

Definitive Radiation Therapy for Extramammary Paget's Disease

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Abstract. *Background: Extramammary Paget's disease (EMPD) is frequently inoperable because of old age and/or coexisting disease. We therefore reviewed the efficacy and toxicity of radiation therapy for EMPD. Patients and Methods: Fourteen patients with EMPD underwent definitive radiation therapy. Three patients had regional lymph node metastases before radiation therapy, but none had distant metastasis. Total doses of 52-80.2 Gy (median=60.6 Gy) were delivered to tumor sites in 26-43 fractions (median=33 fractions). Results: Four patients had developed recurrence at a median follow-up period of 47 months. The 5-year local control and disease-free rates were 71% and 63%, respectively. Two patients died of old age and renal failure at 6 and 51 months, respectively, after irradiation. The 5-year disease-free, cause-specific and overall survival rates were 46%, 100% and 79%, respectively. No therapy-related toxicities of grade 3 or greater were observed. Conclusion: Radiation therapy is effective and safe, and appears to offer a curative treatment option for patients with EMPD.*

Sir James Paget described an intraepidermal neoplasm of the mammary areola in 1874, and it was subsequently named Paget's disease (1). Crocker first reported a similar intraepidermal disease in the scrotum and penis as extramammary Paget's disease (EMPD) in 1888 (2). EMPD is a relatively uncommon malignancy of the skin that is thought to originate in the apocrine gland, although its pathogenesis remains unknown (3). It most commonly occurs in the genital areas in elderly women. Furthermore,

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Key Words: Apocrine gland, extramammary Paget's disease, genitalia, radiation therapy, skin cancer.

at least 30% of patients with EMPD have other concomitant visceral malignancies, and a thorough examination is therefore required prior to treatment for EMPD (4).

Microscopic examination of EMPD typically reveals distinctive Paget's cells, with plentiful clear cytoplasm and large round nuclei, present as single cells or conglomerates within the epidermis and the epithelium of adnexal structures. However, other intraepithelial neoplasms, such as squamous cell carcinoma *in situ* or intraepithelial melanoma, or invasive cancer that has spread to the epithelium, including genitourinary or colorectal carcinomas, sometimes bear a close resemblance to EMPD. Immunohistochemical examination has been used for its differential diagnosis at our institution, and is useful in helping to rule out other malignancies and to provide a definitive diagnosis of EMPD (5, 6). Paget's cells are generally immunoreactive for sweat gland markers, including cytokeratin (CK) 7 and gross cystic disease fluid protein 15, but not for markers of the epithelium and mucous membrane, including CK 20 and CK 34 β E12. Immunohistochemical reactions to hormone receptors, such as androgen receptors, and transcription factors such as CDX2, have recently proven useful in differentiating EMPD from other malignancies (5).

Surgical excision is the standard curative treatment for EMPD (3, 4). However, in many patients, EMPD is inoperable because of old age, severe coexisting diseases, and/or patient refusal of surgery. Although radiation therapy can be a treatment option for these patients, few studies have reported the treatment outcomes. We have previously published a report on the use of radiation therapy for EMPD, but the small number of patients meant that it was not possible to ascertain the efficacy and toxicity of definitive radiation therapy as initial treatment for EMPD (7). In this study, we have therefore updated the patient data and reanalyzed it in further detail. We thus present the treatment outcomes of patients with EMPD and evaluate the validity of definitive radiation therapy as a curative treatment option.

Patients and Methods

Patients. A total of 14 patients with EMPD underwent definitive radiation therapy as initial treatment with curative intent between April 1993 and February 2008. Their ages at irradiation ranged from 52-94 years (median=81 years) and their general conditions were Eastern Cooperative Oncology Group performance status 0-2 (8). Disease in 10 of the 14 patients was medically inoperable because of old age and/or severe coexisting diseases, such as brain infarction, angina pectoris, aortic aneurysm, multiple sclerosis, Parkinson's disease or dementia. The remaining four patients refused surgery. All patients were diagnosed with EMPD on the basis of histopathological examination, including immunohistochemical analysis, of specimens obtained at biopsy. Tumor invasion into the dermis was observed in two patients.

