



MEETING ABSTRACTS

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## ORAL PRESENTATIONS

O1

### Our experience with optical diagnostics of the head and neck

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Optical diagnostics have proved to be a reliable resource that can be used to provide 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, microendoscopy and optical coherence tomography. These have all shown a marked increase in the sensitivity and specificity when compared to both clinical examination and frozen section analysis.

Optical biopsies can be acquired through different modalities; each has its 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. The preliminary results from the application of optical coherence tomography in the head and neck are promising and clinical trials continue.

We describe our experience in the clinical application of elastic scattering spectroscopy, fluorescence spectroscopy, microendoscopy and optical coherence tomography in the head and neck.

O2

### Wide-field and high-resolution optical imaging for early detection of oral neoplasia

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Current procedures for oral cancer screening typically involve visual inspection of the entire tissue surface at risk under white light illumination. However, pre-cancerous lesions can be difficult to distinguish from many benign conditions when viewed under these conditions. We incorporated cross-polarization, narrowband reflectance, and fluorescence imaging modes in a portable, robust, wide-field imaging device to reduce specular glare, enhance vascular contrast, and detect disease-related alterations in tissue autofluorescence.

We have also developed a portable system to enable high-resolution evaluation of cellular features within the oral mucosa *in situ*. This system is essentially a wide-field epi-fluorescence microscope coupled to a 1mm diameter, flexible fiber-optic imaging bundle, capable of imaging nuclear size and nuclear-to-cytoplasmic ratio following topical application of a fluorescent labeling solution. Proflavine solution was used to specifically label cell nuclei, enabling the characteristic differences in N/C ratio and nuclear distribution between normal (b) and cancerous (d) oral mucosa to be quantified. This presentation will discuss the technical design and performance characteristics of these complementary imaging systems. We will also present data from ongoing clinical studies aimed at evaluating diagnostic performance of these systems for detection of oral neoplasia in high- and low-prevalence populations.

O3

### Differential Pathlength Spectroscopy for diagnosis of head and neck cancer

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*Head & Neck Oncology* 2010, **2(Suppl 1):O3**

The development of optical techniques for non-invasive diagnosis of cancer is an ongoing challenge to biomedical optics. For oral cancer biopsy has a low specificity because of a thick keratin layer that often covers potential malignancies. We investigated the possibility of distinguishing potentially malignant visible lesions from benign ones to reduce the number of unnecessary biopsies.

Major challenge here is to measure through the thick keratin layer that often covers the biologically active layers. Differential Pathlength Spectroscopy is a fibre optic measurement technique that samples tissue in a predetermined sampling volume. We constructed a probe for sampling up to 1mm deep into the tissue. By analysing the white light spectrum with a mathematical model developed earlier we could determine scattering parameters, blood volume, micro vascular saturation and the average blood vessel diameter in the sample volume just below the probe.

A total of 110 measurements were performed in 21 patients on 75 suspicious lesions that were biopsied after measurement and 35 clinically normal locations that were not biopsied. Lesions were classified as normal, hyperplasia, inflammation, dysplasia or cancer. With this data we built a logistic regression model that predicts the need for a biopsy (if classification equals dysplasia or cancer) on the basis of the spectra. The model was trained and evaluated using the leave-one-out-approach. The results showed a very good combination of relative sensitivity and specificity with an area under the curve of 0.943. When removing the obvious lesions from the dataset (i.e. the unbiopsied normals and half the samples classified as cancer that were clinically unmistakable, the area under the ROC curve even improved to 0.951. In practice this comes down to reducing the number of biopsies to 50% without reducing the overall sensitivity of the diagnostic procedure, or reducing the number of biopsies by 90% at a loss of 5% relative sensitivity.

We believe Differential Pathlength Spectroscopy is a very promising technique that may help to reduce the costs of healthcare without compromising the quality.

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#### O4

##### **Raman spectroscopy as a tool for the identification and differentiation of neoplasias contained within lymph nodes of the head and neck**

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The development of lymphadenopathy in the neck has many causes, in children it is often found in relation to infection and in a small but significant number it is the first presentation of lymphoma. In adults neoplastic causes predominate for example, lymphoma, squamous cell carcinoma and adenocarcinoma. The treatment modalities and prognosis for these conditions varies enormously and in the case of squamous cell carcinoma an excision biopsy can lead to significant morbidity. A major prognostic factor for the response to treatment for example in lymphoma is the extent of the disease at presentation. Pre-treatment accurate diagnosis is imperative and is a compelling argument for investment in the development of accurate, sensitive and minimally invasive diagnostic techniques, such as Raman spectroscopy.

This work seeks to investigate the ability of Raman spectroscopy to differentiate between the major neoplastic diseases of lymph nodes presenting within the neck. Raman spectroscopy at 830 nm has been used to extensively study lymph nodes from the head and neck and pathology related spectral signatures have been identified.

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#### O5

##### **An optical coherence tomography study for imaging the round window niche and the promontorium tympani**

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Head & Neck Oncology 2010, 2(Suppl 1):O5

Tympanosclerosis may involve the tympanic membrane, the ossicles, as well as the oval and round window niche, respectively. The surgical treatment of the obliterated oval window niche is most challenging. Beside stapesplasty, vibroplasty with coupling the floating mass transducer (FMT) onto the round window niche and into a new, so-called third window is indicated. In the latter situation, drilling a hole into the promontorium is necessary to couple the FMT close to the membranous endosteum. Any damage of the membranous inner ear needs to be avoided. The question was whether OCT is useful to identify the

endosteum and to provide microanatomical information about the round window niche. OCT was carried out on human temporal bone preparations in which a third window was drilled, while leaving the membranous labyrinth and the fluid-filled inner ear intact and removing the overhang of the round window niche. A specially equipped operating microscope with integrated OCT prototype (spectral-domain-OCT) was used. The OCT images and 3D reconstructions demonstrate the usefulness of OCT to measure the drilling cavity, to visualize the inner ear structures, and to obtain microanatomical information about the round and oval window niche. These findings may have an impact on stapes surgery, on cochlea implantation, and on vibroplasty with coupling the FMT onto the round and third window. OCT-guided drilling allows identification of the intact inner ear more precisely.

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#### O6

##### **Assessment of suspicious oral lesions using optical coherence tomography**

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Head & Neck Oncology 2010, 2(Suppl 1):O6

**Introduction/aims:** Optical biopsy systems have been investigated for various clinical applications; however the main interest remains in the diagnosis and monitoring of premalignant and malignant conditions. In this study, we compared findings of optical coherence tomography (OCT) with histopathology results of suspicious oral lesions to assess the feasibility of OCT in identifying pathological tissue.

**Material/methods:** Suspicious oral lesions acquired from 120 patients were subjected to immediate ex-vivo Swept-Source Frequency-Domain OCT. Five OCT parameters were assessed (keratin, epithelial, sub-epithelial layers changes, basement membrane and microanatomical structures). Two clinicians and two pathologists, who were blind to clinical and histopathological diagnosis, examined the OCT images autonomously, provided differential diagnosis, the most probable diagnosis and provided judgment on the need for surgical biopsy. Inter, Intra-observer differences, sensitivity and specificity was calculated.

**Results/statistics:** Basic microanatomical tissue structures were identified on the mainstream of the OCT images. Recognition of the basement membrane was achieved in the majority of the lesions. Identification of changes in the parameters ruled areas of architectural changes. There was a high inter and intra-observer agreement among the two clinicians and two pathologists, who recommended a surgical biopsy when examined all the histologically proven dysplasia and cancer OCT images. Sensitivity and specificity were calculated and proved to be encouraging.

**Conclusions/clinical relevance:** At this phase, OCT can definitely aide clinical examination and monitoring and can be invaluable tool for inexperienced clinicians.

**Acknowledgment:** We would like to thank the BAOMS for supporting this research project.

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#### O7

##### **Assessment of tumour resection margins using optical coherence tomography**

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Head & Neck Oncology 2010, 2(Suppl 1):O7

**Introduction/aims:** 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.

Optical coherence tomography (OCT) is an imaging modality that uses light to determine cross-sectional anatomy in turbid media such as living tissues. In this study, we used this technology to evaluate resection margins acquired from patients with oral squamous cell cancer (OSCC).

**Material/methods:** Twenty-five patients with newly diagnosed T1-T2 OSCC underwent local resection. In the immediate ex-vivo phase, OCT was used to interrogate the surgical margins of these specimens and the results were, then, compared to histopathology. Inter, Intra-observer differences, sensitivity and specificity was calculated.

