucositis in two groups (Group A: asymptomatic or mild ulcers and Group B: severe ulcers or major bleeding pseudo membrane).

Oral cavity D mean, D max, V50Gy, V45Gy, V40Gy, V35Gy, V30Gy, V25Gy and V20Gy were recorded and compared. We used a standard statistical analysis to describe the D mean, D max and volumes with the grade of mucositis appearance. We have compared our results with similar published series.

Results:

The median age of this group was 57 y (range: 45-84y), 12 patients were female and 7 were male with an optimal performance status (Karnofsky Index 90%).

In the group A, 15 patients (78.9%) were assessed with mucositis toxicity grade ≤ 2 and in-group B, only 4 patients (21%) reached a mucositis toxicity grade ≥ 3 with no severe complications.

In the 19 cases the OC volumes mean was 96.4cc accomplishing lower doses in the oral cavity has an organ at risk. We also evaluated the V20, V25, V30, V45 and V50 of the OC. PTV dose compliance was not compromised with the tighter values of D mean 18.8Gy and D max 38.3Gy.

Conclusions: This descriptive study reveals that this oral cavity contouring shows lower D mean and D max in the OC as OAR comparing with the literature available, making possible to achieve tighter constrains dose and decreasing the oral toxicity. Further research comparing different ways of contour the OC is needed to obtain consensus and a lower mucositis profile.
PO-094
Can the mean dose delivered to the superficial parotid lobe predict xerostomia following RT in HNC?
D. Nevens1, S. Nuyts1
1University Hospital Gasthuisberg, Radiation Oncology, Leuven, Belgium

Purpose/Objective: Concurrent (chemo-)radiotherapy (RT) is the current standard of care for patients with locally advanced head and neck cancer (HNC). One of the most frequently reported side effects in these patients is xerostomia due to co-irradiation of the salivary glands. Xerostomia early into treatment may be due to damage to the plasma membrane of acinar cells. Late damage however may be explained by lack of proper cell renewal because of damage to stem cells (SC). The superficial parotid lobe is believed to be a SC rich region. We hypothesize that sparing these SC in the ipsilateral superficial parotid gland could make a difference in the saliva production after parotid sparing RT.

Looking at the correlation between the mean dose to the superficial ipsilateral parotid lobe in patients who were treated with (contralateral) parotid sparing RT and patient/physician scored xerostomia is therefore the purpose of this study.

Materials and Methods: We included 40 patients diagnosed with head and neck cancer who were treated with primary RT up to 72 Gy. In 28 patients the contralateral parotid could be spared to a mean dose less than 26 Gy. Therefore, we conducted the analysis in these 28 patients.

Patients scored toxicity using the University of Michigan Xerostomia Questionnaire (XQ) at 2-6-12 months after the completion of the treatment. Physicians scored toxicity using the RTOG/EORTC late toxicity scoring at 6-12 months. For the statistical analysis, mean doses to the ipsilateral superficial parotid lobe were correlated with xerostomia (for the XQ questionnaire: 0-20, 20-40, 40-60, 60-80; for the RTOG/EORTC late toxicity scoring at 6-12 months. For the statistical analysis, mean doses to the ipsilateral superficial parotid lobe were correlated with xerostomia (for the XQ questionnaire: 0-20, 20-40, 40-60, 60-80; for the RTOG/EORTC scoring: any (≥1), and ≥2). A Wilcoxon Matched Pairs Test was performed to prove correlation.

Results: Regarding patient-scored toxicity we saw no significant correlation between the mean dose to the ipsilateral superficial parotid lobe and xerostomia at all 3 time-points. Concerning physician-scored toxicity we saw no correlation between the mean dose to the superficial parotid lobe and xerostomia nor xerostomia ≥2 at 6 months. At 12 months we saw no significant correlation regarding any xerostomia.

However we observed a statistically significant difference between the mean dose to the superficial ipsilateral parotid lobe and xerostomia ≥2 at 12 months (p=0.001) (Figure 1).

Conclusions: At 12 months we see a significant correlation between physician-scored xerostomia ≥2 and the mean dose to the superficial ipsilateral parotid lobe. Sparing of the superficial ipsilateral parotid lobe, while sparing the whole contralateral parotid gland, could mean a step forward to decrease xerostomia after RT for HNC. We will investigate this hypothesis further in a larger patient cohort and we will take pre-existing xerostomia and other possible confounding dosimetric parameters (mean contralateral superficial parotid lobe dose, mean deep parotid lobe dose, dose to the oral cavity) into account.

PO-095
An evaluation of IMPT versus rotational IMRT for nasopharyngeal carcinoma
T. Williams1, P. Sanghera1, A. Hartley1, G. Heyes1, A. Dumbill1, A. Chalkley1, Y. Roussakis1, J. Cashmore1
1Hall-Edwards Radiotherapy Research Group Queen Elizabeth Hospital Birmingham, Radiotherapy Physics, Birmingham, United Kingdom

Purpose/Objective: Image-guided IMRT with photons is now the accepted standard of care for the treatment of nasopharyngeal carcinoma (NPC). However, there is increasing interest in the use of proton therapy. The extent to which this could impact upon the local control and morbidity remains unclear. The aim of this project was to investigate the potential benefits of IMPT over modern IMRT for NPC.

Materials and Methods: 10 NPC patients, previously treated at the host centre were re-planned using VMAT (Monaco) TomoTherapy (TomoHD) and IMPT (XiO). All patients were planned to receive 65Gy in 30 fractions to the high dose PTV, 60 Gy in 30 fractions to areas of intermediate risk and 54Gy in 30 fractions to at risk nodal regions. Plans were compared by analysing PTV coverage as well as the mean and maximum doses received by critical and normal structures. Significance testing between techniques was performed using a Wilcoxon signed rank test.

Results: All modalities were able to produce plans that would be clinically acceptable for treatment. All 3 techniques were able to achieve critical serial organ dose constraints. No significant difference could be seen in PTV conformity between modalities within this study. IMPT showed significant reductions in mean dose for several distant structures including larynx (p=0.002), brain (p=0.006) and oral cavity (p=0.004).

Conclusions: For the NPC cases studied, plans of high quality could be generated on all three modalities. Minor differences in tumor coverage and homogeneity are unlikely to be of clinical significance. Future clinical studies should investigate whether reduced integral dose to more peripheral structures, such as larynx, brain and oral mucosa lead to meaningful clinical gains.

PO-096
Cetuximab(CET), 5-FU and cisplatin or carboplatin (CA) vs CET, paclitaxel and CA in metastatic head and neck cancer
S. Friesland1, L. Specht1, H. Haugen1, K. Söderström1
1Karolinska institutet, Department of Oncology, Stockholm, Sweden
2University of Copenhagen Rigshospitalet, Department of Oncology, Copenhagen, Denmark
3Jubileumsklinikken Sahlgrenska Universitetssjukhuset, Department of Oncology, Goteborg, Sweden
4Umea Universitet, Department of Oncology, Umeå, Sweden

Purpose/Objective: Primary: To investigate in patients with relapsed or metastatic squamous cell carcinoma of the head and neck (SCCHN) whether progression free survival (PFS) in the arm with cetuximab (CET), paclitaxel and carboplatin (CA) based chemotherapy is not markedly worse than PFS in the arm with CET and 5-FU, cisplatin or CA based chemotherapy. Secondary: to compare in pts with relapsed carcinoma of the head and neck the following study variables between both treatment arms: best Overall response rate (ORR), duration of response, time to treatment failure, overall survival (OS) and safety.

Materials and Methods: One hundred twenty pattiens with histologically or cytologically confirmed SCCHN with at least
one measurable lesion according to RECIST 1.1 will be randomized either to Group A) CET in combination with 5FU and CA or cisplatin for a maximum of 6 cycles, followed by maintenance CET or to Group B) CET in combination with paclitaxel and CA for a maximum of 6 cycles. After completion of chemotherapy the patients with SD, PR or CR will continue with maintenance CET every second week.

HPV status will be analyzed during study (not required before randomisation with surrogate marker p16 or PCR. For pts who provide a separate informed consent, blood-sampling will be collected for future biological analyses at baseline.

**Results:** This Multicentre prospective randomized Phase II trial (CETMET) is ongoing. 50 pts are included by Oct 10, 2014. Toxicity profile will be discussed at the meeting. Preliminary analyses show disease control with 0% CR, 39% PR and 34% SD after 2 cycles; 8% CR after completion of 4 cycles of chemotherapy in combination with CET.

**Conclusions**

The treatment is well tolerated and response rates are promising. The study will be open for further inclusion.

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**Poster: Biology, HPV, immunology and molecular targeting**

**PO-097**

**Genome-scale methylation assessment did not identify prognostic biomarkers in oral tongue carcinomas**

A. Lim, N. Wong, R. Piddles, E. Zontenko, J. Corry, A. Dobrovic, B. Solomon, D. Rischin, S. Clark

1. Peter Mac Callum Cancer Centre, Department of Medical Oncology, Melbourne, Australia
2. Ludwig Institute for Cancer Research Austin Health, Translational Genomics and Epigenomics Laboratory, Melbourne, Australia
3. Garvan Institute of Medical Research, Epigenetics Research Laboratory, Sydney, Australia
4. Peter Mac Callum Cancer Centre, Department of Radiation Oncology, Melbourne, Australia

**Purpose/Objective:** DNA methylation forms an attractive putative biomarker given the use of de-methylating agents in clinical practice and its use for prognostication in other cancer types. A number of studies report the detection of methylation profiles in heterogeneous HNSCC cohorts that were able to predict patient outcome. Thus, we sought to investigate if a prognostic methylation profile could be found in tumour tissue from a single uniform head and neck subsite.

**Materials and Methods:** Using FFPE derived DNA from 120 oral tongue squamous cell carcinoma (OTSCC) samples that were comprehensively annotated for clinicopathological variables, we examined the methylation status of 450,000 loci with the Illumina HumanMethylation450K (HM450K) array. Data pre-processing, quality control and analysis was performed using multiple contemporary R packages (including minfi, methylumi, RnBeads, and ChAMP) and novel machine learning methods. Probes mapping to SNPs, sex chromosomes and unreliable probes were accounted for prior to downstream analyses. The relationship between methylation and patient survival was examined using both agnostic approaches and feature selection. Our cohort was enlarged by the inclusion of 91 TCGA OTSCC samples with HM450K and survival data available.

**Results:** Given the use of FFPE derived DNA, we used stringent quality control criteria to refine our OTSCC cohort to 68 samples. Overall, similar results were found analysing the restricted cohort alone, and analysing the combined cohort of 159 OTSCC samples that had good quality methylation and survival data. With an unsupervised approach, including the use of multidimensional scaling, principal components analysis, and hierarchical clustering, no distinct hypermethylated group of samples was identified, and nor was a prognostic methylation profile identified. The use of multiple feature selection approaches, including a Linear Models for Microarray data (LIMMA), Centroid Feature Selection (CFS), and Recursive Feature Elimination (RFE) support vector machines similarly failed to identify a significant methylation signature to predict patient outcome. The methylation data was not found to be informative for patient prognosis or any clinicopathological data available. Furthermore, we were unable to confirm the prognostic methylation profiles or specific prognostic loci reported within the literature for HNSCC.

**Conclusions:** With genome-scale assessment of DNA methylation in one of the largest OTSCC cohorts to date, we were unable to identify a hypermethylated group of tumours or a prognostic methylation signature. This suggests that either DNA methylation in isolation is not likely to be of prognostic value or larger cohorts are required to identify such a biomarker for OTSCC.

**PO-098**

A re-evaluation of late mucosal toxicity: evidence for a mixed consequential-late effect?

A. Hartley, P. Sanghera, J. Glaholm, C. McConkey, C. Boon, S. Meade

1. Hall-Edwards Radiotherapy Research Group, Cancer Centre Queen Elizabeth Hospital, Birmingham, United Kingdom
2. Clinical Trials Unit, University of Warwick, Warwick, United Kingdom

**Purpose/Objective:** Late mucosal grade 3-4 toxicity (occurring 3 months after the completion of radical radiotherapy for head and neck cancer) is a rare complication. The frequency of this complication may be a marker for the tolerability of a given fractionation schedule. In radiobiological terms it is uncertain whether this is a consequential effect related to the acute response of the mucosa and overall treatment time or a true late effect. Due to this uncertainty an accurate model to predict differences in this endpoint in future randomised studies has not previously been defined.

**Materials and Methods:** Randomised studies of altered fractionation in head and neck cancer reporting late mucosal toxicity were included. Late mucosal biological effective dose (lmBED) was calculating using 3 models: late (αβ=3 Gy with no time correction); acute (consequential) (αβ=10 Gy; α=0.3 Gy(-1); Tβ=2.5Tα; Tα=7 days) and mixed (αβ=0-10Gy; α=0.2-0.6Gy(-1); Tβ=2.5Tα; Tα=7 days). The correlation between percentage (%) changes in lmBED calculated using these models and % changes in late mucosal grade 3-4 toxicity was then examined using the weighted Pearson product moment correlation statistic.

**Results:** A statistically significant correlation was observed when lmBED was calculated using either the late model (p=0.02) or the mixed model (αβ=4Gy; α=0.45 Gy(-1)) (p=0.003). No significant correlation was observed when lmBED was calculated using the acute (consequential) model.

**Conclusions:** These results support the possibility of late mucosal toxicity being either a late or a mixed consequential-late effect. Unlike classical radiobiological late effects, late mucosal toxicity may be related to overall treatment time. Use of the mixed consequential-late model may be helpful in predicting the long term mucosal safety of fractionation schemes for use in future randomised studies.

**PO-099**

Combination of mTOR targeting with cetuximab, and chemotherapy: a preclinical study on head and neck cancer

A. Bozec, N. Ebran, A. Sudaka, M.C. Etinne-Grimaldi, F. Penaud-Llorca, G. Milano

1. Institut Universitaire de la Face et du Cou, Oncologic
5TH ICHNO

Surgery, Nice, France
2Centre Antoine Lacassagne, Oncopharmacology Unit, Nice, France
3Centre Antoine Lacassagne, Pathology, Nice, France
4Centre Jean Perrin, Pathology, Clermont-Ferrand, France

Purpose/Objective: Clinical benefit has been demonstrated in patients with head and neck cancer receiving an anti-epidermal growth factor receptor (EGFR) agent in combination with chemotherapy. Activation of the PI3K/AKT/mTOR signaling pathway is identified as an important mechanism implicated in resistance to EGFR inhibitors. Recent preclinical studies suggest beneficial effects from combining mTOR inhibitors with anti-EGFR drugs. The aim of this experimental study was to investigate the effects of combining the mTOR inhibitor Temsirolimus (Tem) with the anti-EGFR agent Cetuximab (Cet), and conventional chemotherapeutic drugs (Cisplatin (C) and Fluorouracil (F)) on an orthotopic model of head and neck cancer.

Materials and Methods: We evaluated in vivo the anti-tumour efficacy of Tem, Cet and C-F, given alone and in combination. Investigations were performed using a VEGF-secreting human head and neck tumour cell line, CAL33, with a high EGFR content, injected as orthotopic xenografts into the mouth floor of nude mice. Three days after tumour cell injection, Tem (5 mg/kg, 5 days a week), Cet (2.5 mg/kg, once a week) and C-F (C: 4 mg/kg, F: 15 mg/kg, once a week) were administered as intra-peritoneal injection alone or in combination for 12 days.

Results: As compared with the control, the combination of Tem and Cet led to the highest tumor inhibition and induced an almost complete tumor growth arrest (p = 0.01). Tem significantly enhanced the impact of the Cet + C-F combination on tumor growth (p < 0.001). Tem and Cet were well tolerated as indicated by the stability of the mice weight during the treatment period. The highest inhibitory effects of treatments on cell proliferation (Ki67 labelling), MAPK (p42/44 labelling) and PI3K/AKT/mTOR (pS6R labelling) signaling pathways were found with the association Tem-Cet. The addition of Tem-Cet to the C-F treatment significantly decreased tumor vessel formation as compared to C-F treatment alone (p = 0.002).

Conclusions: The results of the present study testing the association of Tem with Cet and chemotherapy could serve as a strong preclinical basis for innovative treatments combining m-TOR/PI3K inhibition with EGFR targeting therapies for an optimal management of patients with head and neck cancer.

PO-100

E6 viral protein ratio correlates with outcomes in human papillomavirus related oropharyngeal cancer
A. Hong1, X. Zhang1, D. Jones1, M. Zhang1, C.S. Lee1, J.G. Lyons1, A.S. Veillard1, B. Rose1
1The University of Sydney, Faculty of Medicine, Sydney, Australia

Purpose/Objective: With the raising prevalence of human papillomavirus (HPV) positive oropharyngeal cancer (OPSCC), a more refined prognostic marker for HPV positive OSCC is needed to guide treatment. The aim of this study was to identify prognostic indicators that could be used in conjunction with the existing clinicopathological approach to improve the management of HPV positive OSCC.

Materials and Methods: We determined the ratio of HPV E6I and E6II splice variants by quantitative RT-PCR in 177 HPV positive OSCC and correlated the findings with other clinicopathological data.

Results: There were significantly more events and deaths among patients whose tumors had an E6I/E6II ratio ≥1 compared with an E6I/E6II ratio of <1 (38.5% vs 20.3%, p=0.015) and (30.2% vs 14.1%, p=0.023) respectively. In the multivariable analysis, patients with E6I/E6II ratio ≥1 OSCC were twice as likely to have an event (HR 2.02, 95% CI 1.06-3.85, p=0.033) and to die (HR 1.95, 95% CI 0.89-4.26, p=0.094) relative to those with E6I/E6II ratio <1 OSCC.

Conclusions: The detection of HPV 16 spliced transcripts may serve to identify risk factors for poorer outcomes for HPV positive OSCC.

PO-101

Podoplanin expression in oropharyngeal cancer influences staging and prognosis only in p16 negative tumors
M.A. Broglie Daeppen1, M. Roessle2, S.Y. Kiessling1, A. Soltermann3, S.R. Haile4, G.F. Huber5, S.J. Stoeckli6
1Kantonsspital St. Gallen, Otolaryngology Head and Neck Surgery, St Gallen, Switzerland
2Cantonal Hospital Graubuenden, Institute of Pathology, Chur, Switzerland
3University Hospital Zurich, Institute of Surgical Pathology, Zurich, Switzerland
4Kantonsspital St. Gallen, Clinical Trials Unit, St. Gallen, Switzerland
5University Hospital Zurich, Otolaryngology Head and Neck Surgery, Zurich, Switzerland
6Kantonsspital St. Gallen, Otolaryngology Head and Neck Surgery, St. Gallen, Switzerland

Purpose/Objective: To assess the impact of podoplanin expression on staging and clinical outcome in relation to HPV status in patients with oropharyngeal cancer (OPSCC).

Materials and Methods: 174 patients were consecutively included with tissue microarray (TMA) construction and immunohistochemical analysis. Estimation of survival times and importance of clinical and immunohistochemical factors for outcome by Kaplan-Meier analysis and Cox proportional hazard models.

Results: For the entire cohort, the 5yr-Overall (OS), disease specific (DSS) and disease free survival (DFS) achieved 71%, 77% and 76%, respectively. Patients with p16 positive tumors had statistically significantly better 5yr-OS (p16 positive vs p16 negative patients 81% vs 60%, p=0.001), DSS (88% vs 66%, p=0.0001) and DFS (87% vs 64%, p=0.0001) than patients with p16 negative cancer. 56/174 (32%) tumor samples were expressing podoplanin. In the entire patient cohort as well as in the p16 positive subgroup no impact of podoplanin expression on nodal stage or survival could be demonstrated. In the p16 negative subgroup podoplanin expressing tumors had a more advanced N-category compared to podoplanin non-expressing tumors and had also a statistically significant worse 5yr-OS (42% vs. 70%), DSS (47% vs. 75%), and DFS (46% vs. 73%).
Podoplanin is a strong and independent prognostic factor for staging and survival in the group of patients with p16 negative but not with p16 positive OPSCC and may be considered as a cofactor in risk stratification and therapeutic decisions in patients with prognostically unfavourable p16 negative OPSCC.

Conclusions: To the best of our knowledge, we report here the largest study where safety and efficacy of re-RT and concurrent EGFR blockade have been investi-gated. We documented significant longer median overall survival if patients developed aceniform rash grade 2-3 compared to patients with- out this cetuximab-related complication (14 months vs. 6 months) and significant shorter survival times in patients who relapsed more than 120 months after finishing primary RT course. Taken together, compared to standard combined therapy (cisplatin,5-Fluorouracil and cetuximab) this therapeutic strategy did not demonstrate survival benefit.

Comparison of VEGF Expression in non malignant, premalignant lesion and squamous cell carcinoma of oral cavity

M. Gupta1, N. Husain2, R. Mehrotra3
1Christian Medical College Hospital, General Pathology, Vellore, India
2RML Medical College & Hospital, Pathology, Lucknow, India
3King George Medical University, Pathology, Lucknow, India

Purpose/Objective: To compare vascular endothelial growth factor (VEGF) expression in non malignant lesion (stratified squamous epithelium overlying pyogenic granuloma), premalignant lesion (leukoplakia) and squamous cell carcinoma (SCC) of oral cavity and further to evaluate expression in relation to grade of the tumour.

Materials and Methods: Immunohistochemical expression of VEGF in 90 cases of oral SCC [30 cases each of well differentiated (WD), moderately differentiated (MD) and poorly differentiated (PD) carcinoma] and 30 cases each of leukoplakia and pyogenic granuloma were evaluated. VEGF expression observed as brown intracytoplasmic staining, was counted in 500 squamous cells in all cases. On the basis of intensity and percentage positivity VEGF score and VEGF grade were calculated.

Conclusions: Podoplanin is a strong and independent prognostic factor for staging and survival in the group of patients with p16 negative but not with p16 positive OPSCC and may be considered as a cofactor in risk stratification and therapeutic decisions in patients with prognostically unfavourable p16 negative OPSCC.

