UC Irvine

UC Irvine Previously Published Works

Title

Photodynamic therapy using topically applied dihematoporphyrin ether in the treatment of cervical intraepithelial neoplasia.

Permalink

<https://escholarship.org/uc/item/69s115tp>

Journal

Gynecologic oncology, 64(1)

ISSN

0090-8258

Authors

Monk, BJ
Brewer, C
VanNostrand, K
et al.

Publication Date

1997

DOI

10.1006/gyno.1996.4463

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

Photodynamic Therapy Using Topically Applied Dihematoporphyrin Ether in the Treatment of Cervical Intraepithelial Neoplasia

BRADLEY J. MONK, M.D.,*¹ CHERYL BREWER, M.D.,* KRISTI VANNOSTRAND, M.D.,* MICHAEL W. BERNIS, PH.D.,†
JERRY L. MCCULLOUGH, PH.D.,‡ YONA TADIR, M.D.,*† AND ALBERTO MANETTA, M.D.*²

*Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, UCI Medical Center, Orange, California 92668;

†The Beckman Laser Institute, University of California at Irvine, Irvine, California 92715; and ‡Department of Dermatology, University of California at Irvine, Irvine, California 92715

Received March 5, 1996

Objective: To perform a phase I study of topically applied dihematoporphyrin ether (DHE) in the photodynamic treatment (PDT) of cervical intraepithelial neoplasia (CIN) using fixed DHE doses and application schedules, and a variable dose of 630 nm red light delivered by an argon-pumped dye laser. **Methods:** Between February 1993 and April 1994, 24 nonpregnant women with a histologic diagnosis of CIN were enrolled. All patients had lesions involving at least 25% of the cervix that were colposcopically visible. Using a cervical cap, 2 ml of a 1% solution of DHE (Photofrin) in a 4% Azone and isopropyl alcohol vehicle were applied to the cervix 24 hr prior to PDT. An argon-pumped dye laser providing light at 630 nm was then used to perform PDT. Light was coupled into a 400- μ m silica fiber optic terminating in a microlens which focused the laser radiation onto a circular field of uniform light intensity perpendicular to the tissue. The entire ectocervix was treated in a single field including a margin of 3–5 mm of normal cervix. Using a constant power density (150 mW/cm²) to avoid thermal injury, the PDT energy was increased every 4 patients in a phase I fashion (40, 60, 80, 100, 120, and 140 J/cm²). **Results:** Thirteen patients with CIN I, 7 patients with CIN II, and 4 patients with CIN III were treated. The maximal energy density was well tolerated. Toxicity was minimal with no patients experiencing local necrosis, sloughing, or scarring; however, a mild vaginal discharge was noted in several patients. Systemic effects were absent. After 12 months of follow-up at 3-month intervals, 22 patients are evaluable of whom 15 (68%) are disease free. One patient was lost to follow-up and in another the cervical cap was dislodged. Four of the 7 failures or recurrences occurred at energy densities of 80 J/cm² or less, while 8 of 11 (73%) patients were treated successfully with PDT at an energy density of 100 to 140 J/cm². **Conclusions:** PDT with DHE and an argon-pumped dye laser at 630-nm wave-

length delivering an energy density of 140 J/cm² is safe and effective in treating CIN. Phase II studies using PDT at the prescribed application schedule and dose are indicated. © 1997 Academic Press

INTRODUCTION

Cancer of the cervix is the second most common cancer affecting women worldwide and is the most common malignancy in developing countries [1]. Although more than 400,000 new cases of invasive cervical carcinoma are diagnosed each year, the predominant trend over the past three decades has been a steady decline in the incidence and the mortality from this disease [2]. Undoubtedly, the explanation for this dramatic decrease in cervical cancer incidence and mortality is a result of widespread cytologic screening followed by effective eradication of premalignant intraepithelial neoplasia [3].

