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### Aspects of photodetection in cervical and ovarian neoplasia

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## **Chapter 6**

# **Fluorescein angiography for the detection of metastases of ovarian tumor in the abdominal cavity, a feasibility pilot.**

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## Abstract

The growth and progression of ovarian tumor metastases at the peritoneal surfaces of the abdominal cavity are coupled with neovascularization. Newly formed tumor vessels show a more diffuse pattern and are more permeable for macromolecules than normal vessels.

We undertook a feasibility pilot study to find out if these tumor properties could be used to detect (small) ovarian metastases in the abdominal cavity by means of fluorescein angiography.

Eighteen patients known with ovarian cancer or with suspicion for this disease and requiring a laparoscopy or laparotomy entered the study. Preceding the required surgery sodium fluorescein was given intra-venously in different doses (0.4-1.6 ml of a 25 % solution) whereafter fluorescence detection by laparoscope was carried out. In 5 patients adhesions hampered laparoscopic inspection, while in 13 patients the abdominal cavity could be inspected with normal white light and subsequently with blue (excitation) light to observe the fluorescence images of the fluorescein. An impression of the distribution patterns of fluorescein was gained from 0 up to 120 min by pooling the data collected in different patients at various time intervals.

Three phases could be discriminated: I. rapid filling (< few minutes) of blood vessels after administration of fluorescein, II diffuse extravasation of fluorescein into surrounding tissues leading to intense generalized staining of vessels and surrounding tissue for at least half an hour; III clearance of fluorescein from vessels and surrounding tissue with gradually fainting of staining. (Small) differences in accumulation of fluorescein could be visualized only after one hour or more. Tissue inspection at blue light more than 60 minutes after administration of fluorescein did not give additional information compared to the inspection using white light, which was confirmed by histology. No clear differences in this pattern were observed for the different doses of fluorescein.

Our overall conclusion is that the concentration gradient differences of fluorescein between healthy and pathological tissue in the abdominal cavity are too small to indicate tumor neovascularization. To our opinion this research should be continued by using fluorescence dyes with larger molecules in order to build up sufficient concentration differences between normal and malignant tissue.

## Introduction

Staging procedures in ovarian cancer are performed to discriminate between early disease, limited to the ovary, and (occult) more advanced disease with spread of tumor into the abdominal cavity. Currently staging is performed by taking of multiple peritoneal biopsies from predilection areas, as small metastases cannot be distinguished macroscopically from normal tissue. Obviously, the risk of understaging by this semi-blind procedure is large. For certain patients understaging will lead to undertreatment and subsequently this may have an adverse effect on the patients' prognosis.

Photodetection is a relatively new diagnostic modality for the detection of small tumors<sup>1-3</sup>. This technique is already successfully used for the detection and localization of bladder, esophagus, skin, colon and lung tumors<sup>4-8</sup>.

Photodetection using the fluorescent dye fluorescein is based on differences in vascular structure and permeability when comparing normal to tumor tissue. Vascular permeability is increased in tumor tissue, which facilitates leakage of i.v. administered drugs into the surrounding tissue. This leakage phenomenon in tumor neovascularization was demonstrated in animal experiments and confirmed by human studies. Experiments in animals with peritoneal carcinosis show that tumor vessels are hyper-permeable and have a larger lumen than normal vessels<sup>9-14</sup>. Similar observations were made in humans<sup>15-18</sup>. In addition, the tumor vessels show a more diffuse pattern and a different flow pattern due to the fact that they contain little or no smooth muscle cells<sup>19</sup>. This last property is already used for the detection of ovarian cancer with transvaginal color doppler ultrasound<sup>20-25</sup>. However, the resolution of this technique is in the order of several millimeters and the penetration is too low to inspect the whole abdominal cavity. A better technique for the visualization of the neovascularization may be laparoscopic fluorescein angiography.