**Results:** The junctional epithelium (between positive and negative margins) can be identified by gradual change in epithelial thickness and basement membrane organisation (integrity) from the normal to pathological. Identified changes in tumour positive margins include hyperkeratinisation, breach of the basement membrane and disorganised epithelial structure. Tumour spread pattern could be identified on the majority of the interrogated tissue. Sensitivity and specificity were calculated and proved to be encouraging.

**Conclusions:** The results from this study are encouraging and suggest the feasibility of using OCT in differentiating between positive and negative surgical margins.

**Acknowledgment:** We would like to thank the BAOMS for supporting this research project.

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## O8

### Real-time volumetric optical coherence tomography OCT imaging with a surgical microscope

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*Head & Neck Oncology 2010, 2(Suppl 1):O8*

Optical coherence tomography is a unique technique to visualize subsurface tissue structures with a resolution below 10µm during microsurgery without tissue contact. Since it was introduced more than 15 years ago imaging speed was boosted by more than three orders of magnitude, from less than 100 to more than 300,000 A-scans per second. Instead of taking only still images of anatomical structures, the increased speed of OCT allows now to image volumes nearly in real time. This enables not only the scanning of larger tissue surfaces, but also opens new application beyond simple diagnosis. A non-contact volumetric imaging with less than 15 µm resolution can guide microsurgery at the eye, in Otolaryngology (ENT) and in other medical disciplines.

Here we present an ultrahigh speed OCT system with more than 200.000 A-scans/second integrated into a surgical microscope (MÖLLER Hi-R 1000, Möller-Wedel GmbH, Wedel, Germany), which is capable of processing, rendering and displaying more than 7 volumes with 12 million pixel per second by using a PC with a high performance graphics accelerator card. Best performance was reached by distributing the calculation of the A-scans to the four cores of the PC, whereas the preprocessing and rendering was done in real-time with dedicated software on graphic processing unit (GPU). Possible applications of the system are OCT guided microsurgery in the middle ear or tumor surgery of the vocal fold.

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## O9

### Automatic segmentation of clinical OCT images for the determination of epithelial thickness changes in laryngeal lesions

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*Head & Neck Oncology 2010, 2(Suppl 1):O9*

Automated classification of laryngeal lesions using optical coherence tomography data can be helpful in making a faster and safer diagnosis. A change in the epithelial layer thickness seems to be an effective indicator for laryngeal cancer and its precursors.

Lesions with different grades of malignancy were scanned with a time domain OCT system during microlaryngoscopy. Every diagnosis was confirmed by performing a biopsy. Each OCT image was separately segmented, manually by an expert and automatically by a segmentation algorithm. Values for the maximal and average epithelial thickness as well as the standard deviations were compared for both segmentations. The results show a thickening of the epithelium from normal over dysplastic

to cancerous tissue. The values for the automatic segmentation are in good agreement with expert segmentation.

In conclusion, automatic segmentation can be used for epithelial thickness measurements as a promising indicator for laryngeal cancer. It would also be possible to extract other characteristics like standard deviation or signal attenuation within the segments. Thus, we laid the foundation for computer-aided diagnosis of laryngeal lesions.

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## O10

### Ultrahigh-resolution 3D full-field optical coherence microscopy of the pulmonary airways ex vivo

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*Head & Neck Oncology 2010, 2(Suppl 1):O10*

Visualizing the respiratory mucosa in pulmonary airways at the sub-cellular level could yield new insights into pathogenesis of many important diseases. However, current imaging modalities to study the respiratory mucosa lack the required resolution to visualize critical subcellular detail such as nuclei and respiratory epithelial cilia.

Full-field optical coherence microscopy (FFOCM) is an emerging technique capable of providing reflectance images in situ with high spatial resolution in all three dimensions. We have developed a FFOCM with an axial sectioning thickness of 1 µm and a high transverse resolution of 0.6 µm. The three-dimensional field of view was 256 (H) x 256 (W) x 400 (D) µm. Three-dimensional images of formalin-fixed, sectioned porcine bronchial segments were obtained immediately ex vivo. Images were compared to H&E stained histology at corresponding sites. Pilot images on fixed human airways from individuals with cystic fibrosis (CF) and Chronic Obstructive Pulmonary Disease (COPD) were also acquired.

Individual epithelial cells and goblet cells, including their subcellular morphologies, were easily seen. Cross-sectional views showed gland ducts containing mucus, cilia, the periciliary layer (PCL), and nuclei. Three-dimensional rendering of the trachea showed the presence of mucus droplets directly above non-ciliated goblet cells, tethered to the surface of these cells by a thin adherent mucus strand.

Our results demonstrate the potential of FFOCM to provide detailed microstructural imaging of pulmonary airways without administration of a contrast medium. The future development of a probe for in vivo monitoring of mucociliary transport, gland function, and airway surface liquid (ASL) depth could provide new avenues for improving our understanding of respiratory mucosal pathophysiology and enable longitudinal assessment of the response to novel drugs.

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## O11

### High-speed three-dimensional imaging of the pulmonary alveoli

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*Head & Neck Oncology 2010, 2(Suppl 1):O11*

Investigating the structure and function of pulmonary alveoli in vivo is crucial for understanding the normal and diseased lung. In particular, understanding the three-dimensional geometry and relationship of the terminal alveoli to their neighboring alveoli, alveolar ducts and acini during respiration would be a major advance. However, the lung is an inherently difficult organ to image in vivo and the peripheral lung has many compounding challenges not limited to its highly scattering micro architecture, large motion artifacts and difficult access through the bronchial tree.

In this study, we image the alveoli of fixed pig lungs using a high-speed high-resolution optical frequency domain imaging (OFDI) system that is endoscopically compatible for future in vivo imaging of human alveoli. Core imaging components include a rapidly swept wavelength source centered at 1310 nm resulting in an A-line depth scan rate of 62,500 Hz, a polarization diverse dual balanced receiver, and a high speed data acquisition system. Whole lungs were excised from normal piglets and inflation fixed at 15 cm H2O pressure using a modified Heitzman fixation technique. Lungs were air dried in a heated oven and sectioned into 500 µm slices. Three-dimensional datasets were acquired from lung slices

with 512 x 512 x 1024 voxels and a voxel dimension of 5 x 5 x 8 μm. Datasets were acquired at 122 frames per second and 0.23 volumes per second - indicating the potential to acquire a three-dimensional volume within a single human respiratory cycle.

OFDI images reveal clear delineation of alveolar septal walls, demonstrating that high-speed three-dimensional visualization of air filled alveoli is feasible. The fixed lung data provides a strong foundation for investigating the 3D structure and function of alveoli in vivo and suggests great promise for advancing our knowledge of the functional unit of the lung.

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## O12

### Reflectance microscopy techniques for 3D imaging of the alveolar structure

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Head & Neck Oncology 2010, 2(Suppl 1):O12

Lung disease involving the alveoli and distal bronchioles are poorly understood and most commonly studied indirectly via lung function tests. Available imaging tools for the non-destructive assessment of the alveolar structure include X-ray computed tomography, intra-vital fluorescence microscopy and Optical Coherence Tomography, which are either limited by long acquisition time, inadequate resolution and contrast, or shallow imaging depth.

In this study, we investigated the potential of two high-resolution reflectance microscopy imaging techniques, Spectrally Encoded Confocal Microscopy (SECM; 1 μm (x) x 1 μm (y) x 5 μm (z) resolution) and Full Field Optical Coherence Microscopy (FFOCM; 1 μm (x) x 1 μm (y) x 1 μm (z) resolution), for imaging alveolar microstructural detail. Two mouse lung samples were imaged with both SECM and FFOCM. The specimens were inflation-fixed using a modified Heitzman fixation technique at 20 cm H<sub>2</sub>O pressure. They were cut in 500 μm thick slices and water immersed for imaging. Images were obtained and analyzed to determine whether or not the resolution and contrast of these techniques are sufficient to visualize the fine structures of the alveolar wall.

Alveolar microstructure could be resolved in three dimensions in images obtained by both technologies. Alveolar septal walls from multiple layers could be clearly identified while sub-cellular structures such as nuclei were also visible in the SECM technique. In conclusion, we have demonstrated that two imaging technologies provide important sub-cellular detail that is required to study alveolar microstructure. Future research to develop these imaging modalities further so that they may be used in vivo is merited.

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## O13

### Three-dimensional microscopy of the human bronchial mucosa

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Head & Neck Oncology 2010, 2(Suppl 1):O13

**Introduction:** Lung cancer is the leading cause of cancer related death, and despite recent efforts to reduce the mortality associated with the disease, patient prognosis remains poor with the current 5-year survival rate under 15%. Detection and diagnosis of lesions arising in the bronchial mucosa remains problematic and as a result they are typically well advanced upon discovery.

