New insights into photodynamic therapy of the head and neck
Karakullukçu, Barış

Citation for published version (APA):

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Chapter 9

General Discussion
This thesis is a combination of critical analysis of clinical mTHPC mediated photodynamic therapy (PDT) of head and neck tumors and developing techniques that can help us understand PDT and improve clinical results.

**Chapters 2 to 3** are retrospective analysis of the clinical experience with superficial PDT of the head and neck area. In the literature considerable data concerning the PDT of the head and neck tumors [1-21] exist, however there has never been an effort to compare PDT to more established conventional methods such as surgery or radiation therapy. The optimal way to compare two treatments is a controlled, blinded, randomized prospective trial. Unfortunately due to the logistic and ethics problems, such a trial was never performed. **Chapter 2** is an effort to mimic a randomized trial retrospectively. PDT of primary oral cavity tumors is limited to thin tumors (<5mm) without regional or distant metastasis. Patients, who were treated with surgery (without neck dissection) for tumors that fit the strict eligibility criteria of PDT, were identified and matched with the patients who underwent PDT at the same center. The non-randomized design of the study and its retrospective design introduce a selection bias inherent to this kind of analysis. To minimize the bias every compared clinical parameter was statistically identical for the two evaluated methods. Thus this analysis provides important evidence that clinically PDT of early stage oral cavity and oropharynx cancers is not inferior to surgery. However, in order to replace an established method, the new technique (PDT in this case) should have advantages, e.g. being more patient-friendly, better function preserving or, even better, superior in clinical outcome. There is room to improve clinical outcomes of PDT of HNSCC.

The published articles (including **Chapter 2** of this thesis) pool all oral cavity cancers together [4,6,9-21]. However tumors of different sub-sites have different clinical courses and prognosis. A cancer of the tongue acts very differently than a cancer of the alveolar process. Also, primary tumors have better prognosis than recurrences or second primaries. Therefore we have performed an in depth analysis of all patients who underwent PDT of the oral cavity and oropharynx to be able to identify clinical scenarios in which PDT needs to be improved. The result was a table stratified for location, T-stage, and primary versus secondary tumors (Table 2, **Chapter 3**). The histologically thinner dysplasia had better response rate than T1 and T2 tumors, but had higher chance of recurrence. The high recurrence rate is not very surprising, since dysplastic leukoplakia is a disease of the mucosa rather than a local problem. Even though easier to treat, by definition dysplasia recurs in the remaining mucosa of the oral cavity. Primary tumors reacted better to PDT than secondary tumors or recurrences. It is known that secondary tumors and recurrences are biologically more resistant to conventional treatments leading to inferior treatment results. Furthermore, prior treatments to the area may have caused unfavorable conditions for PDT. PDT is actually
needed to treat secondary tumors; since the oral cavity is already treated in these patients, further conventional treatments are usually undesirable. Therefore results of PDT need to be improved in the treatment of secondary tumors. Tumors of the alveolar process and retromolar trigon did not react to PDT as well as tumors of the tongue and floor of mouth. The possible reason is the complexity of the geometry in the former locations with areas of possible sub-optimal treatment.

Identification of these areas of sub-optimal treatment is important to improve the results. Spectroscopic analysis of the PDT process can help to detect the sub-optimally treated areas. Since the whole process of PDT is light related, it is only logical that monitoring light related parameters could provide better understanding of the individual treatments. Differences in parameters such as tissue optical properties (scattering and absorption) and subsequent differences in delivered fluence (rate), uptake of photosensitizer and tissue response to PDT can lead to wide variations in the dose delivered during PDT [22-24]. Each of these parameters can be different for individual lesions, patients, and they are interdependent and change dynamically during PDT. These dosimetric uncertainties can easily lead to under treatment of the tumor. Chapter 4 looks into possibilities with optical spectroscopy to evaluate the variables of PDT. By their nature, photosensitizers emit light at certain wavelengths (fluorescence). The amount of fluorescence, if correctly quantified, is representative of the concentrations of the photosensitizer in the tissues. Furthermore, during PDT, the photosensitizer is broken down with the fluorescence reflecting the decrease in photosensitizer content (photobleaching). In order to correctly quantify photobleaching, spectroscopy techniques should reveal data representative of the tissue of interest and able to account for large variations in background absorption and scattering. Fluorescence differential pathlength spectroscopy (FDPS), investigated in this thesis, is a method that has these qualities.

