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Aspects of photodetection in cervical and ovarian neoplasia

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Chapter 1

General introduction, aim of the study

Background

The studies presented in this thesis were performed within the framework of a European project (Biomed no BMH4-CT97-2260) entitled : "Fluorescence imaging for detection, localization and staging of superficial cancer in the female lower genital tract." The participants developed and evaluated several different (fluorescence diagnostic) techniques in laboratory and clinical settings.

The general purpose of the studies as reported in this thesis was to evaluate the possibility to use photodetection for the localization of peritoneal (small) metastases of ovarian carcinoma and the detection of cervical intraepithelial neoplasia.

I will first summarize the currently used methods for identification of ovarian carcinomas and cervical intraepithelial neoplasia (CIN) grades. The specificity and sensitivity of the techniques are included where possible. However, in the literature there is a wide variety in patient inclusion and endpoint criteria. These factors have a large influence on the outcome of the study. Consequently the reported numbers for specificity and sensitivity have to be looked at with care.

Ovarian cancer

The majority of all ovarian carcinomas has metastasized in the abdominal cavity at the time of diagnosis. To determine whether a supplementary therapy is necessary it is important to localize microscopically sized, intra-peritoneal metastasis of the tumor. Currently, staging is performed by taking multiple peritoneal biopsies from suspected areas. Since these metastasis can not be macroscopically discriminated from normal tissue, there is a high risk of understaging.

Ovarian carcinoma has a low incidence but is still the leading cause of death from gynecological malignancies. The probability of survival from ovarian cancer is better if the cancer is found early, and treated before it has spread outside the ovary. Then 95% of women will survive at least five years. However, only 25% of ovarian cancers are found at this early stage. About 78% of all women with ovarian cancer survive at least one year after the cancer is found, and over 50% survive longer than five years. There are approximately 30.000 new cases to be diagnosed in the U.S. this year, 15.000 deaths are expected. These figures imply the necessity for an accurate screening tool. Currently there are no screening modalities available for ovarian cancer. The main problem is that, until now, no premalignant phase has been identified.

CA125: The most commonly used screening tool in ovarian cancer, serum CA 125 concentration measurement, is hardly predictive in pre-menopausal women¹. The problem is that while epithelial ovarian cancer cells produce CA 125, it is also made by normal cells. Some people have naturally high levels of CA 125. In many cases, inflammation or irritation of tissues in the abdomen can cause CA 125 levels to rise. On the other hand, 10 to 20 percent of ovarian cancer patients have normal levels of CA 125 when their tumors are diagnosed. These factors cause the published values for sensitivity and specificity to have a wide range of 50%-99% and 60%-99% respectively²⁻⁵. The sensitivity and specificity increase to 83% and 99.7% respectively when an algorithm (ROC algorithm) is used that incorporates age and the trend that appears with repeated testing as well as absolute levels.⁴.

Ultrasound is also a clinically established technique. Its low values for sensitivity (88%-98%) and specificity(65%-95%) are due to difficulties to discriminate between malignant and benign^{2,3,6,7}. The technique requires experienced sonographers and expensive equipment. Anechoic masses have a higher chance of being benign. As the degree of internal echoes and adhesions increase, and if wall thickening occurs, the likelihood of malignancy increases.

A combination of **CA125 and Ultrasound** results in a sensitivity of 80%-99.9% and a specificity of 78%-92%^{4,6}.

Color Doppler: In addition to grey scale doppler, color doppler and pulsed doppler flow imaging have been proposed as methods that may be useful in differentiating benign from malignant ovarian masses. The techniques use the fact that malignant tumors often have neovascularization consisting of blood vessels that have little or no smooth muscle support. The low resistance of these vessels is visible in the doppler waveform. From this the pulsatile index (PI) or resistance index (RI) can be calculated from the waveform to provide a criterion for discriminating benign from malignant masses. The experience of the sonographer influences the outcome. Sensitivity ranges between 67% and 100% and Specificity is in the range of 53% - 100 %^{2,4,7-10} (PI<0.6). A possible way to improve the technique is to combine color doppler images with the evaluation of the relating vascular morphology in a scoring system (increase to 90%-97.3% and 98% - 100% respectively^{4,8})

MRI and CT: Both MRI (sens: 97.1%, spec: 66.7%¹¹) and CT are too expensive to be used as a routine diagnostic technique. Furthermore, patient acceptability is a problem for CT because of the exposure to ionizing radiation.

Cervical cancer

On a world-wide basis, cervical cancer is still the second most common cancer in woman (after breast cancer)¹². The mortality associated with this disease may be reduced if detection is at an early stage of development. For determination of the right therapeutic strategy exact knowledge of size, depth and localization of the neoplastic tissue is necessary. Currently used techniques for the screening of cervical neoplasms are:

Pap smear: Cervical cytology (pap smear, Papanicolaou & Trout, 1943) is currently used for the routine inspection for CIN and cervical cancer. The reported sensitivity ranges from 50% to 99% and its specificity ranges from 80% to 99%^{13-16 17,18}. A relatively large number of false negatives of 15-60% is reported for this technique. Improvements by using computerized assessment of the samples are currently under investigation.

