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Aspects of photodetection in cervical and ovarian neoplasia

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Summary and conclusions

The studies that are described in this thesis aimed to determine the feasibility of using fluorescence diagnostic techniques for the detection of small volume abdominal metastases of ovarian tumor and for the detection and staging of cervical intraepithelial neoplasia.

The course of the total study was primarily influenced by the results of our safety study (described in chapter 3). In this study we investigated the damage to the intraperitoneal organs of the rat after systemic administration of 5-aminolevulinic acid (ALA) and illumination with a standard white light operating room lamp for two hours. Besides being fluorescent, ALA induced protoporphyrin IX (PpIX) is also a potent photosensitizer, a property that is used in photodynamic therapy but that may also cause damage to healthy tissue during photodetection. The extent of damage that was observed after the first series of experiments was unexpected. Particularly the liver and the bowel turned out to be susceptible to phototoxic injury. To avoid any chance of damage to the healthy tissue, we decided to expand the study to longer time intervals between administration of ALA and the procedure. We assessed maximal tolerable drug doses at different time intervals after administration of ALA. So far, no clinical studies mention any phototoxic damage as a possible side effect of photodetection. This may be either due to the larger mass/ thicker walls of human organs or to the fact that it might have been overlooked.

The next parameter for an optimal introduction in clinical use is the time interval between administration of a certain drug dose and the diagnostic procedure. This timeinterval is determined by PpIX concentration differences in tumor vs. normal tissue, which gives the fluorescence contrast in the different types of tissue. We performed a study on a tumor bearing rat (chapter 4) using three different drug doses ranging from 5 mg/kg to 100 mg/kg. The optimal time after administration of the higher drug doses (25 and 100 mg/kg) turned out to be in the phototoxic dose/time range as assessed in chapter 3. The 5 mg/kg dose turned out to be sufficient to induce significant tumor/normal tissue fluorescence ratios. The risk of damage to healthy tissue is minimal at this low ALA dose.

The pharmacokinetic curves as assessed in chapter 4 were used to extract time constants for the buildup and clearance of PpIX in humans and rats. We were not able to fit conventional first order mathematical reaction rate models accurately on the experimental data. As the conversion of ALA to PpIX is enzyme controlled it seems obvious to use dose dependent enzyme kinetics in the rate equations. This turned out to give an

improved fit of the mathematical model on the experimental data. In chapter 5, we evaluated the use of dose dependent mathematical kinetic models to describe several different data-sets, both from our own experiments and from literature. Implementation of dose dependent reaction rates improved the goodness of fit and enabled interpolation to other drug doses. This last result means that it is not necessary to perform a new series of experiments for every drug dose, which may reduce the amount of pharmacokinetic (animal) experiments

The next logical step would be to clinically evaluate the use of photodetection with ALA in patients with ovarian cancer but besides the amount of time that was needed to complete the toxicity study, it also caused much concern in the medical ethical committee. Approval of the protocol was not possible within the time span of this study.

A new approach was found in using the fact that growth and progression of metastases is directly related to neovascularization. The newly formed vessels have a higher density random pattern and they have a higher permeability for large molecules. These properties suggested the use of fluorescein angiography for the detection of small metastases. In chapter 6, the clinical feasibility study is described. The protocols for this study were quickly approved because of the extensive clinical experience with (i.v.) fluorescein angiography in ophthalmology. Eighteen patients known with ovarian cancer or with suspicion for this disease and requiring a laparoscopy or laparotomy entered the study. Sodium fluorescein was given i.v. in different doses (0.4 -1.6 ml of a 25 % solution) before or at the introduction of anesthesia whereafter fluorescence detection by laparoscope was carried out preceding the required surgery. The abdominal cavity was inspected both under normal white light illumination and under blue light illumination for excitation of the fluorescein. Our overall conclusion is that the concentration gradient differences between normal and pathological tissue are too small in the abdomen to indicate differences.

The second part of the thesis concerns the use of photodetection for localization and staging of cervical intraepithelial neoplasia (CIN).

In chapter 7, a double ratio imaging system is described. With this system it is possible to measure the (relative) concentration of the fluorescent dye, without influences of tissue optical properties, measurement geometries and variations in excitation light power. The validity of the theory is confirmed by several experiments that are also described in

this chapter.

The feasibility of using the double ratio imaging device for the localization and grading of cervical intraepithelial neoplasia (CIN) is evaluated in a clinical study that is described in chapter 8. The value of the double ratio as determined at the site of biopsy correlated in a statistically significant way with the histopathologically determined grade of the disease. It seems to be feasible to localize and grade CIN non invasively using the Double Ratio (DR) technique.

The results of chapter 8 were evaluated mathematically in chapter 9. Monte Carlo simulations were performed on two layered geometries with a 'tumor' embedded in the top layer. With this physicists' model of a progressing epithelial tumor on the cervix, we tried to understand the relations between DR value, tumor thickness and corresponding CIN grade. Several sets of optical properties for excitation light were used to get more insight in the possible mechanism. A relation between thickness of the neoplastic layer, CIN grade and double ratio value was found.

General conclusions

Concerning the feasibility of using photodetection for the localization and grading of CIN we conclude that the results of the studies in this thesis justify further development of the technique. The next logical step will be a large clinical study and refinement of the equipment. A surprising outcome is the possibility to determine the thickness of the CIN layer. A combination of a conventional colposcope with a fluorescence imaging part may be enough to determine the CIN grade without the need for biopsies.

The feasibility to use fluorescence for the detection and localization of ovarian tumor metastases in the abdominal cavity should be explored further in a small scale clinical study. The use of fluorescein for this purpose was not the best choice and the use of ALA induced protoporphyrin IX for this purpose has so far only been evaluated in an animal model. The results of a clinical phase I study must be awaited before the question whether the technique is of clinical value can finally be answered.