Outcome of Radiation Therapy for Locally Advanced Vulvar Carcinoma: Analysis of Inguinal Lymph Node

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Abstract. *Background/Aim:* The aim of this study was to define the outcome of radiation therapy for vulvar carcinoma, and to investigate the effectiveness of therapeutic and prophylactic inguinal lymph node (ILN) irradiation. *Because reports about the treatment of ILN were limited. Patients and Methods:* Thirty consecutive vulvar carcinoma patients were treated using external beam radiation therapy (EBRT) for definitive disease (n=25) or postoperatively (n=5). Twenty-four (80%) had squamous cell carcinoma (SCC). Tumor stages (2002 UICC) ranged from 0 to IVB, with no distant metastases. *Results:* The median total prescribed dose for primary tumor was 64.8 Gy. The 2-year overall survival rate was 25.3%. The outcome was significantly better in patients with ILNs<30 mm (p=0.005) and patients receiving prescribed doses >60 Gy (p=0.002). *Conclusions:* ILN diameters ≤30 mm and prescribed doses over 60 Gy were associated with ILN control in patients with vulvar carcinoma.

Vulvar carcinoma is responsible for 5% of gynecologic malignancies (1) and has an estimated incidence of 5,000 in the US each year, with 1,000 deaths (2). Conversely, the reported incidence of vulvar carcinoma is smaller in Japan compared to the US and European countries, and studies suggest it accounts for 1%-2% of all gynecologic malignancies in Japan (3).

Data on the treatment of inguinal lymph nodes (ILN) and pelvic lymph nodes (PLNs) are limited (1), and only few studies have analyzed PLNs (4) mainly focusing on imaging. Similarly, only a small number of articles have analyzed

ILNs. Katz *et al.*, (5) have found that radiation therapy (RT) alone or in combination with lymph node dissection was an effective treatment. However, the relationships between ILN diameter, number of ILNs, and ILN irradiation dose for vulvar carcinoma remain controversial.

The aim of this study was to report the outcome of RT with or without surgery in a series of cases of vulvar carcinoma, and to investigate the effectiveness of ILN irradiation as well as the role of ILN diameter, irradiation dose for ILN, and number of ILN treatments on its efficacy.

Patients and Methods

Patients. From May 1993 to December 2016, 30 consecutive vulvar carcinoma patients were treated with external beam radiation therapy (EBRT) using three-dimensional radiation therapy (3DCRT) with curative intent at our institution. We retrospectively reviewed these patients' medical records. The determination of clinical stage was based on i) physical examination, ii) chest X-ray, and iii) computed tomography (CT) of the abdomen and pelvis. Almost all patients underwent pelvic magnetic resonance imaging (MRI). All patients were examined prior to their treatment by gynaecologists and radiation oncologists and were classified according to the 2009 Union for International Cancer Control staging system (6). The disease characteristics of the 30 patients are summarized in Table I.

Stage IVB patients showed involvement of pelvic lymph nodes only, with no other distant metastasis. The median diameter of primary tumours was 60 mm (range, 2-100 mm). Involved lymph nodes were defined as a short axis ≥10 mm. This study was approved by the review board of our institution (B180200003), and informed consent was obtained from all patients prior to treatment.

Treatment. Patients received RT with curative intent either postoperatively (n=5) or as a definitive treatment (n=25). The patients who received definitive RT were considered inoperable because of i) old age, ii) complications, or iii) because their tumour had invaded the urethra, anus, or vagina, and, thus, tumour resection would deteriorate their quality of life. Twenty-two patients received RT to the vulva and pelvic and bilateral inguinal nodes, and three patients received only local vulvar irradiation. Five patients received postoperative RT, four for positive or close operative margins and one with suspected pelvic lymph node involvement who was considered high risk.

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Key Words: Vulvar carcinoma, inguinal lymph node, external beam radiation therapy, 3-dimensional radiation therapy, gynecologic malignancies.

Table I. Patient and treatment related characteristics.