**Methods:** We are currently conducting a clinical study aimed at using optical frequency domain imaging (OFDI) to interrogate the bronchial mucosa of patients with the suspicion of lung cancer. During bronchoscopic evaluation, regions of interest suspicious for cancer or precursor lesions were identified and imaged, in addition to regions of normal appearing mucosa. Following OFDI imaging, mucosal biopsies were obtained for histopathologic analysis. Spiral cross-sectional OFDI images were obtained at a rate of 50 frames/sec using a 2.4 Fr catheter (frame size: 1536 x 1024; image resolution: 8 μm x 23 μm x 100 μm).

**Results/conclusions:** The layered structure of the normal bronchial mucosa was clearly visualized in the OFDI images including the identification of the

epithelium, lamina propria, smooth muscle, perichondrium and cartilage layers. In addition, features such as mucosal vasculature, glands, ducts and alveoli were observed. Various features associated with airway disease were also observed including the presence of fibrous debris, airway inflammation, and lymphatic and blood vasculature remodeling. Based on these preliminary results we anticipate that OFDI imaging of the pulmonary airways will enable the early detection of airway features associated with the development of cancer. When used as a screening tool in high-risk patients we hope that early detection of airway associated cancer with OFDI will result in a decrease in patient mortality.

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## O14

### Endoscopic ICG perfusion imaging for flap transplants: technical development

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Head & Neck Oncology 2010, 2(Suppl 1):O14

**Objective:** Endoscopic detection of fluorescence of indocyanine green (ICG) requires excitation in the NIR wavelength range <800 nm and detection at >800 nm. Commercial 3-chip endocameras can be made sensitive for the fluorescence emission in the blue channel by removing infrared blocking filters. It was the objective of the development to combine white light imaging (using the green and red channels only) and fluorescence imaging (using the blue channel) on a single 3-chip camera head. In addition, reliable pharmacokinetics of ICG perfusion images should be established.

**Materials and methods:** Optical filters were designed in a way that white light transmission was much reduced, near IR < 800 nm fully transmitted and light >800 nm completely blocked. These filters were mounted on a filter wheel of an endoscopic light source (D-Light, Karl Storz, Tuttlingen). In front of the camera chip, blue light and the excitation wavelength range was completely blocked, the remainder of the visible wavelength range and NIR fully transmitted. White light remission was used as a reference for semi-quantitative fluorescence measurements.

**Results:** The restoration of a full-colour pseudo-white-light image from the green and blue channels was successfully established with minimal impact on colour perception. Fluorescence can be displayed in a separate window or in false colour overlay. White light remission also was used as reference light for semi-quantitative, online fluorescence measurements. By using motion tracked 'regions of interest' (ROIs) on the corrected data, the recording of fluorescence kinetics was possible without influence of movement, illumination inhomogeneities and tissue geometry. Therefore calculations such as deconvolution of flap perfusion resistance were possible by comparing the fluorescence kinetics of the flap with the ones of the surrounding tissue.

**Conclusions:** Simultaneous recording of white light and ICG-fluorescence images is possible with a single 3-chip camera head. Motion tracking and correction of fluorescence images with white light remission images enables endoscopic ICG-perfusion imaging with semi-quantitative measurements.

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## O15

### Endoscopic ICG perfusion imaging for flap transplants: clinical results

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Head & Neck Oncology 2010, 2(Suppl 1):O15

**Objective:** Malfunction of microvascular anastomoses in the early postoperative period 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:** A total of 25 patients who underwent major ablative surgery followed by free-flap reconstruction of the upper aerodigestive tract took

part in this study. Each participant underwent three ICG-angiographies (intraoperatively, and 24 and 72 h postoperatively). The obtained data were evaluated both online and offline on a 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. Particularly in difficult situations, such as questionable Doppler signals, or flaps situated far down in the pharynx, the method seems to be a welcome adjunct to conventional screening.

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### O16

#### In vivo monitoring of Foscan-mediated photodynamic therapy in clinical head and neck procedures using optical spectroscopy

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*Head & Neck Oncology 2010, 2(Suppl 1):O16*

Photodynamic therapy with m-THPC (Foscan) is an established treatment for superficial squamous cell carcinoma and is also being considered for treatment of larger head and neck tumors. Recently, clinical implementation of Foscan-mediated PDT in the head and neck has not been optimal; a subset of patients has experienced incomplete response. It is well-understood that sufficient quantities of light, drug and oxygen must be present in the targeted tissue in order to deliver sufficient damage. This requirement is complicated by variations in the tissue optical properties and in the photosensitizer uptake rates; however, most clinical protocols do not measure the affect of these factors on the PDT dose delivered to individual patients.

This study represents a first step toward incorporating optical techniques developed to monitor PDT treatments in pre-clinical models into the clinical treatment of head and neck cancer. This clinical study incorporates reflectance and fluorescence spectroscopic measurements into the PDT-treatment protocol. Spectral analysis allows the extraction of Foscan concentrations and the quantitative determination of tissue physiological parameters that are important to the PDT-delivered dose (e.g. blood volume and hemoglobin saturation). The study identifies the practical and technical challenges of translating these techniques into the clinical setting. Moreover, the data presented here contribute to understanding the link between these optical measurements and the PDT-dose delivered to individual patients during treatment.

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### O17

#### Feedback controlled laser system for safe and efficient reshaping of nasal cartilage

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*Head & Neck Oncology 2010, 2(Suppl 1):O17*

In 1992, we identified laser-induced stress relaxation in cartilage. This led to the development of a new laser application in otolaryngology- head and neck surgery for the non-ablative reshaping of cartilage. Laser septochondrocorrection is non-invasive, bloodless, painless procedure which takes only 10 minutes to complete and can be performed in outpatient settings.

The efficacy and safety of this technology can be guaranteed with the feed back control system measuring temperature and stress distribution

in the course of laser treatment. The paper presents recent results of the research and clinical applications of the technology and equipment for laser reshaping of cartilage in the ENT. The new equipment LSC-701 (Arcuo Medical Inc., USA) for laser reshaping of nasal cartilage includes an Erbium doped glass fiber laser (1.56 micrometers in wavelength), special instrument and feedback control system which allow to correct laser settings in the course of laser treatment and to stop the laser when the procedure is completed. The laser technology and equipment are certificated by the Federal Service on Surveillance in Healthcare and Social Development of Russian Federation. The laser septocorrection using LSC-701 has been performed for 120 patients at the ENT Clinics of the Sechenov Medical Academy of Moscow and at the Vladimirskiy Research and Clinical Institute of Moscow Region (MONIKI). The positive results were obtained for 95 percent of the patients in two years follow up. No age limitation (for the patients from 12 until 68 years), no complications and negative secondary effects were observed.

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### O18

#### Methods for evaluating changes in cartilage stiffness following electromechanical reshaping

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*Head & Neck Oncology 2010, 2(Suppl 1):O18*

One component of several otolaryngological surgeries is the reshaping of cartilage. Several previous studies have demonstrated the efficient achievement of this procedure through electromechanical reshaping (EMR), a technique that involves the direct application of voltage to cartilage mechanically deformed in a jig. Two main parameters, voltage and application time, may be varied to achieve varying degrees of shape change. Both maximized shape change and minimized intrinsic tissue damage determine the ideal parameters for EMR. In preceding research, EMR parameters were correlated with degree of shape change. However, it remains necessary to correlate the same parameters with the degree of change in the mechanical properties of tissue. This study satisfies this need by providing comprehensive data on the pre- and post-EMR stiffness of both septal and auricular cartilage over a range of voltages with constant application time (2-8V, 2min, and 2-8V, 3min, respectively). EMR was applied using flat platinum electrodes to one of two 15 mm X 5mm samples obtained from the same cartilage specimen, while the second sample was maintained as a control. Following a 15 min rehydration period, the Young's modulus of the tissue was calculated for both the control and experimental sample from data obtained through a uniaxial tension test. A general reduction in stiffness was observed from beginning at 3V, with the magnitude of reduction increasing at 6V.