Chest X-ray and/or computed tomography (CT), abdominal ultrasonography and/or CT, and pelvic CT were performed in all patients prior to radiation therapy. Lymph node metastasis was confirmed when the short-axis diameter of the lymph nodes had enlarged to ≥ 10 mm on CT. On this basis, three out of the 14 patients had inguinal lymph node metastases, and two of these three had tumor invasion into the dermis. No distant metastases or other underlying malignancies were detected in any patient. Patient and tumor characteristics are shown in Table I. Informed consent was obtained from all patients before treatment.

Radiation therapy. Seven out of the 14 patients, including three with inguinal lymph node metastases, underwent irradiation to the local tumor site and the regional (pelvic and inguinal) lymph node area through antero-posterior opposed ports with 4-6 MV X-rays. This was followed by a local radiation boost to the gross tumor site using 6-13 MeV electrons. The remaining seven patients underwent local irradiation to the tumor site alone, using 4-14 MV X-rays or 6-15 MeV electrons. Radiation fields were set up to include the gross tumors with a 2-5 cm margin. A bolus with a 5-10 mm water-equivalent thickness was used to compensate for the surface dose at the tumor sites. The radiation field was reduced after doses of 44-45 Gy, and total doses of 52-80.2 Gy (median=60.6 Gy) in 26-43 fractions (median=33 fractions) were subsequently delivered to the gross tumors, including enlarged metastatic inguinal lymph nodes in the reduced field. Irradiation took place five days per week and fraction sizes were 1.8-2.2 Gy (median=1.8 Gy). The overall treatment time ranged from 43-69 days (median=50 days).

Follow-up and evaluation criteria. Patients underwent pelvic CT at one month after the completion of irradiation, and were followed up at approximately 3-month intervals. Growth of the irradiated tumor or the appearance of new disease after irradiation was regarded as recurrence. When patients showed no tumor progression within the radiation field and no recurrence after irradiation, the disease was considered to be locally controlled and they were considered to be disease free, respectively. Actuarial disease-control and survival rates were calculated from the beginning of radiation therapy according to the Kaplan-Meier method (9).

Acute and late toxicities associated with radiation therapy were evaluated using the Radiation Therapy Oncology Group (RTOG) acute radiation morbidity scoring criteria, and the RTOG/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme, respectively (10). Acute toxicities were defined as radiation-induced toxicities that occurred within three

Table I. *Patients' and tumor characteristics.*

Number of patients	14
Gender	
Men	3
Women	11
Age (years)	
Range	52-94
Median	81
Performance status	
0	5
1	6
2	3
Tumor location	
Vulva	7
Perineum	5
Scrotum	2
Tumor size (maximum diameter, mm)	
Range	55-150
Median	90
Tumor invasion into the dermis	
Yes	2
No	12
Regional lymph node metastasis	
Yes	3
No	11

months after the beginning of radiation therapy, and late toxicities as those occurring after three months.

Results

Tumor control and failure patterns. All irradiated tumors had disappeared macroscopically within nine months after irradiation, giving an initial complete response rate of 100%. Photographs of the tumor site in one patient both before and after radiation therapy are shown in Figure 1. However, four out of the 14 patients had recurrences at 3-35 months after irradiation; three patients had primary tumor progression within the radiation field and one patient developed distant metastasis in the liver during follow-up periods of 2-150 months (median=47 months). The three patients with primary tumor progression had received total doses of 61.2, 61.6 and 70.2 Gy, respectively. In contrast, the 11 patients without primary tumor progression had received doses of 52-80.2 Gy (median=60 Gy). Two out of the three patients with primary tumor progression were salvaged by surgery. Disease in the remaining patient was medically inoperable and was followed up without further treatment. One patient with liver metastasis, who also had inguinal lymph node metastasis before radiation therapy, refused aggressive treatment such as chemotherapy, and therefore received best supportive care.

The overall local control and disease-free rates were 71% and 63% at both 3 and 5 years, respectively (Figure 2). *Survival.* Two out of the 14 patients died at 6 and 51 months

