

Carcinoma of the Vulva: Clinical Results of Exclusive and Adjuvant Radiotherapy

VINCENZO TOMBOLINI², NICOLA RAFFETTO¹, MARIO SANTARELLI¹,
MAURIZIO VALERIANI², STEFANO NECOZIONE³,
FRANCESCO MASEDU³ and R. MAURIZI ENRICI¹

¹Department of Radiology, University of Rome "La Sapienza";

²Department of Experimental Medicine, Radiotherapy Unit of S.Salvatore Hospital, L'Aquila;

³Department of Internal Medicine and Public Health, University of L'Aquila, Italy

Abstract. *Background:* The aim of this study was to evaluate the historical cohort of 61 patients with carcinoma of the vulva, treated with radiation therapy from 1986 to 1997. *Patients and Methods:* Twenty-seven patients were submitted to radiation therapy alone and 34 received radiotherapy post limited surgery in early stages and post radical vulvectomy in advanced stages. The dose range varied from 59 to 63 Gy in post-operative patients and 65 Gy to 71 Gy in curative patients. *Results:* Five-year Overall Survival (OS) and Disease-Free Survival (DFS) for patients treated with irradiation alone and for those treated with post-operative radiotherapy were 50.8% and 69.7%, respectively, without significant statistical difference. For OS multivariate analysis showed statistical difference for stage and age variables, and for stage variable in the case of DFS. *Conclusion:* In early stage vulvar cancer patients OS and DFS are good, with high control rate and low incidence of adverse effect. In loco-regionally-advanced patients, especially in those with stage IV or with >2 positive lymph nodes, the outcomes are poor.

Vulvar cancer accounts for approximately 4% of gynaecological malignancies. The aetiology of vulvar cancer is unclear, however many risk factors such as obesity, hypertension, diabetes mellitus, antecedent infections and human papilloma virus have been indicated.

If diagnosed at an early stage, vulvar cancer can successfully be treated in a high percentage of cases. Surgery has been the therapy of choice: *en bloc* radical vulvectomy

Correspondence to: V. Tombolini, U.O. Radioterapia, Ospedale S. Salvatore, Via Vetoio 67100 - Coppito - L'Aquila, Italy. Tel/Fax: +39/0862/368797, e-mail: tmbolini52@ciaoweb.it

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and bilateral inguinal-femoral lymph adenectomy has been the standard operation since the first half of the century (1), achieving excellent cure rates of up to 60-70%.

When the disease is loco-regionally advanced, involving the urethra, bladder, anus and rectum, the only surgical option is partial or total exenteration with radical vulvectomy and inguinal-femoral lymph adenectomy, but reported survival rates are poor, ranging from 12% to 70%, depending on patient selection (2-6).

Radiotherapy may play an important role in the reduction of loco-regional recurrence after surgery. In patients who are medically inoperable or refuse intervention and in loco-regionally advanced disease to avoid exenteration, radiation therapy may be curative when used as the exclusive therapeutic approach, its goal being to match curability with cosmetically and functionally excellent results.

Patients with vulvar cancer treated in our institution with exclusive and post-operative radiation therapy were analysed retrospectively. The study was designed and conducted as a historical cohort investigation.

Patients and Methods

A historical cohort of 61 consecutive patients with carcinoma of the vulva, treated from 1986 to 1997 at the Radiotherapy Division, Institute of Radiology, "La Sapienza" University of Rome, Italy, was evaluated retrospectively. The age of patients ranged from 64 to 89 years (average 74 years and median 75). Cases, biopsy proven, treated with radiotherapy alone, were evaluated on clinical and radiological research, while pathological specimen from patients submitted to surgery were evaluated, according to TNM and FIGO criteria. All patients had chest radiographs, complete blood count and chemistry analysis and colposcopic examination. Cystoscopy was performed on 56 patients; abdominal pelvic CT and echotomography were used on all patients; from 1994, also abdomino-pelvic MR was performed in 12 cases. The histological type corresponded in all cases to epidermoidal carcinoma, well-differentiated in 65%, moderately in 29% and anaplastic in 6%.

