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Review Article

Applications of photodynamic therapy in extramammary Paget's disease

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Abstract: Extramammary Paget's disease (EMPD) is a rare form of adenocarcinoma usually found in apocrine gland-containing cutaneous regions. EMPD affects the vulvar area most commonly, followed by the perianal area, scrotum, penis, and axillary region. In its initial form, EMPD presents as an erythematous plaque with well-defined edges, fine scaling, excoriations, exulcerations, and lichenification. Generally, a definitive diagnosis can be made through histopathological analysis. Importantly, associated malignancies should be investigated prior to treatment initiation. Photodynamic therapy (PDT) is a modern, noninvasive treatment strategy for non-oncological diseases as well as various cancers. In recent years, PDT has been widely used to treat EMPD. This present article presents a discussion of the diagnosis and treatment of EMPD as well as the usefulness of PDT in its management.

Keywords: Extramammary Paget's disease, photodynamic therapy, application

Introduction

Paget's disease was described by Sir James Paget in 1874 and was dichotomized as mammary Paget's disease (MPD) and extramammary Paget's disease (EMPD) [1, 2]. EMPD is a rare intraepithelial adenocarcinoma that accounts for 6.5% of Paget's disease [1, 3, 4] and is most commonly observed in patients between the ages of 65-70 years [5, 6]. EMPD usually occurs in the vulva, penis, scrotum, perineum, anus, and axilla [7-9], presenting as adenogenous differentiation of infiltrated tumor cells within the epithelium [2]. The pathogenesis of EMPD remains poorly understood and highly controversial. Current theories suggest that EMPD is primarily an intraepidermal tumor, explaining why only a small number of cases are caused by tumor metastases. EMPD is clinically characterized by well-defined erythema plaques, which can be easily misdiagnosed as eczema or candidiasis and is found in areas with abundant apocrine glands [10]. Skin biopsies often reveal a thickened epidermis, cellular enlargement, a fine-granular cytoplasm, and large and heteromorphic nuclei [3]. Of note, immunohistochemistry analysis can aid in distinguishing primary intradermal Paget's disease from diseases associated with potential adenocarcinoma.

Given that Paget cells invade the epidermis to a greater extent than is visible macroscopically, EMPD is usually treated using extensive surgical excisions. Surgical margins should be approximately 1 to 5 cm away from the lesion edge, and recurrence rates are quite high [11, 12]. Mohs micrographic surgery (MMS) offers excellent outcomes with a low recurrence rate [13, 14]. Nonetheless, some patients may not be able to undergo surgery due to underlying comorbidities or widespread diseases, and others may refuse surgery. Additionally, nonsurgical treatments such as imiquimod, local chemotherapy, and radiotherapy can be used, but their therapeutic effects continue to be inconsistent [15].

In recent years, new treatment modalities, such as photodynamic therapy (PDT), have been developed and extensively used in EMPD treatment. PDT is a treatment method developed in the late 1970s and has been approved by several countries, such as the United States, Britain, Germany, France, and Japan. To date, this technique has been successfully used to treat a number of malignancies. Herein, we review the pathogenesis, clinical features, and diagnosis of EMPD as well as the role of PDT in its treatment.

Overview of EMPD

Clinical features

EMPD typically develops insidiously and is accompanied by bleeding, edema, itching, burning, or pain. Lesions appear as well-defined red or brown patches, which are usually a few centimeters in size, occasionally with uneven surfaces, interspersed with white or gray areas, and occasionally lightly invasive. In later stages, lesions may become aggressive, ulcerated, crusted, or scaly and present with hard nodules, infiltrating or vegetative lesions and enlarged regional lymph nodes, indicating the presence of underlying malignancy. Seborrheic dermatitis, superficial fungi, Bowen's disease, superficial basal cell carcinoma, and sclerosing lichen are possible causes of EMPD [16].

Classification of EMPD

EMPD can occur around the anus, in the armpit, in the male genitalia, in the female vulva, and in some other locations [15], with different characteristics in different areas.

