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Research Report

Incidence and predictors of toxicity in the management of vulvar squamous cell carcinoma treated with radiation therapy

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ABSTRACT

Purpose/Objective: Given the rarity of vulvar cancer, data on the incidence of acute and late severe toxicity and patients' symptom burden from radiotherapy (RT) are lacking.
Materials/Methods: This multi-center, single-institution study included patients with vulvar squamous cell carcinoma treated with curative intent RT between 2009 and 2020. Treatment-related acute and late grade ≥ 3 toxicities and late patient subjective symptoms (PSS) were recorded.
Results: Forty-two patients with predominantly stage III/IV disease (n = 25, 59.5 %) were treated with either definitive (n = 25, 59.5 %) or adjuvant (n = 17, 40.5 %) external beam RT to a median dose of 64 Gy and 59.4 Gy, respectively. Five patients received a brachytherapy boost with a median total dose of 84.3 Gy in 2 Gy-equivalent dose (EQD2). Intensity-modulated RT was used in 37 (88.1 %) of patients, and 25 patients (59.5 %) received concurrent chemotherapy. Median follow-up was 27 months. Acute grade ≥ 3 toxicity occurred in 17 patients (40.5 %), including 13 (31.0 %) acute grade 3 skin events. No factors, including total RT dose ($p = 0.951$), were associated with acute skin toxicity. Eleven (27.5 %) patients developed late grade ≥ 3 toxicity events, including 10 (23.8 %) late grade ≥ 3 skin toxicity events. Patients with late grade ≥ 3 skin toxicity had a higher mean body-mass index (33.0 vs 28.2 kg/m^2; $p = 0.009$). Common late PSS included vaginal pain (n = 15, 35.7 %), skin fibrosis (n = 10, 23.8 %), and requirement of long-term opiates (n = 12, 28.6 %).
Conclusion: RT for vulvar cancer is associated with considerable rates of severe acute and late toxicity and PSS burden. Larger studies are needed to identify risk factors, explore toxicity mitigation strategies, and assess patient-reported outcomes.

1. Introduction

Vulvar cancer is rare, constituting 2 % of all gynecologic malignancies, and the vast majority are squamous cell carcinomas (Siegel et al., 2022). The primary treatment for early-stage vulvar cancer is surgical resection. Adjuvant radiation is generally recommended in the setting of high-risk pathologic features and/or multiple positive lymph nodes (Homesley et al., 1986; Heaps et al., 1990; Greer and Koh, 2016). Definitive or pre-operative chemoradiation is the recommended treatment paradigm for patients with unresectable or locally advanced disease or medically inoperable cases (Moore et al., 2012).

Radiation treatment for vulvar cancer requires targeting the primary vulvar tumor with a wide margin to adequately cover potential areas of microscopic spread. A superficial bolus, a water-equivalent material to generate dose build-up, is frequently placed over the vulva to prevent underdosing of the skin. Radiation dose in the definitive and adjuvant treatment settings range from 64–70 Gy and 56–66 Gy, respectively, with the final dose determined by patient tolerance, tumor size and margin status (Gaffney et al., 2016). Gross unresected lymph nodes are boosted to a total dose of 56–70 Gy. Elective pelvic and inguinal radiation is recommended in most cases due to the high risk of subclinical lymph node involvement (Klapdor et al., 2019).

In early GOG trials evaluating preoperative chemoradiation using 2D or 3D-conformal radiation therapy, over half of patients experienced

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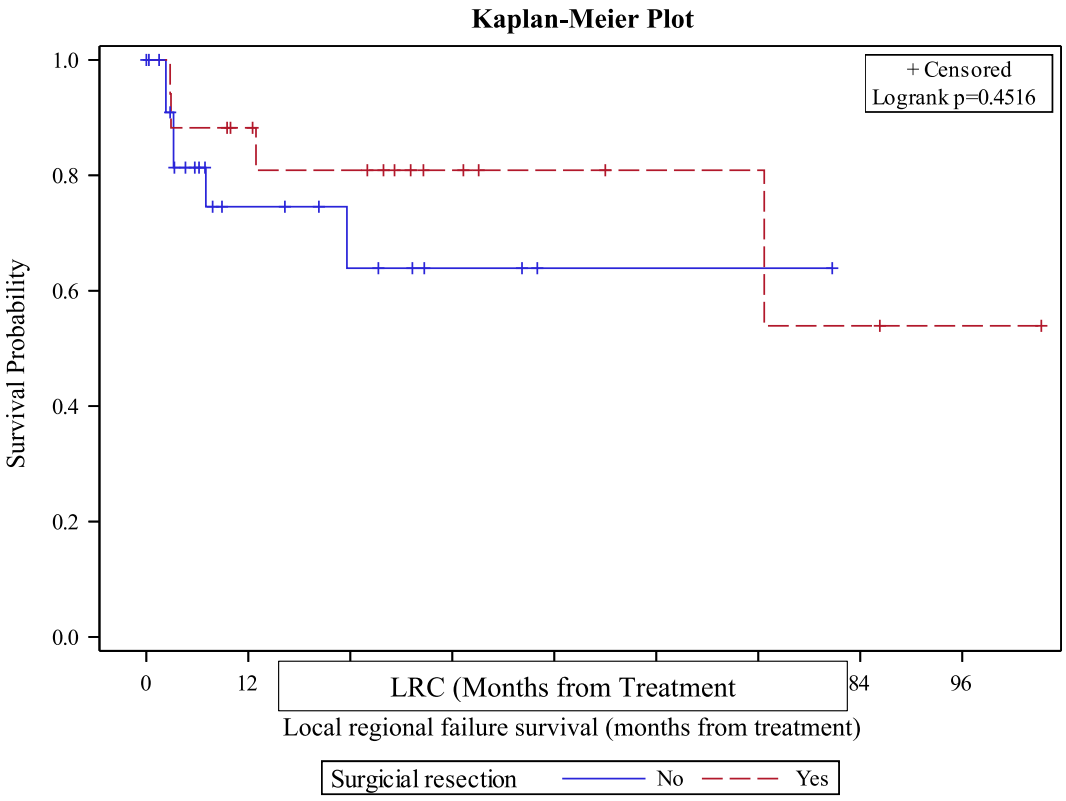

