Radiotherapy as Definitive Treatment of Patients with Primary Vulvar Carcinoma Unfit for Surgery and with Recurrent Vulvar Carcinoma After Primary Radical Surgery: Results of a Retrospective Single-center Study

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Abstract. Aim: To assess the outcome of patients with vulvar carcinoma unfit for surgery treated with radiotherapy for primary disease and for those with recurrent disease after primary surgery. Patients and Methods: The study was conducted on 16 patients with primary disease and 31 with recurrent disease. Results: An objective response and long-term control were obtained in 43.8% and 18.8% of patients with primary carcinoma. Median survival after primary radiotherapy was 15 months. An objective response and long-term control were achieved in 100% and 20% of the 15 patients with local recurrence. Only two out of the 13 patients with groin recurrence were recovered by salvage treatment, and all three patients with distant recurrence died of their disease. Median survival after relapse in the 31 patients was 33 months. Conclusion: Radiotherapy achieves unsatisfactory results in patients with primary vulvar carcinoma who are unfit for surgery as well as in those with recurrent disease after surgery.

Radical vulvectomy with bilateral inguinal-femoral lymphadenectomy by an en-bloc excision has led to similar survival outcome and a reduced morbidity compared to en-bloc vulvectomy (11-14), and radical local excision with a histologically assessed tumor-free margin of 8 mm is considered to be an adequate treatment for T1 unifocal tumor (4, 5, 7, 15, 16). Furthermore, sentinel lymph node mapping appears to be a safe procedure in selected early-stage cases (17, 18).

Besides being used as adjuvant treatment in surgically-treated patients with positive groin nodes (3, 19, 20), radiotherapy or concurrent chemoradiation have been employed as either definitive treatment in patients unfit for surgery or as preoperative treatment followed by tailored surgery in patients with advanced disease to avoid exenterative procedures (5, 6, 21-26). The total irradiation dose recommended by Thomas et al. is approximately 55 Gy for preoperative treatment and 65 Gy for definitive radical treatment (5). Data from the Surveillance, Epidemiology and End Results on 2,292 women with stage III-IV vulvar cancer showed that the use of primary radiation had increased with time from 18.0% in 1988 to 30.1% in 2008 (26). Among women treated with primary radiotherapy, only 17.8% ultimately underwent surgical resection. Radiotherapy and chemoradiation have also been used in patients with recurrent vulvar carcinoma after surgery, often with palliative intent (23, 27-29). High-energy radiotherapy, electrons and both superficial mold and interstitial brachytherapy have been variously integrated to achieve maximum tumor control and minimum morbidity (24).

The aim of the present retrospective study was to assess the clinical outcome of patients with squamous cell carcinoma of the vulva who were unfit for surgery and treated with radiotherapy or chemoradiation for primary disease, and of those with recurrent disease after primary radical surgery.
Patients and Methods

This retrospective study was conducted on 47 patients with squamous cell carcinoma of the vulva who underwent radiotherapy at the Division of Radiotherapy, University of Pisa between 1999 and 2014. Radiotherapy was used as definitive treatment for primary disease in 16 patients (34.0%) and as salvage treatment for recurrent disease after surgery in 31 patients (66.0%). Six of the latter had received prior adjuvant inguinal-peri-aortic radiotherapy for histologically proven tumor-positive groin nodes.

The stage of each primary tumor case was determined according to the 1988 criteria of the International Federation of Gynecology and Obstetrics (FIGO) (30).

External-beam irradiation (EBRT) was delivered with 6-15 MeV photons, whereas brachytherapy was administered with high dose rate (HDR).

Definitive radiotherapy was used in 16 patients unfit for surgery due to severe comorbidities. Fourteen patients underwent EBRT of the vulvar and perineal area up to a total dose of 54-66 Gy and of the bilateral groins and pelvic lymph nodes (oburator, external and internal iliac nodes) up to a total dose of 45-50.4 Gy in 5-6 weeks. Concomitant chemotherapy with 5-fluorouracil with or without cisplatin was used in five out of these 14 patients (35.7%). Two patients received 21 Gy HDR brachytherapy boost (two daily fractions of 350 cGy) to the vulvar/perineal area after EBRT dose of 45 Gy. The remaining two patients were treated with exclusive interstitial HDR brachytherapy to the vulvar area up to a total dose of 45.5 Gy in 7 days (two daily fractions of 350 cGy).

As far as the 31 patients with recurrent disease are concerned, the site of relapse was local in 15 women (48.4%), inguinal in six (19.3%), and local plus inguinal in seven (22.6%) and distant plus local and inguinal in three (9.7%). Distant recurrence involved the bone in one case, the lung in another and both the bone and the lung in one case. Out of the 15 patients with local relapse, 13 underwent EBRT to the vulvar and perineal area up to a total dose of 54-56 Gy in 5-6 weeks and two were treated with interstitial HDR brachytherapy on vulvar area up to a total dose of 45.5 Gy in 7 days (two daily fractions of 350 cGy).

