Vascularity and Uptake of Photosensitizer in Small Human Tumor Nodules: Implications for Intraperitoneal Photodynamic Therapy

Chandrakala Menon, Sara N. Kutney, Shannon C. Lehr, Samantha K. Hendren, Theresa M. Busch, Stephen M. Hahn, and Douglas L. Fraker


ABSTRACT

Purpose: i.p. spread of cancers is a common clinical problem, with limited treatment options leading to morbidity and death. i.p. photodynamic therapy (IP-PDT) combines maximal surgical debulking of gross tumor with intraoperative light delivery to the peritoneum after preoperative i.v. injection of photosensitizer to treat residual disease. An issue of concern in IP-PDT is the potential lack of photosensitizer uptake by residual small tumor nodules (STNs) ≤ 5 mm in maximum diameter and by microscopic residual disease caused by incomplete development of a vascular supply. This study examined the existence of vascularity and Photofrin (PF) uptake in STNs in 12 patients in a Phase II clinical trial for IP-PDT.

Experimental Design: Patients received PF 2.5 mg/kg i.v. 48 h before surgery. STNs obtained during surgery were cryosectioned, immunostained for platelet/endothelial cell adhesion molecule 1, and analyzed by light microscopy. Mean vascular densities in STNs were determined by counting microvessels within a ×200 field (0.28 mm² area). Sections were also examined for PF uptake by fluorescence image analysis using an epifluorescence microscope and IPLab Spectrum software.

Results: Data obtained showed that tumors as small as 1 mm in diameter stained positive for platelet/endothelial cell adhesion molecule 1 and contained PF. A negative control from a patient not given PF showed no detectable fluorescence. The average of all mean vascular densities in STNs was determined to be 100 ± 29.

Conclusions: We conclude that STNs, as small as 1 mm in diameter, have a functional vasculature, because these tumors show PF uptake after i.v. delivery. Both properties are crucial for the treatment of residual STNs by IP-PDT after surgical debulking.

INTRODUCTION

Carcinomatosis and sarcomatosis represent the direct spread of cancer to the serosal surfaces of the peritoneal cavity. Malignant neoplasms of the gastrointestinal tract, the ovaries, and the soft tissues of the bowel and retroperitoneum may spread in this i.p. pattern without evidence of metastasis to any other area of the body. Patients frequently develop an extensive disease burden within the peritoneum, causing significant morbidities such as pain, ascites, and bowel obstruction. Patients frequently succumb to progressive i.p. tumor without evidence of hematogenous or lymphatic spread (1). Unfortunately, treatment options for patients with carcinomatosis and sarcomatosis are limited, and no curative treatments exist.

An effective superficial treatment which can be applied successfully to the complex shape and dimension of the peritoneal cavity may be beneficial in these patients. PDT, which treats superficial neoplasms, is theoretically an ideal therapeutic strategy for widespread i.p. disease. PDT is an antineoplastic treatment that involves the use of a photosensitizer, such as PF, which, when activated by visible light of the wavelength specific for the photosensitizer in the presence of oxygen, leads to reactive oxygen species-mediated cytotoxicity (2). PDT has been used successfully to date for treatment of esophageal, tracheobronchial, bladder, and superficial skin cancers (2).

In our ongoing Phase II clinical trial (3), PF-mediated PDT is used to treat STNs ≤ 5 mm in maximum diameter as well as microscopic residual disease lining the peritoneal cavity after maximal surgical debulking of patients with diffuse intra-abdominal malignancies. The median survival for the first 42 patients treated on this protocol was 21 months (3). The relative contribution of the surgical debulking versus the PDT to patient survival, however, is unknown. The early data indicate an association between the ability to be completely resected free of gross disease and survival (3), a pattern which has been seen...
in several other experimental clinical therapies for carcinomatosis (4, 5).

