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CLINICAL INVESTIGATION **Genitalia**

ROLE OF RADIOTHERAPY AS CURATIVE TREATMENT OF EXTRAMAMMARY PAGET'S DISEASE

Masaharu Hata, M.D.,* Motoko Omura, M.D.,* Izumi Koike, M.D.,* Hidefumi Wada, M.D.,† Etsuko Miyagi, M.D.,‡ Yoshibumi Tayama, M.D.,* Kazumasa Odagiri, M.D.,* Yumiko Minagawa, M.D.,* Ichiro Ogino, M.D.,§ and Tomio Inoue, M.D.*

Departments of *Radiology, †Dermatology, and ‡Obstetrics and Gynecology, Yokohama City University Graduate School of Medicine, Yokohama, Kanagawa, Japan, §Department of Radiation Oncology, Yokohama City University Medical Center, Yokohama, Kanagawa, Japan

Purpose: Extramammary Paget's disease (EMPD) is a relatively rare malignancy that usually arises in the genital areas. Wide surgical excision remains the standard and most reliable curative treatment of EMPD. However, surgery is sometimes not possible, because many patients are elderly, and complete excision can be difficult owing to the tumor location. We, therefore, performed a review to determine the role of radiotherapy (RT) for EMPD.
Methods and Materials: A total of 22 patients with EMPD in their external genitalia (4 men and 18 women, age 52–94 years at RT) underwent RT with curative intent. Nine patients had regional lymph node metastases. A total dose of 45–70.2 Gy (median, 60) was delivered to the pelvis, including the tumors, in 25–39 fractions (median, 33).
Results: In all but 3 patients, the irradiated tumors were controlled during a follow-up period of 8–133 months (median, 42). Of the 22 patients, 13 developed recurrences, including local progression within the radiation field in 3 and lymph node and/or distant metastases outside the radiation field in 10, at 3–43 months after treatment. The 2- and 5-year local progression-free rates were 91% and 84%, respectively. Of the 22 patients, 7 patients had died at 33–73 months after RT. The cause of death was tumor progression in 4, infectious pneumonia in 2, and renal failure in 1 patient. The overall and cause-specific survival rates were 100% for both at 2 years and 53% and 73% at 5 years, respectively. No therapy-related Grade 3 or greater toxicity was observed.
Conclusions: RT is safe and effective for patients with EMPD. It appears to contribute to prolonged survival as a result of good tumor control. © 2011 Elsevier Inc.

Apocrine gland, Extramammary Paget's disease, Genitalia, Radiotherapy, Skin cancer.

INTRODUCTION

Extramammary Paget's disease (EMPD) is a comparatively rare malignancy that often develops in the genital areas, including the vulva, scrotum, penis, and perineal and perianal regions, and less frequently in the axilla and umbilicus, in women aged 50–80 years. This neoplasm is considered to derive from the apocrine gland, but its etiology is still unclear. In 1874, Sir James Paget reported an intraepithelial neoplasm of the areola in the breast that was termed "Paget disease" (1). EMPD, which involved similar intraepithelial lesions in the skin of the scrotum and penis, was first described by Crocker (2) in 1888.

The disease sites generally present as relatively well-defined erythematous eczema or erosions, with or without leukokeratotic plaques, together with complaints of pruritus, irritation, or burning (3–5). However, EMPD will be asymptomatic in approximately 10% of patients. EMPD limited to the epidermis, so-called carcinoma *in situ,* is usually slow growing, with no change in the disease status for a period of ≥10 years in some cases. The diagnosis can accordingly be delayed, and the average interval between the onset of symptoms and diagnosis has been reported to be 2 years (4, 6). However, once the tumor invades into the dermis, it frequently makes rapid progress, resulting in lymph node and distant metastases. No well-established cures exist to treat patients with distant metastases of EMPD, and early detection and treatment while the disease is limited to the epidermis are of great importance. Additionally, EMPD frequently coexists with other internal malignancies; thus, a through examination to identify other malignancies should be performed before treatment (3–6). Racial differences in the frequency of malignancies

Reprint requests to: Masaharu Hata, M.D., Department of Radiology, Yokohama City University Graduate School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama, Kanagawa 236-0004 Japan. Tel: (+81) 45-787-2696; Fax: (+81) 45-786-0369; E-mail: mhata@syd.odn.ne.jp

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coexisting with EMPD have been reported, with the coexistence rate lower for Asian patients than for white patients (0–13% vs. 15–30%) (7).

