Observational multicenter Italian study on vulvar cancer adjuvant radiotherapy (OLDLADY 1.2): a cooperation among AIRO Gyn, MITO and MaNGO groups

Article *in* La Radiologia Medica · September 2022

DOI: 10.1007/s11547-022-01538-w

CITATIONS
0

READS
25

20 authors, including:

Gabriella Macchia
Gemelli Molise spa, Catholic University of the Sacred Heart, Campobasso
486 PUBLICATIONS **3,383** CITATIONS
SEE PROFILE

Calogero Casà
Catholic University of the Sacred Heart
78 PUBLICATIONS **533** CITATIONS
SEE PROFILE

M. Ferioli
68 PUBLICATIONS **194** CITATIONS
SEE PROFILE

Valentina Lancellotta
Policlinico Universitario Agostino Gemelli
175 PUBLICATIONS **694** CITATIONS
SEE PROFILE

La radiologia medica
https://doi.org/10.1007/s11547-022-01538-w

RADIOTHERAPY

Observational multicenter Italian study on vulvar cancer adjuvant radiotherapy (OLDLADY 1.2): a cooperation among AIRO Gyn, MITO and MaNGO groups

Gabriella Macchia[1] · Calogero Casà[2] · Martina Ferioli[3] · Valentina Lancellotta[2] · Donato Pezzulla[1] · Brigida Pappalardi[4] · Concetta Laliscia[5] · Edy Ippolito[6] · Jacopo Di Muzio[7] · Alessandra Huscher[8] · Francesca Tortoreto[9] · Mariangela Boccardi[1] · Roberta Lazzari[10] · Pierandrea De Iaco[11] · Francesco Raspagliesi[12] · Angiolo Gadducci[13] · Giorgia Garganese[14] · Gabriella Ferrandina[15] · Alessio Giuseppe Morganti[3] · Luca Tagliaferri[2]

Received: 9 May 2022 / Accepted: 28 July 2022

Abstract

Background Adjuvant radiotherapy (aRT) has been shown to reduce the risk of local relapse in vulvar cancer (VC). In this multicentre study (OLDLADY-1.2), several Institutions have combined their retrospective data on VC patients to produce a real-world dataset aimed at collecting data on efficacy and safety of aRT.

Methods The primary study end-point was the 2-year-local control, secondary end-points were the 2-year-metastasis free-survival, the 2-year-overall survival and the rate and severity of acute and late toxicities. Participating centres were required to fill data sets including age, stage, tumor diameter, type of surgery, margin status, depth of invasion, histology, grading as well technical/dosimetric details of radiotherapy. Data about response, local and regional recurrence, acute and late toxicities, follow-up and outcome measures were also collected.

Results One hundred eighty-one patients with invasive VC from 9 Institutions were retrospectively identified. The majority of patients were stage III (63%), grade 2 (62.4%) squamous carcinoma (97.2%). Positive nodes were observed in 117 patients (64.6%), moreover tumor diameter > 4 cm, positive/close margins and depth of invasion deeper than 5 mm were found in 59.1%, 38.6%, 58% of patients, respectively. Sixty-one patients (33.7%) received adjuvant chemoradiation, and 120 (66.3%) received radiotherapy alone. aRT was started 3 months after surgery in 50.8% of patients. Prescribed volumes and doses heterogeneity was recorded according to margin status and nodal disease. Overall, 42.5% locoregional recurrences were recorded. With a median follow-up of 27 months (range 1–179), the 2-year actuarial local control rate, metastasis free and overall survival were 68.7%, 84.5%, and 67.5%, respectively. In term of safety, aRT leads to a prevalence of acute skin toxicity with a low incidence of severe toxicities.

Conclusions In the context of aRT for VC the present study reports a broad spectrum of approaches which would deserve greater standardization in terms of doses, volumes and drugs used.

Keywords Vulvar cancer · Adjuvant radiotherapy · Outcomes · Toxicity

Introduction

Vulvar carcinoma (VC) accounts for 3 to 5% of all gynecologic malignancies and 1% of all cancers in women. [1]. Ninety percent of VC histological subtypes are squamous cell carcinoma (SCC), with strong trend toward locoregional dissemination [2]. Traditionally, en bloc radical vulvectomy with bilateral inguino-femoral lymphadenectomy has been considered the cornerstone of therapy [3, 4]. More conservative approaches have been recommended over the last three decades to reduce treatment morbidity and psychosexual impairment without affecting prognosis [5]. Nevertheless, after primary treatment, local recurrence rates for VC have been reported to be as high as 40% at 10 years [6]. Surgical margin and lymph nodes involvement, extracapsular nodal disease, tumor size larger than 4 cm, lymphovascular invasion, and more than 5 mm

✉ Valentina Lancellotta
valentina.lancellotta@policlinicogemelli.it

Extended author information available on the last page of the article

Published online: 10 September 2022

depth of invasion are risk factors for vulvar recurrence [7–12]. Because the 10-year disease-specific survival rate drops from 90% for patients without local failure to 69% for individuals with local recurrence [6, 9], preventing local failure is crucial. In fact, salvage treatment often results in lower curative rates, particularly among patients with nodal relapse or locally advanced malignancies at the time of recurrence. In this context, adjuvant radiation therapy (aRT) has been shown to reduce the risk of local relapse [13–20] and intensity-modulated radiation therapy (IMRT) together with other inverse-planning approaches have become fairly common in the treatment of VC, sparing the organ at risk and allowing for safe dose escalation [21, 22]. As a result, multidisciplinary care has emerged as an appropriate therapeutic issue tool for patients with VC in order to optimize the benefits of technological radiation breakthroughs and provide the best possible treatment. The prospective clinical studies of the Gynecologic Oncology Group (GOG) 37 and GOG 101 demonstrated how a multidisciplinary treatment strategy could provide the most tailored clinical approach [10, 22].With the goal of better targeting doses and volumes in radiation treatment and establishing a shared standard on which to base future prospective research, a consortium of Italian Radiotherapy Centres specialized in the treatment of VC was launched. The OLD LADY (ObservationaL Italian studDy on vuLvar cAncer radical raDiotherapY) trials were authorized and carried out within the Gynecological group of Italian Association of Radiation Oncology (AIRO Gyn) in collaboration with the Multicenter Italian Trials in Ovarian cancer (MITO) group, and the Mario Negri Gynecologic Oncology Group (MaNGO).

