Light Delivery and Light Dosimetry for Photodynamic Therapy

WILLEM M. STAR
Dr. Daniel den Hoed Cancer Centre, Department of Clinical Physics, PO Box 5201, 3008 AE Rotterdam, The Netherlands

Abstract. Photodynamic therapy (PDT) has attracted attention because it was considered to be a selective form of cancer treatment causing minimal damage to normal tissues. This is not exactly true, because the ratio between the photosensitizer concentrations in tumour and surrounding normal tissues is not always much more than one. Nevertheless, tumour destruction by PDT with relatively little damage to normal tissue is possible in many cases. This requires sophisticated light delivery and/or light dosimetry techniques. In this respect the limited penetration of light into biological tissues can sometimes be useful. In this paper a qualitative and sometimes quantitative discussion is given of the physical phenomena determining the energy fluence in a biological tissue. Most important is light scattering, the contribution of which depends on the geometrical conditions. Finite beam surface irradiation, irradiation of hollow organs (bladder) and interstitial irradiation are discussed separately. The emphasis is on light 'dose' and light dose distribution. It is emphasized that PDT dosimetry in general is complicated by photosensitizer distribution (which is usually not known), by photobleaching of the sensitizer, by possible effects of hyperthermia, and by changes in optical properties during and as a result of PDT.

INTRODUCTION

Photodynamic therapy (PDT) is a new form of cancer treatment that is currently evaluated in clinical trials (1, 2, 3). PDT involves the systemic administration of a photosensitizer that is more or less preferentially retained in malignant tissues. A few days after administration of the drug the tumour area is irradiated with a high light dose of suitable wavelength. This excites the photosensitizer, which upon decay to its ground state may transform available oxygen into singlet oxygen, which is probably the most important cytotoxic agent in PDT (4). PDT destroys the (tumour-)tissue blood circulation (5), probably by damaging endothelial cells. Tumour necrosis is therefore most likely an indirect effect and direct tumour cell kill by PDT is relatively unimportant (6).

The photosensitizer almost exclusively used in clinical PDT is haematoporphyrin derivative (HPD) or a substance derived from HPD, enriched in the active fraction, with the trade name Photofrin II (PhII). HPD and PhII can be activated by light of various wavelengths, e.g. $\simeq$400 nm (violet), $\simeq$500 nm (green) or 625–630 nm (red). Red light is least effective, but is preferred because it penetrates best into biological tissues. Lipson et al (7) demonstrated enhanced fluorescence of HPD in transplantable tumours compared to surrounding subcutaneous normal tissue. This has led to the notion of PDT as a selective cancer treatment modality. Subsequent studies have shown, however, that the ratio between photosensitizer concentrations in tumour and normal tissue is often not much larger than two or three. Furthermore, certain normal tissues (liver, spleen) retain more photosensitizer than tumours (8, 9). In the latter case, selective tumour treatment can still be realized by selective light delivery. In cases where the tumour does retain more photosensitizer than the surrounding normal tissue, it should be possible to destroy a superficial tumour and spare the normal tissue, even though both are irradiated with the same dose of light. In all cases, successful application of PDT requires sophisticated light delivery and light dosimetry techniques.

In the following sections the problems and achievements in light delivery and light dosimetry techniques will be illustrated using examples from clinical practice or preclinical animal research.

LIGHT DOSE AND BIOLOGICAL EFFECT

In most cases a laser is used as the light source for PDT. Laser light can be efficiently coupled into an optical fibre, facilitating endoscopic applications. However, for external light delivery properly filtered incandescent light sources or arc lamps have also been successfully employed. The power of a light source is expressed in Watts (=Joules/second) and the energy delivered—if the power is constant—is thus power × irradiation time (s), expressed in Joules.

In PDT usually a surface is irradiated and one is therefore interested in the power per unit area, called the irradiance and expressed in W/m^2 or mW/cm^2. For example, if an area of 5 × 5 cm^2 is uniformly irradiated with 1 W power, the irradiance is 40 mW/cm^2. The energy delivered to the surface in 30 min is 72 J/cm^2. These are numbers (order of magnitude) that are encountered in PDT practice. (Note that the power emitted by the laser must then be larger than 1 W, in this example because the fibre causes loss of light (reflections and also some absorption) and the fibre emits a beam of circular cross section, from which a square beam is obtained using a mask.) One can see that to irradiate a large area several Watts of power are needed. Even with a laser, it is not always easy to obtain a high power (>3 W) at the wavelength most suitable for PDT (625–630 nm). Non-laser light sources emit a broad spectrum of light which for PDT is filtered to obtain a band around the required wavelength. Since this light is not truly monochromatic it is less efficient in exciting the photosensitizer and consequently more energy is needed than with laser light to achieve the same biological effect.