The optimal method of treating cervical intraepithelial neoplasia (CIN) is not known but numerous techniques have been described which have little morbidity and reasonable efficacy. Diverse methods including cold knife excision, electrocautery, cryosurgery, laser ablation, and large loop excision of the transformation zone (LLETZ) have all been efficacious with success rates between 90 and 98% being common [4]. Differences among these techniques are primarily related to cost, unique side effects, distortion of the ectocervix, and the possibility for histologic review of the transformation zone [4, 5]. For example, cold knife cone and LLETZ are more commonly associated with postoperative bleeding but provide tissue for histologic evaluation. Cryotherapy on the other hand frequently makes subsequent colposcopy unsatisfactory and is associated with more vaginal discharge while laser is more costly. Finally, all methods currently employed involve substantial cervical stroma destruction and have potential ramifications on subsequent fertility.

In order to develop a novel treatment modality which would be highly specific to dysplastic cervical epithelium

¹ Present address: Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Texas Tech University Health Sciences Center, Southwest Cancer Center, Lubbock, Texas 79430.

² To whom correspondence should be addressed at Department of Obstetrics and Gynecology, University of California, Irvine, Clinical Cancer Center, Building 23, 101 The City Drive, Orange, California 92668. Fax: (714) 456-6463.

and preserve normal cervical tissue and architecture, we investigated the use of photodynamic therapy (PDT) as a treatment for CIN. Photodynamic therapy refers to the light activation of a photosensitizer to generate highly reactive oxygen intermediates. These intermediates irreversibly oxidize essential cellular components causing local injury and necrosis [6, 7]. The process typically involves intravenous administration of a photosensitizing drug that is retained longer in vascular and highly proliferative tissue [8]. Unfortunately, skin photosensitivity can be a significant side effect limiting the practical use of PDT. For this reason, topical application of photosensitizers has been proposed as a method of minimizing this untoward effect [9]. However, it is not yet clear if mechanisms of tissue destruction following systemic and topical administration of photosensitizers are identical because the efficiency of topical regimes is particularly dependent upon drug distribution and retention in critical cells and subcellular organelles.

Currently, the most commonly used photosensitizers are hematoporphyrins such as dihematoporphyrin ether (DHE), the active fraction of hematoporphyrin, which in clinical practice is usually injected intravenously. DHE is concentrated in various tissues after injection. This predominantly occurs in the liver followed by the spleen, kidney, dysplastic and frankly invasive tumor cells, skin, muscle, brain, and lungs [10]. Due to the differential localization of the photosensitizing agent in neoplastic versus normal epithelial cells, PDT can be used to selectively ablate preinvasive and invasive neoplasms. Photodynamic therapy requires activation of the photosensitizing agent by a monochromatic light, usually a red light at a wavelength of 630 nm delivered by an argon-pumped dye laser. Because of its selectivity and tumoricidal effect, we expanded on the traditional methods of systemic DHE administration and PDT by developing a technique to apply DHE directly to the cervix. We report the first phase I investigation of locally applied DHE in the PDT management of CIN. Through local application, the common systemic toxicity of cutaneous photosensitivity associated with intravenous DHE might be avoided without a compromise in efficacy.

MATERIALS AND METHODS

Approval was obtained from the Human Subjects Review Committee (Institutional Review Board) of the University of California, Irvine and Investigational New Drug (IND) status from the Food and Drug Administration (No. 40,296) was granted. Twenty-four consenting nonpregnant women over the age of 18 with histologically documented CIN were recruited from community sources for a phase I study of locally applied DHE. Patients who were less than 1 year postmenopausal were required to use an acceptable method of birth control during the entire study period. No intravaginal contraceptives were permitted. A negative serum preg-

nancy test was obtained on all women of reproductive age prior to enrolling in the study. Women with a known hypersensitivity to DHE, Azone, isopropyl alcohol, or any components of the formulation were excluded. Patients with abnormal renal or liver function were not eligible.

Patients enrolled in this phase I protocol were referred to and treated at the Beckman Laser Institute and Medical Clinic (Irvine, CA). All participants had cytologic evidence of a low-grade or high-grade squamous intraepithelial lesion on pap smear and a biopsy-proven intraepithelial lesion involving at least 25% of the ectocervix. The cervical biopsy was consistent with the colposcopic and cytologic description of the lesion. All lesions were completely visualized colposcopically. Women with endocervical extension as well as those with any cytologic, histologic, or colposcopic suspicion for invasion were excluded. Patients were not eligible for study if they had undergone treatment for CIN within the previous 3 months.