Fig. 1. *Local-Regional Control (LRC)*. A Kaplan-Meier plot for LRC is shown, stratified according to surgical resection.

acute grade ≥ 3 toxicities; however, late toxicities were not reported in these studies (Moore et al., 2012; Moore et al., 1998). Within the last 15 years, intensity-modulated radiation therapy (IMRT), a radiation technique with improved dose conformality, has emerged as the standard treatment modality for anal, cervical, endometrial cancers. By reducing dose to uninvolved pelvic organs, IMRT has been showed to significantly decrease gastrointestinal, dermatologic, and hematologic toxicities in anal, cervical and endomentrial cancers (Kachnic et al., 2013; Klopp et al., 2018). Data on the incidence of toxicity with IMRT are limited to smaller institutional series that are primarily focused on efficacy. These studies report rates of severe non-hematologic acute and late toxicity rates ranging from 0–29 % and 0–19.2 %, respectively (Rao et al., 2017; Richman et al., 2020; Beriwal et al., 2008; Beriwal et al., 2006; Rishi et al., 2020).

The factors that contribute to toxicity remain poorly described among patients with vulvar cancer treated with modern radiation therapy. The purpose of this study is to report outcomes of patients with vulvar cancer treated with curative intent radiation therapy with a primary focus on the incidence and predictors of severe acute and late toxicity.

2. Methods

2.1. Patient selection

This study was approved by the institutional review board (STUDY00002106). All patients with vulvar cancer who were treated with radiotherapy at one of five hospital centers within the Winship Cancer Institute at Emory University from 2008 to 2021 were retrospectively identified by querying the electronic treatment records for diagnosis codes (n = 77). All patients were reviewed and discussed in our weekly multi-disciplinary tumor board to determine optimal treatment approach. Only patients with biopsy-proven squamous cell carcinoma of the vulvar treated with curative-intent radiation therapy either in the definitive or adjuvant treatment setting were included. Patients with recurrent disease after resection alone without adjuvant therapy were included (n = 6) if the treatment intent was curative. Patients treated with palliative radiation (n = 11) and/or non-squamous cell carcinoma histology (n = 7) were excluded from this analysis and 17 patients were excluded due to incomplete medical records.

Forty-two patients fit the inclusion criteria. Patient-, disease- and treatment-specific factors were abstracted from the medical record. Stage was defined by the 2018 International Federation of Gynecology and Obstetrics (FIGO) staging system. An 18-fluor-deoxyglucose positron emission tomography (PET-CT) was utilized to rule out metastatic disease at the time of diagnosis. All cases were evaluated by a gynecologic oncologist to determine resectability of disease and were discussed at a multidisciplinary tumor board prior to treatment.

2.2. Treatment

Seventeen patients (40.5 %) underwent surgical resection followed by adjuvant radiation and 25 patients (59.5 %) received definitive radiation treatment. Among the 17 patients who underwent resection, 8 (47.1 %) underwent radical vulvectomy; 7 (41.2 %) underwent wide radical excision; two (11.8 %) underwent hemi-vulvectomy. Twelve (70.1 %) of the 17 patients underwent inguinal lymphadenectomy. No patients were managed with sentinel lymph node biopsy (SLNB).

For radiation treatment planning, patients were simulated frog-legged in supine position to reduce skin folds. A customized vacuum-locked immobilization device was placed beneath the patient's lower extremities for setup reproducibility. Superficial radio-opaque wires and beads were used to demarcate the gross tumor and identify urethral meatus and anal verge at discretion of treating physician. Patients with adequate renal function received IV contrast to improve visualization of lymph node regions when clinically indicated. When available, PET-CT and MRI were fused to the CT planning scan to aid in target delineation.

For definitive treatment, radiation target volumes included the

Table 1
Demographic, clinical, and treatment characteristics according to adjuvant or definitive radiotherapy.