Fluorescein is an organic, highly fluorescent, dye. The dye spreads evenly in the body after i.v. administration. Approximately 85% of the circulating fluorescein will be bound to albumin. The circulating fluorescein will rapidly be cleared while the extravasated fluorescein will remain in the extracellular matrix for a longer period. Upon illumination with blue light (peak at 480 nm.) the areas with extravasated fluorescein will emit broad band yellow fluorescence light (peak at 520 nm.).

Fluorescein is an attractive dye to use for the following reasons. Firstly, extensive clinical

experience has been obtained with this fluorescent dye and side effects are well described<sup>26-30</sup>. Secondly, fluorescein has a high fluorescence quantum yield, which favors the detection of very small tumor volumes. Thirdly, the use of fluorescein is attractive in diagnostics because the time interval between administration and extravasation of fluorescein is short.

Fluorescein is widely used for diagnostic procedures in ophthalmology e.g. for the accurate detection of eye tumors. Photodetection with fluorescein is currently under investigation for other tumors. Staining of malignant cells with fluorescein is described by Vinogradova *et al*<sup>31</sup>. Braginskaia *et al.* showed that sodium fluorescein accumulates in experimental gastric cancer in rats<sup>32,33</sup>. Fluorescence levels were higher in tumor tissue than normal adjacent tissue. Ble *et al.* proved the feasibility of fluorescein detection of bladder cancer. Also in benign disorders like Crohn's disease fluorescein detection was applied facilitating early detection of small Crohn's lesions<sup>34</sup>.

In this pilot study we investigated the feasibility of fluorescein photodetection in patients with known or suspected ovarian cancer. Aim of the study was to investigate the distribution pattern of fluorescein in the abdominal cavity and to investigate whether concentration gradients of fluorescein could be found between normal and malignant tissue, as a result of the differences in structure of tumor and normal vessels.

## **Materials and methods**

### **Laparoscopic equipment**

Fluorescence images were recorded using an imaging device that was developed by Karl Storz, Tuttlingen, Germany, for urological applications. The illumination part consisted of a Xe light source (D-light AF-system, Storz, Tuttlingen) with an integrated filter-wheel, which enables selection of white light or blue light (<500 nm. for excitation of the fluorescein). The images were collected through a rigid endoscope that was connected to a camera and a video recorder. A longpass filter (>510 nm.) was placed between the scope and the camera to block the excitation light.

### **Patients**

A total of 18 patients entered this study. Six patients had an indication for exploratory laparotomy because of enlarged adnexal mass. In 3 of these cases, ovarian cancer was diagnosed. Seven patients required an interval debulking while in the remaining 5 patients already treated for ovarian cancer a diagnostic laparoscopy was indicated for

various reasons. Informed consent was obtained to precede the planned surgery with fluorescence laparoscopic inspection of the abdominal cavity. After administration of fluorescein, in 5 of 18 patients the endoscopic inspection could not be carried out due to adhesions.

### **Methods**

White light and blue light laparoscopic video-recorded inspection of the upper and lower abdomen including the pelvis was performed according to a standardized way. Sodium Fluorescein 25% solution prepared at the pharmacy of our hospital was given i.v. as a bolus injection, with a starting dose of 0.4 ml. This dose was increased during the study to 0.8 ml and eventually to 1.6 ml. In the first 7/18 patients an injection of fluorescein was given during laparoscopy after completion of inspection of the abdominal cavity in order to carefully follow the distribution of fluorescein immediately after administration. In the following 11 patients fluorescein was given at an earlier stage preceding the laparoscopic inspection in order to observe the distribution of fluorescein up to 120 minutes after i.v. administration. Dose escalation was carried out after the 7th and again after the 10th patient.

When areas showed a higher fluorescence than the adjacent tissue, blue light inspection was followed by repeated white light inspection and, when possible, biopsies were taken from that area for histological analysis.

According to standard forms, toxicity and endoscopic complications were recorded peri- and post operatively during 48 hours and longer if indicated.

### **Results**

In the first three patients, almost no fluorescence could be visualized after administration of 0.4 ml of the 25% fluorescein solution. After stepwise adaptations of the technical equipment during these first three procedures, a good fluorescence contrast could be observed in the fourth patient, whereafter the equipment settings were maintained in the following 9 patients.

