Role of Locoregional Treatment in Vulvar Cancer With Pelvic Lymph Node Metastases: Time to Reconsider FIGO Staging?

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ABSTRACT

Background: Vulvar cancer with pelvic nodal involvement is considered metastatic (M1) disease per AJCC staging. The role of definitive therapy and its resulting impact on survival have not been defined. **Patients and Methods:** Patients with pelvic lymph node–positive vulvar cancer diagnosed in 2009 through 2015 were evaluated from the National Cancer Database. Patients with known distant metastatic disease were excluded. Logistic regression was used to evaluate use of surgery and radiation therapy (RT). Overall survival (OS) was evaluated with log-rank test and Cox proportional hazards modeling (multivariate analysis [MVA]). A 2-month conditional landmark analysis was performed. **Results:** A total of 1,304 women met the inclusion criteria. Median follow-up was 38 months for survivors. Chemotherapy, RT, and surgery were used in 54%, 74%, and 62% of patients, respectively. Surgery was associated with prolonged OS (hazard ratio [HR], 0.58; $P < .001$) but had multiple significant differences in baseline characteristics compared with nonsurgical patients. In patients managed nonsurgically, RT was associated with prolonged OS (HR, 0.66; $P = .019$) in MVA. In patients undergoing surgery, RT was associated with better OS (3-year OS, 55% vs 48%; $P = .033$). Factors predicting use of RT were identified. MVA revealed that RT was associated with prolonged OS (HR, 0.75; $P = .004$). **Conclusions:** In this cohort of women with vulvar cancer and positive pelvic lymph nodes, use of RT was associated with prolonged survival in those who did not undergo surgery. Surgery followed by adjuvant RT was associated with prolonged survival compared with surgery alone.

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Background

Vulvar cancer is the fourth most commonly diagnosed gynecologic cancer in the United States, with an estimated 6,190 cases annually; it is also the fourth most lethal gynecologic cancer, with an estimated 1,200 deaths per year.¹ Based on the 8th edition of the AJCC Cancer Staging Manual, patients with pelvic lymph node metastasis are classified as having metastatic (M1) disease.² In these patients, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Vulvar Cancer suggest consideration of radiation therapy (RT) with concurrent chemotherapy in larger T2 or T3 lesions not amenable to up-front organ-sparing surgery.³ However, minimal published data, either retrospective or prospective, exists for patients with positive pelvic lymph nodes to guide optimal management. One small retrospective series of 20 patients suggests reasonable overall survival (OS) and disease-specific survival in patients with pelvic nodal involvement.⁴ Given the paucity of data for this clinical situation, we used the National Cancer Database (NCDB) to evaluate the impact of definitive treatment in patients with vulvar cancer and positive pelvic lymph nodes.

Patients and Methods

Data Source

The NCDB, sponsored by the American College of Surgeons and American Cancer Society, includes patient data from >1,500 accredited facilities and captures >70% of newly diagnosed cancer cases in the United States.⁵ The data used in this study were derived from a deidentified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology used or the conclusions drawn from these data by the investigators.

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A total of 55,494 patients diagnosed with vulvar cancer between 2004 and 2015 were identified in the NCDB. Patients were excluded from the study if they had unknown or documented negative pelvic lymph nodes. Furthermore, presence or absence of pelvic nodal involvement and the method of pelvic lymph node identification (clinical, radiologic, biopsy, or lymphadenectomy) are cancer-specific factors that were captured within the vulvar cancer database beginning in 2009, with inconsistent documentation before 2009; therefore, patients diagnosed before 2009 were excluded. All patients in this analysis were diagnosed in 2009 through 2015. We confirmed that all patients were staged based on the 8th edition of the AJCC Cancer Staging Manual, in line with the FIGO 2009 staging.

Patients were also excluded if they had known evidence of lung, liver, bone, or brain metastases; previous treatment with RT or chemotherapy was unknown; they received brachytherapy alone; or they had documented RT to a nonpelvic site. Patients diagnosed or treated at a Commission on Cancer–accredited reporting facility were included. The cohort was stratified into those who received surgery and those who did not (Figure 1). Additional stratification included use of RT or chemotherapy. The primary endpoint was OS.