Total no. of patients (n)	30
Age (years)	
Median (range)	77 (range=59-90) years
RT sequence & doses (n)	
Postoperative	5 (16.7%)
Definitive	25 (83.3%)
Histology (n)	
SCC	24 (80%)
Adenocarcinoma	2 (6.6%)
Verrucous squamous carcinoma	2 (6.6%)
Atypical squamous epithelium	1 (3.3%)
CIS	1 (3.3%)
ECOG PS (n)	
0	17 (56.7%)
1	8 (26.7%)
2	3 (10%)
3	2 (6.6%)
Clinical stage (UICC) (n)	
Stage 0	1 (3.3%)
Stage IB	1 (3.3%)
Stage II	6 (20%)
Stage IIIA	2 (6.7%)
Stage IIIB	5 (16.7%)
Stage IVA	12 (40%)
Stage IVB	3 (10%)
Chemotherapy (n)	3 (12%)
Cisplatin	2
Carboplatin	1

RT: Radiation therapy, SCC: squamous cell carcinoma, CIS: carcinoma in situ, ECOG: Eastern Cooperative Oncology Group, PS: performance status.

Four patients underwent en bloc radical vulvectomy and bilateral inguinal-femoral lymphadenectomy, and one had simple tumour excision due to poor performance status (PS). The pelvic regional lymph nodes included the: i) common iliac, ii) internal iliac, iii) external iliac, iv) obturator, and v) presacral lymph nodes.

The gross tumour volume was defined as the primary tumour of the vulva and the involved lymph nodes, while the clinical target volume (CTV) was defined as the primary tumour plus a 5-mm margin that included the pelvic and bilateral inguinal nodes. The planning target volume was delineated with a 10- to 15-mm margin around the CTV. Normal structures including i) bladder, ii) rectum, iii) small bowel, and iv) femoral heads were contoured as organs at risk in the radiation field.

RT was delivered with photons using 2-4 beams by 3DCRT. In 14 cases, 6 MV was used for the anterior field and 15 MV for the posterior field. The two beams were composed of antero-posterior opposed fields and the four beams were composed of antero-posterior and bilateral fields. Patients received external irradiation at a planned total dose of 60-70 Gy in 30-35 fractions. The fraction size was 1.8-2 Gy and was delivered daily, 5 days per week, using 4-15 MV, X-rays (PRIMUS High-Energy, Toshiba Medical Systems Co., Ltd., Japan), and a shrinking field technique.

The radiation field and prescribed dose data are summarized in Table I. The four patients receiving only local vulva irradiation were treated using 6 MeV electrons or 6 MV photons because of poor PS (n=3) and stage 0 (n=1). The remaining patients received irradiation for whole pelvic and bilateral ILN regions with or without positive

lymph nodes. The pelvic and ILN regions received 40-50.4 Gy prophylactically, and the primary tumour and involved lymph nodes were boosted using photon or electron (6-12 MeV) field arrangement depending on tumour invasion. The bolus material (0.5 cm thickness) was used in all the patients to ensure adequate dose delivery to primary tumours and inguinal regions.

Twenty (66.7%) patients had bilateral ILN involvement, and two (6.67%) patients had unilateral ILN involvement. The median diameter of the ILNs was 20 mm (range=10-75 mm). The median prescribed dose for positive ILNs was 59.4 Gy (range=39-70.2 Gy). ILNs were irradiated with photons with a median of 45 Gy (range=39.6-50.4 Gy) and then were boosted with electrons (6-12 MeV). Of the 26 patients who received irradiation to the pelvic and bilateral inguinal nodes, 19 were treated with two beams and 7 with four beams. Seventeen patients were irradiated after being placed in the frog-leg position.

The median overall treatment time for RT was 50 days (range=12-73 days). Of the 30 patients, 28 (93.3%) completed RT without interruption. Two patients had to quit RT because of the progression of dementia or aspiration pneumonitis. The median prescribed total radiation dose for primary tumours was 64.8 Gy (range=14-79.2 Gy). The median prophylactic prescribed dose delivered (22 definitively and 4 postoperatively) for pelvic and ILNs was 45 Gy (range=39.6-50.4 Gy).

Three patients (12%; definitive, n=2; postoperative, n=1) received simultaneous chemotherapy with cisplatin (40 mg/m²) once a week for five cycles. The reasons chemotherapy was not administered to other patients were due to i) debility, ii) comorbidity, iii) renal disorder, or iv) psychopathic disorder.

Evaluation criteria and statistical analysis. Responses were evaluated by clinical examination and CT, MRI, and biopsy at approximately 4-6 weeks after the completion of treatment. Tumor responses were assessed using Response Evaluation Criteria in Solid Tumors (RECIST v. 1.1) criteria.

When patients exhibited no tumour progression within the radiation field and no recurrence after treatment, the disease was considered to be locally controlled and disease-free. Treatment delay was defined as the period from the patient's first visit to our institution until primary treatment initiation (RT or surgery), and total delay was defined as the period from the patient's first recognition of symptoms until treatment initiation.