Twenty-four hours prior to PDT, and immediately prior to use, 100 mg of lyophilized DHE (light-protected Photofrin, QLT Phototherapeutics, Inc., Vancouver, British Columbia, Canada) was reconstituted with 10 ml of a vehicle containing 4% Azone (American Cyanamid Co., Lederle Laboratories, Pearl River, NY), 48% isopropyl alcohol, and 48% water to yield a 1% solution of DHE. Two milliliters of the 1% DHE/4% Azone solution was then applied to a circular piece of gauze placed in the appropriate size cervical cap (Prentif Cavity Rim Cervical Cap, Cervical Cap Ltd., Los Gatos, CA).

After 24 hr of continuously exposing the ectocervix to the DHE/Azone mixture, the cervical cap was removed and PDT was performed with an argon-pumped dye laser (Coherent, dye Model 920, Palo Alto, CA) providing light at 630 nm (maximum output 0.8 W). This was performed with the patient in the dorsal lithotomy position and without anesthesia. The laser system was coupled into a 400- μ m silica fiber optic (QLT Phototherapeutics, Inc., Vancouver, British Columbia, Canada) terminating in a microlens which focused the laser radiation onto a 10- to 30-mm-diameter circular field of uniform light intensity perpendicular to the tissue. A custom-made vaginal speculum was manufactured (U.S. Patent No. 5,458,595) which allowed stabilization of the optical fiber and focusing of the light spot size by changing the distance of the fiber from the treatment area (Fig. 1). The entire transformation zone was treated in a single field including a margin of 3–5 mm of normal ectocervix. The density of the PDT energy was increased every 4 patients in a phase I fashion (40, 60, 80, 100, 120, and 140 J/cm²) by using a constant power density (150 mW/cm²) in order to avoid thermal injury. Incident energy densities were escalated by increasing the exposure time at a given power output (Table 1).

Patients were monitored for systemic as well as local toxicity 1 and 4 weeks after therapy and the degree of cervical damage and local injury was evaluated grossly as well as

FIG. 1. Photodynamic speculum and light fiber. The spot size can be adjusted to cover the entire lesion by changing the focal length of the microlens and the cervical lesion.

colposcopically. Local toxicity was graded according to the size, depth, and time to healing of the area of destruction. The energy density was then increased only if local necrosis, pain, or nonhealing ulcers were absent in three of the four patients treated at the previous energy density. Response was assessed colposcopically and cytologically 3, 6, 9, and 12 months after PDT. Colposcopically directed biopsies of all abnormal areas were performed. Patients were removed from study and treated by other means (laser or LLETZ) if

biopsy proven CIN II or III was detected or if progression (new lesions) was documented.

RESULTS

Between February 1993 and April 1994, 13 patients with CIN I, 7 patients with CIN II, and 4 patients with CIN III were treated with locally applied DHE in a 4% Azone and isopropyl alcohol vehicle and PDT as previously described. As expected, injury to the underlying normal cervical stroma was minimal and none of the patients experienced local necrosis, sloughing, scarring, or a significant change in the location of the squamocolumnar junction. However, a mild vaginal discharge was noted for the first 2–4 days following PDT. Thus, an energy density of 140 J/cm² was well tolerated. Finally, systemic effects were absent at all energy densities.

At the completion of the 12-month follow-up period, 22 patients were evaluable of whom 15 (68%) are disease free (Table 2). One patient (No. 11 in Table 2) was lost to follow-up after 6 months and in another (No. 24 in Table 2) the cervical cap was dislodged and presumably there was not sufficient sensitization of the diseased area. Four of the 7 failures/recurrences occurred at energy densities of 80 J/cm² or less, while 8 of 11 (73%) patients were treated successfully with PDT at an energy density of 100 to 140 J/cm². Four of the failures/recurrences (patients 1, 7, 15, and 21 in Table 2) were CIN II or III, while 3 were CIN I (patients 6, 10, and 23 in Table 2). One patient (No. 8 in Table 2) developed CIN I 12 months after PDT. When she returned for treatment, no lesion could be identified colposcopically and her cytologic smear was normal. Four other patients (patients 9, 14, 17, and 19 in Table 2) had equivocal colposcopic findings associated with normal exfoliated cytology and yet had biopsy-proven CIN I and koilocytotic atypia at