Variable Definitions

All variables were selected a priori. Sociodemographic variables, including patient age, year of diagnosis (2009–2015), comorbidity score, race/ethnicity, insurance status, median income, distance from facility, facility type, and facility location, were defined according to their respective data fields in the NCDB data dictionary.⁶ Comorbidity was defined based on the Charlson/Deyo comorbidity score.⁷ Race was categorized as non-Hispanic white, black, Hispanic, or other. Insurance status was grouped into government (Medicare/Medicaid/other), private, or uninsured. Income was coded based on census tract estimates and was not patient-specific. Distance from treatment facility to residence was grouped at either ≤ 10 or > 10 miles straight-line distance. Facility locations were grouped into Midwest, Northeast, South, and West regions.

Pathologic factors, including tumor size, clinical nodal stage, and grade, were defined according to the data fields. Cancer-specific factors were also evaluated, including extent of primary disease (including depth of invasion when relevant to primary tumor staging). For multivariate analysis (MVA), all T1 lesions were combined and analyzed as 1 value within the T-stage covariate due to small sample size. Tumor size was grouped with a cutoff of 4 cm to differentiate between larger and smaller T2 lesions.³ Only used as a covariate in surgical patients, number of regional lymph nodes examined and presence of positive regional lymph nodes were grouped as extrapolations of pathologic nodal staging. There is uncertainty

Figure 1. Diagram illustrating exclusion criteria and case selection for the patient cohort.

Abbreviations: NCDB, National Cancer Database; RT, radiation therapy.

within the NCDB coding for vulvar cancer regarding whether pelvic lymph nodes are defined as regional or nonregional, and therefore we omitted distinction between inguinal and pelvic lymph node dissection in the setting of regional lymph node evaluation.

Treatment factors included whether the patient received RT, chemotherapy, or surgery. Extent of surgery was defined as either radical, including total removal plus organ resection, or other, encompassing local excision or extent unknown. Patients documented as undergoing biopsy alone were not defined as undergoing surgery. For MVA, all surgery was combined, turning surgery into a binary covariate similar to receipt of chemotherapy or RT. Concurrent chemotherapy and RT was defined as starting within 2 weeks of each another.

Statistical Analysis

Descriptive statistics for each of the sociodemographic, pathologic, and treatment variables were summarized based on treatment received. OS was plotted using the Kaplan-Meier method, with differences across groups assessed using the log-rank statistic. Survival time was calculated from date of diagnosis until date of death or last contact if alive. Patients alive at last contact were censored at last contact date. Conditional landmark analysis was performed, evaluating only patients who survived at least 60 days from initial diagnosis to allow completion of any planned adjuvant treatment.

Survival analyses were performed using the log-rank test for univariate analysis and Cox proportional hazards regression for MVA. Initial variable selection included all variables discussed previously. Patients with unknown

variables had “unknown” entered as a dummy value to allow analysis without further loss of sample size. The final parsimonious multivariate Cox model was formed by using multivariate hierarchical backward selection of variables at a significance level of $P < .10$. Proportional hazards assumption was assessed for all variables in the final MVA and was not violated.⁸ Additional MVA Cox models were developed for subset analyses in patients undergoing or not undergoing surgery, using the same method as described earlier. A multivariate logistic regression was performed to assess factors predictive of undergoing surgery and RT using multivariate hierarchical backward selection of variables at a significance level of $P < .10$. An alpha threshold of 0.05 was chosen for statistical significance. Statistical analyses were performed using SPSS Statistics, version 24.0 (IBM Corp).

Results

Patient Characteristics

A total of 1,304 patients who met inclusion criteria were identified in the NCDB (Figure 1). Median follow-up was 21 months (38 months for survivors). Table 1 summarizes the sociodemographic, pathologic, and treatment characteristics of the study cohort, stratifying and comparing baseline differences between the surgery and no surgery groups. Significant baseline differences were seen, primarily smaller tumor size and lower clinical nodal stage in patients undergoing surgery.

Patients undergoing surgery were more likely to be treated before 2013, have comorbidities, identify as white, have private insurance, live >10 miles from a treatment facility, and have lower tumor stage, smaller tumors, and a lower clinical nodal stage; they were also less likely to receive chemotherapy or RT. For all patients, 3-year and 5-year OS rates were 46.2% and 37.1%, respectively.

Comparison of Surgery Use and Associated Outcomes

Of the 1,304 patients included, 810 (62.1%) underwent surgical resection. Factors reliant on surgery, such as evaluation of regional lymph nodes and positive nodal count, were not included. Factors that were significant on multivariate logistic regression for higher likelihood of surgery included younger age, treatment before 2013, white race, lower tumor stage, and clinically node-negative disease (Table 2).

