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INTRODUCTORY LECTURE

I1
The surgical resection margin

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Head & Neck Oncology 2009, **1(Suppl 1):**I1

In the treatment of cancer the fundamental surgical goal is to remove all local malignant disease and leave no residual malignant cells. Studies have demonstrated the benefit of achieving negative resection margins in terms of disease free local recurrence and overall survival. The surgical margins for Head & Neck cancer may vary widely depending on the site of disease. This variation reflects the biological and anatomical environment of the tumour site at macroscopic and microscopic levels.

There is no accepted standard for the quantity of normal tissue to be removed and the effect of positive margins on recurrence rate appears to be considerably dependent on the site of the tumour. The extent of tumour volume resection is determined by the need for cancer control and the peri-operative, functional and aesthetic morbidity of the surgery.

Resection margins are assessed intra-operatively by frozen section and retrospectively after definitive histological analysis of the resection specimen. There are limitations to this assessment. The margin may not be consistent in three dimensions and may be susceptible to errors in sampling and histological interpretation. Assigning the true excision margin may be difficult due to post-excision changes secondary to shrinkage and fixation.

Local recurrence occurs even among tumours with extensive histological demonstration of adequate resection margins. Sites with significant recurrence rates after negative resection margins are oral cavity, submandibular region, tonsil and pharynx. Therefore, it is accepted that cancers at these sites require larger margins of excision than tumours elsewhere in the head and neck.

Achieving the histologically adequate margin is insufficient to predict clinical outcome. Multiple parameters in the histological assessment have been developed and refined to predict outcome based on a number of variables including pattern of invasion, keratinisation, nuclear pleomorphism and mitotic rate. Recently molecular technology has been employed to provide a more objective assessment of the margins but these techniques are not yet validated. The current approaches to histological risk assessment and evaluation of the surgical margin in Head & Neck cancer and the limitations will be discussed.

ORAL PRESENTATIONS

O1
Elastic light scattering spectroscopy for the detection of pre-cancer: an overview

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Optical spectroscopy mediated by fibre-optic probes can be used to perform non-invasive, or minimally-invasive, real-time assessment of tissue pathology *in-situ*. The method of elastic-scattering spectroscopy (ESS) is sensitive to the sub-cellular architectural changes, such as nuclear grade and nuclear to cytoplasm ratio, mitochondrial size and density, etc., which correlate with features used by pathologists when performing histological assessment. The ESS method senses those morphology changes without actually imaging the microscopic structure. Clinical demonstrations of ESS have been conducted in a variety of organ sites, with promising results, and larger-scale clinical studies are now ongoing. We have recently developed an analytical model that extracts, from the ESS spectra, the underlying physical correlates of the tissue relating to disease.

O2
The clinical application of elastic scattering spectroscopy in the head and neck

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Optical diagnostics have proved to be a reliable resource that can be used to give an instant diagnosis of soft and, more recently, hard tissue diseases. In the field of head and neck malignancy, most of the experimental spectroscopy work has been performed using fluorescence spectroscopy, Raman spectroscopy, elastic scattering spectroscopy, micro-endoscopy and optical coherence tomography.

Elastic scattering spectroscopy (ESS) has proved to be a promising method for detecting premalignant and malignant changes in oral tissues, with high sensitivity and specificity. Several head and neck tissues, including lymph nodes and bones,

have been interrogated using ESS, which detects changes at the cellular and subcellular level, with very promising results.
We describe our experience in the clinical application of elastic scattering spectroscopy in the head and neck.

O3
Fluorescence spectroscopy and fluorescence imaging for tissue diagnostics – principles and methods

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In an attempt to establish intraoperative tissue diagnosis, tools and methods for an "optical biopsy" have been proposed, some of them exploiting fluorescent properties of endogenous or exogenous fluorochromes.
Fluorescence spectroscopy tries to capture characteristic spectral features of fluorochromes and correlate these with the disease state. Several mathematical methods have been proposed to evaluate recorded spectra to maximize the discrimination between "normal" and "malignant". However, they ignore the influence of tissue parameters on the recorded spectra. Some of these parameters may provide some correlation with the disease progress (epithelial thickness, loosening of collagen matrix), others may cause false positives; because "truly malignant" and "harmless change" have the same influence on the spectral signatures (e.g. blood absorption). Therefore, it may be desirable to eliminate the influence of some of these parameters, which has an influence on the design of the probes used to record the spectra. "Differential pathway spectroscopy", "intrinsic fluorescence" or "single fibre fluorescence" try to solve these problems.
Fluorescence imaging aims at highlighting malignant tissue, especially where it is not evident under white light in a large field of view. Autofluorescence as well as drug-induced fluorescence can be detected and displayed with commercial equipment. They usually rely on capturing fluorescence in one or two colour channels and remission in another channel. Sophisticated image processing to quantify fluorescence or eliminate disturbing signal is only slowly becoming available.
In order to fulfil the requirements for an "optical biopsy", fluorescence techniques will have to be combined with OCT, acousto-optics and con-focal or two-photon techniques.

O4
Diagnosis of head & neck malignancy using fluorescence spectroscopy and imaging

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Upper aerodigestive tract (UADT) carcinomas continue to be the 5th most common cancer. Early diagnosis is often delayed as tumour precursors or early cancers are hardly visible and not picked up by common imaging methods. Fluorescence spectroscopy and imaging seems able to improve the detection and delimitation of these lesions.
Fluorescence diagnostic methods usually pick up a "mixed bag" of signals from endogenous fluorophores such as tryptophan, collagen, elastin, NADH and FAD. As some of these show a tumour specific distribution, this can be exploited to distinguish tissues in vivo. The fluorescence contrast is even slightly enhanced by using exogenously applied fluorescent markers or their precursors (e.g., 5-aminolevulinic acid induced Protoporphyrin IX). Even though the sensitivity to detect malignant lesions seems to be improved by combining fluorescence diagnostic methods with normal inspection according to the literature and to our own experience, the methods are rather unspecific as chronic inflammations cause results similar to neoplastic disease.
Recent advances include the possibility to extract true spectra of single fluorophores ("intrinsic spectra") by mathematically eliminating the undesired influences of scattering and absorption. As well, tumour-specific enzymes are about to be specifically targeted by fluorescent markers (so called "smart probes") in order to improve both sensitivity and specificity.
Due to the lack of specificity, fluorescence spectroscopy and imaging are so far mostly feasible for screening purposes. If combined with other optical techniques such as ESS or OCT, however, a comprehensive non-invasive tissue diagnosis seems possible.

O5
Optical coherence tomography: challenge and opportunity

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Optical coherence tomography (OCT) is an imaging modality based on coherence-domain optical technology. OCT takes advantage of the short coherence length of broadband light sources to perform micrometer-scale, cross-sectional imaging of biological tissue. OCT is analogous to ultrasound imaging except that it uses light rather than sound. The high spatial resolution of OCT enables noninvasive *in vivo* "optical biopsy" and provides immediate and localized diagnostic information. The first *in vivo* endoscopic OCT images in animals and humans were reported in 1997. Since then, a number of clinical applications for endoscopic OCT imaging of respiratory, urogenital, and gastrointestinal tracts have been reported by several groups. This presentation will review the principle of time domain and Fourier domain OCT and the current state-of-the-art OCT technology.
Despite the recent development of Fourier domain OCT that significantly increases imaging speed and sensitivity, the OCT system that achieves both high speed and high sensitivity simultaneously at 1.3 μm is not currently available. I will describe the development of a Fourier-domain-mode-lock (FDML) swept

source based OCT system that can achieves high speed (>100 kHz A-scan rate) and high spatial resolution (<4 μm) simultaneously. In addition, the development of various miniature scanning probes that allow high-speed 3-D OCT imaging will be reported. Finally, a non-iterative digital focusing method to alleviate the compromise between lateral resolution and depth measurement range, which allows high lateral resolution over the full depth measurement range will be described.

O6
The clinical application of optical coherence tomography in the head and neck

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Head & Neck Oncology 2009, **1(Suppl 1):**O6

Optical coherence tomography is an imaging modality that uses light to determine cross-sectional anatomy in turbid media such as living tissues. The axial resolution of conventional OCT exceeds 10 μm and allows identification of specific structural features of the tissue such as the epithelium, basement membrane, lamina propria, and various specialized structures such as glands and ducts. This presentation will review the University of California Irvine experience with OCT imaging in the head and neck (2002–2009) encompassing over 400 subjects in the operating room, ICU, and clinic. Imaging in adults, paediatric cases, and neonates will be discussed as well as instrumentation for use in surgery and the office.

The major clinical applications of OCT in otolaryngology-head and neck surgery that we have explored are: 1) examination of the true vocal folds with the aim of identifying and characterizing pre-cancerous and early stage malignancy and 2) examination of the paediatric/neonatal subglottis. Early stage laryngeal cancer is very difficult to differentiate from many disorders that mimic it, including chronic laryngitis. Biopsy can permanently destroy vocal quality and requires general anaesthesia; thus surgeon is reluctant to obtain diagnostic tissue specimens. OCT imaging has the potential to provide surgeons with a means to better establish indications for microsurgical biopsy, monitor progression of disease, and guide therapy. The subglottic larynx is the "choke" for the neonatal airway and oedema or scar in this region is a major cause of failed extubation. Differentiating oedema from scar is impossible without surgical microendoscopy. OCT imaging can discern subtle differences in the subglottic mucosa and hopefully provide a means to identify patients at risk for extubation failure, and ideally in the future be used in the neonatal ICU to optimize endotracheal tube management.