TABLE 1
Relationship of Power Output and Exposure Time Achieving Various Energy Densities during PDT for CIN^a

Energy density	Spot diameter		
	10 mm	20 mm	30 mm
40 J/cm ²	Power, 118 mW Exposure time, 4 min 27 sec	Power, 471 mW Exposure time, 4 min 27 sec	Power, 1062 mW Exposure time, 4 min 27 sec
60 J/cm ²	Power, 118 mW Exposure time, 6 min 40 sec	Power, 471 mW Exposure time, 6 min 40 sec	Power, 1062 mW Exposure time, 6 min 40 sec
80 J/cm ²	Power, 118 mW Exposure time, 8 min 53 sec	Power, 471 mW Exposure time, 8 min 53 sec	Power, 1062 mW Exposure time, 8 min 53 sec
100 J/cm ²	Power, 118 mW Exposure time, 11 min 7 sec	Power, 471 mW Exposure time, 11 min 7 sec	Power, 1062 mW Exposure time, 11 min 7 sec
120 J/cm ²	Power, 118 mW Exposure time, 13 min 30 sec	Power, 471 mW Exposure time, 13 min 30 sec	Power, 1062 mW Exposure time, 13 min 30 sec
140 J/cm ²	Power, 118 mW Exposure time, 15 min 32 sec	Power, 471 mW Exposure time, 15 min 32 sec	Power, 1062 mW Exposure time, 15 min 32 sec

^a Power density is kept constant at 150 mW/cm².

TABLE 2
PDT in the Treatment of CIN: Patients Information Summarizing Details
Regarding Initial Diagnosis, Light Dose, and 12-Month Follow-up

Patient No.	Pre-PDT Diagnosis	Laser energy (J/cm ²)	3 months	6 months	9 months	12 months
1	CIN I	40	CIN III	Off Study		
2	CIN I	40	Normal	Normal	NA	Normal
3	CIN II	40	CIN I	Normal	NA	Normal
4	CIN I	40	Normal	CINI	Normal	Normal
5	CIN I	60	Normal	NA	Normal	Normal
6	CIN I	60	Normal	CIN I	Off Study	
7	CIN III	60	Normal	CIN III	Off Study	
8	CIN II	60	Normal	Normal	Normal	CIN I ^a
9	CIN III	80	Normal	Normal	CIN I	Normal
10	CIN II	80	CIN I	Normal	NA	CIN I
11	CIN I	80	NA	CIN I	LTFU	
12	CIN II	80	Normal	Normal	NA	Normal
13	CIN I	100	Normal	Normal	NA	Normal
14	CIN I	100	Normal	CIN I	NA	Normal
15	CIN II	100	CIN III	Off study		
16	CIN II	100	Normal	Normal	NA	Normal
17	CIN I	120	Normal	CIN I	Normal	Normal
18	CIN II	120	Normal	Normal	NA	Normal
19	CIN I	120	NA	CIN I	NA	Normal
20	CIN I	120	CIN I	Normal	NA	Normal
21	CIN III	140	CIN I	CIN II	Off Study	
22	CIN I	140	Normal	Normal	NA	Normal
23	CIN I	140	NA	Normal	NA	CIN I
24	CIN III	140	CIN III	Off Study ^b		

Note. Failures are highlighted in boldface. Normal is defined as the absence of biopsy-proven dysplasia. NA means that the results are not available (i.e., patient missed appointment). LTFU means that the patient was lost to follow-up.

^a Subsequent evaluation was normal, therefore this patient was considered free of disease.

^b Cervical cap dislodged.

the location of there previous lesion. These patients ultimately became completely free of disease without further therapy and thus were considered cures. Finally, 3 patients had steady regression of their disease occurring slowly during the study period (patients 3, 4, and 20).

No technical difficulties were encountered with the use of the new vaginal PDT speculum (Fig. 1).