In our clinical experience, it is often possible to excise tumor lesions between 5 and 10 mm in size by dissecting them bluntly off the peritoneal surface. In these instances, particularly for sarcomas and mucinous adenocarcinomas, there is usually little or no visible evidence of bleeding. Because PDT is dependent upon the intravascular delivery and uptake of photosensitizer in the current clinical trial, the vascularity of the residual disease after debulking is crucial for the success of the treatment. The clinical observation that small i.p. tumor nodules can be excised without visible bleeding raises questions about the successful delivery of sensitizer agent given by i.v. injection.

Currently, the size at which metastatic human tumor nodules develop functional blood vessels is unknown. Preclinical models suggest that neovascularization, the process by which growing tumor develops vascular endothelium from normal tissues, is influenced by tumor-derived factors (6, 7). In a classic tumor implant experiment demonstrating neovascularization, tumor fragments or cultured tumor cells were placed in the cornea of a rabbit eye, an avascular site. These implants attracted new capillaries that grew from the limbus to vascularize the cornea of a rabbit eye, an avascular site. These implants afforded us a unique opportunity to study the vascularity of small human tumor metastases present on peritoneal surfaces in the size range of 1–5 mm. In the present study, we evaluate the presence of vasculature and the uptake of PF in STNs. This study is relevant to both IP-PDT treatment outcome as well as to the basic biology of tumor angiogenesis.

MATERIALS AND METHODS

IP-PDT Treatment Regimen. Tumor nodules were obtained from 12 patients enrolled in a Phase II clinical trial for IP-PDT at the University of Pennsylvania Medical Center between September 1998 and April 2000. This trial was approved by the United States Food and Drug Administration, the Institutional Review Board, and the Clinical Trials Scientific Review and Monitoring Committee of the University of Pennsylvania, Philadelphia, PA. Patients with all tumor histologies and prior therapies were eligible for the trial, as long as there was measurable disease in the peritoneal cavity with no evidence of disease outside the peritoneal cavity or evidence of hematogenous liver metastases. The trial was primarily designed for patients with carcinomatosis caused by ovarian or gastrointestinal malignancies and sarcomatosis caused by bowel or retroperitoneal soft tissue sarcomas.

Patients received PF, 2.5 mg/kg, provided by QLT Phototherapeutics Ltd., Vancouver, Canada, i.v. over 15 min, 48 h before surgery. At the time of laparotomy, patients first underwent surgical debulking of gross tumor >5 mm in diameter. Patients were treated for residual disease by exposing them to laser light under controlled conditions as described previously (3). Informed consent was obtained from all patients.

Tissue Acquisition and Cryosectioning. Fresh tumor nodules of different sizes were procured intraoperatively before light treatment. Tumor nodules from a patient undergoing a staging laparotomy who did not receive PF were harvested to be used as negative control for PF studies, and tumor >5 cm in diameter from an IP-PDT patient were used as positive control. The harvested tumor nodules were measured in three dimensions using calipers, rinsed in PBS, and frozen in OCT (Tissue-Tek, Sakura Finetek USA, Inc., Torrance, CA). The following nine cryosections sections were made serially from the peripheral region and from the central region of each tumor nodule in the OCT tissue block: (a) a peripheral 5-μm section for PECAM negative control; (b) a peripheral 5-μm section for PECAM immunostaining; (c) a peripheral 14-μm section for PF uptake analysis; (d) a second peripheral 5-μm section for PECAM immunostaining; (e) a second peripheral 14-μm section for PF uptake; (f) a central 5-μm section for PECAM immunostaining; (g) a central 14-μm section for PF uptake; (h) a second central 5-μm section for PECAM immunostaining; and (i) a second central 14-μm section for PF uptake. The sections for the PECAM immunostaining and PF fluorescence studies were adjacent sections.

Sectioning was performed under minimal ambient light conditions to avoid photobleaching of the photosensitizer. The
cryosections were then stored at −80°C in the dark until additional use.