Cumulative Survival

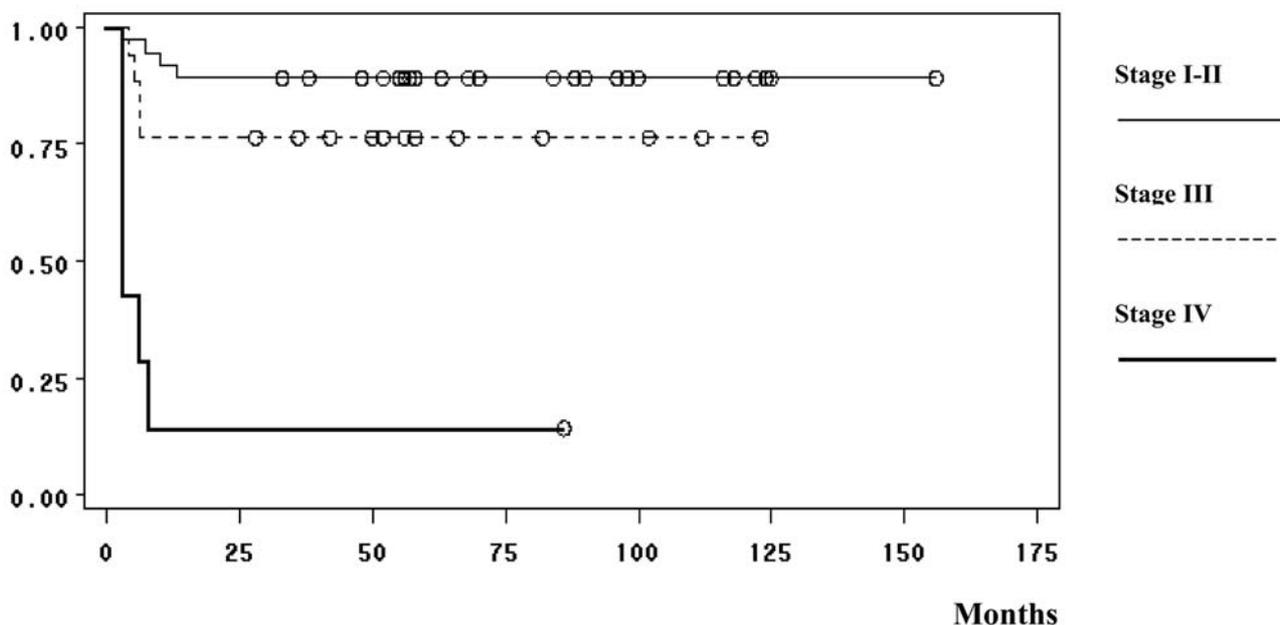


Figure 1. Diseases-free survival for stage.

Twenty-seven patients (44.3%) had radiation therapy alone: 5 (8.2%) cT1N0, 7 (11.5%) cT2N0, 3 (4.9%) cT2N1, 8 (13.1%) cT3N0-N1, 2 (3.3%) cT3N2 and 2 (3.3%) cT4N1. These patients were older than those submitted to surgery (median 79 years, average 78, range 70-89); 15 (24.6%) had mild-severe medical associated problems (heart and cardiopulmonary disease, diabetes) and 10 (16.4%) patients refused surgical intervention.

Thirty-four patients (55.7%) received post-operative irradiation: 10 (16.4%) pT1N0 post wide local excision and 15 (24.6%) pT2N0 post simple vulvectomy, since local excision in T1 patients and simple vulvectomy in T2 patients is not considered safe by our Institute. Five (8.2%) pT3N0-N1 patients, 3 (4.9%) pT3N2 and 1 (1.6%) pT4N1 post radical vulvectomy were submitted to surgery due to groin dissection and resection margins <10 mm (4 pz) or primary tumour >4 cm (5 pz).

The number of inguinal positive nodes was ≤2 in 11 patients, >2 in 7 patients.

The initial localization of the tumor was: labia major and minor in 50 patients (82%), clitoris in 8 (13%) (3 with labia major) and fourchette 3 (5%) (2 with labia).

