Tailoring the Treatment of Locally Advanced Squamous Cell Carcinoma of the Vulva: Neoadjuvant Chemotherapy Followed by Radical Surgery

Results From a Multicenter Study

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Objective: To determine the feasibility of performing neoadjuvant chemotherapy (NCH) followed by radical surgery in patients with locally advanced squamous cell carcinoma of the vulva.

Methods: Prospective and multicenter trial. Thirty-five patients with a diagnosis of previously untreated locally advanced squamous cell carcinoma of the vulva were given 4 schemes of cisplatin-based NCH and 1 NCH regimen with single bleomycin. Then, they underwent radical surgery of the vulva if clinical response was 50% or more. Age, NCH schemes used, toxicity, response to treatment, type of radical surgery performed, and clinical outcome were evaluated.

Results: Thirty-three patients completed the proposed schemes, and 30 were assessed for radical surgery. Finally, 27 patients underwent radical surgery (radical vulvectomy or radical local excision plus bilateral inguinofemoral lymphadenectomy). In 2 cases of persistent rectal involvement, posterior pelvic exenteration was performed. Moreover, 24 of 27 patients remain with no evidence of disease to date. Toxicity was acceptable. Median age was 62 years (range, 54–72 years). Median follow-up was 49 months (range, 4–155 months).

Conclusions: The use of NCH in selected groups may increase surgical feasibility in initially inoperable patients, thus favoring organ preservation and less extensive resections. Adverse reactions were acceptable, and vulvoperineal deleterious effects that may occur after radiotherapy were consequently avoided.

Key Words: Vulvar cancer, Radical surgery, Neoadjuvant chemotherapy

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Carcinoma of the vulva is an uncommon type of cancer, accounting for approximately 4% to 5% of all gynecological malignancies.[1] An estimated 27,000 cases are diagnosed worldwide each year. Incidence declined slightly between 1975 and the mid-1980s to then rise again in the mid-1990s. This is probably due to the higher incidence in young

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women, which has doubled in the past 30 years and is closely related to the induction of human papillomavirus to vulvar intraepithelial neoplasia.[2] The mean age at diagnosis is approximately 70 years,[3] and approximately 75% are squamous cell carcinomas.[4] Although no precise figures have been recorded in Argentina, it is estimated that approximately 1100 new cases are diagnosed each year.[5]

Although vulvar cancer can be cured by means of early detection and proper treatment, it is estimated that 30% to 35% of cases of vulvar cancer will be diagnosed in International Federation of Gynecology and Obstetrics stage III or IV and will require radiation therapy, either primary in unresectable tumors or adjuvant in patients with positive nodes.[4] This percentage is maintained for patients with advanced disease considered unresectable by standard vulvar radical surgery. This entity has not been clearly defined yet, and the definition varies among authors. We have called locally advanced squamous cell carcinoma of the vulva (LASCCV) the inoperable clinical presentation.[6] That is, when radical surgery of the vulva will not remove the tumor successfully with free margins, except for any type of exenterative surgery. This definition might also include those cases in which it is necessary to perform resection of the urethra, the vagina, or the anus without urinary or digestive derivation to achieve adequate radicality. In other words, if the intervention to achieve adequate surgical margins requires resection of the urethra, the vagina, or the anus, with or without exenterative surgery, we would be dealing with LASCCV. Several authors have included both previously untreated and recurrent tumors in the definition.[7–9]

Treatment options include radical primary surgery, pelvic exenteration (ultraradical surgery), radiotherapy (primary or neoadjuvant), concurrent chemoradiation (primary or neoadjuvant), and NCH. The latter option, reported only in a few studies,[10–19] has not been widespread. The aim of this study was to determine the feasibility of performing NCH followed by radical surgery in patients with previously untreated LASCCV.

MATERIALS AND METHODS

The prospective trial was conducted by 2 centers in the Autonomous City of Buenos Aires, Argentina. Two hundred thirty-seven patients were assessed between January 1998 and December 2011 at the Department of Gynecologic Oncology, Oncologic Hospital of Buenos Aires Marie Curie, and the Unit of Gynecologic Oncology, Parmenio Piñero Hospital. Participation in the study was limited to patients with clinical definition of LASCCV, that is, inoperable disease (at least initially). This applies when a standard radical surgery of the vulva will not be useful to remove the tumor with free margins, and so large resections of adjacent organs or any type of exenterative surgery is required. The presence of fixed and/or ulcerated inguinal nodes has been included as part of the definition of LASCCV. Thus, 91 of 237 patients had this diagnosis.