The six patients with groin recurrence underwent EBRT to the inguinal and pelvic areas up to a total dose of 45-50.4 Gy in 5-6 weeks. Only one patient received concomitant chemotherapies with cisplatin. One woman underwent surgical removal of the groin nodes before EBRT and histological examination showed metastatic involvement of the nodes with extracapsular spread.

The seven patients with inguinal and local relapse underwent EBRT to the vulvar and perineal area up to a total dose of 54-66 Gy and to the inguinal and pelvic areas up to a total dose of 45-50.4 Gy in 5-6 weeks. Concomitant chemotherapies with 5-fluorouracil and cisplatin was added for one patient.

All three women with distant plus local and inguinal relapse received systemic chemotherapies (weekly paclitaxel 60 mg/m²). Moreover, the patient with bone metastases received palliative EBRT to the bone up to a total dose of 30 Gy, the patient with lung metastases received palliative EBRT to the lung up to a total dose of 20 Gy, and the patient with bone and lung metastases received palliative EBRT to the bone up to a total dose of 30 Gy.

Statistical analysis. Recruitment of follow-up data was closed in May 2015. Three prognostic factors (age, FIGO stage, tumor size) were assessed in the survival analysis of the patients treated for primary disease and three factors (age, FIGO stage at presentation, and site of recurrence) were considered in the survival analysis of the patients treated for recurrent disease.

Survival curves were calculated using the Kaplan–Meier method and the log-rank test was used to evaluate the differences between curves. Univariate survival analysis was performed including each variable in a Cox regression model and calculating related p-value by Wald test. The results of the Cox regression were expressed using both the hazard ratio (HR) with its related 95% confidence interval (95%CI) and related p-value. Differences were considered significant at p<0.05. Analyses were performed using SPSS v.22 technology (IBM, Armonk, NY, USA).

Results

The median age of the 16 patients who underwent definitive radiotherapy for primary vulvar carcinoma was 76 years (range=45 to 88 years). FIGO stage was Ib in two cases (12.5%), II in five (31.2%), and III in nine (56.3%). Tumor size was <2 cm in three patients (18.8%), 2.1-4 cm in five (31.2%), 4.1-6 cm in six (37.5%), and >6 cm in two (12.5%).

As far as concomitant disease is concerned, severe cardiopathy was present in 12 women (75.0%), out of whom two had had prior stroke, one prior melanoma, one concurrent meningioma, one severe reumathoid arthritis, one recurrent lung embolism, and one had severe obesity. Out of the remaining four patients, one had lymphatic chronic leukemia, one had amyotrophic lateral sclerosis, one had Wegener's granulomatosis, and one had severe psychiatric disease.

Three patients (18.8%) had complete clinical response, four (25.0%) had a partial clinical response, with an overall response rate of 43.8%, seven (43.8%) had stable disease and two (12.5%) had progressive disease. Out of the three complete responders, two were still alive with no evidence of disease after 13 months and 129 months, respectively, from diagnosis, and one experienced recurrence locally after 11 months and died 4 months later. Out of the four partial responders, one was still alive with disease after 16 months, and the others died of disease after 6 months, 13 months and 19 months, respectively. All nine with stable or progressive tumor following definitive radiotherapy died of disease after a median of 13 months (range=2-52 months).

Median survival of the entire group of 16 women with primary vulvar carcinoma was 15 months (range=2-129 months) (Figure 1). There was a trend for worse survival in patients older than 76 years compared to younger ones (14 months versus 18 months, p=0.063) (Table I). Survival was not associated with FIGO stage and tumor size.

The median age of the 31 patients who underwent radiotherapy for recurrent vulvar carcinoma was 71 years (range=38-88 years). Out of the 15 patients with local relapse, 10 (66.7%) achieved a complete response and five (33.3%) had a partial response. Of the 10 complete responders, three were still alive with no evidence of disease after 74, 108 and 132 months, respectively, from relapse. The
remaining seven complete responders died of disease after a median of 13 months (range=5-23 months). Of the five partial responders, four died of disease after 5, 9, 27 and 46 months, respectively, whereas one patient died of myocardial infarction with prolonged partial response after 19 months.

Of the six patients with groin recurrence, four (66.7%) achieved a complete response and two had stable disease. Of the four complete responders, three died of disease after 4, 9 and 16 months, respectively. The remaining patient, who underwent surgical removal of the groin nodes before EBRT, died of primary lung adenocarcinoma after 104 months with no evidence of groin or local recurrence of vulvar carcinoma. The two patients with stable disease died of disease after 5 and 18 months, respectively.