O7
Differential pathlength spectroscopy for diagnosis of head and neck cancer

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Head & Neck Oncology 2009, **1(Suppl 1):**O7

The development of optical techniques for non-invasive diagnosis of cancer is an ongoing challenge to biomedical optics. For head and neck cancer we see two main fields of potential application

1) Screening for second primaries in patients with a history of oral cancer. This requires imaging techniques or an approach where a larger area can be scanned quickly.

2) Distinguishing potentially malignant visible primary lesions from benign ones. Here fiberoptic point measurements can be used as the location of the lesion is known.

This presentation will focus on point measurement techniques.

Various techniques for point measurements have been developed and investigated clinically for different applications. Differential Pathlength Spectroscopy is a recently developed fiberoptic point measurement technique that measures scattered light in a broad spectrum. Due to the specific fiberoptic geometry we measure only scattered photons that have travelled a predetermined pathlength. This allows us to analyse the spectrum mathematically and translate the measured curve into a set of parameters that are related to the microvasculature and to the intracellular morphology. DPS has been extensively evaluated on optical phantoms and tested clinically in various clinical applications.

The first measurements in biopsy proven squamous cell carcinoma showed significant changes in both vascular and morphological parameters. Measurements on thick keratinized lesions however failed to generate any vascular signatures. This is related to the sampling depth of the standard optical fibers used. Recently we developed a fiberoptic probe with a ~1 mm sampling depth. Measurements on several leukoplakias showed that with this new probe we sample just below the keratin layer and can obtain vascular signatures. The results of a first set of clinical measurements will be presented and the significance for clinical diagnostics will be discussed.

O8
Raman spectroscopy in clinical diagnosis of head & neck pathology

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Head & Neck Oncology 2009, **1(Suppl 1):**O8

Introduction: Applications of Raman spectroscopy in the life sciences are still in the early stages of development. Raman spectroscopy is being investigated in a broad spectrum of biological and toxicological sciences. In oncology Raman is being investigated as a diagnostic tool for characterising cancer cells and distinguishing these from normal cells. Raman spectroscopy has the distinct advantage over other optical techniques that it provides information on molecular composition and structure of living tissue. There is a strong rationale for using Raman spectroscopy in epithelial cancer. Although Raman spectroscopy has been investigated for several decades, clinical studies are scarce.

Materials and methods: The existing literature on Raman spectroscopy was evaluated with a Mesh search in Pub med using "Raman spectroscopy" and "Neoplasms" and "Humans" as keywords.

Results: Pub med generated 166 hits on these Mesh terms of which 23 were reviews. Papers were selected to illustrate the most relevant progress in Raman Spectroscopy.

Conclusion: It is apparent that Raman spectroscopy has great potential in becoming an important optical technique in cancer diagnostics. However, there are major technical challenges to be overcome, specifically the design of the fibre-probe and signal to noise ratio. In this presentation our own experience with in vivo

Raman spectroscopy as well as a survey of the literature will be presented to elucidate the current status of this versatile technique.

O9
Role of histopathologic and phenotypic assessment in the development and validation of optical diagnostic devices for head and neck mucosal lesions

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Head and neck squamous carcinoma, including the oral cavity, is the sixth most common cancer worldwide with approximately 270,000 new oral cavity tumours per year. Unfortunately, the majority of these tumours present in late stage with the attended functional, psychological and economic costs on their victims. It's clearly evident that screening and early detection of the cancer and its early precursors have the potential to reduce the morbidity and mortality of this disease. In that context, current oral examination methods including incandescent light or toluidine blue, reflectance visualization and illumination with chemiluminescent light source, are largely subjective, dependent on the experience of the examiner and are considered ineffective tools in primary care settings.

Autofluorescence imaging has recently been shown to improve the detection of premalignant and malignant oral lesions. This method is based on the illumination in the absorption of tissue fluorophore molecules (NADH and FAD in the epithelial layer and collagen, and elastin in the stroma) in ultraviolet visible spectrum leading to the emission of lower energy photon that can be detected as fluorescence from the oral surface mucosa. Studies of these methods in normal oral mucosa have shown increased green fluorescence in comparison to neoplastic lesions upon ultraviolet (UV) or near UV light source. The histopathologic manifestations and heterogeneity of oral squamous lesions and the confounding factors for the validation and the clinical applications of autofluoresence imaging will be presented and discussed.

O10
Ploidy analysis post Sudbø – where are we now?

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Head & Neck Oncology 2009, **1(Suppl 1):**O10

In January 2006 the medical research world was rocked by the discovery that a Norwegian Oncologist, Jon Sudbø, had committed extensive scientific fraud. Four papers in three top medical journals had to be retracted. Two of these papers, both published in the New England Journal of Medicine, described how aneuploidy could be used as a prognostic marker in pre-malignant oral epithelial lesions. There was widespread fallout from this scandal, one of the main casualties being the general reputation of ploidy analysis. However, DNA cytometry research has continued and results suggest that ploidy analysis may well be useful as a screening and prognostic marker in a variety of malignant and pre-malignant conditions. In 2008 Torres-Rendon *et al* published a further study examining the use ploidy as a prognostic marker in oral epithelial dysplasias. Their results, although not as impressive as Sudbø's, do suggest that ploidy analysis is a potentially useful prognostic marker in pre-malignant oral epithelial lesions.

O11
Optical technologies for detection and diagnosis of oral neoplasia

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The goal of our research is to develop an approach to early detection and diagnosis of oral neoplasia using optical-based technologies such as fluorescence spectroscopy and imaging, high-resolution microendoscopy and molecularly-targeted optical contrast agents. Although patients with early disease have better chances for cure and functional outcome, most patients present with advanced tumours when treatment is less successful and often causes severe deficits in speech, swallowing, facial appearance and quality of life. To improve outcomes we must improve detection and diagnosis of early neoplastic changes. Changes in tissue architecture, morphology, and molecular composition that occur during carcinogenesis also produce changes in the optical properties of tissue. These changes can be detected non-invasively, in vivo, and in near real-time using optical spectroscopy and imaging. Our research group has developed multi-spectral imaging devices for wide field visualization of early changes in oral mucosa. We are investigating whether these devices can improve the clinician's ability 1) to improve visualization of early neoplastic changes in oral mucosa that can be difficult to see using normal white light examination in community settings, 2) to choose optimal sites within lesions to perform biopsies, and 3) to visualize the peripheral margins of disease. We have also shown that using computer algorithms and disease probability maps, optical imaging and spectroscopy can provide objective discrimination between normal and abnormal oral mucosa with good sensitivity and specificity – similar to that of oral cancer specialists. We are now developing simplified optical devices to use in screening and diagnosis in community settings.

In addition, we are evaluating the use of molecularly targeted optical contrast agents for non-invasive diagnosis and molecular characterization of oral mucosal lesions. These contrast agents can potentially be used in conjunction with portable microendoscopes and confocal microscopes that have sufficient resolution to visualize cellular features in vivo, to provide non-invasive "optical biopsies" of suspicious areas.

O12
Spectral scatter scanning system for surgical margin detection

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Tumour margin detection in real time without the use of additional molecular stain would be desirable. Surgical use of a

microscopy tool would be ideal, but most systems focus on microscopic disease evaluation, whereas tools for macroscopic scanning of tissue such as enhanced endoscopy imaging are less well developed. A raster scanning scatter spectroscopy system has been evaluated for imaging the spectral signature remitted from tissue, with an online classification algorithm, which maximizes the ability to identify regions of tumour from regions of normal tissue. The system uses a wide band of wavelengths from 400 nm up to 700 nm, and recovers the scatter power, scatter amplitude, and absorption species, from the reflectance from a 100 micron spot, allowing imaging of tissue a high frame rate. The system uses dark field illumination and spectrometer detection in the emission channel together with a scanning mirror. The early prototypes of the system were tested on pancreas tumours and prostate tumour margin detection, and current work is ongoing in breast cancer margin delineation. The automated tissue classification from the data uses a k-nearest neighbours classification, to provide tissue delineation.

O13
Microimaging FT-IR of Head and Neck Tumours. The case of salivary glands

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The potential role of IR spectroscopy in biomedical science has been exploited to distinguish different biomolecules by probing chemical bond vibrations and using these molecular and sub-molecular patterns to define and differentiate pathological from healthy samples.

This technique aims to further exploit the potentiality of infrared spectroscopy in isolating and defining spectral profiles in salivary glands attributable to various kinds of cancer: Warthin tumour, polymorphous low-grade adenocarcinoma, oral epithelium with dysplasia, adenoid cystic carcinoma, lymphoma, and the corresponding healthy tissues. Thirty three samples from patients with diagnosed salivary gland pathology were analyzed. Two adjacent sections of tissues (5 μm thickness) were used for both histopathological and FTIR analysis.