In addition to the definition of LASCCV, the eligibility criteria included absence of concomitant neoplasia, primary tumor, previously untreated tumor, Eastern Cooperative Oncology Group performance status 2 or less and normal renal, hepatic, and hematological functions before treatment. These patients were considered able to tolerate chemotherapy courses and radical surgery including bilateral lymphadenectomy. Before recruitment, the protocol was approved by the respective ethics committees of both participating centers. All the patients signed an informed consent; also, possible therapeutic options as well as the benefits and drawbacks of each of the procedures were fully explained to both patients and their relatives. Neoadjuvant chemotherapy regimens were chosen according to our experience with other squamous cell carcinomas, especially cervical cancer. They were discussed with patients at the time of recruitment.

Neoadjuvant chemotherapy schemes used are shown in Table 1. Age, NCH schemes used, toxicity (graded according to National Cancer Institute Common Toxicity Criteria, version 2.0), response to treatment, type of radical surgery performed, and clinical outcome were evaluated. Overall survival and relapse-free survival were analyzed using Kaplan-Meier curves.[20] Statistical analysis was performed using SPSS version 20. It was not the aim of this study to compare different NCH regimens used.

RESULTS

A total of 35 patients were entered in this study. Patients were administered different NCH schemes as follows: cisplatin + 5-fluorouracil (12/35), cisplatin + paclitaxel (6/35),

TABLE 1. Neoadjuvant chemotherapy schemes used

Cisplatin + 5-fluorouracil (3/3 weeks)	Cisplatin + paclitaxel (3/3 weeks)	Cisplatin + 5-fluorouracil + paclitaxel (3/3 weeks)	Vincristine + bleomycin + cisplatin (3/10 days)	Bleomycin (maximum cumulative dose, 300 U)
Cisplatin 50 mg/m^2 intravenous (IV) on day 1	Cisplatin 50 mg/m^2 per day IV on days 2–3	Cisplatin 50 mg/m^2 per day IV on days 2–3	Vincristine 1 mg/m^2 per day IV on days 1–3	20 U/m^2 IV on days 1–5
5-fluorouracil 800 mg/m^2 per day IV on days 1–4	Paclitaxel 175 mg/m^2 IV on day 1	5-fluorouracil 800 mg/m^2 per day IV on days 1–4	Bleomycin 25 U/m^2 on days 1–3	
		Paclitaxel 175 mg/m^2 IV on day 1	Cisplatin 50 mg/m^2 IV on day 1	

TABLE 2. Clinical response parameter definitions

Partial response (PR)	≥50% decrease in local tumor area with respect to the original lesion ± ≥50% involution of inguinal lymph nodes with respect to the size and fixity
Complete response (CR)	No measurable lesion
Stable disease (SD)	50% decrease in local tumor area with respect to the original lesion ± <50% involution of inguinal lymph nodes with respect to the size and fixity
Progression (P)	Growth in local tumor area ± worsening conditions of the inguinal lymph nodes

cisplatin + paclitaxel + 5-fluorouracil (6/35), vincristine + bleomycin + cisplatin (6/35), and bleomycin alone (5/35). The first 3 schemes were given every 21 days (3 cycles). In the case of bleomycin + vincristine + cisplatin, 3 cycles were given every 10 days ("quick" VBP [vincristine + bleomycin + cisplatin]scheme).[21]

Thirty-three patients (94.2%) completed the proposed schemes. Partial response (PR) was observed in 30 (90.9%) of 33 patients, and stable disease in 3 (9.1%) of 33 patients. The definitions of clinical response parameters used are summarized in Table 2.