Microscopically, Paget's cells classically show abundant clear cytoplasm and large round-to-oval nuclei. They are distributed as single cells, strands, nests, or gland-like structures within the epidermis and epithelium of adnexal structures, with infiltration into the dermis at more advanced stages. However, the epidermal spread of other invasive cancers, such as genitourinary, colorectal, or anal canal carcinoma, or other intraepithelial neoplasms, such as squamous cell carcinoma *in situ* or intraepithelial melanoma, can occasionally mimic EMPD. Immunohistochemistry has been reported to be useful for differentiating between EMPD and these other malignancies and has been routinely used to definitively diagnose EMPD at our institution (8–10). Paget's cells are generally positive for sweat gland markers such as cytokeratin 7 and gross cystic disease fluid protein 15 but are usually negative for markers of the epithelium and mucous membrane, such as cytokeratin 20 and cytokeratin 34βE12.

Wide surgical excision is currently the standard and most reliable curative treatment of EMPD (3, 4). However, surgical excision is sometimes not possible owing to the high incidence of elderly patients and the difficulties associated with aggressive surgery in the areas where the tumors are usually located. Although radiotherapy (RT) is applied to these medically inoperable patients and to patients who refuse surgery, few reports have been published of the results of RT. Therefore, we performed a retrospective review of patients with EMPD treated with RT with curative intent. We present the treatment outcomes and discuss the role of RT in EMPD.

METHODS AND MATERIALS

Patients

Between October 1998 and January 2007, a total of 22 patients with EMPD underwent RT with curative intent at our institution. The exclusion criteria included distant metastases and poor general condition (Eastern Cooperative Oncology Group performance status $\geq$3) (11). Of these patients, 4 were men and 18 were women, and their age at RT was 52–94 years (median, 72). The primary tumor sites were the vulva in 10 patients, perineum in 7, and scrotum in 5. The maximal diameter of the visible tumors at the initial diagnosis was 20–120 mm (median, 83). All 22 patients were definitively diagnosed with EMPD from the results of the histopathologic examinations, including immunohistochemical staining, of the specimens obtained from biopsy or surgical excision. Invasion into the dermis was observed in 12 patients.

The 22 patients were divided into 3 groups according to the indication for RT, as follows: Group 1, 10 patients underwent definitive RT for initial disease; Group 2, 4 patients underwent definitive RT for local recurrences after complete surgical excision; and Group 3, 8 patients underwent RT as postoperative adjuvant therapy.

Of the 22 patients, 9, including 1 patient in Group 1, 2 in Group 2, and 6 in Group 3, had inguinal lymph node metastases. The metastatic inguinal lymph nodes of the 6 patients in Group 3 were surgically removed. The surgical margin of the primary tumor was positive in all 8 patients in Group 3, although the macroscopic tumors were completely excised.

Table 1. Patient and tumor characteristics

Characteristic	Value
Patients (*n*)	22
Gender (*n*)	
Men	4
Women	18
Age (y)	
Range	52–94
Median	72
Performance status (*n*)	
0	9
1	12
2	1
Indication for RT (*n*)	
Definitive therapy	
Initial disease	10
Recurrence after surgical excision	4
Postoperative adjuvant therapy	8
Tumor location (*n*)	
Vulva	12
Perineum	7
Scrotum	3
Initial tumor size (maximal diameter, mm)	
Range	20–120
Median	83
Invasion into dermis (*n*)	
Yes	12
No	10

Abbreviation: RT = radiotherapy.

Before RT, chest X-ray and/or computed tomography, abdominal ultrasonography and/or computed tomography, and pelvic computed tomography were performed in all patients. No distant metastases or underlying malignancies were detected. The patient and tumor characteristics are listed in Table 1. All patients provided informed consent before treatment.

Radiotherapy

Of the 22 patients, 12, including 9 with inguinal lymph node metastases, underwent RT to the regional (pelvic and inguinal) lymph nodes, along with the local tumor site, through anteroposterior opposed ports with 4–6-MV X-rays, followed by a local radiation boost to the gross tumor site using 7–13-MeV electrons. The remaining 10 patients underwent local RT to the tumor site alone, using 4–6-MV X-rays or 6–15-MeV electrons. The radiation fields were set up to include the gross tumors in Groups 1 and 2 and the tumor bed, including the positive surgical margin, in Group 3, with a 2–5-cm margin. A bolus with a 5–10-mm water-equivalent thickness was used to compensate for the skin surface dose. Total doses of 45–70.2 Gy (median, 60) were delivered in 25–39 fractions (median, 33), with a fraction size of 1.8–2.2 Gy (median, 1.8), for 5 d/wk. A total dose of 59.4–70.2 Gy (median, 60.6) was thus delivered to the gross tumor, including the enlarged metastatic inguinal lymph nodes. Patients with positive surgical margins received a dose of 45–64.8 Gy (median, 50) to the tumor bed. The overall treatment time was 35–59 days (median, 48).

Follow-up and evaluation criteria

The patients underwent pelvic computed tomography 1 month after RT completion and were followed up at approximately 3-month