

Conventional radiotherapy and intensity-modulated radiotherapy in carcinoma vulva: An experience from a tertiary medical center of India

Koustav Mazumder, Arun Elangovan, Bhavana Rai, Vanita Suri¹, Vanita Jain¹, Jaswinder Kalra¹, Sushmita Ghoshal

Abstract

Context: Vulvar cancer is one of the uncommon gynecological malignancies. Multimodality treatment with surgery, radiotherapy, and chemotherapy are required for treatment of the disease. **Aims:** The aim of the study was to evaluate clinical outcome in patients of carcinoma vulva, treated at our institution. **Subjects and Methods:** This was a retrospective-cohort study done in 50 patients with squamous cell carcinoma of the vulva, treated at our institution from January 2008 to December 2014. Data were analyzed on the basis of age, stage, type of treatment received, and treatment-related toxicity. Disease-free survival and overall survival were estimated. **Statistical Analysis Used:** Kaplan–Meier survival analysis and Chi-square test were used for statistical analysis. **Results:** Majority of the patients (52%) had presented with Stage III disease. Thirty-six of 50 patients underwent surgery: simple vulvectomy – 2, radical vulvectomy – 34, bilateral inguinal lymph node dissection was done in 32 patients, and 1 patient underwent ipsilateral-inguinal lymph node dissection. Among 40 patients who received radiotherapy and eight patients received palliative radiotherapy. Seventeen patients underwent intensity-modulated radiotherapy (IMRT) and 15 patients received conventional radiotherapy. Significantly less Grade 2 or more skin toxicity ($P = 0.003$) observed in patients who underwent IMRT. Among non-IMRT group, eight patients required treatment break during radiation. At a median follow-up time of 25.5 months, median overall survival was 31 months and median disease-free survival was 25 months. About 42% patients were alive and free of disease at last follow-up. **Conclusions:** Modified radical vulvectomy with inguinal lymph node dissection followed by radiotherapy is the mainstay of management of locally advanced carcinoma vulva. Using IMRT, we could minimize the treatment related radiation toxicity and treatment breaks.

Key words: Radiotherapy, cancer, vulva

Introduction

Vulvar cancer is one of the rare gynecological malignancies accounting for 3%–5% of the gynecological cancers.^[1] It most commonly affects women ≥ 75 years of age. Pruritus, ulceration, and swelling of the vulva are the most common presenting features. It may also present as swelling in the groin, due to lymph nodal spread to inguinofemoral nodes.

It is observed that there are two groups of vulvar cancer patients. One consists of younger patients in whom smoking and human papillomavirus infection are the common risk factors. In addition, association with vaginal intraepithelial neoplasia has been reported. The other group of vulvar cancer patients includes the elderly population, in whom no such risk factors have been associated except for lichen sclerosus and squamous hyperplasia. Among other risk factors are Paget's disease, Bowen's disease, and leukoplakia. The most common histopathological subtype is squamous cell carcinoma, accounting for 85%–90% of the total cases. Other subtypes are less common and include poorly-differentiated carcinoma, verrucous carcinoma, and malignant melanoma.^[2]

The treatment of vulvar carcinoma has evolved over the years. Previously, radical vulvectomy with inguinofemoral lymph node dissection was the primary modality of the treatment in resectable carcinoma vulva. This approach was however associated with significant morbidity. Recently, less radical approaches such as wide-local excision and triple-incision surgery with separate incisions for vulvar, and groin surgery have been standardized.^[3] Adjuvant radiotherapy is indicated in cases with high-risk features such as positive margins, lymphovascular space invasion (LVSI), and depth of invasion >5 mm.^[4]

Patients having locally advanced carcinoma of the vulva are predictably not amenable to surgery. These patients are treated by multimodality approach using neoadjuvant concurrent chemoradiation, followed by surgical resection or by radical chemoradiotherapy alone.^[2] Patients who are medically inoperable are treated by radical chemoradiation, either by conventional, three-dimensional (3D) radiotherapy, or intensity-modulated radiotherapy (IMRT) technique. Metastatic cases are treated with a palliative intent mainly with radiotherapy. Since these tumors are relatively less common, there is a paucity of robust reported data in vulvar carcinoma from India. In our analysis, we present an audit of 50 patients of carcinoma vulva who were evaluated for treatment outcomes and toxicities.

Subjects and Methods

The patients of carcinoma vulva treated in the Department of Radiotherapy, PGIMER, from January 2008 to December 2014 were included in this retrospective analysis. Patients were analyzed for their demographic profile, clinical details, treatment details, complications, and follow-up data including survival analysis. Details of surgery, chemotherapy, and radiotherapy were recorded.

The patients underwent one of the following surgeries: wide-local excision, triple-incision surgery, radical vulvectomy with bilateral inguinofemoral lymph node dissection, or modified radical vulvectomy. Postoperative histopathology report was scrutinized to look for the location, invasion of adjacent structures, margin status, number of resected lymph nodes, presence of lymph nodal metastasis, LVSI, extracapsular extension, etc.