The biological effect in PDT is proportional to the amount of light energy propagating in all directions multiplied by the absorption coefficient of the photosensitizer in the tissue. The first is called the energy fluence rate ψ (W/m^2). Multiplication with the irradiation time yields the energy fluence (J/m^2). If the absorption coefficient μ_p of the photosensitizer is expressed in m^{-1} (linear absorption coefficient), multiplication with ψ yields the power absorbed per second and per unit volume. (If instead of μ_p one uses the mass absorption coefficient, equal to (μ_p/density) and expressed in m^2/kg, the energy absorbed by the photosensitizer is expressed in J/kg.) This is the 'dose' that determines the biological effect of PDT in a well oxygenated tissue. However, since the distribution of photosensitizer concentration in a tissue treated by PDT is often not known, the same is true for the light dose absorbed by the photosensitizer. For simplicity one therefore assumes that for a given dose of photosensitizer administered to an organism the tissue distribution is always the same. In that case the energy fluence (rate) can be used as a measure of the absorbed light dose (rate).

If the surface irradiance exceeds about 200 mW/cm^2, hyperthermia may contribute significantly to (tumour-)tissue response (10). This may be useful, but is also a complicating factor in dosimetry. Avoiding hyperthermia may lead to long treatment times in interstitial PDT (see later section).

Because of the poor penetration of visible light into biological tissues (at most 1 cm for red light and less for light of shorter wavelength), effective PDT of non-superficial tumours requires interstitial light delivery. Here, one or more so-called cylindrical diffusors are implanted. These are optical fibres, modified so that light is emitted more or less uniformly over a length of one or more centimetres (11). The power emitted by a cylindrical diffusor is often expressed in mW per cm of light emitting length. This quantity (like the surface irradiance, above) is important with regard to a possible temperature rise due to the optical energy absorbed by the tissue, which may act synergistically with PDT (see later section). The radiant energy applied in interstitial PDT is sometimes reported as J per cm of light emitting fibre. This is not a useful quantity, because there is no fixed relationship with the actual fluence at any point in the tissue. One should always attempt to either measure or calculate (12) a value for the fluence or fluence rate at critical points in the treated (tumour-)tissue.

SCATTERING, ABSORPTION AND INTERNAL REFLECTION

The irradiance of the incident beam—multiplied by the irradiation time—is often reported as the 'light dose' in superficial PDT. If all other circumstances remain the same (type of tissue, geometry, concentration of photosensitizer) the irradiance can be useful as a reference value. It should be realized, however, that the energy fluence (rate) in the tissue does not have the same value, not even at the air–tissue boundary where the incident light enters the tissue. In fact, if a weakly pigmented tissue in

air is irradiated with a wide beam of red light (irradiance 1 W/m^2), the energy fluence rate in the tissue at the air–tissue interface may be 3–4 W/m^2 (13). After a plateau of a few millimetres, the fluence rate decreases exponentially with increasing depth (13). This behaviour is the result of two phenomena.

Light scattering

In biological tissues the scattering coefficient μ_s for red light is much larger than the absorption coefficient μ_a (to be distinguished from the absorption coefficient μ_p of the photosensitizer). In practice $\mu_a > \mu_p$ so that the light distribution is largely determined by the tissue optical properties. However, the possibility that administration of a photosensitizer may affect the light distribution should be kept in mind. Typical values for μ_s are 20–60 mm^{-1} (14–16). Values of μ_a may be 100–1000 times less. As a result, optical photons entering a tissue are scattered many times before they are either absorbed or diffuse out of the medium. The photons 'stay around' for a longer time than if they were not scattered. This increases the energy fluence rate close to the tissue surface. Another consequence of light scattering is that the fluence rate in tissue depends on the diameter of the incident beam (13). This is because by increasing the beam diameter more tissue is irradiated from which scattered light can reach a given point within the beam.