Out of the seven patients with local plus groin recurrence, five (71.4%) achieved a complete response and two had partial response. Of the five complete responders, four died of disease after 4, 9 and 16 months, respectively. The remaining patient, who underwent surgical removal of the groin nodes before EBRT, died of primary lung adenocarcinoma after 104 months with no evidence of groin or local recurrence of vulvar carcinoma. The two patients with stable disease died of disease after 5 and 18 months, respectively.

All three patients with distant plus local and groin recurrence failed to respond to treatment, and died of disease after 6, 10 and 16 months, respectively.

Median survival after relapse of the entire group of 31 women was 33 months (range=4-132 months) (Figure 2). Survival was significantly better for the patients with FIGO I-II stage compared to those with stage III disease at presentation (54 months versus 23 months, p=0.005) (Table
II). There was a trend for better survival for patients with local recurrence compared to those with other sites of recurrence (median survival=54 months versus 23 months, p=0.098). Survival was not related to patient age.

Discussion

Surgery plays a major role in the treatment of squamous cell carcinoma of the vulva. Primary irradiation or chemoradiotherapy can be used as either neoadjuvant treatment in advanced cases to avoid exenterative procedures or definitive treatment in patients with poor general condition who are unfit for surgery (5, 6, 21-26). In the study of Perez et al. 16 patients with carcinoma of the vulva underwent irradiation alone, obtaining a local tumor control rate greater than 90% in those with T1-3 N0 disease and of 40% in those with T1-3 N1-3 disease (23). In our experience, 16 patients with stage IB-III squamous cell vulvar cancer unfit for surgery due to severe comorbidities underwent definitive radiotherapy. A clinical complete and partial response was obtained in three and four patients respectively, with an overall response rate of 43.8%. However, only three responders were still alive with no evidence of disease at the time of the last follow-up visit. Therefore, long-term control was obtained in only 18.8% of the 16 patients. The median survival for the entire group was 15 months, with a trend for worse survival in patients older than 76 years.

Approximately one-third of patients with squamous cell vulvar carcinoma develop recurrent disease, usually within the first 2 years following primary surgery regardless of adjuvant irradiation (28). The rarity of this malignancy has made it difficult to perform randomized studies to identify the most appropriate treatment modalities, especially for recurrent disease (27). The therapeutic approach mainly depends on the site and extent of recurrence. Most recurrences occur locally near the original resection margins, or at the ipsilateral groin nodes. Isolated local recurrences account for up to 50% of all cases and can be often rescued by surgical resection, whereas those with groin and distant relapses have a poor prognosis (27, 28, 31). For instance, in a large retrospective Italian study on 187 patients with recurrent squamous cell carcinoma of the vulva, the 5-year survival rate was 60% for those with local recurrence, 27% for those with groin and pelvic recurrences, 15% for those with distant recurrences, and 14% for those with multiple recurrences (31). Raffetto et al. retrospectively assessed 20 women with locoregional recurrence of vulvar carcinoma treated with chemoradiation (n=7), neoadjuvant chemotherapy followed by irradiation (n=4) or irradiation alone (n=9), with a total dose of irradiation ranging from 30 to 70 Gy (29). There were six complete responses (30%) and 10 partial responses (50%), and the 5-year overall and disease-free survival for the entire cohort was 20%. Patients with only one site of recurrence, size of lesion ≤3 cm and total radiation ≥64.8 Gy had the best clinical outcome. In the series of Perez et al., radiotherapy alone obtained local tumor control in four out of the 17 patients (27%) with recurrent vulvar cancer, with an actuarial 5-year disease-free survival rate of 11% (23).

In our experience, long-term control was achieved in only 20% of the 15 local recurrences. Only one (16.7%) out of the six patients with groin recurrence and only one (14.3%) out of the seven patients with local plus groin recurrence were recovered by salvage treatment, and all three patients with distant recurrence died of disease. There was a trend to a better survival for patients with local recurrence compared with those with other sites of recurrence.

Literature data have shown that irradiation and chemoradiation lead to good response rates for advanced squamous cell carcinoma of the vulva, and sometimes allow ultraradical surgical procedures to be avoided if employed as neoadjuvant treatment before surgery (5, 6, 21-25). However, definitive radiation therapy achieves unsatisfactory results in patients with primary vulvar carcinoma and debilitating medical conditions precluding surgery as well as concomitant chemotherapy. The use of the newer radiation therapy techniques (32, 33) such as intensity-modulated radiation therapy should reduce radiation-related morbidity thus enhancing tolerance to chemoradiotherapy, allowing this treatment in a higher number of women. Isolated local recurrences should be preferentially treated with wide local excision. Groin recurrences without prior adjuvant irradiation should undergo surgery followed by radiotherapy or chemoradiation, whereas in patients with previous groin irradiation, any excisional procedures should be avoided because of the high rate of complications and brachytherapy should be used for palliation in highly selected cases (27). Radiotherapy and chemotheraphy achieve very dismal results in patients with distant or multiple recurrences (6). Management of this rare malignancy requires a multidisciplinary approach to appropriately optimize therapy.

References


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