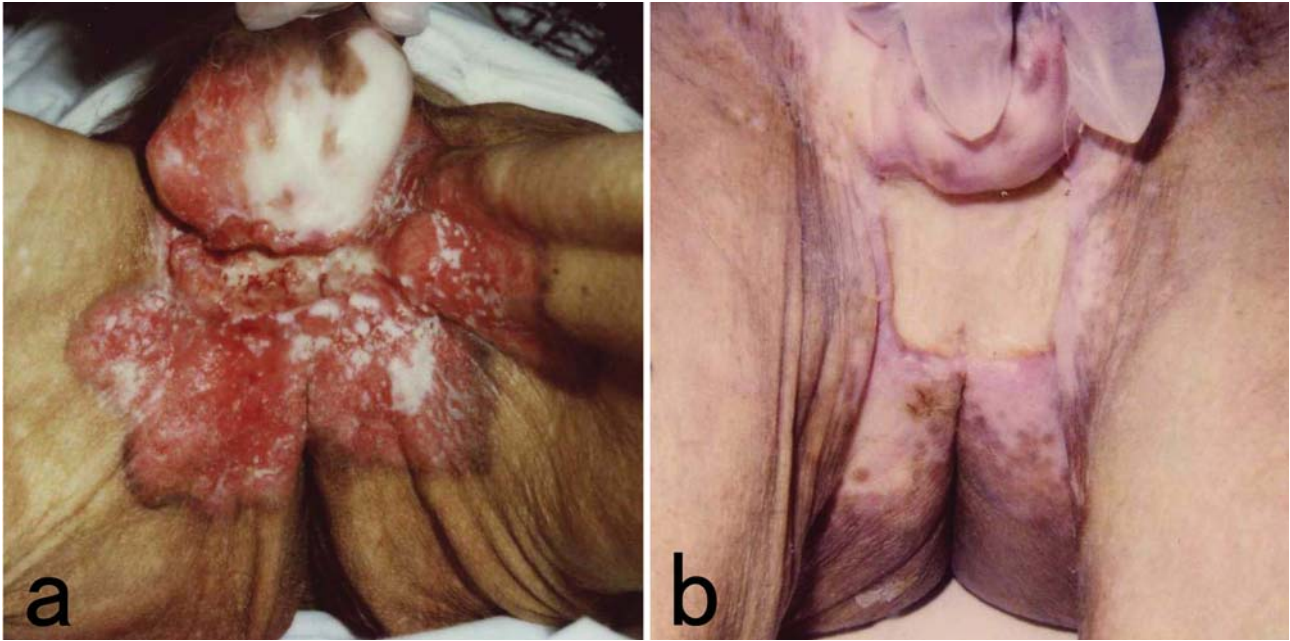


Figure 1. Photographs of a patient with widespread extramammary Paget's disease in the scrotum and the perineum before (a) and one month after (b) radiation therapy. The widespread tumor exhibited erythematous eczema and erosion with leukokeratotic plaques, which completely disappeared after irradiation, leaving a depigmented area.

after irradiation. The causes of death were old age and renal failure, respectively. There was no mortality associated with radiation therapy. The disease-free, cause-specific and overall survival rates in all patients were 58%, 100% and 92% at 3 years, and 46%, 100% and 79% at 5 years, respectively (Figure 3).

Toxicities. Acute reactions were transient and easily manageable. Hematological toxicities of grade ≤ 2 were observed in six patients, including four with leukopenia, three with anemia, and one with thrombocytopenia. All patients developed radiation dermatitis of grade 2, and some patients experienced radiation colitis, cystitis or urethritis of grade 1-2. There were no adverse events of grade ≥ 3 . Therapy-related acute toxicities are shown in Table II.

Regarding late toxicities associated with radiation therapy, three patients had symptom-free telangiectasia of grade 1 within the radiation field, but there were no severe toxicities, including ulceration or necrosis of the skin.

The clinical courses of all patients are summarized in Table III.

Discussion

Surgical excision is widely accepted as the standard and most reliable curative treatment for EMPD (3, 4). However, since EMPD predominantly occurs in the elderly, disease in

Table II. Therapy-related acute toxicities according to RTOG acute radiation morbidity scoring criteria.