Perianal EMPD: Perianal EMPD accounts for approximately 20% of all cases, and the incidence is similar regardless of sex, with a mean age of onset of 63 years [5, 17]. These lesions typically begin near the anus and spread throughout the perineum, genitals, and buttocks, but rarely to the anal canal. The lesion may occasionally swell or bleed, causing pain or itchiness. There is an increased risk of adjacent and distant cancers such as cancers of the rectum, stomach, breast, and ureter in individuals with perianal EMPD, which is occasionally diagnosed by histological examinations of excised specimens of anorectal cancer [18].

Axillary EMPD: Only 0.9% of EMPD patients present with axillary lesions [19, 20]. A previous review summarized 45 cases of axillary EMPD, most of which were Japanese, with males predominating (94.3%) and isolated axillary involvement cases being more prevalent in females (70%) [21]. Axillary EMPD usually presents as well-defined erythema plaques. Brownish to pigmented patches are seen in some cases as a subtype, called pigmented EMPD [22, 23]. In axillary EMPD, the presence of underlying cancers was reported in 35% of cases [21]. EMPD in the armpit may be associated with adenocarcinoma of the breast and apocrine gland.

EMPD in male genitalia: A total of 14% of all EMPD cases involve the male genitalia [6, 24]. Lesions often begin in the scrotum, penis, or folds of the groin and may spread to the abdomen, although in a few instances, they are confined to the glans. Swollen inguinal lymph nodes [25] and edema of the legs can also occur in some patients. In 11% of these cases, EMPD is accompanied by cancers of other sites, such as the prostate, bladder, testis, ureter, and kidney [26].

EMPD in female vulva: More than half of all cases of EMPD occur in the vulva [27-30]. In most patients, the lesions originate from the labia majora before spreading to the pubis, inguinal folds, perineum, inner thigh surface, vagina, and labia minora. Approximately 4-17% of patients with EMPD have adnexal carcinoma, while 11-20% have breast, cervical, vaginal, or cutaneous cancers (basal cell carcinoma or melanoma). Interestingly, scholars have reported observing a correlation between vulvar Paget's disease and breast Paget's disease [31].

Other types of EMPD: Ectopic EMPD usually arises from skin areas without apocrine glands, including the chest, arms, fingers, knees, eyelids, and cheeks [8, 32, 33]. Multiple EMPDs are rare and typically involve anogenital and axillary lesions [34-37]. Axillary lesions occur simultaneously with or after genital lesions and are associated with sweat gland carcinoma in 50% of patients [21]. On the other hand, pure mucosal EMPDs are usually found in the ureter, larynx, esophagus, bronchus, and oral mucosa [38-40].

Pathogenesis

The exact pathogenesis of EMPD has not been fully elucidated. Although the characteristic features of Paget cells have been determined in immunohistochemical studies, the origin of the cells remains elusive. Current evidence suggests that EMPD is a heterogeneous disease. The pathogenesis includes at least two different forms: (1) Primary EMPD appears to originate from the epidermis or apocrine glands. This disease form is not associated with distant adenocarcinoma and is initially confined to the epithelial layers, but it may slowly develop into an aggressive tumor that spreads to the dermis, blood, and lymphatic vessels. During the advanced stages, the tumor may metastasize to the lymph nodes or internal organs, becoming lethal. The progenitors of Paget cells may originate from undifferentiated pluripotent cells in the epidermis or its adnexa. Recently, it has been suggested that Toker cells appearing in the vulvar epidermal layer are benign precursors of Paget cells [41, 42]. (2) Secondary EMPD is associated with potential distant adenocarcinoma and may result from the epidermal invasion of malignant adenocarcinoma cells. This form represents epidermal metastasis of the underlying tumor. The consistent immunohistochemical characteristics between Paget cells and adenocarcinomas strongly support this mechanism.

Diagnosis

Depending on the location of the skin lesions, the following tests for EMPD can be performed separately: cervicovaginal smear, cystoscope, rectal colonoscopy, abdominal ultrasound, computed tomography, gastroduodenal fibroscopy, urography, mammography, and serum tumor markers. Nevertheless, the definitive diagnostic method for EMPD is pathological examination, including surgical biopsy and cytological examination of lesion scrapings. Tumor cells are mostly solid and nested or have glandular structures, often with printed Paget cells [43]. Paget cells are commonly found in the epithelial sheaths of hair follicles, sweat gland excretory ducts, or secretory coils. The epidermis is often hyperplastic, sometimes showing fibroepithelioma-like changes [44]. It should be possible to make an accurate diagnosis by using special staining techniques and immunohistochemical staining. Paget cells occasionally present a signet-ring aspect due to the presence of intracytoplasmic salivary mucins, which explains the positivity of some histochemical stains, such as periodic acid-Schiff (PAS), mucicarmin, alcian blue, aldehyde-fuchsin and toluidine blue [45].