In addition, dose escalation was performed by doubling the dose in patients 9 and 10 (0.8 ml) and again in patients 11, 12 and 13 (1.6 ml) in order to evaluate the effect of dose intensification on the fluorescence contrast in the images. The higher dose did not lead to a gain in fluorescence contrast.

### **Distribution pattern of fluorescein**

Immediately after administration, a strong fluorescence could be observed in the blood vessels during blue light inspection (phase 1). After a few minutes a generalized fluorescence staining appeared in the tissue surrounding the vessels, while also the vessels remained filled with fluorescein. The fluorescence was intense, generalized and non-specific which hampered any diagnostic interpretations (phase 2). This phase was prolonged: from the longer observation time it became clear that this phase lasted for at least half an hour after administration of fluorescein. After this phase a gradual decrease of tissue fluorescence finally led to the phase 3 in which the images started to show some concentration differences expressed by localized patched fluorescent areas at one hour after administration of fluorescein. At 120 minutes, most of the fluorescence had disappeared, both from vessels and surrounding tissue.

### **Biopsies**

Biopsies were only taken in the third phase when more selective accumulation of fluorescein was present. A total number of 16 biopsies were taken. None of the fluorescence directed biopsies gave additional information when compared to the findings of white light inspection: the biopsies that turned out to be positive for tumor were taken out of areas that were also suspected for tumor at white light inspection. When a certain tissue area showed no suspicion for tumor at white light inspection, but showed a higher fluorescence at blue light inspection compared to the surroundings, the fluorescence directed biopsies taken were also negative on histology.

### **Side effects and toxicity**

None of the patients suffered from complications caused by the (additional) endoscopic procedure with fluorescein. A foreseen side effect was the strong yellow-orange discoloration of the urine that was observed from 8 minutes up to 24 hrs afterwards. Some coloring of the eyes was also found in some patients. As expected no other signs of toxicity were noted.

### **Examples of images taken during the procedure.**

Some examples of images that were recorded during the procedure are shown below: Figure 1 shows the extravasation process during the first 16 minutes. The generalized fluorescence that is shown in the picture on the right side was maintained for at least 30 minutes.

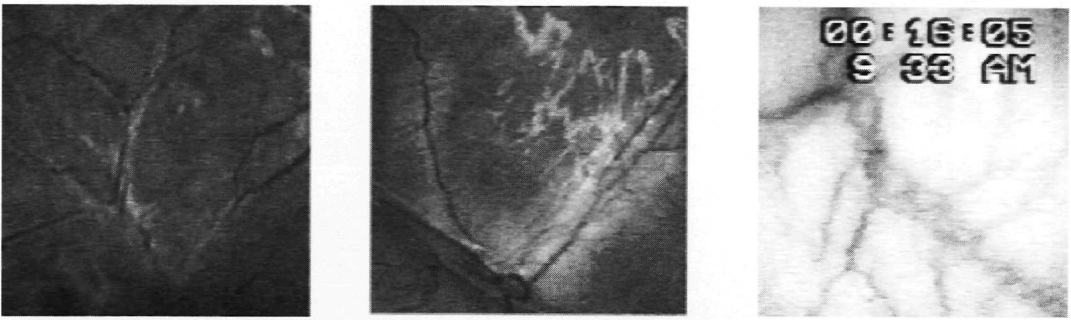


Figure 1: extravasation process of fluorescein at 5, 9 and 16 minutes leading to phase 2.

Figure 2 shows part of the omentum and the small bowel during white light (left picture) and fluorescence (right side) inspection at 45 minutes after administration of fluorescein (phase 2 → 3). The adipose tissue always showed relatively strong fluorescence compared to the organs. The hot spot on the left side in the right picture turned out to be inflammatory tissue area and hence was a false positive finding.