Acute and late toxicities associated with treatment were evaluated according to the Common Terminology Criteria for Adverse Events v4.0 (2009) (7). Acute toxicities were defined as therapy-related adverse events that occurred within 3 months after the beginning of treatment, and late toxicities as those occurring after 3 months. Actuarial survival and tumour control probabilities were calculated from the beginning of RT according to Kaplan-Meier curves, and differences between curves were tested by the log-rank test using the statistical program implemented in IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). A *p*-Value <0.05 was considered significant.

Results

Tumor control and survival. The median follow-up time was 11 months (range=2-179 months). The median treatment delay time was 20 days (range=5-146 days), and the median total delay time was 7 months (range=1-40 months). The reason for the delay in seven patients was that they recognized the

Table II. The last follow-up status and details of all patients.

	Last follow-up status	Details	Median follow-up time
Definitive 25	Alive 12	CR+PR 10	12 months
		Recurrence 2	(range=2-42 months)
	Dead 13	DOD 10	9 months
Postoperative 5		Died of non-cancer-related causes 3	(range=2-11 months)
	Alive 4	CR+PR 4	48 months
	Dead 1	DOD 1	(range=12-79 months)
			35 months

CR: Complete response, PR: partial response DOD: died of disease.

symptoms, but they could not visit a hospital until the disease had advanced. Most patients had symptoms during their first visit to our institute: 7 (23.3%) had vulvar pain, 8 (26.7%) had bleeding, and 15 (50%) recognized a tumour.

In definitive patients (n=23, excluding two patients who could not complete the therapy), 11 (47.8%) achieved CR as confirmed by biopsy, and 12 patients (52.2%) were considered to have PR; the CR + PR rate was therefore 100%. The 1-year overall survival rate (OS) of all 30 patients was 25.3%. In definitive and postoperative patients, OS rates were 21.8% and 53.3%, respectively (Figure 1).

Table II shows details of the last follow-up status. Sixteen (53.3%) patients were alive at the last follow-up in our hospital. Of these, 9 changed hospital following initial treatment so we were unable to obtain any further information, 5 achieved CR, and 2 had primary tumour recurrence. In the initial PR patients, the median local failure time was 4 months (range=2-7 months). Eleven (36.7%) patients died of disease: 5 from primary tumour recurrence, 2 from primary tumour recurrence and ILN metastasis, and 4 from distant metastases, although their primary tumour remained under control. Three (10%) patients died of non-cancer-related causes that included pneumonia and heart failure.

The median diameter and prescribed doses for tumours that relapsed following initial treatment was 60 mm and 65.4 Gy, respectively. This compares to 60 mm and 64.8 Gy, respectively, for tumours that were controlled.

Analysis of inguinal lymph nodes. Of the 16 patients who had clinical lymph node involvement, there were 42 positive ILNs (short axis ≥ 10 mm). Of these, 38 ILNs were in the 14 patients completing RT. Table III shows the outcomes of individual ILNs. When the diameter was ≥ 30 mm the CR+PR rate was 25%, however, when the diameter was less than 30 mm the CR+PR rate was 60% ($p=0.005$).

Two of three patients who had four positive ILNs did not eradicate both their primary tumour and ILNs, but these patients had no distant metastasis. Four of five patients who had ≥ 2 positive ILNs and at least one positive ILN ≥ 30 mm

Figure 1. Overall survival rate in patients with vulvar carcinoma treated with definitive and postoperative radiation therapy.

experienced ILN relapse. One patient who received 70.2 Gy experienced PR. Interestingly, there were no significant differences in the survival of patients with 1-2 positive ILNs vs. 3-4 positive ILNs ($p=0.91$), or 1-3 positive ILNs vs. 4 positive ILNs ($p=0.517$).

Two patients whose prescribed doses were <45 Gy for ILN achieved CR. Their primary tumours were non-squamous cell carcinoma (adenocarcinoma and atypical squamous epithelium). Except for these 2 patients, the 3 patients prescribed >65 Gy experienced CR or PR. In contrast, 6 of 9 patients (66.7%) receiving <65 Gy had recurrences in ILNs. Figure 2A shows a scatter diagram of individual ILN diameters and prescribed doses for SCC. In SCC patients, the outcome was significantly different between those prescribed ≥ 60 Gy and <60 Gy for ILNs ($p=0.002$).