DISCUSSION

Photodynamic therapy is a technique whereby light is used to achieve a toxic effect in photosensitized cells. When excited by red light in the presence of oxygen, photosensitizers such as the hematoporphyrin, DHE, undergo a series of reactions producing a selective cytotoxic effect in areas where the photochemical reaction occurs. Energy from the excited triplet state of the photosensitizer, induced by the absorption of light of the appropriate energy and wavelength, is directly transferred to molecular oxygen producing singlet oxygen. Although it is very unstable and short-lived, singlet oxygen is extremely reactive and capable of oxidizing biologic molecules causing irreversible damage to subcellular organelles such as the cell membrane, mitochondria, and lysosomes [11].

Because DHE is selectively sequestered in neoplastic tissues, PDT has been used extensively in the treatment of bladder, skin, head and neck, brain, and esophageal tumors with minimal surrounding normal tissue toxicity [12–15]. Although less well studied, a few gynecologic malignancies have also been treated with PDT with encouraging results [16–23]. Unfortunately, widespread use of PDT has been hampered by limited optical penetration with effective cytotoxicity of only 4–10 mm in depth [11]. For this reason, clinicians have suggested that PDT is ideally suited for the treatment of intraepithelial lesions such as CIN [16], Barrett's esophagus [24], and carcinoma *in situ* of the bladder [14]. In addition, the development of PDT has been limited by the systemic toxicity of the photosensitizing agent when administered intravenously, predominantly cutaneous photosensitivity [11, 16, 12–23]. In order to overcome these side effects, investigators have recently began to study topically applied photosensitizers [25–27]. Indeed, animal model studies indicate that there is selective retention of hematoporphyrins in areas of chemically induced squamous dysplasia after topical application of hematoporphyrin derivatives (HPD) [16].

On the basis of these animal model studies demonstrating

effective topical delivery and selective concentration in pre-malignant epithelial lesions, we initiated a pilot study of PDT in human intraepithelial neoplasia of the female genital tract [16]. We demonstrated that PDT was more effective in treating nonkeratinizing epithelium such as the vagina and cervix, while it was relatively less effective on the vulva. In addition, further study revealed that Azone with isopropyl alcohol was a more effective photosensitizer vehicle for PDT than Eucerin cream (Biersdorf Inc., South Norwalk, CT) [25, 28]. Therefore, we began to study the treatment of CIN and VAIN, since they were not keratinized, with PDT and locally applied photosensitizers in the Azone vehicle. In unpublished trials, we successfully treated a patient with VAIN using HPD in the Azone vehicle. A similar complete response was seen in a patient with CIN. In addition, HPD was found to readily penetrate vaginal epithelium after three topical applications (every 8 hr) as seen by fluorescence in a tissue biopsy. These encouraging preliminary results provided impetus for this phase I study of topically applied DHE, the active fraction of HPD, in an alcohol and Azone vehicle in the treatment of CIN.

In order to establish a practical and reproducible method of treatment, several logistical considerations of PDT were addressed. First, we report the use of a cervical cap in the application of a photosensitizer. This provided a reliable means of prolonged drug exposure. In addition, a new vaginal PDT speculum was developed and found to be effective (Fig. 1) in facilitating the delivery of reliable doses of laser energy to the ectocervix.

Although PDT was relatively easy to perform and lacked systemic toxicity, the dearth of local toxicity to normal cervical tissues is particularly noteworthy. Undoubtedly, the absence of immediate toxic effects was a result of the constant low power density (150 mW/cm^2) employed in the current protocol, thus limiting acute thermal injury to the cervix. Finally, the lack of subacute side effects as well as long-term morbidity from PDT was probably a result of the inherent selectivity of PDT in producing a cytotoxic effect only in neoplastic tissues. Even systemically administered photosensitizers have little toxic effect on adjacent normal tissues because of the preferential uptake of the photochemical by dysplastic cells compared to normal epithelium. Indeed, it was this selectivity of PDT and the anticipated low morbidity that caused us to study the treatment of CIN with PDT even though numerous other effective treatment modalities for CIN were in current practice.