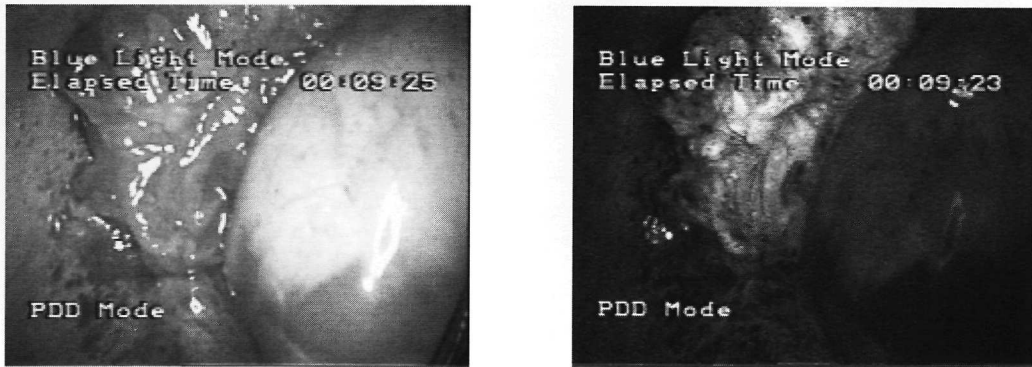
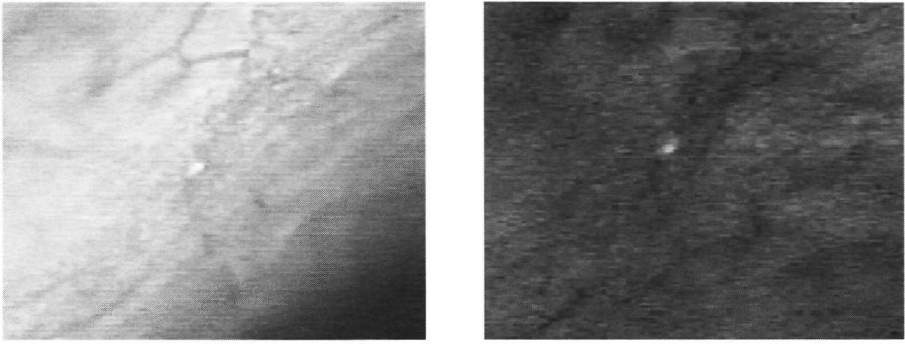


Figure 2: part of the omentum and the small bowel during white light (left picture) and fluorescence (right side) inspection the picture was taken 45 minutes after administration of fluorescein.

Figure 3 shows images of a small tumor metastasis on the abdominal wall under white light inspection (left) and with fluorescence imaging at 90 minutes after administration of fluorescein. The increased fluorescence signal of the tumor is probably caused by the macroscopically white color of the tumor as seen at white light inspection. Because of the white color there is little absorption of the excitation light, which facilitates much deeper penetration of light into the tissue and more fluorescein is excited. The induced fluorescence light can also escape the tissue more easily.

At 90 minutes, most of the generalized tissue fluorescence had decreased to low levels, facilitating the detection of local accumulation of fluorescein. However in some cases



*Figures 3: A small tumor metastasis on the abdominal wall as visualized during white light and blue light (fluorescence) inspection, 90 minutes after administration of fluorescein.*

localized differences in fluorescein concentration were observed at an earlier stage. This was mainly true for larger tumor masses.

Figure 4 shows such an example. At white light inspection a large area was suspected for tumor. This area showed strong prolonged fluorescence at blue light, which could be discriminated from 30 minutes on. On histology the diagnosis of malignant tissue was confirmed.



*Figures 4: An area of tumor tissue visualized using white light illumination (left picture) and illumination with blue light (right picture) at 30 minutes after administration of fluorescein.*

## **Discussion**

The use of fluorescein angiography to identify tumor tissue in the abdominal cavity has not yet been reported in literature. We explored the possible clinical application of fluorescein angiography for the detection of tumor metastases at the peritoneal surfaces in a small-scale study in order to find out whether larger studies would be indicated. As we were to our knowledge pioneers of fluorescein photodetection in the abdominal cavity a number of parameters needed for an optimal application of the technique were unknown, like equipment settings, drug dose and the time interval between administration of fluorescein and laparoscopic blue light inspection.