Spectral data were achieved with Perkin Elmer (PE) Spectrum One FT-IR and Spotlight FT-IR Imaging System 400 spectrometers. Data handling: PE Spectrum v.6.3.1, Grams AI (Galactic) and Pirouette 4.0 (Imfometrix), PE Hyper View Images software. Changes were monitored at the molecular level, probing spectral markers such as Amide I and II, phosphate, nucleic acids, and carbohydrates vibrational modes.

In order to further verify the reliability of our classification, all the spectra from cancerous regions were mixed with those from zones characterized by other tumours obtaining a HCA grouping in excellent agreement with their biochemical and histological characterization.

The results once again demonstrates the capability of infrared microspectroscopy imaging, in combination with multivariate data analysis, to highlight even subtle biochemical and morphological changes, distinguishing various kinds and grades of neoplasia in human tissues. The rapid images acquisition at a high-spatial resolution can be fully satisfied with the use of multi detectors Spotlight system or synchrotron light sources operating at and down the diffraction limit. On considering this and our previous reports, the potentiality of spectral analysis in the study of head and neck neoplasia can be outlined. The complexity of human tissues requires more experimental efforts and statistical evidence to unambiguously formulate a diagnosis of a pathology at a molecular level, mainly at an early stage, this technique has been a valid and synergistic support to the classical histopathological screening.

O14
Characterization of laryngeal carcinoma by confocal endomicroscopy

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Aim: Confocal Endomicroscopy (CEM) is a non invasive imaging tool enabling "optical biopsies" of tissues at cellular level. Clinical studies have successfully reported the accuracy of CEM for the characterization of gastrointestinal, dermatologic and ocular diseases. In this study, we assess the potential use of endomicroscopy in combination with fluorophores clinically approved, to characterize premalignant and malignant lesions in human larynx.

Materials and methods: Twenty-seven fresh pharyngo-laryngectomy surgical specimens were obtained. Normal mucosa, premalignant lesions, and tumoral squamous cell carcinoma were analysed. Five different dyes able to stain cell structures or extracellular matrix were evaluated alone or combined. *En face* images were achieved using both fibered confocal microscopy and conventional confocal microscopy. CEM and confocal images were then compared to the corresponding histological sections.

Results: In normal mucosa samples, a homogeneous and regular nuclear distribution was showed in squamous epithelium with both CEM and confocal imaging. Expected changes in cell density were also seen in basal, intermediate and superficial layers. Imaging of squamous cell carcinoma provided clear information on the heterogeneous distribution of tumour cells surrounded by stroma. Cellular anomalies and disorders of keratinisation such as dyskeratosis and keratin pearls were also discerned by CEM and the images corroborated with histological data.

Conclusion: Our results demonstrated the promising use of fluorescence endomicroscopy for discriminating cancerous and non cancerous region in larynx.

O15

Early experience with in-vivo optical coherence tomography for differentiating lesions of the upper aerodigestive tract

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Head & Neck Oncology 2009, **1(Suppl 1):**O15

Objective: In vivo detection of dysplastic or early invasive mucosal changes is expected to greatly reduce both morbidity and mortality of oral and pharyngeal cancer. Optical Coherence Tomography (OCT) seems to be well suited for this application.
Methods: In this ongoing study, 28 patients with a total of 34 primary, flat mucosal lesions of the upper aerodigestive tract (OADT) were prospectively examined using a time-domain, in vivo OCT (Niris®, Imalux Corporation, USA; lateral resolution 25 μm/axial resolution 15 μm) and the results were compared to the histopathological reports on subsequent tissue biopsies from the same areas. Additionally, an intraoral screening was performed on 52 healthy volunteers.
Results: On the OCT images, surface structures such as the keratin and epithelial layer, the epidermal/dermal junction and areas of cellular crowding were clearly identifiable and showed a good correlation to the histopathological slides down to a depth of approximately 1.5 mm. Of 34 lesions investigated so far, 2 out of 2 early malignant lesions as well as 29 out of 32 non-/premalignant lesions could be correctly differentiated using OCT. The screening resulted in a high degree of variability in the physiological thickness of intraoral epithelium (ø126 μm at the floor of mouth to ø487 μm at the lateral border of tongue).
Conclusion: From these results, the method seems to hold great promise for early in vivo tumour diagnosis and depth measurement in early invasion. Further efforts are currently being undertaken for an enhancement of image quality and contrast.

O16

Immediate ex-vivo optical coherence tomography of suspicious oral lesions

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Background: Optical biopsy systems have been investigated for various clinical applications; however the main interest is in the diagnosis of premalignant lesions.
The aim of this study was to compare findings of optical coherence tomography (OCT) with histopathology of various oral lesions to see if this technique could be used as an adjunct or alternative to histopathology in assessing oral dysplasia. The technique is a non-invasive interferometric tomographic imaging modality which allows millimetre penetration with micrometer-scale axial and lateral resolution.
Materials and methods: Suspicious oral lesions, from 87 patients, were excised and subjected to Swept-Source Fourier-Domain OCT. The acquired OCT images were then compared with histopathology images.
Results: Epithelium, basement membrane, lamina properia, microanatomical histological structures and pathological processes were clearly identified. Normal microanatomical structures identified in these tissues included an overlying keratin layer, papillae, ducts, glands, and blood vessels. Regions of pathologic features studied included leukoplakias, and erythroplakias. Areas of architectural changes were clearly visible and correlated well with the histopathological slides to a depth of approximately 1.5 mm.
Conclusion: This study confirms the feasibility of using OCT to identify various histological structures as well as changes that occurs in these tissues. These preliminary results suggest that OCT may be able to identify dysplasia in oral tissues.

O17

Qualitative diagnostics of oral mucosa by means of multiple fluorophore analysis

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Introduction: Early detection of oral cancer generally occurs by taking a biopsy. The measurement of specific autofluorescence of endogenous fluorophores represents a non invasive method to assess malignant tissue in terms of an "optical biopsy".
Materials and methods: We performed fluorescence measurements of oral mucosa tissue on 19 subjects with a clinical suspicion of a malignant lesion, as well as on 7 healthy controls. A mercury vapour lamp, equipped with appropriate filter sets, was used for the excitation and spectroscopic detection of endogenous fluorophores (NADH, FAD, tryptophan). Additionally, white light remission spectra were recorded from each site. This enabled the calculation of intrinsic fluorescence spectra. Spectroscopy results were then compared to histopathological findings of the subsequently excised lesions.
Results: Quantitative analysis indicated intrinsic fluorescence spectra of endogenous fluorophores from (pre)malignant mucosa to present significant intensity differences compared to healthy tissue. NADH and FAD in particular showed tumour specific fluorescence intensity profiles whereas for tryptophan, no distinct spectral differences were observed. Mucosa of healthy controls yielded similar spectral patterns as did macroscopically innocuous tissues of patients presenting with neoplasia.
Conclusion: The results of this study suggest that MFA, in conjunction with an adequate screening method (e.g. autofluorescence imaging), might be a suitable tool for the discrimination of early neoplastic changes within the oral mucosa.

O18

Fluorescence kinetics of Foscan, Fospeg and Foslip in the window-chamber model

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Head & Neck Oncology 2009, **1(Suppl 1):**O18

Introduction: Foslip and Fospeg are new formulations of the photosensitzer m-THPC, intended for use in Photodynamic Therapy (PDT) of malignancies. Foslip is m-THPC bound to conventional liposomes, Fospeg consists of m-THPC bound to pegylated liposomes. Possible differences in tumour-fluorescence and vasculature kinetics between Foslip, Fospeg and Foscan were studied using the rat window-chamber model.
Materials and methods: In 18 rats a dorsal skinfold window-chamber was installed and a mammary carcinoma was transplanted in the subcutaneous tissue. The dosage used for intravenous injection was 0.15 mg of m-THPC for each formulation. At 7 time-points after injection (5 minutes – 96 hours), mTHPC-fluoresence at its absorption-peak and auto-fluorescence were detected with a CCD. After correction, m-THPC fluorescence images were achieved. Fluorescence intensities of 3 different regions of interest (ROI) were assessed; tumour-tissue, vasculature and surrounding connective tissue.
Results: Shortly after injection vascular m-THPC fluorescence was high for Foscan and Fospeg but not for Foslip. The latter showed a gradual increase in fluorescence. All photosensitizers showed different fluorescence intensity curves in time. Fospeg had higher m-THPC fluorescence in tumour tissue ($p < 0.05$) between 2 and 8 hours and showed this trend at later time-points compared to the other photosensitizers. Maximum tumour fluorescence is reached at 48 hours for Foslip and 24 hours for Foscan and Fospeg. No photosensitizer showed a significant difference between the tumour and surrounding tissue fluorescence.
Conclusion: There are differences in fluorescence intensities of Fospeg, Foslip and Foscan at all time-points. Pegylated liposomes showed higher uptake in tumour. No photosensitizer showed tumour-selectivity.

