

# External Beam Radiotherapy of Extramammary Paget Disease

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## Practice Points

- Elderly patients with extramammary Paget disease (EMPD) usually are multimorbid and frail.
- Nonsurgical options for treatment of EMPD can be advantageous. External beam radiotherapy is a good option for EMPD.

*Extramammary Paget disease (EMPD) is an insidious intraepithelial neoplasm that is difficult to control with surgery, as large resections typically are required. An effective alternative is external beam radiotherapy (EBRT), which typically results in rapid resolution of EMPD. In this study, we analyzed long-term outcomes in 7 patients who were treated with EBRT for EMPD.*

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**E**xtramammary Paget disease (EMPD) is an insidious intraepithelial neoplasm that occurs in areas with a high density of apocrine glands such as the penoscrotal area, the vulva, and occasionally the axillae. It mainly affects patients aged 50 to 80 years.<sup>1</sup> Clinically, EMPD presents as pruritic, nonhealing, red plaques that can be mistaken for eczema. On histology, characteristic Paget cells have abundant pale cytoplasm and atypical nuclear lobuli and are adenocarcinomatous,<sup>1,2</sup> usually infiltrating the epidermis.<sup>2</sup> In approximately 25% of cases, EMPD is associated with neoplastic disease in adnexal structures or organs with a contiguous epithelial lining.<sup>2</sup> Therefore,

screening for an underlying malignancy when EMPD is first diagnosed is indispensable.

Because EMPD tends to be multifocal, presents in elderly patients, and affects functionally important areas such as the anal canal or genitals, treatment often is difficult.<sup>3,4</sup> Surgery generally is considered as a first-line treatment<sup>5</sup>; however, the rate of positive margins ranges from 36% to 67%, and local recurrence is common.<sup>1</sup>

Radiotherapy has been used in EMPD patients mainly when surgery was not an option or was not effective, but several reports have indicated that it should play a more important role in the treatment of EMPD. Luk et al<sup>1</sup> described 6 patients who were treated with different types of radiotherapy. Similar to the results of prior studies,<sup>3,5,6</sup> they concluded that it was an effective treatment of EMPD.<sup>1</sup>

We conducted a retrospective study to analyze long-term outcomes in 7 patients who were treated with external beam radiotherapy (EBRT) for EMPD.

## Methods

Seven patients (6 men and 1 woman) who had been diagnosed with EMPD and were treated with EBRT at the Department of Dermatology at the University Hospital Zurich in Switzerland (1988-2004) were evaluated. The diagnosis was confirmed by a dermatopathologist or pathologist via histology. Data regarding clinical presentation, EBRT regimen, and side effects were retrieved from the medical records. Long-term outcomes were evaluated by an attending dermatologist (1 case), a general practitioner (5 cases), or the hospital's outpatient department (1 case). None of the

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patients showed an associated malignancy at the time of treatment; however, patient 5 had been diagnosed with and treated for a sigmoid colon adenocarcinoma 6 years prior to undergoing EBRT for EMPD. Three patients (patients 3, 5, and 7) received EBRT for local relapse after prior treatment of EMPD (ie, CO<sub>2</sub> laser, multiple local treatments). One patient (patient 2) underwent surgical excision prior to EBRT. The remaining 3 patients had not undergone any prior treatment of EMPD. All patients underwent EBRT with the goal of complete remission.

Six patients received low-energy radiotherapy of 20 to 30 kV at doses of 200 to 400 cGy per day for 2 to 5 days per week until a total dose of 4000 to 5600 cGy was completed. A 0.4- to 0.5-mm aluminum filter was used, and the focus-skin distance (FSD) was 20 cm. One patient was treated with a radiograph of 40 kV at 400 cGy per day for 2 days per week until a total dose of 4800 cGy was completed. A 1.0-mm aluminum filter was used, and the FSD was 10 cm. The field of EBRT included 2-cm margins clear of all visible disease. The treatment parameters for all patients are outlined in the Table.