Toxicity	Grade			
	1	2	3	4
Hematological				
Leukopenia	3	1	0	0
Anemia	3	0	0	0
Thrombocytopenia	0	1	0	0
Skin				
Erythema/moist desquamation	0	14	0	0
Lower GI tract				
Diarrhea	1	2	0	0
Genitourinary tract				
Frequency of urination/dysuria/urgency	5	1	0	0

RTOG, Radiation Therapy Oncology Group; GI, gastrointestinal.

many patients is inoperable. In the present study, we used radiation therapy as a noninvasive and curative treatment for these patients. The local control rate at 5 years was 71%, which compares favorably with those after surgery, which have been reported to vary widely from 39-84% (11-13). Both acute and late toxicities associated with radiation

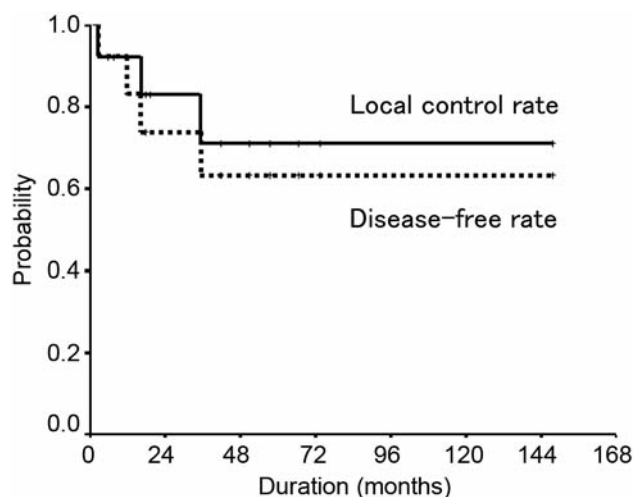


Figure 2. Local control and disease-free rates in patients with extramammary Paget's disease treated with definitive radiation therapy.

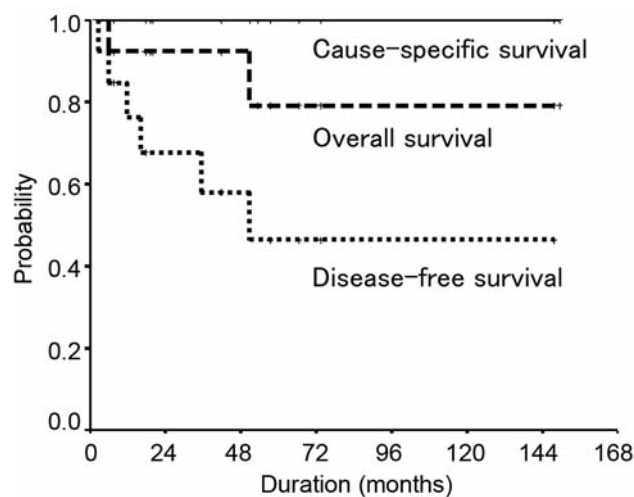


Figure 3. Disease-free, cause-specific and overall survival rates in patients with extramammary Paget's disease treated with definitive radiation therapy.

therapy were negligible, even in our patients with severe coexisting diseases, and no cosmetic impairment of the irradiated genital regions was observed. Radiation therapy therefore appeared to be effective and safe, and to present a promising curative treatment option for patients with inoperable EMPD.

Although the sample size in the present study was small ($n=14$), the rarity of EMPD means that this still represents a larger number of patients treated with definitive radiation therapy than in any previous study. Several authors have previously reported on a few cases of EMPD treated with definitive radiation therapy for initial disease. Among these, only three reports have presented treatment outcomes for four or more patients (14-16). These patients were treated with various dose-fractionation regimens using X- or gamma-rays or electrons. The largest previous study was conducted by Brierley *et al.* and reported treatment results in six patients with EMPD treated with total doses of 30-54 Gy in 3-25 fractions; two out of the six patients in this study experienced local recurrences during follow-up periods of 13-51 months (median=26 months) (14). Burrows *et al.* presented five patients with EMPD treated with a hypofractionated radiation regimen at a total dose of 40.5 Gy at 4.5 Gy per fraction; none of these patients had developed recurrence at the last follow-up of 6-96 months (median=24 months) (15). Besa *et al.* treated four patients with EMPD with external irradiation at total doses of 44-64 Gy in 23-28 fractions, and also added interstitial implants at either 20 or 30 Gy for two of the patients (16). One of the four patients had local failure during follow-up periods of 14-60 months (median=20 months). All these previous reports involved

small numbers of patients and short follow-up periods, making it difficult to evaluate the efficacy of radiation therapy for EMPD. In addition, the wide range of radiation regimens used makes it difficult to assess the optimal total radiation dose and dose-fractionation.