The radiotherapy technique was similar during all the years of the study. Patients were treated in the supine position up to a dose of 45 Gy and, for the boost on the primary site of tumor, in supine frog leg position, with patient's thighs abducted and rotated. External beam radiation therapy to a dose of 45 Gy (minimum 4320 cGy, maximum 4680 cGy, 1.8-2 Gy daily) was delivered to all patients through anterior-posterior (AP-PA) field, using X-photon, 6-15 MV, including primary vulvar tumour, inguinal femoral lymph nodes and lower pelvic nodes, with the upper margin at the bottom of S3 and inferior edge to a minimum of 2 cm from the visible tumour. The lateral margin of the anterior-posterior portals were at 1.5-2 cm from the lateral borders of true pelvic side walls. In most of the patients,

3:2 AP-PA loading was used, in order to increase the dose to the inguinal lymph nodes; a bolus over the primary site was sporadically used. For patients submitted to radiotherapy alone, a boost of 20-26 Gy (median 24 Gy), 2 Gy daily, was administered to the primary tumour and/or positive inguinal nodes with an electron beam reduced portal of energy of 8-18 MeV or X-photon of 6-15 MV, depending on the depth of tumour and inguinal nodes, with a minimum margin of 1 cm. The depth of prescription in the groin for electron-beam therapy was calculated at 3 cm, if patients were N0 and at maximum depth of the nodes seen in echotomography or TC in N+ patients.

In patients submitted to postoperative radiation therapy, a boost of 14-18 Gy / 2 Gy daily (median 16 Gy) was given with en face electron field or X-photon reduced portals to the area of the primary tumour.

Statistical analysis. Survival analysis was used to describe the global mortality of the cohort. Failure-time analysis of prognostic factors was carried out both by univariate and multivariate statistical methods. Univariate analysis (product-limit method) was used to calculate survival probabilities in relation to four clinical variables (stage, lymph nodes, radiotherapy, stage+radiotherapy). Differences between survival curves were assessed using the log-rank test. In the calculation of disease-free survival (DFS), patients dead for causes other than disease were considered as alive at the last follow-up. Relative hazards and 95 percent confidence intervals for prognostic factors (age, lymph nodes, stage, radiotherapy) were calculated with the use of univariate and multivariate Cox proportional-hazard regression models.

In multivariate Cox models, due to high correlation between lymph nodes and stage variables and in order to avoid collinearity, stage was selected as the most clinically relevant variable (7).

All procedures were performed using the SAS/STAT software (8).