O19

Interrogation of skin pathology using elastic scattering spectroscopy

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Introduction: Optical biopsies have been shown to be very effective in providing real time, in situ and non-invasive diagnosis of various tissue pathologies. In the head and neck various tissues have been interrogated using this modality including suspicious oral lesions, tumour resection margins and metastatic lymph nodes.
Elastic scattering spectroscopy (ESS) is one of the optical modalities used to identify inflammatory, ischaemic, premalignant and malignant malformation through changes on the cellular and subcellular level.
The aim of this study was to see if ESS could be used to identify benign and malignant skin lesions.
Materials and methods: Elastic scattering spectroscopy involves firing a xenon-arc lamp light into tissues using a fibre-optic probe. Light undergoes single or multiple scattering events and is then collected by the same probe. The resultant generated spectra are then compared to gold standard histopathology.
In this study, facial skin lesions acquired from 73 patients were subjected to in vivo elastic scattering spectroscopy. Lesions were then surgically resected. The majority of the lesions were classified into four categories: basal cell carcinoma, seborrhic keratosis, fibroepithelial polyp and intradermal nevi.
Results: Results showed that ESS can differentiate between normal and pathological skin conditions as well as benign and malignant skin conditions.
Conclusion: This technology holds great promise. A larger body of data is required to achieve higher sensitivity and specificity. Future data will be acquired from malignant melanoma lesions to enable comparison with benign pigmented skin conditions.

POSTER PRESENTATIONS

P1

Optical diagnostic techniques in the head and neck

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Optical biopsies can be acquired through different modalities; each has it own mechanism of action and requires different modes of data analysis. However, they share the ability of being able to provide a real time, non-invasive and *in situ* optical signature. Most of these techniques have been applied only in clinical trials and are yet to be employed in clinical practice, with the exception of fluorescence spectroscopy. Results from these trials are very promising, and current results indicate the possibility of these techniques being applied in clinical practice in the next few years. This could have a great impact on diagnostics, by reducing the histopathology workload, reducing patient's anxiety, and allowing rapid surgical or adjuvant intervention.
Elastic scattering spectroscopy (ESS) has proved to be a promising method for detecting premalignant and malignant changes in oral tissues, with high sensitivity and specificity. Several head and neck tissues, including lymph nodes and bones, have been interrogated using ESS, which detects changes at the cellular and subcellular level, with very promising results. Fluorescence spectroscopy, unlike ESS, can identify changes

through the fluorophores detected in the tissue, and has been found to be very accurate in detecting oral dysplasia. Raman spectroscopy can detect biochemical changes in tissue, but it has limited clinical applications due to its weak signal. The first application of Microendoscopy in the head and neck was described by Upile et al. at University College Hospital, London; resected tumour margins were examined and the results were impressive; however, a fundamental understanding of histopathology is essential for achieving a high sensitivity and specificity.

P2
Optical coherence tomography in the diagnosis of oral dysplasia

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To date histopathological examination has been considered the gold standard for diagnosing early dysplastic to late cancerous lesions. The prime concern for early detection of the cancer and its precursors in patients is to ensure the appropriate treatment in response to disease progression and also to improve the survival and prognosis. The time taken for conventional invasive histopathological analysis is about 1–2 weeks, whereas the spread of the disease may require diagnosis in real time. Recently new optical non invasive methods has had been introduced to acquire biopsies through different modalities through which diseased tissues can be distinguished from healthy tissues in real time. Optical diagnosis techniques have proved to be a reliable method that can be used to obtain instant diagnosis of soft and recently hard tissue pathologies. During the past few decades most of the experimental spectroscopy work has been performed in head and neck malignancy using Fluorescence spectroscopy, Raman spectroscopy, Elastic scattering spectroscopy, Micro-endoscopy and Optical coherence tomography. All these modalities have shown a marked increase in the sensitivity and specificity when compared to both clinical and histopathological analysis with promising results. Optical coherence tomography is a non invasive, interferometric, topographic imaging modality which allows the millimetre penetration with millimetre-scale axial and lateral resolution. Optical coherence tomography findings when compared with the histopathological results of suspected oral lesions confirm the feasibility of optical coherence tomography to detect the architectural changes in pathological tissues.

P3
Fluorescence spectroscopy in the detection of oral dysplasia

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Head & Neck Oncology 2009, **1(Suppl 1):**P3

Introduction: Fluorescence spectroscopy (FS) is a non-invasive technique which can be used to distinguish normal from abnormal tissue and can identify at an early stage dysplastic changes as well as provide clinical screening in real time without the need for tissue removal or processing.

Modalities: All tissues fluoresce due to the presence of fluorescent chromophores (fluorophores) within them. The commonly fluorophores are NADH, collagen, elastin and co-factors such as flavins (FAD, FMN). FS can detect these substances and provide characteristic spectra that reflect biochemical changes within the tissues. There are three main ways to obtain fluorescence, autofluorescence (induced by UV light) Laser-induced and enhanced/dye which can be by either topical or systemic application of 5-aminolaevulinic acid (5-ALA). Dysplastic and malignant tissues, as well as having different spectral characteristics, tend to have increased red fluorescence and decreased green fluorescence. Therefore, significant increase in the red/green fluorescence ratio is an accurate predictor of dysplasia and malignancy.

Instrumentation in FS consists of a light source such as lamps, a fluorescence interference filter and an optical endoscope for both illumination and detection of the tissue fluorescence. The eyepiece of the endoscope is connected to a highly sensitive single chip, charge-coupled device (CCD) colour camera integrated with red/green/blue (RGB) mosaic filter and the images can be captured by a frame-grabber fitted with an analogue/digital converter (ADC) and analyzed and displayed using a software of a personal computer.

Various clinical studies have been conducted to demonstrate the accuracy of this method in detecting dysplastic lesions. Gillenwater et al found a sensitivity of 88% and a specificity of 100% using autofluorescence in the oral mucosa, Wang et al found a sensitivity of 81.25% and a specificity of 93.75% with a positive predictive value of 92.86%, Van Staveren et al found a sensitivity of 86% and specificity of 100%, Zheng et al found a sensitivity of 95% and specificity of 97%, Sharwani et al found a sensitivity of 83–90% and specificity of 89% by applying 5-ALA in the form of mouthrinse prior to fluorescence imaging.

Conclusion: FS is a valuable tool which can provide real-time diagnosis of premalignant/malignant lesions, it is cost effective and can certainly improve the patient's prognosis.

P4
Raman spectroscopy and oral cancer

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Raman spectroscopy is a spectroscopic technique used in condensed matter physics and chemistry to study vibrational, rational, and other low-frequency modes in a system. Raman spectroscopy is laser-based technique that enables chemical characterization and structure of molecules in sample. Raman spectroscopy methods are being considered as techniques which could be complementary or even alternative to biopsy, pathology and clinical assays in many medical applications.

The aim of this paper is to provide insight regarding Raman spectroscopy and its application in the medical field as a diagnostic method for the early detection and investigation of oral cancer.

Advantage of Raman spectroscopy in medical applications: 1) Raman spectroscopy can be applied to a wide range of

sample morphologies, including single crystals, films, fibres', suspensions, aggregates, or precipitates.
2) Samples require minimal preparation-no need for fixation or staining.
3) Can provide a high degree of information which not easy to obtain by other methods.
4) In comparison with other diagnostic techniques, Raman spectroscopy require small amount of sample.
5) Non destructive, non-invasive method for medical applications.
6) Raman spectra can be acquired quickly.
7) Raman spectroscopy is ideal for studying biological matter.
Disadvantages of Raman spectroscopy: 1) A significant problem associated with Raman applications arises from inherently weak signal produced by the Raman Effect.
2) Biomedical samples are extremely intricate systems which reflect complex Raman spectra. Raman band due to biological constitutes are generally overlapped, making it difficult to identify individual components correctly.
3) Due to the minimal sample preparation encountered in the clinical environment, biomedical sample samples usually produce a strong fluorescent background which may completely obscure the true Raman signals.
Raman spectroscopy is a useful diagnostic method because it is non-invasive and non-destructive. It can either be viewed as a complimentary method to biopsy or an alternative method in some instances. The technique is fast and can be used in situ. It is a technique that is comparable to fluorescence and is not only used for diagnosis of oral cancer, but potentially has many uses in the medical field.

P5
The clinical application of elastic scattering spectroscopy

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The diagnosis of carcinomas currently is facilitated and confirmed by the histopathology examination of a biopsy taken from the site of the lesion. The disadvantages of the traditional biopsy techniques include invasiveness, a delay in the diagnosis of the lesion and the taking of unrepresentative samples. We hope to improve the examination procedures to avoid these problems.
The use of non-invasive or minimally invasive procedure such as light scattering spectroscopy should improve head and neck carcinoma diagnosis. Optical technology can be used to examine the living epithelial tissue without need for its removal. Light scattering spectroscopy can also provide valuable information about the function and the structure of the living tissue by giving information about the nucleus such as size, pleomorphism and the amount of the chromatin.
Light scattering spectroscopy is a non-invasive or minimally invasive way for the examination of epithelial dysplasia or carcinoma in situ and to monitor chemotherapy levels, free flap oxygenation levels. It also enables the assessment of surgical margins and lymph nodes during the surgery. If proven to be successful it would also be fast and cost effective.