The technical specifications of FDPS, and acquisition of the spectra are described in detail in Chapter 5 of this thesis. The data obtained from the FDPS is fitted to an empirical model that incorporates the presence of a background scattering model that is appropriate for tissue, and quantifies the absorption related to various absorbers such as oxy-and deoxyhemoglobin and bilirubin. The model provides quantitative values of the blood volume fraction (BVF), the microvascular oxygen saturation, and the average blood vessel diameter, which can be used to correct the fluorescence for the effects of absorption. This corrected fluorescence is a combination of tissue autofluorescence, mTHPC fluorescence, and a small signal that is attributable to fluorescence from the optical components of the system. Therefore, this method can provide quantitative values with standard deviation for BVF, oxygen saturation, blood vessel diameter, and mTHPC fluorescence. The quality of the data fit can be evaluated...
by the residuals. The basis spectra of the oral cavity were obtained by applying the method to healthy volunteers. The FDPS analysis of three patients undergoing PDT for oral cavity tumors provided consistent high quality fits and correctly demonstrated photobleaching.

After the proof of principle, FDPS was used to monitor patients undergoing PDT of head and neck tumors (Chapter 6). The majority of FDPS acquisitions during the 27 superficial PDT sessions had high quality fits (72%). The fluorescence detected showed inter-subject variation but intra-subject consistency. The intra subject consistency indicates that the inter-subject variability is indicative of variations in pharmacokinetics of mTHPC with different concentrations of mTHPC in different tumors rather than due to variability of the measurement technique. The mean tumor to normal tissue ratio of mTHPC fluorescence was 1.5, with a high standard deviation of 0.66. In some cases the normal mucosa showed more fluorescence than tumor tissue. Consequently, the tumor selectivity of mTHPC is low, and the selective effect of PDT can be attributed to the careful application of light and protection of normal tissue by shielding, rather than selective uptake of the photosensitizer by the tumor. The absence of photobleaching at areas under the shielding (normal mucosa) demonstrates the effectiveness of the used shielding. In the majority of PDT sessions, the expected photobleaching was observed. In this study, three types of possible reasons of treatment failure were identified: low photosensitizer content in tumor, insufficient photobleaching of the tumor and geographic miss/insufficient treatment to the margins. In two patients very low fluorescence in the tumor tissue was observed, while both tumors did not react to PDT. This failure was probably due to extravasation of mTHPC at the injection site. One tumor did not show detectable photobleaching, indicated by almost constant fluorescence intensity before and after PDT. We attribute this finding to the measured high BVF in the tumor. The hemoglobin in the tumor tissue probably acted as a filter absorbing the excitation light. This tumor has shown no response to PDT, indicating that the absence of photobleaching was probably real. The third type of error was insufficient photobleaching at the treated oncologic margins. While this observation does not necessarily mean that the tumor is going to recur, in one patient there was recurrence within 2 months. All of these errors would have not been possible to detect without FDPS. Furthermore, all three types of error are correctable. Tumors with insufficient photosensitizer content should receive adjuvant treatments either in the form of surgery, repeat PDT or radiation therapy. The tumor with insufficient photobleaching should be illuminated again until photobleaching takes place. Areas undertreated should get additional treatment. Therefore incorporating FDPS to clinic will provide an improvement in clinical results by detecting the types of error mentioned above and giving the clinician chance to compensate for them.
For deep-seated recurrent tumors of the head and neck, illumination from the surface is not sufficient [14]. Interstitial PDT might be the solution to treat voluminous tumors. This technique has been applied to deep-seated head and neck tumors in a number of centers [18-21]. We have been applying this technique for several indications and tumors of various histopathologies. **Chapter 7** critically analyzes our experience with iPDT of a subgroup of these patients: those with recurrent base of tongue squamous cell carcinoma. The study had a Phase I/II design and evaluated the feasibility, safety and clinical success. The iPDT technique was feasible without short-term complications. Almost all patients demonstrated response to PDT. In 4 patients long term remissions were achieved, extending over years. These results are very encouraging considering that these tumors have been extensively treated before and no curative options could be offered to the patients anymore. Among the long-term complications, pharyngocutaneous fistulae seen in 6 patients were probably related to inadvertent treatment of normal tissues such as muscle and skin.

