ORIGINAL ARTICLE

Postoperative radiotherapy in the management of vulvar cancer

Radiothérapie postopératoire dans la prise en charge des cancers vulvaires

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Abstract

Background: Vulvar cancer is a rare tumor whose prognosis depends on early treatment.
Aim: The study aimed to evaluate the role of adjuvant radiotherapy (RT) in the treatment of vulvar cancer and to identify the prognostic factors influencing the tumor evolution.
Methods: descriptive and analytical study included 38 patients treated by adjuvant RT, during the period from 1995 to 2020, for vulvar cancer in the oncological radiotherapy department of Farhat Hached University Hospital in Sousse.
Results: All patients underwent adjuvant RT. After a median follow-up of 55 months, 24 patients are in complete remission (63.2%). We noted local and regional recurrences in 23.7% and 13.2% of cases. Two patients had distant bone progression. Overall survival (OS) was 72% at five years and 51% at ten years. The 5-year local (SSRL) and regional (SSRR) recurrence-free survival was 76% and 87%, respectively. In univariate analysis, the factors associated with OS were the size of the tumor (p=0.02), the quality of excision (p=0.000) and age (p=0.04). The quality of excision (p = 0.001) and inguinal dissection (p = 0.05) was associated with SSRL. In addition, those influencing the SSRR were lymph node invasion and the quality of excision.
Conclusion: vulvar cancer requires early diagnosis in order to consider less invasive treatment with advances in RT techniques.

Key words: vulvar cancer, adjuvant radiotherapy, chemotherapy, surgery, prognostic factors

Résumé

Introduction: le cancer de la vulve est une tumeur rare dont le pronostic dépend d'un traitement précoce.
Objectif: l'étude visait à évaluer la place de la radiothérapie (RT) adjuvante dans le traitement des cancers vulvaires et à identifier les facteurs pronostiques influençant l'évolution.
Méthodes: étude descriptive et analytique a inclus 38 patientes traitées par RT adjuvante, pendant la période étalée de 1995 à 2020, pour un cancer de la vulve dans le service de radiothérapie oncologique du CHU Farhat Hached à Sousse.
Résultats: Toutes les patientes ont eu une RT adjuvante. Apres un suivi médian de 55 mois, 24 patients sont en rémission complète (63,2%). Nous avons noté des récidives locales et régionales dans 23,7 % et 13,2 % des cas. Deux patients avaient une progression osseuse à distance. La survie globale (SG) était de 72 % à cinq ans et de 51 % à dix ans. La survie sans récidive locale (SSRL) et régionale (SSRR) à 5 ans était de 76 % et 87 %, respectivement. En analyse uni variée, les facteurs associés à la SG étaient la taille de la tumeur (p=0,02), la qualité d'exérèse (p=0,000) et l'âge (p=0,04). La qualité d'exérèse (p = 0,001) et le curage inguinale (p = 0,05) était associée à la SSRL. De plus, ceux influençant la SSRR étaient l'envahissement ganglionnaire et la qualité d'exérèse.
Conclusion: le cancer de la vulve nécessite un diagnostic précoce afin d'envisager un traitement moins invasif avec les progrès des techniques de la RT.

Mots clés: cancer vulvaires, radiothérapie adjuvante, chimiothérapie, chirurgie, facteurs pronostiques

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Introduction

Vulvar cancer is a rare pathology. It accounts for 3 to 5% of all gynecological cancers worldwide, and 1% of all female cancers. It ranks fourth among gynecological malignancies, after cervical, endometrial and ovarian cancers. This tumor mainly affects post-menopausal women over 60, and most often occurs in estrogen-deficient mucosa. In young women, vulvar cancer is often secondary to infection with the Human Papilloma virus (HPV).(1, 2) Diagnosis is often made at an advanced stage, leading not only to therapeutic issues but also to significant morbidity.

The prognosis for localized forms of vulvar cancer is better than for advanced stages, with a 5-year survival rate ranging from around 86% for stages (I, II), to 53% for stages of federation international of gynecology and obstetrics (FIGO) (III-IVA) and 19% for metastatic disease (IVB). (3)

Management of vulvar cancer is based on two therapeutic weapons: surgery and radiotherapy (RT). The treatment of vulvar cancer has evolved over the years to include conservative surgical techniques to minimize morbidity and preserve sexual function after treatment, as well as advances in RT techniques (IMRT, VMAT, etc.).