Treatment

Eradicating EMPD depends heavily on adequate surgical excision, which should be large enough to remove all tumor tissues. However, Paget cells often invade the epidermis quite extensively, making it difficult to achieve complete excision and leading to high recurrence rates [46]. Therefore, a 2 cm safe cutting edge is usually recommended [47]. A lower recurrence rate can be achieved by utilizing excision biopsy with frozen sections or Mohs micrographic surgery (MMS) [12]. Recently, imiquimod, a local immune response modulator, has been used successfully in a small number of EMPD cases [48] and appears to be effective in controlling superficial lesions. Systemic chemotherapy can be used in patients with contraindications to surgery and radiotherapy [49, 50]. Furthermore, not only can radiotherapy be used for patients with primary EMPD as the first-line therapy, but it may also be applied to the postoperative treatment for patients with positive surgical margins [51]. Dynamic light therapy has produced satisfactory results, but the disease still has a certain recurrence rate [52, 53]. **Table 1** presents the efficacies of several basic treatment methods for EMPD.

Different types of EMPD are subject to different treatment methods with varying therapeutic effects, and we summarize them below.

EMPD in male genitalia: (1) Noninvasive EMPD: Surgical resection is the first-line treatment method [54]. In addition to conventional surgical resection, MMS is also an important surgical procedure. MMS allows maximum preservation of critical anatomical structures typically involved in EMPD while allowing examination of the entire margin. Several studies showed that patients who received conventional surgical treatments had higher overall 5-year survival rates (68% vs. 79%) and recurrence-free survival rates (66% vs. 91%) than those who received MMS. In addition, there are some alternative therapies, such as radiotherapy and

Table 1. Efficacies of main approaches to EMPD treatment

	Treatment effects
Surgical Treatment	Rates of recurrence [12, 13]: MMS: 8% to 26%; Excision: 33% to 60%.
Radiotherapy	Complete response rates: 50% to 100%; Recurrence rates: 0% to 80% [129].
Imiquimod	Complete response rates: 52% to 75%; Partial response rates: 16% to 28% [130-135].
Photodynamic Therapy	Response rates: 66% to 78% [124, 136-139]; Recurrence rates: 33.6% [11].

MMS, Mohs micrographic surgery.

PDT. Currently, discussions of radiotherapy tend to focus on palliative use to relieve pain, despite the risk of frequent radiation dermatitis [55]. PDT is becoming increasingly widely used. One study found no cases of recurrence in 31 patients treated with surgery combined with PDT but one recurrence in 7 patients treated with PDT alone [56]. (2) Invasive EMPD requires wide surgical resection with a lateral margin of 2 cm and deep excision in front of the tumor to ensure that the fascia is removed [57]. (3) Metastatic EMPD: The treatment mainly relies on chemotherapy, which can be performed using taxane or cisplatin combined with 5-fluorouracil.

EMPD in female vulva: The recurrence rates (RR) with radical vulvectomy, radical hemi-vulvectomy and wide lesion excision (WLE) were 15%, 20% and 43%, respectively [58]. In addition, the RR with MMS as therapy for the vulvar EMPD was 27%. Imiquimod has been reported as a successful treatment alternative to surgery. In a series of recent studies, imiquimod was more likely to cure the disease than WLE [59]. Chemotherapy can also play a role. Local chemotherapy drugs for treating EMPD include 5-fluorouracil and bleomycin [7, 60-63]. Despite playing an important role in multimodal treatment strategies to control symptoms of inoperable or recurrent diseases, chemotherapy is not recommended as the primary treatment modality [64, 65]. Radiotherapy is mainly indicated for patients who are not suitable for surgery or as an adjuvant treatment to surgery in patients with underlying adenocarcinoma [7]. A study presented the final radiotherapy results of nine patients categorized in the intraepithelial Paget's (IEP) and invasive disease groups, finding that the RR after radiotherapy was 50% in the invasive group, and no local recurrences were found in the IEP group [66]. The role of carbon dioxide laser as a primary treatment is limited to the treatment of superficial lesions [46, 67], with a RR of approximately 31% to 67% [67, 68].