Cumulative Survival

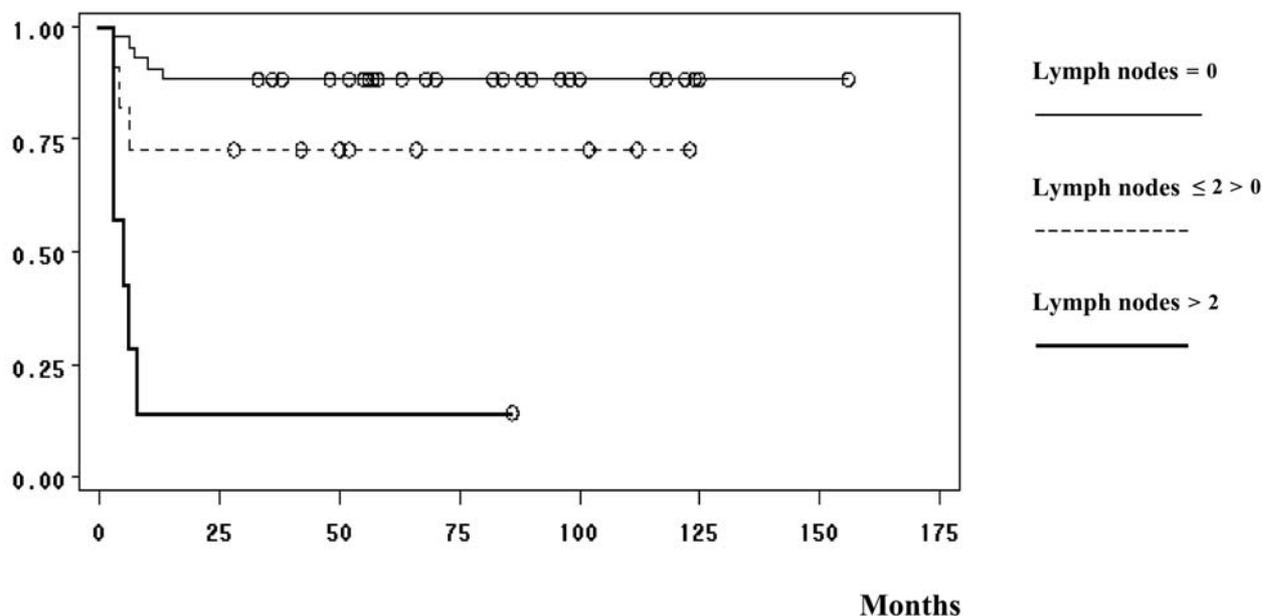


Figure 2. DFS for number of positive lymph nodes.

Results

The median follow-up was 86 months (range 58-116 months).

In the group of 27 patients treated exclusively with radiotherapy, 5-year overall survival (OS) and disease-specific survival (DSS) were respectively 50.8% and 70.4%; 16 (59.2%) patients died, 8 (29.6%) of other causes and 8 (29.6%) of relapse: 2/7 stage II, 3/11 stage III, 3/4 stage IV. In the group of 34 patients submitted to radiotherapy after surgery, 5-year OS and DSS were 69.7% and 82.3%, respectively; 20 (58.8%) patients died, 14 (41.2%) of other causes and 6 (17.6%) of disease: 2/15 stage II, 1/5 stage III, 3/4 stage IV. Between these two groups, no statistical difference in terms of OS and DSS ($p=0.0933$ and 0.2994 , respectively) was found.

Five-year OS and DSS in stage I-II patients were 71.6% and 89.2%, respectively, in stage III 58.4% and 76.5%, and in stage IV both were 14.3%. There was statistical difference in terms of OS and DSS between stage I-II, III and IV in all patients ($p<0.0001$) (Figure 1).

In the women submitted to post-operative irradiation, 5-year OS in stage I-II was 74.5%, in stage III 80%, and in stage IV 25% ($p=0.0008$) and 5-year DSS was 92%, 80% and 25%, respectively ($p=0.0016$). In patients with exclusive radiotherapy, 5-year OS was 65.6%, 43.7% and 33.3%, respectively, for stage I-II, III and IV ($p<0.0001$), and 5-year DSS was 83.3%, 75% and 33.3%, respectively ($p<0.0001$).

Table I. Results of Cox proportional-hazard models.

Disease-Free Survival (DFS)				
Variable	Hazard Ratio Univariate (95% CI)	<i>p</i>	Hazard Ratio Multivariate (95% CI)	<i>p</i>
Age				
≤70	1.00 (reference group)	0.372	1.00 (reference group)	0.867
>70	1.97 (0.44-8.84)		1.15 (0.23-5.80)	
Lymph nodes				
≤2	1.00 (reference group)	<0.0001	-	-
>2	10.86 (3.60-32.76)			
Stage				
I, II, III	1.00 (reference group)	<0.0001	1.00 (reference group)	<0.0001
IV	11.39 (3.78-34.38)		12.69 (3.94-40.85)	
Radiotherapy				
Exclusive	1.00 (reference group)	0.313	1.00 (reference group)	0.202
Post-operative	1.72 (0.60-4.90)		2.06 (0.65-6.56)	

In patients with N0 5-year OS was 67.6%, in those with $\leq 2 > 0$ positive lymph nodes it was 72.7% and in women with > 2 positive lymph nodes it was 14.3% ($p < 0.0001$); DFS was 88.4%, 72.7% and 14.3%, respectively ($p < 0.0001$) (Figure 2).

In the Cox model analysis, stage I-II patients were grouped with stage III patients and, N0 with $\leq 2 > 0$ positive-lymph-node patients since they presented a similar outcome in univariate analysis (log-rank) in terms of both OS and DFS; these two new groups were compared with stage IV and > 2 positive-lymph-node patients, respectively. The results of univariate and multivariate analysis with Cox proportional-hazard models are shown in Table I.

