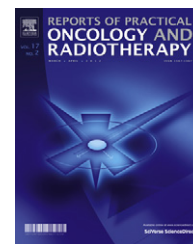


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## Case report

# HDR-plesiotherapy for the treatment of anogenital extramammary Paget's disease

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## ARTICLE INFO

## Article history:

Received 11 September 2011

Received in revised form

7 January 2012

Accepted 10 March 2012

## Keywords:

Extramammary Paget's disease

Anogenital region

Superficial brachytherapy

HDR plesiotherapy

Custom-made mold

## ABSTRACT

**Background:** Extramammary Paget disease (EMPD) is a rare condition that most commonly affects the anogenital region in the elderly. It may be associated with an underlying invasive carcinoma. Surgical excision is nowadays considered a standard treatment for extramammary Paget's disease, although this approach might not be suitable for all patients. Good rates of local control and cosmetic outcome have been achieved by using high-dose-rate (HDR) plesiotherapy in the treatment of skin tumors arising in different locations.

**Material and methods:** We present the results observed in a patient with EMPD treated by HDR plesiotherapy with a custom-made mold up to a final dose of 54 Gy in 12 fractions of 450 cGy over 4 weeks.

**Results:** After a follow-up of 18 months, the patient is alive and without evidence of local or distant relapse. Acute toxicity was acceptable and cosmetic result was considered as excellent.

**Conclusion:** This technique represents an attractive alternative for those patients who are not candidates for surgical procedures because of unacceptable risk of disfigurements or functional impairment, medical contraindications or patient preference.

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## 1. Background

Paget's disease (PD) is a rare type of intraepithelial adenocarcinoma characterized by the presence of malignant Paget's cells lying within the epidermis of the skin, first described by Sir James Paget in 1874.<sup>1</sup> Extramammary Paget's disease (EMPD) expresses the occurrence of this entity in areas containing apocrine glands such as the perianal region, vulva, penis, scrotum, perineum and axilla, different from the breast

nipple. The first case of EMPD of the anogenital area was reported by Crocker in 1888, and until 2010 almost 300 cases have been published.<sup>2–4</sup> The disease sites present as patchy and well-circumscribed, erythematous eczema or erosions together with itching, bleeding or burning.<sup>5</sup> The prognosis of simple EMPD is relatively favorable, reaching disease-free and overall survival rates of above 70% at 5-year after curative intention treatment.<sup>6</sup> Wide surgical excision remains to be the mainstream of therapy for vulvar Paget's disease. However, local recurrence rates range from 12% to 58% of treated

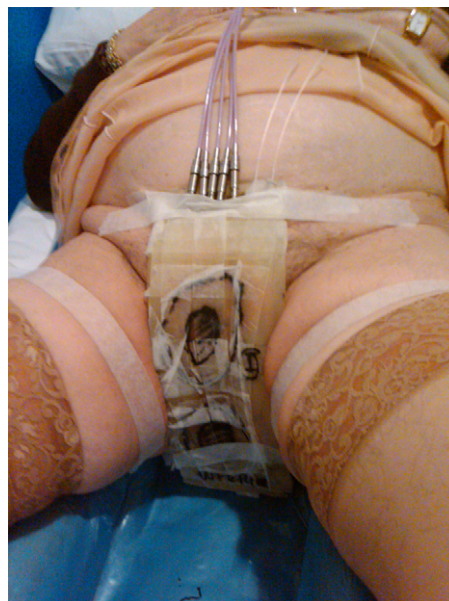
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**Fig. 1** – Patient with two biopsied lesions of EMPD located in the right labium majus and on perianal skin.



