For clinical photodynamic therapy basic knowledge on light transport in tissue is essential for the development of devices and strategies for delivering light to the tissue being treated. The dosimetry of light in the patient during treatment is essential to check the actually delivered fluence rates and enables compensation of changes in light distribution that occur during therapy.

New applications of PDT in head and neck tumours

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Head and Neck Cancer

Squamous cell carcinoma of the head and neck is world wide one of the major malignancies. Nasopharynx carcinoma (NPC) occurs sporadically in the west of the world but it is endemic in Southern China where it is the third most common form of malignancy among men with incidence rates of between 15 and 50 per 100.000. The geographical pattern of incidence suggests an interaction between environmental and genetic factors. The usual treatment of nasopharyngeal cancer consists of (neo-adjuvant) chemotherapy followed by high dose radiotherapy or, more recently, the concomitant chemo-radiation protocols. The high radiation dose necessary for this treatment requires the use of high-precision techniques such as brachytherapy and stereotactic radiotherapy, in order to limit the exposure of critical structures such as the spinal cord, the optic nerve and the optical chiasma. In practice this leads to external radiotherapy followed by a local booster using brachytherapy or stereotactic radiotherapy. This approach has several lasting side effects such as xerostomia (dry mouth). As this therapy is aimed at giving the maximum tolerable radiation dose possible to the critical structures, additional radiotherapy is not possible in cases of recurrence because sub-critical damage to normal tissue is long-lasting. Even in the treatment of small tumors in the oral cavity, tonsil and tongue, surgery and radiotherapy can cause considerable morbidity, such as xerostomia, disfiguration, and impairment of important vital functions (swallowing and speech).

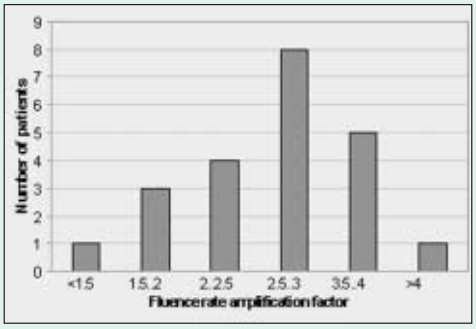

Figure 1. *The importance of in vivo dosimetry. Fluence rate amplification factors, measured in 22 patients receiving PDT for Barrettís oesophagus. Dosimetry based on an average fluence rate amplification factor of 2.75 would result in serious overtreatment of 6 out of 22 patients and a serious under-treatment of 8 out of 22.*

At present we are investigating the possibilities for PDT in this field as an alternative or additional treatment modality. We are focussing on 2 fields: intra-cavitary treatment of cancer in the nasopharynx and interstitial treatment of tumours in the base of the tongue. There is considerable experience with the photosensitiser Foscan for lesions in the oral cavity. The challenge we face is to facilitate an accurate, controllable and reproducible approach to the delivery and monitoring of light to these tumour regions that are more difficult to acces. This is essential for local control of the tumour, while limiting the PDT induced tissue damage to critical structures.

In vivo light dosimetry

The study of light propagation and light dosimetry in mammalian tissues began with the development of dermatological phototherapy and PDT in the early 1980's. Since then, measurement and theoretical calculation of the light distribution in various tissue have developed in parallel with PDT. The propagation of light in biological tissues is strongly influenced by the strong scattering of light. With typical mean-free paths of less than 0.1 mm, the light is scattered many times before it is absorbed. Hence, highly diffuse light distributions are generated. In the wavelength bands used for PDT the diffuse penetretration of light ranges from a few mm to 1 cm. Initially, light dosimetry consisted of estimating the delivered dose from measurement of the surface irradiance. Measurement of the diffuse light, the fluence rate, proved to be much more accurate, especially in hollow organs. In hollow organs the actual fluence rate

at the surface is strongly increased due to multiple diffuse reflections from the tissue. This ***fluence rate amplification*** varies with the shape of the cavity, but has been reported to be as high as a factor of 7.5 for the bladder. Special fluence rate detectors were developed for measurement of diffuse light in vivo, but accurate calibration of these devices is still a matter of scientific discussion. In situ fluence rate measurements in complicated geometries, such as the bladder, the oesophagus, the oral cavity, the thoractic cavity and the bronchi emphasised the need for dedicated light delivery systems with an integrated in situ fluence rate measurement. In the past, such a device was successfully developed for the bladder, and recently a prototype for the oesophagus has been developed in our group. We have done an extensive clinical evaluation of this device for PDT of Barrett's mucosa (early cancer of the esophagus). The results showed a dramatic variation between patients, indicating that it is of vital importance to further develop instrumentation for integrated light delivery and in situ light dosimetry. Such instrumentation may be of great clinical (and commercial) value because it may significantly contribute to an increase in clinical response and a decrease in complications due to overtreatment.