Due to the rarity of vulvar cancer, prospective randomized trials evaluating the place of postoperative radiotherapy (PORT) are extremely rare, and most data are based on retrospective studies. As a result, the indications for adjuvant irradiation in the treatment of vulvar cancer remain a matter of debate.

Methods

Type of study

This is a retrospective descriptive and analytical study of patients with primary invasive vulvar cancer treated in the oncology and radiotherapy department of Farhat Hached Hospital in Sousse-Tunisia over a period of 25 years.

Study population

A total of 38 patients with vulvar cancer were included. Patients of any age with histologically confirmed vulvar cancer treated by curative surgery followed by adjuvant radiotherapy were included. Exclusion criteria were metastatic vulvar cancer. External radiation therapy was delivered by Cobalt in 60% of cases and with Three-dimensional conformal radiotherapy in 40% of the cases. The mean dose was 59.4% [50.4-70Gy].

Data collection

Data were collected in the radiotherapy department from clinical records and patient data sheets.

We studied the epidemioclinical, the anatomopathological data, the therapeutic modalities and their complications, and the follow up of the disease after complete treatment.

Data management and analysis

Cancers were classified according to the TNM classification and the classification of the International Federation of obstetricians (FIGO) 2009. Survival was calculated using the Kaplan-Meir method with the log-rank test and multivariate Cox proportional hazards modeling. Recurrence-free survival and overall survival (OS) were analyzed. The 5% risk of error was accepted for our study.

Ethical aspects

Data were processed anonymously.

This work presents no conflict of interest.

Results

In our study, the frequency peak was observed during 2017 at a rate of 15.8% (6 cases) followed by that of 2011 at 13.2%. The average age was 64-year-old [44 to 85]. Only five patients were single. Multiparty presented 71% of cases. Almost half of our patients had a pathological history (diabetic: 10.5%; cardiovascular disease: 31.6%; obesity: 2.6% of cases). Positive HPV status was present in 5.3% of patients. Furthermore, 2 patients had vulvar intraepithelial neoplasia and only one patient was followed for lichen sclerosis. No patient had a personal history of neoplasia. In addition, 7.9% had a history of cancer in the family, 2 cases of endometrial cancer in the mother and one case of gastric cancer in a maternal cousin.

The consultation delay ranged from 1 month to 60 months, with a median of 12 months. The main reason for consultation was pruritus and a vulvar mass in respectively 65.8% and 63.2% of cases. The tumor was predominantly unifocal in (84.2%) of cases and labial in (76%). The mean tumor size was 41 mm [6-150 mm]. Node involvement was noted on clinical examination in 65.8% of cases, with bilateral involvement in 35% of cases. (Table 1).

Staging of the disease was based on radio clinical and anatomopathological findings. Abdominopelvic ultrasound was performed in 79% of patients. Pelvic MRI was only done in 10.5% of cases with a multifocal tumor to evaluate tumor extension to neighboring organs. Cystoscopy und rectoscopy were performed in 16% and 10.5% of cases. One patient had urethral invasion.

These clinical and anatomopathological findings were similar with different retrospective data evaluable in the literature.

In our study, all patients had total vulvectomy except one had partial vulvectomy for a lateral small tumor. Bilateral inguinofémoral dissection was performed in 76.3% of cases. Bilateral sentinel node technique was performed in only two patients (5%) who were clinically node negative. The median time to surgery was 9 weeks [1-28 weeks].

Resection limits were positives in 21% of cases and less then 8mm in 50% of cases. Depth of invasion was > 5 mm in 34.2% of cases. Vascular emboli and perineural invasion were present in 8% and 5% of cases respectively.

Lymph node invasion was noted in 47% of cases, associated with capsular rupture in 13% of cases. Involvement of 2 or more lymph nodes was noted in 42.1% of cases. Histological type was dominated by squamous cell carcinoma, with well-differentiated grade in 47% and moderately differentiated grade in 50% of cases. HPV-positive status was present in 5.3% of cases. In addition, 2 patients were carriers of a vulvar intraepithelial neoplasia and only one patient was followed for lichen sclerosis. The tumor was classified as FIGO stage I, stage II and stage III in 42.1%, 10.5% and 47.3% respectively (Table 2).