P6
Developing fluorescent, tumour-specific "smart probes": Transketolase-like 1 (TKTL1) expression und function in primary carcinomas of the head and neck

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Introduction: The development of tumour-specific, fluorescent smart probes has the potential to improve the early diagnosis of cancer and metastatic spread. TKTL1 thereby seems an interesting enzyme to target, as it has been described to be overexpressed in a number of malignancies. It plays a central role in the pentose phosphate pathway, and its overexpression might lead to a selection advantage in tumour cells as their metabolism might become widely independent of the presence of oxygen. Therefore, they can survive under the common hypoxic conditions within tumours, while at the same time lactate and CO_2 production increase, which in turn promotes matrix degradation and favours metastasis formation.
Methods: The aim of this preliminary project is the analysis of TKTL1 expression in upper aerodigestive tract epithelial cells of different sites. Prior to this it seemed mandatory to verify the specificity of the commercially available TKTL1 antibody. Therefore, we analysed stable transfectants of HEK 293 cells via immunoblot and siRNA transfection. Furthermore, TKTL1 mRNA levels in carcinoma cell lines were determined via RT-PCR.
Results: The main protein band of TKTL1 at 65 kD was detected, however along with two additional protein bands, which occurred in control cells, too. Downregulation of TKTL1 via specific siRNA showed an effect on the main protein band, while the additional protein bands remained unaffected. These results suggest an unspecific binding of the antibody in addition to the specific TKTL1 detection.
Conclusion: Some future experiments with stable transfectants and siRNA should show if TKTL1 expression mediates a proliferation advantage in head and neck carcinomas.

P7
Spectroscopic evaluation of QDs encapsulated with a novel biocompatible polymer for cancer diagnosis

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Introduction: Quantum dots (QDs) are new class of fluorescent inorganic nanocrystals which have been used for in vitro

and in vivo imaging. Their unique optical properties such as broad excitation spectra, narrow emission spectrum and resistance to photobleaching make them ideal for biological labeling. Sentinel lymph node biopsy is a means of ultra-staging cancer metastasis and is now the standard of care in breast cancer surgery. Localisation of sentinel nodes is also important in the treatment of *head and neck* cancer. Current tracers for SLN biopsy include the blue dye have various limitations that could be overcome by quantum dots that emit in near infrared range (>700 nm). To safely deliver QDs they must be encapsulated in a biocompatible coating. In this study we encapsulate CdTe QDs with new nanocomposite material based on a silsesquioxane modified poly (carbonate-urea) urethane polymer, and evaluated their spectroscopic properties.

Aim: Developing new biocompatible QDs and investigating their spectroscopic properties versus that of un-coated one.

Materials and methods: QDs solution was irradiated with 670 nm laser diode (Hamamatsu LD 4000) to examine the photostability of the QDs, using CCD spectrometer. Fluorescence lifetime was measured using time-correlated single photon counting method.

Results: Encapsulation with the polymer enhances the aqueous solubility and biocompatibility of the nanocrystals, and provides an opportunity to modify the surface for biomedical applications. QDs are relatively resistance to photobleaching, the presence of the polymer coating did not appear to significantly modify the photobleaching threshold and the fluorescence lifetime of the quantum dot.

P8
Treatment of Kimura disease with photodynamic therapy: a case report

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Head & Neck Oncology 2009, **1(Suppl 1):**P8

Background: Kimura disease (KD) is a chronic inflammatory disorder with a secondary vascular component. The aetiology is unknown. It is mostly reported in Asian populations and has a 6:1 male/female ratio. Clinical manifestation is often as a painless unilateral cervical lymphadenopathy or as subcutaneous masses in the head and neck region. KD is generally limited to the skin, lymph nodes and salivary glands.

Conventional management includes conservative, intra-lesional steroids, chemotherapeutic drugs, radiotherapy and surgical excision. Unfortunately none of which are curative as the lesion inevitably recurs.

Photodynamic therapy has previously been shown to reduce the bulk of vascular malformations.

Case report: A 58-year-old Asian man, diagnosed with Kimura disease at 40 years of age, was referred for further management of facial disfigurement after recurrence.

Initially, he presented with an asymptomatic, slowly enlarging, right-sided facial swelling. Biopsy and imaging confirmed the diagnosis. He subsequently underwent surgical debulking of the lesion and superficial parotidectomy, which left him with a mild facial weakness. Following recurrence, it was felt that further surgery or medical management was not the optimal choice. Interstitial PDT was performed using a baseline MRI scan as a guide. Clinical and radiological assessments at follow-up showed a promising reduction in lesional size.

Conclusion: The authors propose PDT as a repeatable treatment option in shrinkage of this lesion.

P9
Photodynamic therapy in the treatment of recurrent nasopharyngeal cancer

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Head & Neck Oncology 2009, **1(Suppl 1):**P9

Background: Nasopharyngeal carcinoma (NPC) is a condition that predominantly affects the population of South China (2–3 cases/100 000). At the present time, the conventional treatment of NPC is with chemoradiotherapy. This has revolutionised the prognosis and 5-year survival rates are of the order of 50–70%, size dependent. Treatment of recurrence is however difficult. Surgery is an option but suited to small localised recurrence; re-irradiation can cause demyelination and chemotherapy has very small complete response rates. Photodynamic therapy (PDT) is approved for the treatment of advanced or recurrent head and neck cancers.

Materials and methods: We describe a series of 5 patients treated with PDT for recurrent NPC all of whom had unsuccessful conventional therapy. The patients were treated with Foscan 0.15 mg/kg, 4 days prior to illumination with red light of 652 nm from a diode laser. The technique of light application is described as well as the clinical response.

Results: Of the 5 patients treated, local control was achieved in 4/5 patients. A standard regimen of controlled exposure to light was followed over a 4–6 weeks period and no phototoxic events were recorded. Apart from transient pain and swelling, there were no complications or side effects from the treatment itself. It should be noted that some patients underwent more than one PDT treatment.

Conclusion: In this group who had failed previous conventional therapy, PDT is clearly a useful therapeutic option. It has low morbidity, is repeatable and is not prejudiced by prior therapy.

P10
Ultrasound guided interstitial photodynamic therapy of deep seated lesions

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Introduction: Photodynamic therapy is a minimally invasive therapy that results from the interaction between a photosensitiser, oxygen and light. The delivery of light can by either by surface illumination or interstitial application.

We describe the intraoperative application of ultrasound in guiding light delivery in photodynamic therapy.

Materials and methods: A total of 60 patients with various deep seated pathologies in the head & neck, upper and lower limbs were treated with mTHPC-photodynamic therapy. 2D Ultrasound was used to guide the needle insertion in the diseased area.
Results: It was possible to clearly identify the needles during insertion in all treatments and it was possible to guide parallel needle insertions using ultrasound. Although the resolution of ultrasound is not as good as other imaging modalities (i.e. CT, MRI) it was satisfactory in identifying the centre and the peripheries of the pathological lesions.
Ultrasound is very easy to perform, non-invasive, relatively inexpensive, quick and convenient, suited to imaging soft tissues and does not cause any discomfort.
Conclusion: Ultrasound can be used to guide 'real-time' photodynamic therapy of deep seated tumours and other malformations and can augment the information from other imaging modalities without affecting the patient's treatment outcome.

P11
Chondrosarcoma of the hyoid treated with interstitial photodynamic therapy

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Introduction: Primary cartilaginous tumors of the larynx are rare neoplasms. Chondrosarcomas constitute less than 1% of all laryngeal tumors. They are more commonly reported in Asian populations and have a 6:1 male/female ratio. Their clinical manifestation is often as painless unilateral cervical lymphadenopathy or as subcutaneous masses in the head and neck region.
Photodynamic therapy has previously been shown to reduce the bulk of tumours and vascular malformations.
Case report: A 74-year-old Caucasian male presented with asymptomatic, slowly enlarging swelling of the anterior neck. Radiological and histopathological investigation revealed a low grade chondrosarcoma of the hyoid bone and extending to involve most of the base of tongue and anterior laryngeal wall.
The patient was offered surgical excision of the sarcoma which would require sacrificing the larynx, base of tongue and the hyoid, but rejected. It was felt that other medical management (i.e. chemo-radiotherapy) was not the optimal choice.
Interstitial PDT was performed using a baseline MRI scan as a guide. Clinical and radiological assessments at follow-up showed a promising reduction in lesional size.
Conclusion: Conventional management of chondrosarcoma includes conservative, intra-lesional steroids, chemotherapeutic drugs, radiotherapy and surgical excision. Unfortunately none of which are curative as the lesion inevitably recurs. The authors commend PDT as a repeatable treatment option in management of these lesions.