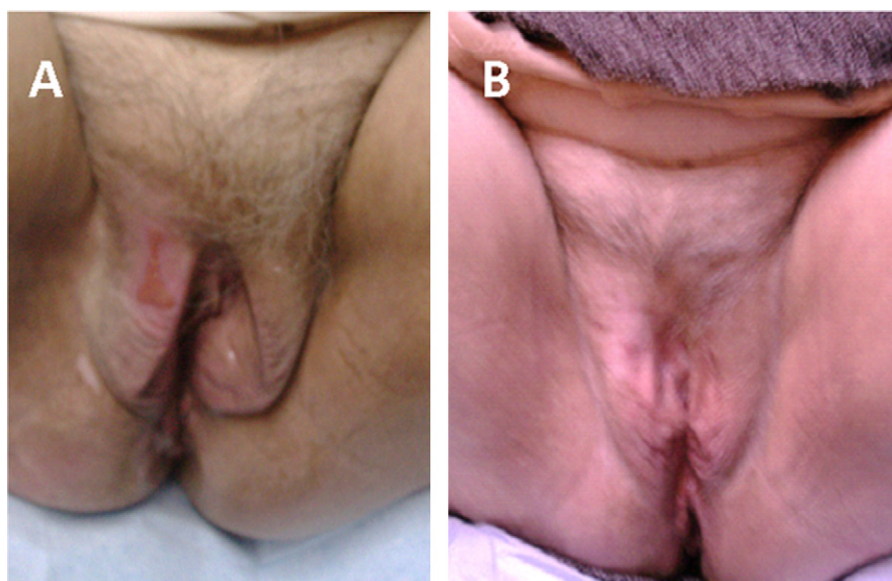
**Fig. 2** – Patient with the custom-made mold in place for plesiotherapy during irradiation.

women during the follow-up time, even after extensive local resections.<sup>7-9</sup> On the other hand, radical surgery morbidity can be high, especially in the elderly. Radiotherapy has been used only occasionally in this condition. Primary radiotherapy was indicated in patients not suitable for surgery because of the presence of irresectable tumors or co-morbidities precluding radical surgery. Radiotherapy was also used occasionally in the adjuvant setting following surgery or with palliative intention after recurrent disease.<sup>10,11</sup> Recently, a curative role for radiation therapy of EMPD has been proposed.<sup>12</sup> We present a case of vulvar and perianal Paget's disease treated by HDR brachytherapy with a custom made mold (plesiotherapy) with curative intention.

## 2. Case report

A 79-year-old woman presented with a 2-year history of redness and pruritus in the vulvar and perianal region. Clinical examination revealed two well-circumscribed erythematous plaques with some scattered whitish points on her right labium majus and on perianal skin (Fig. 1). No enlarged inguinal lymph nodes were detected. Both areas were biopsied evidencing the presence of multiple Paget cells, forming irregular nests and scattering individually in a pagetoid pattern in the epidermis, leading to the diagnoses of extramammary Paget's disease. Additional exams, including whole-body CT, colonoscopy and gynecological examination did not reveal an underlying malignancy. The patient was treated initially by means of topical applications of imiquimod cream but in the absence of response she was referred to the Radiation Oncology Department. A treatment by means of HDR superficial brachytherapy (plesiotherapy) with a custom-made mold encompassing both lesions with a security margin of at least 2 cm surrounding the visible disease was proposed and the patient gave her consent to the treatment.

Our technique of HDR plesiotherapy based upon custom-made molds has been previously described.<sup>13</sup> Briefly, personalized molds consist of a flexible pad of silicone rubber, 10 mm thick, with a customizable array of 6F plastic catheters embedded separated by 1 cm that easily conforms to the shape of surfaces. The number of plastic tubes and the separation between them depended on the size of the area to be treated. This area was defined by the radiation oncologist being wide enough to include an adequate margin of uninvolved skin of at least 1 cm around the tumor or the surgical bed. A CT scan carrying the mold with wire dummies inserted on the plastic tubes were obtained from each patient at 1-mm-thin intervals. The macroscopic tumor/surgical tumor bed with a margin (planning target volume (PTV)), along with the surrounding organs at risk were contoured on these CT slices before calculation. PTV dose distribution and additional treatment parameters were calculated by using the 3D treatment planning software PLATO developed by Nucletron (Nucletron BV, Veenendaal, the Netherlands). Treatment dose was prescribed at 5 mm depth from the surface of the mold. At the moment of treatment, the personalized mold was applied to the tumor lesion, placed in direct apposition to the skin of the involved area, and kept in place by adhesive tape (Fig. 2). The mold was then connected to a HDR equipment containing a 192-iridium radioactive source (Microselectron Nucletron BV, Veenendaal, the Netherlands). Radiation treatment was administered in 12 fractions of 450 cGy, 3 fractions a week over 4 weeks, until a total dose of 54 Gy (equivalent dose in 2-Gy fractions (EQD2): 65.3 Gy) was reached. Adverse effects of plesiotherapy included acute grade 3 epithelitis on the treated areas that resolved with topical measures 2 weeks after treatment cessation. Postradiotherapy evaluation revealed a complete disappearance of the Paget's disease areas 3 months after discharge. On the last follow-up at 18 months after plesiotherapy,