Three patients could not undergo surgery (1 patient was lost to follow-up, another patient had performance status worsening, and still another patient refused to undergo surgery and finally underwent concurrent chemoradiation). Twenty-seven (90%) of 30 patients with PR then underwent radical surgery of the vulva: 14 patients underwent radical vulvectomy and 13 patients underwent radical local excision. The decision to perform either surgery was unrelated to the clinical response obtained or the NCH regimen given. Bilateral

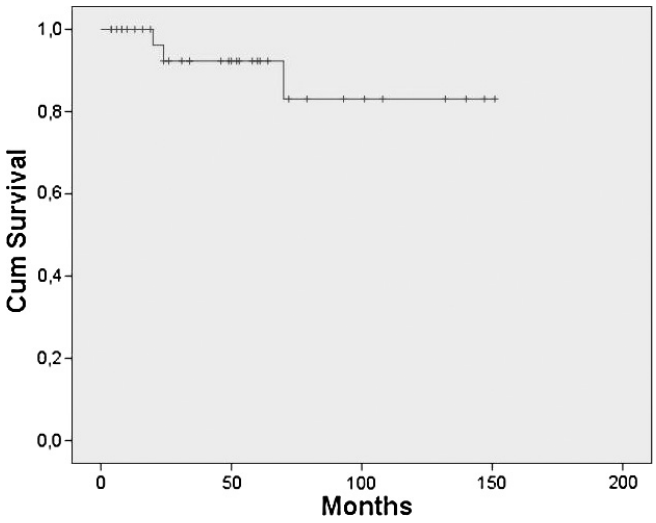

FIGURE 1. Overall survival.

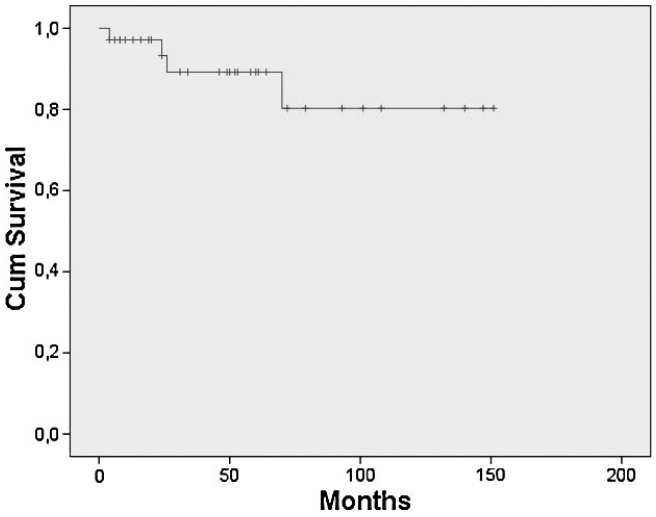

FIGURE 2. Relapse-free survival.

inguinofemoral lymphadenectomy could not be performed only in 2 of the 27 patients (owing to intraoperative instability). Two of the 27 patients showed considerable local response; however, owing to persistence of rectal involvement, they underwent posterior pelvic exenteration and radical vulvectomy plus bilateral inguinofemoral lymphadenectomy.

One patient could not undergo lymphadenectomy; she presented nodal progression and died 4 months after surgery. Three patients presented local recurrence. One of them was rescued by local re-resection. Twenty-four (68.5%) of 35 initial patients have not shown evidence of disease to date. The Kaplan-Meier curves are shown in Figures 1 and 2. The 5-year overall survival rate was 92.3%, and the mean overall survival was 133.6 months (95% confidence interval, 114.9–152.2). The 5-year relapse-free survival rate was 89.5%, and the mean relapse-free survival was 129.5 months (95% confidence interval; 109.9–149.2).

Sixteen patients presented unresectable fixed nodes together with the vulvoperineal lesion. All of them exhibited PR to NCH. The specimen of the lymph nodes was histologically positive in 11 of them, who underwent adjuvant chemoradiation.

As for toxicity, 1 (2.8%) of the 35 patients developed grade 4 gastrointestinal adverse effects (after the second cycle of the cisplatin + paclitaxel + 5-fluorouracil scheme, which was interpreted as an unusual event) and discontinued treatment. Five (14.2%) of the 35 patients developed grade 3 hematologic toxicity. Therefore, neoadjuvant treatment was interrupted temporarily to restore bone marrow function. Four of these patients resumed and completed NCH. We have noted that patients with a poorer Eastern Cooperative Oncology Group performance status were more likely to develop significant toxicity, requiring withdrawal from the study in the aforementioned case. None of the patients on bleomycin developed pulmonary fibrosis.