Patterns of failure. Fourteen patients (23% of total), 8 (29.6%) after radiotherapy alone and 6 (17.6%) after post-operative radiotherapy, experienced a failure after a median time of 9 months (range 3-17). All 14 patients died of disease after 6-24 months (median 16 months) from the end of primary therapy. No relapse was registered in 15 stage I patients regardless of therapy, while in 22 stage II patients the rate of relapse was 28.6% in the 7 women submitted to radiotherapy alone and 13.3% in the combined therapy group. Tumour control at the vulvar primary site was 85.2%, with 4/27 (14.8%) recurrence in the exclusive radiotherapy group and 5/34 (14.7%) in the post-operative irradiation group. Tumour control at the inguinal lymph nodes was 82%, with 6/27 (22.2%) recurrence in the exclusive radiotherapy group and 5/34 (14.7%) in the combined therapy group.

Tumour recurrence at pelvic nodes in N0 patients was 7% (3/43), 1 marginal (at level of S3) and 2 inside the field of irradiation, in 2 cases associated with lumbar-aortic lymph nodal recurrence and in 1 with pulmonary metastases.

In the N1-N2 patient group, pelvic recurrence was observed in 5/18 (28%), 2 marginal, 2 inside and 1 outside (at level of L5-S1) the field of irradiation, and associated with lumbar-aortic lymph node recurrence in 1 patient.

Distant metastases were recorded in 8 patients (13%). The incidence of distant metastases in N0 patients was 4.6% (2/43), while in N1-N2 patients it was 33.3% (6/18). One patient T4N2 submitted to exclusive radiotherapy developed only distant metastases 3 months after the end of radiation therapy, with no evidence of local disease; in the other 7 patients, distant metastases were associated with recurrence at the primary site in 4 cases and/or at the groin in 2, and/or at the pelvic lymph nodes in 4.

Morbidity. Acute treatment morbidity included 12 (19.7% of total) grade 2-3 proctitis, 10 (16.4%) grade 2-3 cystitis, 21 (34.4%) moist desquamation and 6 (9.8%) vulvar infections. Interruption of radiation therapy because of cystitis and/or

proctitis was necessary for up to 14 days (range 4-14 days, median 7 days) in 19 patients (31.1%).

Late toxicity included 7 (11.5%) moderate leg oedema, 6 (9.8%) vaginal stenosis and 1 (1.6%) recto-vaginal fistulae.

Leg oedema was recorded in 3/9 (33%) patients irradiated after radical vulvectomy and lymph adenectomy, in 2/15 (13%) patients irradiated after simple vulvectomy, and in 2/27 (7.4%) patients submitted to exclusive radiotherapy. Vaginal stenosis was observed in 5/27 (18.5%) patients treated with exclusive radiotherapy and in 1/15 (6.7%) patients treated with radiotherapy after local excision. Recto-vaginal fistula was observed in 1 patient submitted to radiotherapy after biopsy (total dose: 70 Gy). Hip fractures or other hip complications were not observed.

No surgical corrections for rectal stricture, skin necrosis, rectal or vaginal necrosis were reported.

Discussion

In carcinoma of the vulva the treatment of choice is generally radical surgery, with inguinal and femoral lymph adenectomy in more advanced stages (9-10). Since the major proportion of failures after surgery is local or loco-regional, radiotherapy, pre- or post-operatively, may play an important role. The main risk factors for recurrence in the vulva are surgical margins less than 8 mm and tumour size greater than 2 to 4 cm (11-14), while the most important prognostic factors for survival are the presence and the number of lymph node metastases, which cause a 50% reduction in long-term survival (12-18). Curative radiotherapy is difficult to evaluate in terms of the number of studies carried out, heterogeneity of dosage and schedule, and in terms of different criteria for patient selection (19-25).