Reirradiation and cetuximab in patients with recurrent, unresectable previously irradiated head and neck cancer

D. Milanovic1, A.L. Grosu1, M. Henke1
1Universitätsklinik Freiburg, Department of Radiation Oncology, Freiburg, Germany

Purpose/Objective: The treatment of patients with locoregionally recurrent, unresectable and previously irradiated head and neck cancer (HNSCC) is a continuing challenge. Due to the fact that the predominant cause of death of these patients is local controlled growth, it has been supposed that reirradiation (re-RT) may play important role achieving local control, but median survival achieved with this therapeutic modality is approximately 10 months. The overexpression of epidermal growth factor receptor (EGFR), which is not only responsible for progression but also for increased resistance toward RT, is one of the most important molecular biological characteristics of HNSCC. We propose that better response to re-RT will be reached in case of simultaneous EGFR inhibition with cetuximab. The purpose of this retrospective study was to investigate the feasibility, toxicity, and outcome of re-RT combined with cetuximab in pa-tients with inoperable, previously irradiated recurrent HNSCC.

Materials and Methods: Between June 2008 and August 2014, 34 patients with inoperable and previously irradiated HNSCC were reirradiated Concomitant EGFR blockade (cetuximab) was given initially at 400 mg/m² two days prior to re-RT and weekly (250 mg/m²) thereafter.

Results: 31 patients completed Re-RT (50.4-66.6 Gy, 5 X 1.8 Gy/Week) and received cetuximab as prescribed. One patient died of anaphylactic shock, two discontinued study-participation on their own request. Grade 3 side effects were documented for dermatitis (25.8%), dysphagia (12.9%), aceniform rash (22.5%), mucositis (9.6%), voice change (9.6 %) and pain (9.6%). Median overall and progression-free survival times were 10.4 and 5.2 months, respectively.

Conclusions: The intensity of VEGF staining in individual cells was graded as negative, +, ++, +++.

Number of cells showing VEGF expression of varying intensity was counted and VEGF score was calculated as below

Number of cells with negative VEGF expression × 0 = A
Number of cells with 1(+) intensity × 1 = B
Number of cells with 2(++) intensity × 2 = C
Number of cells with 3(+++) intensity × 3 = D

VEGF score = A+B+C+D

VEGF score for individual cases was calculated and mean score was obtained for each of the 5 groups.

VEGF grading on the basis of the score obtained for each tumour was done in the following way:

**VEGF grade VEGF score**

Grade 0: 0-50
Grade 1: 51 - 500
Grade 2: 501-1000
Grade 3: 1001 - 1500
Results:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Mean VEGF score</th>
<th>Mean VEGF grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well differentiated</td>
<td>1121.0 ± 288.3</td>
<td>3</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>922.0 ± 313.0</td>
<td>2</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>237.6 ± 176.1</td>
<td>1</td>
</tr>
<tr>
<td>Leukoplakia</td>
<td>479.9 ± 152.6</td>
<td>1</td>
</tr>
<tr>
<td>Pyogenic granuloma</td>
<td>479.8 ± 73.1</td>
<td>1</td>
</tr>
</tbody>
</table>

Conclusions: We observed significant decrease in VEGF expression as the degree of differentiation declined in oral squamous cell carcinoma with poorly differentiated tumors demonstrating negligible VEGF expression. Low VEGF expression was present in leukoplakia and epithelium overlying pyogenic granuloma. VEGF acts through tyrosine kinase receptors on the endothelial cell surface causing them to dimerize and become activated through transphosphorylation. This results in vascular proliferation. It appears that in well differentiated SCC, this mechanism is active for tumor vascularization. It is speculated that vascular proliferation in poorly differentiated SCC occurs through a different mechanism. There is controversy in literature regarding the expression of VEGF in relation to the grade of the tumor.

PO-104
HPV 16 E7 seropositivity in head and neck squamous cell carcinoma compared to healthy controls

T. Zahoor1, V. Green2, N. Stafford2, J. Greenman2
1Department of Cancer Research, Hull and York Medical School, Cottingham, United Kingdom
2Department of Cancer Research, Daisy Research Building University of Hull, Cottingham, United Kingdom

Purpose/Objective: It has already been established that infection with Human Papilloma Virus (HPV) 16 confers better outcomes and survival rates in those who have HPV positive Head and Neck squamous cell cancer (HNSCC) compared with their negative counterparts, regardless of treatment modality. The HPV viral oncoproteins E6 and E7, have been implicated in the pathogenesis of tumourigenesis by inactivating the tumour-suppressor proteins p53 and retinoblastoma respectively. Although it has been demonstrated that seropositivity to E6 and E7 in HPV positive HNSCC confers much better survival rates, little information is available which compares serum antibody titres to those in healthy controls. The aim therefore was to compare serum E7 antibody levels in both HPV positive HNSCC patients and healthy controls.

Materials and Methods: The presence of HPV16 was determined in patients with established laryngeal or oropharyngeal HNSCC (n=85) using p16 immunohistochemistry (CinTec®). Patients and healthy controls (n=25) were also tested for seropositivity to the HPV 16 viral oncoprotein E7 with an ELISA developed in house.

Results: Of the 75 patients tested 21 were found to be p16 positive. No significant difference in E7 antibody level was observed amongst the HPV positive and negative patients and notably not all HPV positive patients mounted an antibody response to HPV 16 E7. Interestingly almost half of the healthy subjects also displayed an antibody response to E7 and no significant difference between E7 antibody response in HPV positive HNSCC patients vs. normal healthy subjects was detected.

Conclusions: Although seropositivity has been shown to confer better outcomes in HPV positive HNSCC patients, the presence of a similar level of antibody response to E7 in healthy subjects suggests antibody titres against this antigen are not useful as a diagnostic tool.
Hofman1, A. Bozec1, G. Orend1, A. Sudaka3
1Institute of Biology Vairose, CNRS UMR7277 - INSERM U1091 - UNS, Nice, France
2CHU Nice, Laboratory of Clinical and Experimental Pathology, Nice, France
3Centre A. Lacassagne-IUFC, Surgery, Nice, France
4INSERM U1109, Microenvironmental Niche in Tumorigenesis and Targeted Therapy, Strasbourg, France
5Centre A. Lacassagne-IUFC, Pathology, Nice, France

Purpose/Objective: Malignant progression of Head and Neck Squamous Cell Carcinomas (HNSCC) is controlled by functional interplay between tumor cells and their pre-tumoral tissue environment thus a thorough understanding of these interactions is essential for the development of effective therapies. The Extracellular Matrix (ECM) is a non-cellular component of the HNSCC microenvironment that provides not only a molecular scaffold but also a signaling platform for growth, immunomodulatory, and angiogenic factors and transmits chemical and physical cues to malignant and non-malignant cells via signaling receptors of the integrin family. Here we sought to identify ECM components and their receptors that contribute to the invasive behavior of HNSCC. Further, we set out to compare the matrix environment of HPV-negative and HPV-positive HNSCC, two clinically distinct entities with different outcomes.

Materials and Methods: A binary ex vivo system, composed of human HNSCC lines and a de-cellularized ECM produced by patient-derived fibroblasts was set up to observe the motile behavior of tumor cells by videomicroscopy and to identify relevant integrin receptors and signaling pathways. The composition of the fibroblast ECM and associated proteins (termed matrisome) was determined by mass spectrometry. Expression of selected matrix proteins and integrins in human tumors was analyzed by immunohistochemistry on a defined set of 97 loco-regionally advanced HNSCC (including 41% HPV-positive tumors, as determined by p16 immunostaining and high-risk HPV CISH), and a larger independent cohort of primary HNSCC.

Results: Proteomic analyses identified oncofetal fibronectin and tenasin-C as the most abundant ECM components of the HNSCC-derived fibroblast matrisome. Fibronectin overexpression in HNSCC, predominantly by stromal cells, correlated with poor prognosis and higher locoregional recurrence in patients (n=436). Tenasin C (expressed by tumor and stromal cells) localized to pre-invasive areas. The fibronectin and tenasin C-binding integrins v86 and p981, upregulated in human tumors, were found to regulate collective migration of tumor cells on the HNSCC-derived ECM. Results from analyses of HPV-related matrix components, integrin expression and signaling pathways will be presented.

Conclusions: Our results validate an ex-vivo model for further mechanistic investigations and a platform for the development of translational studies. Proteomic analysis of the fibroblast-derived ECM has provided an inventory of the matrisomal proteins that could engage in functional interactions with tumor cells. Immunoprofiling of human tumors should provide biologically and clinically relevant information about the roles of ECM and related molecules in HPV-related disease progression, treatment response and tumor recurrence.

PO-107
Gain of copy number of PIK3CA and MET in head and neck cancers (HNSCCs)

D. Brauswetter1, K. Danos2, E. Birtalan1, L. Tamas1, I. Peták1
1Semmelweis University, MTA-SE Pathobiocchemy Research Group, Budapest, Hungary
2Semmelweis University, Department of Oto-Rhino-Laryngology Head-Neck Surgery, Budapest, Hungary

Purpose/Objective: Mutations and copy number gains (CNG) resulting in increased activity of the MET receptor tyrosine kinase or PI3K/Akt/mTOR pathway have a known and important role in the pathogenesis of head and neck cancers. However, the importance of these pathways in the different subtypes of HNSCCs and their relation to HPV-positivity is still unclear.

The use of target therapies is currently increasing, therefore predictive biomarkers of sensitivity are becoming more important and necessary. PI3K and MET are remarkable targets in cancer cells, accordingly, examination of their gene status is up-to-date and relevant.

Materials and Methods: Tumor samples of 132 patients were examined with fluorescence in situ hybridisation method (FISH) to investigate the copy number gain of PIK3CA (catalytic subunit of PI3K) and MET in head and neck cancers. Six minor groups were distinguished: negative, low trisomy, high trisomy, low polysomy, high polysomy and gene amplification. Subsequently, we divided the results into two major groups (normal or CNG), performed statistical analysis with SPSS and looked for correlations with clinical parameters, localization and previously studied biomarkers (Ki67, p53, p16, EGFR).

Results: We found no amplification of MET gene in the tumor samples examined in our study. The rate of MET polysomy (low and high) was 33.5%. PIK3CA amplification and high polysomy were observed in 28.5% of the samples. Comparing the patients’ survival according to the PIK3CA or MET copy number, we found that patients with CNG had significantly worse survival rate than those with normal copy number of the gene (p=0.032 HR=1.65; p=0.013 HR=1.779 respectively). Significant correlation was revealed between tumor size (T) and PIK3CA CNG (p=0.008): CNG was associated with higher T status. In addition, we found correlations between p16 positivity and copy number gain both of PIK3CA and MET. The rate of CNG was significantly higher in the p16-negative cases (p=0.026;p=0.023 respectively).

Conclusions: Although we found no amplification, MET polysomy proved to be a prognostic biomarker in HNSCCs. We observed less PIK3CA amplification than written in scientific literature, but this can be caused by the difference in the used methods (quantitative real-time PCR or FISH). According to our results, copy number elevation of PIK3CA is also a prognostic biomarker in this type of cancers and has a strong correlation with the tumor size. Both examined biomarkers are more prevalent in p16-negative tumor samples.

PO-108
The role of circulating HPV-16 DNA detection in HNSCC patients treated by definitive radiation or chemo-radiation

A.B. Hajduk1, T. Rutkowski1, A. Mazurek2, K. Skladowski1
1Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology III Dept, Department of Radiation Oncology, Gliwice, Poland
2Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology III Dept, Center for Translational Research and Molecular Biology, Gliwice, Poland

Purpose/Objective: Human papillomavirus (HPV) infection and the head and neck squamous cell carcinoma (HNSCC) development have been well established. Patients with HPV-positive tumors present better prognosis in reverse with HPV-negative ones, so the confirmation of HPV-HNSCC origin may be crucial for treatment decision. Despite of favorable outcome for these patients, locoregional or distant failure still could be observed. The assessment of plasma circulating HPV DNA is an attractive noninvasive method for virus detection in the blood. If the response to treatment is reflected in HPV detection, it may become feasible tool in monitoring of treatment results in aspect of locoregional and distant relapse. The study is focused on preliminary results of
HPV-16 DNA detection as a marker for diagnosis and monitoring of the response to the radiotherapy (RT) or radiochemotherapy (RCHT) in HNSCC patients.

**Materials and Methods:** The collection of blood plasma from 287 patients before definitive RT/RCHT due to HNSCC was performed. After DNA extraction from plasma, the presence of HPV was assessed by qPCR using E6/7 specific primer/probe sets. In all cases HPV-16 type was found. Sensitivity and specificity of HPV detection in blood was established in comparison to HPV detection in paraffin embedded tumor specimens. For HPV-positive patients, blood collections were carried out during RT/RCHT (before, after induction therapy, after treatment completion) and during follow-up period.

**Results:** 43 HPV-positive patients (14.6%), mostly oropharyngeal carcinoma 28/43 (65%), was identified. For all that patients virus was also detected in paraffin embedded tumor specimens. The sensitivity and specificity of the method has been established on 62% and 100%, respectively. The assessment of early treatment outcome showed total tumor regression in 41/43 (95%) of HPV-positive patients after RT/RCHT. Serial measurements demonstrated that HPV-16 DNA become undetectable in plasma in all cured patients and was still observed in those with treatment failure 2/43 (5%). HPV-16 DNA was also re-detectable during follow-up period because of recurrence disease 2/41 (5%).

**Conclusions:** Preliminary results indicate that detection of HPV-16 in cell-free DNA is a feasible method to confirm HPV-positive tumors. Detection of HPV-16 DNA in blood plasma correlates also with clinically observed tumor regression after treatment completion and with relapse disease.

**PO-109**

**Prognostic value of Connexin 43 expression in head and neck cancers**

K. Dános¹, D. Brauswitter², J. Petáki², L. Tamás¹
I. Semmelweis University, Dept. of Oto-Rhino-Laryngology
Head-Neck Surgery, Budapest, Hungary
II. Semmelweis University, MTA-SE Pathobiomarkers Research Group, Budapest, Hungary

**Purpose/Objective:** Gap junctions are transmembrane channels playing a role in the exchange of small molecules and ions between cells. Gap junctions are composed of connexons formed of connexins. Connexins have an established prognostic value in several cancer types, e.g. melanomas, renal cell carcinomas. Our objective was to evaluate the prognostic role of Connexin 43 (Cx43) in head and neck squamous cell carcinomas (HNSCCs).

**Materials and Methods:** 90 patients having HNSCCs were enrolled into our study. We prepared Tissue Microarrays (TMA) made from the patients’ tissue samples and used immunohistochemical staining for detecting Cx43 and other relevant biomarkers (Ki67, p53, EGFR, p16INK4). The histological evaluation was performed on computers using the Panoramic Viewer software. Regarding the Cx43 expression, four groups were distinguished according to the percentage of positively stained tumor cells: 0-5, 5-20, 20-60 and 60-100%. Expressions of the other markers were considered positive when more than 25% of tumor cells were stained. For statistical analysis, Kaplan-Meier estimations with log-rank tests, Cox-regression and Pearson’s Khi-square tests were used.

**Results:** We found significant correlation between the level of Connexin 43 expression and survival of patients: The loss of Cx43 expression was associated with poorer survival (p=0.005). Among the other clinicopathological parameters studied, Cx43 showed significant inverse correlation with tumor grade (p=0.034), and significant direct correlation with p53 expression (p=0.036), however there was no significant association with tumor stage, T, N, or M level.

**Conclusions:** Connexin 43 expression proved to be a prognostic biomarker in head and neck squamous cell carcinomas. Further studies are needed to evaluate its role as a possible predictive biomarker.

**PO-110**

**Excellent survival in patients with non-hypoxic, HPV-positive oropharyngeal squamous cell carcinoma**

J. E. Swartz¹, A. J. Pothen¹, P. M. W. Van Kempen¹, I. Stegeman¹, S. M. Willems¹, W. Groffman¹
¹UMC Utrecht, Department of Otorhinolaryngology, Utrecht, The Netherlands
²UMC Utrecht, Department of Otorhinolaryngology and Brain Center Rudolph Magnus, Utrecht, The Netherlands

**Purpose/Objective:** Hypoxia in solid tumors is associated with resistance to (radio-)therapy, as well as a more aggressive tumor phenotype. Under hypoxia, the transcription factor HIF-1 alpha (HIF-1α) is upregulated to promote cellular survival and inhibit apoptosis. HIF-1α is considered a biomarker for hypoxia and HIF-1α overexpression is known to be associated to therapy resistance and worse survival in oropharyngeal squamous cell carcinoma (OPSCC). Moreover, HPV-associated OPSCC shows better response to therapy, compared to HPV-negative OPSCC. Unfortunately, no evidence is available on the role of hypoxia in the difference in treatment response. We investigated the effect on survival of tumor hypoxia in relation to HPV-status in OPSCC.

**Materials and Methods:** In a cohort of 207 OPSCC patients treated between 1998 and 2007, immunohistochemical analysis of HIF-1α expression and its downstream targets GLUT-1 and CA-IX was performed. Analyses were restricted to patients treated with curative intent for a first primary OPSCC (n=181). Cutoff for positivity was set at 15% nuclear expression. Kaplan-Meier and Cox-regression analyses were performed for the entire cohort and stratified for HPV status.

**Results:** HIF-1α, CA-IX and GLUT-1 expression was available for 169, 176 and 166 of the 181 patients, respectively. In the other patients, tumor cores were not evaluable on the tissue microarray slides. Overexpression of HIF-1α was observed in 61.9% of cases and was weakly correlated to CA-IX and GLUT-1 expression (r=0.297 and 0.278 respectively, p=0.001 and clinical T-stage (r=0.272, p=0.006), but not to HPV-status (p=0.075). In univariate Cox-regression, HIF-1α overexpression was associated with worse survival (HR=1.654, p=0.032). In multivariate analysis, HPV status was a strong predictor of survival (HR=2.96, p=0.002), while HIF-1α overexpression was not (p=0.232). However, in patients with HPV-associated tumors (n=37), low HIF-1α expression was associated with significant better survival (5-year survival: 93.8% versus 55.6%, HR=9.479, p=0.034). In this subgroup, survival in HIF-1α overexpressing tumors was only marginally better than patients with HPV-negative tumors. In the subgroup of patients with HPV-negative tumors, HIF-1α expression was not related to survival (p=0.804).

**Conclusions:** In our cohort, overexpression of HIF-1α was associated with significantly worse survival. However, differences in survival between hypoxic and normoxic tumors were especially apparent in HPV-associated OPSCC. This finding supports the hypothesis that HPV-associated OPSCCs have a distinctly different biology from HPV-negative tumors. HIF-1α overexpression did not influence survival in HPV-negative OPSCC. Possibly, response to therapy of these tumors is already so poor that treatment resistance induced by HIF-1α is no longer clinically relevant. Although these results should be validated in a larger cohort, low HIF-1α expression might be a good predictor of excellent prognosis in patients with HPV-positive OPSCC.
PO-111
FGFR1 is a potential therapeutic target in oral and oropharyngeal squamous cell carcinoma
K. Koole1, D. Brunen2, R. Nooral1, P.M.W. Van Kempen4, W.W. Braunius3, R.J.J. Van Es1, R. Koole1, P.J. Van Diest1, R. Bernard2, S.M. Willems1
1UMC Utrecht, Pathology, Utrecht, The Netherlands
2Netherlands Cancer Institute, Molecular carcinogenesis, Amsterdam, The Netherlands
3UMC Utrecht, Oral and Maxillofacial Surgery, Utrecht, The Netherlands
4UMC Utrecht, Ortholaryngology, Utrecht, The Netherlands

Purpose/Objective: Head and neck cancer is the sixth most common cancer worldwide. Since current treatment regimens cause severe side-effects and survival rates for head and neck cancer have not improved over the last 20 years, novel therapeutic targets are needed. Therefore, we have investigated whether fibroblast growth factor receptor 1 (FGFR1) could serve as a prognostic biomarker or novel therapeutic target in oral and oropharyngeal squamous cell carcinoma (OSCC, OPSCC).

Materials and Methods: Formalin-fixed paraffin embedded tissue of 450 oral and oropharyngeal squamous cell carcinomas was constructed into tissue microarrays and clinical data of these tumors was collected. Both FGFR1 protein expression and FGFR1 gene copy-numbers were determined by fluorescent in situ hybridization (FISH) and immunohistochemistry on these tissue microarrays. FGFR1 protein expression was correlated to survival and clinicopathological characteristics. In a panel of six head and neck cancer cell lines, the anti-tumor effect of inhibiting FGFR1 with selective FGFR-inhibitor AZD4547 was assessed using short-term colony assays and downstream signaling pathway analysis.

Results: FGFR1 protein was overexpressed in 46% (97/212) of OSCC and 78% (186/238) of OPSCC. Overexpression of FGFR1 was related to poor overall survival in OSCC (HR: 1.8; 95%CI: 1.2-2.6; p=0.004). The FGFR1 gene was amplified in 3% (3/97) of OPSCC showing overexpression of FGFR1. Inhibiting FGFR1 with AZD4547 suppressed tumor cell proliferation and downstream FGFR1 signaling in head and neck cancer cell lines.

Conclusions: FGFR1 is frequently overexpressed in both OSCC and OPSCC. Inhibiting FGFR1 suppresses tumor proliferation in vitro. Concerning clinical applications, FGFR1 may serve as a prognostic biomarker in OSCC and novel therapeutic target in both OSCC and OPSCC.

PO-112
Prediction of local control using maximal standard uptake value in early glottic carcinoma
J. Park1, S. Lee1, E. Choi1, J. Kim1, S. Ahn1, S. Song1, S. Yoon1, S. Kim1, Y. Kim1, J. Joo1
1Asan Medical Center, Radiation Oncology, Seoul, Korea Republic of

Purpose/Objective: To investigate that the SUV\textsubscript{max} can predict local tumor control in early glottic cancer (Tis, T1 and T2).

Materials and Methods: A total of 59 patients were treated with definitive radiotherapy for early glottic cancer. We evaluate the pretreatment SUV\textsubscript{max} in region of interest around original tumor site. Local tumor control and survival outcome were estimated by the Kaplan-Meier method. Receiver operating characteristic (ROC) curves were used to assess the SUV\textsubscript{max} on local control.