**PECAM Immunostaining of Cryosections.** Immunostaining with a mouse antihuman PECAM antibody using the avidin-biotin-peroxidase complex method was performed to evaluate the presence and extent of vascularity in the collected tumor nodules. Cryopreserved 5 μm tumor tissue sections were fixed in cold acetone on ice for 5 min and then blocked with PBS containing 4% BSA and 5% horse serum. The sections were incubated overnight with a mouse antihuman PECAM antibody (a generous gift from Dr. Steven Albelda, University of Pennsylvania, Philadelphia, PA). Thereafter, the sections were incubated sequentially with biotinylated horse antimouse secondary antibody (Vector Labs, Burlingame, CA) and avidin-biotin-peroxidase complex (ABC Elite kit; Vector Labs). After washing with PBS, the color reaction was developed with the Vector VIP Peroxidase Substrate kit (Vector Labs). The sections were air-dried and mounted in glycerol. Tumor sections that were processed without primary antibody were used as negative control. A tumor cryosection from the central region of a 9 × 5 × 5 cm tumor was used as positive control. The slides were viewed and photographed under a light microscope at a total magnification of ×200.

**MVD Measurements.** MVD was assessed by light microscopy without prior knowledge of the histology of the excised tumor. Areas of most intense vascularization were picked out by scanning PECAM-immunostained tumor sections under a light microscope using a ×100 objective. Individual microvessels were then counted within a ×200 field equal to a 0.28-mm² area. Any brown-staining endothelial cell or endothelial cell cluster that was clearly separate from adjacent microvessels and tumor cells was considered a single countable microvessel. Vessel lumens, although sometimes present, were not necessary for a structure to be defined as a microvessel. All counts were performed separately by two investigators. A mean of 2–3 fields was computed for each tumor section, and the MVDs were calculated separately for peripheral and central sections of each tumor. MVD for each tumor nodule was then computed by calculating the mean of all counts from both the peripheral and central sections and was expressed as MVD ± SD.

**Fluorescence Image Analysis of PF Distribution.** Air-dried, 14-μm tumor sections were photographed for PF fluorescence under low ambient light conditions by using a fluorescence microscope fitted with a custom tube filter (Omega Optical) for excitation at 410 ± 15 nm and emission at 640 ± 40 nm. This microscope was a Nikon Lab-Photofluorescence microscope equipped with a 100-W high-pressure mercury arc lamp, a cooled (−25°C) charge coupled device camera (Photometric “Quantex”), and an automatic stage advancement (Ludl Electronic Products). Digital control of the camera and stage was provided by a Macintosh 9600 Power PC running IPLab Spectrum software (Scanalytics, Inc.). Images of each tissue section were collected as several individual images, and composites were made with IPLab Spectrum software. Field-flattening was performed by subtraction of an image of an empty field acquired with the same exposure as for the section of interest. Tumor sections from a patient not given PF were used as negative control. Tumor >5 cm in maximum diameter from an IP-PDT patient was used as positive control. The presence or absence of PF

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (yr)</th>
<th>Tumor type</th>
<th>Tumor burden</th>
<th>Surgical procedure</th>
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</thead>
<tbody>
<tr>
<td>1</td>
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<td>Gastrointestinal stromal tumor, small bowel</td>
<td>&gt;1000 nodules</td>
<td>Small bowel resection, omentectomy, peritoneectomy</td>
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<tr>
<td>2</td>
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<td>50</td>
<td>Appendiceal carcinoma</td>
<td>100–500 nodules</td>
<td>Bilateral oophorectomy, small bowel resection, colon resection, omentectomy, peritoneal stripping</td>
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<tr>
<td>3</td>
<td>F</td>
<td>63</td>
<td>Uterine leiomyosarcoma</td>
<td>100–500 nodules</td>
<td>Small bowel resection, colon resection, cholecystectomy, vaginectomy</td>
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<tr>
<td>4</td>
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<td>37</td>
<td>Colon adenocarcinoma</td>
<td>5–10 nodules</td>
<td>Colon resection, small bowel resection, peritoneectomy</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>62</td>
<td>Gastrointestinal stromal tumor, small bowel</td>
<td>100–500 nodules</td>
<td>Aborted procedure; unable to adequately debulk disease</td>
</tr>
<tr>
<td>6</td>
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<td>8</td>
<td>F</td>
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<td>F</td>
<td>51</td>
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<td>M</td>
<td>74</td>
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<td>10–100 nodules</td>
<td>Peritoneectomy</td>
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</tbody>
</table>