Table 1. characteristics of patients

Characteristic	Subgroups	Percentage %
Age	≤ 50 year-old	10.5%
	[51-70]	71.1%
	>70-year-old	18.4%
parity	Multiparity	71%
	Nulliparity	8%
Menopausal statute	Menopausal	97.4%
	Non-menopausal	2.6%
Main symptom	Pruritus	65.8%
	Vulvar mass	63.2%
	Ulceration	13.2%
	Bleeding	7.9%
	Vulvar pain	2.6%
Localization	Labial	79%
	Clitoral	18%
	Posterior	3%
Size of the tumor	≤4cm	57.9%
	>4cm	42.1%
Number	Unique	84.2%
	Multiple	15.8%
Lymph node involvement	Present	65.8%
	Bilateral	35%

Table 2. Anatomopathological results

Criteria	Subgroups	Percentage %
Quality of excision	R0	28.9%
	< 8mm	50%
	R1	21.1%
Depth of invasion (in mm)	>5mm	34.2%
	≤5mm	8%
	Unspecified	57.8%
Tumor size (in cm)	≤ 4cm	58%
	> 4cm	42%
Vascular emboli's (VE)	Present	8%
	Absent	13%
	Unspecified	79%
Perineural invasion	Present	5%
	Absent	13%
	Unspecified	82%
Lymph node involvement	N x	18.4%
	N0	34.2%
	N+	47.4%
Extra capsular extension	Present	13%
	Absent	87%
Pre-neoplastic lesions	Lichen sclerosis	40%
	Vulvar intraepithelial neoplasia (VIN)	19%
FIGO stage	Stage I	42.1%
	Stage II	10.5%
	Stage III	47.4%
Tumor grade	Well-differentiated	50%
	Moderately differentiated	47%
	Undifferentiated	3%

All patients underwent adjuvant radiotherapy (Table 3). The median time from surgery to the start of radiotherapy was 17 weeks [22-125 weeks]. Only two young patients (< 50 years) with lymph node involvement had chemotherapy concomitant with radiotherapy based on weekly cisplatin underwent chemotherapy concomitantly with radiotherapy (cisplatin: 40mg/m2/, once a week).

RT was delivered by Cobalt in 60% of cases. The mean dose was 59.4% [50.4-70Gy]. Target volumes were respectively tumor bed, inguinal nodes and pelvic nodes in 100%, 73% and 60% of cases.

Radiotherapy was well tolerated in the majority of cases. Vulvar radiotherapy may be indicated in the presence of EV or deep infiltration (≥ 5 mm), a size > 4 cm, a margin < 8 mm and the lymph node involvement.

No cases of grade IV toxicity were observed. Acute toxicities of radiotherapy were mainly radio dermatitis GIII in 15.8% and radiomucositis GIII in 2.6% of cases. Skin fibrosis was the major late toxicity related to RT (15.6%) (Table 4).

Table 3. Characteristics of radiotherapy treatment

Criteria	Value
RT dose (Gy)	59.4Gy [50.4-70Gy]
RT techniques	2D : 60% ; 3D :40%
Target volumes	Tumor bed: 100% Inguinal nodes: 73% Pelvic lymph nodes: 60%.
Duration (weeks)	7 weeks [5-10weeks]

Table 4. Acute and chronic toxicities

Toxicities	Number	Percentage%
Acute radiomucositis		
No radiomucositis	22	57.9
GI	5	13.2
GII	10	26.3
GIII	1	2.6
Acute radiodermatitis		
No radiodermatitis	4	10.5
GI	5	13.2
GII	23	60.5
GIII	6	15.8
Acute cystitis	5	13.2
Acute diarrhea	3	8
Acute rectitis	1	2.6
chronic pruritus	4	10.5
skin fibrosis	6	15.6

After a median follow-up of 55 months, 24 patients were in complete remission (63.2% of cases). Local recurrence was noted in 9 patients (23.7% of cases). Inguinal recurrence was noted in 13.2% of cases. Two patients had bone metastatic progression. The ulterior treatment was either RT, surgery or monitoring and sometimes palliative care.

In our series, overall survival was 72% at 5 years (figure 1). Survival free of local and regional recurrence was 76% and 87% at 5 years respectively.

In the univariate analysis, the factors significantly associated with OS were tumor size, quality of excision

and patient's age (Table 5). Factors associated with local recurrence-free survival were the quality of excision and inguinal dissection (Table 5). Factors associated with regional recurrence-free survival were lymph node involvement and quality of excision (Table 5). None of these criteria was an independent survival factor in multivariate analysis.