**Fig. 3 – EMPD lesions at the end (A) and after 18 months (B) of treatment.**

no signs of tumor recurrence were noted with only two small areas of hypopigmentation on the primary tumor bed (Fig. 3).

### 3. Discussion

According to latest literature reviews, anogenital presentation represents 6.5% of all cases of PD. EMPD of the vulva accounts for less than 1% of all vulvar tumors.<sup>8</sup> Unlike the presentation in the nipple, where PD is almost invariably associated with the existence of a ductal adenocarcinoma, EMPD of the anogenital region is less frequently associated with the presence of an underlying malignancy with incidence ranging from 33% to 86%.<sup>6,7</sup>

Therapeutic management of EMPD is highly related to the existence of an underlying neoplasia and possible regional or systemic spread. Surgery is the treatment of choice for EMPD. Wide excision of the lesion with a margin of at least 3 cm beyond the clinically affected area with subsequent reconstruction of the tissue defect or abdominoperineal excision has been recommended. Mohs micrographic surgery (MMS) represents an alternative to wide surgical resections, allowing to spare more normal tissue than conventional surgery. Nevertheless, local recurrence after different surgical excision techniques is a common problem. In the vulvar region, vulvectomy has a 15% recurrence rate, Mohs micrographic surgery has a 27% recurrence rate and a wide local excision has a 43% recurrence rate. Perianal EMPD recurs in 28% of patients after MMS and in 50% of patients after a wide local excision.<sup>6-9</sup> Due to the aggressiveness of radical operative procedures, surgical excision cannot always be accomplished. Many of these patients are not candidates for surgical procedures because of medical contraindication, old age or risk of disfigurements or functional impairment. Alternative treatments for EMPD, including systemic chemotherapy, chemo-radiotherapy, photodynamic therapy and more recently topical therapies with

5-FU or imiquimod, have been shown to be effective in treating anogenital EMPD.<sup>14-20</sup>

Radiotherapy could be considered a reliable alternative for EMPD. Irradiation may be used as a definitive treatment in patients refusing surgery or with poor conditions that contraindicate operation as well as an adjunctive therapy after primary local excision. Although there are no randomized controlled trials comparing surgical excision and radiotherapy in the initial management of EMPD, results from published reports suggest a possible beneficial role for this modality of treatment. However, despite the existing evidence, discrepancies between studies on the total dose, dose per fraction and the irradiation technique used (i.e. external photons or electrons, interstitial brachytherapy, pliesotherapy), make it difficult to establish a definitive indication of radiotherapy in EMPD.<sup>10-12,21</sup> While most results come from reports limited to one or at most two case-reports,<sup>22-26</sup> some groups have communicated results for larger series. Hata et al.<sup>12</sup> reported a clinical course of 22 patients with EMPD, with 10 patients undergoing EBRT. With a follow-up ranging between 0.6 and 11 years, 13 out of the 22 patients suffered a disease recurrence. Only 3 patients developed a local relapse within the radiation field, whereas regional nodal or distant metastases were seen in 10 patients, with an interval between 3 and 43 months after irradiation. Besa et al.<sup>27</sup> treated 4 patients with primary EMPD with EBRT alone or EBRT plus an interstitial LDR brachytherapy implant to a total dose of 44–64 Gy. With a follow-up of 1.2–5 years, no cases of local in-field relapse were noted. Brown et al.<sup>28</sup> published an extensive literature review on the use of radiotherapy in EMPD together with 6 cases of their own. Exclusive irradiation was indicated in patients with inoperable tumors and in those who had severe medical contraindications. Postoperative radiotherapy was indicated in the adjuvant setting following surgery with close/positive margins or as salvage treatment in recurrent disease. The authors concluded that radiation doses of 50 Gy (EQD2Gy) should be the minimum dose required for