**Table 1** Patient characteristics, tumor burden, and surgical procedures at the time of tumor debulking and photodynamic therapy
**Fig. 2** Upper panel, photomicrographs of tumor cryosections of a large tumor nodule (13 × 10 × 10 mm) excised from a patient who did not receive PF. Lower panel, photomicrographs of tumor cryosections of a tumor (9 × 5 × 5 cm) excised from a patient who received PF 48 h before surgery. Tumor section immunostained with antihuman PECAM antibody (A) and PF-specific fluorescence micrograph of adjacent tumor tissue section (B). Tumor from this patient was used as negative control for PF uptake, showing no background fluorescence. Tumor section immunostained with antihuman PECAM antibody (C) and PF-specific fluorescence micrograph of adjacent tumor tissue section (D). Tumor from this patient was used as positive control for PF studies and shows PF uptake, which is uniformly distributed in the tumor cryosection.

**Fig. 3** Photomicrographs of cryosections of STNs from IP-PDT patients. Tumor nodules with a maximum diameter of 1 mm (A), 2 mm (C), and 4 mm (E) that were immunostained with antihuman PECAM antibody. Fluorescence micrographs of adjacent tumor tissue cryosections showing PF uptake in 1 mm (B), 2 mm (D), and 4 mm (F) tumor nodules. All STNs show both vasculature and PF uptake uniformly distributed throughout the tumor.
was qualitatively assessed and the data were presented in tabular form using a "++", "+++" grading system after visual examination of the field-flattened images where, ++ indicates positivity for PF with a relatively lesser number of “dots” that are sparsely dispersed, and +++ represents positivity for PF with a relatively greater number of dots that are densely dispersed.

**Statistical Analysis.** The Graphpad Instat and Microsoft Excel software were used to perform statistical analysis of the MVD data. Comparisons were made between MVDs obtained for 1–2 mm maximum diameter (small) and 3–5 mm maximum diameter (medium) tumor nodules. SDs were calculated, and the unpaired t test or the unpaired t test (Welch corrected) was used to calculate levels of significance.

**RESULTS**

The gross appearance of the disease to be treated by IP-PDT is typically multiple mesenteric, serosal, and parietal peritoneal nodules. Fig. 1 is an intraoperative photograph of a patient with sarcoma showing multiple mesenteric nodules. Patients with carcinomatosis or sarcomatosis may have literally hundreds of individual nodules of various sizes on the peritoneal surfaces (Fig. 1).

Tumor nodules of varying sizes and histologies were harvested intraoperatively from different areas of the peritoneum from 12 human patients that were enlisted in our Phase II IP-PDT clinical trial. The clinical characteristics of the patients and the extent of tumor and debulking surgery are shown in Table 1. Tumor nodules from two of the patients appeared necrosed by H&E staining and were considered unusable for additional study by PECAM immunohistochemistry and for PF uptake analysis. The data from the remaining 10 patients and from the patients used as negative and positive controls are presented here. Fig. 2A is a representative PECAM immunostaining of a peripheral cryosection from a human sarcoma tumor nodule that was approximately 13.10 mm in dimension. This tumor nodule was harvested from a patient who had not received PF, and it was used as negative control for PF uptake studies. The vasculature appeared normal, dense, and uniformly distributed throughout this tumor nodule by PECAM immunostaining. MVD for this tumor section was determined to be 187 ± 11. There was no significant difference between the MVD of the peripheral and central tumor sections. Analysis of a 14-μm serial section from the same tumor nodule by fluorescence microscopy using a filter specific for PF showed no visible fluorescence (Fig. 2B), indicating that other endogenous molecules which have an overlapping or similar excitation/emission spectrum to that of PF.

