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Prognostic role of inguinal lymphadenectomy in vulvar squamous carcinoma: younger and older patients should be equally treated. A prospective study and literature review

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HIGHLIGHTS

- Prognostic role of nodal status in very elderly patients also.
- Number of positive nodes and of lymphnodes removed impact survival.
- Literature review about variable associated to nodal status and lymphadenectomy.

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ABSTRACT

Objective. This study analyzed the prognostic significance of nodal involvement in vulvar squamous carcinoma and its correlation with other prognostic factors, focusing the research on comparison between <75 and ≥75 years old patients.

Methods. We prospectively enrolled patients with >1-mm-deep stromal invasion, Ib–III stage vulvar cancer. Patients underwent unilateral or bilateral inguinal lymphadenectomy, according to tumor localization.

Results. In total, 131 patients met inclusion criteria; 93 (71%) underwent bilateral and 38 (29%) unilateral lymphadenectomy with 36 (27%) of them presenting nodal disease. At Kaplan–Meier analysis factors associated to prognosis were nodal status (in very elderly patients also) and number of resected nodes both in bilateral and unilateral lymphadenectomy groups. In univariate analysis, covariates associated with survival included age, in terms of overall survival (OS) but not with disease free-survival (DFS) and disease-specific survival (DSS), grading, nodal status, the presence of bilateral nodal metastases, the number of resected nodes in both unilateral, in terms of OS and DSS but not of DFS and bilateral lymphadenectomy and the number of metastatic nodes. In multivariate analysis covariates associated with survival were age, the number of positive nodes and the number of resected nodes in bilateral lymphadenectomy.

Conclusions. Results confirm the prognostic role of nodal status in very elderly patients also. Although DSS in older patients resulted worse, lymphadenectomy is not associated with more complications, suggesting its importance in older patients too. Furthermore, the resection of less than 15 lymph nodes in bilateral lymphadenectomy seems to have a negative impact on survival.

1. Introduction

Vulvar cancer represents 4% of all female gynecologic malignancies with 4580 estimated new cases and 1030 deaths in USA in 2014 [1].

Most of vulvar carcinomas are squamous cell carcinomas (SCC).

This tumor predominantly occurs in elderly women; 54% of patients with the diagnosis of vulvar carcinoma are 70 years or older; no more than 15% are younger than 50 years [2,3].

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Until 1980, the standard treatment of vulvar cancer consisted of en bloc radical vulvectomy and bilateral dissection of the upper and deep groin lymph nodes, even if associated with high morbidity rates. From that time on, surgeons began to implement a less invasive surgery, trying to ensure better aesthetic results with the development of different techniques without compromising cancer-related outcome.

These surgical innovations have led to lower morbidity and complication rates while the local recurrence rate has remained unchanged.

Lymph-nodal spread represents one of the most important prognostic factors for vulvar carcinoma, such as FIGO staging system revised the classification in 2009, including all cases with nodal involvement in all stage (irrespective of tumor diameter) [4].

Lymph-nodal status is strictly related to other parameters such as tumor size, depth of stromal invasion, histological grade, and lymph vascular space involvement [5–12]. Generally, lateralizing lesions (>1 cm beyond the midline) drain to the ipsilateral superficial inguinal lymph nodes, whereas midline lesions can drain to either side [9].

Therefore, the indication to inguino-femoral lymphadenectomy is limited to patients with more than 1 mm of stromal invasion and contralateral inguinal lymphadenectomy could be safely omitted for lateral tumors when ipsilateral lymph nodes are negative [13].

Furthermore, in an effort to reduce the almost inevitable inguinal dehiscence, other variations were proposed regarding groin lymphadenectomy technique.

Some authors have recommended either the use of sentinel node sampling [14] or superficial nodal dissection with saphenous vein preservation [15].

Due to the lack of established long-term oncologic outcomes as well as experience with sentinel node procedures in most centers, this approach remains experimental.

On the other hand, patients undergoing superficial inguinal node dissections have been reported to have a slight but significant increase in the rate of inguinal recurrences compared to those having a complete groin dissection [4,16].

In this prospective study we reported our experience about lymphadenectomy in vulvar squamous carcinoma, evaluating characteristics of lymph-nodal involvement in this tumor, its prognostic role and its possible correlation with other prognostic factors. Moreover we analyzed the role of nodal status in patients older than 75 years, usually defined as very elderly population [17].