Covariate	Level	Overall N = 42 (%)	Adjuvant N = 17 (%)	Definitive N = 25 (%)	P-value*
Median Age		64 (Range: 32–98)	62 (Range: 32–86)	71 (Range: 38–98)	0.032
Race	White	19 (45.2)	3 (17.7)	16 (64.0)	0.003
	Black	23 (54.8)	14 (82.35)	9 (36)	
KPS	80–100	37 (88.1)	17 (100.0)	20 (80.0)	0.049
	50–70	5 (11.9)	0 (0.0)	5 (20.0)	
BMI (kg/m^2)		29.4 ± 5.3	31.7 ± 4.8	27.7 ± 5.1	0.013
Smoking status	Active smoker/Former smoker	23 (54.8)	7 (41.2)	16 (64.0)	0.145
	Never smoker	19 (45.2)	10 (58.8)	9 (36.0)	
Diabetes Mellitus	Non-insulin dependent	7 (16.7)	3 (17.7)	4 (16.0)	0.610
	Insulin dependent	3 (7.1)	2 (11.8)	1 (4.0)	
	No diabetes	32 (76.2)	12 (70.6)	20 (80.0)	
HIV status	Positive	6 (14.3)	4 (23.5)	2 (8.0)	0.158
	Negative	36 (85.2)	13 (76.5)	23 (92.0)	
HPV Status	Positive	20 (38.5)	10 (58.8)	10 (40.0)	0.176
	Negative	2 (4.76)	0 (0.0)	2 (8.0)	
	Unavailable	20 (38.5)	7 (41.2)	13 (52.0)	
FIGO stage	Stage I/II	17 (40.5)	9 (52.9)	8 (32.0)	0.175
	Stage III/IV	25 (59.5)	8 (47.0)	17 (68.0)	
Multifocal disease	Yes	8 (19.0)	2 (11.76)	6 (24.0)	0.322
	No	34 (81.0)	15 (88.2)	19 (76.0)	
Location of tumor	Right/Left labia	12 (29.3)	7 (43.8)	5 (20.0)	0.083
	Clitoral hood	1 (2.4)	0 (0.0)	1 (4.0)	
	Forchette	4 (9.8)	3 (18.8)	1 (4.0)	
	Overlapping sites	24 (58.5)	6 (37.5)	18 (72.0)	
Grade	Well differentiated	7 (21.2)	1 (7.7)	6 (30.0)	0.302
	Moderately differentiated	20 (60.6)	9 (69.2)	11 (55.0)	
	Poorly differentiated/High-grade dysplasia	6 (18.2)	3 (23.1)	3 (15.0)	
Tumor size		5.16 ± 2.54	4.26 ± 2.76	5.78 ± 2.23	0.057
Largest gross nodal disease size (cm)		2.57 ± 1.21	2.75 ± 1.38	2.48 ± 1.16	0.617
Pathologic T stage	pT1a/pT1b	–	15 (88.2)	–	–
	pT2	–	2 (11.8)	–	–
Pathologic N stage	pN0/pN1a/pN1b	–	8 (66.7)	–	–
	pN2a/pN2b/pN2c	–	3 (25.0)	–	–
	pN3	–	1 (8.3)	–	–
Margin status	Macroscopic Complete Resection	–	13 (76.5)	–	–
	Macroscopic Positive margin	–	4 (23.5)	–	
Radiation treatment	EBRT alone	37 (88.1)	15 (88.2)	22 (88.0)	0.982
	EBRT + Brachytherapy	5 (11.9)	2 (11.8)	3 (12.0)	
EBRT dose, category	< 54	6 (14.3)	5 (29.4)	1 (4.0)	0.003
	54–59.9	16 (38.1)	9 (52.9)	7 (28.0)	
	≥ 60	20 (47.6)	3 (17.7)	17 (68.0)	
High Dose CTV + PTV Margins (cm) †		1.5 (Range: 0–3.0.	1.3 (Range: 0.5–3.0)	1.5 (Range: 0.0–3.0)	0.994
Total RT Dose in EQD2 (Gy)		64.8 (Range: 44.0–90.4)	59.4 (Range: 44.0–90.4)	64.8 (Range: 50–88.6)	0.08
No. of fractions with Bolus	<10	20 (47.5)	10 (58.8)	10 (40.0)	0.231
	≥10	22 (52.4)	7 (41.2)	15 (60.0)	
Concurrent Chemotherapy	Yes	25 (59.5)	7 (41.2)	18 (72.0)	0.046
	No	17 (40.5)	10 (58.8)	7 (28.0)	
Chemotherapy type	Cisplatin	23 (92.0)	6 (85.7)	17 (94.4)	0.223
	Carboplatin/Paclitaxel	1 (4.0)	1 (14.3)	0 (0.0)	
	Other	1 (4.0)	0 (0.0)	1 (5.6)	

KPS: Karnofsky Performance Status **EBRT**: External Beam Radiation Therapy; **CTV**: Clinical Target Volume; **PTV**: Planning Target Volume; **No**: Number.