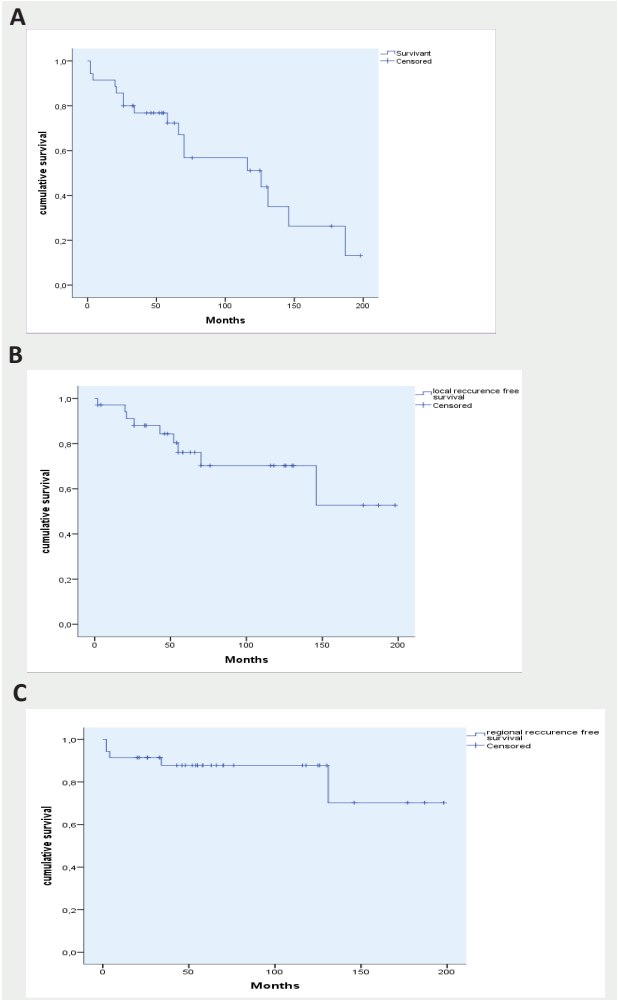

Figure 1. (A) overall survival curve, (B) local recurrence free survival curve, (C): regional recurrence free survival curve

Table 5. Factors significantly associated with OS, LRFS and RRFS on univariate analysis

Survival	Criteria	Subgroups	Survival %	P value
5-years-OS	Tumor size	≤4cm > 4 cm	83% 52%	0.02
	Age	< 70 years ≥ 70 years	74% 60%	0.04
	Quality of excision	R0 < 8 mm R1	78% 74 % 25 %	0.000
5-years-LRFS	Inguinal dissection	Done Not done	64% 42%	0.05
	Quality of excision	R0 < 8 mm R1	77% 59% 0%	0.001
5-years-RRFS	N status	PN0 PN+ Nx	100% 91% 50%	0.000
	Quality of excision	R0 < 8 mm R1	80% 47% 20%	0.002

Discussion

Given the rarity of vulvar cancer and the lack of prospective data, the indications for postoperative irradiation remain a subject of discussion.

The first data on adjuvant RT were published by GOG 37.(4, 5) Patients were randomized to receive pelvic lymphadenectomy or adjuvant inguinal and pelvic RT at a dose of 45 Gy to 50 Gy without vulvar irradiation. OS at 2 years was better in favor of adjuvant RT 68% versus 54% (P = 0.03). The inguinal recurrence rate was 5% compared to 24% in the absence of RT. Acute or late morbidity was similar between the two arms. The 6-year OS benefit in the RT arm persisted in patients with ulcerated or fixed inguinal lymph nodes (P = 0.004) and in case of two or more positive inguinal lymph nodes (P < 0.001). The positive effect of RT on OS and on the rate of inguinal recurrence in GOG37 is linked to inguinal and not pelvic irradiation, particularly in patients with 2 or more positive inguinal lymph nodes. The large retrospective AGO-CaRE-1 study demonstrated significantly better progression free survival (PFS) in the adjuvant RT or radiochemotherapy arm (54.6%) versus observation (3-year PFS of 39.6% versus 25.9%, P = 0.004). The RT volume most often included the inguinal and pelvic areas ± the vulva in 49% of cases and an inguinal ± vulvar RT in 27.6% of cases.(6)

There are conflicting data on the benefit of PORT in patients with a single positive lymph node. Some studies in the literature have reported no benefit from adjuvant RT.(7) A recent study revealed a low single-node inguinal recurrence rate of 2% with disease-specific survival, OS and recurrence free survival (RFS) of 79%, 62.5% and 97% respectively.(8) However, another analysis revealed a significant improvement in 5-year disease-specific survival with adjuvant RT (77% versus 61.2%, p=0.02). (9) The survival benefit was more pronounced in patients who underwent less extensive dissection (≤12 lymph nodes removed) (76.6% versus 55.1%).