Median follow-up in patients who did not undergo surgery was 15 months (34.5 months for survivors) compared with 24 months (39 months for survivors) in those who did undergo surgery. Survival outcomes favored patients undergoing surgery on univariate analysis, with 3-year OS of 53.2% versus 32.4% in patients not undergoing

surgery ($P < .001$) (Figure 2). MVA revealed that receipt of surgery was associated with prolonged OS (hazard ratio [HR], 0.58; 95% CI, 0.48–0.72; $P < .001$) (Table 3). Receipt of RT was also associated with prolonged OS (HR, 0.75; 95% CI, 0.62–0.92; $P = .004$). Other factors associated with prolonged OS included younger age, lack of comorbidities, uninsured, treatment in an academic/research facility, smaller tumor size (<4.0 cm), and being clinically node-negative (all $P < .05$).

Use of RT and Outcomes in Patients Undergoing Surgery

When evaluating only the 810 patients who underwent surgical resection, we observed that 572 (70.6%) also underwent RT (Table 1). In MVA, factors significant for increased likelihood of RT use in these patients included more recent year of diagnosis, distance of ≤ 10 miles from facility, treatment at a community facility, having 2 or 3 positive lymph nodes at time of surgery, and receipt of chemotherapy (all $P < .05$) (supplemental eTable 1, available with this article at JNCCN.org).

Survival analyses of patients undergoing surgery showed that addition of RT was associated with prolonged OS (3-year OS, 55.4% vs 48.0% without RT; $P = .033$) (Figure 3A). The association of RT with prolonged OS was maintained in MVA (HR, 0.78; $P = .048$) (supplemental eTable 2). Other factors associated with prolonged OS included younger age, lack of comorbidities, smaller tumor size, and having no positive lymph nodes (all $P < .05$). Use of chemotherapy was not associated with survival in this patient population.

Outcomes in Patients Not Undergoing Surgery

Of 494 patients who did not undergo surgery, 389 (78.7%) received RT. Most patients were treated with both chemotherapy + RT ($n = 299$; 60.5%) (Table 1). RT was associated with prolonged survival in univariate analysis (3-year OS, 35.5% vs 17.1% in patients not receiving RT; $P < .001$) (Figure 3B). Use of RT and chemotherapy was associated with prolonged OS in MVA (HR, 0.66; $P = .019$) (supplemental eTable 3). Other factors associated with prolonged OS included younger age, nongovernment insurance, and tumors ≤ 4 cm. Receipt of chemotherapy did not significantly improve OS in this patient population.

Timing of Surgery, RT, and Chemotherapy

A total of 572 patients received both surgery and RT, 550 (96.2%) of whom had evaluable time point data for both variables. Among patients who received surgery and RT, 90% received RT after surgical resection. A total of 643 patients received both chemotherapy and RT, 621 (96.6%) of whom were evaluable. Concurrent treatment was the most common method of combining these modalities, used in 85% of the studied patients.

Table 1. Baseline Characteristics of Study Cohort

	All Patients n (%)	No Surgery Cohort n (%)	Surgery Cohort n (%)	P Value
Total, N	1,304	494	810	
Sociodemographic factors				
Median age (IQR), y	67 (56–78)	66 (57–80)	67 (56–78)	
Year of diagnosis				<.001 ^a
2009–2012	673 (51.6)	209 (42.3)	464 (57.3)	
2013–2015	631 (48.4)	285 (57.7)	346 (42.7)	
Charlson/Deyo comorbidity score				.018 ^a
0	928 (71.2)	374 (75.7)	554 (68.4)	
1	279 (21.4)	88 (17.8)	191 (23.6)	
≥2	97 (7.4)	32 (6.5)	65 (8.0)	
Race				.002 ^a
Non-Hispanic white	1,058 (81.1)	381 (77.1)	677 (83.6)	
Black	121 (9.3)	64 (13.0)	57 (7.0)	
Hispanic	86 (6.6)	37 (7.5)	49 (6.0)	
Other	39 (2.9)	12 (2.4)	27 (3.3)	
Insurance status				.012 ^a
Government ^b	840 (64.4)	341 (69.0)	499 (61.6)	
Private	380 (29.1)	118 (23.9)	262 (32.3)	
Uninsured	65 (5.0)	28 (5.7)	37 (4.6)	
Unknown	19 (1.5)	7 (1.4)	12 (1.5)	
Median income (residential area)				.058
<\$38,000	271 (20.8)	117 (23.7)	154 (19.0)	
\$38,000–\$47,999	324 (24.8)	123 (24.9)	201 (24.8)	
\$48,000–\$62,999	356 (27.3)	117 (23.7)	239 (29.5)	
≥\$63,000	345 (26.5)	132 (26.7)	213 (26.3)	
Unknown	8 (0.6)	5 (1.0)	3 (0.4)	
Distance from treatment facility				<.001 ^a
≤10 miles	618 (47.4)	261 (52.8)	357 (44.1)	
>10 miles	678 (52.0)	227 (46.0)	451 (55.7)	
Unknown	8 (0.6)	6 (1.2)	2 (0.2)	
Facility type				.69
Community/Comprehensive community	606 (46.5)	229 (46.4)	377 (46.5)	
Academic/Research	501 (38.4)	197 (39.9)	304 (37.5)	
Integrated health network	157 (12.0)	55 (11.1)	102 (12.6)	
Unknown	40 (3.1)	13 (2.6)	27 (3.3)	
Facility location				.66
Midwest	351 (26.9)	129 (26.1)	222 (27.4)	
Northeast	285 (21.9)	117 (23.7)	168 (20.7)	
South	477 (36.6)	182 (36.8)	295 (36.4)	
West	151 (11.6)	53 (10.7)	98 (12.1)	
Unknown	40 (3.1)	13 (2.6)	27 (3.3)	