*P-values were calculated using ANOVA for numerical variables and chi-square for categorical variables
† Represents the sum of the anatomically modified CTV and PTV margin expansions for the highest dose level of EBRT.

primary gross tumor with a 1–2 cm margin and inclusion of the entire vulvar electively in primary clinical target volume (CTV). For post-operative treatment, the primary CTV included the post-operative bed with 1–2 cm margin as well as the entire vulva. If the vagina, urethra, bladder, or rectum was involved, additional margin into these structures was included to cover potential areas of microscopic spread. Most patients received radiation to the primary site, bilateral inguinal and pelvic lymph node regions (n = 40), whereas 2 patients received radiation to post-operative bed only. Pre-sacral (n = 26) and mesorectal (n = 5) lymph nodes were treated electively at the discretion of the treating physician. After 45–50.4 Gy was delivered to the primary site, entire vulva and nodes (if treated), a sequential boost was delivered to the residual gross disease or the post-operative bed with a median 1.0 cm CTV margin (range 0–2 cm) to the total prescribed dose. A median planning target margin (PTV) of 0.5 cm (range: 0.4–1 cm) was utilized to account for daily setup variation. Gross undissected nodes were generally treated with a 5–7 mm PTV margin without a CTV margin.

Thirty-seven (88 %) patients received intensity-modulated radiation therapy (IMRT), 3 (7.1 %) patients received 3D-conformal radiation and 2 (4.8 %) patients received a combination of IMRT and 3D-conformal techniques. Representative axial slices from an IMRT plan for a patient treated with definitive chemoradiation are shown in **Supplemental Data,** Fig. 1**.** The median dose to the elective lymph node regions was 45 Gy (range 44 Gy-50.4 Gy). The median total dose to the primary site treated with EBRT was 64 Gy (range 50–74 Gy) and 59.4 Gy (range 45–64.8 Gy) in the definitive and adjuvant treatment settings, respectively. Five (11.9 %) patients received a boost with brachytherapy, including 3 patients treated definitively and 2 patients post-

operatively due to macroscopic positive margins. The median combined dose in 2 Gy equivalent fractions (EQD2) for patients that received brachytherapy was 83.3 Gy (Range: 63.0–90.4 Gy).

2.3. Response and toxicity assessment

Patients were evaluated at 3 months post-radiation and subsequently every 3–6 months for the first 2 years. Surveillance imaging was obtained when clinically indicated based on symptoms and/or examination findings. A pelvic examination was performed at each follow up visit. A clinical complete response was defined as no visible tumor on exam. Pathologic complete response was defined as no evidence of tumor on biopsy or surgical specimen.

Acute and late adverse events graded by the physician using the Common Terminology Criteria for Adverse Events (CTCAEv5) during radiation and throughout the follow-up period were recorded. Acute toxicity was defined as occurring < 90 days from radiation initiation and late toxicity was defined as occurring ≥ 90 days from completion of radiation. Non-hematologic severe toxicity was defined as a CTCAEv5 grade ≥ 3 adverse event. Late (≥90 days from completion of radiotherapy) patient-reported subjective symptoms (PSS) documented by the physician in the medical record were also recorded.

2.4. Statistical analysis

Demographics, clinical, and treatment characteristics were tabulated using frequency and percentage and median and interquartile range (or mean standard deviation) according to data structure. Comparative analysis between radiotherapy type, acute and late grade skin toxicity status were conducted using analysis of variance (ANOVA) for continuous variables, and Chi-square or Fischer exact test for categorical variables. Kaplan Meier curves were created to calculate median follow-up, estimates, and log rank test of local regional control stratified by surgical resection. Further analyses were conducted with univariate Cox regression models with covariates of interest. All analyses were performed in SAS 9.4 (SAS institute; Cary, North Carolina) with a significance level of $P < 0.05$, two-tailed.

3. Results

3.1. Patients

The median follow-up time for the 42 patients included in this analysis is 27 months (95 % CI: 9.5–32.7 months). Demographic, clinical, and treatment variables are shown in Table 1, according to the receipt of adjuvant vs definitive radiation therapy. Patients treated with adjuvant radiation were more likely to be Black and have a higher Karnofsky performance status (KPS) and body-mass index (BMI). Higher radiation dose and concurrent chemotherapy were more common in the definitive radiation treatment setting. Ten patients (23.8 %) were followed until their death. The two-year OS estimate for the whole cohort was 81.2 % (95 % CI: 54.3 %-90.6 %), and median survival was not yet reached (95 % CI: 81.3 months-not reached).

3.2. Local-regional control

Eleven (26.2 %) patients developed recurrent disease during the follow-up period. Isolated local or regional recurrence occurred in 6 (14.29 %) of patients, and five patients (11.9 %) developed distant metastatic disease. The median LRC time was not reached (95 % CI: 72.7 months-not reached) among the entire cohort. The two-year rate of LRC was 73.1 % (53.8 %-85.3 %) overall. There was no significant difference in LRC among patients who underwent resection vs those treated definitively ($p = 0.452$) (Fig. 1).

Factors associated with LRC are shown in Supplementary Data, Table 1. Notably, larger tumor size (HR: 1.27; 95 % CI: 1.02–1.57; p =

Table 2
Factors associated with acute grade ≥ 3 skin toxicity.