In the current paper, the latter Institutions have combined retrospective data on their patients to produce a real-world dataset aimed at collecting data on efficacy and safety of adjuvant (chemo) radiation, as well as preparing the ground to define the best potential treatment in terms of doses and volumes.

Methods

Study design and end-points

This is a multicenter, retrospective study (OLDLADY-1.2) aimed at assessing the efficacy and safety of aRT in VC patients treated in 9 Italian Radiation Oncology Institutions.

The primary study end-point was the 2-year-local control, secondary end-points were the 2-year-metastasis free-survival, the 2-year-overall survival and the rate and severity of acute and late toxicities.

Procedures

A specific data set for standardized data collection was developed by the Principal Investigators (GM, LT and MF). All performed procedures were under the ethical standards of the institutional, national research committee and with the Helsinki declaration. No specific ethical approval was required for retrospective studies in our institution at the time of the data collection. Participating centres were required to fill data sets including age, stage, tumor diameter, type of surgery, margin status, depth of invasion, histology, grading as well technical/dosimetric details of radiotherapy. The Margin Status following tumor resection (AJCC 8th Edition) was classified as negative (R0), microscopic (R1) or macroscopic positive (R2) according to absence, microscopic or grossly presence of tumor at the surgical margins, respectively. Moreover, margins within 8 mm were considered as close, according to literature [23–26]. Data about response local and regional recurrence, acute and late toxicities, follow-up and outcome measures were also collected. Patients have to be diagnosed with histological proven primary vulvar cancer and have given their informed consent for treatment and the use of their clinical data for research or educational purposes. The toxicity was reported and a posteriori scored using the Common Terminology Criteria for Adverse Events (CTCAE) version 5 scale [27].

Analysis of data and statistical methods

Data were gathered from the historical database of Radiation Oncologists who took part in the study; data were centrally collected at the Radiation Oncology Department of Policlinico Gemelli IRCCS, and entered into an electronic database. The data processing was carried out by CC, LT, VL, and GM.

Descriptive statistics were performed on patient, tumor, and treatment characteristics. To compare categorical variables and continuous variables the $\chi 2$ tests and t-tests or Wilcoxon rank sum tests were used, respectively. Local control (LC), metastasis free-survival (MFS) and overall survival (OS) curves were generated using the Kaplan–Meier methods. Actuarial Local control (LC) was defined as the time interval between the date of aRT and the date of "in site" radiotherapy field relapse/progression of disease or the date of the last follow-up. Actuarial metastasis free-survival (MFS) was defined as the time interval between the date of aRT and the date of out of field progression or the date of the last follow-up. Overall survival (OS) was defined as the time interval between the date of aRT and the date of death of disease or the

date of the last follow-up. Kaplan–Meier curves were compared using the log-rank test. Univariate and multivariate Cox proportional hazards regression models were used to ascertain predictors of LC, MFS and OS. All the variables were supposed to have a clinically significant impact; as a result, rather than using a specific *p*-value from the univariate analysis as a cut-off, all variables were used for either the univariate or multivariate analysis. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, N.Y., USA).

Results

Patient, tumor, and treatment characteristics

One hundred eighty-one patients with invasive VC treated at 9 different Radiation Oncology Institutions were retrospectively identified, covering 20-year time interval (February 2000- November 2019). Table 1 details patient and lesion characteristics. Briefly, median age at diagnosis was 71.5 years (range: 17–90). The majority of patients were stage III ($N=114$, 63%), grade 2 ($N=113$, 62.4%) squamous carcinoma ($N=176$, 97.2%) with depth of invasion (DOI) over 5 mm in 105 (58.0%) patients. Surgery was the primary treatment in the overall series.

Seventy three (40.4%) patients underwent wide local excision (WLE) or deep partial vulvectomy and 108 (59.6%) underwent total deep vulvectomy according to the glossary of terminology proposed by Micheletti et al. [28] The surgical excision encompassed the lesion with a free margin of at least 1 cm of clinically normal skin, and removed a portion of the vulva in all its thickness from the surface to the urogenital diaphragm. Deep partial vulvectomy indicated that the vulvar excision was limited to a portion of the vulva, whereas deep total vulvectomy denoted the removal of the whole vulva. Unilateral and bilateral inguinofemoral lymphadenectomy (IFLD) was performed for 17 (9.3%) and 141 (77.9%) patients, respectively. Five patients (2.7%) received sentinel node dissection (SND). In terms of risk factors for adjuvant treatment positive inguinal lymph nodes were observed in 117 patients (64.6%), moreover tumor diameter larger than 4 cm, positive/close margins and depth of invasion deeper than 5 mm were found in 59.1%, 38.6%, 58% of patients, respectively (Table 1).

As per adjuvant treatment is concerned, 61 patients (33.7%) received adjuvant chemoradiation, and 120 (66.3%) received aRT alone. The median time for radiotherapy treatment start was 3 months after surgery in 92 patients (50.8%). Distribution of VC features and treatment data according to adjuvant scenario (radiotherapy alone versus chemoradiation) is reported in Table 2. Younger age, positive lymph node status and higher mean dose to tumor bed were