Results: All patients were observed laryngoscopic complete response. But 11 patients were experienced local failure. There was no distant metastasis. Only one patient died due to local failure. The five patients lost their larynx. Median follow up duration was 61.5 months (range: 6.2-123.4 months). The five year local progression free survival (LPFS) was 84.7% and laryngeal preservation survival was 89.6%. Median SUV\textsubscript{max} was 2.2. The SUV\textsubscript{max} was used to predict actuarial local tumor control through ROC curve analysis, with 3.4 as the cut-off. The glottic cancer with SUV\textsubscript{max} ≥ 3.4 was poorer LPFS than the tumor with SUV\textsubscript{max} < 3.4 (5 year LPFS: 53.4% vs. 95.4% [p < 0.01]), respectively. Multivariate analysis confirmed that high SUV\textsubscript{max} could predict predictive factor for LPFS (p = 0.006).

Conclusions: 18\textsubscript{F}FDG-PET evaluation using SUV\textsubscript{max} is useful predictive tool of LPFS in early glottic cancer with definitive radiotherapy. Early glottic cancer with 18\textsubscript{F}FDG uptake should be needed aggressive local treatment and careful surveillance.

PO-113
Role of 18\textsubscript{F}-FDG PET/CT in chemo-radiotherapy response of nasopharyngeal cancer
L. Belgioia1, D. Agnese2, A. Bacigalupo2, M. Marcenaro2, F. Pupillo3, S. Morbelli4, R. Corvo2
1IRCCS San Martino IST, Radioterapia, Genova, Italy
2IRCCS San Martino IST, Radiation Oncology, Genova, Italy
3IRCCS San Martino IST, Medical Physics, Genova, Italy
4IRCCS San Martino IST, Nuclear Medicine, Genova, Italy

Purpose/Objective: There is still no consensus which is the most effective method to evaluate the response to chemoradiotherapy (CT/RT) treatment in nasopharyngeal carcinoma (NPC). Magnetic resonance imaging (MRI) may be difficult to interpret because poorly distinguishes post-actinic outcomes from any residual disease. The 18\textsubscript{F}-Fludeoxyglucose Positron Emission Tomography/Computer Tomography (18\textsubscript{F}-FDG PET/CT) widely entered in oncology practice as it provides important information on the metabolic characteristics of tumors, stage and the therapeutic response. The aim of our study was to evaluate the effectiveness of this method in monitoring the response to treatment CT / RT in NPC.

Materials and Methods: We retrospectively analyzed 22 patients (pts) with NPC (median age 53 years; 1 patient (pt), 5 pts, 6 pts, 3 pts and 1 pt in stage I, stage II, stage III, stage IVA, stage IVC and stage IVC respectively) subjected to RT +/- CT. All pts have performed an initial inspection with MRI at 2 months and with 18\textsubscript{F}-FDG PET/CT between 3 and 5 months after the end of treatment and were monitored over time with these methods.

Results: At the first control, 8 pts (36.4%) showed absence of disease both on MRI and on 18\textsubscript{F}-FDG PET / CT. Of these, 2 have relapsed in the lymph nodes at 12 and 36 months after treatment end and were referred to salvage surgery; actually they are in complete response (CR). 14 pts (63.6%), however, presented a negative 18\textsubscript{F}-FDG PET/CT between 3 and 5 months after the end of treatment and were monitored over time with these methods.
Conclusions: 18F-FDG PET/CT is an effective method to evaluate the response after CT/RT in the treatment of NPC and in our series did not give false positives. Because some pts may recur despite a first negative control (9.1%), it is advisable to keep a close clinical and instrumental follow-up at least in the early years.

PO-114 Performance of SPECT/CT compared to bone scan in the assessment of free-flap bone grafts in mandible reconstruction

M. J. Ouvrier1, C. Zwarthoed1, A. Bozec2, G. Poissonnet1, O. Dassonville2, J. Darcourt2
1Centre Antoine Lacassagne, Nuclear Medicine, Nice, France
2Centre Antoine Lacassagne, Head and Neck Surgery, Nice, France

Purpose/Objective: The aim of this study was to compare the performance of planar bone scintigraphy (BS) and SPECT/CT in the assessment of microvascular bone grafts in mandible reconstruction 24 hours after surgery.

Materials and Methods: Twelve mandible reconstructions were performed on 11 patients (8M/3F, 56 ± 13 y/o) with cancer (squamous cell carcinoma n=5, adenoid cystic carcinoma n=3, rhabdomyosarcoma n=1) and 2 with osteoradionecrosis. Reconstruction of the mandible consisted of an autogenous microvascular bone grafting with a fibular free-flap with a skin pedicle. Fourteen planar BS and SPECT/CT were performed 24 hours after surgery. Patients were injected with 99mTc-HMDDP (10MBq/kg). BS were acquired on a Siemens Symbia T2 240 minutes after injection, systematically followed by a SPECT/CT. Images were reconstructed in 3-mm slices every 2 mm. SPECT images were reconstructed using CT for attenuation correction and using iterative reconstruction. Planar and SPECT/CT BS were analyzed semi-qualitatively by two nuclear physicians. Consensus was found between the two physicians when there was a discrepancy. They were rated as certainly not viable, probably viable, equivocal, probably viable, and certainly viable. Follow-up was used as gold standard.

Results: Seven patients were free of complications, 2 had partial muscular necrosis, 1 had infectious complication but no necrosis and 1 had bone necrosis on 2 different free-flaps. Two planar BS were rated as certainly not viable, 1 probably not viable, 2 equivocal, 3 probably viable and 6 certainly viable. Three SPECT/CT were rated as probably not viable, none were rated as probably not viable nor equivocal, 4 were rated as probably viable and 7 as certainly viable. For planar BS and SPECT/CT, sensitivity was respectively 82% and 100%.

Conclusions: MRI is of limited diagnostic value for evaluating residual/recurrent nodal disease. There is a lack of consensus on the optimal strategy to determine residual/ recurrent nodal disease in all cases of advanced nodal disease, others reserve surgery for salvage in case of persistent nodal disease after radiotherapy.

At our institution, patients are evaluated with MRI two months after treatment. Patients with an MRI-scan positive for residual neck disease are offered lymph node excision and/or neck dissection.

The purpose of this study was to assess the diagnostic value of magnetic resonance imaging (MRI) for response evaluation of metastatic neck lymph nodes after curative radiotherapy in patients with node-positive oropharyngeal cancer.

Materials and Methods: Retrospective cohort study. Medical records, pathology reports and imaging reports were electronically available. Recurrent neck disease, diagnosed in the course of follow-up, served as gold standard for comparison with MRI report.

Results: 100 consecutive patients with node-positive oropharyngeal cancer diagnosed in 2010 - 2012 met the study inclusion criteria, 74 p16-positive and 26 p16-negative. The majority of patients, 63, had tonsil cancer, and 85 patients had stage IV disease. All patients underwent curative radiotherapy, 66-68 Gy in 33-34 fractions. Sixty-seven patients received concomitant cisplatin, and 14 patients were treated with zalutumumab as part of a randomized trial.

MRI was performed after a median of 8 weeks after radiotherapy, showing persistent nodal disease in 60 patients. After response evaluation, 60 patients underwent neck dissection or lymph node biopsy, whereas the rest of the cohort was observed. After a median follow-up of 2 years (minimum 1 year), 11 patients were diagnosed with residual/recurrent nodal disease.

From these results, MRI for the diagnosis of residual neck nodal disease had a sensitivity of 64 %, and a specificity of 40 %.

Positive predictive value (PPV) was 12 %, and negative predictive value was 90 %. Thus, the overall diagnostic accuracy was 43 %.

There was a high rate of false positive scans at 53 %, particularly in the group of p16-positive patients (64 % versus 23 % for group of p16-positive and p16-negative respectively, p = 0.0005). As a consequence, PPV was only 6 % among p16-positive patients.

Conclusions: MRI is of limited diagnostic value for evaluating neck response two months after radiotherapy for advanced oropharyngeal cancer, particularly in patients with p16-positive disease.

There is a lack of consensus on the optimal strategy to evaluate treatment response, as well as precise criteria for interpretation of imaging in this setting. Improved management algorithms and imaging methods are needed.

### Table

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Characteristics of included patients.
PO-116
Confocal laser endomicroscopy in diagnosis and treatment of ENT lesions: a feasibility study, preliminary results
G. Chantrain1, A. Ruiz Rodriguez1, N. De Saint Aubin2
1University Hospital St Pierre, Department of ENT and Head and Neck Surgery, Brussels, Belgium
2Bordet Institute, Department of Pathology, Brussels, Belgium

Purpose/Objective: Confocal laser endomicroscopy is a novel imaging technique that is routinely used in gastroenterology, pulmonology and urology for the in vivo real time microscopic characterization of malignant and pre-malignant lesions. This study aims at evaluating the feasibility and the safety of performing probe-based confocal endomicroscopy (pCLE) and needle-based confocal endomicroscopy (nCLE) in the oral cavity, thyroid, lymph nodes, pharynx and larynx organs. It also aims at creating a first atlas of CLE images.

Materials and Methods: In vivo pCLE and nCLE was performed on 15 patients with ENT lesions. Among them, 9 patients were scheduled for open surgery procedures and 6 patients were scheduled for a panendoscopic evaluation aiming at obtaining diagnosis or to evaluate the tumoral extension. CLE images were reviewed offline by an ENT expert pathologist in order to interpret them, together with the corresponding histological slides.

Results: Cases included buccal (2), pharyngeal (2), laryngeal (6), thyroidal (4) lesions and masses (1). There were no device malfunctions. Technical challenges were encountered in 4 out of 15 attempts which led to develop specific modifications to improve the operational procedure. Technical feasibility to perform imaging with pCLE was achieved in all cases. 8 out of 10 cases had good to very good image quality, using the GastroFlex UHD. No adverse events occurred.

Fig 1: Images of vocal folds - laryngoscopy. Endomicroscopic view of healthy vocal fold: vessels with red cells (A) and well organized squamous cells with white dots (B), view of a polyp with disorganized black cells (C), and arytenoid cartilage (D) with vessels and fibers. Imaged with GastroFlex UHD

Conclusions: CLE is feasible and safe in ENT organs. It enables good quality imaging of healthy tissues and showed modifications of malignant ENT tissues, at a microscopical scale and in real time. Thus, CLE could be a great tool for the diagnosis of ENT lesions and the real time evaluation of resection margins.

PO-117
Overestimation of tumor volume of laryngeal/hypopharyngeal cancer on MRI in clinical radiotherapy practice
E.A. Jager1, T. Schakel1, J. Caldas-Magalhaes1, H. Ligtgenberg1, N. Kasperts1, M.E.P. Philippens1, F.A. Pameijer2, C.H.J. Terhaard1, S.M. Willems1, C.P.J. Raaijmakers1
1UMC Utrecht, Radiation Oncology, Utrecht, The Netherlands
2UMC Utrecht, Radiology, Utrecht, The Netherlands
3UMC Utrecht, Pathology, Utrecht, The Netherlands

Purpose/Objective: Validation of MRI delineation, with and without guidelines for tumor delineation, by using the histopathology outline from surgical specimens.

Materials and Methods: Twenty-two patients (median age, 61 years; range, 49-79 years; two female and 20 male) with T3(N=4) or T4 (N=18) laryngeal or hypopharyngeal cancer underwent an MRI scan before total laryngectomy. After surgery, whole-mount hematoxylin-eosin stained (H&E) sections were obtained from the surgical specimen. One pathologist delineated the tumor on the H&E sections (tumorH&E). The specimen was reconstructed and registered to the MRI scan in order to compare the GTV to the tumorH&E in 3 dimensions. To compare the GTV delineation with the actual tumor, volumes were compared, overlap parameters and tumor extensions outside the GTV were determined. The overlap was quantified as sensitivity, that is the part of the tumorH&E volume that was included in the GTV and more gadolinium uptake on T1 weighted MRI than the tumor bulk were considered as peritumoral changes and not included in the GTV. The specimen was reconstructed and registered to the MRI scan in order to compare the GTV to the tumorH&E in 3 dimensions. To compare the GTV delineation with the actual tumor, volumes were compared, overlap parameters and tumor extensions outside the GTV were determined. The overlap was quantified as sensitivity, that is the part of the tumorH&E volume that was included in the GTV and positive predictive value (PPV), that is the part of the GTV that actually was tumor. The distance from each point of the common contour to the closest point on the contour of the tumorH&E in 3D orientation was measured for tumor extensions outside the GTV. This measure quantifies the underestimation of the tumor for each observer.

Results: In a clinical setting the GTV overestimates the actual tumor volume as determined by histopathology and which improved considerably by the implementation of guidelines (figure). These guidelines decreased the sensitivity slightly. This might be explained by registration uncertainties which appear more prominent when the accuracy of the delineation increases.
PO-119
Does adaptive threshold based MTV and SUL have predictive value in head-neck cancers treated with radiotherapy?

O. Ozkaya Akagunduz1, R. Savas2, K. Kocacelebi3, S. Alanyali1, M. Esassolak1
1Ege University Faculty of Medicine, Radiation Oncology, Izmir, Turkey
2Ege University Faculty of Medicine, Radiology, Izmir, Turkey
3Ege Rad Imaging Center, Nuclear Medicine, Izmir, Turkey

Purpose/Objective: To evaluate the predictive value of SUVmax (standardized uptake value), SULmax (lean body mass - SUV) and adaptive threshold based MTV (metabolic tumor volume) of PET-CT in treatment response and disease outcome in head and neck cancer patients.

Materials and Methods: Sixty-two patients treated with curative radiotherapy (RT) /chemoradiotherapy (CRT) between May 2010-February 2013 were retrospectively reviewed. The median age of the patients were of 56 (range 23-83). Tumor site was hypopharynx and larynx in 22 (35.5%), nasopharynx in 14 (22.5%), and oropharynx in 14 (22.5%) of the patients. Twelve (19.2%) of the patients had tumors of other head and neck sites. Chemotherapy was part of their treatment in 55 (89%) of the patients. All diagnostic PET-CT scans were performed on a PET-CT unit (Discovery STE; GE Healthcare, Wisconsin) and all reconstructed images were transferred to a research workstation for tumor volume analysis. PET-CT images were evaluated at an Advantage Workstation AW4.6 (GE Healthcare, Wisconsin, USA) by a nuclear medicine physician and a radiologist. Semi quantitative and volumetric analyses were performed using the PET VCAR (Volume Computer Assisted Reading) software.

Results: Treatment response were evaluated 3 months after the completion of RT/CRT with PET-CT. Primary tumor response was complete in 46 (74.2%), partial in 15 (24.1%) and progressive disease was observed in 1 (1.6%) of the patients. Within a median follow-up of 18 months (range 5-41 months) 3 year local control, disease-free and overall survival rates were 66%, 44% and 67% respectively. MTV had significant impact on treatment response (p=0.011), local recurrence (p=0.050), disease-free survival (p=0.03) and overall survival (p=0.024). There is a significant relationship between SULmax and local recurrence (p=0.03) and disease-free survival (p=0.024). However SUVmax was not found as a prognostic or predictive factor in our analysis. ROC analysis shows negative predictive values for MTV with >14,00 mL and for SULmax with >10,15.

Conclusions: In our study we found that adaptive threshold based MTV and SULmax values of initial PET-CT had important prognostic and predictive value for head and neck cancer patients. We believe these PET-CT based predictive and prognostic markers will help clinicians to individualize treatment.
PO-120
Clinical impact of metabolic and anatomic imaging in nasopharyngeal carcinoma treated with chemoradiotherapy
S. Ghosh Laskar1, A. Pilar1, H. Purandare2, V. Rangarajan2, A. Budrukkar1, T. Gupta1, V. Murthy1
1Tata Memorial Hospital, Department of Radiation Oncology, Mumbai, India
2Tata Memorial Hospital, Department of Bio Imaging, Mumbai, India

Purpose/Objective: To correlate anatomic tumour volumes (gross tumour volumes) , maximum standardized uptake value (SUV max), metabolic tumour volume (MTV) and total lesional glycolysis (TLG) with loco regional control (LRC), disease-free survival (DFS), distant metastases free survival (DMFS) and overall survival (OS).

Materials and Methods: Between 2008 and 2012, 61 patients treated with chemo-radiotherapy, were evaluated. Gross tumour volumes (GTV) were contoured on the contrast enhanced CT of the pre-treatment FDG-PET-CT. SUV max was automatically generated. MTVs were delineated on the pre-treatment FDG-PET-CT. MTVs were generated at different thresholds of absolute SUV (MTV2, 3, 4, 5) and percentage SUV max (MTV20, 30, 40, 50). TLG was calculated for each MTV (8, for each patient) as the product of the corresponding MTV and SUV mean. All parameters were generated separately for primary tumour (primary GTV/MTV) and nodal disease (nodal GTV/MTV) and combined to get a total volume (Total GTV/MTV). Post treatment FDG-PET-CT was utilized to assess response. In case of residual disease, GTV and MTV were generated for the residual disease. The impact of GTV, SUV max, MTV, TLG and post treatment metabolic response on LRC, DFS, DMFS and OS was evaluated.

Results: Seventy seven percent patients had stage III/IV disease. At a median follow-up (FU) of 35 months (range 11-87months), 3-year LRC, DFS, DMFS and OS were 87.0%, 71%, 87% and 89%, respectively. At last FU, 18 patients (29%) had failed, 7 had loco regional failure, 10 had distant metastases and 1 had a second primary. Seven patients died of disease. Median time to first failure was 9.5months (range 1-59 months).

All MTVs correlated well with GTV (R² range 0.93-0.69); however the best correlation was seen with MTV 2.0. Of all the MTVs, highest statistical significance for prediction of outcomes was seen with absolute SUV of 2.0. Hence, all further results are restricted to MTV 2.0.

On univariate analysis, nodal GTV, total GTV were significant predictors of DFS, DMFS and OS (hazard ratio range 1.15-1.20, p value < 0.03).MTV node had an impact on DFS and DMFS (hazard ratio range 1.10-1.15 p value < 0.03) but no impact on OS. Total MTV had no impact on DFS and OS but showed an impact on DMFS (hazard ratio = 1.16, p value=0.001).

Post treatment metabolic response (MR) had no impact on DFS, DMFS and OS but patients with partial MR (PMR) had a significantly poorer local control (91% vs. 67% p=0.042) and regional control (96% vs. 71% p=0.016) compared to patients with complete MR (CMR). There was a significant association between total MTV and MR, patients with PMR having higher mean MTV than patients with CMR (114.1 ±49.5 vs. 63.9 ± 52.6, p=0.003).

Conclusions: Nodal volume and GTV significantly impact DFS, DMFS and OS. Total MTV has an impact on DMFS. PMR results in poor local and regional control. There is significant association between total MTV and MR, patients with PMR having higher MTV.

PO-121
Computer-aided quantitative interpretation to HIF-1α, c-MYC and p53 expression in oral submucous fibrosis
A. Anura1, S. Conjeti2, M. Pal3, R.R. Paul3, J. Chatterjee1
1Indian Institute of Technology Kharagpur, School of Medical Science and Technology, Kharagpur, India
2Technische Universität München, Chair for Computer Aided Medical Procedures and Augmented Reality Fakulät für Informatik, Boltzmannstraße3 Garching bei München, Germany
3Guru Nanak Institute of Dental Science and Research, Department of Oral and Maxillofacial Pathology, Kolkata, India

Purpose/Objective: Oral submucous fibrosis (OSF), a high-risk precancerous condition embeds progressive fibrosis of lamina propria in association with chronic inflammation and atrophy of overlying epithelium. The development of epithelial hyperplasia is often observed during OSF progression. The disorganized complex interplay amongst various molecular markers (cellular proliferation-c-MYC, regulator of apoptosis-p53 and hypoxia- HIF-1α) could have crucial role in epithelial dysplasia and advancing malignant potentiality of OSF. Assessing molecular marker impact on precancer pathobiology with the help of computer-aided quantitative analysis framework would help in evaluating advancing states in OSF and could improve the diagnostic interpretation of malignant potentiality towards carcinoma.

Materials and Methods: The expression of c-MYC, HIF-1α and p53 were evaluated in sixty eight biopsy sample of oral buccal mucosa (normal mucosa, OSF with hyperplasia and OSF with atrophic epithelium) by immunohistochemistry. The digital immunohistochemical microphotographs were used for image analysis which includes stain separation of an original chromogenic immunohistochemical image into haematoxilin counter-stain (blue) and immunoreaction product (brown diaminobenzidine; DAB) followed by quantification of DAB expression. Further, biologically relevant features of molecular expression (spatial distribution and intensity) were extracted considering biological sites (nuclear/cytoplasmic).

The altered state and trends of relevant features characterizing the diseased condition are statistically evaluated by Mann-Whitney U-Test and Spearman's rank correlation coefficient.

Results: In this study, an increased HIF-1α expression in epithelium and sub-epithelium was observed in OSF in comparison to NOM. c-MYC+ nuclei were restricted to basal layers of epithelium in NOM. OSF with atrophic epithelium showed a reduction in expression intensity of c-MYC, whereas the upper epithelial layer showed c-MYC expression along with significant increase in expression intensity in hyperplastic epithelium. On observing p53 expression in OSF with atrophic epithelium, it was found that density as well as intensity of its expression was significantly higher in atrophic epithelium to that of hyperplastic epithelium. The expression of p53 depicted a negative correlation with c-MYC in atrophic and hyperplastic epithelium of OSF.

Conclusions: The incorporation of both intensity and spatial features into the proposed quantitative IHC scoring system led to a greater diagnostic value and may help in decision making for marker discovery. Through the above analysis, it has been postulated that, c-MYC, p53 and HIF-1α could have emerged as potential screening markers. Along with that, vital role of dysregulation of antagonist expression of c-Myc and p53 in oral epithelium in development of hyperplastic/atrophic epithelium during OSF Progression cannot be denied.
**Poster: Supportive care, quality of life, rehabilitation**

**PO-122**

Pre-radiation feeding tube marks a poor prognostic subset of postoperative p16+ oropharyngeal cancer

V. Verma1, J. Liu2, J.S. Lewis3, D.R. Adkins4, B. Nussenbaum5, W.L. Thorstad6, H. Gay6

1University of Nebraska Medical Center, Radiation Oncology, Omaha, USA
2Washington University in St. Louis School of Medicine, Biostatistics, St. Louis, USA
3Washington University in St. Louis School of Medicine, Pathology, St. Louis, USA
4Washington University in St. Louis School of Medicine, Medical Oncology, St. Louis, USA
5Washington University in St. Louis School of Medicine, Otolaryngology, St. Louis, USA
6Washington University in St. Louis School of Medicine, Radiation Oncology, St. Louis, USA

**Purpose/Objective:** This study explores variables associated with poor prognosis in postoperative p16 positive oropharyngeal squamous cell carcinoma (OPSCC) patients undergoing adjuvant radiotherapy or chemoradiotherapy. Specifically, analysis was done related to timing of feeding tube insertion relative to radiotherapy.