Colposcopy: In case of an abnormal cervical smear, a diagnostic procedure called colposcopy (white light examination of the cervical surface after application of acetic acid) is performed. With this technique, the most atypical site is identified for biopsy. The outcome of this procedure is strongly influenced by the level of experience of the colposcopist. This explains the wide range of reported sensitivity (73%-99%) and the relative low specificity (50-66%)^{18,19}

HPV screening has a high sensitivity but a too low specificity to be used as a routine screening technique²⁰.

For both ovarian carcinoma & CIN it can be concluded that specificity and sensitivity of the currently used standard diagnostic techniques, though sometimes acceptable, are far from optimal. This justifies the search for and development of more accurate diagnostics. In this context it is worthwhile to study the clinical value and applications of photodetection in these gynecological neoplasias.

Aim of the study

The aim of this thesis is to evaluate the use of photodetection for:

- 1) the localization of peritoneal metastases of ovarian tumor and
- 2) the detection and possibly staging of cervical intraepithelial neoplasia.

In the last few years, photodetection emerged as a useful tool to detect superficial neoplastic layers in various medical fields. The two possible applications that are studied in this thesis were selected because the neoplastic layer or volume is in both cases very superficial and because of the need for more sensitive detection techniques.

Introduction of a technique into clinical practice requires optimization of parameters like drug dose, excitation wavelength and power, detection device etc. We performed several pre-clinical and clinical studies to assess these parameters.

Outline of the thesis

The thesis is divided into two parts. Chapters 3 to 6 focus on the detection of ovarian tumor metastases and chapters 7 to 9 describe the studies that were performed on the detection of CIN.

Chapter 2 gives an overview of past and current research on photodetection in gynecology. In particular work on the detection of cervical neoplasia and on the detection of small abdominal metastases of ovarian tumor will be analyzed. The importance of research in this area is clear from the fact that over the last decade, mortality has not dropped significantly. Early discovery and accurate staging must be the key factors to change this.

Chapter 3 describes work that assesses the risk on phototoxicity during photodetection with ALA induced protoporphyrin IX of small volume metastases in the abdominal cavity. Internal organs of rats, photosensitized by protoporphyrin IX, are exposed to bright light during surgery. The damage to intestines, liver, and other exposed organs was macroscopically and histologically scored.

Chapter 4 gives the results of a pre-clinical animal study that was performed to optimize the treatment parameters like drug-dose and time-interval between administration of ALA and the diagnostic procedure. We assessed the time of maximal difference of fluorescence between the tumor and the surrounding tissue for three drug doses. The

results were combined with the results of the toxicity study (chapter 3) to give an optimal drug/dose-time interval combination for the procedure.

Chapter 5 is a theoretical analysis of the fluorescence kinetics of PpIX after administration of ALA. We incorporated dose dependent enzyme kinetics (Michaelis-Menten) in a mathematical compartmental model that describes the subsequent steps in the conversion of ALA to PpIX. This model and a conventional first order model were fitted to several published PpIX fluorescence kinetics datasets to determine whether our model would describe the experimentally determined curves more accurately.

In **chapter 6** a photodetection technique based on the detection of fluorescein for the localization and staging of ovarian tumor in patients is evaluated. The idea behind this is the fact that metastatic growth and progression of ovarian cancer depends on neovascularization. These vessels have a higher permeability for large molecules, which may be used for the delivery of the fluorescent dye fluorescein to these areas, and a different, more dense and chaotic growth pattern. We looked for changes in vascular patterns and for stained areas over an extensive period of time after administration of fluorescein.

In **chapter 7**, the technical details and first experiments of a fluorescence imaging system that is based on the Double Ratio technique is described. By using this technique, fluorescence measurements can be performed that are independent of tissue optical properties, measurement geometry and variations in excitation intensity.

Chapter 8 gives the results of a clinical fluorescence imaging study on detection of cervical neoplasia. For this study, joint measurement sessions were organized between the groups from Rotterdam (DdHK) Amsterdam (AMC/AVL) and Munich (LFUK). The measurements were performed in Munich in the 'Laser-Forschungslabor' of the hospital 'Großhadern' of the University of Munich. In the study described here, the feasibility to use the double ratio setup for localization and staging of cervical intraepithelial neoplasia was investigated.

In **chapter 9**, the results of chapter 8 are analyzed using mathematical simulations. The dependency of the Double Ratio on the thickness of a fluorescent layer was studied. This is important for the interpretation of fluorescence images for diagnostic purposes. A Monte Carlo calculation method was used to calculate excitation light distribution in the tissue and the subsequent escape of the fluorescence light from the tissue.

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