Internal reflection

The refractive index n of biological tissues is about 1.41 (17). If a light beam in air strikes an air–tissue interface, it is therefore partially reflected. The reflection coefficient is only a few percent, however (18). When light *within* the tissue strikes the tissue–air boundary, it will be totally reflected back into the tissue if the angle of incidence is larger than the critical angle, defined by $\arcsin(1/n) = 45°$. On the average, for diffuse light in the tissue striking the boundary, the reflection coefficient can be approximated by $[\cos\{\arcsin(1/n)\}]^2 = 0.50$ (19). Light that would otherwise have been scattered back cannot leave the tissue, causing an additional increase of the energy fluence rate in tissue at the air–tissue interface. If the tissue were embedded in water this effect would be much less. The refractive index of water is 1.33 so that the diffuse internal reflection coefficient is approximately $[\cos\{\arcsin(1.33/1.41)\}]^2 = 0.11$. This difference can be important if localized tumours in a water-filled bladder are treated by PDT using focal irradiation (see later section).

NARROW BEAM SURFACE IRRADIATION

Malignant tumours often arise at a tissue surface, either in the skin or at a surface in a body cavity (oral mucosa, gastrointestinal tract, lung, bladder). If the tumour to be treated is superficial, surface irradiation can be adequate.

Laser light can easily be coupled into an optical fibre. This facilitates irradiation of surfaces in body cavities by passing the fibre through an endoscope. The light intensity in a cross-section of the beam emitted by an optical fibre usually decreases as a function of the radial distance from the optical axis. The beam profile is bell shaped, whereas a 'rectangular' shape is preferred, i.e. the same irradiance at each point in a cross-section of the beam. McKenzie (20) has proposed a trick to manipulate this profile. A more elegant way is the use of a microlens (21), which can be small enough to pass through an endoscope. A somewhat more bulky device using a microscope objective lens has been proposed by Allen et al (22). This can be easily manufactured and emits a nearly perfectly uniform beam, but can only be used outside the body.

Even though the profile of the incident light beam may be rectangular, inside the tissue it becomes bell shaped again, due to scattering. This effect becomes more pronounced with increasing depth in the tissue. When irradiating a tissue for PDT it is therefore important to include a margin of normal tissue in the treatment field.

If a tumour is superficial and contains more photosensitizer than the surrounding normal tissue, selective PDT by surface irradiation is possible. The energy fluence rate in a tissue decreases with increasing depth. Thus, when the thickness of a tumour increases the surface light dose must be increased to achieve a tumoricidal dose at the deepest tumour boundary. Eventually, the required surface dose will cause necrosis of the superficial normal tissue as well. The limit of selective PDT is thus determined by the difference between tumour and normal tissue in retention of the photosensitizer and by the penetration depth of the activating light. But even when the conditions are not fulfilled,

for a well circumscribed tumour selective PDT is often still possible by selective irradiation: laterally by limiting the beam diameter and at depth by the natural limit of light penetration.

As mentioned earlier, the energy fluence (rate) in a tissue depends on the diameter of the incident beam (13), in particular if this diameter is small (of the order 1 cm). This has never been taken into account. In fact, little is known about the energy fluence rate in tissues for a given irradiance as a function of depth and beam diameter. Therefore, experience obtained with a given tissue cannot be transferred to different tissues, but can only be used as a guideline. Care must be taken that the geometry is the same. This will be illustrated with clinical experience obtained from PDT of bladder cancer in the next section.

PDT IN HOLLOW ORGANS: THE BLADDER

PDT in the urinary bladder has been applied in two different ways, viz. by focal irradiation of a limited area of a few centimetres diameter and by irradiation of the whole bladder wall.

For focal irradiation a fibre is entered into the bladder and light is applied to the target area under cystoscopic control. To control the amount of delivered light it is important to know the distance from the fibre to the surface and to keep it fixed. Up to 300 J/cm^2 incident fluence has been applied (23). Benson (24) reports using 100–150 J/cm^2. As disussed earlier, the energy fluence in the bladder mucosa will be larger due to light scattering. The effect of internal reflection is of minor importance here if the irradiated bladder is filled with water. We have estimated (25) that the energy fluence in the mucosa is twice the incident fluence, so that Benson effectively delivers 200–300 J/cm^2 with focal irradiation. It is interesting to compare this with a typical light dose applied to skin lesions, e.g. 72 J/cm^2. The actual fluence in the skin (in air) is estimated to be $3.5 \times 72 = 250$ J/cm^2 [see earlier and (13)]. The tissue light dose values for bladder and skin, derived from clinical practice, thus appear to be quite similar. The real meaning of this similarity is determined by the photosensitizer concentrations retained in these tissues.