PDT in the nasopharyngeal cavity

The nasopharyngeal cavity is located deep in the skull and can be accessed through the nose or through the oral cavity. For interstitial radiotherapy a flexible silicone device was developed in the past that can be positioned in the nasopharynx through the mouth (fig 2a). We have developed a modified device that can be used for delivering light while at the same time shielding critical areas we do not to damage. Fig 2b shows a drawing of the light applicator inside the skull with the optical fiber used for delivering light present. The red line of the optical fiber represents the cylindrical diffusing end where the light from the laser is radially emitted. Additional fibers for measurement of the fluence rate during treatment can be entered through the mouth or the nose. The light delivery device has been tested in 5 healthy volunteers and showed a reproducible fluence rate distribution with a reasonable homogeneity in the target area and very low values at the critical areas such as the soft palate. A typical result from a volunteer is given in figure 3. Early 2005 a pilot study comprising the experimental treatment of 25 patients will start in Indonesia.

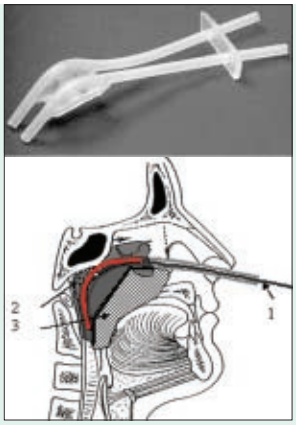

Figure 2. *a) Basic shape of the light applicator originally developed for Brachytherapy and b) Position of the light application device with respect to the anatomical location. For treatment, an optical cylindrical diffuser fibre (1) that emits the laser-light diffusely over a 60mm length will be used. The tumour (2) is usually localised along the outer curve of the applicator. The thick black line represents an example of a structure intended to shield light*

Interstitial PDT

The limited penetration of light in tissue (~10 mm) limits the size of the tumours that can be treated successfully by irradiating the surface. Hence for the treatment of larger tumour volumes, like recurrent cancers in the base of the tongue, it is necessary to place multiple fibers inside the tumour volume. Interstitial PDT may offer an excellent alternative for surgery. The general approach we developed starts by inserting several needles (under total anaestesia) into the tumour volume. The needles are then replaced by transparent hollow catheters that can be visualised by X-ray using a wire with lead beads. Based on X-ray images taken under different angles combined with prior knowledge on the precise location of the tumour boundaries we can then determine the position and length of the linear diffusers needed for treatment. Treatment planning in interstitial PDT is essential, as in such a complicated geometry it is easy to generate a 'cold spot' that receives insufficient light and may cause the tumour to re-grow rapidly. Figure 4 describes a clinical example. The results so far indicate an excellent local control of the tumour, while keeping the nerves and vasculature of the tongue relatively undamaged. Based on our extensive knowledge on light dosimetry for PDT we can develop succesful treatment strategies for PDT in complex and geometries that are difficult to access such as the nasopharynx and embedded solid tumors.

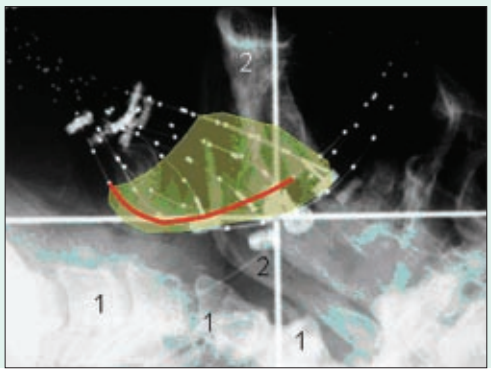

Figure 4. *X-ray image used for PDT treatment planning (1 spinal column, 2 lower jaw). In this patient a total of 8 catheters were inserted through the tumour. For taking the X-ray image each catheter contained a wire with equidistant (10 mm) lead beads. The yellow shaded area indicates the target area; i.e. the tumour plus a treatment margin. For each catheter the length and position of the optical fiber with linear diffuser is determined. The red line shows an example of this. For treatment each optical fiber is connected to the laser and laser light delivered to the tumor.*