Table 1 Patient- and tumor characteristics of the study population

All patients, *n*	181
Median age, years (range)	71.5 (17–90)
Surgery	
Radical vulvectomy	108 (59.6)
Partial vulvectomy/WLE	73 (40.4)
Unilateral IFL	17 (9.3)
Bilateral IFL	141 (77.9)
SLNB /sampling	5 (2.7)
No lymphadenectomy	16 (8.8)
Missing	2 (1.1)
AJCC prognostic stage group	
IA	6 (3.3)
IB	47 (26.0)
II	10 (5.5)
IIIA	55 (30.4)
IIIB	39 (21.6)
IIIC	20 (11.0)
IV	4 (2.2)
Pathologic tumor stage	
pT1a	15 (8.3)
pT1b	137 (75.7)
pT2	27 (14.9)
pT3	2 (1.1)
Pathologic nodal status	
pN0	45 (24.9)
pN+	117 (64.6)
pNx	19 (10.5)
Histology	
Squamous cell carcinoma	176 (97.2)
Other	5 (2.8)
Grading	
G1	17 (9.4)
G2	113 (62.4)
G3	47 (26.0)
missing	4 (2.2)
Vulvar tumor size	
< 4 cm	74 (40.9)
≥ 4 cm	107 (59.1)
Margin status	
Negative	111 (61.5)
Close	30 (16.5)
R1	35 (19.3)
R2	5 (2.7)
Depth of invasion	
≤ 5 mm	71 (39.2)
> 5 mm	105 (58)
missing	5 (2.8)
Adjuvant treatment	
Exclusive radiotherapy	120 (66.3)
Concomitant chemoradiation	61 (33.7)

AJCC: American Joint Committee on Cancer; *n*: number; SLNB; sentinel lymph node biopsy, IFL; inguinofemoral lymphadenectomy; WLE: wide local excision

Table 2 Distribution of Vulvar Cancer features according to adjuvant treatment

	Radiotherapy N (%)	Chemoradiation *N* (%)	*p* value[a]
All lesions	120 (66.3)	61 (33.7)	
Age, years			
< 72	49 (40.8)	38 (62.3)	**0.006**[b]
≥ 72	71 (59.2)	23 (37.7)	
Histotype			
Squamous	116 (96.6)	60 (98.4)	0.511[b]
Other	4 (3.4)	1 (1.6)	
Vulvar tumor size, cm (%)			
< 4	75 (62.5)	33 (54.1)	0.276[b]
≥ 4	45 (37.5)	28 (45.9)	
Depth of Invasion, mm (%)			
≤ 5	52 (43.3)	21 (34.5)	0.245[b]
> 5	66 (5.0)	39 (63.9)	
Missing	2 (1.7)	1 (1.6)	
Lymph nodes status			
negative	58 (48.3)	6 (9.9)	**< 0.0001**[b]
positive	62 (51.7)	55 (90.1)	
Margin status			
Negative	79 (65.8)	32 (52.5)	0.275[b]
Close	18 (15.0)	12 (19.7)	
R1	21 (17.5)	14 (22.9)	
R2	2 (1.7)	3 (4.9)	
Grading			
1	13 (10.8)	4 (6.5)	0.158[b]
2	78 (65.0)	35 (57.4)	
3	26 (21.7)	21 (34.5)	
missing	3 (2.5)	1 (1.6)	
Tumor bed Total dose, Gy (mean ± SD)	50.5 ± 5.7	53.6 ± 6.1	**0.001**[b]
Overall treatment time, days (mean ± SD)	45.8 ± 13.6	48.8 ± 12.7	0.144
Type of vulvar surgery			
Radical vulvectomy	67 (55.8)	40 (65.6)	0.208[b]
Partial vulvectomy/WLE	53 (44.2)	21 (34.4)	
Type of nodal surgery			
No surgery/sampling/sentinel lymph node	17 (14.2)	4 (6.5)	0.122
IFN/pelvic lymphadenectomy	101 (84.1)	57 (93.4)	
missing	2 (1.7)	0	
IFN negative node dose, Gy (mean + SD)	48.1 ± 3.7	47.3 ± 2.6	0.164
IFN positive node dose, Gy (mean + SD)	57.8 ± 6.4	56.5 ± 6.4	0.295
Pelvic negative node dose, Gy (mean + SD)	46.9 ± 2.3	46.6 ± 2.3	0.524
Pelvic positive node dose, Gy (mean + SD)	50.0[c]	55.8 ± 6.8	–

[a]calculated by the *t*-test, [b]calculated by the Chi-square test,[c]insufficient data for test

Abbreviations: n: number; SD: standard deviation; Gy: gray; IFN: inguinofemoral lymphadenectomy; VC: vulvar cancer; WLE: wide local excision

registered in patients undergoing chemoradiation compared to patients receiving radiotherapy alone. No other differences in term of tumor characteristics or type of treatment were found (Table 2).

Heterogeneity in term of prescribed volumes and doses was recorded according to margin status and presence of nodal disease in the overall population. In case of negative margins, tumor bed received a median dose of 50 Gy/2 Gy fraction (range 44–64 Gy), in case of close or R1 or R2 margins, median doses were 50 Gy/2 Gy fraction (range 45–66 Gy), 60 Gy/2 Gy fraction (range 54–70 Gy) and 60 Gy/2 Gy fraction (range 50–70 Gy), respectively. The

median total doses administered to negative and positive inguinal nodes were 46/1.8 Gy fraction (range 44–65 Gy) and 60/2 Gy fraction Gy (range 45–70.4 Gy), respectively. The median total doses administered to negative and positive pelvic nodes were 45/1.8 Gy (range 43.2–50.4 Gy) and 52.2 Gy (range 45–65 Gy), respectively. Cisplatin plus 5-fluorouracil (16 patients, 8.8%) or cisplatin alone (40 patients, 22%) were the most commonly used drugs for chemoradiation. In details, cisplatin (20 mg/m^2, 2-h intravenous infusion, Days 1–4) and 5-fluorouracil (1000 mg/m^2, 24-h continuous intravenous infusion, Days 1–4) during the first and last weeks of radiotherapy, or, in alternative, cisplatin (40 mg/m^2, 2-h intravenous infusion once a week, were administered. No data was collected on the temporary or definitive suspension of radiation treatment, as well as on the used radiotherapy technique.

Treatment outcomes

Overall, 61 patients (33.8%) relapsed at the tumor bed, 33 patients (18.2%) at lymph nodes, and 17 patients (9.4%) at both sites, totalling 77 recurrences (42.5%). Thirty patients (16.5%) developed distant metastases. Median time to vulvar and nodal recurrence was 14 (range 1–96) and 5 (range 1–85) months, respectively. As per adjuvant therapy, we registered 45 (37.5%) tumor bed and 23 (19.1%) lymph node failures in patients treated by radiotherapy versus 16 (26.2%) tumor bed and 10 (16.3%) nodal relapses in patients treated by chemoradiation. No differences in nodal or tumor bed relapses according to type of surgery were found (data not shown).