**Materials and Methods:** From 1997-2009, of 376 consecutive patients with OPSCC, 220 received adjuvant intensity-modulated radiotherapy (IMRT), and 97 were p16 positive and eligible. Of these, 23 had feeding tube placement before IMRT (B-FT), 32 during/after IMRT (DA-FT), and 42 had no feeding tube (NO-FT). Feeding tubes were not placed prophylactically. These three groups were analyzed for differential tumor, patient, treatment, and feeding tube characteristics as well as differences in overall survival (OS), disease free survival (DFS), and distant metastasis free survival (DMFS).

**Results:** Pre-RT FT insertion was associated with higher tumor size and depth, T (but not N) and overall stage, comorbidities, presence of chemotherapy, and less use of transoral laser microsurgery/transoral bovie. Additionally, time from surgery to IMRT completion was also statistically longer in the B-FT group. The feeding tube was permanent in 52% of patients in the B-FT group versus 16% in the DA-FT group (p = 0.0075). The 5-year OS for the NO-FT, DA-FT, and B-FT groups was 90%, 86%, and 50%, respectively. The 5-year DFS for the NO-FT, DA-FT, and B-FT groups was 87.6%, 83.6%, and 42.7%, respectively. Multivariate analysis showed that for OS and DFS, feeding tube placement timing and smoking history were statistically significant.

**Conclusions:** Due to the poor prognosis of early FT insertion, the presence of FTS at time of radiotherapy consultation can be used as an alternate marker to identify a subset of p16 positive OPSCC patients that have a poor prognosis.

**PO-123**

Bupivacaine lozenge induces no risk of toxic plasma concentration in healthy subjects and head/neck cancer patients

C. Treldal1, S. Mogensen2, K. Sveindottir1, K. Jensen1, C.A. Kristensen2, J. Jacobsen2, M. Kreigaard2, J. Petersen2, O. Andersen1

1Copenhagen University Hospital Hvidovre, Clinical Research Centre, Hvidovre, Denmark
2Aarhus University Hospital, Department of Oncology, Aarhus, Denmark
3Rigshospitalet, Department of Oncology, Copenhagen, Denmark

**Purpose/Objective:** Oral mucositis is a common but serious complication to cancer treatment which often leads to insufficient treatment of the patient. Mucositis is caused by a damage of the mucosa in the oral cavity and pharynx, which induces severe oral pain. There is currently no sufficient pain management for patients with oral mucositis. This has led to the development of a bupivacaine lozenge as a new local anesthetic treatment. It is novel to administrate bupivacaine as a topical oral anesthetic lozenge.

The objective of the safety study was to investigate the potential side effects and plasma concentrations after the local administration of a bupivacaine lozenge, in both healthy subject with normal mucosa and in head and neck cancer patients with a damaged mucosa due to oral mucositis.

**Materials and Methods:** The bupivacaine plasma concentration was measured after administration of a 25 mg bupivacaine lozenge as single dose. A baseline blood sample was drawn before administration of the lozenge and followed by ongoing blood samples for six hours for 10 healthy subjects and three hours for 10 head and neck cancer patients. The blood samples from the healthy subjects were collected from Marts to May 2011, at The Zelo Phase One Clinic, Copenhagen University Hospital, Bispebjerg, Denmark and blood samples from the patients were collected from Marts 2013 to Marts 2014 at the Department of Oncology, Rigshospitalet, Denmark.

The blood samples were analyzed using a HPLC system and the plasma concentration of bupivacaine was detected using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS).

**Results:** The theoretical toxic plasma concentration of bupivacaine is estimated to 2-4000 ng/ml. The maximum bupivacaine plasma concentration were 376 ng/ml in the healthy subjects and 664 ng/ml in the head and neck cancer patients after administration of one lozenge containing 25 mg bupivacaine.

**Conclusions:** The results show that the plasma concentrations of bupivacaine are below the toxic limit in both healthy subjects and the head and neck cancer patients. The bupivacaine lozenge can be used safely by patients as pain management without the risk of toxic side effects.

**PO-124**

New local anesthetic lozenge induces no risk of aspiration in healthy subjects and head/neck cancer patients

S. Mogensen1, K. Sveindottir1, C. Treldal1, A. Nygaard2, A. Mohammad2, C.A. Kristensen2, J. Petersen2, O. Andersen1

1Copenhagen University Hospital Hvidovre, Clinical Research Centre, Hvidovre, Denmark
2Rigshospitalet, Department of Diagnostic Radiology, Copenhagen, Denmark

**Purpose/Objective:** Oral mucositis induces severe oral pain and is a serious complication to cancer treatment with severe negative influence on the patient’s nutritional status. Many patients undergoing high-dose chemotherapy or radiation treatment for head and neck cancer develop oral mucositis. There is currently no sufficient pain management for oral mucositis and there is an urgent need for new treatments. This has led to the development of a local anesthetic lozenge containing 25 mg bupivacaine. The anesthetic effect of the lozenge in the oral cavity and pharynx was investigated. However, it has previously been assumed that pharyngeal anesthesia with local anesthetics induces a risk of aspiration, because it affects the self-regulating swallowing reflex.
The objective of this safety study was to investigate the risk of aspiration after anesthetizing the oral cavity and pharynx with a bupivacaine lozenge, when administered as topical anesthesia to healthy subjects and head and neck cancer patients with oral mucositis.

**Materials and Methods:** In 10 healthy subjects the risk of aspiration was studied before and after administration of 25 mg bupivacaine lozenge, as a single dose to healthy subjects and head and neck cancer patients with oral mucositis.

The patients swallowed 20 ml barium-contrast agent and its path through the pharynx and the esophagus was recorded using video radiography. The videos were thereafter analyzed for aspiration by an experienced physician.

**Results:** None of the 10 healthy subjects or the 10 head and neck cancer patients showed any signs of aspiration before or after administration of the bupivacaine lozenge.

**Conclusions:** The results show that the bupivacaine lozenge is safe to use as local anesthetic for head and neck cancer patients with oral mucositis and can therefore be used by the patients as local pain management with no food and drink restrictions.

**PO-125**
Toxicity and feasibility of adjuvant chemotherapy in nasopharynx carcinoma: a retrospective study

**Materials and Methods:** We performed a retrospective review of all cases of patients (pts) treated with chemoradiotherapy (cCRT) followed by adjuvant chemotherapy (aCT), having started and completed treatment in our center between Jan/2009 and July/2014. cCRT followed by aCT, having started and completed treatment in our center between Jan/2009 and July/2014.

**Results:** Of 69 pts, with a median age of 49 years (17-72); 50 (73%) were male. Twenty-eight (41%) had stage II disease; 51 (74%) were WHO III. Initial Karnofsky Performance Status was > 60% in all pts. Fifty-one pts (74%) completed 3 cycles of cisplatin+radiotherapy. Nine (13%) pts did not receive aCT, 6 due to toxicity during cCRT, 2 due to insufficient compliance with the treatment and 1 because of diagnosis of metastatic disease in the end of cCRT. Of the 60 pts who received aCT, all reported toxicity; 24 pts (40%) had grade ≥ 2 toxicity; 11 pts with grade 3, 12 with grade 4 and 1 pt died. Mucositis and infection were the grade 4 toxicities most frequently reported during aCT (8.3% and 5%, respectively). As to grade 3, the events more often reported were neutropenia, ototoxicity, mucositis and infection (13%, 12%, 10% and 8.3%, respectively). Of the 60 pts who received aCT, 45 pts (75%) completed 3 platin-based cycles. The main reason for not completing aCT was toxicity (12 pts; 20%); toxicity also lead to a change in dosage/protocol in 12 cases (20%). One toxic death occurred during aCT.

**Conclusions:** Toxicity ≥ grade 3 during aCT was reported in almost half of the patients. Grade limiting toxicities were similar to the ones described in published data and have a potential impact in quality of life (mucositis, infection, hearing impairment). Therefore, large multicentric randomized trials are needed to assess the benefit-risk ratio of adding aCT to cCRT to treat advanced NC.

**PO-126**
Early percutaneous endoscopic gastrostomy and nutritional supplementation in H&N cancer: an Italian survey.

**Materials and Methods:** 106 Italian centers of radiation oncology and 100 centers of otorhinolaryngology were interviewed using a SurveyMonkey online interface questionnaire. Statistical analysis was performed to establish significant differences between answers of two respondent groups.

**Results:** We obtained a response rate of 63% and 27% for RO and OL respectively. The majority of RO declared to not use any preventive nutritional supplements while OL preferred nasogastric tube and other nutritional supplemental patches. In 73.1% and 88.9% of cases PEG is positioned in case of necessity by RO and OL respectively. Indeed 82.1% (RO) and 92.6% (OL) of physicians argued that the preventive placement of the endoscopic percutaneous gastrostomy should not be a standard procedure. Nutritional counseling before starting of treatment is not routinely performed but 88.1% and 85.2% of respondents (RO and OL respectively) stated that this should represent a standard procedure.

**Conclusions:** It is current opinion that a reactive approach should be preferred to an early endoscopic percutaneous gastrostomy placement, but firm evidences are lacking. The survey showed a good agreement about both timing and criteria for endoscopic percutaneous gastrostomy placement; however management of nutritional supplementation in head and neck cancer globally appeared quite variable and deserving of focused studies. The present study, to our knowledge, represent the first Italian Survey about this topic.

**PO-127**
Prevention and treatment of oral mucositis in patients treated with chemoradiotherapy with head and neck cancer

**Materials and Methods:** In 10 healthy subjects the risk of aspiration was investigated after the administration of the lozenge. The risk was also investigated in 10 patients with oral mucositis before and after administration of the lozenge. Data from the healthy subjects was collected from Marts to May 2011, at the Radiology department, Copenhagen University Hospital, Hvidovre, Denmark. Data from the patients was collected from Marts 2013 to June 2014 at the Department of Diagnostic Radiology, Righospitalitaet, Denmark.

The risk of aspiration was studied before and after administration of 25 mg bupivacaine lozenge, as a single dose to healthy subjects and head and neck cancer patients with oral mucositis.

The patients swallowed 20 ml barium-contrast agent and its path through the pharynx and the esophagus was recorded using video radiography. The videos were thereafter analyzed for aspiration by an experienced physician.

**Results:** None of the 10 healthy subjects or the 10 head and neck cancer patients showed any signs of aspiration before or after administration of the bupivacaine lozenge.

**Conclusions:** The results show that the bupivacaine lozenge is safe to use as local anesthetic for head and neck cancer patients with oral mucositis and can therefore be used by the patients as local pain management with no food and drink restrictions.

**Purpose/Objective:** Aim of this study was to survey the opinions of Italian radiation oncologists (RO) and ototrhynolaringologists (OL) regarding the role of nutritional supplementation and early placement of endoscopic percutaneous gastrostomy in patient with head and neck (H&N) cancers receiving radiotherapy or radio-chemotherapy.

**Materials and Methods:** 106 Italian centers of radiation oncology and 100 centers of otorhinolaryngology were interviewed using a SurveyMonkey online interface questionnaire. Statistical analysis was performed to establish significant differences between answers of two respondent groups.

**Results:** We obtained a response rate of 63% and 27% for RO and OL respectively. The majority of RO declared to not use any preventive nutritional supplements while OL preferred nasogastric tube and other nutritional supplemental patches. In 73.1% and 88.9% of cases PEG is positioned in case of necessity by RO and OL respectively. Indeed 82.1% (RO) and 92.6% (OL) of physicians argued that the preventive placement of the endoscopic percutaneous gastrostomy should not be a standard procedure. Nutritional counseling before starting of treatment is not routinely performed but 88.1% and 85.2% of respondents (RO and OL respectively) stated that this should represent a standard procedure.

**Conclusions:** It is current opinion that a reactive approach should be preferred to an early endoscopic percutaneous gastrostomy placement, but firm evidences are lacking. The survey showed a good agreement about both timing and criteria for endoscopic percutaneous gastrostomy placement; however management of nutritional supplementation in head and neck cancer globally appeared quite variable and deserving of focused studies. The present study, to our knowledge, represent the first Italian Survey about this topic.

**Purpose/Objective:** Evaluate the benefit of the supersaturated calcium phosphate solution (SCPS) in the prevention and treatment of mucositis in patients who were
treated with chemoradiotherapy (QRT) for head and neck cancers (HNC).

**Materials and Methods:** It is a prospective unicentric non-randomized clinical study with an unblinded sample allocation for convenience. It was compared the prevention and treatment of mucositis with SCPS versus lidocaine and bicarbonate solution (LBS). The eligibility criteria were: patients with squamous-cell carcinoma from HNC by biopsy; stage III and IVa; treatment with QRT with no prior chemotherapy; competence for self-care; cisplatin (100mg/m²) each 3 week and Intensity Modulated Radiation Therapy (IMRT), doses from 60 to 69.96 Gy. A consent form was signed by each patient. In the two arms (SCPS and LBS) it was performed a first assistance by doctor and nurse, to assure the self-care. At the beginning QRT, each arm started the mouthwashers 3 times daily SCPS (study arm) and LBS (control arm). At time of mucositis grade 1 or 2, it was increased for 6 times; at time of mucositis grade 3 or more it was increased for 8 times per day. To evaluate the prevention, it was considered the time when mucositis grade 1 or more occurred and to evaluate the treatment response it was considered the reduction at least one grade of the mucositis. Patients had 3 times consults with nurse per week and one time consult with the doctor per week, at the beginning. With mucositis, patients were assisted by nurse daily, till the end of the treatment. Four weeks after the ending of QRT, patients had a consult with nurse and doctor. For second endpoints, it was also evaluated the use of morphine, tube feeding and inpatient ward due to mucositis. To evaluate the mucositis it was used the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. For statistical analysis it was used the following tests: Wilcoxon-Man Withney, Fisher, Logrank and Pearson.

**Results:** Out of 34 patients (17 patients, each arm) median age of 56 years old (control arm) and 61 years old (SFCS arm), p=1,001, 98% were men (control arm) and 100% at the SFCS arm (p=0,426) and the dose of radiotherapy was 60Gy (2 patients control arm, 0 patients at the SFCS arm), 66 Gy (4 patients control arm, 5 patients SFCS arm) and 69,96 Gy (11 patients control arm and 12 patients SFCS arm), p= 0,552. 10 patients were submitted to surgery (control arm) and 11, in the SFCS arm. Mucositis occurred in 3 weeks after the beginning of QRT at control arm versus 4 weeks at the SFCS arm (p=0,046). The reduction of mucositis at least one grade occurred in 87,5% during QRT and 4 weeks after QRT at the SFCS arm (p=0,00386). There were no statistical differences in terms of tube feeding, use of morphine or inpatient ward.

**Conclusions:** Due to logistic reasons this was a non-randomized and an unblinded study; however, SFCS has an important role either on prophylactic and in treatment of mucositis in patients with HNC. We also conclude the importance of nurse care assistance in the prevention of oral mucositis, optimizing a better self care to this patients.

**PO-128**

How does radiotherapy impact on swallowing in head and neck cancer? Short-term results of a prospective study

S. Ursino1, V. Secchia1, P. Cucuzza1, P. Ferrazza1, T. Briganti1, P. Giusti1, M. Grosso1, M. Morganti1, B. Fattori1

1University Hospital, Radiation Oncology, Pisa, Italy

Purpose/Objective: To report the initial results of a prospective clinical trial aimed to assess instrumental swallowing function in nasopharynx and oropharynx cancers after radio or chemoradiotherapy using intensity-modulated radiotherapy (IMRT).

**Materials and Methods:** IMRT was delivered aiming to spare the swallowing organ at risk (SWOARs) for Stage II–IV naso and oropharynx cancer. Objective instrumental assessment included Videofluoroscopy (VFS), Fiberoptic Endoscopic Evaluation of Swallowing (FEES) and Oro-Pharyngeal-ESophageal Scintigraphy (OPES) at baseline and 1,6 and 12 months after radiotherapy. Dysphagia parameters scores were calculated and reported at each exam both after liquid (L) and semi-liquid (SL) bolus intake: pre-swallowing penetration, aspiration, pharyngeal transit time (PTT) and hypopharyngeal retention index (HPRI). Results: Overall 20 patients (6 Nasopharynx and 14 Oropharynx) completed treatment and instrumental assessment after one month. Correlations between the pre and post-treatment changes in HPRI scores resulted statistically significant both at FEES-L (p=0,021) and SL (p=0,02) and at VFS-L (p=0,008) and SL (p=0,005). Moreover, significant relationships between baseline and 1 month HPRI score at FEES-L and FEES-SL (p=0,005) as well as at VFS-L and VFS-SL (p=0,001), were observed. Differently, PTT resulted not significantly affected by radiotherapy (p=0,2). Only few patients experienced pre-swallowing penetration (1 patient with base of tongue cancer at FEES-L and SL) and aspiration (1 patient with nasopharynx cancer at OPES-L and FEES-SL) after radiotherapy.

**Conclusions:** Our early results showed that radiotherapy significantly increased the post-swallowing HPRI. Longer follow-up will be necessary to evaluate if the increase of HPRI is related to a high risk to develop late aspiration.

**PO-129**

Late xerostomia in VMAT for oropharyngeal cancer: dosimetric analysis of parotids outside the PTV

S. Schipani1, M. Thomson2, R. Ferguson2, D. Grose2, A. James1, C. Lamb2, C. Paterson2, S. Smith2, M. Rizwanullah2

1Institute of Cancer Sciences University of Glasgow, Radiation Oncology, Glasgow, United Kingdom

2Beatson Cancer Centre, Radiation Oncology, Glasgow, United Kingdom

Purpose/Objective: Mean dose (Dm=24-26 Gy) to 'whole contralateral' parotid is commonly referenced as dose constraint in step-and-shoot head&neck IMRT. Both parotids are generally partially included inside the PTV in locally advanced oropharyngeal cancer (OPC), and a dose spillage to the bilateral parotids cannot be avoided with Volumetric Modulated Arc Therapy (VMAT). We considered the parotids as a pure whole parotid organ, analysed and correlated the dosimetric data of both parotids outside the PTV (Par_outPTV) with late xerostomia.

**Materials and Methods:** Patients with locally advanced OPC treated with VMAT with radical or post-operative intent between September 2010 and November 2012 were retrospectively reviewed. Patients were immobilised with a thermoplastic mask, and contrast enhanced CT was used for treatment planning. High risk and low risk regions were included in PTV1 and PTV_LR respectively. Organs at Risk were defined as per institutional protocol. Parotids and Par_outPTV were contoured separately. Treatment planning was optimised with the AAA algorithm for Rapid Arc (Varian). A dose of 65-68 Gy and 54-60 Gy in 30-34 fractions was prescribed to PTV1 and PTV_LR respectively, and Dmax 24 Gy was the constraint for the Par_outPTV. Dosimetric data were retrospectively reviewed for Par_outPTV, and correlated with late xerostomia graded with CTCAE v4 criteria. Mann-Whitney test was used for statistical analysis.

**Results:** A total of 114 patients were reviewed. Radical and post-operative treatment was given in 94 (82%) and 20 (18%) patients. The tumour was lateralised in 93 individuals (82%),
Induction and concomitant chemotherapy was given in 30 (26%) and 90 (79%) patients respectively. A dose of 65 and 68Gy was given to 97 (85%) and 17 (15%) cases. Median follow-up was 20.6 (2.3-4.5) months. Tumour complete remission was achieved in 96 (84%) patients. Tumour progression was registered in 18 cases (16%) with a time to progression of 11.4 (2.8-25.4) months. Twenty-one patients (18%) deceased at 12 (5.5-25.6) months. Grade ≤2 and ≥2 xerostomia at >18 months (n87) resulted in 54 (62%) and 33 (38%) patients. In this group of patients Par_outPTV volume(cc), Dm(Gy), V10(%), V20(%), V25(%), V40(%) resulted ≥G2 xerostomia respectively. The ratio between Par_outPTV and both parotids (R) was 0.62 (0.25-0.89) and 0.67 (0.15-1) in the 2 sub-groups. Significant difference (p<0.05) was demonstrated for V10(%), V20(%), V25(%), V40(%) and R.

Conclusions: The partial volume low doses (V10%, V20%, V25%, V40%) of the parotids outside the PTV should be minimised to avoid late ≥G2 xerostomia.

PO-130 Disseminating best practice in oral care
M. Thomson1, B. Quinn2, J. Horn3, F. Campbell4, A. Beasley5, S. Hoy6, D. Houghton7
1Inst. of Cancer SciencesUniv. Glasgo The Beatson West of Scotland Cancer Center, Beatson Oncology Center, Glasgow, United Kingdom
2Chelsea and Westminster NHS, Chelsea, London, United Kingdom
3Aberdeen Royal Inf., Haematology, Aberdeen, United Kingdom
4Beatson west of Scotland Cancer Centre, Oncology, Glasgow, United Kingdom
5CNS, Surgery, Cardiff, United Kingdom
6Royal Marsden NHS, Oncology, London, United Kingdom
7Ramsay healthcare, Pharmacy, London, United Kingdom

Purpose/Objective: Oral mucositis (OM) continues to be a challenge in the head and neck cancer setting. Despite advances made in understanding the pathophysiology of OM and the variety of treatment options available clinical teams struggle to address oral damage secondary to disease and treatment in a consistent manner. The United Kingdom oral Mucositis in Cancer Care (UKOMiC) a multi professional expert group was formed over 2 years ago to address the challenges of oral complications secondary to disease and treatment in the cancer and palliative care setting. This is of particular interest in head and neck cancer where it is reported 97% of patients receiving radiotherapy (with or without chemotherapy) will suffer from some degree of OM Kostler et al (2001).