### Results

Complete remission was initially obtained in 6 of 7 patients. In patient 3, an erosive perianal plaque remained following treatment with EBRT that was locally treated with imiquimod cream 3%. The patient relapsed 2.5 years later with a lesion in the vaginal area that was treated with imiquimod cream 3% and later via surgical excision. Complete remission was never achieved, and the patient died 7 years after EBRT treatment due to unrelated causes. Patient 5 relapsed after 6 years of remission following treatment with EBRT and also was treated with imiquimod.

At the time of this study, 1 patient remained in full remission (patient 1: 12 years) and 2 had died while in remission (patient 2: 14 years; patient 4: 6.5 years). Two patients were lost to follow-up while in remission (patient 6: 6 months; patient 7: 3 years); however, they did not show any signs of relapse. The Figure shows patient 6 at baseline and at 4 and 8 months after starting treatment with EBRT.

The most commonly reported side effect was mild dermatitis with reddening and desquamation. Patient 2 developed erosive radiodermatitis 4 days after the first treatment with EBRT. All acute reactions resolved with local treatment. Late side effects of EBRT were hyperpigmentation (patients 1 and 4) and mild skin atrophy (patient 4).

### Comment

Because EMPD is such a rare disease, data regarding long-term treatment outcomes are mostly from small

studies and case reports; evidence in the literature regarding treatment of EMPD with EBRT is especially limited. However, the good initial healing in most reported cases, the relatively low and late relapse rate, and the mild side effects reported in most cases make EBRT an effective treatment of EMPD. In the current study, initial complete remission was achieved in 6 of 7 patients. Patient 3 did not show complete macroscopic remission following EBRT but had a poor response to treatment in general, as she had already been unsuccessfully treated with several local treatments prior to EBRT; also, surgical and topical intervention following EBRT was not successful. Patient 5 relapsed after 6 years, but this case exceeds the follow-up period of many cases of EMPD found in the literature.

Overall, EBRT was well tolerated by the patients included in our study. All patients showed mild dermatitis following treatment as an acute reaction to EBRT. In most cases, these reactions resolved on their own or with topical treatment. Two patients developed late hyperpigmentation and one developed mild skin atrophy in the treatment area. One patient who was treated until a total dose of 5600 cGy was achieved developed erosive radiodermatitis, whereas the other patients were only treated 2 to 5 times per week. Side effects can therefore be considered as mild and/or easily controlled.

Luk et al<sup>1</sup> also observed a low rate of long-term relapse in patients with EMPD, but consistent EBRT with similar doses and settings were applied in our study. The following parameters showed the best results in treatment response, low side effects, and relapse rate: total dose of 4000 to 4800 cGy; 20 to 30 kV; electron current of 10 to 20 mA; 0.4- to 0.5-mm aluminum filter; 20-cm FSD. This dose is at the low end of those for the standard fractionation regimen, which is a total dose of 4200 to 7000 cGy using 200-cGy fractions.<sup>1</sup> The dose we used was slightly lower than the total dose recommended by Besa et al<sup>5</sup> who treated 65 patients with radiotherapy for EMPD in 1992 (>50 Gy). It is equivalent to the doses used by Burrows et al<sup>6</sup> and by Moreno-Arias et al<sup>3</sup> (40–50 Gy). Lower radiograph doses may put treatment outcome at risk.<sup>7</sup>

Surgery is considered the first-line therapy for EMPD. Positive margin rates vary from 36% to 67% depending on the size of the lesion and the type of surgery that is used.<sup>5</sup> Positive margin rates lead to a significant increase in recurrence rate ( $P < .001$ ).<sup>8</sup> Relapse rates for surgical intervention vary in the literature from 19% to 44%<sup>8</sup> and 40% to 45% within 4 years of surgery.<sup>4</sup> Wang et al<sup>8</sup> reviewed long-term outcomes of surgical treatment in 130 Chinese patients with penoscrotal EMPD. They recommended