Covariate	Level	Not Present N = 29 (%)	Present N = 13 (%)	P-value*
Age (years)	< 65 yr	16 (55.2)	6 (46.2)	0.588
	≥65 yr	13 (44.8)	7 (53.9)	
Race	White	13 (44.8)	6 (46.2)	0.936
	Black	16 (55.2)	7 (53.9)	
KPS	80–100	26 (89.7)	11 (84.6)	0.641
	50–70	3 (10.3)	2 (15.4)	
Smoking status	Active smoker/ Former smoker	16 (55.2)	7 (53.9)	0.936
	Never smoker	13 (44.8)	6 (46.2)	
Lichen Sclerosis	Yes	4 (13.8)	0 (0.0)	0.159
	No	25 (86.2)	13 (100)	
Body Mass Index (kg/m2)		28.5 ± 4.9	31.1 ± 5.8	0.144
Diabetes Mellitus	Non-insulin dependent	5 (17.2)	2 (15.4)	0.986
	Insulin dependent	2 (6.9)	1 (7.7)	
	No diabetes	22 (75.9)	10 (76.9)	
HIV status	Positive	6 (20.69)	0 (0.0)	0.076
	Negative	23 (79.3)	13 (100.0)	
FIGO stage	Stage I/II	12 (41.4)	5 (38.5)	0.859
	Stage III/IV	17 (58.6)	8 (61.5)	
Surgical resection	Yes	13 (44.8)	4 (30.8)	0.391
	No	16 (55.2)	9 (69.2)	
Inguinal Lymphadenectomy		9 (31.0)	3 (23.1)	0.598
Margin status	Macroscopic Complete Resection	10 (76.9)	3 (75.0)	0.937
	Macroscopic Positive margin	3 (23.1)	1 (25.0)	
Tumor size (cm)		5.3 ± 2.5	5.0 ± 2.8	0.750
Size of nodal disease	≤3 cm	10 (58.8)	5 (62.5)	0.861
	>3 cm	7 (41.2)	3 (37.5)	
EBRT dose (Gy)	< 54	5 (17.2)	1 (7.7)	0.448
	54–59.9	12 (41.4)	4 (30.8)	
	≥60	12 (41.4)	8 (61.5)	
Total RT Dose in EQD2 (Gy)		62.7 ± 11.6	62.9 ± 10.4	0.951
High Dose CTV + PTV Margins (cm)†	<1.5 cm	10 (34.5)	5 (38.5)	0.804
	≥1.5 cm	19 (65.5)	8 (61.5)	
No. of fractions with Bolus	< 10	14 (48.3)	6 (46.2)	0.899
	≥10	15 (51.7)	7 (53.9)	
Concurrent Chemotherapy	Yes	16 (55.2)	9 (69.2)	0.972
	No	13 (44.8)	4 (30.8)	

KPS: Karnofsky Performance Status **EBRT**: External Beam Radiation Therapy; **CTV**: Clinical Target Volume; **PTV**: Planning Target Volume; **No**: Number; **EQD2**: Equivalent Dose in 2 Gy Fractions.

(*continued on next page*)

Table 2 (*continued*)

Covariate	Level	Not Present N = 29 (%)	Present N = 13 (%)	P-value*

*P-values were calculated using ANOVA for numerical variables and chi-square for categorical variables
† Represents the sum of the anatomically modified CTV and PTV margin expansions for the highest dose level of EBRT.

0.030), presence of a nodal disease > 3.0 cm (HR: 6.08; 95 % CI: 1.26–29.40), and multifocal disease (HR: 4.02 95 % CI: 1.11–14.61) were associated with inferior LRC.

3.3. Acute and late toxicity

Acute grade ≥ 3 non-hematologic toxicity occurred in 17 patients (40.5 %), which included 13 (31.0 %) patients who developed grade 3 skin toxicity. The remaining 4 patients with grade 3 toxicity included a patient with diarrhea and nausea requiring hospital admission, 2 patients with severe fatigue, and a patient that developed a urinary tract infection resulting in hospital admission. Given the predominance of severe skin toxicity, a univariate analysis to identify predictors of acute skin toxicity was performed, as shown in Table 2. There were no factors associated with acute grade 3 skin toxicity including smoking status, BMI, diabetes mellitus, HIV status, tumor size, resection status and radiation dose.

Eleven patients (27.5 %) developed late grade ≥ 3 toxicity events, 10 of which were skin toxicity (23.8 %). There were 4 events of grade 4 late toxicity events in 3 patients, whose disease and treatment characteristics are shown in Table 3.

All three patients developed grade 4 skin necrosis or perineal wounds, one of which had also developed grade 4 fecal incontinence requiring emergent diversion in the setting of gross residual disease after definitive chemoradiation treatment. Each patient was managed with surgical debridement. There were no grade 5 toxicities. Factors associated with late grade ≥ 3 skin toxicity are shown in Table 4. BMI was significantly higher among patients who had developed late grade ≥ 3 skin toxicity (33.03 ± 5.0 vs 28.19 ± 4.86 kg/m^2; p = 0.009); however, there were no other significant associations.

3.4. Patient subjective symptoms

Late (≥90 days from completion of radiotherapy) PSS, or patient reported complaints documented by the provider during follow-up, are shown in Fig. 2. Subjective symptoms were not recorded for six (14.3 %) of patients. The most common complaints were skin discoloration (23.8 %), vaginal pain (35.7 %), and pain requiring continued opiate use (28.6 %).