With a median follow-up of 27 months (range 1–179 months), the two-year actuarial LC rate was 68.7% (Fig. 1a). Univariate analysis of variables predicting LC rate showed that older age was significantly associated with a lower probability of LC rate (Table 3). This finding was lost at the multivariate analysis ($p = 0.163$). As per MFS in concerned, the two-year actuarial MFS was 84.5% (Fig. 1b). Univariate analysis of variables predicting MFS rate showed that older age and concurrent chemotherapy were significantly associated with a lower MFS rate. At the multivariate analysis age and positive nodal status correlated with a worse MFS (Table 3). Lastly, overall survival (OS) was 67.5% (Fig. 1c). Univariate analysis of variables predicting OS rate showed that older age was significantly associated with a lower probability of OS rate (Table 3). The impact of older age was also confirmed at the multivariate analysis.

Toxicity

Acute and late toxicities were limited to the skin, lymphovascular system and vagina. No data on gastrointestinal and genitourinary toxicities were collected. Due to the

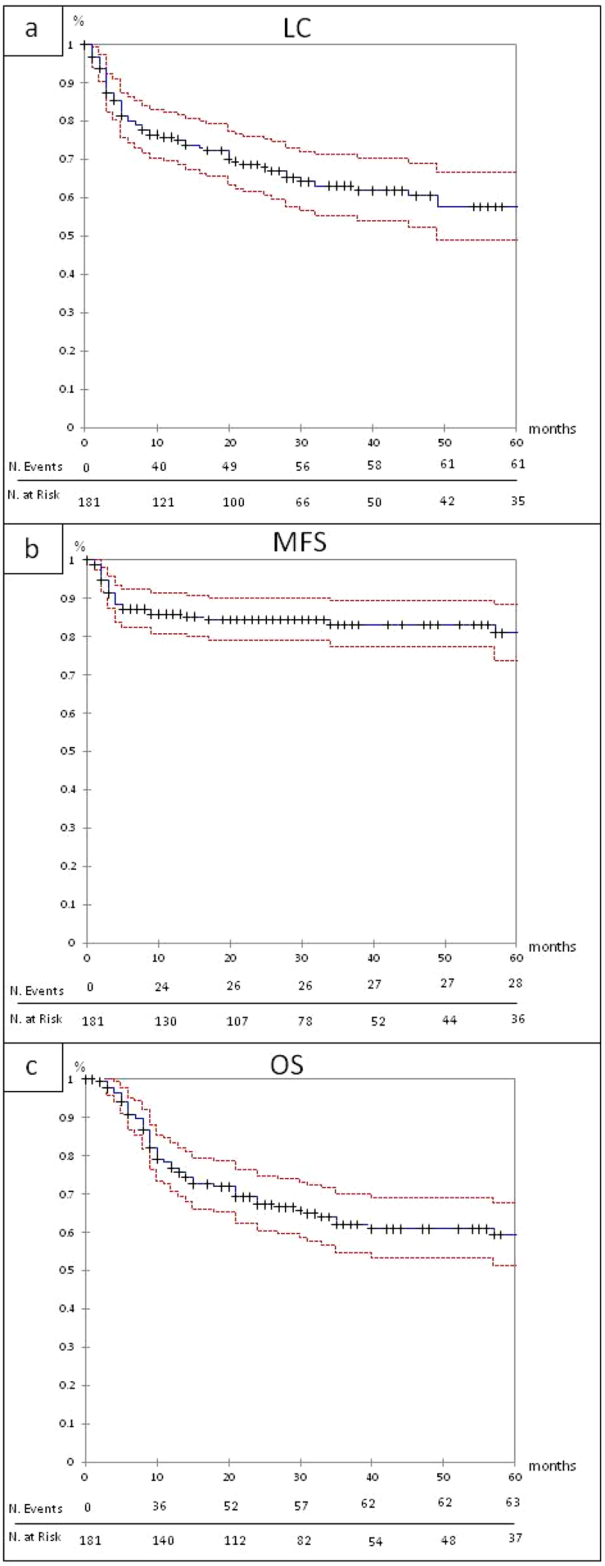

Fig. 1 Kaplan–Meier curves: **a** local control (LC); **b** metastasis free-survival (MFS); **c** overall survival (OS)

Table 3 Univariate and multivariate analysis of pathological features, as prognostic factors for local control, metastasis free-survival and overall survival in the whole population