Bladder cancer often occurs multifocally and carcinoma in situ in particular is not easy to detect cystoscopically. Consequently, local treatment by e.g. transurethral resection does not yield satisfactory results. Even after treating the whole bladder, by instillation with chemotherapeutic drugs or BCG, recurrencies practically always occur after some time. Therefore, PDT has been proposed as a possible alternative. By irradiating the whole bladder wall, it may be possible to destroy visible and invisible tumour, and spare normal mucosa. Obviously, it is important to irradiate the bladder wall as uniformly as possible. For this purpose, Jocham et al (26) use a light scattering suspension in the bladder. A practical advantage of this method is that a flat cut fibre can be used. Most other investigators use a fibre with a diffusing bulb (24, 26–30), emitting light isotropically, and water in the bladder. If the bladder approximates a sphere, both methods can yield a uniform light distribution, if the fibre tip is properly centred. It has been shown (25) that with a light scattering medium the uniformity of the light distribution across the bladder wall is much more sensitive to the position of the light source than with water in the bladder. Therefore, an alternative for the light scattering suspension is being studied (31). But even with water in the bladder in a clinical situation it is difficult to achieve and maintain a uniform light distribution (28). It is therefore not justified to draw conclusions on possible complications of whole bladder wall PDT (32) if no data can be given on the light distribution.

Initially, light doses of 60–70 J/cm^2 (incident, unscattered light) to the bladder wall were given in whole bladder PDT (26, 27). Complications indicated that this was too much. Currently, 20–25 J/cm^2 is recommended (24, 33). Due to scattering, the actual fluence at the bladder wall is five to six times larger (25, 28). This should be compared with the factor of three to four for surface irradiation (see earlier). The difference is caused by the fact that during surface irradiation some back scattered light is lost. In whole bladder PDT back scattered light re-enters the bladder wall elsewhere. Thus, the true fluence in a bladder irradiated with 20–25 J/cm^2 is approximately 100–150 J/cm^2. This is less than, but approaches the value estimated above, for focal irradiation. In this context it should be realized that a small area (volume) of tissue usually tolerates a larger does than large area (volume).

The preceding discussion illustrates the importance of adequate light delivery and light dosimetry techniques both for safe PDT-treatments and for the understanding of PDT-treatment results.

INTERSTITIAL PHOTODYNAMIC THERAPY

It has been shown that experimental non-superficial tumours can be effectively treated by PDT in a single session of interstitial irradiation (34, 35). In principle, the amount of light energy to be administered can be determined by measuring (13, 34, 36) or calculating (12, 36) optical isofluence curves (or 'optical isodoses') and combining these for multiple fibre insertions (36, 37). Subsequently, one estimates the energy fluence rate at the tumour boundary for the given geometry and fibre output to prescribe the treatment time. There are a number of complicating factors.

1. For calculations one needs the optical constants of the tissue and a suitable mathematical model. The Monte Carlo model can in principle be used for calculations in an arbitrary geometry, but the optical constants are generally not known.
2. The photosensitizer in the tissue affects the light distribution (34).
3. During interstitial irradiation, the light penetration may change due to PDT-induced changes in the optical properties (13).
4. Tissue heating may occur if more than about 100 mW per cm of light emitting length is applied to a cylindrical diffusor (35). A synergistic effect of interstitial PDT combined with interstitial hyperthermia has been demonstrated (38), of which one can take advantage. However, if uncontrolled hyperthermia occurs, this complicates relating light dose to response.

Practically the only reported clinical applications of interstitial PDT are for palliative treatments of obstructing oesophageal (39, 40) and lung tumours (40, 41). Usually one cylindrical diffusor is inserted into the tumour and the amount of delivered light energy is reported as Joules per cm. It appears from the literature that the power limit for hyperthermia has been exceeded in many cases. Avoiding hyperthermia in interstitial PDT may lead to long treatment times [1 h or more (35)]. If hyperthermia is avoided, J/cm is still not a good measure of effective light dose, because the latter depends on the tumour volume and on the distribution of the implanted cylindrical diffusors over this volume. In our opinion, the only way to apply interstitial PDT in a controlled fashion is to use an in situ light dosimetry probe (13, 34). This is only feasible for accessible tumours. For applications in the lung or oesophagus there appears to be no other possibility than to rely on clinical experience.