Perianal EMPD: The basic treatment for perianal EMPD is surgical resection. Local excision is associated with a high recurrence rate (40%) [44]. Wide surgical excision with a sphincter-saving technique is a better treatment method [5, 69-72], which can give patients more chances to be cured and survive [72-77]. MMS has been shown to reduce the risk of recurrence to 28% [46, 78]. When the disease is associated with underlying anal or rectal cancers, the choice of treatment modality is the abdominoperineal resection with wide excision of the cutaneous lesions [79]. Several noninvasive treatments, including radiotherapy, chemotherapy, and PDT, may be proven to be reasonable alternatives to surgery, but there are currently insufficient data to assess the efficacies of noninvasive treatments.

Prognosis and follow-up

The prognosis of EMPD depends on the presence of underlying distant cancers. The prognosis for primary/epidermal extramammary Paget's disease is generally favorable. However, if the lesion invades and its depth of invasion exceeds 1 mm, the prognosis can become worse. Due to the risk of recurrence, clinical follow-up of EMPD patients is recommended. For noninvasive EMPD, follow-up every six months for three years, followed by annual monitoring for ten years, is recommended. On the other hand, for invasive EMPDs or EMPDs associated with underlying tumors, follow-up should be more frequent (3 or 4 times per year), with biopsies performed for any suspicious skin lesions.

Correlation between EMPD and MPD

Paget's disease has been classified into EMPD and MPD, which share many clinicopathologi-

Table 2. Correlation between mammary and extramammary Paget's diseases

	Mammary Paget's disease	Extramammary Paget's disease
Epidemiology	Accounting for 0.7-4.3% of all breast cancers [140-142].	Accounting for 6.5% of all Paget's disease cases [4].
Onset age	Mean age 57 years.	Aged between 65 and 70 years [5, 6].
Clinical features	Insidious; oozing erythema of nipple and areola; invariably unilateral and very exceptionally bilateral [143]; itch, tingling, burning or pain.	Insidious; well-demarcated red or brown plaques; bleeding, oedema or subjective symptoms (itch, burning or pain).
Pathological features	The invasion of epidermis by Paget cells; expressing keratin 7, epithelial membrane antigen, carcinoembryonic antigen, GCDFP-15, the oncoproteins c-erb-B2/HER-2/neu, p53, cell-cycle-related antigens (p21, Ki-67, cyclin D1) and androgen receptors [144-147].	Paget cells; the positivity of some histochemical stains: periodic acid-Schiff, mucicarmin, alcian blue, aldehyde-fuchsin and toluidin blue.
Pathogenesis	Paget cells originate from the underlying mammary carcinoma and migrate via the lactipherous ducts to invade the epidermis of the nipple and areola.	Two different forms: 1. Primary or cutaneous EMPD: originate in the skin, initially limited to the epithelium, slowly progress to an invasive tumour, spreading to the underlying dermis, blood and lymphatic vessels; 2. Secondary form of EMPD: associated to an underlying adenocarcinoma; due to epidermal invasion of malignant adenocarcinoma cells.
Treatment	1. Surgical excision [148]; 2. Radiotherapy [149, 150]; 3. Chemotherapy [151].	1. Surgical excision [46, 47]; 2. Laser excision [152]; 3. X-ray treatment; 4. Intralesional interferon [153]; 5. Systemic chemotherapy [49, 50]; 6. Dynamic phototherapy [52, 53].

cal features but also exhibit some differences in certain aspects, such as pathogenesis and correlations with potential malignancies. **Table 2** shows the characteristics and correlations of EMPD and MPD.