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### O19

#### Using optical coherence tomography to monitor effects of electromechanical reshaping in septal cartilage

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*Head & Neck Oncology 2010, 2(Suppl 1):O19*

Electromechanical reshaping (EMR) of cartilage is a promising noninvasive technique with potential for broad application in reconstructive surgery. EMR involves applying direct current electrical fields to localized stress regions and then initiating a series of oxidation-reduction reactions, thus effecting a shape change. Previous EMR studies have focused on macroscopic structural measurements of the shape change effect or monitoring of electrical current flow. Only limited investigation of structural changes in the tissue at the histologic level have been performed, and not in real time. This study is the first to use optical coherence tomography (OCT) to examine structural changes in cartilage during EMR. Two platinum needle electrodes were inserted into fixed rectangular rabbit nasal septal cartilage specimens. The spectral domain OCT probe was then positioned above the anode needle. A constant voltage of 6V was applied for 3 minutes, and images were obtained (8 frames/second). OCT was also performed in specimens undergoing dehydration under ambient conditions and during pH changes produced

by the addition of HCl, as both processes accompany EMR. The OCT data identified distinct findings among the three conditions, suggesting that EMR causes a much greater degree of reshaping on a molecular level than dehydration or a change in pH alone. OCT provides a means to gauge structural changes in the tissue matrix during EMR. The application of OCT to image the EMR process will add to our understanding of the mechanisms of action involved and potentially facilitate optimization of this process.

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## O20

### Comparison of bend angle measurements in fresh cryopreserved cartilage specimens after electromechanical reshaping

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Head & Neck Oncology 2010, **2(Suppl 1):O20**

Cryopreservation of cartilage has been investigated for decades and is an established protocol. However, the reliability and application of cryopreservation of cartilage for use in electromechanical reshaping (EMR) has not been studied exclusively. A system to cryopreserve large amounts of tissue provides a steady source of similar quality cartilage for future experimentation. This will reduce error that may arise from different cartilage stock, and have the potential to maximize efficiency under time constraints. Our study utilizes a unique methodology to cryopreserve septal cartilage for use in electromechanical reshaping studies. Septal cartilages were extracted and placed in one of three solutions (Saline, PBS, and 10% DMSO by volume in PBS) for four hours in a cold room. Then, each cartilage specimen was vacuumed and sealed in an anti-frost plastic bag and placed in freezer for 1 to 3 week durations. EMR was performed using 2 volts for 2 minutes to create a bend. Bend angle measurements of the cryopreserved cartilage specimens were compared to the bend angles of fresh cartilage which underwent EMR using the same parameters. Results demonstrate that Saline, PBS, and DMSO were effective in cryopreservation, and indicated no significant differences in bend angle measurements. Our methodology to cryopreserve cartilage specimens provides a successful approach for use in electromechanical reshaping studies.

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## O21

### Monitoring of electrical current in rabbit and porcine cartilage tissue during electromechanical reshaping

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Head & Neck Oncology 2010, **2(Suppl 1):O21**

Electro Mechanical Reshaping (EMR) with platinum needle electrodes has been recently developed to shape cartilage without conventional cut and suture surgery. This study investigates the relationship between the voltage applied, the electrical current measured during EMR with platinum needles, and the resulting shape. Monitoring the electrical current provides information to model the electro-chemistry, which will aid in determining the onset of shape stabilization. Rabbit septal, rabbit auricular, porcine auricular, and porcine costal grafts were bent into a 90° angle using a moulage. Platinum needle electrodes were then placed in contact with the cartilage and a constant voltage was applied for a set time. The electrical current was measured during the process and total charge transferred was calculated. The cartilage specimen was then removed from the jig and photographed after one minute in order to determine the resulting bend angle.

Results show that a higher current in tissue is produced with increasing applied voltage. Each current trace is unique and is dependent on tissue thickness and inter-electrode distances. Understanding the electrical current process ultimately leads to optimizing EMR and feedback control. Voltage, for example, could be varied in real-time during EMR to produce a constant chemical reaction rate and potentially reduce total tissue dehydration in contact with electrodes.

In conclusion, electric current traces provide information about chemical kinetics during EMR that depend on exposure settings, and monitoring these traces is an important step in optimizing the reshaping process.

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## O22

### Numerical analysis of costal cartilage warping after laser modification

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Head & Neck Oncology 2010, **2(Suppl 1):O22**

Grafts obtained from peripheral regions of costal cartilage have an inherent tendency to warp over time. Laser irradiation provides a potential method to control the warping process, thus yielding stable grafts for facial reconstructive surgery. In our current study, we propose a simple and well-fitting model that numerically describes the degree of warping of laser irradiated costal cartilage grafts. Using an Nd:YAG laser ( $\lambda = 1.32 \mu\text{m}$ ) at various exposure settings, grafts harvested from the peripheral regions of porcine costal cartilage were irradiated. The resulting graft geometry was fitted to a curve using a quadratic regression model. The coefficient of determination demonstrated a very strong fit for all grafts modeled. A quadratic regression is simple to perform and results in a single numerical value that appropriately describes the degree of cartilage warping. Our proposed model is valuable in assessing the effect of laser irradiation on the warping process of costal cartilage.

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## O23

### A laser device for fusion of nasal mucosa

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Head & Neck Oncology 2010, **2(Suppl 1):O23**

A patent pending device has been created, and successfully used, to fuse tissue membranes as an alternative to sutures or staples. The joining, or coaptation, is accomplished through the controlled application of laser heating to induce protein denaturation and subsequent renaturation across the interface. Lasers have been used by a number of researchers to close wounds in controlled laboratory tests over the last 15 years. Many encouraging results have been obtained; however, no commercial delivery systems are currently available. This is due primarily to two factors: requiring an inordinate amount of experience on the part of the operator to detect changes in tissue appearance, and attempting to achieve general applicability for multiple tissue systems. The present device overcomes these barriers as it is tailored for the particular application of septal laser fusion, namely for the coaptation of mucoperichondrial membranes.

The important parameters involved in fusing biological tissues using radiation from laser sources are identified. The development of the device followed from computational modeling of the fusion process based on engineering first-principles from heat transfer, fluid dynamics and optics, and from experimental results on a particular tissue system. The experiments were designed and analyzed using orthogonal arrays, employing a subset of the relevant parameters, i.e., laser irradiance, dwell time and spot size, for a range of wavelengths. The in vitro fusion experiments employed 1 cm by 1 cm sections of equine nasal mucosa having a nominal thickness of 1 mm.

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## O24

### The role of photodynamic therapy in the management of oral dysplasia

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Head & Neck Oncology 2010, **2(Suppl 1):O24**

**Introduction:** Photodynamic therapy (PDT) is a minimally invasive surgical intervention used in the management of tissue disorders. It can be applied before, or after, any of the conventional modalities, without compromising these treatments or being compromised itself. PDT is valuable for potentially malignant disorders.

**Materials and methods:** In this prospective study, a total of 147 consecutive patients with potentially malignant disorders were treated with surface illumination PDT, using 5-ALA or mTHPC as the photosensitizer. The average age was  $53 \pm 8.9$  years. Patients' recovery was uneventful and no complications reported. Comparisons with the clinical and histopathological features and rate of recurrence as well as malignant transformation were

made. These patients were followed-up for a mean of 7.3 years, and biopsies taken in case of changes indicative of malignant development.

**Analysis and results:** The results were analysed by an independent statistician using SPSS 17. The results were cross tabulated and the Chi-squared statistic was used to test for differences in the case-mix.

Homogenous leukoplakias were identified in 55 patients, non-homogenous leukoplakias in 73 patients, whereas 19 patients had erythroplakias. Ex- and current lifelong smokers formed 84.4% of the recruited patients. While people who currently smoke and drink formed 38.1% (56 patients) of the cohort. Erythroplakias were mainly identified in heavy lifelong smokers. The most common identified primary anatomical locations were the lateral border of tongue, floor of mouth and retromolar area. Moderate dysplasia was identified in 33 patients while 63 patients had severe dysplasias; and 32 patients had a histopathological diagnosis of carcinoma *in situ*.

The rate of first recurrence in laser surgery was approximately 11.6%. The rate of recurrence had no significant association with the location or the severity of epithelial dysplasia. Malignant transformation was observed in 11 patients (7.5%), in the tongue, floor of mouth and retromolar area. Recurrence and malignant transformation was mainly identified in erythroplakias and non-homogenous leukoplakias. The final outcome of the cohort showed that 11 (7.5%) suffered from progressive disease, 5 (3.4%) has stable disease, 12 (8.2%) were considered partially responsive to the therapy. Complete response was identified in 119/147 patients (81%).

**Conclusion:** 5-ALA-PDT and/or mTHPC-PDT offer an effective alternative treatment for potentially malignant oral disorders. It is associated with excellent functional and cosmetic results and can be used in conjunction with other standard therapies.