4. Discussion

Radiation plays a key role in the treatment of vulvar cancer; however, data regarding the incidence and predictors of acute and late morbidity from radiation are limited. In this study, with a median follow up 27 months, we report a 2-year locoregional control rate of 73 %, which did not differ among patients that underwent surgery versus those treated with definitive radiation treatment. With a median external beam dose of 64 Gy and 59.4 Gy in the definitive and adjuvant treatment settings, respectively, we report incidence of grade ≥ 3 acute toxicity was 40.5 %, the majority of which were skin toxicity. Furthermore, 30.9 % of patients developed severe late toxicity, including 23.8 % of patients with late severe skin toxicity. Importantly, there were no grade 5 toxicities in our study.

This study is unique in that we assessed factors that may predict acute and late toxicity. Interestingly, we did not identify any factors associated with acute skin toxicity including smoking status, presence of comorbid conditions, or radiation dose, which is likely due to the relatively small cohort and lack of statistical power. However, patients who developed late grade ≥ 3 skin toxicity tended to have higher BMI, a finding that has also been reported in patients with anal cancer treated with definitive chemoradiation. (Mitra et al., 2017) One reason for this association may be increased dose to the skin because of skin folds among patients with higher BMI. Another possibility is coinciding metabolic disease, which complicates recovery of normal tissue following radiotherapy. (Yusuf et al., 2017).

These data suggest a higher incidence of severe toxicity compared to previous studies. For example, GOG-205 was a non-randomized prospective phase II trial predating the IMRT era of neoadjuvant cisplatin-based chemoradiation in patients with unresectable (T3-T4) vulvar cancer. (Moore et al., 2012) This trial reported a rate of acute grade ≥ 3 skin desquamation of 17.6 %, however, the median dose in this study was 57.6 Gy, and the rates of late toxicity were not reported. In the setting of dose-escalated IMRT for locally advanced vulvar cancer to a median dose of 66 Gy, one institutional series of 49 patients (24 treated preoperatively, 25 definitively) reported an overall acute grade ≥ 3 non-hematologic toxicity rate of 29 % and a late toxicity rate of 6 %. (Richman et al., 2020) Similarly, Stecklein et al. reported a late toxicity in 9 % of patients in a cohort of vulvar cancer patients with lymph node involvement who were treated to 56–70 Gy (Stecklein et al., 2018). Rishi et al. observed a severe late toxicity rate of 19 % in 26 patients treated with definitive radiation, although this study included patients with prior pelvic radiation. (Rishi et al., 2020) Finally, a phase II study of definitive IMRT or 3D-CRT with concurrent capecitabine reported an acute grade ≥ 3 skin toxicity rate of 54 %; however, only 10 % of patients developed late skin toxicity (van Triest et al., 2021). The explanation for the higher incidence of acute and late toxicity observed in our study with prior reports ultimately unclear. Certainly, target delineation, disease extent and burden, radiation dose, and concurrent therapies may play a role. While retrospective assessment of toxicity is inherently limited, severe toxicities requiring an intervention are generally less susceptible to subjectivity. Nevertheless, the rates of severe toxicity observed in our study are consistent with rates of grade ≥ 3 toxicity observed in cervical cancer (Pötter et al., 2021) and anal cancer (Kachnic et al., 2013; Kachnic et al., 2022), both of which are generally treated to lower radiation doses with concurrent chemotherapy.

These data highlight the need for better measures to reliably assess and grade toxicity outcomes. Patient-reported outcomes (PROs) have proven to provide valuable insight on patients' perceived toxicity and its

Table 3
Summary of late Grade 4 toxicity events.

Patient	FIGO Stage	Surgery	EBRT Dose (Gy)	Brachy-therapy Boost Dose	Concurrent Chemo	Toxicity	Management	Gross disease present
1	III	Wide local excision with gross residual disease	59.6	24 Gy in 6 BID fractions (interstitial)	None	Grade 4 Skin	Hyperbaric Oxygen, Debridement	No
2	III	None	66	None	Weekly Cisplatin	Grade 4 Skin	Debridement	No
3	III	None	64	None	Weekly Cisplatin	Grade 4 Skin, Grade 4 Bowel	Debridement, Bowel Diversion	Yes

Table 4
Factors associated with late grade ≥ 3 skin toxicity.