	Local control				Metastasis free-survival				Overall survival			
	Univariate	*p* value	Multivariate	*p* value	Univariate	*p* value	Multivariate	*p* value	Univariate	*p* value	Multivariate	*p* value
Age, yrs												
<72	Ref		Ref		Ref		Ref		Ref		Ref	
≥72	1.632 (1.035–2.573)	**0.035**	1.428 (0.866–2.357)	0.163	2.252 (1.048–4.839)	**0.037**	1.776 (1.742–12.044)	**0.002**	2.074 (1.313–2.074)	**0.002**	2.144 (1.291–3.558)	**0.003**
Tumor size, cm												
<4	Ref		Ref		Ref		Ref		Ref		Ref	
≥4	0.901 (0.568–1.428)	0.657	1.076 (0.644–1.797)	0.779	1.498 (0.731–3.070)	0.27	1.143 (0.523–2.502)	0.737	1.056 (0.675–1.654)	0.811	1.257 (0.780–2.026)	0.78
Depth of invasion, mm												
≤5	Ref		Ref		Ref		Ref		Ref		Ref	
>5	0.778 (0.496–1.220)	0.274	0.794 (0.485–1.300)	0.359	1.933 (0.856–4.367)	0.113	1.139 (0.454–2.857)	0.781	0.814 (0.524–1.286)	0.362	0.761 (0.465–1.246)	0.277
Margin status												
Negative	Ref		Ref		Ref		Ref		Ref		Ref	
Close	0.960 (0.466–1.977)	0.912	0.941 (0.447–1.984)	0.874	2.038 (0.815–5.099)	0.128	1.754 (0.654–4.706)	0.264	1.087 (0.559–2.112)	0.807	0.943 (0.470–1.891)	0.47
R1	1.547 (0.907–2.638)	0.109	1.468 (0.809–2.665)	0.207	1.839 (0.770–4.394)	0.17	2.717 (0.951–7.760)	0.062	1.349 (0.775–2.348)	0.289	1.335 (0.721–2.470)	0.721
R2	1.138 (0.275–4.701)	0.858	1.591 (0.363–6.965)	0.538	1.302 (0.170–9.986)	0.799	2.106 (0.250–17.751)	0.494	0.522 (0.122–12.240)	0.382	0.992 (0.224–4.396)	0.224
Lymph nodes status												
negative	Ref		Ref		Ref		Ref		Ref		Ref	
positive	0.821 (0.515–1.309)	0.407	1.052 (0.601–1.841)	0.86	2.162 (0.882–5.300)	0.092	3.315 (1.058–10.389)	**0.04**	0.951 (0.596–1.516)	0.831	1.320 (0.761–2.290)	0.323
Grading												
G1	Ref		Ref		Ref		Ref		Ref		Ref	
G2	0.533 (0.281–1.012)	0.054	0.545 (0.276–1.079)	0.082	1.238 (0.284–5.388)	0.776	1.757 (0.373–8.2.72)	0.476	0.476 (0.255–0.877)	**0.019**	0.585(0.295–1.159)	0.295
G3	0.532 (0.255–1.108)	0.092	0.601 (0.277–1.301)	0.196	2.054 (0.450–9.379)	0.353	1.772 (0.355–8.837)	0.485	0.607 (0.301–1.225)	0.163	0.693 (0.325–1.478)	0.325
Time from surgery to RT, mts												
≤3												
>3	Ref		Ref		Ref		Ref		Ref		Ref	
	1.290 (0.819–2.032)	0.272	1.189 (0.728–1.942)	0.489	1.392 (0.674–2.872)	0.371	0.892 (0.400–1.987)	0.78	0.805 (0.515–1.258)	0.341	0.700 (0.435–1.126)	0.141

Table 3 (continued)

	Local control				Metastasis free-survival				Overall survival			
	Univariate	*p* value	Multivariate	*p* value	Univariate	*p* value	Multivariate	*p* value	Univariate	*p* value	Multivariate	*p* value
Adjuvant treatment												
RT	Ref		Ref		Ref		Ref		Ref		Ref	
Concomitant chemoradiation	0.777 (0.470–1.284)	0.324	0.861 (0.480–1.543)	0.615	2.192 (1.068–4.500)	**0.032**	1.776 (0.743–4.247)	0.196	0.963 (0.602–1.539)	0.873	1.039 (0.595–1.815)	0.892

cm: centimeters; mm: millimeters; mts: metastases; RT: radiotherapy; yrs: years

Bold values indicate the statistically significant

retrospective study design, data were not available for the overall series. All grade acute and late skin toxicity were recorded in 171 (94.4%) and 101 (57.0%) patients, respectively. The most frequently reported short-term side effects were grade 1–2 skin toxicities (71.8%), followed by acute localized edema (21.1%). Acute skin toxicity higher than grade 2 was reported in 41 patients (22.6%), the majority of them ($N=38$) had grade 3 and a minority ($N=3$) had grade 4.

Severe late toxicity rates (grade 3) were reported in 6 (3.4%) patients, suffering from skin ulcerations (1.7%), chronic lymphedema (1.1%) and vaginal stenosis (0.6%). No grade 4 late toxicity was recorded.

Discussion

Summary of the main results

The present paper investigates adjuvant (chemo)radiation treatment in a large multi-institutional series of VC over a 20-year time period and evidenced low radiotherapy doses, heterogeneity of treatment volumes and reduced chemotherapy association. A higher than expected locoregional rate of relapses (42.5%) and a disappointing two-year actuarial LC rate of 68.7% were registered. Despite the risk factors that should have led to more aggressive treatment throughout the series, the patients appear to be undertreated. Indeed, two third of patients had advanced stage, pathologic positive lymph nodes, and around 60% had positive/close margins or deep invasion, but only one third of patients received chemoradiation. The higher toxicity of the combination could justify the lower application of chemoradiation in the frail setting of postoperative VC. Moreover, the median time to start treatment appears to be longer than recommended by international guidelines, with half of patients starting radiotherapy three months following surgery. Furthermore, about 25% of patients suffered from grade ≥ 3 toxicity leading us to speculate that the treatment was halted to recover from the toxicity, and that the interruptions may have affected recurrence. In term of radiobiology, temporarily treatment breaks have an important impact in VC since it is a disease with high *Dprolif* (i.e., the dose to compensate 1 day of treatment interruption) which would require dose recovery for the suspensions. All of the aforementioned factors could have influenced the findings of this multicenter trial.

Results in the context of published literature

According to international guidelines, (chemo)radiotherapy is often used in the management of patients with locally advanced VC as adjuvant therapy following initial surgery and is informed by primary tumor risk factors and nodal

surgical pathology [24, 29, 30-Khullar, 31-U. Mahantshetty]. However, due to the rarity of the disease and the lack of randomized prospective trials, there is still a wide variability among institutions in terms of the aRT doses and volumes as well in terms of combination with concomitant chemotherapy, despite the supporting literature [32-Han]. Therefore, the optimal patient selection criteria and adjuvant therapy regimens to address nodal disease remain a challenge. Most of the indications for adjuvant therapy after surgery arise from retrospective studies with low number of patients, heterogeneous stage of disease, and treatment [13–20]. In term of recommendations of adjuvant chemoradiotherapy, the literature data considered as major criteria the nodal and margin status, nodal extracapsular spread, and depth of tumor invasion [20, 24, 29]. As well, minor criteria are considered the lympho-vascular space invasion, tumor size larger than 4 cm, multifocality, grade 3, anterior tumor site, and local recurrence after previous surgery [20, 23, 29, 33].