Fig. 2, C and D, show PECAM immunostaining and PF distribution, respectively, in a cryosection from the central region of a 9 × 5 × 5-cm sarcoma from a patient who was given PF 48 h before surgery. Again, the vasculature appeared normal, dense, and uniformly distributed throughout the section by PECAM immunostaining. MVD for this tumor section was determined to be 190 ± 5. Uniform distribution of PF was observed in this tumor section. A section from the above tumor

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**Fig. 4** PECAM immunostaining and PF distribution in peripheral and central cryosections of a 1-mm tumor nodule from an IP-PDT patient. Immunostaining for PECAM in the peripheral cryosection (A) and in the central cryosection (B) of a 1-mm tumor nodule. PF distribution in the peripheral cryosection (C) and in the central cryosection (D) in the same 1-mm tumor nodule. Data shows that both central and peripheral sections had similar distributions of blood vessels and PF. (Note: a portion of the tumor cryosection in (D) was folded over in the top left corner during sectioning).
that was not treated with primary antibody was used as negative control for PECAM immunostaining and did not show any immunostaining for blood vessels. Having thus established the validity of the technique to study uptake and distribution of PF in human tumors, the study was extended to small human tumor nodules ranging from 1 to 5 mm in maximum diameter.

Fig. 3 summarizes the results of PECAM immunostaining and PF uptake in a 1-mm, a 2-mm and a 4-mm tumor nodule. These size measurements are the maximum diameters of the individual nodules. PECAM immunostaining (left column) shows endothelial cells that seem to be organized into blood vessels, even in the 1-mm tumor nodule. Again, the endothelial cell clusters that apparently constitute blood vessels were uniformly distributed throughout each tumor cryosection. Analysis by fluorescence microscopy showed distribution of PF in localized dots that were not concentrated in any one area but distributed uniformly throughout the tumor section (right column). PECAM immunostaining and PF analysis of peripheral and central cryosections showed equal distribution of both blood vessels and PF dots in the peripheral and central sections alike (Fig. 4).

MVDs of small (1–2 mm maximum diameter; n = 6) and medium (3–5 mm maximum diameter; n = 4) tumor nodules were determined to be 93 ± 28 and 115 ± 27, respectively. The difference between these values was determined to be significant using the unpaired t test (P = 0.045; Fig. 5A). MVD of the two larger tumors used as positive and negative controls in the PF studies was determined to be 189 ± 4. Statistical analysis comparing the MVDs of the 1–5 mm tumors (n = 10) and of the larger tumors (n = 2) by the unpaired t test (Welch corrected) showed that the difference was very significant (P < 0.0001; Fig. 5B).

The MVDs in relation to tumor size and PF content are summarized in Table 2. Data collected indicate that irrespective of tumor histologies and tumor sizes, all tumor nodules harvested from IP-PDT patients stained positively for PECAM and showed PF uptake. Also, larger tumors (patient 11) were found to contain more PF. It seems that this is a direct result of larger tumors having relatively higher MVDs than tumors of smaller diameters (Table 2).

### DISCUSSION

An i.p. pattern of tumor spread is common in adenocarcinomas arising in the colon, appendix, stomach, and pancreas (11, 12), cancer of the ovaries (13), and soft tissue sarcomas of the bowel, intra-abdominal cavity, and retroperitoneum (14–16). Peritoneal seeding of cancers can occur in one of two ways. First, free malignant cells may be released directly from tumors into the peritoneal cavity (e.g., ovarian cancers, soft tissue sarcomas, or pancreatic cancer). Second, adenocarcinomas arising on the mucosal surface of the bowel wall may gain access to the peritoneal cavity via transmural penetration of the bowel wall.

