Clinical Applications of Photodynamic Therapy

David I. Rosenthal and Eli Glatstein

This is a review of photodynamic therapy, which is a classic binary system involving the use of a photosensitizer and light of very specific wavelength, consistent with the absorption characteristics of that sensitizer. As a binary system, its effects are almost entirely limited to tumour cells, but the major drawback is its limited penetration because it utilizes physical light within the visible spectrum. For Photofrin II, which is the only approved sensitizer for clinical use in this country, the effects are limited to approximately 0.5 cm or less, depending on the tissue and the amount of blood, etc. Newer sensitizers offer more penetration and the opportunity to repeat treatments, because the newer sensitizers do not have the very long (up to 10 weeks) period of enhanced skin sensitivity to sunlight. A summary of the results of photodynamic therapy by individual sites is included.

The use of newer sensitizers, which represent much purer substances than Photofrin II, should give an opportunity for repeated treatments, which should eventually make this form of treatment far more important than it has been up to now.

Key words: lasers; neoplasms; therapeutic radiology, experimental.

(Annals of Medicine 26: 405–409, 1994)

Introduction and Background

Photodynamic therapy (PDT) involves a classic binary system which combines the use of a photosensitizer and light of an appropriate wavelength that is consistent with the absorption of that sensitizer. Both the sensitizer and the light must be at the same place at the same time for biological impact to result. Its use has been developing steadily in Japan and somewhat more sporadically in the United States.

The origin of PDT can be traced back to the turn of the century when Raab described the lethal effect of light on paramecia treated with an acridine dye (1). What makes the treatment of extreme clinical interest is its relative specificity. Lipson reported in 1961 on the use of haematoporphyrin derivative (HPD) for fluorescent detection of tumour tissue (2). It seems that when the porphyrins are injected intravenously, they are dispersed ubiquitously throughout the body. Normal tissues seem to eliminate this compound in a matter of several hours, while the porphyrins are retained either in or on tumour cells for a few days. Thus, there is a window of time during which the biological effects can be confined almost exclusively to tumour, rather than normal tissues. At certain wavelengths, fluorescence of tumour occurs; at other wavelengths, cytotoxicity results. These specific wave lengths are entirely dependent on the absorption characteristics of the specific photosensitizer. It is the tissue specificity and the relative freedom from lethal complications of treatment that make this treatment attractive clinically. However, it is limited in scope because it is dependent upon the penetration of light in tissues.

Dougherty first reported in 1975 on the eradication of transplanted animal tumours with HPD and red light without excessive damage to surrounding uninvolved skin (1). It is these observations, along with the development of lasers and fibreoptic systems for light delivery, which provide the major impetus for the current interest in this field.

Although the exact mechanisms of action are not entirely defined, it is clear that PDT involves the interaction of oxygen, photosensitizer and light (Fig. 1). The photosensitizer is excited and activated by the light and interacts with molecular oxygen to yield reactive singlet ($^1O_2$), the proposed mediator of photodynamic cytotoxicity. An activated sensitizer also has the potential

From the Department of Radiation Oncology, Harold C. Simmons Comprehensive Cancer Center, The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas, USA.

Address and reprint requests: David I. Rosenthal, M.D., Department of Radiation Oncology, Harold C. Simmons Comprehensive Cancer Center, The University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Dallas, TX 75235-8590, USA.

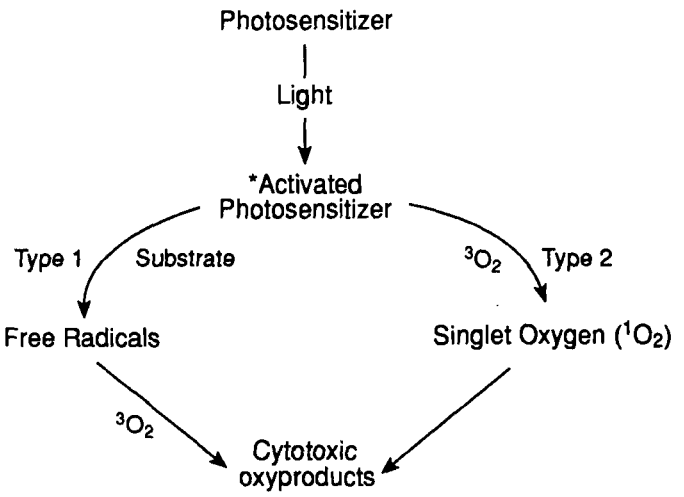

Figure 1. Interaction of oxygen, photosensitizer and light. Adapted with permission from Delaney (3).

to fluoresce when returning to the ground state, thus permitting the fluorescent detection of tumours.