Photodynamic therapy

Overview of photodynamic therapy

PDT has emerged as a strategy for cancer treatment in recent years [80]. PDT utilizes photosensitizers, light, and oxygen molecules to selectively treat malignant lesions through photodynamic reactions. PDT can generate reactive oxygen species (ROS) under specific laser irradiation, thereby killing tumor cells and inhibiting tumor growth. Photosensitizers such as hematoporphyrin and temoporfin have been used to treat clinical tumors. Notably, PDT has become a novel modality for the treatment of advanced tumors and has been successfully used to treat some skin malignancies, such as Bowen's disease and superficial basal cell carcinoma [81]. The advantages of PDT include the following: (1) minimal toxic side effects compared to systemic drug administration since ROS production is induced locally to promote cellular apoptosis; (2) no drug resistance; (3) minimal effect on adjacent organs or skin tissues (PDT is a better treatment option for patients with serious heart and brain diseases that are not suitable for resection); (4) the treatment of PDT is more thorough. Employing PDT helps to avoid missing small lesions that are invisible to the naked eye during surgery, thus improving patient prognosis [80].

Clinical studies on PDT

The clinical application of PDT for cancer dates back to the late 1970s, when a study was published about the effects of hematoporphyrin derivative (HPD) combined with light on five patients with bladder cancer [82, 83]. In 1978, Dougherty et al. reported the first series of patients successfully treated with PDT [84]. Complete or partial responses were achieved in 111 of the 113 malignant lesions. Several systematic reviews indicated that PDT could be used to treat malignant and precancerous nonmelanoma skin lesions [85, 86]. PDT in the treatment of skin malignant cancers has been widely studied [87, 88]. PDT has also been successfully applied to the treatment of early cancers of the oral cavity, pharynx and throat, allowing the normal tissues and the important functions of speech and swallowing to be retained [89]. A large multicenter phase 2 trial evaluating temoporfin-mediated PDT in the

treatment of primary oropharyngeal cancer showed a complete response rate of 85% (97 of 114 patients) at 12 weeks and a 2-year disease-free survival rate of 75% [90]. In addition, several other studies have demonstrated that PDT could be used to treat digestive system tumors [91], intraperitoneal malignancies [92], urinary system tumors [93], and brain tumors [94].

PDT in combination with chemotherapy

Combination therapies using two or more treatment strategies are known to reduce toxicity and improve the efficacy of a single therapy. PDT combined with chemotherapy via drug delivery systems (DDSs) can increase the effects while reducing the toxic side effects of chemotherapy alone [95-99]. To synergistically deliver chemotherapeutic drugs and photosensitizers, researchers loaded Ce6 via π-π stacking interactions with doxorubicin (DOX), which was then connected to a personality polymeric carrier through the terminal thione bond (PEG-PBCTKDOX) sensitive to ROS. In this system, the ROS generated by PDT can cause nanocarrier degradation and promote drug release. Therefore, nontargeted chemotherapeutic drugs will only release the minimum toxic dose at the position where the excitation light is focused. This strategy is very suitable for inducing additional tumor growth inhibition to improve efficiency and reduce toxicity [100].

PDT in combination with radiotherapy

Radiotherapy is a local therapeutic method for tumors. Approximately 70% of cancer patients receive radiotherapy as a part of their cancer treatment and usually obtain appropriate therapeutic outcomes [101-103]. The effectiveness of radiotherapy depends on radiosensitivity, lesion location, tumor type, etc., among which radiosensitivity is closely related to the proliferation cycle and pathological stage of tumors. In addition, the radiosensitivity of tumor tissue is also considerably influenced by O_2 levels [104-106].

Similar to the combined use of chemotherapy and PDT, PDT-based radiotherapy has an important synergistic therapeutic effect, which can reduce the radiotherapeutic dose and adverse reactions. In particular, the self-lighting PDT developed in recent years no longer requires additional light sources, and its combination with radiotherapy not only reduces the radiation dose but also effectively solves the problems of weak penetration of external light sources and poor PDT-inducing effects. The damage of X-rays to biological macromolecules such as DNA and proteins involves both direct energy transfer and indirect effects of water ionization that produce massive amounts of free radicals. The main damage occurs in the nucleus. Photosensitizers mainly aggregate at membrane structures such as mitochondria, endoplasmic reticulum, Golgi apparatus and cell membrane, causing membrane injury and activating corresponding apoptotic pathways extranuclearly [107]. However, PDT can not only cause phototoxicity through $^1O_2$ but also lead to several types of DNA damage [108], thus resulting in a synergistic effect with their combination. The combined effect may be related to various factors, including photosensitizer properties, irradiation intensity of PDT, radiation dose, cell line and the interval between radiotherapy and PDT. For example, photosensitizers with radiosensitization are more likely to exhibit synergistic effects.