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Departments of Radiotherapy and Oncology and 'Gynecology and obstetrics, Postgraduate Medical Education and Research, Chandigarh, India
Correspondence to: Dr. Bhavana Rai,
E-mail: bhavana1035@gmail.com

Details of radiation therapy including the type of radiation therapy (conventional/3D-conformal/IMRT), energy used, dose delivered, treatment interruptions, early and late toxicities, and the use of concurrent chemotherapy were recorded. Response to treatment was assessed at the end of 6 weeks. Follow-up period assessed from the completion of the primary management. Elaborate clinical history was taken and clinical examination was done at each follow up visit.

Results

Case records of the 50 patients included in the retrospective analysis were retrieved. The median age of presentation was 61.5 years (Range: 33–84 years). Comorbidities, either diabetes or hypertension, were present in 16 of the patients. Majority of patients were ≥60 years (58%) and presented in locally advanced stages (66% patients were in Stages III and IV). Thirty-six patients (72%) had undergone surgery: wide-local excision was done in 2 patients, radical vulvectomy in 20 patients (55.6%), and modified radical vulvectomy in 14 patients (38.8%). Thirty-two patients underwent inguinal lymph node dissection. The average number of lymph nodes dissected was 15 (Range: 9–25). Bilateral inguinal lymph node dissection was performed in 31 patients, out of which 6 patients had centrally located tumor and 15 patients had disease extending across the midline. Unilateral lymph node dissection was performed in one patient with a well-lateralized tumor at the labia majora.

Radiotherapy was given in forty patients (90%) [Figure 1]. Thirty-two patients (80%) received radical radiation therapy among whom, IMRT was done in 17 (53.1%) patients and conventional radiotherapy was delivered in 15 (46.9%) patients. Eight patients (20%) received palliative radiotherapy. Before 2010, the patients were treated with conventional radiotherapy. Thereafter, the patients were treated with both IMRT and conventional radiotherapy techniques. The choice of treatment with IMRT/conventional radiotherapy was based on logistic and disease-related factors including intent of treatment (radical vs. palliative). Conventional radiotherapy was delivered by Theratron Co-60 machine or by a linear accelerator. Postoperative adjuvant radiotherapy was indicated in 23 patients and among them 14 (60.86%) patients received radiotherapy by (IMRT technique) and nine patients received conventional radiotherapy. Of those treated with conventional radiation, two patients were treated with a wide anterior- and narrow posterior field with matched inguinal electron fields. The rest of the patients were treated with anterior-posterior fields. Eight (16%) patients who were not fit for surgery were offered radical radiotherapy and among them, IMRT was done in two patients, conventional radiotherapy in six patients, and one patient received neoadjuvant IMRT. The target volume comprised of the vulva, inguinal lymph nodes, external iliac, internal iliac, and obturator lymph nodes. For patients receiving adjuvant treatment at a dose of 45 Gy – 50.4 Gy/1.8 Gy/fraction was prescribed to the primary tumor, groin, and pelvic lymph nodes. In patients who underwent adequate inguinal lymph node dissection, irradiation to inguinal lymph nodes was excluded in case of negative or ≤1 lymph node positive. Patients treated with

definitive radiotherapy received a dose of 45 Gy–50.4 Gy over 5 weeks prescribed initially to tumor, pelvic, and inguinal lymph node, followed by 16 Gy–20 Gy in 8–10 fractions to the gross disease (tumor and nodal). Those receiving palliative radiotherapy were prescribed a dose 30 Gy in 10 fractions over 2 weeks.

Chemotherapy was administered to four patients: one patient received neoadjuvant concurrent chemoradiation (with cisplatin) and two patients received neoadjuvant chemotherapy followed by the surgery and adjuvant radiation therapy (IMRT). Adjuvant chemotherapy was administered in one patient, in a view of gross residual disease and inoperability after radical radiation therapy.

Acute Grade 2 and 3 skin toxicities occurred in 13 (86.6%) of the 15 patients treated with conventional radiotherapy. On the contrary, only four (23.5%) of the 17 patients experienced Grade 2 and 3 skin toxicity, when IMRT technique was used ($P = 0.002$ [Figure 2]). Acute Grade 2 mucosal toxicity was observed in two patients and acute Grade 2 gastrointestinal toxicity was seen in one patient treated by conventional technique.

Eight patients treated by conventional methods experienced treatment breaks with a mean break time of 15.5 days (ranging from 2 to 25 days). Further treatment was stopped after 15 radiotherapy fractions in one patient. Treatment compliance was significantly better when IMRT was utilized. Amongst patients treated with IMRT, only one patient had a break in treatment which occurred nearing completion of adjuvant radiation (after 44Gy). No other patients treated with IMRT-experienced treatment interruptions. Chronic toxicity in the form of vaginal fibrosis, and vaginal telangiectasia was seen in three and two patients, respectively, in those treated by conventional methods.

