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Highlight Article (Invited)

In vivo Tissue Evaluation Reveals Improvements in Explicit PDT Dosimetry†

Alexander Greer[1,2]*

[1]Department of Chemistry, Brooklyn College of the City University of New York, Brooklyn, NY
[2]Ph.D. Program in Chemistry, The Graduate Center of the City University of New York, New York, NY

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ABSTRACT

Progress is needed before explicit photodynamic therapy (PDT) dosimetry can treat peritoneal carcinomatosis and yet spare all healthy tissue. A report by Cengel et al. in this issue of *Photochemistry & Photobiology* on tissue evaluation in a canine model may bring that goal a step closer and may even be *dog*ma-changing.

COMMENTARY

Selectivity for treating peritoneal carcinomatosis and sparing of healthy cells is a major challenge. Such diseased tissue, for example, can be eradicated by photodynamic therapy (PDT), which generates cytotoxic singlet oxygen and oxygen radicals—in response to sensitized photooxidation. Now, photodynamic inroads have been accomplished in a canine (peritoneal) model system, as reported by Cengel et al. in this issue of *Photochemistry & Photobiology* (Fig. 1) (1). The canine study enables advancements to the PDT of peritoneal carcinomatosis using a probe which monitors tissue properties upon sensitizer administration. The monitoring then provides insight to help optimize PDT dosing in an explicit fashion.

Explicit dosimetry is used to guide light delivery (2), and also PDT is used as an adjuvant to surgery (3,4), in particular by researchers at the University of Pennsylvania. Alternatives to chemotherapy and traditional radiation therapy are needed due to their shortcomings in toxicity and tissue selectivity. Ultimately, PDT as an adjuvant to surgery is an area where important contributions have been made and with continued success will have a big impact (5,6). Despite PDT's success when applied after surgery, these peritoneal tissues are highly diverse, and devising dosimetry strategies are needed.

Early PDT dosimetry efforts were carried out by Dougherty et al. (7) with subsequent effectiveness found in the peritoneal cavity (8). Efforts by Busch et al. at the University of Pennsylvania have helped in this regard which include advanced parameters for PDT reactive oxygen species modeling and explicit PDT modeling (9–18). For example, about 4.6×10^7 singlet oxygen molecules are required to kill each tumor cell when using benzoporphyrin derivative (BPD) as the sensitizer (12). But among the problems that persist is the amount of sensitizer in tissue neither fully correlates with the PDT dose nor with amount of singlet oxygen delivered. Further, current PDT protocols rarely assess oxygenation level of tissue and whether it changes as a result of PDT damage to the vascular system. Nonetheless, medical physicists have made inroads in developing tools to measure optical properties of tissue *in vivo* (19–25); one such tool is explicit PDT dosimetry. But despite explicit PDT dosimetry effectiveness, advances can be made through tissue analysis. Tissue (spectroscopic) properties can be sampled in the treatment sites based on three main components—light, oxygen and photosensitizer.

A trio of tissue evaluations improve explicit PDT dosimetry

Cengel et al. (1) have used these three components in their study and find substantial differences among tissue sites with respect to optical properties, oxygenation levels and BPD sensitizer uptake, which can influence the photodynamics. The three components are found to vary among tissue sites, and also from canine-to-canine. The tissues studied were the abdominal wall, aorta, bladder, bowel, colon, gallbladder, kidney, liver, rectum, spleen and stomach.

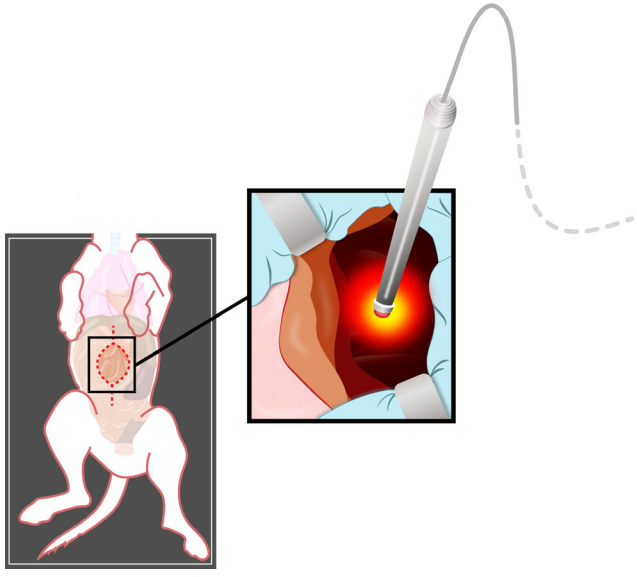

Figure 1. Illustration of canine with incision made from xiphoid to pubis in which the abdominal contents were explored.