## O25

### Photodynamic therapy of laryngeal cancers

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Head & Neck Oncology 2010, 2(Suppl 1):O25

Carcinoma of the larynx accounts for 25–30 percent of all carcinomas of the head and neck. Early carcinomas of the larynx (Tis or T1) and severe dysplasia are presently treated with either radiation therapy or surgery alone. Radiation therapy, however, has significant disadvantages including mucositis during and for potential prolonged periods after therapy, permanently altered voice quality, dysphagia, chondroradionecrosis of the larynx and trachea, and the extensive length of therapy (6–7 weeks). Surgical therapy for early carcinomas of the larynx includes performing a partial cordectomy or hemilaryngectomy. Although cure rates are high, surgical removal of portions of the vocal cord or hemilarynx results in significant alteration of the quality of voice.

Photodynamic therapy has been demonstrated to be effective in the treatment of early carcinomas of the larynx, Tis and T1, with cure rates of 90% with follow-up to 236 months. The advantage of PDT therapy for early carcinomas of the larynx is the ability to preserve normal endolaryngeal tissue while effectively treating the carcinomas. This results in improved laryngeal function and voice quality. Furthermore, PDT requires a short duration of therapy as compared to radiation therapy, is repeatable and carries less risk than surgical therapy and is performed as an outpatient noninvasive treatment. Importantly, the use of PDT does not preclude the use of radiotherapy or surgery in the future for new primary or recurrent disease.

## O26

### Ultrasound-guided interstitial photodynamic therapy for deeply seated pathologies: assessment of outcome

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Head & Neck Oncology 2010, 2(Suppl 1):O26

**Introduction:** Photodynamic therapy, the fourth oncological intervention modality has proved its successfulness in the management of variety of pathologies involving the human body.

Our aim in this prospective clinical study was to evaluate the outcome following ultrasound-guided iPDT of pathologies involving the head and neck region as well as the upper and lower limbs. Patients' reports on quality of life with clinical and radiological evaluation were the main end point parameters used to assess the outcome.

**Materials and methods :** One hundred and ten patients were referred to the UCLH Head and Neck Centre for treatment of various deep-seated pathologies. These included tumours in the head and neck as well as vascular and hamartomatous malformations of the limbs. After multidiscipline discussion, all patients underwent interstitial photodynamic therapy under general anaesthesia, using 0.15 mg/kg mTHPC as the photosensitising agent. Following treatment, patients were followed-up for a mean of 26 months.

**Results:** All 4 patients who presented with visual problems reported improvement after treatment. Also, 17/24 reported improvement of breathing. Improvement of swallowing was reported by 34/40 patients; while speaking improvement was evident in 18/26 patients and 39/47 reported reduction in the disfigurement caused by their pathology. 6/8 patients with impeded limb function reported some degree of improvement.

Clinical assessment showed that more than half of the patients had "good response" to the treatment and a third reported "moderate response". Radiological assessment comparing imaging 6-week post-PDT to the baseline showed moderate response in half of the patients and significant response in 17 patients.

**Conclusion:** This study on 95 patients with deep-seated pathologies undergoing interstitial photodynamic therapy provided evidence that PDT can be the fourth modality in the management of tissue disease.

## O27

### Photodynamic therapy as the "last hope" for tongue-based carcinoma

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Head & Neck Oncology 2010, 2(Suppl 1):O27

**Introduction:** The management of base of tongue carcinoma continue to be a major challenge in head and neck oncology. Our aim in this prospective study was to evaluate the outcome following ultrasound-guided interstitial photodynamic therapy (US-iPDT) of stage IV tongue base carcinoma. Patients' reports on quality of life with clinical and radiological evaluation were the main end point parameters used to assess the outcome.

**Material/methods:** Thirty-three consecutive patients were referred to the UCLH Head and Neck Centre for treatment of advanced tongue base cancer. Two-thirds of the patients had not been offered further treatment. It was decided that the only available option is to offer US-iPDT under general anaesthesia, using mTHPC as the photosensitising agent. Following treatment, patients were followed-up for a mean of 18 months (Min 8, Max 44).

**Results:** 11/14 patients who presented with breathing problems reported improvement after treatment. Also, 28/33 reported improvement of swallowing. Improvement of speaking was reported by 15/18 patients.

Clinical assessment showed that two-thirds of the patients had "good response" to the treatment and a third reported "moderate response". Radiological assessment comparing imaging 6-week post-PDT to the baseline showed stable pathology with no change in size in 6 patients, minimal response in 7 patients, moderate response in 12 patients and significant response in 5 patients.

Eleven patients died; Seven of which due to locoregional metastasis. Kaplan-Meier survival curve was generated from the survival and follow-up data.

**Conclusions:** Photodynamic therapy is a successful palliative modality in the treatment of advanced tongue base carcinoma.

## O28

### The effect of PDT on H. influenzae biofilm in vivo

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Head & Neck Oncology 2010, 2(Suppl 1):O28

**Introduction:** Biofilm formation has been demonstrated for many mucosal pathogens such as Haemophilus influenzae. The presence of

mucosal biofilms with chronic otitis media with effusion (COME) suggests that bacteria do not clear by antibiotics.

**Aim:** To test the effect of photodynamic therapy (PDT) on *H. influenzae* induced biofilm in vivo.

**Methods:** Sixteen bullae of 8 gerbils were injected with 200µl (107CFU/ml) of *H. influenzae* and formation of biofilms in the bullae was obtained by 5 days. The bullae were divided into control, laser, photofrin, and PDT groups. The control group received no treatment. For laser group, 120 J/cm<sup>2</sup> (100 mw x 20 min) of 632 nm LD laser was irradiated into the bullae by a fiber inserted directly into the bullae. For photofrin group, photofrin 40 µl (1 mg/ml) were injected into the bullae. For PDT group, photofrin same as in photofrin group was injected into the bullae and LD laser was irradiated into the bullae same way as in laser group. The mucosal tissues in bullae were examined by H/E staining, and SEM.

**Results:** The control, laser, and photofrin groups have shown well formed biofilm. Two third of the PDT group bullae have shown well resolved biofilm while 1/3 of the bullae have shown incompletely resolved biofilms.

**Conclusion:** The results of this study demonstrated that PDT appears to be effective to treat experimental *H. influenzae* induced biofilms in vivo. Further trial in different dose combinations of photosensitizer and laser needs to be tried for better results in PDT group.

**Clinical implication:** PDT may be an alternative to antibiotic treatment on otitis media with biofilm formation.

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## O29

### Toward endoscopic ultrafast laser microsurgery of vocal folds

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Head & Neck Oncology 2010, 2(Suppl 1):O29

Vocal fold scarring can arise from disease or post-surgical wound healing and is one of the predominant causes of voice disorders. Focused ultrafast laser pulses have been previously demonstrated to create tightly confined sub-surface ablation in a variety of tissue, including vocal folds. Here, we demonstrate how we can take advantage of this unique ability of ultrafast laser ablation to create sub-surface vocal fold microsurgeries with a goal for eventually creating a plane in tough sub-epithelial scar tissue into which biomaterials can be injected. Specifically, we create sub-epithelial ablations in vocal fold tissue in under 1 minute using sub-µJ pulses from a compact, commercially available amplified ultrafast laser system from Raydiance Inc., operating at a 500 kHz repetition rate. The use of relatively high repetition rates, with a small number of overlapping pulses, is critical to achieving ablation in reasonable amounts of time while still avoiding significant heat deposition. Additionally, we use multiphoton fluorescence of the ablation region and SHG imaging of collagen fibers to obtain visual feedback of tissue structure and confirm successful ablation. Lastly, we demonstrate microsurgery using amplified ultrafast laser pulses delivered through over 1 meter of air-core photonic crystal fiber to a laser scanning microsurgery probe, illustrating the feasibility of developing an ultrafast laser surgical laryngoscope. We aim to further develop this clinical tool through demonstration of laryngeal microsurgery using a compact laser system in conjunction with a larynx-specific fiber-based surgery probe.

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## O30

### Femtosecond laser microstructuring and bioactive nanocoating of titanium surfaces in relation to chondrocyte growth

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Head & Neck Oncology 2010, 2(Suppl 1):O30

**Introduction:** Titanium implants can be regarded as the current gold standard for restoration of sound transmission in the middle ear following destruction of the ossicular chain by chronic inflammation. Many efforts have been made to improve prosthesis design, while less attention had been given to the role of the interface. We present a study on chemical nanocoating on microstructured titanium contact surface with bioactive protein.

**Materials and methods:** Titanium samples of 5 mm diameter and 0,25 mm thickness were structured by means of a Ti:Sapphire femtosecond laser operating at 970 nm with parallel lines of 5 µm depth, 5 µm width and 10µm inter-groove distance. In addition, various nanolayers were applied to PVDF foils, while bone matrix protein 7 (BMP-7) was linked to the outer coating layer.