OTHER GEOMETRIES

In the foregoing sections the factors determining light dosimetry have been discussed for the most common geometries in which PDT is applied. A few other applications should be mentioned. Wilson et al [42] have published a study on light delivery and light dosimetry for intraoperative PDT of brain tumours [43]. A balloon with a light scattering medium is used to distribute the light as evenly as possibly over the tumour bed that is to be irradiated.

Superficial tumours in tube-like organs such as the oesophagus are not easily irradiated with a flat-cut fibre fitted with a microlens. Van den Berg [44] reports the construction of a cylindrical diffusor of 5 cm light emitting length which is kept centred using a transparent cylinder of 20 mm diameter. Here too, one must take into account that the energy fluence at the surface in the tissue is larger than the irradiance of unscattered light. The multiplication factor will be somewhere between three (for wide beam surface irradiation) and six (for whole bladder wall irradiation).

DISCUSSION

Light delivery and light dosimetry for PDT are complicated by the strong scattering of light in tissues and by the strong attenuation, leading to small penetration depths and high gradients of the energy fluence rate. With a few exceptions (28, 43) light dosimetry in clinical PDT has been rather primitive. This situation should improve, because without proper knowledge of the light dose it will not be possible to establish the factors that determine success or failure of PDT. Complications or failures of PDT should not be attributed to the modality when the light dose data to correlate response with dose are lacking (32). Otherwise, possible applications of PDT could be rejected for the wrong reasons. If for any reason sophisticated light dosimetry is not possible, the least one can do is detailed recording and reporting of the treatment parameters, to allow other investigators to reproduce and compare the results.

The strong light scattering in tissues is sometimes an advantage, for example in whole bladder wall PDT. If only light absorption would

play a role, the energy fluence rate at the bladder surface would vary as R^{-2}, where R is the distance from the isotropic light source to the bladder surface. Instead, due to the strong scattering, the energy fluence rate at the bladder surface varies approximately as R^{-1}. This means smaller deviations from uniform light distribution if the light source is displaced from the centre.

One phenomenon that may play a role in all PDT applications (depending on the type of photosensitizer used) is photobleaching (45). Due to the destructive effect of the activating light on the photosensitizer, a minimum tissue concentration is necessary to achieve tissue necrosis; otherwise stated, the level of tissue damage that can be achieved depends on the tissue concentration of the photosensitizer. If a superficial tumour retains more photosensitizer than the surrounding normal tissue, it may be possible to administer a drug dose that will allow destruction of the tumour with a certain minimum light dose, whereas at the same time it will not be possible to cause normal tissue necrosis, no matter how large the applied light dose. In such a situation light dosimetry becomes less critical. However, it could be that the required reduction of the photosensitizer concentration leads to longer treatment times that are undesirable for certain applications (e.g. bladder). More research is needed before a more detailed discussion is justified.

ACKNOWLEDGEMENT

The author thanks Hans Marijnissen for critical reading of the manuscript and for constructive comments.