It is difficult to assess the efficacy of the current PDT protocol in the therapeutic approach to CIN since the majority of the lesions studied were low grade. Indeed, the spontaneous regression of low-grade squamous intraepithelial lesions has been reported, although the precise resolution rate is unknown varying between 0 and 78% [29, 30]. Nevertheless, numerous dramatic responses to PDT were documented in the current study. Moreover, many of the PDT failures

may instead represent recurrences and thus not accurately reflected the true effectiveness of PDT in the treatment of CIN. Therefore, phase II studies of high-grade lesions and/or phase III studies comparing PDT to existing established modalities will determine the role of PDT in the current management of intraepithelial neoplasia of the cervix. In addition, second generation photosensitizers such as 5-aminolevulinic acid, and Benzo-Prophyrin derivative, may offer improved penetration following topical application and should also be tested for this indication.

REFERENCES

1. Parkin, D. M., Pisani, P., and Ferlay, J. Estimates of the worldwide incidence of eighteen major cancers in 1985, *Int. J. Cancer*, **54**, 594–606 (1993).
2. Muñoz, N., and Bosch, F. X. Epidemiology of cervical cancer, in *Human papillomavirus and cervical cancer* (N. Muñoz, F. X. Bosch, O. M. Jensen, Eds.), International Agency for Research on Cancer Scientific Publications, No. 94, Lyon, pp. 9–39 (1989).
3. Miller, A. B. Control of carcinoma of cervix by exfoliative cytology screening, in *Gynecologic oncology: Fundamental principles and clinical practice* (M. Coppleson, Ed.), Churchill Livingstone, Edinburgh, 2nd ed., pp. 543–556 (1992).
4. DiSaia, P. J., and Creasman, W. T. Preinvasive disease of the cervix, in *Clinical gynecologic oncology* Mosby Year Book, St. Louis, 4th ed., pp. 1–36 (1993).
5. Coppleson, M., Atkinson, K. H., and Dalrymple, J. C. Cervical squamous and glandular intraepithelial neoplasia: Clinical features and review of management, in *Gynecologic oncology: Fundamental principles and clinical practice* (M. Coppleson, Ed.), Churchill Livingstone, Edinburgh, 2nd ed., pp. 571–608 (1992).
6. Dougherty, T. J. Photodynamic therapy (PDT) of malignant tumors, *Crit. Rev. Oncol. Hematol* **2**, 83–116 (1984).
7. Kretmer-Birnbaum, M. Modified porphyrins, chlorins, phthalocyanines, and purpurines: Second generation photosensitizers for photodynamic therapy, *Semin. Hematol* **26**, 157–173 (1989).
8. Kimel, S., Tromberg, B. J., Roberts, W. G., and Berns, M. W. Singlet oxygen generation of porphyrins, chlorins, and phthalocyanines, *Photochem. Photobiol.* **50**, 175–183 (1989).
9. Chapman, J. A., Tadir, T., Tromberg, B. J., Yu, K., Manetta, A., Sun, C. H., and Berns, M. W. Effect of administration route and estrogen manipulation on endometrial uptake of Photofrin, *Am. J. Obstet. Gynecol.* **168**, 685–692 (1993).
10. Gomer, C. J., and Dougherty, T. J. Determination of [^3H] and [^{14}C] hematoporphyrin derivative distribution in malignant and normal tissue, *Cancer Res.* **39**, 146–151 (1979).
11. Spitzer, M., and Krumholz, B. A. Photodynamic therapy in gynecology, *Obstet. Gynecol. Clin. North Am.* **18**, 649–659 (1991).
12. Kato, H., Horai, T., Furuse, K., Fukuoka, M., Suzuki, S., Hiki, Y., Ito, Y., Mimura, S., Tenjin, Y., Hisazumi, H., et al. Photodynamic therapy for cancers: A clinical trial of porfimer sodium in Japan, *Jpn. J. Cancer Res.* **84**, 1209–1214 (1993).
13. Laws, E. R., Cortese, D. A., Kinsey, J. H., Eagan, R. T., and Anderson, R. E. Photoradiation therapy in the treatment of malignant brain tumors: a phase I (feasibility) study, *Neurosurgery* **9**, 672–678 (1981).
14. Hisazumi, H., Misaki, T., and Miyoshi, N. Photoradiation therapy of bladder tumors, *J. Urol.* **130**, 685–687 (1983).
15. Hayata, Y., Kato, H., Okitsu, H., Kawaguchi, M., and Konaka, C.