In the case of positive sentinel lymph node (SLN) with micrometastases (≤2 mm), PORT reduces the rate of inguinal recurrence with acceptable morbidity and, therefore, constitutes a safe alternative to inguinofemoral (IF) lymph node dissection. Whereas for patients with macrometastases, dissection remains the standard of treatment given the increased risk of inguinal recurrence rate. According to the GROINSS V-II trial (10) including patients with a positive SLN, adjuvant RT was administered at a dose of 50 Gy. Isolated ipsilateral inguinal recurrence at 2 years was 1.6% compared to 11 .8% in the absence of RT. In the case of macro metastases, this rate was 22% in the RT group compared to 6.9% in those who underwent inguinofemoral dissection (with or without adjuvant radiotherapy) (p = 0.011). Among these patients, only 7 women received chemotherapy (13.7%). No inguinal recurrence was observed. The GROINSS-V-III recently began including patients. This trial studies the effectiveness and safety of cisplatin-based chemo radiotherapy in patients with macro metastasis (>2 mm) in the SLN. PORT is administered at a dose of 48 to 50 Gy to the inguinofemoral fossa and external iliac lymph node

regions, with an additional dose to the affected inguinal fossa to a dose equivalent of 56 Gy over 5 to 6 weeks with the simultaneous integrated boost technique.(11)

The benefit of PORT of the tumor bed in patients with positive surgical margins has been well demonstrated in the literature. In a retrospective study including 257 women, 65 of whom had insufficient or positive surgical margins, the 5-year OS was significantly improved by adjuvant primary site RT (67.6% vs. 29%; P = 0.038) and was similar compared to those with negative margins. (12)

Its place remains questionable depending on the various other prognostic factors and their impact on local control. The literature data remains controversial. According to the various recommendations and in the absence of prospective data, vulvar radiotherapy may be indicated in the presence of vascular emboli or deep infiltration (≥ 5 mm), a tumor size > 4 cm, excision margin < 8 mm and the involvement of lymph nodes. In our series, the irradiated volumes were the tumor bed in all patients, the inguinal fossa and the pelvic lymph node areas in 73% and 60% of cases respectively.

The optimal dose in adjuvant treatment remains uncertain. Old literature data suggested that doses of 45 to 50 Gy were appropriate. Furthermore, more recent data have demonstrated a lower risk of recurrence in patients receiving a dose (≥56 Gy) compared to those receiving a dose (≤50.4 Gy) in the case of positive or insufficient margins.(13) The impact of adjuvant radiotherapy on OS and the dose-response relationship was studied using data from the National Cancer Data Base (NCDB) including 3075 women. This large analysis demonstrated that 3-year OS increased from 58.5% to 67.4% (P < 0.001) with a dose between 54 and 59.9 Gy compared to a dose < 54Gy. There was no benefit in terms of OS for a dose ≥ 60 Gy.(14) Currently, the recommended dose at the tumor bed is 45 to 50 Gy in 5 weeks with an additional dose by external RT or interstitial brachytherapy at a dose of 15 Gy on positive or insufficient margins. In the case of involvement of at least 2 nodes and/or extracapsular rupture, adjuvant treatment with pelvic and inguinal radiotherapy is recommended, at a dose of 45 to 50 Gy.(4) In our series, the dose delivered was between 50.4 Gy and 70 Gy. The median dose was 59.4 Gy.