PDT combined with radiotherapy can substantially reduce symptoms, improve quality of life, and prolong survival in cancer patients [109, 110]. There have been a series of studies on the effects of PDT plus radiotherapy. Previous studies have shown that PDT combined with radiotherapy can improve the sensitivity of tumors to radiotherapy and improve treatment outcomes [111, 112]. Furthermore, it can also shorten the exposure time or reduce the radiation dose. PDT has been widely used as a rescue procedure for patients with recurrent cancers after radiotherapy, and this practice has shown promising results [113]. In one study, PDT was used to treat patients with end-stage head and neck squamous cell carcinoma who had previously received surgery, chemotherapy, and radiotherapy. The results showed an overall response rate of 68%, with a median progression-free survival of 33 months in patients with tumors showing responses [114]. In addition, PDT can also work synergistically with radiotherapy. A previous clinical study tested the effect of PDT combined with radiotherapy on Bowen's disease. The results showed that after the treatment, all lesions disappeared,

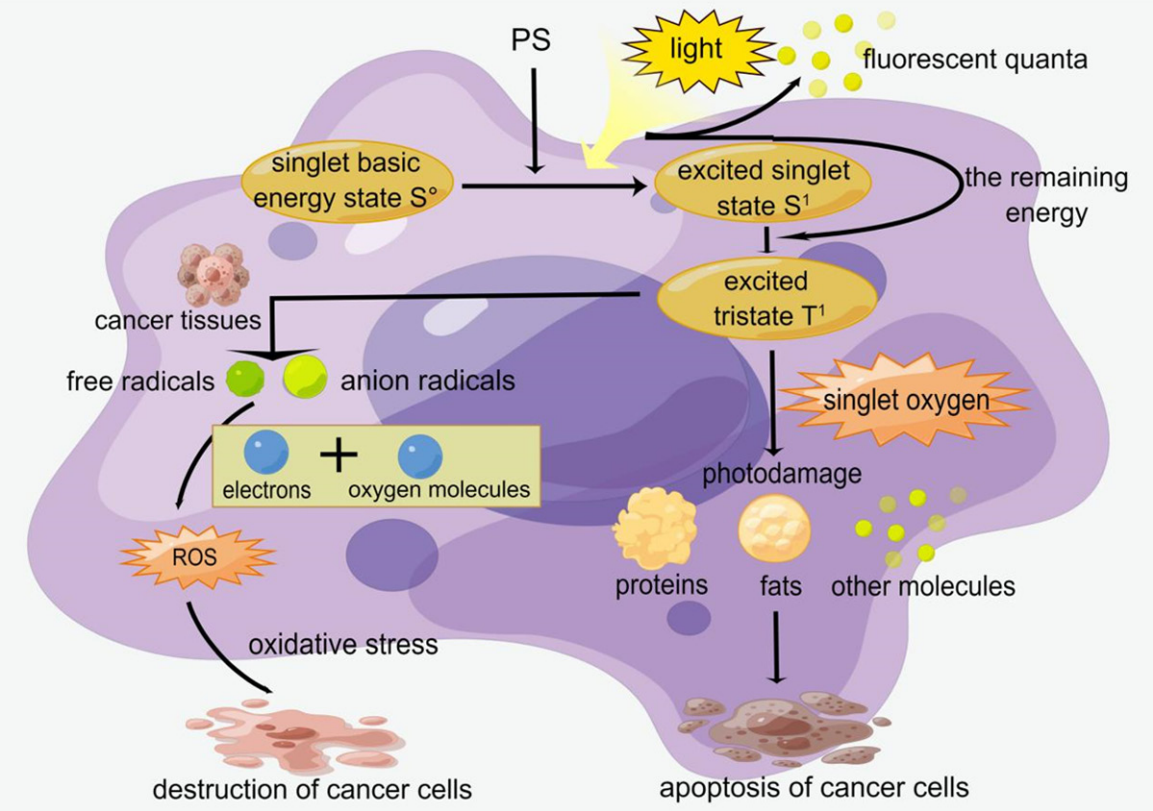

Figure 1. Mechanism of photodynamic therapy killing tumor cells.

and there was no recurrence during follow-up for 14 months.