2. Materials and methods

We prospectively enrolled patients affected by invasive SCC of the vulva who were amenable to radical surgery comprehensive of inguinal lymphadenectomy. Patients were afferent to “Campus Biomedico” University of Rome and “Sapienza” University of Rome and were recruited from 1998 to 2012. The study protocol was approved by the ethical committee. Written informed consent was obtained from all patients. Eligibility criteria were as follows: histologically documented squamous vulvar carcinoma with >1-mm-deep stromal invasion; stages Ib–III, according to the International Federation of Gynecology and Obstetrics (FIGO) new classification (all patients treated before 2009 were restaged according to the new criteria), performance status 0–2 according to ECOG classification, and informed consent to treatment and follow-up. Ineligibility criteria were as follows: unresectable disease; distant metastasis (other than pelvic lymph-nodes); impaired renal (creatinine clearance <50 ml/min) or hepatic function tests (transaminase level elevated more than 1.5 times the upper limit of normal range); other severe systemic diseases significantly limiting treatment feasibility or other concomitant malignancies. Preoperatively, all patients underwent complete diagnostic workup, consisting of complete history, physical and gynecologic examination, complete laboratory analyses, electrocardiogram and chest X-ray. Total-body computed tomography (CT) scan was carried out in order to exclude distant metastases and vulvoscopy was performed to estimate local tumor extension. Patients with lateralizing lesions underwent unilateral superficial and deep inguino-femoral lymphadenectomy if ipsilateral nodes were negative at frozen section analysis; in the other cases a bilateral nodal resection has been carried out.

Lymphadenectomy started with a 7–9-cm-long skin incision parallel to the inguinal ligament. The incision was performed about 3 cm above the inguinal cutaneous fold.

The subcutaneous tissue was cut down to Camper's fascia, which was identified, incised, exposed, and tapered by Kelly clamps.

Inguinal skin flaps were prepared by resecting all the lympho-fatty tissue from the inferior border of the superficial Camper's fascia, whereas the tissue above was not resected, in order to obtain two well-perfused skin flaps to avoid skin necrosis.

Clinical data analyzed were age, type of vulvar surgery and lymphadenectomy. Pathological evaluation included tumor size, depth of invasion, number of resected nodes, tumor stage, grading and nodal involvement. All data were accurately stored in an appropriate database. Disease-free survival (DFS) was defined as the time from surgery to the date of recurrence or last follow-up. Overall survival (OS) was defined as the time from surgery to the date of death or last follow-up.

Disease-specific survival (DSS) was the time from surgery to the date of death due to vulvar cancer or last follow-up. The association between parametric variables was assessed by chi-square or Fischer's exact test. Overall survival was estimated by the Kaplan–Meier method. Survival curves were constructed by life table with log-rank significance test. A Cox proportional hazards model was used to adjust the prognostic role of the factors considered for multiple parameters.

The results had been considered statistically significant when p value was less than 0.05.

3. Results

In total, 163 consecutive patients affected by histologically documented invasive squamous vulvar carcinoma were enrolled into the study.

Among these patients 32 did not meet inclusion criteria: 22 presented too extensive and/or metastatic disease (16 of these underwent neoadjuvant chemotherapy), 10 were excluded for poor performance status or for important concomitant pathologies leading them to be not amenable to surgical procedure. Median age was 69,5 (range 48–90).

Seventy-nine patients (60%) were younger than 75 years, while 52 patients (40%) were older than 75 years (thus considered as very elderly patients).

Eight patients (6%) underwent wide local excision, 57 (44%) hemivulvectomy and 66 (50%) radical vulvectomy; in all cases unilateral or bilateral lymphadenectomy was performed. Lymphadenectomy was bilateral in most of the cases (93 patients, 71%) and unilateral in the remaining (38 patients, 29%). Clinical, surgical and pathological characteristics are reported in Table 1. Postoperative complications, related to inguinal lymphadenectomy, occurred in 43 patients (33%): in 24 out of 79 (30%) patients younger than 75 years and in 19 out of 52 (33%) patients older than 75 years, with no statistically significant difference (p = NS). Among these 43 patients, 45 complications occurred consisting of 26 (58%) wound breakdown, 11 (24%) lymphedema, 4 lymphocyst (9%) and 4 deep venous thrombosis (9%);

2 patients had both wound breakdown and lymphedema. No intra or postoperative death occurred. Median follow-up was 80 months (1–187). In total, 47 (36%) deaths have been recorded, of which 35 were due to cancer. The median number of resected nodes was 18 (range, 4–43) per patient: 23 (range, 10–43), when a bilateral lymphadenectomy was performed, 12 (range 4–19) when the lymphadenectomy was unilateral.

All patients amenable to unilateral lymphadenectomy, having metastatic nodes at frozen section, were subjected to contralateral lymphadenectomy and consecutively to adjuvant chemotherapy. In total lymph-nodal metastases were histologically verified in 36 (27%)