Materials and Methods: 10 prospectively collected consecutive out clinic patients with oral cancer treated with episil® oral liquid during RT were evaluated for oral mucositis (WHO grade 0-4), pain (VAS-scale), analgesic consumption, feeding tube-dependency (FTD) and inpatient time. 10 consecutive out clinic patients undergoing RT for oral cancer before the introduction of episil® oral liquid at the same institution were drafted as controls. The intervention group was monitored weekly by dentist and RTT separately. Data on side-effects for the controls were collected retrospectively from the patient chart. Feeding tube administration, analgesic consumption and hospitalization was managed according to clinical practice. All patients were and treated with a combination of surgery and radiotherapy. RT was delivered with either standard fractionation to total dose of 60 to 68 Gy or an intensified protocol with accelerated treatment or chemoradiotherapy. As the intensified treatment protocols are correlated with significantly worsened acute mucositis, patients were stratified for treatment in the analysis.

Results: All tests were two-sided and a p-value of <0.05 was considered significant. The mucositis and pain scores were analysed in an ANOVA with baseline as covariate. The Kaplan-Meier method and the log rank test were used to evaluate time to event.

Results: The mean age for all patients was 62.2 years (range: 31-79), 65.4 years in the controls and 58.9 years for the intervention group. 50 % of the controls and 60 % of the intervention group were male. 30 % of the patients, equally distributed between the groups, received an intensified treatment. Two patients discontinued episil® oral liquid due to emesis. There was no significant difference in assessed mucositis or in assessed pain between the groups. There was no significant difference in time (weeks) to continuous opioids (6.4 vs 4.6 (p 0.223) or hospitalization (2 vs. 0 events (p= 0.404)). There was a trend towards improved outcome for FTD with 3 events in the control group and none in the intervention group (p = 0.097).

Conclusions: The major finding of the study is that episil® oral liquid is well tolerated and the trend towards less FTD and a possible reduction in inpatient time is promising.
However, as this was a small pilot study of the introduction of a registered medical device into the clinical setting, the aim was descriptive and more prospective studies are needed to validate the results in the clinical setting. Since the mucositis and pain scoring for the controls were done retrospectively there is a substantial risk of misclassification due to unstructured reporting in the patient chart illustrating the need for standardized side effect registration in day to day clinical practice for ongoing/future clinical evaluation.

PO-132
Management of anemia in (chemo)radiotherapy for head and neck cancer: policies in EORTC centers
S. Nuys1
On behalf of EORTC ROG -University Hospital Gasthuisberg, Radiation Oncology, Leuven, Belgium

Purpose/Objective: There is clinical evidence indicating that hypoxia may be a critical factor when treating carcinomas of the head and neck with radiotherapy. Some of the evidence for the influence of hypoxia on radiation response comes indirectly from the relationship between tumor control and hemoglobin level. Anemia can be corrected with red blood cell transusions or with erythropoietin stimulation agents but the value of these therapies is heavily debated. We therefore wanted to investigate the current policies on the management of low hemoglobin in HNSCC treatment amongst EORTC centers.

Materials and Methods: A questionnaire was sent out to all EORTC radiotherapy centers member of the radiation oncology group and/or head and neck cancer group using a web based form. The questionnaire included questions concerning the measurement of hemoglobin pre-, per- and post-treatment and inventoried the different therapeutic options to manage anemia.

Results: 72 different radiotherapy centers answered the questionnaire (28.3% of the contacted centers). 89% of the responding centers checked hemoglobin levels before the start of (chemo)radiotherapy for head and neck cancer. Pretherapy hemoglobin levels were determined in both primary and postoperative setting in 95.5%, only in the primary setting in 3% and only in postoperative setting in 1.5%. 22.8% of centers would only check in locally advanced stages while 77.2% determine hemoglobin pretherapy in all stages. 83% of the centers would start a supportive treatment to correct for anemia when the hemoglobin level is below a certain threshold: 75% would use blood transfusion, 12.5% uses erythropoietin and 33% iron therapy. The cut off to start a supportive treatment to correct for anemia was below 10g/dl in 53.2% (<6 g/dl in 1.6% - < 12 g/dl in 4.8%). The level of hemoglobin aimed for varied from 8 to 17g/dl. During radiotherapy, hemoglobin was measured in 87.5% of centers and 83% would correct using blood transfusion (79%), erythropoietin (18%) and iron (28%). The majority (61%) would check hemoglobin levels weekly. The cut off to start a supportive treatment to correct for anemia during treatment was below 10g/dl in 50.9% (<6 g/dl in 3.5% - < 12 g/dl in 3.5%).

Conclusions: There exists a large variety amongst EORTC centers how to manage anemia in HNSCC. The vast majority of centers measure hemoglobin before the start of radiotherapy and start corrective measures to increase hemoglobin levels. Most used adjustment remains blood transfusion, although erythropoietin is used in up to 18% of centers, despite the knowledge that correction of low hemoglobin by blood transfusion or erythropoietin stimulating agents does not improve outcome. Moreover, some studies suggest an inferior outcome with erythropoietin. This questionnaire could be used as a starting point to develop guidelines on the management of low hemoglobin in HNSCC.

PO-133
The effect of normal tissue doses on quality of life in nasopharyngeal carcinomas treated with 3D-CRT
M. Akın1, L.Z. Arican1, B. Aydin1, C. Umay1, A. Cinkaya1, F. Akman1
1Dokuz Eylul University, Department of Radiation Oncology, Izmir, Turkey

Purpose/Objective: To compare the quality-of-life (QOL) results assessed by the EORTC Core QOL questionnaire (QLQ-C30) and QLQ-H&N35 modules for nasopharyngeal carcinomas (NPC) survivors who received treatment with three dimensional conformal radiotherapy (3D-CRT) according to the normal tissue doses.

Materials and Methods: This cross-sectional study was a retrospective review analyzing QOL data of 25 cancer free patients with NPC. All patients were irradiated definitively with 3D-CRT (non-coplanar 5-7 beams) between January 2004 and October 2011 by a multidisciplinary team. The standard approach was conventionally fractionated RT (66-70 Gy/33-35 fractions/6-7 weeks) with concurrent chemotherapy. The study group compromised the patients who answered the EORTC QLQ-C30 and H&N35 QOL questionnaires during their routine follow-up between October 2011 and October 2013. The global, functional and symptom scales scores of each patient were determined with using EORTC QLQ-C30 and H&N35 questionnaires. The relationship between radiation oncologist. The doses of each tissue were calculated and generated their volume histograms (DVH). These DVHs were analyzed with the EORTC QLQ-C30 and H&N35 scores. The relationship between RTQG late side effects and doses of each tissue was evaluated with using Kendall correlation. The doses and volumes of each tissue, EORTC QLQ-C30 and H&N35 QOL scores were analyzed by SPSS 18.0 software®.

Results: The mean age was 48 (20-74). A positive effect of female gender (p:0,028) on the 'physical function' and negative effect of neoadjuvant and/or concurrent chemotherapy administration on 'swallowing problem' (p: 0,04), 'trouble with social eating' (p: 0,039) and 'sexuality' (p: 0,01) symptom scores were found statistically significant. The symptom scores of 'feeling ill' were found statistically significant (p: 0,044) on the non-smoker patients prior to RT. A significant relationship between the late side effects of mucosa, saliva and the different doses, volumes of GTV, parotid, submandibular glands, and constrictor muscles were found. In patients with no comorbidity, 'swallowing problem’ symptom scores were found higher than patients with comorbidity (p: 0,038). There were no significant relationship between the skin, subcutaneous parts, esophagus, medulla spinalis, late side effects and each tissue doses.

Conclusions: The doses of the GTV and major salivary glands have a significant impact on dry mouth, sticky saliva, difficulty in swallowing, speech problems, feeling ill, less sexuality symptoms as well as on emotional, social function and global health parameters of QOL. Adjusting the normal tissue doses and volumes of dose received may use to predict the risk of late toxicity and improve the QOL for survivors of NPC.

PO-134
Dose related efficacy of LMS-611 in Radiotherapy Induced Xerostomia from an ex vivo study
C. Paterson1, M. Thomson1, B. Caldwell1, S. Porteous1, A. McLean1, G. Park1, C.A. Messow2
1The Beatson West of Scotland Cancer Center, Clinical Oncology, Glasgow, United Kingdom
2The Beatson West of Scotland Cancer Center, Therapy
Purpose/Objective: Radiotherapy induced xerostomia (RIX) is the most common permanent side effect of radiotherapy (RT) to the head and neck (H&N) with no effective treatment. LMS-611 is a mimetic of a natural lamellar body which has been shown to have the potential to reduce the 'stickiness' of oral cavity secretions following RT. Our pre-clinical study was designed as an ex vivo, efficacy, proof of concept study as a preparatory step towards our clinical study of LMS-611 in RIX.

Materials and Methods: Patients with H&N cancer who were booked for RT or chemoRT (CRT) as primary treatment were recruited. Patient reported xerostomia scores were collected using the Groningen RIX (GRIX) questionnaire at baseline, weeks 2, 4 and 6 of radiotherapy. Saliva samples were also collected and adhesiveness and viscosity tested by assessing time taken to travel 5cm on an inclined plane (IP). LMS-611 was added to saliva samples and IP test repeated.

Results: 30 patients were enrolled. All patients had a pathologically confirmed diagnosis of squamous cell carcinoma (SCC) oropharynx. Mean age 54.8 years, range 42-67. 80% were male and the majority stage III and IV disease (96.6%), 90% received CRT. The mean IP test results (seconds) are as follows baseline 31.3; week 2 49.7; week 4 51.1; week 6 55.7 indicating increasing saliva adhesiveness and viscosity as RT progresses. The increase was significant from baseline to week 2 with only moderate increases from week 2 to 4 and week 4 to 6. Wide inter-patient variability was seen at baseline. GRIX scores increased as RT progressed, figure 1. Differences between GRIX scores at weeks 2, 4 and 6 were statistically significant when compared with pre-treatment scores. Modest variability in GRIX scores was seen at baseline and this remained constant.

Figure 1

The IP test results were compared with GRIX scores, Spearman Correlation Co-efficient was -0.06 at baseline, 0.25 at week 2, 0.12 at week 4 and 0.08 at week 6, therefore no relevant correlation was seen.

The addition of saline, LMS-611 2.5mg/ml or 5mg/ml to the saliva samples does not reduce saliva adhesiveness and viscosity. However, when LMS-611 in concentrations of 10mg/ml and 20mg/ml are added a significant reduction is seen in the IP test (not shown). Analysing the inclined plane results as survival data separately for each time point and overall adjusting for week of RT demonstrates this statistically significant difference using cox proportional hazards model, see table 1.

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline untreated</td>
<td>vs. 0.115</td>
<td>(0.045, 0.294)</td>
</tr>
<tr>
<td>2.5 mg/ml untreated</td>
<td>vs. 0.283</td>
<td>(0.125, 0.639)</td>
</tr>
<tr>
<td>5 mg/ml untreated</td>
<td>vs. 0.593</td>
<td>(0.337, 1.042)</td>
</tr>
<tr>
<td>10 mg/ml untreated</td>
<td>vs. 4.957</td>
<td>(3.132, 7.846)</td>
</tr>
<tr>
<td>20 mg/ml untreated</td>
<td>vs. 30.687</td>
<td>(17.852, 52.750)</td>
</tr>
</tbody>
</table>

Conclusions: Saliva becomes more visco-adhesive and patient reported xerostomia worsens as RT progresses. However, there is no relevant correlation between objective and subjective measures of xerostomia. The addition of LMS-611 to thick, sticky saliva restores its fluidity ex-vivo at concentrations of 10mg/ml and 20mg/ml.

PO-135
Nasopharynx IMRT: DVH parameters of constrictor muscles and parotid glands correlated to dysphagia and xerostomia

L. Deantonio1, M. Paolini1, S. Cozzi1, L. Masini1, G. Loi1, M. Brambilla1, M. Krenghi1
1University Hospital Maggiore della Carità, Radiotherapy, Novara, Italy
2University Hospital Maggiore della Carità, Medical Physics, Novara, Italy

Purpose/Objective: To analyse the frequency and severity of swallowing dysfunction and xerostomia in patients affected by nasopharyngeal cancer treated by intensity-modulated radiotherapy (IMRT) and in relation to dosimetric data and volumetric changes of pharyngeal constrictor muscles and parotid glands.

Materials and Methods: Twenty-five patients, who underwent adaptive IMRT for nasopharyngeal cancer, were included in the present study. Ninety percent of patients (22/25) received concurrent radio-chemotherapy and 84% (21/25) were in a locally advanced stage.

The volumetric and dosimetric parameters related to constrictor muscles (superior constrictor muscle, scm, middle constrictor muscle, mcm, inferior constrictor muscle, icm), and parotid glands were analyzed using dose volume histograms (DVHs). All patients underwent replanning CT scan after 5 weeks of radiation therapy and the target and OARs were recontoured on fusion images after co-registration. The volumetric variations were measured. Dosimetric and volumetric parameters were associated to acute and late dysphagia and xerostomia in terms of CTCAE RTOG morbidity score for acute and late effects, respectively.

Results: The dose-volume parameters are reported in Table 1. There was an increase in the volumes of constrictor muscles after 5 weeks of RT by 30% in scm, 12% in mcm and 7% in icm respectively. There was a decrease in the volume of parotid glands by 31%.

At the end of the RT, 48% of patients experienced grade G0-1 acute dysphagia, and 52% grade G2-3, 40% of patients experienced G0-1 acute xerostomia and 60% G2.

At a median follow-up of 2 years (range 6-48 months), 20% of patients experienced G2-3 late dysphagia and 16% of patients G2 late xerostomia.

The analysis of the correlation of dosimetric/volumetric data with clinical findings is ongoing.
Materials and Methods: This is to assess treatment interruptions according to repletion by cancer cells during the treatment break. and overall survival, possibly because of a rapid clonal repletion by cancer cells during the treatment break. The purpose of this analysis is to assess treatment interruptions according to repletion by cancer cells during the treatment break. The purpose of this analysis is to assess treatment interruptions according to repletion by cancer cells during the treatment break.}

Results: Forastiere AA, 1, R. Ciérvide Jurío1, E. Sanchez Saugar1, O. Hernando Requejo1, J. Valero Albarran, M. Lopez Rodriguez, A. Rodriguez Gutierrez, D. Zucca Aparicio, A. Gomez Pinillos2, C. Rubio Rodriguez2
1Hospital Universitario Madrid Sanchinarro - Grupo Hospital de Madrid, Radiation Oncology Department, Madrid, Spain
2Hospital Universitario Madrid Sanchinarro - Grupo Hospital de Madrid, Medical Oncology Department, Madrid, Spain

PO-136

7-year experience with the use of PEG in head and neck cancer patients treated with Radiation Therapy
M. Garcia-Aranda Pez1, R. Ciérvide Jurío1, E. Sanchez Saugar1, O. Hernando Requejo1, J. Valero Albarran, M. Lopez Rodriguez, A. Rodriguez Gutierrez, D. Zucca Aparicio1, A. Gomez Pinillos2, C. Rubio Rodriguez2
1Hospital Universitario Madrid Sanchinarro - Grupo Hospital de Madrid, Radiation Oncology Department, Madrid, Spain
2Hospital Universitario Madrid Sanchinarro - Grupo Hospital de Madrid, Medical Oncology Department, Madrid, Spain

Purpose/Objective: The use of percutaneous endoscopic gastrostomy (PEG) as a feeding support in the multimodal management of head and neck cancer patients (HNCP) receiving radiotherapy remains controversial. The purpose of this analysis is to assess treatment interruptions according to the use of gastrostomy regarding that longer treatment interruptions significantly reduce progression-free survival and overall survival, possibly because of a rapid clonal repletion by cancer cells during the treatment break. Materials and Methods: We have analyzed 258 HNCP that have been irradiated at our institution with adjuvant or radical radiotherapy between November 2007 and June 2014. Gastrostomy has been selectively used in patients with tumors located in pharynx, oral cavity and locally advanced laryngeal tumors treated with concomitant chemoradiotherapy or induction chemotherapy followed by chemoradiation. It was inserted prophylactically before the beginning of radiation treatment. For those patients with tumors located in glottis, salivary glands and nasal cavities without chemotherapy, gastrostomy was not inserted. Radiation technique (Intensity modulated radiation therapy or 3D conformal radiotherapy) was chosen according to tumor location and proximity of organs at risk.

Results: Regarding location, there were 14 (5%) nasal cavity and sinuses tumors, 48 (19%) oral cavity tumors, 84 (32%) pharyngeal tumors, 19(7%) salivary gland tumors, 2 (1%) thyroid gland tumors and 91 (36%) laryngeal tumors. From the 123 patients with gastrostomy (pharynx, oral cavity and locally advanced laryngeal tumors), 109 (89%) completed treatment with no interruptions, 9 (7%) completed with interruptions and 5 (4%) did not complete it. From the remaining 135 patients without gastrostomy (glottis, salivary glands and nasal cavities without chemotherapy), 117 (87%) completed without interruptions, 11 (8%) completed with interruptions and 7 (5%) did not complete. The completion of the treatment was almost similar in both groups and fairly good compared with historical studies (Where patients without gastrostomy had 59% of interruptions compared to those with PEG with 37,7% of interruptions; p=0,01).

In addition, the use of IMRT (195 patients; 76%) and IGRT (100%) in our group could impact in a better tolerance and compliance of treatment.

Conclusions: Our experience shows that the selective use of gastrostomy in pharyngeal, oral cavity and locally advanced laryngeal cancer patients plus the use of IMRT and IGRT with chemotherapy is related with very low radiation treatment interruptions which could impact in a better progression free survival.

PO-137

Health-related quality of life in head and neck cancer patients
M. Mäkikie1, V. Loimu2, K. Aro1, L. Bäck1, K. Saarilaiti1, H. Sintonen2, P. Räsänen3, R.P. Roine4
1Helsinki University Central Hospital, Dept. of Otolaryngology - Head & Neck Surgery, Helsinki, Finland
2Helsinki University Central Hospital, Dept. of Oncology, Helsinki, Finland
3University of Helsinki, Dept. of Public Health, Helsinki, Finland
4Helsinki and Uusimaa Hospital Group, Group Administration, Helsinki, Finland

Purpose/Objective: Health-related quality of life (HRQoL) remains as one of the most important management outcomes for head and neck cancer. Disease-specific HRQoL instruments alone may not give an appropriate view of this multidimensional disease.

Materials and Methods: An observational follow-up study using the 15SD, a 15-dimensional standardized and self-administered generic HRQoL instrument, was performed for the first time in this patient population. This instrument can be used as a profile and as a single index utility score measure. HRQoL results were compared with those of an age-standardized sample of the general population. We have earlier presented 15SD HRQoL results in a subset of these patients managed with definitive (chemo)radiotherapy (Loimu et al. Eur Arch Otorhinolaryngol. 2014 Jul 2. [Epub ahead of print]). Two hundred and ten patients (66% male; mean age 63 years; range 27-85) entering treatment for a head and neck malignancy filled in the 15SD HRQoL questionnaires before and at 3, 6 and 12 months after the treatment onset.

Results: Mean (SD) HRQoL score (on a 0-1 scale) of the patients entering treatment was only slightly, but statistically significantly worse than that of age-standardized controls. The total HRQoL score showed a slight initial deterioration but then remained fairly constant during the rest of the 12-month follow up. The most affected HRQoL dimensions were eating, speech, usual activities, distress and sexual activity. After initial decrease, the scores for depression, sleep and distress improved towards the end of the follow-up period compared with their baseline scores. Compared with baseline, the 15SD score was slightly, but statistically significantly worse on all follow-up points. Regarding the various dimensions, the most consistent impairment was seen on the dimensions of eating and speech.

Conclusions: The present study gives an overall view of the HRQoL in this patient population during the first year after treatment. The 15SD instrument seems feasible for evaluation
of HRQoL in head and neck cancer patients. It is noteworthy that there was a significant improvement on certain dimensions after treatment.

PO-138
Data from DETERMIN RCT: Patient preferences for commonly-used, head and neck cancerspecific QOL questionnaires
H. Mehanna1, B. Carter1, A. Hartley2, H. Kirkby2, J. Jones2, L. Fresno, L. Moss3, T. Jones4, S. Rogers4, R. Morton4
1University of Birmingham, Institute of Head and Neck Studies and Education School of Cancer Sciences, Birmingham, United Kingdom
2University Hospitals Birmingham, Hall-Edwards Radiotherapy Research Group, Birmingham, United Kingdom
3University of Birmingham, Cancer Research Clinical Trials Unit School of Cancer Sciences, Birmingham, United Kingdom
4University Hospitals Coventry and Warwickshire, Department of Oncology, Coventry, United Kingdom
5Velindre Cancer Centre, Department of Oncology, Cardiff, United Kingdom
6University of Liverpool, Department of Oncology, Liverpool, United Kingdom
7Edge Hill University, Department of Oncology, Liverpool, United Kingdom
8Auckland University, Department of Oncology, Liverpool, New Zealand

Purpose/Objective: To determine patients’ preferences and willingness to use the common head-and-neck cancer (HNC), quality-of-life (QoL) instruments in routine follow-up clinic.

Materials and Methods: Mixed methods analysis of a RCT of 583 subjects in follow-up after treatment for oropharyngeal or laryngeal cancer. Subjects completed 4 questionnaires: 3 validated instruments - EORTC, FACT, and UW-QOL - and one unstructured open list, and rated which they found most helpful to communicate their health concerns to their clinicians. Order of questionnaire presentation was randomized, and subjects were stratified by disease site and stage.

Results: Of the respondents, 82% (457/558) found that HNC QoL questionnaires helped them communicate their health concerns with their clinician (OR=15.76, 95% CI 10.83-22.94; p-value = 0.001). Patients preferred the validated, structured disease-specific instruments (OR 8.79; 95% CI 5.99-12.91; p=0.001). An open list was the most disliked by patients (OR=4.25; 95% CI 3.04-5.94). More women preferred the FACT (OR=3.01, 95% CI 1.05-8.62, p=0.04) and patients under 70 preferred EORTC (OR=3.14, 95% CI 1.37-7.59, p=0.01). Despite this, only 55% wanted to complete questionnaires routinely in the clinic. Age and gender were significant determinants, with younger patients preferring validated, structured QoL instruments and the elderly less willing to complete questionnaires in the clinic, preferring shorter questionnaires (eg UW-QOL). Women preferred FACT, and younger patients preferred EORTC.