**Results:** Chondrocytes could be cultured on microstructured surfaces without reduced rate of vital/dead cells compared to native surfaces. Chondrocytes also showed contact guidance by growing along ridges particularly on 5µm lines. On PVDF foils, chondrocyte growth was doubled in contact with BMP-7 compared to hydrogel layer or native surface.

**Discussion:** According to these results, relative preference for cell growth on titanium prosthesis contact surfaces compared to non-contact surfaces (e.g. prosthesis shaft) can be achieved by nanocoating. Relative selectivity induced by microstructures for growth of chondrocytes compared to fibrocytes is subject to further evaluation.

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## O31

### Laser hearing aids

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Visible light is a source of energy known to activate the visual system through absorption by photoreceptors in the eye. When the so-called stress-confinement condition is fulfilled, laser light can induce an acoustic signal through an optoacoustic effect. We sought to assess, if visible light with parameters that induce an optoacoustic effect (i.e., 532 nm, 10 ns pulses) could be used to stimulate the peripheral hearing organ at ear drum and middle ear level.

Auditory brainstem responses (ABRs) were recorded preoperatively in anesthetized guinea pigs to confirm normal hearing. After opening the bulla, a 50-µm core-diameter optical fiber was positioned first in the outer ear canal directed towards the tympanic membrane and then within the bulla directed towards the bony structures within the middle ear as well as towards the round window membrane.

Optically-induced ABRs (OABRs), similar in shape to those of acoustic stimulation, were elicited with single pulses after stimulation within the outer as well as the middle ear. The OABR peaks increased with energy level (0.6-23 µJ/pulse) but varied in magnitude depending on the location of stimulation.

Our findings demonstrate that visible light can be used to activate the peripheral hearing organ when applied at the ear drum level or on bony structures within the middle ear that can transmit vibrations to the cochlea or inner ear. We propose that this novel, non-contact laser stimulation method could be used to improve implantable and non-implantable hearing aids as well as for research purposes.

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## O32

### CO2 laser myringoplasty using handheld waveguide

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Head & Neck Oncology 2010, 2(Suppl 1):O32

**Introduction:** Eustachian tube dysfunction is very common and is the predominant cause of otitis media with effusion. Negative middle ear pressure generated by Eustachian tube dysfunction can cause deformation of the collagen layer in the ear drum. Collagen becomes stretched and loses its orderly array. Over time, deep retraction pockets form. If left untreated, the tympanic membrane becomes prone to cholesteatoma formation. CO2 laser energy interacts with collagen and causes it to return to its natural configuration.

**Objective:** To describe and review our results treating tympanic membrane retraction pockets using laser myringoplasty with a novel hand-held flexible photonic band gap fiber CO2 laser.

**Methods:** A hand-held flexible fiber CO2 laser system (Omniguide BeamPath) was used to treat tympanic membrane retraction pockets. The fiber tip was held approximately 3 mm from the membrane surface



producing a spot size of 570 microns at the setting of 2 watt per 100 millisecond pulse. Pulses were administered until the desired level of membrane contraction was achieved. A tympanostomy tube was then placed in the affected ear.

**Results:** We reviewed our results with this procedure on 22 patients (40 ears). The average pre-operative air bone gap (ABG) pure-tone average (PTA) was 15 dB. The average post-operative ABG PTA was 6 dB ( $p=0.002$ ). All patients had satisfactory contraction of the atelectatic segment. There were no adverse events recorded.

**Conclusion:** Laser myringoplasty using the Omniguide hand-held flexible fiber CO<sub>2</sub> laser provides immediate hearing improvement and eardrum contraction. Long-term results are pending.

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### O33

#### The use of CO<sub>2</sub> laser in tumour resection of the oropharyngeal region

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Head & Neck Oncology 2010, 2(Suppl 1):O33

**Introduction/aims:** The incidence of oral squamous cell carcinoma (OSCC) remains high. Oral carcinomas are the sixth most common cancer in the world.

This prospective study evaluated the oncological outcomes following transoral CO<sub>2</sub> laser resection of T1/T2 N0 OSCC. Patients' three-year disease-specific survival and disease-free survival were evaluated, including postoperative complications.

**Material/methods:** The patients' data included a range of clinical, operative and histopathological variables related to the status of the surgical margins. Data collection also included recurrence, cause of death, date of death and last clinic review.

Ninety patients participated in this study. Their mean age at the 1<sup>st</sup> diagnosis of OSCC was 63.5 years. Two-thirds of the patients were Caucasians. Primary sites were mainly identified in the tongue, floor of mouth and buccal mucosa. Pathological analysis revealed that half of the patients had moderately differentiated OSCC.

**Results:** Tumour clearance was primarily achieved in 73 patients. Follow-up resulted in a 3-year survival of 87.8%. Recurrence was identified in 12% of the patients. The mean age of 1<sup>st</sup> diagnosis of the recurrence group was 76.4 years. Most common oral sites included the lateral border of tongue and floor of mouth. Recurrence was associated with clinical N-stage disease. The surgical margins in this group were also evaluated.

**Conclusions:** Squamous cell carcinoma of the oral cavity has a poor overall prognosis with a high tendency to recur at the primary site and extend to involve the cervical lymph nodes. The overall results of this study were comparable with those of other, larger studies.

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### O34

#### CO<sub>2</sub> laser ablation of oropharyngeal dysplasia

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Head & Neck Oncology 2010, 2(Suppl 1):O34

**Introduction:** The use of CO<sub>2</sub> laser in the management of oral dysplastic lesions have been put into practice for more than a few years now. The main advantage is the decrease in local tissue morbidity. Very few studies have evaluated recurrence, malignant transformation and overall outcome in patients undergoing such procedure.

**Materials and methods:** In this prospective study, a total of 123 oral dysplastic lesions from 77 consecutive patients were treated with CO<sub>2</sub> laser (resection and/or ablation). The average age was 58±4.8 years. Patients' recovery was uneventful and no complications reported. Comparisons with the clinical and histopathological features and rate of recurrence as well as malignant transformation were made. These patients were followed-up for a mean of 6.4 years, and biopsies taken in case of changes indicative of malignant development.

**Analysis and results:** The results were analysed by an independent statistician using SPSS 17. The results were cross tabulated and the Chi-squared statistic was used to test for differences in the case-mix.

Homogenous leukoplakias were identified in 31 patients, non-homogenous leukoplakias in 34 patients, whereas 12 patients had erythroplakias. Ex- and lifelong smokers formed 88.3% of the recruited patients. While people who currently smoke and drink formed 55.8% (43 patients) of the cohort. Erythroplakias were solely identified in heavy lifelong smokers. The most common identified primary anatomical locations were the lateral border of tongue, floor of mouth and buccal mucosa. Moderate dysplasia was identified in 42 patients while 18 patients had severe dysplasias.

Laser resection margins in selected cases (68 patients) were clear in 53 and showed mild-moderate dysplasia in the involved margins. The rate of recurrence had no significant association with the location or the severity of epithelial dysplasia. The rate of first recurrence in laser surgery was approximately 19.5%. Malignant transformation was observed in 8 patients (10.4%), in the tongue and the floor of mouth. Recurrence and malignant transformation was mainly identified in erythroplakias and non-homogenous leukoplakias.

**Conclusion:** Recurrence and/or malignant transformation of oral dysplasia have been observed following laser surgery. Laser resection/ablation is recommended for oral dysplasia to prevent not only recurrence and malignant transformation, but also postoperative oral dysfunction encountered by other conventional modalities. In this study, smoking and drinking were associated with oral erythroplakia formation; the latter was identified to recur and transform into squamous cell carcinoma more than other lesions.

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### O35

#### Fiber-based microendoscopic multiphoton imaging

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Head & Neck Oncology 2010, 2(Suppl 1):O35

We developed a multiphoton microscope which integrates an all normal dispersion fiber laser, a double cladding photonic crystal fiber and a MEMS mirror scanner based hand-held probe. The fiber laser has a central wavelength of 1.06  $\mu$ m, a repetition rate of 76MHz and maximum average output power of more than 1W. The MEMS mirror based probe is compact and Second harmonic generation and two photon excited fluorescence images of biological sample were demonstrated.