Eight of the 27 patients who developed PR had a pathological complete response. Interestingly, one of the patients who underwent posterior exenteration due to persistent rectal involvement after NCH had no residual lesion in the surgical specimen.

TABLE 3. Clinical characteristics and outcomes

Patient	Clinical Stage	NCH Scheme	Toxicity	Clinical Response	Surgery	Time to Progression
1	T3N0	B		PR	RV + BL RV + BL	
2	T3N1	VBP		PR		
3	T3N2	B		PR	RV + BL	24 months
4	T2N0	CP		PR	RV + BL	
5	T2N1	CPF	G3-H	PR	RV + BL	
6	T3N0	CF		PR	LFU*	
7	T2N0	B		SD		
8	*T3N0*	VBP		PR	LRR + BL	
9	T2N0	CF	G3-H	PR	LRR + BL	
10	T2N0	CF		PR	RV + BL	
11	T3N1	CP	G3-H	PR	RV + BL	70 months
12	T3N2	CF		PR	RV	4 months
13	T2N0	CPF	G4-GI			
14	T2N0	B		PR	LRR + BL	
15	T3N1	VBP		PR	RV + BL	
16	T3N2	CF		PR	Refused	
17	T3N1	CP		PR	LRR + BL	
18	T2N0	CPF	G3-H	PR	LRR + BL	
19	T3N0	CF		SD		
20	T2N1	VBP		PR	LRR + BL	26 months
21	T3N0	B		PR	RV + BL	
22	T3N0	CF	G3-H			
23	T4N2	VBP		PR	RV + PE + BL	
24	T2N0	CF		PR	LRR + BLL	
25	T4N2	CP		SD		
26	T2N0	CPF		PR	RR + BL	
27	T4N2	CPF		PR	RV + PE + BL	
28	T3N0	VBP		PR	LRR + BL	
29	T3N0	CF		PR	LRR + BL	
30	T2N0	CF		PR	PSW†	
31	T3N2	CP		PR	RV + BL	
32	T3N1	CF		PR	LRR	
33	T2N0	CPF		PR	RV + BL	
34	T4N2	CP		PR	LRR + BL	
35	T3N2	CF		PR	LRR + BL	

*Lost to follow-up.

†Performance status worsening.

B, bleomycin; BL, bilateral lymphadenectomy; CF, cisplatin + 5-fluorouracil; CP, cisplatin + paclitaxel; CPF, cisplatin + paclitaxel + 5-fluorouracil; G3-H, grade 3 hematologic; G4-GI, grade 4 gastrointestinal; LRR, local radical resection; PE, pelvic exenteration; RV, radical vulvectomy; VBP, vincristine + bleomycin + cisplatin.

The median age was 62 years (range, 54–72 years). The median follow-up was 49 months (range, 47–155 months). Patients' characteristics and outcomes are shown in Table 3.

DISCUSSION

The selection of candidates for some kind of therapeutic strategy depends not only on the extent of the tumor but also on the performance status and general characteristics of each patient. As the critical objectives of any given treatment are to achieve locoregional control of the disease and minimize the functional and cosmetic damage observed after treatment, every diagnosis poses a therapeutic dilemma.[22–25]

We consider that the concept of LASCCV has more to do with the spread of cancer to adjacent structures, and

the possibility of becoming radical enough, rather than with tumor size itself. It was understood that this entity usually features close or overt involvement of the bladder, proximal urethra, anus, and/or rectum. It is often associated with extensive and unresectable inguinal metastases and usually corresponds to International Federation of Gynecology and Obstetrics stages III and IV.

Preoperative radiation therapy was developed in the 1980s by Boronow[26] and Hacker,[27] and the results were encouraging enough to avoid pelvic exenteration. In the same period, chemoradiation was developed for anal cancer. Bonorow's experience indicates that radiotherapy is good to achieve regression of locally advanced disease to the point that a more limited resection may be performed and therefore preserve the function of adjacent organs and improve quality of life. However, radiation followed by radical surgery led to a marked increase in morbidity, greater than with each treatment separately.