Figure 2. A. The diameter of individual inguinal lymph node (ILN) and prescribed doses for ILN in squamous cell carcinoma (SCC) patients. The relationship among the treatment outcome of individual ILN, the diameter of individual ILN and prescribed doses for ILN in case of SCC patients. B. The diameter of individual ILN and primary tumor diameter in definitive treatment patients. The relationship among the treatment outcome of individual ILN, the diameter of individual ILN and primary tumor diameter in case of definitive treatment patients (excluding postoperative treatment). CR: Complete response, PR: partial response, SD: stable disease, PD: progressive disease.

Table III. The outcome of individual ILN, number, diameter, and prescribed doses.

Initial outcome	n	ILN diameter	ILN prescribed dose
CR	15	20 (range=10-30) mm	54 (range=39.6-70.2) Gy
PR	4	20.5 (range=14-46) mm	55.8 (range=50.4-63) Gy
SD	12	22 (range=12-75) mm	61.2 (range=54-69) Gy
PD	6	31 (range=18-66) mm	58.5 (range=50.4-69) Gy

CR: Complete response, PR: partial response, SD: stable disease, PD: progressive disease.

Figure 2B shows a scatter diagram of individual ILN diameters and the diameters of primary tumours. When the primary tumour was >100 mm no ILNs achieved CR, and when ILNs were >30 mm only one ILN achieved CR, regardless of the primary tumour diameter. In the 7 patients who developed primary tumour recurrence, 4 had PD in the ILNs, two had SD, and one achieved CR but developed contralateral ILN metastasis. In the two patients whose primary tumours were >100 mm, both the primary tumour and ILN involvement recurred. In 5 patients with successful treatment of the primary tumour, 3 had no ILN recurrence. One patient had a primary tumour that was successfully treated, but persistent ILN involvement was followed by bone metastases. The other patient also had ILN disease, and eventually developed carcinomatous peritonitis. Two patients had only unilateral positive ILNs; they received 70.2 Gy to

these ILNs and achieved CR. However, one patient developed primary tumour recurrence and metastasis to the ILN on the other side.

Eleven patients without ILN involvement underwent radiation to the primary tumour plus a median of 45 Gy prophylactic RT to the ILNs. None of them developed any ILN metastases.

Toxicity. Pain, dermatitis, radiation-induced diarrhoea, and oedema were observed as acute toxicities (Table IV).

Four patients had bleeding from desquamated skin. One patient who had grade 3 radiation-induced intermittent diarrhea required intravenous hydration. Two patients had grade 4 myelosuppression temporally but recovered without serious infection. The acute toxicities were manageable and tolerated, and most of the pain diminished 1-2 months following treatment.

Table IV. *Acute toxicities.*

	Grade 1	Grade 2	Grade 3	Grade 4
Hematology toxicity				
Leukopenia	2	1	3	1
Neutropenia	0	3	1	1
Anemia	11	3	2	0
Thrombocytopenia	5	1	0	0
Skin				
Pain (irradiated skin)	12	11	5	0
Dermatitis in the vulva	5	18	5	0
GI				
Radiation-induced intermittent diarrhea	14	0	1	0
General disorders				
Edema in lower legs	3	2	0	0

GI: Gastrointestinal.

Therapy-related late toxicities included two cases of rectovaginal fistula; both cases had bulky tumours and suspected rectum invasion. No other late toxicities >grade 3 were observed.

Discussion

The aim of this study was to report the outcome of RT with or without surgery or chemotherapy for vulvar carcinoma, and especially to investigate the effectiveness of ILN irradiation. Few reports have previously analyzed ILNs for vulvar cancer. Katz *et al.*, (5) have reported that RT alone or in combination with lymph node dissection was effective, but there are no guidelines for the prescribed dose for ILNs. Moreover, the relationships between tumour diameter, prescribed dose, number of ILNs, and inguinal lymph node dose are unclear.

Our results show the outcome was significantly better in patients with ILNs < 30 mm, although the number of involved ILNs had no significant effect on outcome. However, if the patient had ≥ 4 involved nodes, surgery before radiation was helpful. In cases prescribed >65 Gy for ILN, initial CR and PR rates were 100%, while cases receiving <65 Gy had an ILN recurrence rate of 66.7%. In SCC patients, the outcome was significantly better in patients who received ≥ 60 Gy for ILNs. A previous study reported an optimal dose to unresected gross nodal disease of 60-70 Gy, but this lacked statistical analysis (1). We suggest that optimal doses may be >60 Gy.