REFERENCES

1 Manyak MJ, Russo A, Smith PD, Glatstein E. Photodynamic therapy. *J Clin Oncol* 1988, **6**:380–91
2 Dougherty TJ. Photosensitizers: therapy and detection of malignant tumors. *Photochem Photobiol* 1987, **45**:879–89
3 Gomer CJ. Photodynamic therapy in the treatment of malignancies. *Seminars Hematol* 1989, **26**:27–34
4 Weishaupt KR, Gomer CJ, Dougherty TJ. Identification of singlet oxygen as the cytotoxic agent in photoinactivation of a murine tumor. *Cancer Res* 1976, **36**:2326–9
5 Star WM, Marijnissen JPA, Van den Berg-Blok AE et al. Destruction of rat mammary tumor and normal tissue microcirculation by hematoporphyrin derivative photoradiation, observed in vivo in sandwich observation chambers. *Cancer Res* 1986, **46**:2532–40
6 Henderson BW, Waldow SM, Mang TS et al. Tumor destruction and kinetics of tumor cell death in two experimental mouse tumors following photodynamic therapy. *Cancer Res* 1985, **45**:572–6
7 Lipson RL, Baldes EJ, Olsen AM. The use of a derivative of hematoporphyrin in tumor detection. *J Natl Cancer Inst* 1961, **26**:1–11
8 Gomer CJ, Dougherty TJ. Determination of ^{3}He- and ^{14}C-hematoporphyrin derivative distribution in malignant and normal tissue. *Cancer Res* 1979, **39**:146–51
9 Eckhauser ML, Persky J, Bonaminio A et al Biodistribution of the photosensitizer dihematoporphyrin ether. *Lasers Med Sci* 1987, **2**:101–5
10 Svaasand LO. Photodynamic and photothermic response of malignant tumors. *Med Phys* 1985, **12**:455–61
11 Arnfield M, Gonzalez S, Lea P et al. Cylindrical irradiator fiber tip for photodynamic therapy. *Lasers Surg Med* 1986, **6**:150–4
12 McKenzie AL. How may external and interstitial illumination be compared in laser photodynamic therapy? *Phys Med Biol* 1985, **30**:455–60
13 Marijnissen JPA, Star WM. Quantitative light dosimetry in vitro and in vivo. *Lasers Med Sci* 1987, **2**:235–42
14 Flock ST, Wilson BC, Patterson MS. Total attenuation coefficients and scattering phase functions of tissues and phantom materials at 633 nm. *Med Phys* 1987, **14**:835–41
15 Jacques SL, Alter CA, Prahl SA. Angular dependence of He–Ne laser light scattering by human dermis. *Lasers Life Sci* 1987, **1**:309–33
16 Marchesini R, Bertoni A, Andreola S et al. Extinction and absorption coefficients and scattering phase functions of human tissues in vitro. *Appl Opt* 1989, **28**:2318–24
17 Bolin FP, Preuss LE, Taylor RC, Ference RJ. Refractive index of some mammalian tissues using a fiber optic cladding method. *Appl Opt* 1989, **28**:2297–303
18 Orchard SE. Reflection and transmission of light by diffusing suspensions. *J. Opt Soc Am* 1969, **59**:1584–97
19 Star WM, Marijnissen JPA, van Gemert MJC. Light dosimetry: status and prospects. *J Photochem Photobiol B:Biol* 1987, **1**:149–67
20 McKenzie AL. How to control beam profile during laser photoradiation therapy. *Phys Med Biol* 1984, **29**:53–6
21 Doiron DR. Photophysics of and instrumentation for porphyrin detection and activation. In: Doiron DR, Gomer CJ (eds) *Porphyrin localization and treatment of tumors*. New York: Alan Liss 1985:41–73
22 Allen V, Essex TJH, McKenzie AL. A simple projector for superficial laser photodynamic therapy. *Phys Med Biol* 1989, **34**:927–30
23 Hisazumi H, Misaki T, Miyoshi N. Photoradiation therapy of bladder tumors. *J Urol* 1983, **130**:685–7
24 Benson R. Treatment of bladder cancer with hematoporphyrin derivatives and laser light. *Urology* Suppl 1988, **31**:13–7
25 Star WM, Marijnissen JPA, Jansen H et al. Light dosimetry for photodynamic therapy by whole bladder wall irradiation. *Photochem Photobiol* 1987, **46**:619–24
26 Jocham D, Staehler G, Baumgartner R, Unsöld E. Die integrale Photodynamische Therapie beim multifokalen Blasenkarzinom. *Urologe [A]* 1985, **24**:316–9
27 Nseyo UO, Dougherty TJ, Boyle DG et al. Whole bladder photodynamic therapy for transitional cell carcinoma of bladder. *Urology* 1985, **26**:274–80
28 Marijnissen JPA, Jansen H, Star WM. Treatment system for whole bladder wall photodynamic therapy with