The mechanism of PDT for EMPD

The molecular mechanism underlying photodynamic therapy is based on the interaction of three nontoxic components: photosensitizers (PSs), light of appropriate wavelength, and dissolved oxygen in the targeted pathological tissues [115]. Upon entering the cell, the photosensitizer is exposed to light of a wavelength matching its absorption spectrum, causing it to convert from the singlet basic energy state S° to the excited singlet state S^1. Part of the energy is radiated out in the form of fluorescent quanta, while the remaining energy guides the photosensitizer molecule into the excited tristate T^1 [116, 117]. The subsequent reaction occurs through two forms: (1) In the excited state T^1, photosensitizers transfer energy from the surrounding environment to the biomolecules. Between the photosensitizer with the state of T^1 and the cancerous tissues (substrate), a hydrogen or electron is transferred, which causes the formation of free radicals and anion radicals of the photosensitizer and the substrate. Electrons interact with oxygen molecules, which maintain their basic energy state, leading to the production of ROS, which culminates in a cancer killing effect [118]. (2) When the photosensitizer molecule transforms into an excited tristate, the energy is directly transferred to the oxygen molecules in the basic energy state (the basic tristate), producing excited oxygen particles, known as singlet oxygen, which possesses extremely strong oxidative properties [119]. Excited photosensitizer particles cannot damage the structures of organic cells but only react with oxygen molecules dissolved in the cytoplasm [120]. Highly reactive oxygen can cause photodamage to proteins, fats, and other molecules, leading to the immediate death of tumor cells via apoptosis or necrosis [121]. The detailed reaction process is shown in **Figure 1**.

Research progress in the treatment of EMPD by PDT

Cases of local and systemic PDT used in combination with surgery, radiotherapy, and chemo-

therapy for EMPD have been reported [52, 53, 122]. Notably, PDT is a well-tolerated outpatient procedure that does not affect anatomical structures or functions. It may be particularly suitable for patients who are not candidates for resection. Additionally, PDT can be used to treat recurrent diseases following surgery. Since PDT acts in situ, requires no tissue removal and may induce host immune responses, the treatment results may not be apparent until several months after treatment [123]. PDT has several advantages in the treatment of EMPD: it is safe, reusable, can protect the functions and appearances of the patient's organs, and can be used in combination with other therapies.

To evaluate the efficacy of PDT in patients with EMPD, a search from the PubMed database was conducted to identify clinically or histologically confirmed EMPD cases treated with PDT between 2013 and 2022. The search terms used were "photodynamic therapy" and "extramammary Paget's disease", and a total of 44 articles were obtained. The titles and abstracts of these studies were assessed to determine their eligibility, followed by a full inclusion review. Meanwhile, the exclusion criteria were as follows: reports that were not in English and reviews, unpublished clinical trials, and articles with nonrelevant topics. In the end, 18 studies or case reports were included. Detailed information on each study is depicted in **Table 3**.

Effectiveness of PDT in the treatment of EMPD

Although the primary treatment for EMPD remains surgical resection, PDT can offer several advantages over other modalities [11]. In addition to providing a great response rate, PDT can reduce lesion size and symptoms in nonoperative patients. Improvements in quality of life have also been found in a few studies [124, 125]. Moreover, PDT can preserve good appearance and function, providing similar or lower recurrence rates compared to other approaches [40, 126, 127]. Unlike radiotherapy, PDT can be repeated according to patient tolerance, without dose limiting factors [52]. PDT can also be used to observe tumor margins. The affected tissues show more vasodilation, resulting in higher photosensitizer concentrations [128]. Finally, PDT can be combined with other treatment methods to produce higher complete response rates and lower recurrence rates. Therefore, PDT possesses unique advantages and effectiveness in the treatment of EMPD.

Conclusion

Overall, PDT is a reliable strategy for managing EMPD and its associated symptoms. Nonetheless, the majority of current studies are retrospective analyses or case reports, which lack sufficient validations. Therefore, future randomized controlled trials are needed to further substantiate the efficacies of PDT in EMPD management.