The mean follow-up in patients treated with conventional radiotherapy was 47 months and for those treated with IMRT was 27.5 months. The 2-year disease-free survival was 77.7% and 87.5%, respectively ($P = 0.56$). None of the eight patients who were offered radical radiotherapy in a view of inoperability achieved a complete response.

At a median follow-up time of 25.5 months, the median overall survival was 31 months and the median disease-free survival was 25 months for the entire cohort [Figures 3 and 4]. About 42% patients were alive and free of disease. On comparing the various prognostic factors affecting overall survival of carcinoma vulva patients, that is, age (≤ 60 years vs. > 60 years), Stages (I and II vs. III and IV), lymph node dissection, lymph node status (positive vs. negative), a higher (statistically non-significant) overall survival was observed in patients with favorable factors. Similarly, a higher (statistically non-significant) median local recurrence-free survival was observed

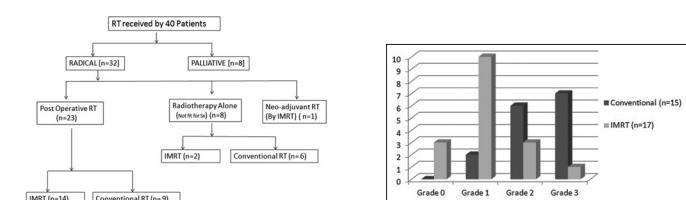


Figure 1: Radiotherapy details

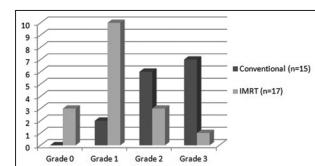
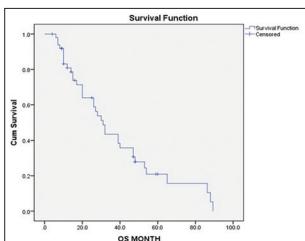
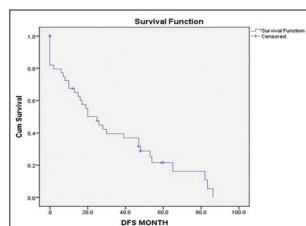


Figure 2: Skin toxicity

**Figure 3: Overall survival****Figure 4: Disease-free survival**

on comparing the prognostic factors affecting the local recurrence-free survival of patients, that is, margin status, lymphovascular invasion, and involvement of midline structures depth of invasion (≤ 5 mm vs. >5 mm).

Discussion

Vulvar cancer is one of the rare gynecological malignancies. Very few studies from India have reported regarding its management. Bafna *et al.*^[5] studied 37 patients of carcinoma vulva among which 33 were of squamous cell carcinoma histology and the majority of patients presented in advanced stages (Stages III and IV). This is in contrary to the European studies and Surveillance, Epidemiology, and End Results report, where most patients present in early stages with localized disease.^[6]

The surgical approach of carcinoma vulva has evolved from radical vulvectomy with inguinofemoral lymph node dissection^[3,7] to radical vulvectomy with bilateral groin lymphadenectomy through separate groin incisions.^[8] Recent studies have shown modified radical vulvectomy to be efficacious for invasive squamous cell carcinoma of the vulva. Hence, the current surgical standard method is modified radical vulvectomy with bilateral groin lymphadenectomy.

Similarly, radiation therapy to treat carcinoma vulva has evolved from the conventional and 3D-conformal radiotherapy modalities to IMRT, which is currently the widely practiced treatment approach for vulvar carcinoma patients treated with a radical intent. IMRT has shown a significant benefit in reducing treatment-related toxicities. Our study was done to analyze our practice and outcomes from the era of conventional radiotherapy to the use of IMRT in vulvar cancer.

Separate electron fields are delivered to cover the inguinal lymph nodes.^[9] Studies have shown that significant acute as well as chronic toxicities arise with the use of conventional radiotherapy techniques in vulvar cancers and often, the dose distribution is unpredictable.^[10] IMRT ensures adequacy of target coverage while reducing doses to the organs at risk. The literature available on using IMRT in carcinoma vulva patients continues to be sparse. The studies in IMRT in vulva by Beriwal *et al.*^[11] reported no Grade 3 or higher acute toxicities with the use of IMRT in vulvar cancer. Various dosimetric studies have also shown that IMRT provides better plans and

decreased toxicity.^[12,10] In our study, patients who received radiotherapy using IMRT technique reported significantly lesser acute Grade 2 and 3 skin toxicities. Furthermore, treatment breaks were significantly reduced compared to conventional treatment. The patients who received radiation therapy by conventional methods experienced late toxicities in the form of vaginal fibrosis and vaginal telangiectasia, but no such complications observed in patients who received IMRT. In the postoperative setting, when comparing the IMRT with conventional therapy, it was seen that the 2 year disease-free survival was comparable (87.5% vs. 77.7%). Thus, although IMRT did not add benefit to survival; however, it reduced treatment-related toxicity.

Conclusion

In our experience from using both conventional radiotherapy and IMRT in vulvar cancers, IMRT results in decreased normal tissue toxicity and hence, should be the preferred radiation modality in vulvar cancers.

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Conflicts of interest

There are no conflicts of interest.

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