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Abbreviations: DOI, depth of invasion; IQR, interquartile range; RT, radiation therapy.

^aStatistically significant.^bIncludes Medicare, Medicaid, and other.

Table 1. Baseline Characteristics of Study Cohort (cont.)

	All Patients n (%)	No Surgery Cohort n (%)	Surgery Cohort n (%)	P Value
Pathologic factors				
Extent of primary disease				<.001 ^a
T1				
DOI ≤1.0 mm	43 (3.3)	5 (1.0)	38 (4.7)	
DOI >1.0 mm	457 (35.0)	16 (3.2)	441 (54.4)	
DOI unknown	236 (18.1)	89 (18.0)	147 (18.1)	
T2	318 (24.4)	188 (38.1)	130 (16.0)	
T3	190 (14.6)	146 (29.6)	44 (5.4)	
Unknown	60 (4.6)	50 (10.1)	10 (1.2)	
Tumor size				<.001 ^a
0–4.0 cm	491 (37.7)	103 (20.9)	388 (47.9)	
≥4.1 cm	585 (44.9)	237 (48.0)	348 (43.0)	
Unknown	228 (17.5)	154 (31.2)	74 (9.1)	
Clinical N stage				<.001 ^a
N0	265 (20.3)	12 (2.4)	253 (31.2)	
N1	326 (25.0)	143 (28.9)	183 (22.6)	
N2	405 (31.1)	225 (45.5)	180 (22.2)	
N3	109 (8.4)	86 (17.4)	23 (2.8)	
Unknown	199 (15.3)	28 (5.7)	171 (21.1)	
Grade				<.001 ^a
Well or moderately differentiated	718 (55.1)	220 (44.5)	498 (61.5)	
Poorly or undifferentiated	347 (26.6)	97 (19.6)	250 (30.9)	
Unknown	239 (18.3)	177 (35.8)	62 (7.7)	
Positive regional lymph nodes				<.001 ^a
Not examined (ie, nonsurgical)	429 (32.9)	362 (73.3)	67 (8.3)	
0	23 (1.8)	7 (1.4)	16 (2.0)	
1	374 (28.7)	51 (10.3)	323 (39.9)	
2–3	263 (20.2)	21 (4.3)	242 (29.9)	
≥4	137 (10.5)	10 (2.0)	127 (15.7)	
Unknown	78 (6.0)	43 (8.7)	35 (4.3)	
Regional lymph nodes				<.001 ^a
Not examined (ie, nonsurgical)	429 (32.9)	362 (73.3)	67 (8.3)	
1–10	481 (36.9)	69 (14.0)	412 (50.9)	
≥11	313 (24.0)	20 (4.0)	293 (36.2)	
Unknown	81 (6.2)	43 (8.7)	38 (4.7)	
Treatment factors				
RT				.001 ^a
No	343 (26.3)	105 (21.3)	238 (29.4)	
Yes	961 (73.7)	389 (78.7)	572 (70.6)	
Chemotherapy				<.001 ^a
No	603 (46.2)	166 (33.6)	437 (54.0)	
Yes	701 (53.8)	328 (66.4)	373 (46.0)	

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Abbreviations: DOI, depth of invasion; IQR, interquartile range; RT, radiation therapy.