Covariate	Level	Not Present N = 32 (%)	Present N = 10 (%)	P-value*
Age (years)	<65	18 (56.3)	4 (40.0)	0.369
	≥65	14 (43.8)	6 (60.0)	
Race	White	15 (46.9)	4 (40.0)	0.703
	Black	17 (53.1)	6 (60.0)	
KPS	80–100	29 (90.6)	8 (80.0)	0.365
	50–70	3 (9.4)	2 (20.0)	
Smoking status	Active smoker/ Former smoker	19 (59.4)	4 (40.0)	0.283
	Never smoker	13 (40.63)	6 (60.0)	
Lichen Sclerosis	Yes	4 (12.5)	0 (0.0)	0.240
	No	25 (87.5)	10 (100)	
Body Mass Index (kg/m^2)		28.2 ± 4.0	33.0 ± 5.0	0.009
Diabetes Mellitus	Non-insulin dependent	5 (15.6)	2 (20.0)	0.859
	Insulin dependent	2 (6.3)	1 (10.0)	
	No diabetes	25 (78.1)	7 (70.0)	
HIV status	Positive	4 (12.5)	2 (20.0)	0.554
	Negative	28 (87.5)	8 (80.0)	
FIGO stage	Stage I/II	14 (43.8)	3 (30.0)	0.439
	Stage III/IV	18 (56.3)	7 (70.0)	
Surgical resection	Yes	12 (37.5)	5 (50.0)	0.482
	No	20 (62.5)	5 (50.0)	
Inguinal Lymphadenectomy		8 (25.0)	4 (40.0)	0.359
Margin status	Macroscopic Complete Resection	10 (83.3)	3 (60.0)	0.301
	Macroscopic Positive margin	2 (16.7)	2 (40.0)	
Tumor size (cm)		4.9 ± 2.3	6.0 ± 3.1	0.217
Size of nodal disease, category	≤3 cm	12 (66.7)	3 (42.9)	0.275
	>3 cm	6 (33.3)	4 (57.1)	
EBRT dose, category (Gy)	<54	5 (15.6)	1 (10.0)	0.665
	54–59.9	11 (34.4)	5 (50.0)	
	≥60	16 (50.0)	4 (40.0)	
Total RT Dose in EQD2 (Gy)		62.8 ± 11.3	62.7 ± 11.2	0.973
High Dose CTV + PTV Margins (cm)[†]	<1.5 cm	9 (28.1)	6 (60.0)	0.066
	≥1.5 cm	23 (71.9)	4 (40.0)	
No. of fractions with Bolus	<10	15 (46.9)	5 (50.0)	0.863
	≥10	17 (53.1)	5 (50.0)	
Concurrent Chemotherapy	Yes	19 (59.4)	6 (60.0)	0.972
	No	13 (40.6)	4 (40.0)	

KPS: Karnofsky Performance Status **EBRT**: External Beam Radiation Therapy; **CTV**: Clinical Target Volume; **PTV**: Planning Target Volume; **No**: Number; **EQD2**: Equivalent Dose in 2 Gy Fractions.

*P-values were calculated using ANOVA for numerical variables and chi-square for categorical variables

[†] Represents the sum of the anatomically modified CTV and PTV margin expansions for the highest dose level of EBRT.

impact on their overall health-related quality of life (HRQoL). In comparison to other gynecologic malignancies, PRO and HRQoL data among patients with vulvar cancer are limited. GOG-244 prospectively evaluated the risk of lymphedema and PROs in 1,054 females undergoing gynecologic surgery, of which only 42 patients had a diagnosis of vulvar cancer (Carlson et al., 2020; Carter et al., 2021). The most recently published cooperative group vulvar cancer trial, GROINS-VII, a single arm phase II trial evaluating inguinofemoral radiation among patients with positive SN micrometastases, has not reported PROs (Oonk et al., 2021).

In this retrospective cohort spanning from 2008 to 2021, PROs were not collected. Therefore, we aimed to assess the patients' experience based on subjective complaints reported by the provider in the medical record during the follow up period. Interestingly, we identified a significant burden of treatment-related morbidity based on patient subjective symptoms as documented by the provider that did not meet the criteria for high-grade toxicity. Most notably, 35.7 % of patients were still experiencing vulvovaginal pain at least three months from treatment with 28.5 % requiring opiate pain medication. Similarly, 16.7 % of patients in our study complained of late dyspareunia. Sexual toxicity following radiotherapy for vulvar cancer is understudied in comparison to other gynecologic and anorectal cancers (Marshall et al., 2022; Yerramilli et al., 2020). As a result of an increasing rate of HPV infection, the incidence of vulvar cancer particularly in women <60 years old is gradually increasing, implying a greater need to understand the late effects of radiation treatment on patients with vulvar cancer (Kang et al., 2017). These data, together with the well-established divergence between patient and physician-reported toxicities (Bruner et al., 2015), underscores the importance of capturing PROs to better understand the impact of cancer treatments on symptom burden and HRQoL.

Several strategies may prove effective in reducing the morbidity of vulvar cancer treatment. For patients with early-stage, clinically node-negative vulvar cancer, SLNB affords many patients the option to forego inguinofemoral lymphadenectomy in the setting of negative SLNs (Oonk et al., 2021; te Grootenhuis et al., 2016). This has been shown to reduce the risk of wound healing issues, cellulitis and long term lymphedema. In the setting of positive SLN with micrometastases (≤2mm), inguinofemoral lymphadenectomy can be safely replaced with radiation therapy which resulted in lower rates of lymphedema at 12 months (10.7 % versus 22.9 %) (Oonk et al., 2021). However, availability of SLNB may be limited in a low-resource environment.