The HPD compound is a complex mixture of porphyrins produced by the acid treatment of haematoporphyrin. Dougherty purified a more active oligomeric porphyrin fraction (1) from HPD with a high proportion of the active moiety, which has been proposed to be a dihaematoporphyrin ether (1) or ester (4). This oligomeric porphyrin fraction (termed polyporphyrin or dihaematoporphyrin ether, DHE) provided a higher therapeutic ratio (tumour compared to skin reaction) in animal testing than the previous employed HPD. The preparation of DHE (Photofrin II) is presently the only drug approved by the FDA for photodynamic therapy. Most of the work has been performed at 630 nanometers (nm) of wavelength. At this wavelength, red light is the most penetrating of the light forms and will penetrate reliably into 0.5 cm of most tissues. It should be noted, however, that a newer compound has been produced by the Quadralogic Company in Vancouver, British Columbia, which absorbs at 690 nm (in the infrared zone) (5). At this wavelength, there is more penetration (reliably about 1 cm into tissues) and there is no absorption by haemoglobin and relatively little by melanin, thereby maximizing the penetration in tissue. In addition, this newer compound BPD-MA (benzoporphyrin derivative, monoacid ring A) does not appear to be associated with the major UV skin reactions that are evident sometimes 6–10 weeks after the administration of HPD. Any skin reaction associated with the BPD compound would be apparent for approximately 1 week. Thus far, BPD-MA not only has a greater wavelength of absorption which means greater penetration in tissues, but it also seems to have a similar degree of tumour cell retention that is associated with Photofrin II (5). Normal tissue clearance for BPD-MA is also reported to be much greater than for Photofrin II.

Concerning the mechanism it is important to point out that, although the concentrations of HPD in liver, spleen and kidney are more consistently higher than those in tumour, there is no particular toxicity associated with those concentrations, unless light is exposed to those organs during that period. Higher HPD concentrations are consistently seen in mouse tumours than in skin and muscle (6). The precise mechanism of preferential localization of HPD in tumours is not understood at present. There is little difference in the effect of photodynamic therapy on *in vitro* cell lines derived from tumours versus normal tissue (7). Tumour stroma retains more labelled HPD than tumour cells, suggesting that a higher vascular permeability and inefficient lymphatic clearance may account for some of the differential retention in tumour tissues (8). The most hydrophobic HPD components appear to be involved in tumour localization (9). Porphyrins bind to low density lipoproteins in the serum, and it has been proposed that LDL receptors may play an important role in porphyrin localization in or on tumour cells (10).

Membrane targets, especially in mitochondria, are probable sites of cellular killing by HPD and light (11). Currently, many investigators believe that photodynamic damage due to tumour cell tissues represents a secondary effect produced by photodynamic destruction of tumour microvasculature (12). However, there is almost certainly a direct anti-tumour cell effect as well, since this binary system is very effective *in vitro*, where there are no vessels. In addition, when treatment is administered clinically, effects are usually seen within a matter of minutes to a few hours, which is a much faster course than we associate with cytotoxic therapy (i.e. chemotherapy or radiation therapy). Thus, the hypothesis has evolved that the mechanism is related to membrane

Table 1. Lasers vs. function.

Laser type	Wavelength (mm)	Mechanism of action	Use
CO_2	10500	Vaporization	Cutting
Nd-Yag	1050	Heat	Thermal coagulation
Argon dye	400–600 (visible light spectrum)	Cytotoxic only with sensitizer	Photodynamic therapy

Table 2. Summary of PDT results by site.