Conclusions: Most HNC patients found QoL instruments helpful in communicating their health needs to their clinicians, preferring validated, structured disease-specific, questionnaires over open unstructured lists. However, only just over half of patients support routine questionnaire use in follow-up clinics, with males and the elderly less willing to complete questionnaires in the clinic, preferring shorter questionnaires (eg UW-QOL). Women preferred FACT, and younger patients preferred EORTC.

Acknowledgments: The study was funded by Macmillan Cancer Research, who were not involved in the conduct, analysis or interpretation of the study.

Poster: Minimal invasive and reconstructive surgery

PO-139
Photodynamic therapy as an adjuvant treatment after TORS of recurrent SCC of the base of tongue
J. Meulemans1, V. Vander Poorten1, P. Delaere1, S. Nuyts2, P. Clement2, R. Hermans4
1University Hospitals Leuven, Otorhinolaryngology - Head and neck surgery, Leuven, Belgium
2University Hospitals Leuven, Radiotherapy, Leuven, Belgium
3University Hospitals Leuven, Medical Oncology, Leuven, Belgium
4University Hospitals Leuven, Radiology, Leuven, Belgium

Purpose/Objective: For selected patients with recurrent base of tongue squamous cell carcinoma (BOT-SCC) after IMRT with or without concomitant chemotherapy, transoral robotic surgery (TORS) has been implemented in the salvage setting. Because of the difficult preoperative surgical margin assessment in this post-radiotherapy setting, the definitive pathologic report frequently shows involved resection margins. In this report, we assessed the feasibility of using temoporfin-mediated photodynamic therapy (PDT) as an adjuvant treatment in patients with involved resection margins after TORS salvage surgery for post(chemo)radiotherapy recurrent BOT-SCC.

Materials and Methods: 2 patients with recurrent BOT-SCC after primary treatment with radiotherapy (patient 1) or concomitant chemoradiotherapy (patient 2) were offered salvage TORS. Unfortunately definitive pathologic specimen revealed involved resection margins. Both patients consented to postoperative PDT. We secured the airway using a tracheostomy, since both edema of the upper airway and aspiration can be expected after both TORS and PDT, especially in the postradiotherapy setting. For the same reason, a 4 to 6 weeks recovery period after TORS was incorporated, before proceeding to PDT. Expecting severe interference with the swallowing mechanism, nasogastric tube (NGT) feeding was accounted for to ensure adequate caloric intake following TORS and PDT.

Results: The NGT could be removed 7 days after TORS and 19 days after PDT in patient 1, and 15 days after TORS in patient 2. In the latter patient, observing no important dysphagia after PDT, oral feeding was not interrupted after PDT. The tracheal cannula was removed 19 days and 4 days after PDT, respectively. At hospital discharge after PDT, 19 days in patient 1, and at 4 days in patient 2, both were able to eat, breathe and speak normally. We observed oncological disease control at 40 months for patient 1 and at 22 months for patient 2, which would have been very unlikely without adjuvant PDT.

Conclusions: In selected patients, with involved resection margins following salvage TORS for recurrent BOT-SCC after primary radio(chemo)therapy, our preliminary experience suggests that temoporfin-mediated PDT can achieve locoregional tumor control, while preserving speech, respiration and swallowing. This approach merits further study concentrating on long-term locoregional control and functional outcome in larger groups of patients.

PO-140
Transnasal endoscopic medial maxillectomy for maxillary and ethmoid sinus tumor- our three experience
T.C. Wang1, H.C. Liao2, C.H. Chen1
1Tainan Municipal Hospital, Otolaryngology, Tainan, Taiwan
2Tainan Hospital Ministry of Health and Welfare, Otolaryngology, Tainan, Taiwan

Purpose/Objective: To determine patients’ preferences and willingness to use the common head-and-neck cancer (HNC), quality-of-life (QoL) instruments in routine follow-up clinic.

Materials and Methods: Mixed methods analysis of a RCT of 583 subjects in follow-up after treatment for oropharyngeal or laryngeal cancer. Subjects completed 4 questionnaires: 3 validated instruments - EORTC, FACT, and UW-QOL - and one unstructured open list, and rated which they found most helpful to communicate their health concerns to their clinicians. Order of questionnaire presentation was randomized, and subjects were stratified by disease site and stage.

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Conclusions: Most HNC patients found QoL instruments helpful in communicating their health needs to their clinicians, preferring validated, structured disease-specific, questionnaires over open unstructured lists. However, only just over half of patients support routine questionnaire use in follow-up clinics, with males and the elderly less willing to complete questionnaires in the clinic, preferring shorter questionnaires (eg UW-QOL). Women preferred FACT, and younger patients preferred EORTC.

Acknowledgments: The study was funded by Macmillan Cancer Research, who were not involved in the conduct, analysis or interpretation of the study.

Poster: Minimal invasive and reconstructive surgery

PO-139
Photodynamic therapy as an adjuvant treatment after TORS of recurrent SCC of the base of tongue
J. Meulemans1, V. Vander Poorten1, P. Delaere1, S. Nuyts2, P. Clement2, R. Hermans4
1University Hospitals Leuven, Otorhinolaryngology - Head and neck surgery, Leuven, Belgium
2University Hospitals Leuven, Radiotherapy, Leuven, Belgium
3University Hospitals Leuven, Medical Oncology, Leuven, Belgium
4University Hospitals Leuven, Radiology, Leuven, Belgium

Purpose/Objective: For selected patients with recurrent base of tongue squamous cell carcinoma (BOT-SCC) after IMRT with or without concomitant chemotherapy, transoral robotic surgery (TORS) has been implemented in the salvage setting. Because of the difficult preoperative surgical margin assessment in this post-radiotherapy setting, the definitive pathologic report frequently shows involved resection margins. In this report, we assessed the feasibility of using temoporfin-mediated photodynamic therapy (PDT) as an adjuvant treatment in patients with involved resection margins after TORS salvage surgery for post(chemo)radiotherapy recurrent BOT-SCC.

Materials and Methods: 2 patients with recurrent BOT-SCC after primary treatment with radiotherapy (patient 1) or concomitant chemoradiotherapy (patient 2) were offered salvage TORS. Unfortunately definitive pathologic specimen revealed involved resection margins. Both patients consented to postoperative PDT. We secured the airway using a tracheostomy, since both edema of the upper airway and aspiration can be expected after both TORS and PDT, especially in the postradiotherapy setting. For the same reason, a 4 to 6 weeks recovery period after TORS was incorporated, before proceeding to PDT. Expecting severe interference with the swallowing mechanism, nasogastric tube (NGT) feeding was accounted for to ensure adequate caloric intake following TORS and PDT.

Results: The NGT could be removed 7 days after TORS and 19 days after PDT in patient 1, and 15 days after TORS in patient 2. In the latter patient, observing no important dysphagia after PDT, oral feeding was not interrupted after PDT. The tracheal cannula, was removed 19 days and 4 days after PDT, respectively. At hospital discharge after PDT, o
PO-142 Microsurgical reconstruction of the tissues of the oral cavity and pharynx by visceral flaps in cancer patients A. Polyakov1, A. Kaprin2, I. Reshetov2, M. Ratushny1, O. Matorin1, F. Svrkov1, M. Filushin1, V. Vasilev1, I. Rebrikova1
1Moscow Gertzen Institute, Microsurgery, Moscow, Russian Federation
2Moscow Gertzen Institute, Director, Moscow, Russian Federation
3I.M.Sechenov First Moscow State Medical University, Plastic surgery, Moscow, Russian Federation

Purpose/Objective: Surgical treatment of malignant locally advanced oropharyngeal tumors is a challenging task in terms of obtaining good long-term oncological results, on the one hand, and providing social rehabilitation of the patients, on the other. We tried to develop a method of surgical rehabilitation after extensive resections that will not compromise oncological outcome and will improve quality of life in the given group of patients.

Materials and Methods: 124 patients with malignant locally advanced oropharyngeal tumors were operated between 1995 and 2013. Tumors were located in oral cavity (35), tongue (15), oropharynx (11), laryngopharynx (23), larynx (17), maxilla (18), mandible (4) and soft tissues (6). In all cases patients presented with significant cosmetic and functional defects of the upper digestive and respiratory tracts. We used gastro-omental (60 pts), colon-omental (49 pts) and jejunum (15) flaps from microsurgical reconstruction of oral and pharynx.

Results: Necrosis of the flap was found in 6 patients (4,8%). Good functional qualities of the transplant contributed to the complete healing of salivary fistulas in 15 patients (12,1%). There were no complications associated with abdominal cavity. Four patients (3,2%) died in the postoperative period. Feeding per os started from the 14th day after surgery. Natural food intake was restored in 120 patients. All patients were dacanulates within 3-7 weeks after surgery. In 8 cases a vocal function was applied after trachea-esophageal shunting with establishing voice protez. The general life expectancy of patients within 36 months after operation has made: 63,5% at use gastro-omental flap and 58,7% at use colon-omental flap. Several patients were alive for 10 years after surgery.

Conclusions: Patients with locally advanced oropharyngeal tumors are treated most effectively using multimodal approach - chemoradiation with extensive surgical resection. The use of visceral free flap autotransplantation helps restore vast defects after resections and improves quality of life in such patients.

PO-143 Microinvasive access to visceral autoflaps - microsurgical reconstruction laryngopharynx and upper third esophagus A. Polyakov1, A. Kaprin2, I. Reshetov2, M. Ratushny1, O. Matorin1, F. Svrkov1, M. Filushin1, V. Vasilev1, I. Rebrikova1
1Moscow Gertzen Institute, Microsurgery, Moscow, Russian Federation
2Moscow Gertzen Institute, Director, Moscow, Russian Federation
3I.M.Sechenov First Moscow State Medical University, Plastic surgery, Moscow, Russian Federation

Purpose/Objective: Microinvasive diagnostic and surgery is one of the most promising lines of up-to-date oncology. In the P.A. Hertzen Moscow Cancer Research Institute was developed a method of microinvasive abdominal access to form the visceral autoflaps in cancer patients.

Materials and Methods: We have an experience of treatment 50 patients aged from 16 to 55 years (male 19, female 31)
with malignant local extended craniofacial (27) and oropharyngeal tumors (23).

In 17 cases it was the tumor of the scalp, 5 - maxilla, 5 - cellae ethmoidales, 4 - oral cavity, 5 - tongue, 3 - oropharyngeal, 5 - laryngeal pharynx, 1 - face soft tissues, 1 - mandible, 4 - parotid gland. For plastic closing the large postoperative defect were used the abdominal organs. We chose a umbilical incision as the appropriate access to the abdominal cavity with minimal external trauma of the anterior abdominal wall. Using video assisted technique (video endoscopy system) aponeurosis was dissected along median line centerline. Donor’s organs (omentum, greater curve of the stomach, transverse colon, jejunum) were delivered through the minilaparotomy wound on the anterior abdominal wall, then vessel's peduncle of free flap was exposed (right gastroomental vessels, vessels colicae media, vessels jejunum) and visceral autoflap was formed. Dissection away the transplant followed by the extracorporal forming of the organs’ anastomosis. In 3 cases was made an attempt to form the 1 gastrointestinal and 1 colon-omental autoflaps and in 1 case at adiposity during formation omental flap. After inspection the abdominal cavity usual upper median laparotomy was performed. The massive commissural process in the abdominal cavity caused the widening of the access. The plan of the operation among these 3 patients was fulfilled; the flaps were formed and transported on recipient’s wound.

Results: In 47 cases the operation was completely made through the minimal access (3 patients had abdominal operative intervention before). It was formed and prepared for autotransplantation 26 omental free flaps, 7 gastrointestinal, 15 colon-omental and 2 jejunum flaps. There were no intra- postoperative abdominal complications. Based on the results of clinical and morphological data comparison there were no reliable feature of any structural and functional changes of gastric and omental flap mucous. The follow up period was up to 1 year.

Conclusions: Microinvasive technology to form visceral autoflaps for head and neck reconstruction allows to minimize operative trauma and to shorten the period of postsurgical treatment. We recommend using this access when operating the weak cancer patients and young women to avoid additional undesirable scar on donor’s site.

PO-144
Test of calcium phosphate cement for reconstruction maxillofacialis zones in vitro
A. Polyakov1, M. Filushin1, I. Reshetov1, E. Kiseleva1, E. Batutina1, I. Rebrikova1, A. Shevalgin1, Y. Panaseykin1
1Moscow Gertzen Institute, Microsurgery, Moscow, Russian Federation
2I.M. Sechenov First Moscow State Medical University, Plastic Surgery, Moscow, Russian Federation

Purpose/Objective: Developing the method of oropharyngeal region morphotypical tissue reconstruction in cancer patients using bioengineered autologic flaps.
Materials and Methods: 32 patients with locally advanced tumors of the oropharyngeal region were included in the study. Orostoma or pharyngostoma were formed for local control after tumor resection in all patients. Patients were divided into two groups (16 in each) depending on the localization of epithelium used - nasal or oral cavity. Micrografts of autologic epithelium of nasal or oral cavity were implanted on the fibers of pectoralis major muscle. Implanted fragments of the mucous membrane were placed in the artificial pocket on the anterior pectoral wall for 30-45 days. Pharynx reconstruction was performed during the second stage; fragments of implanted mucous membrane were taken for morphological testing.
Results: Full flap survival was registered in all patients in 1st and 2nd group. Full organ function recovery was noticed in 87.5% (n=14) cases in group #1, and in 93.75% (n=15) cases in group #2. In 2 patients in group #1 and 1 patient in group #2 the postoperative period was complicated by ligature fistulas that were closed during a period from 12-24 days after conservative therapy without a negative impact on bioengineering flap.
Morphological testing demonstrated the presence of mature epithelium in 56.25% (n=9) of cases in group #1 and in 81.25% (n=13) cases in group #2. Stratified squamous epithelium of the oral mucosa can adapt and grow on muscle fascia much better than stratified cylindrical epithelium of the nasal cavity.

**Conclusions:** Using the method of morphotypical tissue reconstruction of oropharyngeal area using bioengineered autologic flaps allows to improve results of defect elimination with restoration of mucous membrane and soft tissues and provides a complete anatomical and functional rehabilitation. Implantation of oral mucous fragments is an optimal method of creating a mucous membrane on muscle fascia.

**PO-146 Anatomical substantiation of microsurgical autotransplantation of parathyroid glands**

I. Reshetov, A. Golubtsov, F. Sevrukov, O. Krekhno, E. Kirpa

1. I. M. Sechenov First Moscow State Medical University, Plastic surgery, Moscow, Russian Federation
2. P. A. Hertzen Moscow Cancer Research Institute, Microsurgery, Moscow, Russian Federation
3. Oncological Dispensary Research Institute, Medical University, Surgical, Toliatte, Russian Federation

**Purpose/Objective:** The purpose of this work is to justify the method for the prevention and treatment of parathyroid insufficiency in patients with thyroid cancer from the point of view of the vascular anatomy of the parathyroid glands, based on microsurgical autotransplantation of the parathyroid glands, that provides reliable and stable results.

**Materials and Methods:** We applied the method of assessing blood flow in 14 parathyroid glands (4 right top, 5 bottom right, 2 left top and 3 bottom left), in 7 patients (6 women from 24 years to 71 years, 1 male 34 years) operated for thyroid cancer (6 thyroidectomies, 1 right hemithyroidectomy). On the day of surgery for 2.5-3 hours prior to intubation oral accepted drug alsens (30 mg/kg). Intraoperatively performed fluorescence navigation of the parathyroid glands. Upon detection of fluorescent areas is urgent Cytology (confirmation that the parcel fabric of the parathyroid gland). Next, using optical magnification and microsurgical instruments is the study of the blood supply to the parathyroid glands: estimated primary and possible additional sources of blood supply, their length and diameter, type of branching. Next estimated the number of arteries and veins diverging from the main supply vessel, their length from the branch directly to the parathyroid glands, the diameter ratio to each other. Data is logged, photoregistration was performed. Next, excision of tumour with preservation of the parathyroid glands is performed.

**Results:** As a result of application of the method described, discovered that the upper parathyroid glands have blood supply with the vessels of smaller diameter than the bottom ones. The diameter of the upper arterioles is from 0.4 to 0.8 mm, the diameter of the upper venules is from 0.5 to 0.9 mm, while the diameter of the bottom arterioles varies from 0.6 to 1.0 mm, the diameter of the bottom varies venules fromathy 6 to 1.1 mm. Bottom feeding arterioles and venules different parallel arrangement in a single vascular bundle, the upper arterioles and venules often bypass the parathyroid gland with two sides. In most cases thyroid artery departs at 1 main supply vessel to the parathyroid glands, and only in one case, the branch from the bottom right thyroid veins merged from two independent parallel to each other venules.

**Conclusions:** Based on the obtained data it is possible to assume that autotransplantation of the parathyroid glands is possible by using the vascular bundles of the thyroid vessels, but not arterioles and venules, directly feeding the parathyroid gland, because they have a large diameter (1 mm), and it is more favorable factor for successful vascular anastomosis. It is also possible to assume that the lower parathyroid glands more suitable for autologous transplantation on vascular legs because of the nature of their blood supply - the larger diameter of the supply vessels and their location in one vascular bundle.

**PO-147 Facial nerve and its branches reconstruction during surgery for head and neck tumors**


1. PA Gertzon Moscow Research Oncological Institute, Microsurgery, Moscow, Russian Federation
2. I. M. Sechenov First Moscow State Medical University, Plastic Surgery, Moscow, Russian Federation

**Purpose/Objective:** Evaluation of facial nerve branch reconstruction efficiency during radical surgery in patients with head and neck tumors.

**Materials and Methods:** Retrospective analysis of surgeries for malignant and benign head and neck tumors with facial nerve injury on different levels was performed. 98 patients underwent surgical treatment including 44 males (44.89%) and 54 female (54.11%). Average age was 55 (min 23, max 87) years. 63 (64.2%) cases of malignant tumors were presented with parotid gland cancer (35), skin cancer (9), mixed tumor of parotid gland (2), primary multifocal metachronic cancer (4), submandibular salivate gland cancer (2), tongue cancer (2), oropharyngeal cancer (2), lower eyelid skin cancer (1), dermatofibrosarcoma of facial soft tissues (1). 35 (35.8%) benign tumors included parotid gland adenoma (31), neurofibroma of parotid gland (2), cyst in parotid gland (1), lipoma of the neck (1). In surgery for malignant tumors radical tumor resection with nerve or branch transection was performed. Nerve sparing resections were made in case of benign tumors.

**Results:** All cases with nerve injury were analyzed. The type of facial nerve surgery was influenced by the volume of tumor resection and the level of injury. Neurolysis was performed in 78 cases (59.6%), plastic restoration of the nerve in 20 cases (40.4%). Nerve reconstruction was performed via anastomosis with descending branch of hypoglossal nerve (8), cervical branch of hypoglossal nerve (6), nerves of cervical plexus (3), glossopharyngeal nerve (1). Method of neural insertions was used in 4 cases using parts of descending branch of hypoglossal nerve (2), great auricular nerve (1) and subcutaneous branch of transverse cervical nerve (1). In the majority of cases there was no need for additional cover of defect (81), in other cases the most frequently used materials were omental flap (10), sternocleidomastoid muscle flap (2), posterior cervical flap (1), free cervical flap (1), partial sternocleidomastoid muscle fibers flap (1), surrounding soft tissues (1), musculo-cutaneous flap (1). Complete function restoration of facial nerve was achieved in 65% cases, partial recovery in 23%, in 12% no function restoration was noticed.

**Conclusions:** Facial nerve of its branches transection is a necessary component of radical head and neck tumor surgery in a certain cases. It requires mandatory nerve reconstruction in order to achieve functional rehabilitation and quality of life improvement.

**PO-148 Videoassisted resections of larynx with radio frequency thermal ablation in cancer patients**


1. PA Gertzon Moscow Research Oncological Institute, Microsurgery, Moscow, Russian Federation

**Purpose/Objective:** The purpose was to modify and confirm methods of malignant tumor resection and reconstruction in larynx with decreased functional and esthetic quality of life improvement.

**Materials and Methods:** Videoassisted resections of larynx with radio frequency thermal ablation in cancer patients with head and neck tumors. All cases with nerve injury were analyzed. The type of facial nerve surgery was influenced by the volume of tumor resection and the level of injury. Neurolysis was performed in 78 cases (59.6%), plastic restoration of the nerve in 20 cases (40.4%). Nerve reconstruction was performed via anastomosis with descending branch of hypoglossal nerve (8), cervical branch of hypoglossal nerve (6), nerves of cervical plexus (3), glossopharyngeal nerve (1). Method of neural insertions was used in 4 cases using parts of descending branch of hypoglossal nerve (2), great auricular nerve (1) and subcutaneous branch of transverse cervical nerve (1). In the majority of cases there was no need for additional cover of defect (81), in other cases the most frequently used materials were omental flap (10), sternocleidomastoid muscle flap (2), posterior cervical flap (1), free cervical flap (1), partial sternocleidomastoid muscle fibers flap (1), surrounding soft tissues (1), musculo-cutaneous flap (1). Complete function restoration of facial nerve was achieved in 65% cases, partial recovery in 23%, in 12% no function restoration was noticed.

**Conclusions:** Facial nerve of its branches transection is a necessary component of radical head and neck tumor surgery in a certain cases. It requires mandatory nerve reconstruction in order to achieve functional rehabilitation and quality of life improvement.
Purpose/Objective: Treatment results of patients with locally-advanced larynx cancer may be improved with modern surgical technologies.

Materials and Methods: Videoassisted endolaryngeal resections with radiofrequency thermal ablation with the use of endovideoscopic complex and radio frequency thermal ablation device ‘Metatom-Z’ are performed in P.A.Herzen Moscow Cancer Research Institute since 2006. Extent of operations varies from cordectomy to thyroid cartilage-sparring frontolateral and horizontal resection after total laryngectomy.

Results: 64 patients with larynx cancer stage T1-2N0M0 underwent separate surgical treatment or combined treatment with pre- or post-operation radiation therapy. Decannulation was performed on 2-3 day after operation. Continued tumor growth has been detected in 7 patients since 2006 making surgical treatment in volume of laryngectomy necessary.

Conclusions: This method renders possible saving supporting, respiratory and phonal functions, decreases risk of complications such as bleeding and larynx stenosis, prevents lymphogenic and blood dissemination of tumor cells, and reducing bed days in hospital.

