Gynecologic Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Effectiveness of definitive radiotherapy for squamous cell carcinoma of the vulva with gross inguinal lymphadenopathy

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HIGHLIGHTS

- We studied outcomes following definitive RT for vulvar SCC with gross inguinal lymph node metastases.
- Definitive RT results in excellent local control of metastatic lymph nodes.
- There is low risk of serious long-term toxicity with definitive RT.
- Definitive RT is indicated for patients with unresectable disease and those at high risk of major morbidity from surgery.

ARTICLE INFO

Article history:
Received 15 November 2017
Received in revised form 6 January 2018
Accepted 8 January 2018
Available online xxxx

Keywords:
Vulvar cancer
Inguinal lymph node metastases
Advanced disease
Radiotherapy
Chemoradiation

ABSTRACT

Objective. To evaluate the effectiveness and long-term side effects of definitive groin radiotherapy for vulvar cancer with grossly involved inguinal lymph nodes.

Methods. The records of 407 women with vulvar squamous cell carcinoma treated with radiotherapy at one institution during 1992–2014 were reviewed to identify patients who had radiographic or histologic evidence of grossly involved inguinal lymph nodes. Patients with lymphadenectomy before radiotherapy and patients treated for recurrent disease were excluded. Actuarial incidences of vulvar, inguinal, and distant recurrences, the relationship between vulvar recurrence and inguinal recurrence, and overall survival were analyzed using the Kaplan–Meier method.

Results. Thirty-three patients were identified. The median age at diagnosis was 64 years. The median long-axis radiographic diameter of the largest inguinal lymph node or lymph node mass was 2.5 cm (range, 1.4–8.7). Sixteen patients (48%) also had evidence of pelvic lymph node metastasis. The median radiation dose delivered to grossly involved nodes was 66.0 Gy (range, 60.0–70.0). The 3-year actuarial incidences of vulvar, groin, and distant recurrences were 24.2%, 17.7%, and 30.3%, respectively. With a median follow-up time of 28 months (range, 2–196), four patients (12%) had groin recurrence, of whom three also had vulvar recurrence. There were few major late adverse effects of regional radiotherapy. The 3-year overall survival rate was 51%.

Conclusions. High-dose volume-directed radiotherapy achieves a high rate of local control with low risk of serious long-term toxic effects in patients with vulvar squamous cell carcinoma and grossly involved inguinal lymph nodes.

1. Introduction

Although the presence of clinically evident lymph node metastases is an adverse prognostic factor for patients with vulvar cancer, many patients with this finding can be cured if regional disease can be controlled. A widely accepted approach to the treatment of patients with vulvar cancer and grossly involved nodes is radical inguinal lymphadenectomy followed by adjuvant radiotherapy [1]. Although this approach is effective in many cases, it is associated with a high rate of perioperative complications, including wound dehiscence, wound infection, and lymphocyst formation [2, 3]. Although rarely life-threatening, these complications can delay the initiation of adjuvant radiotherapy, which can in turn compromise the effectiveness of treatment. In addition, radical lymphadenectomy can cause chronic lymphedema, a potentially serious long-term adverse effect. In the hope of reducing these sequelae, Hyde et al. [4] have advocated a more selective nodal debulking operation followed by radiotherapy; in a small retrospective study, they reported an 80% regional control rate with this

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https://doi.org/10.1016/j.ygyno.2018.01.007
0090-8258/

procedure, which was not significantly different from the regional control rate achieved with radical lymphadenectomy. However, for patients with extensive lymphadenopathy, debulking still may require a very extensive, potentially morbid lymphadenectomy. Definitive radiotherapy is a potentially attractive alternative for patients who have very extensive or bulky nodal metastases and for patients who are poor operative candidates for medical reasons. In this study, we reviewed our institutional experience to evaluate the effectiveness and long-term side effects of definitive radiotherapy for vulvar cancer with grossly involved inguinal lymph nodes.

2. Methods

2.1. Patients

The records of all women treated for stage I-IVB vulvar squamous cell carcinoma according to the 2009 International Federation of Gynecology and Obstetrics (FIGO)/American Joint Committee on Cancer (AJCC) staging system at The University of Texas MD Anderson Cancer Center from March 1992 through December 2014 were reviewed to identify patients who received definitive radiotherapy for grossly involved inguinal lymph nodes. Patients who had lymphadenectomy before radiotherapy, except for patients who underwent diagnostic excisional biopsy of a single node, were excluded. Patients who received radiotherapy for recurrent disease, who had metastases to paraaortic lymph nodes or other distant sites at presentation, or who were treated with palliative intent were excluded. To be included, patients had to have histologic evidence or strong clinical (palpable nodes) or radiographic evidence (fixed, matted, or grossly enlarged nodes) of regional metastasis; patients with equivocal clinical or radiographic findings were excluded. In the interest of consistency, all patients treated before 2009 were retrospectively assigned a T category according to the 2009 FIGO/AJCC staging system.