The initial technique used for iPDT does not allow precise planning to treat the tumor homogenously while avoiding damage to normal tissues. Therefore we have developed a new treatment protocol to provide us with better control over iPDT. **Chapter 8** describes a treatment protocol, which consists of the treatment simulation, implantation of light sources, verification, modification of the treatment plan if necessary and illumination. This method aims to standardize the delivered light dose to the tissue by introducing simulations based on the assumption of a circumferential PDT effect of 8mm radius around the light source. For these simulations a brachytherapy software was customized for the assumed light distribution. The word assumed is used because the distribution of light in tissues is dependent on many factors such as the tissue optical properties and the output of the diffuser. Therefore a uniform distribution cannot be achieved. However based on the penetration of 652nm light and previous experiments, 8mm radius of effect was elected. The simulation based on virtual light sources placed on MR images gives insight in whether the whole volume of the tumor can be illuminated, the needed approximate number of light sources and the angle of insertion. Based on the simulation, the clinician has an operation plan on the day of light source implantation. In practice, the light sources cannot be exactly placed as planned in the simulation. Therefore the actual places of the light sources are verified with CT imaging. The simulation is run again to visualize the distribution of light (based on the assumed 8mm radius). Next, the treatment is modified by inserting additional light sources to places of possible under-illumination and the length of the light diffusers are adjusted to protect normal tissue as much as possible. This method is an important step to optimize the delivered treatment and document the technique used. By incorporating FDPS to the iPDT algorithm, photobleaching an be detected in order to help identify undertreated
areas. Although this last step is a challenge, as FDPS probe placed in the tumor should not be interfering with the treatment, we have already explored the possibilities of evaluation of iPDT with the help of FDPS.

**FUTURE PERSPECTIVES**

PDT of the head and neck should be evaluated in two categories: superficial PDT and iPDT. Treatment of primary early stage cancer with PDT - even though the equivalency to surgery can be demonstrated - remains controversial until an advantage of the new technique over the established technique has been demonstrated. By incorporating ways to monitor PDT, like FDPS, clinical success can be improved, potentially making it favorable to surgery. Further trials should also concentrate on function sparing effects of PDT.

Superficial PDT of secondary or recurrent tumors is more commonly accepted as a viable option. Improving the clinical success by incorporating FDPS measurements can increase the acceptance of PDT for this indication. Interstitial PDT can offer a curative option to patients with no other options. The technique is very young and immensely complicated to understand, because many variables that can affect the success of iPDT exist. Due to the change of the parameters during PDT, the process becomes even more complicated. The protocol described in this thesis is an important step forward in order to optimize iPDT. However, many more steps have to be taken, such as light dosimetry and screening of tissue oxygenization and photobleaching during iPDT in order to deliver a predictable treatment to the whole tumor volume. The evolution of dosimetry and quality control of PDT and iPDT should follow the footsteps of the development of ionizing radiation therapy in the last century. Especially the development of brachytherapy serves as a template for developing better iPDT techniques.

Recurrences in difficult to treat areas create an opportunity to use PDT. For example recurrent tumors located in the paranasal sinuses bordering on the anterior skull base or growing intracranially cannot receive curative treatment. Currently we are evaluating if a combination of limited surgery and adjuvant PDT is feasible.
REFERENCES