Tumour type	Pts/sites	Light dose J/cm²	CR	PR	NR	Comment	Reference
Cutaneous or subcutaneous							
Basal cell	3/38	90	100			None recurred at 35 months	16
Basal/sq CCA	6/9	8/60	100			Follow-up 8–24 months	17
Basal/SCCA	6/53	30	68	NA	NA	Most recurrences by 6 months	18
Basal/breast	7/61	60–100	50	31	19	Follow-up 40–16 months	19
Basal/SCCA	37/151	56–216	88	12	—	61% PR retreated to CR	20
Breast	14	26–288	15	69	15	Palliative–longest CA 6 months	21
Head and neck							
Squamous	10	60–100	80	10	10	Early or advanced	22
Squamous	17	NA	59	24	17	Early stage	23
Squamous	21	17–91	29	52	19	1° site	24
Squamous	10	17–91	20	30	50	Regional soft tissue	24
Squamous	6	34–390	—	100	—	1° site	25
Brain							
Glioma/met	23	70–230	NA	NA	NA	No toxicity	26
Glioma	32	8–68	19	13	68	25% cerebral oedema	27
Eye							
Melanoma	24/24	300–3000	41	6	53	CRs in small tumours	28
Melanoma	9/9	50–400		22	66	12 CR non-pigmented	29
Retinoblastoma	6/9	50–400		11	78	11 All later recurred	29
Lung and bronchus							
Lung	38/40	54/675	35	NA	NA	CRs in small lesions	30
Lung	8/8	120–240	75	25		Early stage lesion	31
Lung met	10/13	250 J/cm		80		80% reopened	32
Lung met	35/35	100 J/cm		80		If tumour endobronchial, 80% reopened	33
Lung	54/64	150–1575		84		No recurrences after 3 years	34
Oesophagus and gastric							
Oesophagus	40	300–660	10	NA	NA	Most improved swallowing	35
Oesophagus	14	60–337	14	86	—	All improved swallowing	36
Oesophagus	4	270–360	50	50	—	Early stage, CRs NED	37
Oesophagus	5	270–360	—	100	—	Advanced stage	37
Gastric	4	34–960	100	—	—	3/4 recurred by 27 months	38
Gastric	12	34–960	Resected post PDT			5/12 no tumour in specimen	38
Bladder							
TCCa	4	150 F	100	—	—	CIS, recurrences elsewhere	39
TCCa	8	120–360 F	100	—	—	Ta–T1 2 recurred 6, 18 months	40
TCCa	9/36	50–300 F	50	19	31	Ta, T1 all CR less than 2 cm	41
TCCa	19/50	100–200 F	24	50	26	Ta, T1, CIS	42
TCCa	10	WB 25–45	60	20	20	CIS or CIS and T2	39
TCCa	7	WB 25	78	—	22	4/7 developed contracted bladder	43
Gyn							
Vagina	5/5	NA	40	60	—	CRs durable at 10, 12 months	44
Vulva	2/2	NA	50	—	50	CR in CIS	45
Vagina/skin	6/9	20–40	22	45	33	Treatment not well tolerated	46
Vagina	15/15	60–240	53	40	7	Duration of CR 2.5–25 months	47
Vulva/vagina	5/5	Variable	80	20	—	Follow-up 5–15 months	48

Pts: patients.
J: joules.
CR: complete response.
PR: partial response.
NR: no response.
NED: no evidence of disease.
TCCa: transrectal cell carcinoma.
SCCa: squamous cell carcinoma.
Met: metastases.
CIS: carcinoma *in situ*.
Ta: papillary tumour confined to mucosa.
T1: tumour invading lamina propria.
T2: tumour invading muscle superficially.
F: focal.
WB: whole bladder.
NA: not available.
Energy: measured in joules.
PDT doses of light expressed in joules, joules/cm of fibre, joules/cm².
Power is work/unit time; measured in watts.
1 watt = 1 joule/s of treated surface area.
Laser power measured and expressed in watts.

damage of the cell or mitochondrion, as opposed to a direct DNA target.

HPD is generally been administered by intravenous injection followed within 48–72 hours by light delivery to the affected area. This schedule was developed empirically for the treatment of skin lesions from the observation that tumour destruction relative to surrounding normal skin was greater during this time period than at 24 hours. Serum half life of the HPD is about 3 hours in mice and about 25 hours in humans. The whole body half life of HPD has been measured at 396 hours (13). Because HPD is a mixture of porphyrins, it has been difficult to assess drug levels in tumours by direct techniques.

Phototoxicity can be avoided by shielding from the sunlight and by use of sunscreens. Normal indoor activity is possible. Since the porphyrins are metabolized in the liver, the drug must be used with caution in patients who have impaired hepatic function.