2.2. Treatment

All patients were evaluated in a multidisciplinary clinic at MD Anderson Cancer Center. Patients were treated using 3-dimensional conformal radiotherapy (3D-CRT), intensity modulated radiotherapy (IMRT), or a combination of 3D-CRT and IMRT techniques according to the policies of the time. All patients received an initial radiation dose of 40 to 50 Gy of external beam radiotherapy to the vulva, bilateral inguinal regions, and pelvis. According to plan, various techniques were then used to bring the total dose to all sites of known or suspected gross disease to a minimum of 60 Gy. Some patients also received concurrent chemotherapy with cisplatin (40 mg/m^2 per week) or a combination of cisplatin and 5-fluorouracil.

2.3. Data analysis and statistical methods

The actuarial rates of vulvar, groin, and distant (including pelvic) recurrence and overall survival were calculated using the Kaplan–Meier method. Times to recurrence were calculated from the date of completion of definitive radiotherapy to the date when recurrent disease was first detected in that site. Survival was calculated from the date of completion of definitive radiotherapy to the date of death; patients alive at the date of last contact were censored at that time. The relationships between long-axis radiographic diameter of the largest inguinal lymph node, target radiotherapy dose, and disease control were evaluated.

3. Results

3.1. Patient and treatment characteristics

Our final study cohort included 33 patients. Two patients underwent diagnostic excisional biopsy of a single lymph node before radiotherapy; none of the other patients underwent lymphadenectomy before radiotherapy. Demographic, disease, and treatment characteristics are summarized in Table 1. Most patients had locally advanced primary tumors and were recommended definitive radiotherapy because their primary disease was considered unresectable or could not be resected without sacrifice of critical structures. Twenty-nine patients (88%) had palpable inguinal adenopathy on clinical examination, and all patients had radiographic evidence of inguinal lymph node metastasis. Eight patients (24%) had biopsy proof of inguinal lymph node metastases. Sixteen patients (49%) also had radiographic evidence of pelvic lymph node metastases and thus had FIGO/AJCC stage IVB disease. Ten patients received 3D–CRT, eight received 3D–CRT plus IMRT, and 15 received IMRT alone. Twenty patients received concurrent chemotherapy. Twenty-nine of 33 patients (88%) completed groin radiotherapy within 7.5 weeks. The remaining four patients had treatment delays, with cumulative groin treatment times of 57 days (N = 2), 59 days (N = 1), and 77 days (N = 1).

3.2. Recurrence and survival outcomes

Of the 33 patients in the cohort, six had a recurrence in the vulva, four had a recurrence (n = 3) or disease progression (n = 1) in one or both groins, and eight had a recurrence in distant sites. At three years, the actuarial incidences of vulvar, groin, and distant recurrence were 24.2%, 17.7%, and 30.3%, respectively (Fig. 1A). All vulvar, groin, and distant recurrences occurred within 1 year of the completion of definitive radiotherapy, and all patients who had recurrence died with active disease (Fig. 1B and C). Three of the four patients who experienced recurrent or progressive groin disease also had

Table 1
Patient, disease, and treatment characteristics.

Variable	Value
Median age (range)	64 years (31–91 years)
Race/ethnicity, N (%)	
White	21 (64)
Black	8 (24)
Hispanic	4 (12)
FIGO 2009 stage, N (%)	
IIIA	12 (36)
IVA	5 (15)
IVB[a]	16 (48)
FIGO 2009 T category, N (%)	
T1b	3 (9)
T2	24 (73)
T3	6 (18)
Findings on clinical nodal exam, N (%)	
Normal	4 (12)
Enlarged mobile	21 (64)
Fixed	6 (18)
Ulcerated	2 (6)
Bilaterality (radiologic), N (%)	
Unilateral	16 (48)
Bilateral	17 (52)
Median node size (range)	2.5 cm (1.4–8.7 cm)
Histologic confirmation, N (%)	
No	25 (76)
Yes	8 (24)
Radiotherapy and chemotherapy, N (%)	
Radiotherapy modality	
3D-CRT	10 (30)
3D-CRT/IMRT	8 (24)
IMRT	15 (46)
Concurrent chemotherapy	
None	13 (39)
Weekly cisplatin	15 (46)
Cisplatin and 5-fluorouracil	5 (15)

3D-CRT, three-dimensional conformal radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; IMRT, intensity modulated radiotherapy.
[a] Patients with metastatic disease beyond the pelvic lymph nodes were excluded.

Please cite this article as: S.R. Stecklein, et al., Effectiveness of definitive radiotherapy for squamous cell carcinoma of the vulva with gross inguinal lymphadenopathy, Gynecol Oncol (2018), https://doi.org/10.1016/j.ygyno.2018.01.007