Complete surgical resection of all malignant disease in patients with carcinomatosis and sarcomatosis is not possible for curative intent. A radical surgical resection or peritonectomy involves the complete removal of all omental tissue and stripping of the peritoneum from the lateral side walls, subdiaphragmatic spaces, and pelvis. Although a difficult surgical procedure, peritonectomy is technically feasible. However, the shortcoming of peritonectomy is that the majority of the peritoneal surfaces at risk for malignant spread of cancers cannot be removed with this surgical approach without life-threatening blood loss (17). For example, the capsules of the liver and spleen, the serosa of the small bowel and colon, and the peritoneum lining the bowel mesentery cannot be completely removed. Stripping of the peritoneum from the diaphragm, abdominal wall, and pelvis removes only a portion of the surface at risk for tumor implantation. Radiation therapy is of limited use in the treatment of carcinomatosis and sarcomatosis because of the toxicities to normal tissue within the peritoneal cavity with total abdominal radiation. Systemic and i.p. chemotherapy have yielded very limited results because of drug delivery problems and the lack of effective agents. Thus, meaningful treatment options are extremely limited for patients with disseminated i.p.

![Graphs comparing MVDs of i.p. tumors of different sizes.](image_url)
cancer, and these patients uniformly fail with progressive tumor in the peritoneal cavity.

PDT as a surface treatment may be advantageous in the treatment of i.p. malignancies, because the major clinical issue after surgery is not the bulk of tumor but rather the large surface area of the peritoneum. This surface potentially contains either STNs too numerous to be resected or microscopic disease that is always present in this clinical setting. Although light dispersion in the peritoneal cavity sometimes could be hampered by contamination of blood, it is theoretically possible that the large surface areas of the peritoneum could be exposed to light. Moreover, the effective treatment depth of PDT caused by light penetration is only a few millimeters in tissue, thus avoiding life-threatening toxicity (18, 19).

Uptake and retention of i.v. administered photosensitizer by tumor tissue is one of several fundamental determinants of the clinical effectiveness of PDT. It is important therefore that the residual tumor tissue that needs to be treated is well vascularized. Also, the cytotoxicity of PDT is dependent on oxygen as a substrate to create free radicals important in cell death. This requirement for oxygen is yet another reason that residual tumor tissues must be vascularized. Although photosensitizer uptake has been studied by several different methods in preclinical models (20–23), it has not been evaluated in small human tumor nodules. Also, the extent of vascularity in peritoneal malignant small human tumor nodules from clinical specimens has not been reported thus far. Therefore, the study presented here is an important one not only for its relevance to IP-PDT treatment and other therapies for carcinomatosis and sarcomatosis but also for our understanding of the process of vascularization of STNs in metastatic disease.

The data presented in this study indicate that small human tumor nodules ≤ 5 mm in diameter have blood vasculature as shown by PECAM immunostaining of tumor sections. It is, however, difficult to discern by this method as to whether the blood vessels have lumens and whether or not they are functional, especially in the 1–2-mm tumors. The study is limited by the fact that conventional invasive methods used in preclinical animal models to test the patency of blood vessels cannot be applied intraoperatively in human patients. Also, noninvasive methods such as Doppler ultrasound are not sensitive enough to measure blood flow in vessels of the size found in small human tumor nodules. Nonetheless, PECAM immunostaining suggests that endothelial cells, that seem to be blood vessels, are present in small human tumor nodules studied.

On the basis of this work, fluorescence image analysis of tumor tissue sections is a feasible method to assay for tumor uptake and distribution of photosensitizer in PDT. Uptake of systemically administered photosensitizer in STNs was observed uniformly in this study, and therefore, does not seem to be a limiting factor in the treatment of residual STNs by IP-PDT. Although we have not quantitated the amount of PF present in the nodules studied, a qualitative assessment of the data would indicate that the smaller nodules in the range of 1–2 mm may have less PF than the larger nodules. An as yet unanswered question in the context of IP-PDT is whether the PF seen in STNs after intravascular delivery produces sufficient quantum yields of reactive oxygen species and other deleterious species to result in tumor cell kill.

Limitations of currently used techniques for the detection and tissue processing of tumor lesions that are < 1 mm in thickness did not allow their inclusion in this study, although they frequently form part of the treated residual disease in IP-PDT. It is possible that these microscopic surface lesions are thin enough to fall within the diffusion limits of neighboring blood vessels in the peritoneum, which is a relatively well-perfused area of the body, although there currently does not exist any evidence in support of this idea.

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REFERENCES


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