In the current study, most of the 14 patients received conventional irradiation at 1.8-2 Gy per fraction, and the median follow-up period of 47 months was longer than in any of the previous studies. Three patients with local recurrences underwent irradiation at total doses of 61.2-70.2 Gy to the primary tumors. All these total doses were higher than the median total dose (60.6 Gy) for all patients in this study. Thus even a total dose of >60 Gy may be insufficient to eradicate a subset of EMPDs. The primary tumors in the three patients with local recurrences were 55, 55 and 120 mm, respectively, two of which were smaller than the median size (90 mm) for all patients. In addition, none of the three patients with local recurrences had tumor invasion into the dermis. These results suggest that tumor size and depth may not be related to local control. Furthermore, all three patients with local recurrences had primary tumors in the vulva, and the significance of tumor location in local recurrence risk is currently unknown. Both of the two patients with tumor invasion into the dermis had inguinal lymph node metastases at initial diagnosis, while another patient with inguinal lymph node metastasis developed liver metastasis after radiation therapy. Previous studies of patients with EMPD treated with surgery have reported invasion into the dermis as being a risk factor for metastasis, and inguinal lymph node metastasis as a prognostic factor for survival (17, 18).

Table III. Clinical courses of 14 patients with extramammary Paget's disease treated with definitive radiation therapy.

Patient no.	Age (years)/gender	PS	Tumor location	Tumor size (MD, mm)	Tumor invasion into the dermis	Regional lymph node metastasis	Radiation field	Total dose (Gy/fractions)	Pattern of failure	Follow-up period (months)	Recent status
1	80/F	1	Perineum	80	No	No	Local	52/26	No	73	Alive with NED
2	81/M	2	Scrotum	150	Yes	Yes	Local + RLN	80.2/43	No	6	Dead of old age
3	68/F	0	Vulva	55	No	No	Local + RLN	61.2/34	Primary	150	Alive with recurrence
4	63/F	0	Perineum	60	No	No	Local + RLN	59.4/33	No	148	Alive with NED
5	72/F	0	Vulva	55	No	No	Local	61.6/28	Primary	20	Alive with recurrence
6	73/M	1	Scrotum	100	Yes	Yes	Local + RLN	59.4/33	No	51	Dead of renal failure
7	94/F	1	Vulva	100	No	No	Local	70.2/39	No	18	Alive with NED
8	82/F	0	Vulva	85	No	No	Local	70.2/39	No	58	Alive with NED
9	52/M	0	Vulva	90	No	No	Local	60/30	No	67	Alive with NED
10	84/F	1	Vulva	120	No	No	Local	70.2/39	Primary	53	Alive with recurrence
11	83/F	2	Perineum	90	No	No	Local	60/30	No	8	Alive with NED
12	74/F	1	Vulva	120	No	Yes	Local + RLN	59.4/33	Liver	19	Alive with recurrence
13	82/F	1	Perineum	70	No	No	Local + RLN	60/30	No	42	Alive with NED
14	85/F	2	Perineum	120	No	No	Local + RLN	61.2/34	No	2	Alive with NED

PS, Performance status; MD, maximum diameter; M, male; F, female; RLN, regional (pelvic and inguinal) lymph node; NED, no evidence of disease.

Other nonsurgical treatments, such as topical and systemic chemotherapy, photodynamic therapy and CO₂ laser therapy, have been also used to treat EMPD. Several case reports have documented the successful treatment of patients with EMPD with the topical immunomodulating agent imiquimod (19, 20). Although imiquimod cream is known to be effective for basal cell carcinoma, its use for EMPD remains tentative (21). Other case reports have recorded the effective treatment of advanced and metastatic EMPD with chemotherapeutic agents such as cisplatin, 5-fluorouracil, paclitaxel or docetaxel, and recombinant monoclonal antibodies such as trastuzumab (22-24). However, these are noncurative treatments, and no first-line regimen has yet been established. Photodynamic and CO₂ laser therapies are promising and less invasive, but data in large numbers of patients with long follow-up periods are still lacking (25, 26). In addition, these treatments are unfortunately only effective for superficial disease, and are ineffective in cases with lymph node metastasis.

In conclusion, initial treatment with definitive radiation therapy was found to be effective and safe, and to represent a potentially curative treatment option for patients with EMPD. However, further studies involving more patients and longer follow-up periods are required to confirm the validity of radiation therapy as a curative treatment for EMPD.

Conflict of Interest

Authors have declared that no actual or potential conflicts of interest exist.

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Received April 23, 2012
Revised June 25, 2012
Accepted June 26, 2012