The study was started with a (rather arbitrary) low initial drug dose, when compared to the dose commonly used for visualization of vessel abnormalities in ophthalmology, which is 3 ml 25% sodium fluorescein solution. This low starting dose was chosen to avoid any phototoxicity to the vulnerable organs in the abdominal cavity, although the publications of phototoxic effects after administration of fluorescein are limited<sup>26-30</sup>. During the study it became clear that even a low dose of 0.4 ml fluorescein solution already leads to massive generalized fluorescence. Nevertheless we increased the dose twice, - still below the dose used clinically in ophthalmology - mainly to see whether this would improve fluorescence contrast in the images in the third phase. As described in the results this was not the case. The option to lower the dose to induce more specific fluorescence in the phase 2 was not investigated in this limited study. However, considering the distribution pattern of fluorescein, with generalized nonspecific extravasation, this option seems not very attractive and will probably not lead to better images.

Besides the drug dose the optimal time interval between administration of fluorescein and the diagnostic procedure had to be assessed. We were able to identify three phases after administration of fluorescein. Almost immediately after administration, a rapid filling (< few minutes) of blood vessels was observed. In theory tumor induced vascularization can be recognized during this first phase, due to their more diffuse and dense pattern and other vascular structure which facilitates prompt leakage. However, because of the short duration of the first phase which was only a few minutes, it is impossible to carefully inspect the whole abdominal cavity. Following phase 1 the diffuse extravasation of fluorescein from all (tumor and normal) vessels into surrounding tissues caused an intense non specific, generalized staining of vessels and surrounding tissue which lasted for at least half an hour, during which period no images could be obtained for any diagnostic purpose. At longer time intervals when the staining gradually faded, areas were distinguishable that showed prolonged accumulated fluorescence levels. This indicates that only this third phase is suitable for tumor diagnostics. The optimal time period to perform laparoscopic fluorescein angiography is therefore somewhere between 30-60 and 90 minutes.

However when comparing the images obtained at stage 3 to those obtained at white light inspection, the latter are much easier to interpret and clearer considering discrimination between normal tissue and tissue suspected for metastasis. We did not find areas suspected for tumor metastases as indicated by fluorescein accumulation that were not already recognized by normal white light inspection. In addition, other conditions like

inflammation may also lead to fluorescein accumulation, which indicates that fluorescein photodetection is not highly specific.

Our general impression is that local concentration differences in fluorescence angiography are too small to add to white light diagnostics. This is in contrast to the findings in ophthalmology. Most likely the blood to tissue barrier in the eye prevents from massive extravasation of fluorescein from the normal vessels into the surrounding tissue in contrast to pathological disorders. These other conditions facilitate diagnostics in phase 1. Our overall conclusion is that the applicability of photodetection with fluorescein in the abdominal cavity is disappointing. Based on the findings of this pilot study it is not indicated to continue our studies with fluorescein photodetection. Though the numbers of patients in our studies are small, this conclusion is justified in our opinion as our data about the distribution pattern and concentration gradients of fluorescein were uniform for all our patients and therefore seem conclusive.

Nevertheless the idea of diagnostics of neovascularization with fluorescence techniques remains attractive. To make the technique work, we need larger molecules. One possibility is to fluorescein-label a large dextran molecule. An other possibility is to use Indocyanine Green (ICG) which may be a more suitable dye for photodetection of tumor vessels. ICG has a high molecular weight (twice as great as that of fluorescein) and is amphiphilic (both hydrophilic and lipophilic)<sup>35</sup>. After administration, ICG will bind to plasma proteins and will therefore have limited extravasation from the normal vessels<sup>35</sup>. In this way the different tumor vessel structure may be visualized without background-fluorescence from extravasated fluorophores. A disadvantage of the use of ICG might be the low fluorescence efficiency of only 4% of that of fluorescein.

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