The disappointing results in our series could be related to the treatment type, mostly radiotherapy alone, underweighted considering the high percentage of registered risk factors. Indeed, as reported by Gill and coll., in a National Cancer Data Base [NCDB] analysis, the adjunction of adjuvant chemotherapy significantly reduced the risk of death in node-positive vulvar carcinoma patients who received adjuvant radiotherapy, with a hazard ratio [HR] of 0.62 (95%CI = 0.48–0.79) [34]. Also delays to postoperative radiotherapy were frequent (about 51%) and can be associated with poorer oncologic outcomes as reported in head and neck cancer patients [35].

Indeed, oncologic outcomes of this pooled analysis in terms of 5-year OS (59.6%) are comparable with data reported in a recent literature review [9] on this topic. On the contrary, 2-y-local control is low if compared with Tagliaferri et al. data that reported 88.6% at 2 years in a small series of 35 patients with squamous vulvar cancer treated with adjuvant radiotherapy ± chemotherapy [8]. However, as noted by the authors [8], the interdisciplinary tailored approach to the care of vulvar cancer benefits the outcomes of this series. The frustrating local control in our series fits with the large number of registered local failures. Indeed, the overall recurrence rate (42.5%) was comparable to the rate reported by Zapardiel et al. that in a large series of 1727 VC registered a total of 41.3% patients recurring, of whom 27.9% locally and 13.4% distantly [33]. In these Authors experience, multivariate analysis showed that factors significantly associated with the risk of global recurrence of squamous cell VC when adjusted to FIGO stage were age, number of positive inguinal nodes, tumor resection margins, not undergoing chemotherapy, and not undergoing any radiotherapy [33]. In our pooled analysis, only old age and positive nodal status were associated with poorer outcomes, consistently with other reports [33, 36–39]. On the other hand, tumor size, deep stromal invasion, margin status, treatment type and time to adjuvant treatment had no impact on oncological outcomes. These findings suggest that the doses and volumes discrepancies may mask the effect on outcomes, emphasizing the importance of shared technical guidelines and treatment protocols for VC.

In term of safety, aRT leads to a prevalence of acute skin toxicity with a low incidence of severe toxicities. These data were comparable with recent data reporting on multidisciplinary management of locally advanced VC [9]. Indeed, the skin toxicity may pose a barrier to the delivery of proper radiation, so high-volume institutions, so high-volume institutions developing preventive and supportive therapy regimens could be beneficial in the management of this challenging treatment.

Strengths and weaknesses

This study has some weaknesses, including potential effects from occult bias due to the retrospective study design, which affected data collection, treatment, and follow-up and underpowered some analyses because of low number of events. Moreover, the already mentioned discrepancies in terms of doses and fractions delivery during daily practice is a limit for drawing conclusions. The rarity of disease and the lack of shared guidelines resulted in the reported disagreement. VC, in our opinion, should be treated in experienced centres with a large range of available techniques and a large number of VC patient referred. Zapardiel et al. reported that the case volume at each center was among the factors impacting overall survival [33]. Indeed, the discussion of clinical cases in an expert multidisciplinary team increases the homogeneity of treatment approaches and improves clinical outcomes [8].

One of the strengths of the work is the consortium of several Italian centers that deal with this pathology, laying the foundations for future multicenter prospective studies. We have also added our case series to the retrospective studies that underline the importance of adjuvant treatment in this setting.

Implications for practice and future research

The present paper aims to contribute to discussion and proposal about VC adjuvant treatment issue. Since the lack of prospective randomized trials and the rarity of the disease contrast an evidence-based approach, patients with VC should be enrolled in prospective studies, aimed to focus on risk factors to triage patients to treatment escalation when deemed appropriate. To uniform the treatment of vulvar carcinoma will be crucial the patient' path of care optimization, through scheduled multidisciplinary board sessions that offer the highest quality of personalized medicine [8].

Nevertheless, a smart tool in patient counselling could be the use of predictive models which have proven to be efficacious in different context [40–44].

Conclusion

The present study reports a broad spectrum of therapeutic options in the context of adjuvant VC, which would deserve greater standardization in terms of doses, volumes and drugs used. Cooperative prospective studies are worthwhile for improving outcomes.

Acknowledgements The Authors thank the Scientific Committee and Board of the AIRO for the critical revision and final approval of the paper.

Funding The authors did not receive support from any organization for the submitted work.

Declarations

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Ethical approval Ethical approval was waived by the local Ethics Committee of University A. Gemelli in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Consent informed Consent was obtained from all individual participants included in the study.