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### O36

#### Design, conduct and challenges of a clinical trial utilizing elastic light scattering spectroscopy in the thyroid

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Head & Neck Oncology 2010, 2(Suppl 1):O36

Thyroid cancer is the most common endocrine malignancy. The standard of care in the management of a patient with a thyroid nodule is fine-needle aspiration biopsy (FNA) with cytological evaluation. While 5–10% of nodules are malignant, 10–25% of FNAs are indeterminate. Consequently, about twice as many patients undergo surgery for a suspicious lesion that turns out to be benign as undergo surgery for a known malignant lesion. A more accurate molecular and ultrastructural based algorithm would be useful to improve diagnostic accuracy. Noninvasive optical tissue diagnosis mediated by fiber-optic probes can be used to perform non-invasive, or minimally-invasive, real-time assessment of tissue pathology in-situ. Elastic light-scattering spectroscopy (ESS) is a point spectroscopic measurement technique, which is sensitive to cellular and subcellular morphological features. Normal and abnormal tissues can generate different spectral signatures as a result of changes in nuclear size, density, and other sub-cellular features, the optical-spectroscopy equivalent of histopathological readings. ESS is optimal for use in the small-volume area as found in thyroid FNA. An important advantage of ESS is that it provides an objective and quantitative assessment of tissue pathology that may not require on-site special expertise and subjective image interpretation as in conventional histopathology. Here we will describe our experience in the clinical application of elastic scattering spectroscopy in the thyroid.

### O37

#### CO<sub>2</sub> laser transoral laser microsurgery of head and neck cancer: lessons learned over ten years

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*Head & Neck Oncology* 2010, **2(Suppl 1)**:O37

**Background:** CO<sub>2</sub> transoral laser microsurgery (TLM) is an emerging technique for the management of laryngeal cancer and other head and neck malignancies. This technique has become more widely used by head and neck surgeons progressively replacing traditional open surgical procedures because it is better at preserving organ function with lower overall morbidity. The CO<sub>2</sub> laser is coupled to a micromanipulator and microscope, which provides enhanced tumor visualization and the ability to perform precise tissue cuts, obtain excellent hemostasis, and avoid damaging the surrounding tissues and structures that are transected during open surgical procedures.

**Objectives:** To summarize our experience using the CO<sub>2</sub> laser for the transoral resection of head and neck cancer, and discuss strategies and solutions for situations encountered during laser resections.

**Material and methods:** The basic principles and approach of performing TLM using CO<sub>2</sub> laser for different otolaryngologic malignancies will be discussed. The benefits of using CO<sub>2</sub> TLM over traditional surgery, common complications, and different settings used depending on the location of the tumor and as well as the several lessons learned over the years will also be discussed.

**Conclusion:** CO<sub>2</sub> laser is the best-suited laser for TLM in treatment of head and neck cancer. Over the years the improved instrumentation, demonstration of oncologic effectiveness, clinical experience using TLM and decreased morbidity has led to an increased utilization of TLM by head and neck surgeons. Successful surgery requires adequate visualization, precise cutting, controlled depth of tissue penetration, and ability to obtain tissue hemostasis. The full spectrum of laser power settings, spot sizes and energy pulse delivery modes is utilized to resect mucosa, fat, muscle, connective tissue and cartilage while avoiding inadvertent damage to nerves and large vessels, and obtaining adequate hemostasis.

### O38

#### Lasers, a tool for soft cochleostomies

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*Head & Neck Oncology* 2010, **2(Suppl 1)**:O38

Advancements in implantable auditory prostheses now demand preservation of residual auditory function following the surgery. Atraumatic cochleostomy formation is essential to this goal. Clinically reported hearing outcomes in human implantation are still quite variable in this regard. The objective of the study was to determine whether a CO<sub>2</sub> laser operated with a handheld hollow waveguide can consistently produce cochleostomies without damaging the residual auditory function. Human temporal bones were used to present a novel method creating a cochleostomy and adult guinea pigs were used to test whether cochlear function will be affected by the procedure. Baseline cochlear function was determined by recording compound action potential thresholds evoked by acoustic tone pips. Measurements were conducted at 6 steps per octave and 5 octaves starting at 50kHz. The sound level as attenuated from 0 to 80dB in steps of 5dB.

The human temporal bones were mounted and a standard approach through the facial recess was used to access the cochlea. The lateral bone was thinned at the basal turn with a motorized drill (Anspach Effort<sup>®</sup>, Palm Beach Gardens, FL, USA). Care was taken not to open the cochlea. The final opening of scala tympani was made with the handheld CO<sub>2</sub> laser fiber (BeamPath<sup>®</sup> OTO-S, OmniGuide<sup>®</sup> Inc., Cambridge, MA, USA) and a Sharplan 20C CO<sub>2</sub> laser (Lumenis<sup>®</sup>, Yokneam, Israel). In addition to describing the surgical approach, our experiments have demonstrated that for a careful selection of the laser's power, the safety range for the laser is superior to the safety range of drilling. Particularly

important is the finding that multiple laser pulses through the same cochleostomy do not further increase the initial compound action potential (CAP) threshold elevation. Moreover, multiple laser pulses at different locations of the cochlea do not further increase the initial CAP threshold elevation observed after the first laser pulse. When opening the inner ear, safe laser settings would be up to 4W, at pulse durations of 100ms in single pulse mode.

### O39

#### Current Munich status concerning in-vivo optical coherence tomography for differentiating lesions of the upper aerodigestive tract

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**Objective:** Non-invasive differentiation of pre- and early malignant mucosal changes may be helpful to reduce the morbidity and shorten the time to diagnosis for the patients concerned. Optical Coherence Tomography (OCT) seems to be well suited to reach this goal.

**Methods:** 61 patients with a total of 82 primary leukoplakic or erythroplakic mucosal lesions of the upper aerodigestive tract (OADT) were prospectively examined using an in-vivo, time-domain OCT (Niris<sup>®</sup>, Imalux Corporation, USA; lateral resolution 25 µm / axial resolution 15 µm) so far. The results were subsequently correlated to histopathology of tissue biopsies taken from the same areas. Additionally, intensity profiles of OCT images were evaluated concerning their ability to differentiate dysplasia from hyperplasia.

**Results:** Down to a depth of 1.5 mm, microanatomical structures were clearly identifiable on the OCT images. Concerning the ability to differentiate non- and early invasive lesions, OCT reached a sensitivity of 100% and a specificity of 92% or 75% (investigator unblinded or blinded to visual inspection), respectively. False positive findings were mostly hyperplastic lesions with a significant broadening of the epithelial layer. Epithelial thicknesses measured on OCT images and histological slides correlated well ( $\kappa=0.63$ ), but were no indicators of either epithelial hyperplasia or different grades of dysplasia. Yet, OCT intensity profiles showed a statistically significant difference between dysplastic and hyperplastic lesions in a subset of cases (n=44).

**Conclusions:** The method seems highly promising for early, non-invasive tumour diagnosis in the UADT. Technical advances and an increase in patient numbers will help to define its clinical value in the near future.

### O40

#### Utilizing 5-aminolevulinic acid and pulsed dye laser for photodynamic therapy of oral leukoplakia – pilot study

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**Objective:** Determine the safety and efficacy of photodynamic therapy (PDT) in the treatment of oral leukoplakia with 5-aminolevulinic acid (5-ALA) and pulsed dye laser (PDL).

**Methods:** A total of 24 subjects, between 18 – 80 years old, with a confirmed diagnosis of leukoplakia with or without dysplasia, measuring at least 10 mm in diameter were enrolled in cohorts of 3 within 24 months. Twenty percent solution of 5-ALA, Levulan Kerastick<sup>™</sup> were applied to the lesions, for 1 to 3 hours, by utilizing custom fixtures made from hygienic polymer. The drug application was confirmed with Fluorescence diagnosis system (Dyaderm<sup>™</sup>). High power pulsed dye laser emitting 585-nm wavelength was used to activate the 5-ALA. The laser

dose was escalated from 6 to 8 J/cm<sup>2</sup>. The safety was evaluated via clinical observation 48 hours post treatment, and the clinical and pathological efficacy were evaluated 30 and days after treatment, respectively. Histopathology and immunohistochemistry were conducted on fixed tissue samples collected at screening and 90 days post treatments, from the lesion and an adjacent healthy site.

**Results:** No significant adverse events and minor pain (3 out of 10) was observed, during and following PDT in the safety phase of the study. The maximum tolerated dose was 8 J/cm<sup>2</sup>. Partial response was observed in 54% of the treated subjects and significant response was observed in 46% of the subject treated in the efficacy phase of the study.

**Conclusions:** Photodynamic therapy (PDT) with 5-Aminolevulinic Acid (5-ALA) and PDL could be use to regress oral leukoplakia. The treatment is safe and well tolerated. Thick and progress lesions require multiple treatments. An application time of 2 hours and laser radiant exposure of 8 J/cm<sup>2</sup> were found to be the best settings, in this study. The high power laser allows completing the laser therapy within 1-3 minutes. More work is underway to determine the optimal laser radiant exposure and drug application to improve the rate of complete regression.