In our series, stage I-II patients showed similar 5-year OS and DFS when treated either with limited surgery plus radiotherapy or with radiotherapy alone. However, the patients with T2N0 treated exclusively with radiotherapy had double the recurrence rate (28%) when compared to those treated by simple vulvectomy plus radiotherapy (13%), but the small number of patients did not allow clear conclusions. Balat *et al.* (10), in their study of 73 patients with vulvar cancer, reported 52% 5-year DFS in stage II-IV patients treated with radiotherapy post wide local excision, without significant difference in the 5-year DSS and OS between radiotherapy post excision and radical vulvectomy with bilateral lymph adenectomy plus pre- or post-operative radiotherapy. Perez *et al.* (23) noted, in patients with biopsy-local excision and irradiation, an actuarial 5-year DFS of 87% for T1N0, 62% for T2-3N0 and 30% for T1-3N1: the doses higher than 50 Gy were associated with slightly better tumor control. No statistical difference was observed for OS and DSS in our stage III and in stage IV patients between

those who underwent radiotherapy alone and those subjected to radical surgery plus radiotherapy, although the former were clinically staged and the latter had adverse prognostic factors, such as inadequate resection margins and/or primary tumour >4 cm.

There is no agreement as to whether or when it is necessary to irradiate all pelvic nodes, lower pelvic nodes from S3 or only groin nodes in patients with clinically negative or positive nodes (23-25). We treated all patients on lower pelvic nodes up to the bottom of S3. No recurrence was observed in 15 T1N0 patients, whereas 3/22 (13.6%) stage T2N0 patients experienced pelvic recurrence. The incidence of pelvic node recurrence in N0 patients was 7% (3/43), and in N1-2 patients 28% (5/18). In 11 patients with ≤ 2 positive inguinal nodes, the incidence of pelvic node recurrence was 18% (2/11), while in 7 patients with number >2 it was 43% (3/7): the difference between these two subgroups was significant in terms of OS and DFS. In our series, 3 of the 8 pelvic recurrences were marginal, at the level of S3, and 1 outside, at the level of L5-S1, the field of irradiation. It seems reasonable that, at least in patients with positive groin nodes, pelvic nodes must be irradiated up to the bottom of L5.

Univariate analysis of our series evidenced statistical difference in terms of stage, number of positive lymph nodes and age for OS, while age was not significant for DFS. This difference between OS and DFS regarding age may be explained by the relatively high rate of intercurrent deaths, without recurrence of disease, in patients with a median age >70 years, which therefore influenced OS analysis (in contrast, for DFS, patients who died due to causes other than disease were considered alive at the last follow-up). The high hazard ratio (10.86) in terms of DFS for patients with >2 positive lymph nodes indicated a very poor prognosis in this group, even if the small number of patients examined does not permit extrapolation to a definitive conclusion. The multivariate analysis confirmed the statistical significance of the age variable for OS, and IV stage proved to be an adverse prognostic factor in terms of both OS and DFS. The type of therapy was not statistically significant. In T3-T4, N0-N2 patients of the current series, local control was poor. We observed 5/12 (41.7%) loco-regional relapses in the group submitted to radiotherapy alone and 4/9 (44.4%) in the group submitted to radical vulvectomy followed by radiation therapy. The rate of distant metastases was also high, that is 33.3% (6/18) in N1-N2 women, in comparison to 4.6% (2/43) of N0. In advanced stage vulvar carcinoma, radical surgery and/or radiotherapy do not seem to ensure good rates of local control and survival; concurrent chemo-radiotherapy, especially if used in a pre-operative manner, seems to be the treatment of choice with a major response of 40-67% (24, 26-30). Akl *et al.* (31) reported 100% of complete response

to chemoradiation as primary treatment for early stage T1-T3, N0 vulvar carcinoma, with 3-year DFS of 84%. The Gynecologic Oncologic Group GOG study by Moore *et al.* evidenced 46.5% of patients with no visible cancer at the time of planned surgery (24) after pre-operative chemoradiation for advanced vulvar cancer.

The morbidity of radiation therapy in our series was low, without statistical difference between the sub-groups, and was similar to other analyses (10, 22, 31). Leg oedema was more frequent in patients irradiated after radical vulvectomy and lymph adenectomy. Vaginal stenosis was observed mainly in patients submitted to exclusive radiotherapy (5/27, 18%), without significant symptoms. No rectal stricture was recorded. In conclusion, in patients with stage I-II vulvar cancer, radiotherapy alone or post limited surgical intervention yields good results with high control rates, low incidence of adverse effects and high quality of life. In patients with locally advanced tumours, radiotherapy alone or radical surgery followed by radiation therapy have similar but poor results, especially in those patients with stage IV or with >2 positive lymph nodes.

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