References

1. Siegel RL, Miller KD, Jemal A (2015) Cancer statistics, 2015. CA Cancer J Clin 65:5–29
2. Eifel PJ, Berek JS, Markman MA (2011) Cancer of the cervix, vagina, and vulva. In: DeVita VT Jr, Lawrence TS, Rosenberg SA (eds) DeVita, Hellman, and Rosenberg's cancer: principles and practices of oncology. Williams & Wilkins, Philadelphia
3. Morley GW (1976) Infiltrative carcinoma of the vulva: results of surgical treatment. Am J Obstet Gynecol 124:874–888. https://doi.org/10.1016/s0002-9378(16)33392-0
4. Podratz KC, Symmonds RE, Taylor WF et al (1983) Carcinoma of the vulva: analysis of treatment and survival. Obstet Gynecol 61:63–74
5. Andersen BL, Hacker NF (1983) Psychosexual adjustment after vulvar surgery. Obst Gynecol 62:457–462
6. Te Grootenhuis NC, van der Zee AG, van Doorn HC et al (2016) Sentinel nodes in vulvar cancer: long-term follow-up of the Groningen international study on sentinel nodes in vulvar cancer (GROINSS-v) I. Gynecol Oncol 140:8–14. https://doi.org/10.1016/j.ygyno.2015.09.077
7. Heaps JM, Fu YS, Montz FJ et al (1990) Surgical-pathologic variables predictive of local recurrence in squamous cell carcinoma of the vulva. Gynecol Oncol 38:309–314. https://doi.org/10.1016/0090-8258(90)90064-r
8. Tagliaferri L, Garganese G, D'Aviero A et al (2020) Multidisciplinary personalized approach in the management of vulvar cancer - the Vul. Can Team experience. Int J Gynecol Cancer 30:932–938. https://doi.org/10.1136/ijgc-2020-001465
9. Tagliaferri L, Lancellotta V, Casà C et al (2021) The radiotherapy role in the multidisciplinary management of locally advanced vulvar cancer: a multidisciplinary vulcan team review. Cancers (Basel) 13:5747. https://doi.org/10.3390/cancers13225747
10. Homesley HD, Bundy BN, Sedlis A et al (1991) Assessment of current international federation of gynecology and obstetrics staging of vulvar carcinoma relative to prognostic factors for survival (a Gynecologic Oncology Group study). Am J Obstet Gynecol 164:997–1003. https://doi.org/10.1016/0002-9378(91)90573-a
11. Federico F, Forte S, Ardighieri L et al (2019) Multivariate analysis of prognostic factors in primary squamous cell vulvar cancer: the role of perineural invasion in recurrence and survival. Eur J Surg Oncol 45:2115–2119. https://doi.org/10.1016/j.ejso.2019.07.029
12. Miljanović-Špika I, Drežnjak Madunić M, Topolovec Z et al (2021) Prognostic factors for vulvar cancer. Acta Clin Croat 60:25–32. https://doi.org/10.20471/acc.2021.60.01.04
13. Chapman BV, Gill BS, Viswanathan AN et al (2017) Adjuvant radiation therapy for margin-positive vulvar squamous cell carcinoma: defining the ideal dose-response using the National Cancer Database. Int J Radiat Oncol Biol Phys 97:107–117. https://doi.org/10.1016/j.ijrobp.2016.09.023
14. Kunos C, Simpkins F, Gibbons H et al (2009) Radiation therapy compared with pelvic node resection for node-positive vulvar cancer: a randomized controlled trial. Obstet Gynecol 114:537–546. https://doi.org/10.1097/AOG.0b013e3181b12f99
15. Swanick CW, Eifel PJ, Huo J et al (2017) Challenges to delivery and effectiveness of adjuvant radiation therapy in elderly patients with node-positive vulvar cancer. Gynecol Oncol 146:87–93. https://doi.org/10.1016/j.ygyno.2017.05.004
16. Parthasarathy A, Cheung MK, Osann K et al (2006) The benefit of adjuvant radiation therapy in single-node-positive squamous cell vulvar carcinoma. Gynecol Oncol 103:1095–1099. https://doi.org/10.1016/j.ygyno.2006.06.030
17. Mahner S, Jueckstock J, Hilpert F et al (2015) AGO-CaRE-1 Investigators. Adjuvant therapy in lymph node-positive vulvar cancer: the AGO-CaRE-1 study. J Natl Cancer Inst 107:426. https://doi.org/10.1093/jnci/dju426
18. Gill BS, Bernard ME, Lin JF et al (2015) Impact of adjuvant chemotherapy with radiation for node-positive vulvar cancer: a National Cancer Database (NCDB) analysis. Gynecol Oncol 137:365–372. https://doi.org/10.1016/j.ygyno.2015.03.056
19. Ignatov T, Eggemann H, Burger E et al (2016) Adjuvant radiotherapy for vulvar cancer with close or positive surgical margins. J Cancer Res Clin Oncol 142:489–495. https://doi.org/10.1007/s00432-015-2060-9
20. Gaffney DK, King B, Viswanathan AN et al (2016) Consensus recommendations for radiation therapy contouring and treatment of vulvar carcinoma. Int J Radiat Oncol Biol Phys 95:1191–1200. https://doi.org/10.1016/j.ijrobp.2016.02.043
21. Grégoire V, Guckenberger M, Haustermans K et al (2020) Image guidance in radiation therapy for better cure of cancer. Mol Oncol 14:1470–1491. https://doi.org/10.1002/1878-0261.12751
22. Moore DH, Thomas GM, Montana GS et al (1998) Preoperative chemoradiation for advanced vulvar cancer: a phase II study of