#### O41

##### Emerging applications for OCT in the head and neck

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**Objectives:** To describe the current and promising new applications of the Optical Coherence Tomography (OCT) as a helpful tool when imaging the different sites in the head and neck. Using the OCT Niris system, which is the first commercially available OCT device for applications outside the field of ophthalmology.

**Methods:** We obtained OCT images of normal, benign, premalignant and malignant lesions in different areas of the head and neck. The OCT imaging system has a tissue penetration depth of approximately 1-2 mm, a scanning range of 2 mm and a spatial depth resolution of approximately 10-20 μm. Imaging was performed using a flexible probe in two different situations, the outpatient clinic and the operating room.

**Results:** High-resolution cross-sectional images from the larynx were obtained with the patient awake, without the need of general anesthesia. The OCT probe was inserted through the nasal cavity and placed in slightly contact with the laryngeal tissue, under direct visualization with a flexible fiberoptic. Images of other sites, such as the oral cavity, nasal cavity, and ears were also obtained in various settings.

**Conclusions:** This system is non invasive and easy to incorporate into the operating room as well as to the outpatient clinic. It requires minimal set-up and requires only one person to operate the system. OCT has the distinctive capability to obtain high-resolution images, where the microanatomy of different sites can be observed. OCT technology has the potential to offer a quick, efficient and reliable imaging method to help the surgeon not only in the operating room but also in the clinical setting to guide surgical biopsies and aid in the decision making of different head and neck pathologies, especially those arising from the larynx.

#### O42

##### Measurement of epithelial thickness within the oral cavity using optical coherence tomography (OCT)

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Head & Neck Oncology 2010, 2(Suppl 1):O42

Optical coherence tomography (OCT) is a promising method in the early diagnosis of oral cavity cancer. The objective of the present study is to determine normal values of epithelial thickness in the oral cavity, as no such data are to be found in the literature. In healthy test persons, epithelial thickness of the oral mucosa was determined with the help of

OCT separately for each side at nine different locations. Special attention was directed to those sites having the highest incidence for the development of dysplasias and carcinomas. Depending on the location within the oral cavity, the epithelium demonstrated a varying thickness. The highest values were found in the region of the tongue and the cheek, whereas the floor of the mouth showed the thinnest epithelium. Our data serve as reference values for detecting oral malignancy and determining the approximate grade of dysplasia. In this circumstance, a differentiated view of the different regions is important due to the variation in thickness of the epithelium within the normal oral cavity.

#### O43

##### Towards early dental caries detection with OCT and polarized Raman spectroscopy

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In recent years, we have been developing optical coherence tomography (OCT) and polarized Raman spectroscopy (PRS) for the detection of early non-cavitated dental caries. OCT provides high resolution morphological depth imaging of incipient caries. With OCT, early lesions can be readily identified as regions of high light backscattering with depth into the enamel as compared to health sound enamel. From the OCT images, the lesion depth can be approximated to provide clinically useful information to guide treatment decisions. In addition, we have derived a parameter known as the optical attenuation coefficient in order to distinguish sound from carious enamel non-subjectively. OCT is being combined with PRS since regions of high light backscattering not related to caries development can lead to false-positive results. PRS provides biochemical specificity along with molecular structural/orientational information. With PRS, the Raman depolarization ratio calculated from the main phosphate vibration at ~959 cm<sup>-1</sup> from parallel- and cross-polarized Raman spectra allows discrimination between sound and early developing caries. Early studies on lab bench instrumentation are now being translated into fibre-optic based devices for intra-oral use in patient volunteers for clinical validation. In combination, OCT and PRS have potential for detecting and monitoring early lesions with high sensitivity and high specificity.

#### O44

##### Photochemical internalization

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**Introduction/aims:** Photochemical internalization (PCI) is a novel technology facilitates the delivery of macromolecules into cytoplasm. The initial mechanism and practical application was described by Berg et al. in 1999.

This, first in human trial, is an open, phase I dose escalating study to evaluate the safety and tolerance of the photosensitizer (amphinex) that is used to initiate the photochemical internalization process with bleomycin as the chemotherapeutic agent. We present our preliminary report following the management of 11 patients with head and neck tumours.

**Material/methods:** Patients monitoring and follow-up start from Day -14 and continue to Day 28. The drug safety and tolerance are assessed by measuring the concentration (PK) of amphinex in plasma and urine after centrifugation and samples freezing under -20°C. Assessment of amphinex accumulation in skin is performed by fluorescence spectroscopy. Skin sensitivity testing is conducted using white light.

**Results:** The 11 patients in this trial received 0.25-1.0 mg/kg amphinex (Day 0) approximately 93hrs prior to a slow bleomycin infusion (15000 u/m<sup>2</sup>) and subsequent illumination (Day 4) with 652 nm diode laser with 60 J/cm<sup>2</sup>

to initiate PCI. No immediate clinical symptoms were reported prior to amphinex administration and no immediate drug adverse events were identified.

**Conclusions:** The most striking finding is the dramatic tumour responses. Complete tumour response of the target lesions of 10/11 patients was achieved. The starting dose of Amphinex for the study was set at a level not expected to trigger a PCI response, however there appeared to be a localized synergistic effect with photo-activation.

#### O45

##### Treatment planning for Interstitial Photodynamic Therapy for head and neck cancer

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We are investigating the feasibility of interstitial (iPDT), using multiple linear light sources positioned within the tumour. In an on-going feasibility study, 16 patients with incurable SCC at the base tongue have been treated with iPDT as a last treatment option. Preliminary results are encouraging with a long-term complete response in 8 out of 16 patients who have failed standard treatment. There is strong evidence that the partial responders are a direct result of inadequate light delivery. Accurate light dosimetry has not yet been performed during iPDT in head and neck, we therefore propose the development of dedicated iPDT verification and planning technology to improve the clinical response and reduce the occurrence of side effects.

We propose to develop a 3-step approach: 1) Pre-treatment planning, based on MRI in which a tumour and a risk volume are identified. A simple planning algorithm will then estimate the optimal positions, amount and lengths of the linear light sources. 2) Verification 3D imaging e.g. X-ray C-arm of the source locations after placement, 3) Modification of the pre-treatment planning based on the actual source locations. The modification step will be executed in two phases; initially aiming to implement a simple planning strategy. This approach will be based on iPDT induced tissue damage and does not take into account any patient specific PDT parameters. In the second phase we aim to investigate methods to measure the actual light transport within the tumour and risk volumes. These measurements enables for a patient tailored inverse planning strategy aiming for improved accuracy. The performance of the proposed planning strategies and their clinical results will be evaluated by mutual comparison and previous results.

The clinical results so far indicate good conservation of functions i.e. swallowing, and excellent local control of the tumour. Interstitial PDT may offer an excellent alternative or adjuvant for conventional treatment modalities.

#### O46

##### Non-invasive measurement of photosensitiser concentration using fluorescence differential path-length spectroscopy: validation for different liposomal formulations of m-THPC: Foscan, Foslip and Fospeg

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As previously described, Fluorescence differential path length spectroscopy (FPDS) can determine chromophore concentrations non-invasively after injection with m-THPC (Foscan) in the rat liver [1]. Our first aim is to validate FDPS for two other, liposomal formulations of m-THPC; pegylated liposomes (Fospeg) and conventional liposomes (Foslip), and compare them to Foscan. As a proof of principle we use the highly vascularised, optically homogenous liver of the rat [1] Validation of the FDPS-measurements was done by chemical extraction of the same liver [2].

Our second aim is to validate FDPS measurements of the tongue, which is optically less homogenous, but clinically more relevant. After successful validation in both liver and tongue tissue, the pharmacokinetic-profile in other tissue types could be assessed by FDPS alone. Therefore, FDPS can lower the need for labour-intensive chemical extraction. Fifty-four male Wistar rats were intravenously injected with one of the three formulations of m-THPC; eighteen rats for each formulation. All rats were injected with 0.15 mg kg m-THPC. FDPS measurements were performed on liver, palate, tongue, spleen and kidney 2, 4, 8, 24, 48, and 96 h after m-THPC administration. For validation of our FDPS measurements, liver and tongue were harvested for chemical extraction [2]. Concentration estimates in liver and tongue measured by FDPS are here compared with chemical extraction.

At the HNODS-meeting we will present the results of our first step in the validation of FDPS; the correlation of FDPS measurements with chemical extraction for the three different formulations in the liver.

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Cite abstracts in this supplement using the relevant abstract number, e.g.: de Visscher *et al.*: Non-invasive measurement of photosensitiser concentration using fluorescence differential path-length spectroscopy: validation for different liposomal formulations of m-THPC: Foscan, Foslip and Fospeg. *Head & Neck Oncology* 2010, 2(Suppl 1):O46