Moore et al[28] and Montana et al[29] evaluated concurrent chemoradiation and concluded that a combined treatment is feasible in patients with advanced vulvar cancer and reduces the need for more radical surgery including pelvic exenteration. They also stated that follow-up is short and the sample is too small (125 patients from 1989 to 1994) to make a thorough analysis of survival or failure patterns. In this regard, a review of the Cochrane database published in 2006[30] concluded that patients with inoperable vulvar cancer benefit from chemoradiation if followed by surgery. If exenteration is required, complications of neoadjuvant therapy might outweigh complications of exenterative surgery. The authors also added that neoadjuvant therapy is not justified in patients with tumors that may be adequately treated with radical vulvectomy and bilateral groin node dissection alone, and secondary adverse effects are considerable. Authors who are in favor of chemoradiation consider that the results of radical surgery are unacceptable with respect to local control and morbidity, and the best treatment should combine surgery, radiation, and chemotherapy to increase the therapeutic ratio.[31] Nevertheless, a recent and new Cochrane Database review reported no evidence of a survival advantage when chemoradiation (primary or neoadjuvant) was compared to primary surgery for women with locally advanced vulvar cancer.[32]

In 1985, Bortolozzi et al[10] at the University of Milan and Strzinar et al[11] in former Yugoslavia were the first to publish encouraging results with polychemotherapy followed by surgery in advanced cancer of the vulva. These studies motivated Professors Di Paola and Sardi at the University of Buenos Aires, who tried to match the results obtained with NCH in locally advanced cervical cancer using quick VBP fast scheme in patients with locally advanced vulvar cancer.[12] Later, Shimizu et al[13] reported that a combination of bleomycin, vincristine, cisplatin, and mitomycin C might be used to reduce a previously inoperable vulvar tumor. In 1993, Benedetti-Panici et al[14] tested 3 cycles of cisplatin, bleomycin, and methotrexate in advanced disease without showing therapeutic relevance: local control in 57% of cases and survival rate of 24% in 3 years. Wagenaar et al EORTC study[16] underlined the role of bleomycin, methotrexate, and lomustina in locally advanced and recurrent disease and in the palliative care of these patients. Geisler et al[17] published very promising results including a combination of cisplatin and 5-fluorouracil followed by radical vulvectomy and lymphadenectomy considering that 5-fluorouracil would be the most important drug. A subsequent EORTC study[18] using paclitaxel showed moderate response rates in local control of advanced disease. Finally, Domingues et al[19] compared 3 schemes: paclitaxel, 5-fluoruracil + cisplatin, and bleomycin, highlighting the activity of the latter drug (25 patients in total).

In our study, the fact that patients were allocated to 5 different chemotherapy schemes instead of 1 or 2 is assumed as a self-criticism. This had to do with our initial inexperience in the field of vulvar cancer, which has been improving since the start of recruitment. The use of single bleomycin was considered at the time that the study was designed according to some trials that were analyzing the role of single bleomycin in the treatment of gynecological cancer and other malignancies.[33–35] It is also important to point out that the few publications available up to now have shown a variable response to the different and possible chemotherapy regimens. Furthermore, none of them has clearly excelled over the others.[24–33]

Combined treatment modalities seem to involve greater local morbidity.[23,36] Although it is not part of the objectives of this study, we could emphasize the importance of this situation when considering oncoplastic surgery. In this sense, it is known that well-vascularized and previously nonirradiated tissues are essential to decrease morbidity.[37–39]

Our analysis indicates that the use of NCH in selected groups of patients increases surgical feasibility in LASCCV cases, encouraging the preservation of adjacent structures. In patients with persistent rectal involvement, although they underwent posterior pelvic exenteration, NCH favored vulvoperineal surgical conditions and allowed less extensive resections. Adverse reactions were acceptable, and locoregional deleterious effects related to radiotherapy were avoided. The latter could be beneficial with oncoplastic reconstruction prospects, which surely will be material for further research. A randomized trial comparing neoadjuvant chemotherapy with the current standards of care would be useful to achieve a better understanding of this disease.

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