the Gynecologic Oncology Group. Int J Radiat Oncol Biol Phys 42:79–85. https://doi.org/10.1016/s0360-3016(98)00193-x
23. Aragona AM, Cuneo NA, Soderini AH et al (2014) An analysis of reported independent prognostic factors for survival in squamous cell carcinoma of the vulva: Is tumor size significance being underrated? Gynecol Oncol 132:643–648. https://doi.org/10.1016/j.ygyno.2013.12.022
24. Greer BE, Koh WJ (2016) New NCCN guidelines for vulvar cancer. J Natl Compr Canc Netw 14:656–658
25. Dudley S, Viswanathan A (2019) Margins in vulvar cancer: challenges to classical clinicopathologic vulvar recurrence risk factors. Gynecol Oncol 154:253–254. https://doi.org/10.1016/j.ygyno.2019.07.007
26. Te Grootenhuis NC, Pouwer AW, de Bock GH et al (2019) Margin status revisited in vulvar squamous cell carcinoma. Gynecol Oncol 154:266–275. https://doi.org/10.1016/j.ygyno.2019.05.010
27. Common Terminology Criteria for Adverse Events (CTCAE) Version 5. Published: November 27. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute
28. Micheletti L, Preti M, Zola P et al (1998) A proposed glossary of terminology related to the surgical treatment of vulvar carcinoma. Cancer 83:1369–1375
29. Jolly S, Soni P, Gaffney DK et al (2015) ACR appropriateness criteria adjuvant therapy in vulvar cancer. Oncology 29:867–875
30. Khullar K, Patrich T, Jabbour SK, Hathout L (2022) Adjuvant radiation in early stage vulvar cancer: a review of indications and optimal dose. Appl Radiat Oncol 11:14–20
31. Mahantshetty U, Naga P, Engineer R et al (2017) Clinical outcome of high-dose-rate interstitial brachytherapy in vulvar cancer: a single institutional experience. Brachytherapy 16:153–160
32. Han SC, Kim DH, Higgins SA, Carcangiu ML, Kacinski BM (2000) Chemoradiation as primary or adjuvant treatment for locally advanced carcinoma of the vulva. Int J Radiat Oncol Biol Phys 47:1235–1244
33. Zapardiel I, Iacoponi S, Coronado PJ et al (2020) Prognostic factors in patients with vulvar cancer: the VULCAN study. Int J Gynecol Cancer 30:1285–1291. https://doi.org/10.1136/ijgc-2019-000526
34. Gill BS, Bernard ME, Lin JF et al (2015) Impact of adjuvant chemotherapy with radiation for node-positive vulvar cancer: a National Cancer Data Base (NCDB) analysis. Gynecol Oncol 137:365–372
35. Lee CW, Dupré S, Marlborough F et al (2022) Postoperative radiotherapy delay in head and neck cancer patients undergoing major resection and free flap reconstruction. J Plast Reconstr Aesthet Surg. https://doi.org/10.1016/j.bjps.2022.02.038
36. Burger MP, Hollema H, Emanuels AG et al (1995) The importance of the groin node status for the survival of T1 and T2 vulval carcinoma patients. Gynecol Oncol 57:327–334. https://doi.org/10.1006/gyno.1995.1151
37. Raspagliesi F, Hanozet F, Ditto A et al (2006) Clinical and pathological prognostic factors in squamous cell carcinoma of the vulva. Gynecol Oncol 102:333–337. https://doi.org/10.1016/j.ygyno.2005.12.027
38. Rhodes CA, Cummins C, Shafi MI (1998) The management of squamous cell vulval cancer: a population based retrospective study of 411 cases. Br J Obstet Gynaecol 105:200–205. https://doi.org/10.1111/j.1471-0528.1998.tb10053.x
39. Sun X, Zhang Y, Sun J, Feng S, Yan M, Cheng H (2012) The comparative study of former and latest FIGO staging of vulvar cancer. Minerva Chir 67:187–195
40. Tagliaferri L, Budrukkar A, Lenkowicz J et al (2018) ENT COBRA ONTOLOGY: the covariates classification system proposed by the Head & Neck and Skin GEC-ESTRO Working Group for interdisciplinary standardized data collection in head and neck patient cohorts treated with interventional radiotherapy (brachytherapy). J Contemp Brachyther 10:260–266. https://doi.org/10.5114/jcb.2018.76982
41. Tagliaferri L, Gobitti C, Colloca GF et al (2018) A new standardized data collection system for interdisciplinary thyroid cancer management: thyroid COBRA. Eur J Intern Med 53:73–78. https://doi.org/10.1016/j.ejim.2018.02.012
42. Tagliaferri L, Pagliara MM, Masciocchi C et al (2017) Nomogram for predicting radiation maculopathy in patients treated with Ruthenium-106 plaque brachytherapy for uveal melanoma. J Contemp Brachyther 9:540–547. https://doi.org/10.5114/jcb.2017.71795
43. Meldolesi E, van Soest J, Alitto AR et al (2014) VATE: VAlidation of high TEchnology based on large database analysis by learning machine. Colorectal Cancer 5:435–450. https://doi.org/10.2217/crc.14.34
44. Lancellotta V, Guinot JL, Fionda B et al (2020) SKIN-COBRA (Consortium for Brachytherapy data Analysis) ontology: the first step towards interdisciplinary standardized data collection for personalized oncology in skin cancer. J Contemp Brachytherapy 12:105–110. https://doi.org/10.5114/jcb.2020.94579

Authors and Affiliations

Gabriella Macchia[1] · Calogero Casà[2] · Martina Ferioli[3] · Valentina Lancellotta[2] · Donato Pezzulla[1] · Brigida Pappalardi[4] · Concetta Laliscia[5] · Edy Ippolito[6] · Jacopo Di Muzio[7] · Alessandra Huscher[8] · Francesca Tortoreto[9] · Mariangela Boccardi[1] · Roberta Lazzari[10] · Pierandrea De Iaco[11] · Francesco Raspagliesi[12] · Angiolo Gadducci[13] · Giorgia Garganese[14] · Gabriella Ferrandina[15] · Alessio Giuseppe Morganti[3] · Luca Tagliaferri[2]

[1] Radiation Oncology Unit, Gemelli Molise Hospital – Università Cattolica del Sacro Cuore, Campobasso, Italy

[2] Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

[3] Radiation Oncology, Department of Experimental, Diagnostic and Specialty Medicine – DIMES, IRCCS Azienda Ospedaliero, Universitaria di Bologna - Alma Mater Studiorum University of Bologna, Bologna, Italy

[4] Radiotherapy Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

[5] Department of New Technologies and Translational Research, Division of Radiation Oncology, University of Pisa, Pisa, Italy

[6] Radiation Oncology, Università Campus Bio-Medico, Rome, Italy

[7] Dipartimento di Oncologia P.O. S. Anna - SS Radioterapia, A.O.U "Città della Salute e della Scienza", Turin, Italy

[8] Fondazione Poliambulanza, U.O. di Radioterapia Oncologica "Guido Berlucchi", Brescia, Italy

[9] U.O.C. Radiotherapy, S. Giovanni Calibita Fatebenefratelli Hospital - Amethyst Radioterapia Italia, Rome, Italy

[10] Division of Radiotherapy, IEO European Institute of Oncology IRCCS, Milan, Italy

[11] Division of Oncologic Gynecology, IRCCS Azienda Ospedaliero, Universitaria di Bologna - Alma Mater Studiorum University of Bologna, Bologna, Italy

[12] Gynecologic Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

[13] Department of Clinical and Experimental Medicine, Division of Gynecology and Obstetrics, University of Pisa, Pisa, Italy

[14] Gynecology and Breast Care Center, Mater Olbia Hospital, Olbia, Italy

[15] Unità Operativa Complessa Ginecologia Oncologica, Dipartimento per la Salute della Donna e del Bambino e della Salute Pubblica, Fondazione Policlinico Universitario A. Gemelli, IRCCS – Università Cattolica del Sacro Cuore, Rome, Italy