PO-149
Methods of soft tissues defect restoration in surgical treatment of head and neck skin melanoma
I. Reshetov1, A. Poljakov2, N. Babakina3
1I.M. Sechenov First Moscow State Medical University, Plastic surgery, Moscow, Russian Federation
2PA Gertzen Moscow Research Oncological Institute, Microsurgery, Moscow, Russian Federation

Purpose/Objective: Surgical treatment of skin melanoma is specific because of wide excisions made to perform radical operation causing vast defects of soft tissues. Plastic reconstruction is of high value especially when tumor is localized on head or neck due to necessity of both functional and aesthetic results.

Materials and Methods: Basing on experience of head and neck skin melanoma surgical treatment in P.A.Hertzen Moscow Cancer Research Institute a retrospective investigation was performed to evaluate methods of soft tissues defect restoration. 88 operations were performed in microsurgical department of P.A.Hertzen Moscow Cancer Research Institute on skin and mucosal melanoma, 45 of them in volume of soft tissue excision in cases of head and neck skin melanoma with a single-step plastic.

Results: Local tissue reconstruction was performed in 29 cases (64,4%), including double-end, sliding and Z-grafts, and also a helix double-step plastic with advanced graft. Autodermoplasty was performed in 9 cases (20%) - a defect was restored with a perforated full-thickness skin graft, in 7 cases (15,6%) both autodermoplasty and local flaps were used to restore the defect. Local fasciocutaneous flaps plastic provided best functional and aesthetic results in compare with other methods. Unfortunately vast postoperative defects and lack of soft tissue plastic material in head and neck area limit usage of these methods. Combined local-flap plastic and autodermoplasty on limited areas also showed good aesthetic and functional results (cosmetic results were inverse-proportionally connected with area size of autodermoplasty reconstruction). Autodermoplasty being usually a forced plastic method because of wide defects or possible healing failure of wound provided poor aesthetic results but proved to be satisfactory in functional aspect.

Conclusions: Local tissue reconstruction is wildly recommended as a method of plastic defect rebuilding in patient with head and neck skin melanoma undergoing surgical treatment because of good aesthetic and functional results in a single-step procedure. Autodermoplasty as a single method or combined with local-flap plastic may be used in case of plastic material deficit mainly for the purpose of a functional profit but is not recommended to be used as a routine method of surgical defect restoration.

PO-150
Histopathologic features of irradiated and non-irradiated vessels in head and neck microvascular reconstruction
C. Piazza1, L. Morassi2, F. Del Bon3, L. Brescia1, M. Schiavolina4, A. Paderno1, A. Grammatica1, V. Taglietti5, P. Nicolai6
1University of Brescia, Otorhinolaryngology - Head and Neck Surgery, Brescia, Italy
2University of Brescia, Pathology, Brescia, Italy

Purpose/Objective: Microvascular reconstruction has a key role in head and neck (HN) surgery but debate in the literature is still present around its feasibility after radiation (RT) or chemoradiation (CRT). Aim of this study is to evaluate the histopathological features of recipient and donor vessels in relation to previous RT/CRT and other clinical variables.

Materials and Methods: Specimens of recipient and donor vessels were histopathologically analyzed in 40 patients undergoing free flaps for tumors of the HN. Patients’ data were collected in a prospective database and comorbidities were assessed using the Charlson comorbidity index (CCI). Vessels were divided in 3 groups: Group A (N=26; HN vessels exposed to RT/CRT), Group B (N=32; HN vessels not exposed to RT/CRT), and Group C (N=73; vessels of the flap pedicle). An histopathological score (HS) was developed in order to quantify the alterations observed in the vessels.

Results: Overall flap success rate was 95%. Flap failure occurred in 2 patients for arterial thrombosis (both reconstructed with an anterolateral thigh, one in Group A and the other in Group B). No statistically significant association was found between flap failure and CCI, HS, preoperative RT/CRT, and type of free flap. Similarly, preoperative RT/CRT and CCI did not significantly influence the HS. Regarding Group C (free flap pedicles), no significant difference in the HS was found in relation to the type of flap donor site.

Conclusions: It is not possible to find a significant difference in the histopathologic appearance of irradiated and non-irradiated vessels. Microvascular surgery should therefore be considered feasible and safe even in patients after RT/CRT.

PO-151
Initial experience on near-infrared guided surgery for sentinel lymph node biopsy for oral cavity carcinoma
A.L. Carvalho1, C. Scapulatempo Neto2, E.T. Rocha3, R.C. Capuzzo4
1Hospital de Cancer de Barretos, Teaching and Research Institute, Barretos, Brazil
2Hospital de Cancer de Barretos, Pathology Department, Barretos, Brazil
3Hospital de Cancer de Barretos, Nuclear Medicine Department, Barretos, Brazil
4Hospital de Cancer de Barretos, Head and Neck Department, Barretos, Brazil

Purpose/Objective: Sentinel lymph node biopsy (SLNB) for initial stage oral cavity cancer is nowadays an accepted procedure to pathologically stage the neck. The Head and Neck Department at Barretos Cancer Hospital is using SLNB as a standard procedure for those patients since 2009, this procedure was based only on Tc-99 radioguided technique. The objective of this study is to describe our initial experience using the near-infrared (NIR) guided surgery for SLNB.

Materials and Methods: This is a prospective study evaluating the feasibility of NIR guided surgery for SLNB. Inclusion criteria were: T1-T2 squamous cell carcinoma of the oral
PO-153 Losing teeth attenuate the anti-cancer defense of oral fluid
M. Narges1, N. Nafisheh2
1Shahid Sadoughi University of Medical Sciences, Oral Medicine, Yazd, Iran Islamic Republic of
2Shahid Sadoughi University of Medical Sciences, N/A, Yazd, Iran Islamic Republic of

Purpose/Objective: The burden of cancers is so great that it would be a huge step if we could prevent them instead of struggling for cure, specifically for a cancer with poor prognosis such as oral squamous cell carcinoma. A recent trend in cancer research highlighted the possible role of poor oral hygiene in upper digestive tract carcinomas. However, no study has yet carried out to explain that relationship. We studied the correlation between decayed, missed, and filled teeth and total anti-oxidant capacity of whole saliva, which is a known defense against carcinogenesis.

Materials and Methods: Ninety healthy adults (30 to 49 years of age) participated in the study. Their unstimulated whole saliva total anti-oxidant capacities and the scores for decayed, missed, and filled teeth were measured and were analyzed.

Results: Number of extracted and decayed teeth correlates negatively with saliva total anti-oxidant capacity (P < 0.001).

Table 1: TAC and D, M, and F Scores

<table>
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<th>TAC</th>
<th>D</th>
<th>M</th>
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<tr>
<td>-0.337</td>
<td>-0.416</td>
<td>0.391</td>
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<tr>
<td>P</td>
<td>0.001</td>
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Test: Pearson’s Correlation

Conclusions: Findings indicated that losing normal dentition weakens the anti-oxidant defense of oral cavity.

Poster: Epidemiology and prevention

PO-154 Head and neck cancer case-control study: UK Biobank
T.V. Macfarlane1, G.J. Macfarlane1
1University of Aberdeen, School of Medicine and Dentistry, Aberdeen, United Kingdom

Purpose/Objective: To confirm associations of head and neck cancer (HNC) with smoking, alcohol consumption and markers of poor diet and to investigate novel risk factors such as medical history in a national UK study.

Materials and Methods: A nested case-control study within UK Biobank, a national population study conducted in 2006-2010 and which recruited over 500,000 people (www.ukbiobank.ac.uk/). Participants are followed-up via record linkage to cancer registry data. Cases of HNC diagnosed at least 6 months after attendance at assessment centres were identified. Controls were selected in a ratio of 10:1 (where possible), matched by gender, age (within 2 years), assessment centre and ethnicity. Analysis was by conditional logistic regression with results expressed as Odds Ratios (OR) (adjusted for smoking and deprivation) with 95% Confidence Intervals (CI).

Results: There were 135 incident (primary) cases of HNC and 1,340 matched controls. There was an increased risk associated with Townsend Deprivation Index (OR=2.1, 95% CI 1.2-3.8 in the highest quintile), current smoking (OR=6.1, 95% CI 3.7-10.0) and reporting adding salt to food (OR=2.2, 95% CI 1.2-4.1 for always compared to never). There was an inverse association with history of any allergy (OR=0.4, 95% CI 0.1-1.2), asthma (OR=0.5, 95% CI 0.3-1.0) and fruit and vegetable consumption (OR=0.6, 95% CI 0.3-1.3 for five or more per day compared to one or less). There was an increased risk associated with self-reported autoimmune diseases (OR=2.4, 95% CI 1.3-4.5) and painful gums (OR=2.5, 95% CI 1.2-5.3).

None of the HNC cases reported history of viral infections...
such as HIV/AIDS, Measles / Morbillivirus; Rubella / German measles; Varicella zoster virus / chickenpox / shingles; Herpes simplex; Infectious mononucleosis / glandular fever / Epstein Barr Virus; Mumps / epidemic parotitis.

Conclusions: This study confirms the findings of previous studies on risk factors for HNC and adds new information related to medical history. As HNC cases accumulate, the study will provide more precise estimates of associations.

PO-155
Second primary tumors in a cohort of almost 600 patients with head and neck cancer

B. Cirauqui1, V. Quiroga1, M. Gil1, L. Vilà1, A. Indacochea1, S. Ahlal1, M. Hardy-Werbin1, I. Teruel1, C. Pollán1, M. Margeli2
1Institut Català d’Onkologia. Badalona, Medical Oncology, Badalona, Spain
2Hospital Germans Trias i Pujol. Badalona, Otolaringology, Badalona, Spain

Purpose/Objective: Second primary tumors are a common problem in patients with head and neck cancer. The aim of this review is to try to assess their frequency in a cohort of patients treated in our department.

Materials and Methods: We retrospectively analyzed records of 589 patients treated at the department of Medical Oncology at our center between 2004 and 2014, and we selected those with a history of cancer before the diagnosis of head and neck cancer or who had developed a synchronous and metachronous second primary tumor.

Results: 108 of the 589 patients had a second primary tumor (14.65%), and a total of 132 different malignancies. The main characteristics of patients are in Table 1. No data about HPV status are available.

90 (97%), 17 (2%) and 1 (1%) patients had a single, two and three second primary tumors, respectively. Lung cancer was the most frequent (27%) followed by a head and neck second tumor (15%), colorectal adenocarcinoma (11%), esophageal squamous cell carcinoma (9%) and bladder tumor (8%). 54% of patients developed a metachronous second primary tumor, 26 % had a cancer history at diagnosis, 14% were synchronous and 6% had it before and after cancer diagnosis head and neck. The median overall survival from diagnosis of head and neck cancer was 60 months. If we analyze the cause of death of the 63 dead patients, 46 % was due to second primary tumor, 28 % to head and neck cancer and 26% to other causes.

Conclusions: Our data confirm that patients with head and neck tumors have an important rate of second primary tumors and this is the cause of death in a high percentage of them, despite being in a cohort of patients with advanced malignancies.

PO-156
Pitfalls for diagnosis of pigmented skin lesions

1Federal University of Rio de Janeiro, Head and Neck Surgery Department, Rio de Janeiro, Brazil
2Institute of Oncology Aldenora Bello, Head and Neck Surgery Department, São Luís, Brazil
3Institute of Oncology Aldenora Bello, Dermatology Department, São Luís, Brazil
4Institute of Oncology Aldenora Bello, Pathology Department, São Luís, Brazil

Purpose/Objective: The classification of various Pigmented Lesions of the skin and its relation to the development of melanoma are not well defined. Melanocytes are originally derived from the neural crest and are defined by their ability to produce melanin pigment, having specific organelles (melanosomes). As these do not possess intercellular junctions, premelanosomes and even developed melanosomes may be transferred to epidermal keratinocytes, which may undergo a process of melanin colonization. The distinction between different types of pigmented lesions interferes with proper treatment and better prognosis. To the present, a classification that defines pigmented lesions is not completely established.
To describe the main clinical and histopathological criteria for the diagnosis of Pigmented Lesions and thus set in a better way the variety of them and consequently assist in the effective treatment of injuries.

M. Delmelle3, H. Nguyen4, D. Larsimont5, M. Lemort6, M. Paesmans7

1Institut J. Bordet, Surgery Department, Brussels, Belgium
2Institut J. Bordet, Nuclear Medicine, Brussels, Belgium
3Institut J. Bordet, Medicine, Brussels, Belgium
4Institut J. Bordet, Anatomopathology, Brussels, Belgium
5Institut J. Bordet, Radiotherapy, Brussels, Belgium
6Uludag University School of Medicine, Radiotherapy, Uludag, Turkey
7CRLC Paul Lamarque, Radiotherapy, Montpellier, Turkey
8Fujian Province Tumor Hospital, Radiotherapy, Fujian, China
9Centre Antoine-Lacassagne, Radiotherapy, Nice, France

Materials and Methods: Observation of clinical and histopathological findings related to Pigmented Lesions, and analysis of numerous papers proposed to classify the different injuries.

Results: Numerous cases of different Pigmented Lesions were analyzed. The Pigmented Lesions have certain characteristics that aid in diagnosis, as the relation of edges and pearly sun-exposed areas with Basal Cell Carcinoma (BCC); the periluminal comedo and homogenous halo of color with melanoma; warty surface suggests Pigmented Seborrhoeic Keratosis; longstanding trend suggests Nevus, among others. Despite these features, which are not always easily distinguishable, the fact that the lesions are pigmented does not necessarily indicate melanocytic origin. Thus, the staining of BCC and Seborrhoeic Keratosis Pigmented, for example, stems from the colonization of melanin and basal keratinocytes of the epidermis, respectively. Furthermore, there are no studies in the literature that could define, in a precise manner, the Pigmented Lesions.

Conclusions: The main importance of Pigmented Lesions distinction lies in the possibility of their relationships with Cutaneous Melanoma, which is the skin cancer with greater potential lethality. Furthermore, its incidence has increased in recent decades, constituting the leader among cancers that affect young adult population. Thus, for the diagnosis of varied pigmented skin lesions and effective treatment, it is necessary to evaluate the clinical and histopathological criteria.

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

PO-157

Medullary thyroid cancer (MTC): improved survival with new imaging

G. Andry1, E. Willemsse1, A. Digonnet1, M. Quiriny1, C. Garcia2, M. Delmelle3, H. Nguyen4, D. Larsimont5, M. Lemort6, M. Paesmans7

1Institut J. Bordet, Surgery Department, Brussels, Belgium
2Institut J. Bordet, Nuclear Medicine, Brussels, Belgium
3Institut J. Bordet, Medicine, Brussels, Belgium
4Institut J. Bordet, Radiotherapy, Brussels, Belgium
5Institut J. Bordet, Medical Imaging, Brussels, Belgium
6Uludag University School of Medicine, Radiotherapy, Uludag, Turkey
7CRLC Paul Lamarque, Radiotherapy, Montpellier, Turkey
8Fujian Province Tumor Hospital, Radiotherapy, Fujian, China
9Centre Antoine-Lacassagne, Radiotherapy, Nice, France

Purpose/Objective: MTC represents 5% of all thyroid cancers, surgery is the main step of treatment. Calcitonin is a specific marker in the serum, carcinoembryonic antigen (CEA), may be also elevated. MRI and Pet CT have made possible to localize occult recurrence and treat patient more selectively.

Materials and Methods: From 1965 till December 2010, 54 consecutive Patients (PTS) (36 women, 18 men) were treated in our Institute for MTC. Analysis of treatment, results, complications, prognostic factors (T N M/Stage (St), calcitonin, CEA) recurrences and survival. PTS had a total thyroidectomy and selective lymph node dissection - lateral if suspicious nodes (sonography or MRI). After incomplete resection or lymph node involvement with capsular rupture, postoperative external radiation was applied.

Results: Median age was 54.5 yrs. Stage distribution was St I: 6; St II: 16; St III: 26; St IV: 4; unknown : 2. Fourteen PTS were referred after incomplete surgery done elsewhere, additional hemithyroidectomy was performed in 4 PTS leading to total thyroidectomy in 53 PTS; 42 PTS underwent lymph node dissections; 10 PTS had postop. Complications: recurrent unilateral nerve paralysis (4); hypoparathyroidism (3); deep venous thrombosis (1); Horner’s syndrome (1), paresia (1). Postop. radiation was applied to 18 PTS, chemotherapy to 3 PTS. There were 26 deaths among which 11 due to MTC, 6 due to other causes, 9 unknown cause. Median F.U. for PTS alive: 12.3 yrs (0.4 to 21.7). Overall survival at 5 and 10 yrs were 74% (C1: 95%: 62-86%) and 55% (C1: 95%: 40-70%) respectively. Predictive factors for worse survival were: ST > II (HR= 3.10, C1 95%: 1.28-7.51), lymph node invasion (HR= 2.98, C1 95%: 1.22-7.26), postop. external radiation (HR= 5.23, C1 95%: 2.21-12.39). Ten PTS with normalised calcitonin (< 15) 9 are alive NED, 1 died of other cause, whereas in 38 PTS with persistently elevated calcitonin the survival was compromised (logrank test on survival curves: p=0.02). Nevertheless 21 PTS survive for long periods (median 12.4 yrs, r: 4 to 22 yrs) with persistently elevated calcitonin levels. In 5 out of 9 PTS with this elevated calcitonin, 18-FDG PET or octreotid PET could localize tumoral tissue, 2 of those PTS had successful salvage surgery, 3 other PTS had disseminated metastases.

Conclusions: Formerly hyper radical surgery has been advocated for MTC, but nowadays novel tools: MRI and PET (5 FDG or/and octreotid) are able to provide useful localization of tumoral deposits, that could be surgically removed selectively. This tailored treatment should improve the survival and lessen the morbidity. Elevated calcitonin levels after initial treatment is a sign of persistent disease but the PTS can survive for prolonged periods and should be carefully monitored and treated accordingly.

PO-158

The Role of concomitant radiochemotherapy in Anaplastic Thyroid Carcinomas (ATC): A study of the Rare Cancer Network

X.S. Sun1, J. Khalifa2, J.C. Faiivre3, T. Sio4, G. Bar-Sela5, C. Demirao6, P. Boisselier7, J.J. Pan8, R.C. Miller9, J. Thariat9

1Hôpital Univ. Jean Minjoz CHU Minjoz & Belfort-Montbéliard Hospital, Radiotherapy, Besançon, France
2CAC Toulouse, Radiotherapy, Toulouse, France
3COL Lille, Radiotherapy, Lille, France
4Oncology Mayo Clinic, Radiotherapy, Rochester Minnesota, USA
5Rambam-Health Care Campus and Faculty of Medicine, Radiotherapy, Haifa, Israel
6Uludag University School of Medicine, Radiotherapy, Uludag, Turkey
7CRLC Paul Lamarque, Radiotherapy, Montpellier, Turkey
8Fujian Province Tumor Hospital, Radiotherapy, Fujian, China
9Centre Antoine-Lacassagne, Radiotherapy, Nice, France

Purpose/Objective: Anaplastic Thyroid Carcinomas (ATC) are rare diseases and among the most aggressive human malignancies with median survival 10 months. The objective of this study was to estimate the impact on the overall survival according to the multimodal therapeutic strategy.

Materials and Methods: The patients affected by ATC treated in a dose of at least 40 Gy in the centers of the group of the rare cancer network were analyzed.

Results: In total, among 140 patients affected by ATC: 25 % had a composite differentiated and undifferentiated component, 13 patients received neoadjuvant chemotherapy (with various protocols), and 63 % of the patients have a partial response. Among 68 patients having been operated (among which 63 % by total thyroidectomy, 70 % with cervical lymph node dissection), 18 % had a complete resection. 80 % of the patients had a concomitant radiochemotherapy (including doxorubicin, docetaxel, cisplatin, carboplatin). 80 % of the patients had wide fields external radiotherapy, 20 % with limited fields, and a median dose of 60 Gy was delivered. The medians of locoregional control, survival without metastasis and overall survival were respectively of...
16, 14 and 17 months. The multivariate analysis showed that with surgery and high-dose radiotherapy are independent predictors of overall survival. Patients who received IMRT treatment seem to have better results. Conclusions: High-dose IMRT with docetaxel concomitant probably gives the best result, but needs more patients up to confirm this trend. This study is ongoing.

PO-159
Orbit preservation with chemoradiation for orbit invasive cancer of the paranasal sinuses
M.J. Amsbaugh1, C.A. Perez2, J. Bumpous3, K. Potts1, C. Silverman1, N.E. Dunlap1, M. Berke1
1University Of Louisville Brown Cancer Center, Radiation Oncology, Louisville, USA
2University Of Louisville Brown Cancer Center, Medical Oncology, Louisville, USA
3University Of Louisville Brown Cancer Center, Otolaryngology - Head and Neck Surgery, Louisville, USA

Purpose/Objective: To compare an organ preservation (OP) strategy to standard treatment in patients requiring orbital exenteration for orbit-invasive sinonasal cancer. Materials and Methods: All patients treated for locally advanced cancer of the paranasal sinuses at our institution were retrospectively reviewed. Eighteen patients, determined by a multidisciplinary team to require orbital exenteration as part of definitive surgery, were identified. The Kaplan-Meier method was used to estimate overall survival (OS) and progression free survival (PFS). Factors influencing survival were analyzed using proportional hazards regression. Toxicity data, collected weekly during radiation therapy (RT) and at all follow up visits, were graded according to the Common Terminology Criteria for Adverse Events version 3.0.