- Photodynamic therapy with hematoporphyrin derivative in cancer in the upper gastrointestinal tract, *Surg. Oncol.* **1**, 1–11 (1985).
16. Rettenmaier, M. A., Berman, M. L., DiSaia, P. J., Burns, R. G., Weinstein, G. D., McCullough, J. L., and Berns, M. W. Gynecologic uses of photoradiation therapy, in *Porphyrin localization and treatment of tumors* (D. R. Doiron and C. J. Gomer, Eds.), A. R. Liss, New York, pp. 767–775 (1984).
 17. Hetzel, H., Muller-Holzner, E., Marth, C., and Kostrom, H. Photodynamic therapy in patients with recurrent gynecologic cancers, *Geburts. Frauenheil.* **53**, 333–336 (1993). [in German]
 18. Lele, S. B., Piver, M. S., Mang, T. S., Dougherty, T. J., and Tomczak, M. J. Photodynamic therapy in gynecologic malignancies, *Gynecol. Oncol.* **34**, 350–352 (1989).
 19. Caughan, J. S., Schellhas, H. F., Lomano, J., and Bethel, B. H. Photodynamic therapy of gynecologic neoplasms after presensitization with hematoporphyrin derivative, *Lasers Surg. Med.* **5**, 491–498 (1985).
 20. Rettenmaier, M. A., Berman, M. L., DiSaia, P. J., Burns, R. G., and Berns, M. W. Potoradiation therapy of gynecologic malignancies, *Gynecol. Oncol.* **17**, 200–206 (1984).
 21. Corti, L., Tomio, L., Maluta, S., Minucci, D., Fontana, M., Cittar, H., *et al.* Recurring gynaecologic cancer treated with photodynamic therapy, *Photochem. Photobiol.* **46**, 949–952 (1987).
 22. Gray, M. J., Lipson, R. L., Maeck, J. V. C., Parker, L., and Romeyn, D. Use of hematoporphyrin derivative in detection and management of cervical cancer, *Am. J. Obstet. Gynecol.* **99**, 766–771 (1967).
 23. Sindelar, W. F., Delaney, T. F., Tochner, Z., Thomas, G. F., Dachoswki, L. J., Smith, P. D., *et al.* Technique of photodynamic therapy for disseminated intraperitoneal malignant neoplasms, *Arch. Surg.* **126**, 318–324 (1991).
 24. Falk, G. W. Barrett's esophagus, *Gastroenterol. Endocrinol. Clin. North Am.*, **4**, 773–789 (1994).
 25. McCullough, J. L., Weinstein, G. D., and Berns, M. W. Topical hematoporphyrin derivative (HPD) photodynamic therapy for psoriasis, *Laser Res. Med. Dent. Surg.* **64**, 35–39 (1988).
 26. Wyss, P., Tromberg, B. J., Wyss, M. T., Krasieva, T., Schell, M., Berns, M. W., and Tadir, Y. Photodynamic destruction of endometrial tissue using topical 5-aminolevulinic acid (5-ALA) in rats and rabbits, *Am. J. Obstet. Gynecol.* **171**, 1176–1183 (1994).
 27. Wyss, P., Tadir, Y., Tromberg, B. J., Liaw, L., Krasieva, T., and Berns, M. W. Benzo-Porphyrin derivative (BPD): A potent photosensitizer for photodynamic destruction of the rabbit endometrium, *Obstet. Gynecol.* **84**, 490–414 (1994).
 28. McCullough, J. L., Weinstein, G. D., Lemus, L. L., Rampone, W., and Jenkins, J. J. Development of a topical hematoporphyrin derivative formulation: Characterization of photosensitizing effects in vivo, *J. Invest. Dermatol.* **81**, 528–532 (1983).
 29. Montz, F. J., Monk, B. J., Fowler, J. M., and Nguyen, L. Natural history of the minimally abnormal Papanicolaou smear, *Obstet. Gynecol.* **80**, 385–388 (1992).
 30. Richart, R. M., and Wright, T. C. Controversies in the management of low-grade cervical intraepithelial neoplasia, *Cancer* **71**, 1413–1421 (1993).