Although HPD absorbs light most strongly in the UV and blue region around 400 nm (14), 630 nm of red light is generally used in the clinic because of its superior penetration. PDT with 630 nm of light can produce tumour necrosis to a depth of 5 mm and rarely as deep as 10 mm. Though some carcinomas *in situ* and certain early stage invasive lesions and some dermatological malignancies and even some intraperitoneal carcinomatoses may be confined to such dimensions, externally directed red light will not penetrate deeply enough to sterilize many gross tumours with a single treatment. Hence, effective use of haematoporphyrin derivative with red light may require several treatments, or the placement within the tumour of interstitial optical fibres or combined modality therapy using surgery, radiotherapy or chemotherapy to reduce the bulk of the tumour, followed by PDT to sterilize the residual tumour within a tumour bed. To give multiple exposures, the period of risk for the cutaneous reactions must be short enough that multiple injections over a finite period are safe.

Light is expressed in joules (J) or energy density, such as joules per square centimetre (J/cm^2). Light may also be expressed as energy output per centimetre of light diffusing fibre (J/cm) for interstitially placed fibres. Lasers and optical fibres allow light delivery to deep seated tumours using endoscopic, interstitial or intercavitary techniques. The laser (light amplification by stimulated emission of radiation) provides light of an appropriate wavelength at sufficiently high power to excite the photosensitizer retained in the tumour. Clinical PDT lasers include argon pumped dye lasers or pulsed metal vapour lasers, which can yield up to 5 watts of usable light (15). More recently, solid state lasers have been developed which may offer even greater reliability at lower costs than currently employed systems.

It is worthwhile to contrast briefly the different types of lasers in clinical use (see Table 1). The carbon dioxide laser is a cutting or ablative instrument which emits at approximately 10600 nm. Thus, it is a surgical tool used for cutting. By contrast, the neodynium YAG laser works on the principle of heat coagulation of tissues. Emitting at 1060 nm, the tip of the laser is put in direct contact with tissues. Heat derived from the laser is sufficient to cause coagulation necrosis. By contrast, the gold vapour or pulsed argon dye laser emit in the visible light spectrum, generally under 700 nm of wavelength. At such wavelengths, the light by itself does not cause any biological effect that is recognizable in tissues. At those wavelengths, it must be combined with a photosensitizer and oxygen in order to cause any injury to tissues.

Although HPD and DHE have been used for clinical trials, DHE is the preferred agent, as it is the only approved investigational agent (in the US). It has been applied to a variety of superficial carcinomas with results as shown in Table 2. The use of such established treatment in these various types of tumours is already established in terms of efficacy (see Table 2).

We hypothesize that phototherapy has a potential curative role to play in selected neoplasms and situations. The future will see investigations in randomized controlled clinical trials being conducted to prove that PDT can deliver an important 'knock-out' punch for ovarian cancer patients who respond well to chemotherapy and also for colorectal patients undergoing end-to-end anastomosis. Additional animal studies must demonstrate the ability of various organs and tissues to withstand repeated weekly treatments. The new BPD-MA sensitizer is associated with a maximum 1-week period of enhanced skin reaction to sunlight; this makes weekly treatments feasible. The astonishing aspect of PDT is that most of the published data have been achieved by a single application of PDT. The future should see an actual course of PDT and improvements in outcome that can respond to this development.

References

1. **Dougherty, TJ.** Photosensitization of malignant tumors. *Semin Surg Oncol* 1986; 2: 24–37.
2. **Lipson RL, Baldes EJ, Olsen EM.** *Hematoporphyrin derivative for detection, and management of cancer.* Proc IX International Cancer Congress, Abstract 393, 1966.
3. **Delaney T.** Photodynamic therapy. In: Moosa AR, Schrimpff SC, Robson MC, eds. *Comprehensive Textbook of Oncology, 2nd edn.* Baltimore: Williams & Wilkinson, 1990.
4. **Kessel D, Thompson P, Musselman B, Chang CK.** Chemistry of hematoporphyrin-derived photosensitizers. *Photochem Photobiol* 1987; 46: 563–8.
5. **Lui H, Hruzhh L, Kollias N, et al.** Photodynamic therapy of malignant skin tumours with benzoporphyrin derivative-mono acid ring A (BPD-MA). Preliminary observations. *International Society for Optical Engineering* (in press).
6. **Gomer CJ, Dougherty TJ.** Determination of [3H] and [14 c] hematoporphyrin derivative distribution in malignant normal tissue. *Cancer Res* 1979; 39: 146–51.
7. **Henderson BW, Bellnier DA, Ziring B, Dougherty J.** Aspects of the cellular uptake and retention of hematoporphyrin derivative and their correlation with the biological response to PRJ *in vitro*. In: Kessel D, Dougherty TJ, eds. *Porphyrin Photosensitization*. New York: Plenum Press, 1983; 129–38.
8. **Bugelski PJ, Porter CW, Dougherty TJ.** Autoradiographic distribution of HPD in normal and tumor tissue of the mouse. *Cancer Res* 1982; 41: 4606–12.
9. **Kessel D, Chow, T.** Tumor-localizing components of the porphyrin preparation hematoporphyrin derivative. *Cancer Res* 1983; 43: 1994–9.
10. **Barel A, Jaro G, Perin A, Ramandini P, Ragnan A, Biffanti S.** Role of high, low, and very low density lipoproteins in the