microscopic disease, whereas higher doses may be necessary in the presence of gross tumor or an underlying invasive adenocarcinoma. Brierley et al.<sup>29</sup> reported results of radiotherapy as primary treatment in 6 patients with EMPD. The total dose ranged between 36 and 54 Gy with a fraction size of 2–10 Gy using either photons or electrons. Local relapse occurred in 20% of patients. Luk et al.<sup>30</sup> reported results observed in 6 patients with anogenital EMPD, 2 of them with an underlying adenocarcinoma, treated by radiotherapy with doses ranging from 42 Gy to 70 Gy. All 4 patients with EMPD alone remained alive and disease-free at 2–14.8 years of follow-up. Only one patient underwent salvage surgery for local relapse in the outer margin of the radiotherapy field. Finally, Burrows et al.<sup>21</sup> and Moreno-Arias et al.<sup>31</sup> treated 5 and 4 patients, respectively, with superficial orthovoltage to a total dose ranging from 39.6 Gy to 40.5 Gy. During follow-up, no cases of local relapse were observed.

Brachytherapy techniques have a long history in the treatment of cancer and continue to play an important role in cancer therapy. New developments in recent years have opened up several new treatment possibilities enabling treatments to be individualized.<sup>32,33</sup> In this patient, we found that the most suitable treatment was superficial brachytherapy, the so-called plesiotherapy, due to her performance status and her refusal of surgical management. Comparatively, the outcome of the treatment with radiotherapy was favorable for anogenital EMPD. Acute tolerance was acceptable, with moderate epithelitis resolving soon after completion of treatment. To our knowledge, only two previous cases have been treated by a custom-made mold HDR-plesiotherapy technique.<sup>30</sup> Plesiotherapy involves the use of surface applicators in direct contact with the tumor or surgical tumor bed. Our result is consistent with those previously reported, suggesting similar tumor control rates and clinical outcomes to external radiotherapy. Plesiotherapy offers the additional advantage of a better targeting of radiation and minimizing irradiation of surrounding healthy tissue, as compared to other radiotherapy techniques. In our opinion, plesiotherapy using an afterloaded custom-made mold appears to be an ideal alternative for elderly patients with comorbidities, not candidates for aggressive surgical management presenting with superficial tumors without infiltration in depth.

Prognosis of EMPD is closely related to the presence of invasive disease. For in situ lesions, overall survival exceeds 75%, but when EMPD becomes invasive, survival rates decrease by 33% irrespective of the aggressiveness of local treatment, since distant metastases are frequent even at the time of diagnosis.<sup>34</sup>

#### 4. Conclusion

Anogenital EMPD is a rare disease usually associated with adnexal and visceral infiltrating tumors but sometimes may present as a purely intraepithelial lesion prone to a definitive treatment. In spite of the fact that surgery is usually the preferred treatment, radiotherapy offers a reasonable alternative in patients who are not candidates for surgery or refuse it. Doses above 50 Gy, and even higher, in the presence of an underlying infiltrative neoplasia, are required to guarantee

acceptable local control. HDR-plesiotherapy with custom-made molds is a worth-considering technique that shows an acceptable outcome with good tolerance and appears to be an ideal alternative for elderly patients, not candidates for aggressive surgical impairment.

#### Conflict of interest

None declared.

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