The technique of radiotherapy has evolved from conventional and 3D conformal radiotherapy to intensity modulated irradiation (IMRT), which is currently the recommended technique. IMRT allows for better adequacy of target volume coverage while reducing doses to organs at risk. Studies have demonstrated a reduction in short- and long-term toxicity with the use of IMRT thereby reducing treatment-related discontinuations.(15–17) In a study by Kaustov and al, 2-year DFS was similar when comparing 2D/3D RT versus IMRT (77.7% vs. 87.5%, p=0.56). Several dosimetric studies have demonstrated the potential benefit of adjuvant IMRT to reduce the dose to organs at risk (OAR) in cervical and endometrial cancer. (18,19) According to Beriwal et al, the median volume of the small intestine, rectum and bladder receiving doses above 30 Gy (V30) was significantly reduced by 27% (p 0.03), 41% (p 0.03), 01) and 26% (p 0.004), respectively, with IMRT compared to 3D RT.(20)

There are few series published in the literature studying the benefit of dose escalation in vulvar cancer. A study compared sequential boost, simultaneous integrated boost (56 Gy/28 Fr, 2Gy/Fr) and simultaneous integrated boost with dose escalation (67.2Gy/28 Fr, 2.4 Gy/Fr) by IMRT in the treatment of locally advanced vulvar cancer. In terms of doses to the OAR (rectum, bladder and femoral head), the study did not demonstrate significant differences between the 3 groups. Furthermore, for the small intestine, the results were in favor of the boost with dose escalation (Dmean, V30, V40, V45).(17)

There is little data in the literature on the place of brachytherapy in the treatment of vulvar cancer. Some retrospective studies, including small numbers and using a low dose technique in the majority of cases, have suggested the possibility of integrating brachytherapy as an exclusive irradiation modality or as a complement to external RT. (21–24) In published series, brachytherapy was most often proposed when surgery was contraindicated or had high morbidity. In addition, the target volume is more difficult to define in the context of postoperative treatment. A recent study, including 26 patients, demonstrated that interstitial brachytherapy (at a median total dose at the primary site of 60Gy in EQD2) used in the treatment of locally advanced or recurrent (11 cases) or postoperative (15 cases) was feasible and well tolerated (toxicity ≤ grade 2). DFS and OS at 3 years of 57% and 81% respectively.(24) In the largest series using high-dose (HD) brachytherapy (definitive (n=29), postoperative (n=6) or salvage (n=3)), 29 patients (76.3%) were in remission after a median follow-up of 30 months. At 5 years, DFS and local control rate were 51% and 77%, respectively.(25) In a recent series including 18 cases of which 8 had vulvar cancer, external RT was delivered at a median dose of 45 Gy in 25 fractions, followed by image-guided HD brachytherapy (15 to 27.5 Gy in 3 to 5 fractions), 5 patients (27.8%) recurred, three of whom (16.7%) had a local recurrence. Acute grade 3 toxicities were vaginal stenosis (5.6%), radiodermatitis (33.3%), vaginal pain (11.1%) and vulvar infection (5.6%). Grade 3 late toxicities included 3 cases (17.7%) of vaginal pain and 1 case (5.9%) of skin necrosis. There was no grade 4 or higher toxicity.(26)

As for other squamous cell carcinomas (HPV-related), the addition of chemotherapy improves local control results as well as survival (the example of cervical cancer). Commonly used drugs are platinum derivatives, 5-fluorouracil and mitomycin C concomitantly with radiotherapy. In a large analysis by Gill et al including 1797 patients, there was a significant reduction in mortality risk of 38% in node-positive patients by the addition of chemotherapy to adjuvant RT (median survival was 44 months versus 29.7 months; P < 0.001). (27) Another study including 2779 patients demonstrated that only those with 2 or more positive nodes benefited from the addition of CT to RT (p=0.022). (28) In the AGO-CaRE study, the addition of chemotherapy to radiotherapy reduced the risk of death with an HR of 0.62. In a recent series, adjuvant chemo radiotherapy improved 5-year RFS and DFS by 58.5% and 81.8% compared to 41.7% and 55.6%

in RT alone.(29)in our study, only two young women with lymph node involvement received chemotherapy.
Our study remains the first evaluating the role of PORT in vulvar cancer in Tunisia as an African country. However, its limits are the retrospective character, the limited number of patients included and the lack of data related to prognostic factors in some cases.

Conclusion

Vulvar cancer remains a rare tumor diagnosed mostly at an advanced stage in our country. Innovations in terms of conservative surgery and radiotherapy techniques aimed to reduce both acute and late toxicity. Therefore, more research in this regard are needed in order to explore the interest of these innovations in the treatment of vulvar cancer especially in the postoperative context in order to enhance the quality of life of those patients while achieving better oncological outcomes both on local or overall survival. Our study showed similar results as found in the literature in terms of the role of PORT in vulvar cancer treatment with the different prognostic factors involved in the recurrence of the disease.

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