P12
Subglottic carcinoma effectively treated with surgery and adjuvant photodynamic therapy

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Head & Neck Oncology 2009, **1(Suppl 1):**P12

Introduction: Subglottic cancers are extremely rare as a primary malignancy representing < 8% of all laryngeal cancers. Typical age at presentation is in the 5th decade. Recent reports have suggested a female preponderance.
There are three main types of subglottic carcinoma. Adenocarcinoma is uncommon and is typically a lung parenchymal disease and the prognosis is often poor. Mucoepidermoid carcinoma arises from submucosal glands and is extremely malignant. Adenoid cystic carcinoma is the most common neoplasm of the trachea. It is slowly progressive with an equal gender distribution.
Photodynamic therapy has previously been shown to reduce the bulk of tumours and vascular malformations. It also causes tissue destruction through an interaction beween a photosensitizing drug and light. The authors commend photodynamic therapy as an adjunct to surgical management of subglottic carcinoma.
Case report: A 54-year-old Caucasian male presented to his general medical practitioner in May 2007 with a 2–3 month history of haemoptysis. Radiological examination revealed a radiopacity neck to the right heart border. Panendoscopy showed a pedunculated lesion projecting into the trachea from the cricoid. Excisional biopsy was performed and histopathology showed fragments of a non-cystic epithelial tumour. Further tests showed characteristics of adenocarcinoma.
The patient was offered surgical excision (subglottic resection) and free flap reconstruction, but declined this option. Radiotherapy was not a viable option, having had previous radiotherapy for Non-Hodgkins lymphoma. The patient was offered a photodynamic therapy and underwent three cycles of "intraluminal" treatment via bronchoscope.
Clinical and histopathological assessment at 3/12 after the last photodynamic therapy treatment shows no signs of residual disease.
Conclusion: Treatment of subglottic carcinoma is commonly with surgical resection or external beam radiation. We have shown photodynamic therapy to be an appropriate adjuvant treatment for patients who do not wish to undergo surgical treatment and are unsuitable for radiation therapy.

P13
Investigation of photochemical internalisation in HN5 head and neck carcininoma cells and in an *in vivo* rat model

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Head & Neck Oncology 2009, **1(Suppl 1):**P13

Aim of study: Early diagnosis of cancerous lesions renders them suitable for minimally invasive therapy. Photochemical

internalisation (PCI) is a new technique which involves sub-lethal photodynamic treatment to modify the intracellular distribution of co-administered drugs and other agents which are sequestered in lyso/endosomes. In this study, we investigated the PCI effect induced by a new photosensitiser, $TPCS_{2a}$, in combination with a cytotoxic macromolecular drug, saporin, both *in vitro* and *in vivo*.

Materials and methods: The cytotoxicity experiments in combination with saporin were carried out with HN5 carcinoma cells by the MTT assay. Using a rat liver model, various light and drug doses were evaluated for optimizing the PCI conditions. The surface area and volume of necrosis induced after light treatment in the liver were measured 3 days later.

Results: With saporin (25 nM) and $TPCS_{2a}$ (0.1 μg/ml), PCI enhanced the cell kill, reducing the cell viability by a factor of 27 after 3 min light exposure compared to saporin treatment alone. Under optimum PCI conditions ($TPCS_{2a}$: 0.25 mg/kg; light dose:10 J; saporin given 1 hr prior to light treatment), the size of necrosis on the liver was 3 times larger in surface area and more than 3.5 times in volume in combination with 250 μg/kg saporin compared to saporin free groups.

Conclusion: In combination with saporin, $TPCS_{2a}$ PCI displayed a synergistic inhibition of cell growth with HN5 cells and showed a significant enhancement in inducing the necrosis on normal rat liver. PCI may be a useful modality for treating small tumours or local recurrence. Further studies in tumour models are in progress.

P14
Integrin αvβ6 promotes TGF-β1-dependent myofibroblastic transdifferentiation in oral submucous fibrosis

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Head & Neck Oncology 2009, **1(Suppl 1):**P14

Introduction: Oral submucous fibrosis (OSF) is a chronic progressive fibrosing disorder of the oral cavity. Commonly in fibrosis, TGF-β1 promotes the transdifferentiation of fibroblasts into α-smooth muscle actin (SMA)-secreting myofibroblasts. Integrin αvβ6 is not detectable on normal oral keratinocytes but is upregulated during tissue remodelling. αvβ6 is a key activator of TGF-β1 through its interaction with its latency associated peptide.

Objective: To investigate the role of αvβ6 integrin in the pathogenesis of OSF.

Methods: αvβ6 expression was examined in 41 OSF cases compared with 14 cases of fibroepithelial hyperplasia by immunohistochemistry. TGF-β1 activation assays were carried out using a keratinocyte cell line expressing high levels of αvβ6 (VB6). VB6 cells were co-cultured with HFFF2 fibrblasts and SMA expression examined by Western blotting and confocal microscopy.

Results and conclusion: αvβ6 was highly expressed in 54% of OSF cases. αvβ6 activated TGF-β1, which was significantly reduced by antibody blockade. Co-culture experiments revealed markedly increased SMA expression by fibroblasts, indicating myofibroblast transdifferentiation, which was αvβ6-dependent. *In vitro* findings were confirmed by immunochemistry, which demonstrated SMA-. pSmad2 and Smad4-positive myofibroblasts in OSF connective tissue. Finally, treating oral keratinocytes with the areca nut alkaloid arecoline upregulated αvβ6 expression. In summary, we show that αvβ6 integrin is strongly expressed in OSF, and that it promotes myofibroblast transdifferentiation by activating TGF-β1. These data suggest a possible mechanism for the chronic fibrosis seen in OSF.

P15
Vascular mimicry in head and neck tumours

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Head & Neck Oncology 2009, **1(Suppl 1):**P15

Introduction: Angiogenesis has been extensively investigated in several tumour models; however, chemotherapeutic agents based upon these models have not been very effective. It is logical to assume this lack of efficacy is due to the host tumour interface. Furthermore, it is a reasonable hypothesis that the transition between the host vasculature and tumour is not binomial but a gradual transition from tumour and mosaic vessels to host capillaries. The existence of such pure tumour and mosaic vessels would suggest the possibility of tumour vascular mimicry in the connecting vessels.

Materials and methods: Primary and metastatic tumour cells lines were developed 'in-house' and checked to be free from mycoplasma infection. A positive control HUVEC (vascular endothelial cell line) was used. An anti-endothelial antibody was then used. The growth of the cell lines was assessed. Other tumour cell lines were then investigated for similar properties as were primary and metastatic cell lines.

Results: Certain head and neck tumours display the phenomena of vascular mimicry when grown on collagen substrate ($p < 0.001$). This is more so in cell lines derived from metastases than primary tumours. This was found in some other non head and neck tumour cell lines. The cell lines had a reduced capacity to undergo vascular mimicry when exposed to specific anti-endothelial growth factor antibodies.

Conclusion: The phenomenon of tumour vascular mimicry has important implications for future chemotherapeutic drug design.

P16
The use of specific anti-growth factor antibodies to abrogate the oncological consequences of transfusion: an in-vitro study

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Head & Neck Oncology 2009, **1(Suppl 1):**P16

Introduction: Peri-operative blood transfusion is associated with reduced prognosis in a number of solid malignancies. We

investigate its role in a head & neck squamous cell cancer cell line. Growth of these cell lines was analogous to endothelial growth. Direct exposure to transfusion products exaggerated this effect. It was logical therefore to assess the effects of anti-endothelial antibodies on this interaction.

Materials and methods: Control (HUVEC) and tumour cell lines were exposed to transfusion products. The pre-incubation of the transfusion product with anti-endothelial growth factors was assessed by a growth assay.

Results: The antibody did not directly reduce growth in the tumour cell line, however there was a significant reduction ($p < 0.001$) in tumour cell line growth caused by transfusion products pre-incubation with anti-endothelial growth factor antibody. This was found in several other tumours.

Conclusion: We have shown some of the prognostically deleterious effects of peri-operative transfusion in head & neck cancer patients is caused by the transfusion products release of endothelial growth factors. This is found to be the case in several of the tumour groups (Colonic and Prostate) for which this phenomena has been previously reported. It can now be hypothesized that this is due to the specific expression of receptors to these growth factors in these tumour types which are not universally found. It would also explain why this phenomenon does not occur for all tumour types.

P17
Clinicopathological parameters and outcome of 115 (T1–T2) oral squamous cell carcinoma patients

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Head & Neck Oncology 2009, **1(Suppl 1):**P17

Introduction: This study analysed the outcome of patients undergoing surgery for T1–T2 oral squamous cell carcinoma (OSCC) in order to identify the prognostic value of several clinical characteristics.

Materials and methods: A total of 115 patients were studied who had undergone surgery for OSCC between 1992 and 2001, of which 25 had received postoperative radiotherapy.

For each patient, personal data, age at first OSCC, histological findings, treatment, and outcome were recorded and analysed statistically. Survival curves were calculated using the Kaplan-Meier algorithm, and the difference in survival among subgroups was examined.

Results: The overall 5-year survival rate in the 115 patients was 82%. Clinical, operative and pathological parameters including recurrence, site of origin, vascular, perineural and osseous involvement and length of surgery as discriminators were found to affect survival at 5 years.

Conclusion: The overall survival rate was within the (previously) reported range. The prognostic value of many parameters is widely recognized; the combined evaluation of 'composite factors' might uncover other clinical characteristics which might affect the survival in this group of patients.