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Disclosure of conflict of interest

None.

Abbreviations

MPD, Mammary Paget's disease; EMPD, Extramammary Paget's disease; MMS, Mohs micrographic surgery; PDT, Photodynamic therapy; PAS, periodic acid-Schiff; RR, recurrence rates; WLE, wide lesion excision; IEP, intraepithelial Paget's; ROS, reactive oxygen species; HPD, hematoporphyrin derivative; DDSs, drug delivery systems; DOX, doxorubicin; PS, photosensitizers.

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Table 3. Basic information on studies using PDT to treat EMPD

Study	Number and gender of patients	Age	Site of lesion	Other treatment methods	Results
Li X, 2022 [154]	7 (5 males and 2 females)	53-76 years old	Scrotum, penis and vulva	Surgery	Only one distant recurrence under the armpit in 2.9 years
Wang D, 2022 [155]	11 (9 males and 2 females)	50-93 years old	Vulva, penis, scrotum and perianal region	Surgery (2 cases)	72.7% of the subjects (8/11) showed CR in 17.4 months
Lin JD, 2021 [156]	1 (female)	48 years old	Perianal region	Topical imiquimod cream	No recurrence in 2 years
Ferrara F, 2021 [157]	10 (females)	67-92 years old	Vulva	Surgery (4 cases); carbon dioxide (CO_2) laser abrasion; occlusive application of aminolaevulinic acid (ALA)	Complete remission (2 cases) and recurrence (8 cases) in 12 months
Zhou P, 2021 [158]	36 (males)	Experimental group: 57-83 years old; control group: 63-75 years old	Scrotum, penis	Experimental group: 5-ALA-PDT; control group: wide local excision	No significant differences in recurrence rate between two groups
Chen M, 2020 [159]	16 (males)	68.44 years old (mean age)	Scrotum	Surgery	Two patients developed metastases followed up for 3 to 42 months
Rioli DI, 2018 [160]	13 (females)	70.1 years old (mean age)	Vulva	Imiquimod (10 cases), surgery (8 cases), and carbon dioxide laser treatment (6 cases)	All patients relapsed after a median time of five months
Bauman TM, 2018 [161]	1 (male)	69 years old	Scrotum	Imiquimod	No recurrence in 6 years
Apalla Z, 2018 [162]	2 (1 female and 1 male)	Female: 48 years old; male: 62 years old	Female: genital and perianal area; male: pubic area	Female: imiquimod; male: steroids and imiquimod	No recurrence for 12 months
Shen S, 2018 [163]	1 (male)	78 years old	The perineal region	None	Symptoms were relieved after 3 sessions of treatment
Vicentini C, 2017 [164]	1 (female)	62 years old	Vulva	Imiquimod, localized surgery and laser therapy	Disappearance of the pruritus and pain after three sessions
Youssef AA, 2016 [165]	1 (male)	86 years old	The right parietal scalp	None	No invasion in 12 months
Park YJ, 2015 [166]	1 (male)	68 years old	Scrotum	Surgery and radiotherapy	No recurrence in 18 months
Gao Y, 2015 [56]	38 (males)	55-100 years old	Scrotum and penis	Surgery (31 cases); without surgery (7 cases)	Surgery and PDT group: overall one-year recurrence rate was 29.03%; simple PDT group: overall recurrence rate of 14.29%
Jing W, 2014 [167]	2 (males)	56 and 72 years old	Scrotum and inguinal area	Imiquimod	No clinical recurrence after 24 and 36 months
Fontanelli R, 2013 [124]	32 (females)	48-90 years old	Vulva	Surgery; radiotherapy	Patients who initially achieved a complete response recurred after 6, 10 and 18 months
Wang HW, 2013 [139]	13 (12 males and 1 female)	56-83 years old	Lower abdomen, penis, pubic hair, scrotum and inguen egions	Surgery alone or ALA-PDT combined with surgery	Local recurrences in two patients (40%) at 3 or 6 months
Magnano M, 2013 [168]	1 (female)	84 years old	Vulva	Topical antibiotic	No recurrence in six months

5-ALA-PDT, Wood's lamp examination combined with 5-aminolevulinic acid and photodynamic therapy.

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