Results: Twelve patients underwent OP (two refused concurrent chemoradiation and were treated with RT alone), and six patients underwent primary surgery followed by chemoradiation (CRT). Treatment groups were well balanced with respect to age, sex, site, stage, and histology. Performance status was higher in patients undergoing OP (median KPS 80 vs 70, p = 0.04). Four patients in the OP group had complete disease response at time of surgery. Median follow-up was 18.8 months. Crude local control was 67% in patients treated with upfront surgery and 75% in patients receiving OP. Patients undergoing OP had similar median OS (18.77 vs 28.33 months, p = .74) and PFS (16.36 vs 18.27 months p = 0.65) as patients receiving upfront surgery. Patients with higher T-stage had worse local-regional progression free survival (HR 0.76, 95% CI 0.01 - 0.74) regardless of treatment group. No patients receiving neoadjuvant therapy required an upfront orbital exenteration regardless of its amount, is considered. All three systems of grading were tested for inter-observer concordance and prediction of prognosis. Results: Inter-observer concordance for grading ACC according to Perzin et al/ Szanto et al and Spiro et al, proved to be moderate with Kappa Scores of 0.393 and 0.433, respectively. Our alternative grading system yielded inter-observer concordance with a Cohen’s kappa result of 0.990. All systems were comparable in discriminating patients with poor clinical outcome. Histopathological grade proved to be an independent prognosticator. Conclusions: The presence of any solid component in ACC is a negative prognosticator, and can histopathologically be diagnosed with a high reliability. These results suggest to merely register the presence or absence of a solid tumor component since its inter-observer variability is very low, its reproducibility is high and its predictive value is comparable to the traditional grading systems used.

PO-161
Abstract withdrawn

PO-162
Multiple primary malignancies of thyroid and nasopharyngeal carcinoma
N. Sellami1, W. Minejja1, W. Siala1, N. Toumi2, M. Ghorbel3, M. Frihka1, J. Daoud1
1Hopital Habib Bourguiba, Radiation Oncology, Sfax, Tunisia
2Hopital Habib Bourguiba, Oncology, Sfax, Tunisia
3Hopital Habib Bourguiba, Head and Neck Surgery, Sfax, Tunisia

Purpose/Objective: Multiple primary malignancies of thyroid and nasopharyngeal carcinoma are relatively rare with an incidence ranging from 1.8% to 11%. This incidence is increasing in recent decades. This may be the result of progress in diagnostic and therapeutic strategies of cancer. We report 4 cases of multiple primary cancers in the nasopharynx and thyroid. Materials and Methods: We retrospectively reviewed 590 records of patients treated for nasopharyngeal cancer between 1993 and 2014 in the department of Radiation Oncology of Sfax. We found 4 cases of multiple primary cancers involving nasopharyngeal and thyroid carcinoma. Results: In our study, the incidence of the association nasopharyngeal - thyroid cancer was 0.67%. The characteristics of patients are listed in the table below.
Materials and Methods:

Tissues.

Simultaneously maintain the required volume removed.

During the performing of VFLND in the neck were visualized and saved all the most important anatomical structures (internal jugular vein, branch of the accessory nerve, branches of brachial and cervical plexus, great auricular nerve thoracic duct). During operation on the left side thoracic duct was visualized and adequately klipped. Time of operation was not significantly different by standard techniques. Number of remove nodes was 20-35 pieces on one side. There were no intraoperative and postoperative complications. According to lateral metastasis all the patients were treated by radioactive iodine in the postoperative period. During the observation, for three years, recurrent metastases in zone of operation have not been identified. All patients rated the cosmetic effect as excellent.

Conclusions: Thus, according to the result, VFLND, may be alternative to the conventional surgical methods with small amounts high-grade thyroid cancer metastases, without the distribution out of the capsule. Should be performed more detailed study of this technique, as well as develop of criteria for selection of patients for such operations. Also requires a comparative analysis of conventional and videoassisted neck dissection.

PO-164

PACSA: Phase II study of pazopanib in patients with progressive recurrent or metastatic salivary gland carcinoma

D. Cupissol1, C. Even2, J. Fayette3, F. Rolland4, B. Laguerre5, F. Peyrady5, K. Buffard5, F. Bidal8, A. Auperin9, J. Guigay10

1Institut Regional du Cancer, Medical Oncology, Montpellier, France
2Gustave Roussy, Medical Oncology, Villejuif, France
3Centre Leon Berard, Medical oncology, Lyon, France
4Institut de Cancérologie de l’Ouest, Medical oncology, Saint Herblain, France
5Centre Eugene Marquis, Medical oncology, Rennes, France
6Centre Antoine Lacassagne, Medical oncology, Nice, France
7Unicancer, R&D, Paris, France
8Gustave Roussy, Medical Imaging, Villejuif, France
9Gustave Roussy, Bio statistics, Villejuif, France
10Centre Antoine Lacassagne, Medical Oncology, Nice, France

Purpose/Objective: Salivary gland carcinomas of the head and neck (SGCHN) are rare tumors (less than 5% of Head and Neck cancers) including many histological subtypes. SGCHN are treated mainly with surgery and radiation. For patients with recurrent or metastatic (R/M) SGCHN, there is no standard systemic treatment: disease control is usually low with chemotherapy, and only rare objective responses to targeted agents have been previously recorded. Pazopanib, an oral inhibitor of VEGFR, PDGFR and KIT, may be an active agent according to previous data.

Materials and Methods: PACSA is a multi-center phase II single-arm study that aims to evaluate the activity and safety of single agent pazopanib in patients with R/M SGCHN including adenoid cystic carcinoma (ACC) and non-ACC, not amenable to curative surgery or radiotherapy. Patients with confirmed SGCHN (centralized pathological review) and progression within 6 months before inclusion are eligible and receive pazopanib, 800 mg daily until progression. Response is assessed every 12 weeks, according to RECIST 1.0 (centralized review).

Primary endpoint is progression-free survival (PFS) at 6 months. Secondary endpoints include response rate (CR/PR), overall survival, toxicity, time to next therapy, quality of life (QLQ-C30 questionnaire), and modification of tumor growth rate under treatment as compared to before treatment, an innovative endpoint which is assessed with radiological

Table: Characteristics of patients

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>First primary (NPC) Staging(Thyroid) Treatment</th>
<th>Interval between 2 cancers</th>
<th>Second primary (thyroid) Histology Treatment</th>
<th>Evolution</th>
</tr>
</thead>
</table>
| case 1
| case 2
| case 3
| case 4
| 42 years
| 42 years
| 42 years
| 42 years
| T2b N1 M0 Induction CT - RT (70 Gy)
| T2b N2b M0 Induction CT - RT (70 Gy)
| T4 N2b M0 Induction CT - concurrent CT-RT (70 Gy)
| T4 N2b M0 Induction CT - concurrent CT-RT (70 Gy)
| synchronous
| synchronous
| synchronous
| synchronous
| 92 months
| Total Thyroidectomy + neck dissection + Iodine therapy
| Total Thyroidectomy + neck dissection + Iodine therapy
| Total Thyroidectomy + neck dissection + Iodine therapy
| Total Thyroidectomy + neck dissection + Iodine therapy
| In remission at 2 y
| In remission at 13 y
| Living in progression
| Currently in treatment

NPC: nasopharyngeal Carcinoma; CT: Chemotherapy; RT: radiation therapy

Conclusions: The incidence of multiple primary cancers has experienced in the recent years a fairly significant increase. They can be synchronous or metachronous. The most common sites are successively: the digestive system, the pelvis and head and neck. The mechanisms implicated in the genesis of multiple primary cancers are not yet well known. For the association nasopharynx - thyroid, genetic predisposition and exposure to ionizing radiation are the most predisposing factors. The cooccurrence of thyroid cancer in patients treated for nasopharyngeal carcinoma is not associated with a poor prognostic factor, however regular monitoring of these patients allows early detection and therapeutic treatment which improves chances of recovery.

PO-163

Videoassisted functional lateral neck dissection (VFLND) about metastases of high grade thyroid cancer (TC)

A. Polyakov1, I. Reshetov2, F. Svrakov3, Y. Panaseykin4

1Moscow Gertzen Institute, Microsurgery, Moscow, Russian Federation
2I.M. Sechenov First Moscow State Medical University, Plastic surgery, Moscow, Russian Federation

Purpose/Objective: Over the last 20 years the disease of thyroid cancer has doubled; in mainly due to the young and middle age, which mainly observed high grade forms of thyroid cancer. Risk of metastasis in neck nodes reaches 40%, high grade forms of thyroid cancer. The most frequent localization of lateral thyroid cancer metastases are 6, 5, and then 4, 3 groups. Metastasis in the first group is extremely rare and only in advanced stages of the disease. Standard methods of surgery of high grade thyroid cancer with metastases in lateral nodes in the neck, is thyroidectomy, central dissection and selective lateral neck dissection of 2-6 neck groups. For adequate exposition of surgical field at the lateral neck dissection requires a large surgical incision. The young age of the patients, histological type of cancer, and a favorable prognosis all of these factors make us muse on fall.

Materials and Methods: Since 2011 in Herzen Institute was performed 13 VFLND by using the cosmetic access. VFLND were conducted in patients with metastatic papillary Thyroid cancer at age <45 y.o., absence of distant metastasis, lesion of nodes of one side with the diameter of metastases <2 cm., without of reliable signs involvement of the main vascular and rows without departing from the capsule. All patients were female between the ages of 23-45 years, wishing to obtain a minimal cosmetic defect after surgery. During the operation was made a mini incision (in 4-7 cm length) on the posterior edge of the sternoclevicularmastoideus muscle.

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| In remission at 2 y
| In remission at 13 y
| Living in progression
| Currently in treatment

Conclusions: All patients rated the cosmetic effect as excellent.

Then, using videoassisted hardware performed lateral dissection of 3, 4, 5 and 6th cervical group. Nodes were removed en bloc. The quality of dissection was evaluated by routine histological study.

Results: During the performing of VFLND in the neck were visualized and saved all the most important anatomical structures (internal jugular vein, branch of the accessory nerve, branches of brachial and cervical plexus, great auricular nerve thoracic duct). During operation on the left side thoracic duct was visualized and adequately klipped. Time of operation was not significantly different by standard techniques. Number of remove nodes was 20-35 pieces on one side. There were no intraoperative and postoperative complications. According to lateral metastasis all the patients were treated by radioactive iodine in the postoperative period. During the observation, for three years, recurrent metastases in zone of operation have not been identified. All patients rated the cosmetic effect as excellent.

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PO-164

PACSA: Phase II study of pazopanib in patients with progressive recurrent or metastatic salivary gland carcinoma

D. Cupissol, C. Even, J. Fayette, F. Rolland, B. Laguerre, F. Peyrady, K. Buffard, F. Bidal, A. Auperin, J. Guigay

1Institut Regional du Cancer, Medical Oncology, Montpellier, France
2Gustave Roussy, Medical Oncology, Villejuif, France
3Centre Leon Berard, Medical oncology, Lyon, France
4Institut de Cancérologie de l’Ouest, Medical oncology, Saint Herblain, France
5Centre Eugene Marquis, Medical oncology, Rennes, France
6Centre Antoine Lacassagne, Medical oncology, Nice, France
7Unicancer, R&D, Paris, France
8Gustave Roussy, Medical Imaging, Villejuif, France
9Gustave Roussy, Bio statistics, Villejuif, France
10Centre Antoine Lacassagne, Medical Oncology, Nice, France

Purpose/Objective: Salivary gland carcinomas of the head and neck (SGCHN) are rare tumors (less than 5% of Head and Neck cancers) including many histological subtypes. SGCHN are treated mainly with surgery and radiation. For patients with recurrent or metastatic (R/M) SGCHN, there is no standard systemic treatment: disease control is usually low with chemotherapy, and only rare objective responses to targeted agents have been previously recorded. Pazopanib, an oral inhibitor of VEGFR, PDGFR and KIT, may be an active agent according to previous data.

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Primary endpoint is progression-free survival (PFS) at 6 months. Secondary endpoints include response rate (CR/PR), overall survival, toxicity, time to next therapy, quality of life (QLQ-C30 questionnaire), and modification of tumor growth rate under treatment as compared to before treatment, an innovative endpoint which is assessed with radiological
modern tools. Ancillary studies are planned with biomolecular analysis. For the ACC population, a one-stage phase II study design was chosen. The unacceptable 6-month rate of PFS is 20% and the promising rate 40%. 43 patients are to be treated. A total of 13 non-progressions or more at 6 months are required to make the drug worthy of further study (a=0.07, B=0.07). In the non-ACC SGCHN population, assessment of pazopanib activity is exploratory without a predetermined study design, with up to 20 patients. A planned interim analysis of acute toxicities was conducted 3 months after the 14th non-ACC inclusion and results are provided below:

Results: 14 non ACC patients have been enrolled, 13 were eligible: 8 males, 6 females, median age 58 years (45-70), 6 (43%) adenocarcinoma, 2 (14%) salivary duct carcinoma, 1 (7%) acinar cells carcinoma and 5 (36%) other types. The main grade 3 severe treatment-related adverse events were hepatitits in 1 patient (7%), asthenia in 1 patient. The Independent data monitoring committee recommendations were: add euthyroidism as inclusion criteria, resume enrolment of non ACC patients, and continue ACC patients' enrolment. The accrual of patients (52 patients /63 needed) is higher than expected as showed in the following graph.

Conclusions: Completion of patient recruitment and data analyses are awaited.

PO-165 Long-term results of locally-advanced and metastatic thyroid cancer surgical treatment

I. Reshetov, A. Polyakov, A. Golubtsov

1I.M.Sechenov First Moscow State Medical University, Plastic surgery, Moscow, Russian Federation
2P.A.Hertzen Moscow Cancer Research Institute, Microsurgery, Moscow, Russian Federation

Purpose/Objective: Number of patients with recurrence and metastatic thyroid cancer does not decrease in spite of early diagnostic development. Un satisfactory treatment results of such patients (esp. in stage IV) may be improved by modern surgical techniques.

Materials and Methods: The research was conducted in 2000-2012 in P.A.Herzen MSOI in 314 stage III-IV patients, which were arranged into 4 clinical groups. 1st group included 101 patients with T3N0M0 and T4N0M0 stages with continued tumor growth or recurrent thyroid cancer. 2nd group included 120 patients with T3NlaM0, T3NlbM0, T4NlaM0, T4NlbM0 stages, continued tumor growth or recurrence after surgical treatment, with tumor involving surrounding tissues, with metastasis of thyroid cancer in lymphatic nodes of neck and anterior upper mediastinum. 3rd group included 73 patients with recurrence or continued growth of metastasis in lymphatic nodes of neck and anterior upper mediastinum. 4th group included 73 patients with recurrence or continued growth of metastasis in lymphatic nodes of neck and anterior upper mediastinum after surgical or combined treatment.

Results: Long-term results were followed up in 293 patients (93,3%), further clinical history is known in 21 cases (6,7%). Adverse prognostic factors: distant metastasis of medullar cancer, metastasis in lymphatic nodes of neck and upper anterior mediastinum in males, age over 60, were revealed in comparative study of patients' survival rates. Long-term results of treatment of patients with locally-advanced and metastatic thyroid cancer showed equal 10-year survival rate in 1-3 groups: 1st group - 85.7%; 2nd group - 80.1%; 3rd group - 83.3%. Treatment results of patients with distant thyroid cancer metastasis (combined affection) were worse, 10-year survival rate was 49.0%. General 5- and 10-year survival rate were 86,3% and 80,5% respectively.

Conclusions: The developed tactics and strategy of treatment of patients with locally-advanced or metastatic thyroid cancer consists in surgical removal of all accessible focuses of a disease (excluding metastasis in pulmonary parenchyma) with modern physical, vascular, surgical, microsurgical and endoscopic methods of treatment. It removes a direct life treat and offers an opportunity for additional treatment extending life of patients so that most of them reaches 5- and 10-years survival grade.
Conclusions: Uniform classification of rare melanoma types does not exist because of absence of tumor affection accurate measure methods. Main treatment tactics is still surgical including cases of recurrent tumors. Rationality point of regional lymphadenectomy and its' volume is to be discussed individually in every case. Necessity of available chemotherapy and development of modern local methods and targeted therapy as prophylaxis of local recurrence and process generalization.

PO-167
Rational approaches to surgical treatment of head and neck skin melanoma.
A. Polyakov1, O. Matorin1, M. Ratushnyy1, M. Filushin1, K. Kydri1
1PA Gertzen Moscow Research Oncological Institute, Microsurgery, Moscow, Russian Federation

Purpose/Objective: Skin melanomas of head and neck averages 22-46% (according to different authors) of all melanomas. Main treatment strategy is still surgical, for both primary and recurrent tumors it is wide excision. The tumor is removed with adjacent part (on 1 to 3 sm distance from tumor - based on tumor stage) of visually unaffected skin. Hypoderm is also removed in block at a depth of aponeurosis or muscle fascia with a single step plastic.

Materials and Methods: In microsurgical department of PA Gertzen Moscow Research Oncological Institute different types of flaps including advanced and free flaps with vascular pedicles are used to restore defects after wide tumor excision.

Results: Fasciocutaneous defects of scalp are mainly restored with sliding flaps from unaffected scalp area prefabricated with tissue expanders. Combined defects of facial area can be rebuilt with microsurgical free flaps - radial or thoracodorsal musculocutaneous flaps, musculo-serosocutaneous flaps formed from rectus abdominis muscle. Free partial thickness perforated dermal flap (from anterior abdominal wall, humerus, huckle) can be used to restore small defects to avoid scar deformation. Biopsy of sentinel lymph node with lymphphotopic or radio diagnostic drugs is to be performed in case of Clark invasion level is III. In case of morphologically proved invasion of 4 and higher level wide excision of primal tumor with underlying muscle tissue or radio frequency thermal ablation of tumor bed with a full-volume neck lymphadenectomy (1-5 groups) and cellular tissue of preauricular and occipitalis regions are advisable.

Conclusions: Main principles of head and neck skin melanomas are equal to threatening methods of other localizations, but it is important to mention complex anatomical arrangement of tumors requiring in most cases reconstructive operations after wide excisions. The attention must be paid to the point of lymph nodesectomy in cases of invasive melanoma forms.

PO-168
Experience in using radiofrequent thermoablation in tumors of the mouth
A. Polyakov1, O. Matorin1, M. Filushin1, M. Ratushnyy1, F. Sevrukov1
1PA Gertzen Moscow Research Oncological Institute, Microsurgery, Moscow, Russian Federation

Purpose/Objective: Oral cavity cancer is a heterogenous condition not only in terms of the type of tumors and localizations, but also in the incidence, risk factors, optimal treatment methods and results. That is the reason why it is important to search for new and modern treatment approaches for this difficult group of patients, and radiofrequent thermo ablation is one of them.

Materials and Methods: 50 patients were treated for oral cavity cancer and tongue at our medical facility. Primary evaluation of the tumors was made using ultrasound, CT and needle biopsy. The histological structure of the tumors: squamous cell cancer. 70% of the patients were male, 30% - female. The age was between 25-78 years. The stages were as follows: 2 stage - 50%, 3 stage - 40%, 4 stage - 10%. 80% of the tumors were primary, and 20% were recurrent tumors of a previous disease. The previous treatment of these patients was radio therapy or combined chemo- and radiotherapy. Depending on the tumor location, the patients received either endotracheal general anesthesia or local potentiated infiltrative anesthesia. The follow up period for these patients varied from 2-64 months.

Results: The efficiency of the performed treatment was confirmed by the physical examination, follow up ultrasound studies and follow up core-needle biopsy. The follow up exams were scheduled once in every three weeks, which allowed a timely evaluation of the efficiency of the performed treatment and allowed to notice any complications in time. The mean number of procedures performed for each patient - 3. The follow up period for these patients varied from 3-64 months. 28 patients were disease free during that period (note that a disease free period longer than 3 years was observed in 11 patients) stabilization of the disease without further local growth of the tumor was observed in 12 patients (RFA was also performed), further growth of the tumor was observed in 10 patients. The complications of the procedures were as follows: 2 hemorrhages that required clipping of the external carotid artery on the affected side were observed at 10-14 days after the procedure. 5 patients had superficial dry skin necrosis in the area where the electrodes were applied, but it didn't require surgical intervention.

Conclusions: The procedure proved to be efficient and brought positive results in patients with tumors of this localization and should be used in a multidisciplinary treatment approach. RFA can become an important step in surgical treatment of patients with oral cavity tumors.

PO-169
Fine needle aspiration biopsy of thyroid at the Institute of Oncology Aldenora Bello-São Luís-Brazil
S.P. Silva1, L.A.R. Porfírio2, L.K.R. Porfírio1, L.N.R. Porfírio1, D.V.S. Silva1, M.S. Azevedo1, A.A. Lourenço1, R.R. Silva1
1Institute of Oncology Aldenora Bello, Head and Neck Surgery Department, São Luís, Brazil
2Federal University of Rio de Janeiro, Head and Neck Surgery Department, Rio de Janeiro, Brazil
3Institute of Oncology Aldenora Bello, Pathology Department, São Luís, Brazil

Purpose/Objective: Epidemiological studies suggest that about 4% of women and 1% of men have palpable thyroid nodule. The vast majority is benign, however, 5% to 10% are malignant lesions, demonstrating the importance of adequate management of thyroid nodules. A fine needle aspiration biopsy (FNAB) is the initial diagnosis method with higher accuracy and cost-benefit for the distinction of the nature of the lesion in malignant or benign and subsequent appropriate treatment. This study aims to determine the diagnostic accuracy of fine needle aspiration biopsies performed at the Institute of Oncology Aldenora Bello (IMOAB), comparing them with the histopathological finding of their surgical specimens.

Materials and Methods: 93 patients were submitted to clinic, cytologic and histopathologic analysis. Patients were treated surgically in these cases: malignant FNAB result; indeterminate follicular lesion, follicular neoplasm or suspicious; two punctures with unsatisfactory samples; or benign lesion in patients who presented with clinical examination or ultrasound risk factors for malignancy, aesthetic or functional disorders. Histopathologic examination was considered the gold standard for diagnosis.
Results: FNAB samples and biopsies from 93 patients were analyzed. Among the histological results, 43 (46.2%) had diagnoses of benign lesions and 50 (53.8%) were classified as malignant. Statistical analysis was performed comparing the FNAB findings with histopathology. Thus, the following results were found: 8.64% False positive; 12.34% False Negative; sensitivity (75%); specificity (82.9%); positive predictive value (81%); negative predictive value (77.27%); accuracy (79%).

Conclusions: Nodular thyroid disease is highly prevalent in the general population and therefore selective surgical management of patients with thyroid nodules is necessary. A fine needle aspiration biopsy, associated with appropriate clinical evaluation, is successfully used as an initial diagnostic tool in these patients. We conclude with the study that the FNAB is a proper method for the low cost, simple implementation and has good diagnostic accuracy and was able to establish trust with the diagnosis in 68.81% of cases, reducing the number of surgeries and increasing the number of operated carcinomas.
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