*Corresponding author email: agreer@brooklyn.cuny.edu (Alexander Greer)
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Cengel et al. (1) examined the intraperitoneal cavity of healthy canines, where an incision was made from the lower part of the sternum to the pubis to expose the contents of the abdomen. The procedure also included a partial bowel resection. Diffuse reflectance and fluorescence measurements were carried out with a custom-built probe using a white light source (tungsten lamp) and a 403-nm diode laser, respectively. The canines were administered BPD and analyzed prior to and after irradiation with 690 nm light.

Tissue spectroscopy

The light distribution was measured by the optical properties including light absorption (μ_a), reduced scattering (μ_s') and effective attenuation (μ_{eff}) coefficients. The μ_{eff} is the effective attenuation coefficient and is determined from μ_a and μ_s'. Red light at 690 nm was used to irradiate organs in the cavity with a diffusing light wand. This wand was maneuvered in the cavity to provide near uniformity of distributed light. BPD absorbed the light as it was administered to the dogs several hours prior to irradiation. The μ_a and μ_s' optical parameters were measured before and after light administration, and the fluence was monitored by isotropic detectors in the cavity and on the bowel. The probe light sources included one for fluorescence and another for reflectance measurements. Reduced light penetration depth is seen in tissues with higher μ_a and μ_s'.

The results show that μ_a is higher for the liver and spleen (~0.2–0.8 cm^{-1}) and to some extent the gallbladder and kidney. The μ_a is lower in other tissues, such as the abdominal wall and stomach. It can be noted that tissues with higher μ_a generally yield higher μ_s' and μ_{eff}, such as in the kidney, liver and spleen. The oxygen saturation (StO_2) was assessed in the canine tissues. O_2 concentrations in tissue were highest in the spleen and aorta ~90%, but lower in the liver and kidney ~25–75%. Other tissues were at about 75% StO_2. This tissue spectroscopy provides important insight to potentially boost the effectiveness of explicit PDT dosimetry.

A deeper tissue PDT effect

Long-wavelength absorption of sensitizers along with selective localization in diseased tissue are needed. The better sensitizers for deep tissue PDT are red absorbers for the formation of ROS such as singlet oxygen (26–28). The sensitizer used by Cengel et al. (1) for longer wavelength absorption at 690 nm was BPD, as it has better light penetration depth than the 630 nm used for Photofrin. But there are still needs in this area, including improved sensitizer localization in the tumor (29,30). In the Cengel studies (1), the BPD concentration is obtained by diffuse fluorescence spectroscopy in each particular tissue. Interestingly, irradiation in the presence of BPD did not appear to reduce the oxygenation of tissue. Although after irradiation, BPD concentrations were lower in the abdominal wall, bowel and kidney.

The report of Cengel et al. (1) forms part of a growing body of work not only using PDT as an adjuvant to surgery (29–38), but also in advancing explicit PDT dosimetry (39,40). Their work stands as an important contribution in assessing tissue optical properties and oxygenation, and sensitizer effects in the peritoneal cavity. Advances in probe devices in general can open up potential advantages. For example, recent work suggests probes may be used to directly interrogate the three essential PDT components. The development of probes has increased in recent years for devices oriented to the PDT field (41). One technique (42) delivers sensitizer, oxygen and red light through a device tip directed at the tumor site. This device helps avoid damage to healthy cells by focusing the laser light, O_2 and sensitizer drug within the tumor site.

CONCLUSION

Better explicit PDT dosimetry from tissue analysis

There is no denying that PDT's use in peritoneal carcinomatosis will require improvements. Cengel and colleagues' data on tissue type show that we can understand where the challenges are. They characterize the effects of photodynamics on three essential components tissue optical properties, tissue oxygenation levels and BPD sensitizer effects for insight to explicit PDT dosimetry. Their work on explicit PDT dosimetry may well create more *explicit* discussions among photobiologists (this is a play on words). With their information in hand, application to humans is envisioned to fit in with peritoneal applications suited to PDT *following* surgery and spare health tissue.

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