## Patient Overview and Treatment Parameters

Patient No.	Age, y (Sex)	Location of Lesion	Prior Treatment	Associated Malignancy	ERBT Treatment Parameters				Treatment Outcome (Relapse-Free Period)		
					Voltage, kV	Electron Current, mA	Total Dose (Fraction, n)	Al Filter, mm		FSD, cm	Side Effects
1	86 (M)	Penis, pubic area	None	None	20	20	4000 cGy (10)	0.4	20	Mild dermatitis, hyperpigmentation	Complete remission (12 y) <sup>a</sup>
2	84 (M)	Penis, scrotum	Surgical excision	None	30	10	5600 cGy (28)	0.5	20	Erosive radiodermatitis	Complete remission (14 y) <sup>b</sup>
3	82 (F)	Perianal region	5-FU, PDT, imiquimod	None	30	10	4000 cGy (10)	0.5	20	Mild dermatitis	No full remission, even after excision and imiquimod (no remission)
4	64 (M)	Pubic and inguinal regions	None	None	40	10	4800 cGy (12)	1.0	10	Mild dermatitis, hyperpigmentation, late atrophy	Complete remission (6.5 y) <sup>b</sup>
5	75 (M)	Perianal region	CO <sub>2</sub> laser	Sigmoid colon adenocarcinoma 6 y prior	20	20	4000 cGy (10)	0.4	20	Mild dermatitis	Complete initial remission; relapsed after 6 y, treated with imiquimod (6 y)
6	73 (M)	Inguinal region	None	None	30	10	4800 cGy (12)	0.5	20	Mild dermatitis	Complete remission (6 mo) <sup>c</sup>
7	76 (M)	Inguinal region	CO <sub>2</sub> laser	None	30	10	4400 cGy (18)	0.5	20	Mild dermatitis	Complete remission (3 y) <sup>c</sup>

Abbreviations: ERBT, electron beam radiotherapy; Al, aluminum; FSD, focus-skin distance; M, male; F, female; 5-FU, 5-fluorouracil; PDT, photodynamic therapy.

<sup>a</sup>In full remission at the time of this study.

<sup>b</sup>Died while in remission.

<sup>c</sup>Lost to follow-up.



A 73-year-old man with extramammary Paget disease in the inguinal region at baseline (A) and 4 (B) and 8 (C) months after starting treatment with electron beam radiotherapy.

3-cm surgical margins and frozen section pathological examination for complicated conditions. A local recurrence rate of 9.9% was reported, which is remarkably lower than in many other studies in the literature.<sup>8</sup> Nevertheless, the severe possible side effects of surgery cannot be easily put aside.

Electron beam radiotherapy should be considered as an alternate therapy in EMPD given its low risks and moderate side effects. In our study, the relapse rate was 28.6% (2/7), which is not remarkably higher than reports in the literature of relapse rates associated with surgical excision. Electron beam radiotherapy should be especially considered when extensive margin-controlled surgery is not an option, such as EMPD in sensitive areas or for an extensive circumference of the lesion, as surgery might then produce functional disfiguring results. Adequate limiting ray (grenz ray) or low-energy radiograph treatment has proved to preserve function, especially in the area of the vulva and glans penis.<sup>9</sup> Furthermore, EBRT may be the treatment of choice in patients with an increased risk for morbidity from surgery, such as elderly patients<sup>5</sup> or those with wound healing disorders (eg, diabetes mellitus).

### Conclusion

Given that EMPD patients typically are elderly with multimorbidities, surgery should be carefully considered in this patient population, particularly because EMPD without underlying malignancies has an excellent survival rate.<sup>5</sup> Highly invasive treatments

should therefore be thoughtfully considered. Because of the inconsistent data on relapse rates and the small number of patients with EMPD who have been studied, further study with more cases is needed.

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