in vivo monitoring and control of light dose rate and dose. *J Urol* 1989, **142**:1851–5
29 McKenzie AL. How to construct a bulb-tipped fibre: part 1—theory. *Lasers Med Sci* 1988, **3**:267–72
30 McKenzie AL. How to construct a bulb-tipped fibre: part 2—application. *Lasers Med Sci* 1988, **3**:273–5
31 Unsöld E, Beyer W, Heinze A, Sroka R. Irradiation modalities for photodynamic therapy. In: Müller G (ed) Proceedings of the first plenary workshop on safety and laser–tissue interaction (European community medical laser concerted action programme). *Lasers Med Sci* Suppl 1989:159–64
32 Harty JI, Amin M, Wieman TJ et al. Complications of whole bladder dihematoporphyrin ether photodynamic therapy. *J Urol* 1989, **141**:1341–6
33 Shumaker BP, Hetzel FW. Clinical laser photodynamic therapy in the treatment of bladder carcinoma. *Photochem Photobiol* 1987, **46**:899–901
34 Marijnissen JPA, Versteeg AAC, Star WM. In vivo light dosimetry for interstitial photodynamic therapy: results of clinical importance. In: Dougherty TJ (ed) *Photodynamic therapy, mechanisms.* SPIE-Proceedings no. 1065. Bellingham, WA 1989:109–14
35 Marijnissen JPA, Versteeg AAC, Star WM. Tumor and normal tissue response to interstitial photodynamic therapy. Submitted for publication
36 Arnfield MR. Optical dosimetry and photodynamic therapy of experimental prostate tumors. PhD Thesis, University of Alberta, Edmonton, Alberta, Canada 1989
37 Arnfield MR, Tulip J, Chetner M, McPhee MS. Optical dosimetry for interstitial photodynamic therapy. *Med Phys* 1989, **16**:602–8
38 Levendag PC, Marijnissen JPA, De Ru VJ et al. Interaction of interstitial photodynamic therapy and interstitial hyperthermia in a rat rhabdomyosarcom—a pilot study. *Int J Radiat Oncol Biol Phys* 1988, **14**:139–45
39 McCaughan JS Jr, Williams TE Jr, Bethel BH. Palliation of esophageal malignancy with photodynamic therapy. *Ann Thorac Surg* 1985, **40**:113–20
40 McCaughan JS. Overview of experience with photodynamic therapy for malignancy in 192 patients. *Photochem Photobiol* 1987, **46**:903–9
41 Balchum OJ, Doiron DR, Huth GC. HPD Photodynamic therapy for obstructing lung cancer. In: Doiron DR, Gomer CJ (eds) *Porphyrin localization and treatment of tumors.* New York: Alan Liss, 1984:727–45
42 Wilson BC, Muller PJ, Yanch JC. Instrumentation and light dosimetry for intra-operative photodynamic therapy (PDT) of malignant brain tumors. *Phys Med Biol* 1986, **31**:125–33
43 Muller PJ, Wilson BC. Photodynamic therapy of malignant primary brain tumors: clinical effects, postoperative ICP, and light penetration of the brain. *Photochem Photobiol* 1987, **46**:929–35
44 Van den Berg H. Light and porphyrins in cancer therapy. *Chemistry in Britain* 1986, **22**:430–7
45 Potter WR, Mang TS, Dougherty TJ. The theory of photodynamic therapy dosimetry: consequences of photodestruction of sensitizer. *Photochem Photobiol* 1987, **46**:97–101

Key words: Photodynamic therapy; Light delivery; Light dosimetry; Tissue optics; Scattering; Absorption; Diffusor; Dosimetry probe

DISCUSSION

P. Muller: The relationship between penetration depth for PDT and wavelength has been well demonstrated. Is there a relationship between penetration depth and (a) power density; (b) dose rate; (c) other?

W.M. Star: Power density and dose rate have no effect on penetration depth. If a beam with finite diameter is used, penetration depth may depend on beam diameter and is smallest for the smallest beam. Beyond a certain diameter, penetration depth is constant. The size of this 'critical' beam diameter depends on tissue optical properties.

G. Jori: Light scattering from a tissue depends on the size of the tissular constituents (e.g. size and shape of cells, or type of organelles-ribosomes, etc.). Would these details be important enough to require a specific consideration when one needs to estimate the amount of light scattered by a tissue under different physiological, metabolic conditions?

W.M. Star: Most likely, the differences in optical properties among various tissues are much larger than the differences that might be caused by different physiological conditions. So, one should be satisfied with a reasonably accurate set of optical constants for a given tissue. The effect of photosensitizer in the tissue on the optical properties can be quite important, however.