transport and tumour delivery of hematoporphyrin *in vivo*. *Cancer Lett* 1986; 32: 145–50.
11. **Kessel D.** Effects of photoactivated porphyrins at the cell surface of leukemia L-1210 cell. *Biochemistry* 1977; 16: 3343–449.
12. **Henderson BW, Waldow SM, Mang JS, Patter WR, Malone PB, Dougherty TJ.** Tumor destruction and kinetics of tumor cell death in 2 experimental mouse tumours following photodynamic therapy. *Cancer Res* 1985; 45: 572–6.
13. **Brown SB, Vernon DI, Stribbling S.** Fate of HPD after intravenous administration. *Photochem Photobiol* 1990; 51 (Suppl.): 97s, (abstract).
14. **Moan J, Sommer S.** Action spectra for hematoporphyrin derivative, and photo II with respect to sensitization of human cells in vitro to photo inactivation. *Photochem Photobiol* 1984; 40: 631–4.
15. **Wilson BC, Patterson MS.** The physics of photodynamic therapy. *Phys Med Biol* 1986; 31: 327–60.
16. **Kennedy J.** HPD photoradiation therapy for cancer at Kingston and Hamilton. In: Kessel D, Dougherty TJ, eds. *Porphyrin Photosensitization*, New York: Plenum Press, 1983; 53–62.
17. **Waldow S, Lobraico RV, Lohler IK, et al.** Photodynamic therapy for treatment of malignant cutaneous lesions. *Lasers Surg Med* 1987; 7: 451–6.
18. **Pennington, DJ, Waner, M, Knox, A.** Photodynamic therapy for multiple skin cancers. *Plast Reconstr Surg* 1987; 82: 1067–71.
19. **Bandieramonte C, Marchesini R, Melloni E, et al.** Laser phototherapy following HPD administration in superficial neoplastic lesions. *Tumori* 1984; 70: 327–34.
20. **Wilson BD, Mang TS, Cooper M, Stoll H.** A clinical evaluation of photodynamic therapy for the treatment of basal cell carcinoma. Presented at International Photodynamic Association Meeting, Buffalo, NY, 1990.
21. **Schuh M, Nseyo UO, Potter WR, Dao TL, Dougherty TJ.** Photodynamic therapy for palliation of locally recurrent breast carcinoma. *J Clin Oncol* 1987; 5: 1766–70.
22. **Grossweiner LI, Hili JH, Lobraico RV.** Photodynamic therapy of head and neck squamous cell carcinoma: optical dosimetry and clinical trial. *Photochem Photobiol* 1987; 46: 911–7.
23. **Gluckman JL, Waner M, Shumrick K, Peerless S.** PTD: a viable alternative to conventional therapy for early lesion of the upper neurodigestive tract. *Arch Otolaryngol Head Neck Surg* 1986; 112: 949–59.
24. **Wile AG, Novotny J, Mason GR, Passy V, Berns MW.** Photoradiation therapy: photodynamic therapy of head and neck cancer. In: Dovion DR, Gomer CJ, eds. *Porphyrin Localization and Treatment of Tumors*. New York: Alan R. Liss, 1984; 681–91.
25. **Takata C, Imakiire M.** Cancer of the ear, nose and throat. In: Hyata Y, Dougherty TJ, eds. *Lasers and Hematoporphyrin Derivative in Cancer*. New York: Igaku-Shoin, 1983; 70–1.
26. **Kaye AH, Morstyn G, Brownbili D.** Adjuvant high dose photoradiation therapy in the treatment of cerebral glioma: a phase 1-2 study. *J Neurosurg* 1987; 67: 500–5.
27. **Muller, PJ and Wilson, BC.** Photodynamic therapy of malignant primary brain tumours: clinical effects, post-operative ICP and light penetration of the brain. *Photochem Photobiol* 1987; 46: 929–35.
28. **Bruce RA Jr, McCaugh JS Jr.** Lasers in uveal melanoma. *Opthal Clin North Am* 1989; 2: 597–604.