P18
The effect of smoking, drinking and smoking cessation on morbidity and mortality in oral cancer: a controlled study

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Head & Neck Oncology 2009, **1(Suppl 1):**P18

Background: Smoking and Alcohol have been implicated in the development and maintenance of squamous cell carcinoma with an almost synergistic effect. We review the effect and timing of smoking, drinking and smoking cessation upon the peri-operative morbidity and mortality for oral cancer surgery.

Materials and methods: A controlled cohort involved 67 patients who were diagnosed with oral squamous cell carcinoma. The smoking and drinking habits of this groups was recorded, in addition cessation of smoking after diagnosis was assessed; these were compared to TNM, depth of invasion, pattern of invasion, dysplasia at margin, vascular and nerve invasion, recurrence, 3 and 5 years survival and cause of death.

Results: Smokers are nearly twice as likely to suffer worsened prognosis as non smokers with ex-smokers in an intermediate deleterious position ($p < 0.01$). Alcohol is associated with a detrimental effect but the effect was not significant, this may be due to the small sample size.

Conclusion: Smoking does have an adverse effect on peri-operative outcome and eventual prognosis. We would commend patients to stop smoking to improve outcomes especially during treatment (i.e. surgery or radiotherapy).

P19
cTNM vs. pTNM: are we as good as we think?

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Head & Neck Oncology 2009, **1(Suppl 1):**P19

Background: Accurate clinical staging of oral squamous cell cancer can be quite difficult to achieve especially if nodal involvement is identified. Radiologically-assisted clinical staging is more accurate and informs the clinician of locoregional and distant metastasis. Locoregional metastasis is radiologically assessed by MRI of the head and neck region and 2D-US of the neck followed by FNAC of any identified neck lump when indicated. Distant metastasis is usually assessed by either a PA-CXR or a CT chest.

Materials and methods: In this study an analysis was performed that involved 245 patients with oral squamous cell carcinoma. Clinical TNM (cTNM) staging involved clinical examination of the tumour and neck nodes, MRI of the head and neck, US neck (± FNAC) and PA-CXR or CT chest). Pathological TNM (pTNM) is provided by the pathologist following the surgical resection of the tumour with or without the lymphatic chain. Both cTNM and pTNM were then compared.

Results: There are occasional significant discrepancies between clinical and pathological staging TNM however in general there is a good correlation between staging (Spearman rank correlation coefficient, 0.9787).

Conclusion: It is debatable that inaccurate registration of nodal involvement during the clinical examination is unlikely to affect the patient's prognosis. Histopathological grading would rectify the error and the patient would undergo an adjuvant therapy (i.e. radiation) that would be delivered anyway in the postoperative phase.

P20
Pathological tissue processing time vs. morbidity and mortality

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Background: It is well documented that delay in diagnosing tumours in the head and neck region can affect morbidity and mortality. Delay in processing a biopsy can also affect the patient as it can delay surgical treatment or adjunct therapy.
Methods: We have retrospectively analysed information acquired from 168 patients treated following recurrent squamous cell cancer. Pathological tissue processing time was identified at 4 intervals (first diagnostic biopsy, first surgical resection, second diagnostic biopsy for recurrence and second surgical resection). This was compared to primary sites, recurrence sites, TNM staging and survival over 3 and 5 years.
Results: We show that the processing time for the biopsy of the original and recurrence does have a significant effect on prognosis ($p < 0.01$).
Conclusion: The Royal College of Pathologists have released recent guidelines as to the quality of their delivered head and neck pathology reports however little guidance has been given as to timing. We now show that delay does have an adverse prognostic effect.

P21
Comparison of laser resistant tracheal tubes subjected to CO_2 laser beam

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Introduction: This study was designed to compare how robust four different laser resistant endotracheal tubes would be when subjected to CO2 laser beam.
Materials and methods: The laser was directed perpendicularly onto the shaft; 'saline-filled cuffs and tips of the tubes. A gas flow of 6 L/min of oxygen was delivered to each tube. The laser was set on continuous mode with power set at 6, 12, and 25 W. The time until tube penetration under microscopic vision was noted. Four different products were studied, all marketed as laser resistant:
1) Xomed laser-shield@ II endotracheal tube: aluminium wrapped shaft with an unprotected fluroplastic cuff and tip.
2) Sheridan laser-trach@ tracheal tube: copper wrapped shaft with an unprotected red rubber cuff and tip.
3) Mallinckrodt laser-flexTM tracheal tube: stainless steel shaft with an unprotected plastic cuff and tip.
4) Norton tube: entirely metal with no cuff.
Results: The Norton tube was the only entirely laser resistant tube, surviving greater than 5 minutes lasering at 25 Watts. The shafts of the other three tubes were also laser resistant. However the unprotected cuffs and tips of these three tubes were all penetrated within two seconds, even at minimum power, frequently exhibiting flaring.
Conclusion: Airway fires are possible with laser resistant tubes. The risk of a fire increases with increasing power and duration of the laser beam on the tube. This study demonstrates the ease of penetration of the unshielded components of these laser tubes.

P22
Laser assisted uvulopalasty: the use of the reinforced laryngeal mask airway

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Introduction: The use of laser assisted uvulopalatoplasty (LAUP) is now established as a recognised technique for the treatment of snoring. The traditional anaesthetic management of this surgical procedure requires the placement of a laser-resistant endotracheal tube to facilitate ventilation.
In this preliminary study, we assessed the laser-resistant properties of the reinforced Laryngeal Mask Airway (rLMA) followed by retrospective series of 924 patients who underwent LAUP with the use of the rLMA.
Materials and methods: We compared the incendiary characteristics of the reusable and disposable rLMA to power densities at 4.0×10^3 watts/cm^2 (the commonly used laser settings for LAUPs). Once the rLMA was deemed safe for use with laser surgery, a retrospective survey was conducted over a period of 5 years with the use of the rLMA.
Results: The laser penetrated with the reusable rLMA at 20 min, but could not be ignited. However the laser did penetrate the disposable rLMA after 0.3 seconds and ignited at 2 seconds. A retrospective analysis of 924 patients undergoing LAUP over a period of 10 years with the use of the reusable rLMA revealed no reports of damage or adverse incident with the use of the rLMA.
Conclusion: The use of the reusable rLMA for LAUP is safe and effective.

P23
Oropharyngeal complications of using laryngeal mask airway-case series

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Introduction: The reinforced Laryngeal Mask Airway (LMA) is now increasingly being used for head and neck procedures. However, their use is not without complications and attendant morbidity. We report three cases of postoperative sore throat due to severe pharyngeal trauma following the use of a reinforced LMA.
Series report: In the first and second cases, a 27-year-old male and a 56-year-old male underwent septoplasty, submucosal diathermy to inferior turbinates and bilateral antral washouts. While in the third case, a 44-year-old-female underwent bilateral temporomandibular joint arthroscopy and arthrocentesis.

Size 4 LMA was used in all cases. No throat pack was used. Each procedure took less than an hour. A plastic Yankauer sucker was used under direct vision to clear the supraglottis and the posterior pharynx of retained secretions and blood. The LMA was then removed by the anaesthetist on recovery of the patient. Postoperatively the patients complained of a severe sore throat with evidence of significant palatal abrasions and uvular swelling on examination. On later review the sore throat was reported to have lasted around 5–10 days. At the six week outpatient review, all patients reported full recovery with no visible evidence of residual palatal or uvular scarring or other anaesthetic sequelae.
Conclusion: LMAs are useful and occasionally life saving airways adjuncts but are not without complications. Both the surgeon and anaesthetist should recognise and ensure trauma is minimised to the oropharynx during all stages of surgery.

P24
Advances in the understanding of chondrodermatitis nodularis chronica helices: the perichondrial vasculitis theory

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Introduction: Chondrodermatitis Nodularis Chronica Helicis usually presents as a painful nodule affecting the pinna. The aetiology of the disease is unknown. Several theories have been suggested.
We suggest a possible explanation based upon pathophysiological treatment correlations to new histopathological evidence.
Materials and methods: A detailed histopathological review of 16 confirmed cases of Chondrodermatitis Nodularis Chronica Helicis was undertaken.
Results: Review of cases revealed arteriolar narrowing in perichondrium region of pinna most remote from arterial blood supply, i.e. helix. This has lead to ischaemic changes and death of the metabolically active underlying cartilage with necrosis and extrusion.
Conclusion: This is the first report of specific perichondrial arteriolar changes as the possible cause of underlying cartilage necrosis resulting in Chondrodermatitis Nodularis Chronica Helicis.