We found that if the primary tumour recurred it was difficult to control ILN involvement. Moreover, if the primary tumour was successfully treated but ILN disease persisted, there was a high risk of distant metastasis. According to Katz *et al.*, (5) primary tumour recurrence is

the only significant predictor of ILN recurrence. The group has also reported a rate of ILN recurrence of 9.8% for patients who had not had a primary recurrence and who were treated with inguinal RT. We observed that when the primary tumour was >100 mm or the ILN diameter >30 mm, it was difficult to control the ILNs (Figure 2A).

Prophylactic chemoradiation therapy (CRT) to the inguinal regions has been suggested as effective because the “negative” ILNs is expected to have occult metastases more than 20% of the time (8). Most of these studies report on postoperative RT. In a series presented by Hallak *et al.*, (9) the inguinal relapse-free survival rate was 75% both for patients treated with adjuvant inguinal irradiation without lymphadenectomy and patients treated with primary lymphadenectomy with or without inguinal irradiation. They received 47.5 to 54 Gy by various methods. In definitive RT, Katz *et al.*, (5) have reported an ILN recurrence rate of 11% for patients treated with RT alone for clinically negative nodes. In general, bilateral ILN coverage for the CTV is suggested (1).

In our series, prophylactic bilateral ILN RT was delivered to 11 patients who did not develop any ILN involvement following RT, with a median prescribed dose of 45 Gy. We suggest that prophylactic RT for ILN should be delivered in such cases. One patient developed ILN involvement and died of bleeding from the tumour invasion of vessels; however, >G3 toxicity was not associated with ILN irradiation. From the above findings, we suggest that ILNs should receive sufficient radiation doses. To our knowledge, this is the first report to analyze the outcomes of ILN in terms of size and number following irradiation.

Few studies have investigated the outcome of definitive RT for vulvar carcinoma. The 5-year OS has been reported to be 10% for only RT included brachytherapy, EBRT, and a combination for vulvar carcinoma (10). Some previous reports suggested the superiority of CRT over RT alone (11,12). Mak RH *et al* reported, in CRT studies, the 2-year disease-free survival rate was 58.1% (11). Moore DH *et al* reported that 4% of T3-T4 patients administered CRT have been recently shown to have a complete CR of the primary tumour (12). In surgery and radiation combination treatment, studies have reported a 3- to 4-year OS of 32%-64% (13-15). However, differences in therapy make it difficult to compare outcomes. In our study, most patients received only RT, which explains the relatively poor outcome. Cameron *et al.* (13) observed a 24% 5-year OS following surgery and adjuvant RT. The median patient age of that study was 78 years, similar to our own, so the outcomes are comparable.

The reasons for diagnostic and treatment delays in gynaecological malignancies have previously been investigated (16). Vulvar cancer was reported to take the most time to diagnose out of all gynaecological malignancies and treat because the recognition of warning symptoms is difficult, and it is common in older people. In

this earlier study, the median treatment delay was 18 days and the total delay was 170 days, which compares with 20 days and approximately 210 days, respectively, in the present study. Total delays were considered one reason for poor outcome. The outcome of adjuvant RT for margin-positive vulvar cancer reported that a prolonged treatment period and delays in diagnosis and treatment significantly affected OS (14).

The limitations of our study were that the number of patients was small, the median follow-up time was short, it was a retrospective review, and the treatment method was only 3DCRT. Recently, some reports have investigated intensity-modulated radiation therapy (IMRT) as a possible means of improving outcome by reducing toxicities (17-19). Future studies could compare these treatments.

We assessed the effectiveness of ILN irradiation in the treatment of vulvar carcinoma. We observed that prophylactic RT for ILNs was effective. We suggest that an ILN diameter >30 mm should be considered as high risk for relapse after initial treatment. We suggest that prescribed doses <60 Gy may be insufficient to control both ILNs and primary tumour. The dose escalation and suppressing dermatitis are an issue to be addressed in the future.

Conflicts of Interest

None of the Authors have any conflicts of interest associated with this study.

Authors' Contributions

Y.M. analyzed the patient data and major contributor in writing the manuscript. M.H. advised the analysis and writing. All Authors read and approved the final manuscript.

Acknowledgements

The Authors thank Libby Cone, MD, MA, from DMC Corp. (www.dmed.co.jp <<http://www.dmed.co.jp/>>) for editing drafts of this manuscript. We also thank H. Nikki March, Ph.D., from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

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Received October 11, 2019

Revised October 25, 2019

Accepted November 4, 2019