29. **Murphree AL, Cote M, Gomer CJ.** The evolution of photodynamic therapy techniques in the treatment of intraocular tumors. *Photochem Photobiol* 1987; 46: 919–23.
30. **Edell ES, Cortese DA.** Bronchoscopic phototherapy with hematoporphyrin derivative for treatment of localized bronchogenic carcinoma: a 5 year experience. *Mayo Clin Proc* 1987; 62: 8–14.
31. **Kato H, Konaka C, Kawate N, et al.** Five year disease free survival of a lung cancer patient treated only by photodynamic therapy. *Chest* 1986; 90: 768–70.
32. **Pass Hi, Delaney TF, Smith PD, Bonner R, Russo A.** Bronchoscopic phototherapy at comparable dose rates. *Ann Thorac Surg* 1989; 47: 693–9.
33. **Balchum OJ, Doiron DR.** Photoradiation therapy of endobronchial lung cancer. *Clin Chest Med* 1985; 6: 255–75.
34. **Furuse K, Fukuoka M, Kato H, et al.** A prospective Phase II study on photodynamic therapy with Photofrin II for centrally located early stage lung cancer. *J Clin Oncol* 1993; 11: 1852–7.
35. **McCaughan JS Jr, Nims TA, Guy JT, et al.** Photodynamic therapy for esophageal tumors. *Arch Surg* 1989; 124: 74–80.
36. **Thomas RJ, Abbott M, Bhathal PS, et al.** High dose photo irradiation of esophageal cancer. *Ann Surg* 1987; 206: 193–9.
37. **Aida M, Hiroshima T.** Cancer of the esophagus. In: Hayata Y, Dougherty TJ, eds. *Lasers and Hematoporphyrin Derivative in Cancer*. New York: Igaku-Shoin; 1983: 57–62.
38. **Hayata T, Kato H, Okitsu H, et al.** Photodynamic therapy with hematoporphyrin derivative in cancer of the upper gastrointestinal tract. *Semin Surg Oncol* 1985; 1: 1–11.
39. **Benson RC.** Laser photodynamic therapy for bladder cancer. *Mayo Clin Proc* 1986; 61: 859–64.
40. **Tsuchiya A, Obara N, Miwa M, et al.** Hematoporphyrin derivative and laser photo radiation in the diagnosis and treatment of bladder cancer. *J Urol* 1983; 130: 79–82.
41. **Hisazumi H, Misaki T, Miyoshi N.** Photo radiation therapy of bladder tumors. *J Urol* 1983; 130: 685–7.
42. **Prout GR Jr, Lin C, Benson R, et al.** Photodynamic therapy with hematoporphyrin derivative in the treatment of superficial transitional cell carcinoma of the bladder. *N Engl J Med* 1987; 317: 1251–5.
43. **Harty JI, Amin M, Wieman TJ, et al.** Complications of whole bladder dihematoporphyrin ether photodynamic therapy. *J Urol* 1989; 141: 1341–6.
44. **Ward BG, Forbes IJ, Cowied PA, et al.** The treatment of vaginal recurrences of gynecologic malignancy with phototherapy following hematoporphyrin derivative pretreatment. *Am J Obstet Gynecol* 1982; 142: 356–7.
45. **Dahlman A, Wile AG, Burns RG, et al.** Laser photo radiation therapy of cancer. *Cancer Res* 1983; 43: 430–4.
46. **Rettenmaier MA, Berman ML, Disaia PJ, et al.** Gynecologic uses of photo radiation therapy. In: Doiron DR, Gomer CJ, eds. *Porphyrin Localization and Treatment of Tumors*. New York: Alan R. Liss, 1984; 767–75.
47. **Corti L, Tomio L, Maluta S, et al.** Photodynamic therapy in gynecologic cancer. *Lasers Med Sci* 1989; 4: 155–8.
48. **McCaughan JS Jr, Schellhas HF, Lomano J, Bethel BH.** Photodynamic therapy of gynecologic neoplasms after presensitization with hematoporphyrin derivative. *Lasers Surg Med* 1985; 5: 491–8.