Toxicity mitigation strategies for locally advanced or unresectable disease are less robust. Establishing the optimal radiotherapy dose and treatment volume may improve the therapeutic ratio. Expert consensus guidelines recommend a wide range of definitive doses between 60 and 70 Gy (Gaffney et al., 2016). Several institutional studies have demonstrated improved local control and survival outcomes associated with p16 + vulvar cancer (Yap et al., 2018; Lee et al., 2016; Dohopolski et al., 2019; Horne et al., 2018). Further study into the influence of HPV status and disease biology may offer an avenue for radiotherapy dose de-escalation similar to HPV-related oropharyngeal cancer (Ferris et al., 2022). The potential utilization of circulating tumor HPV-DNA as a biomarker, which has shown to be prognostic in both HPV-positive oropharyngeal and cervical cancers (Cheung et al., 2019; Chera et al., 2020), may be valuable in identifying patients suitable for dose de-escalation in a clinical trial setting. Furthermore, consensus

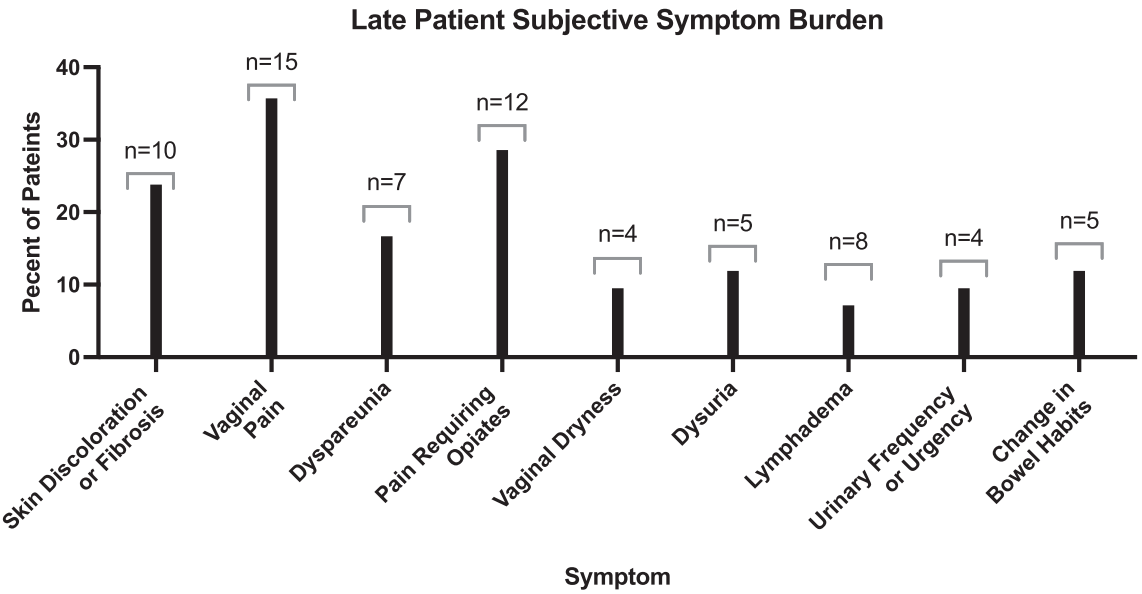

Fig. 2. *Late Patient Subjective Symptom (PSS) Burden.* Subjective symptoms were defined as patient-related complaints documented by providers during follow-up. These data include patients who had developed acute or late grade $\geq$ 3 toxicities. PSS were not well documented in six (14.3 %) of patients, though the plot is representative of the entire cohort (n = 42).

recommendations for CTV expansions are not well-defined. Patterns of failure data are needed to identify areas at risk of disease spread to reduce the amount of healthy tissue irradiated.

Our study has several limitations, including those inherent to a single-institution retrospective study. This cohort includes a heterogeneous vulvar cancer population, including patients with both early and locally advanced disease treated either definitively or adjuvant and with or without concurrent chemotherapy. A strength of this study, however, is its includes a racially-diverse cohort comprised of 54.8 % Black patients, a group that has been poorly represented in vulvar cancer trials (Moore et al., 2012; Carlson et al., 2020; Oonk et al., 2021; Carlson et al., 2008). Additionally, the surgical management of the groins must be considered in the generalizability this study since none of the patients with early-stage vulvar cancer were managed with SLNB. Furthermore, groin dissection was only performed for medically operable patients in the presence of clinical or radiographic nodal disease. Our instutitional approach is to stage these patients with PET/CT rather than SLNB. While the sensitivity and specificity of PET/CT are limited, other studies have demonstrated that radiation doses between 45 and 50 Gy are adequate in controlling possible micrometastaic disease in the PET/CT-negative groin (Richman et al., 2020).

In summary, this multi-center, single-institution comprehensive evaluation of toxicity among women with vulvar cancer treated with radiation demonstrated a high incidence of acute and late toxicity in a real-word treatment setting. Larger prospective studies are needed to identify risk factors, investigate toxicity mitigation strategies, and evaluate patient-reported outcomes in this patient population.

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The contribution of authors to this manuscript were as follows:

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Project development, manuscript writing and editing: TYE, JWS, SH, PRP, ABP, TEC, NK, CHH, ANG, KDS.

Statistical analysis: AAM-V, JMS.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2022.101086.

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