P25
Unilateral versus bilateral thyroarytenoid Botulinum toxin injections of in adductor spasmodic dysphonia

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Introduction: In this prospective study, we compared unilateral and bilateral thyroarytenoid muscle injections of Botulinum toxin (Dysport®) in 31 patients with adductor spasmodic dysphonia, who had undergone more than 5 consecutive Dysport® injections (either unilateral or bilateral) and had completed 5 concomitant self-rated efficacy and complication scores questionnaires related to the previous injections. We also developed a Neurophysiological Scoring (NPS) system which has utility in the treatment administration.
Materials and methods: Data were gathered prospectively on voice improvement (self-rated 6 point scale), length of response and duration of complications (breathiness, cough, dysphagia and total voice loss). Injections were performed under electromyography (EMG) guidance. NPS scale was used to describe the EMG response. Dose and unilateral/bilateral injections were determined by clinical judgment based on previous response. Time intervals between injections were patient driven.
Results: Low dose unilateral Dysport® injection was associated with no significant difference in the patient's outcome in terms of duration of action, voice score and complication rate when compared to bilateral injections. Unilateral injections were not associated with any post treatment total voice loss unlike the bilateral injections.
Conclusion: Unilateral low dose Dysport® injections are recommended in the treatment of Adductor Spasmodic Dysphonia.

P26
Primary Burkitt's lymphoma of the postnasal space

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Introduction: We present the first reported case of a primary Burkitt's lymphoma of the postnasal space occurring in an adult Caucasian male.
Case report: The patient presented with a 6-week history of a productive cough and a painless left sided cervical swelling.
Examination of the neck revealed a 5 × 5 cm hard mass in the left anterior triangle by the angle of the mandible with no other palpable masses. Fibre-optic nasendoscopy revealed a 3 × 3 cm mass extending from his left Eustachian cushion towards the midline.
A CT scan of the head and neck showed a soft tissue swelling in the post nasal space, with extensive lymphadenopathy along the carotid sheath and deep to the sternomastoid, with the lowest enlarged lymph node being at the level of the hyoid bone.
Immunohistochemical staining and in-situ hybridisation for Epstein-Barr Virus (EBV) revealed the tumour to be EBV RNA negative suggesting this was a rare sporadic form of the tumour. The case further serves to illustrate the diversity of histological subtypes of malignancies that may develop at this concealed site.
Conclusion: Review of the literature suggests nasopharyngeal Burkitt's lymphoma occurs only in childhood. To our knowledge, this is this is the first reported case in the world literature of primary nasopharyngeal Burkitt's lymphoma presenting in an adult Caucasian male.

P27
Intra-cranial pathology masked by temporomandibular disorder

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Head & Neck Oncology 2009, **1(Suppl 1):**P27

Introduction: Pain in the orofacial region can arise from a distant site. The symptoms of non-temporomandibular disorders, including

intra-cranial lesions, may mimic or be masked by symptoms of temporomandibular disorders, and thus not be detected.
We describe a case of a patient who presented with temporomandibular disorder masking the underlying intra-cranial pathology.
Case report: A 45-year-old Caucasian female presented initially with bilateral temporomandibular disorders. The symptoms in the left TMJ indicated a surgical exploration. Unfortunately the symptoms persist in both joints and a diagnostics arthroscopy and arthrocentesis followed by intra-articular morphine injection was performed. The images from the arthroscopy confirmed that both joints are pathology free. In the immediate postoperative phase, the patient reported weakness of the right oculomotor and trochlear nerves as well as vertigo.
The MRI scan report showed high signals in the right temporal lobe and cavernous sinus; the diagnosis of a '**cavernoma**' was reached.
Conclusion: The clinician must be aware of this diagnosis and maintain a high level of suspicion when the patient fails to respond to treatment or develop unusual postoperative complications.

P28
Analysis of the compatibility of dental implant systems in fibula free flap reconstruction

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As a result of major ablative surgery, head and neck oncology patients can be left with significant defects in the orofacial region. The resultant defect raises the need for advanced reconstruction techniques. The reconstruction in this region is aimed at restoring function and facial contour.
Endosteal implants are being used to restore the masticatory function by the way of prosthetic replacement of the dentition. Implant rehabilitation usually leads to improved facial appearance, function, restoration of speech and mastication.
Suitable dental implant placement's site requires satisfactory width, height and quality of bone. Reconstruction of hard tissue defects therefore will need to be tailored to meet the needs for implant placement.
The aim of this study was to assess the compatibility of five standard commercially available dental implant systems (Biomet 3i, Nobel Biocare, Astra tech, Straumann and Ankylos) for placement into vascularised fibula graft during the reconstruction of oromandibular region.
Radiographs of the lower extremities from 142 patients in the archives of the Department of Radiology in University College London Hospital (UCLH) were analysed in this study. These radiographs were from 61 females and 81 males. Additionally, 60 unsexed dry fibular bones, 30 left side and 30 right side, acquired from the collection of the Department of Anatomy, University College London (UCL) were also measured.
In the right fibula (dry bone), 90% of the samples measured had a width of 13.1 mm. While in the left fibula (dry bone), 90% of the samples measured had a width of 13.3 mm; fibulas measured on radiographs had a width of 14.3 mm in 90% of the samples.
The length ranges of the dental implants used in this study were: 7–13 mm (Biomet 3i), 10–13 mm (Nobel biocare), 8–13 mm (Astra Tech), 8–12 mm (Straumann) and 8–11 mm (Ankylos).
This study concludes that the width of fibula is sufficient for placement of most frequently used dental implants for oral rehabilitation after mandibular reconstructive procedure.

P29
Endoscopic examinations of free flap perfusion in the head and neck region using red-excited Indocyanine Green

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Objective: Malfunction of microvascular anastomoses is regarded as the main reason for failure of free tissue transfer. It was the aim of the current investigation to prove the feasibility and to explore the clinical benefit of endoscopically guided free flap perfusion measurements in the head and neck region using red-excited Indocyanine Green (ICG).
Methods: 25 patients who underwent reconstructive surgery including free tissue transfer to the head and neck region took part in this study. Each participant underwent 3 ICG-angiographies (intraoperatively, 24 hrs and 72 hrs postoperatively). The obtained data were evaluated online and offline on PC, and the results compared to the clinical outcome.
Results: There were no partial or complete losses of transplants. Two flaps with an early arterial failure were successfully salvaged by revision surgery. The ICG-angiographies were tolerated well. The gain of fluorescence was delayed in the transplanted tissue when compared to the surrounding tissue, whereas the final maximum fluorescence intensities were comparable. The two flaps with the initial compromise in perfusion showed relative fluorescence maxima (transplant vs. surrounding) of 33% or 37%, respectively, whereas these values lay above 64% for all other examinations.
Conclusion: It was possible to prove the feasibility of endoscopic ICG angiographies in patients with free tissue transfer to the upper aerodigestive tract. The method is easy to perform and there were no adverse events. Especially in difficult situations (e.g. questionable Doppler signals, flaps situated far down in the pharynx...) the method seems to be a welcome adjunct to conventional screening.

P30
Bilateral sinonasal inverted papilloma with orbital invasion

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This case reports a 28 year old male who presented with left sided nasal obstruction and rhinorrhoea. He had undergone two

previous endonasal surgeries for removal of left inverted papilloma at a different hospital. Clinical and radiological findings were suspicious of disease recurrence, for which an endoscopic clearance was performed, confirming the diagnosis. He however developed further aggressive recurrences, with areas of severe dysplasia involving the orbit and disease in nasal septum, frontal sinuses and sphenoid bilaterally, necessitating five further endoscopic procedures – two combined with external approach and one assisted by image guidance.

The multiple bilateral recurrences in this young patient are an unusual presentation. It compels us to draw a comparison with laryngeal papillomatosis, HPV being a known aetiopathological factor for this and also reported with recurrences of disease in the nose. We also wonder about the possible benefits of an HPV vaccination in a case like ours. The role of image guidance in revision endoscopic surgery with loss of most anatomic allandmarks is well borne out with this case.

P31
How we do it: endoscopic trans-nasal repair of CSF rhinorrhoea

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Endoscopic repair of CSF rhinorrhoea was first described in the early 1980s. Since then the endoscopic approach has overtaken the intracranial route as the procedure of choice due to superior visualisation of the operative field, reduced operating time & lower complication rates. Various autogenous, allogenic and synthetic patching materials have been used to augment repair. We describe a step wise technique of patching the skull base defect using a combination of septal mucoperichondrial flap and tensor fascia lata graft.

P32
Carotid artery by-pass and head and neck squamous cell carcinoma: Geneva's experience. Should we be afraid of the carotid artery?

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Purpose: To determine the survival, the neurologic morbidity, the post-operative surgical complications, and the predictive factors of patients undergoing a radical neck dissection with carotid by-pass for squamous cell carcinoma of the head and neck (SCCHN).

Materials and methods: A retrospective study of 11 patients operated between 1991 and 2007. Besides survival and recurrence, the type of vascular graft, previous radiation, histological carotid invasion, and major complications were evaluated.

Results: The 5-year survival rate was 39%. All deceased patients had a loco-regional recurrence. Salvage surgery and histologic invasion of the carotid artery are negative predictive factors, with an odd-ratio of respectively 6 and 2.5. The rate of neurological morbity is 9% and post-operative complications were found in 18% of patients.

Conclusion: Radical neck dissection with carotid by-pass achieves a good survival rate considering the advanced disease stage of the patients. Autologous venous or arterial graft should be preferred to avoid neurologic complications. Caution should be observed in case of salvage surgery.