^aStatistically significant.^bIncludes Medicare, Medicaid, and other.

Table 1. Baseline Characteristics of Study Cohort (cont.)

	All Patients n (%)	No Surgery Cohort n (%)	Surgery Cohort n (%)	P Value
Treatment factors (cont.)				
Surgery				<.001 ^a
None	494 (37.9)	494 (100)	0 (0)	
Radical surgery	435 (33.4)	0 (0)	435 (53.7)	
Other surgery	375 (28.8)	0 (0)	375 (46.3)	
Treatment combinations				
Observation	76 (5.8)	76 (15.4)	0 (0)	<.001 ^a
RT alone	90 (6.9)	90 (18.2)	0 (0)	
Chemotherapy alone	29 (2.2)	29 (5.9)	0 (0)	
Surgery alone	209 (15.8)	0 (0)	209 (25.8)	
Surgery + RT	228 (17.5)	0 (0)	228 (28.1)	
Surgery + chemotherapy	29 (2.2)	0 (0)	29 (3.6)	
Chemotherapy + RT	299 (22.9)	299 (60.5)	0 (0)	
Surgery + chemotherapy + RT	344 (26.3)	0 (0)	344 (42.5)	

Abbreviations: DOI, depth of invasion; IQR, interquartile range; RT, radiation therapy.

^aStatistically significant.

^bIncludes Medicare, Medicaid, and other.

Discussion

This study shows that in patients with vulvar cancer metastatic to pelvic lymph nodes, consideration should be given to definitive management using ≥ 1 locoregional treatment. Patients who underwent surgery had significantly different baseline characteristics from those who did not, limiting the possible conclusions about benefit of surgery, even with standard methods of limiting confounding, such as propensity score adjustment or propensity score matching. If patients are surgically resectable, consideration could be given to surgical therapy. Patients who underwent surgical resection seemed to benefit from adjuvant RT; however, adjuvant chemotherapy appeared to have no effect. Patients who did not undergo surgical resection seemed to benefit most from RT. The role of chemotherapy in either surgical or nonsurgical patients was not well elucidated in this study. Although no statistically significant improvement in OS was seen with addition of chemotherapy, this may be due more to a heterogeneous patient population and limitations of sample size than to a true lack of benefit of chemotherapy.

Previous research determining the role of definitive treatment in patients with vulvar cancer with limited metastases to pelvic lymph nodes is limited to a small single-institution series of 20 patients treated with combinations of surgery, RT, and chemoradiation, showing 5-year OS of 43%.⁴ Our study shows similar outcomes when evaluating all patients. The question posed by Thaker et al⁴ regarding reconsideration of the FIGO staging system is a relevant one, echoed in our study.

Multiple studies in vulvar cancer show significantly worse outcomes in patients with regionally node-positive disease, with 2- to 5-year survival outcomes ranging between 30% and 60%.^{9–12} These previously published rates of OS are similar to the 3- and 5-year OS rates of 46.2% and 37.1%, respectively, seen in our study. Patients who underwent both surgery and RT also had a 3-year OS rate as high as 55%. Additionally, patients with positive pelvic lymph nodes seemed to have better survival than the 2-year OS of approximately 10% reported in those with distant metastases.¹³

Current management of vulvar cancer in either the definitive, neoadjuvant, or postoperative setting includes purposeful RT of lower pelvic lymph nodes, including obturator, external iliac, and internal iliac, when nodal volumes are being treated.¹⁴ The superior aspect of the pelvic RT field, however, is slightly more nebulous and dependent on clinical scenario. In GOG 37, RT went as high as the midpelvis,¹² and in GOG 101 to the inferior sacroiliac joint.¹⁵ The ongoing GROINSS-V II/GOG 270 study of postoperative vulvar cancer (ClinicalTrials.gov identifier: NCT01500512) mandates coverage of the lower half of the external iliac lymph nodes when lymph node RT is performed. Given that coverage of pelvic lymph nodes is routine in the prophylactic setting, treatment of involved pelvic lymph nodes would be consistent with the treatment approach of other pelvic malignancies, such as anal and cervical cancer.

Increased knowledge of cancer biology, together with improvements in both systemic and locoregional therapy, has redefined patients previously considered to have metastatic disease in multiple disease sites.

Table 2. Multivariate Analysis of Use of Surgery by Baseline Characteristics

	Odds Ratio ^a (98% CI)	P Value
Total, N		
Sociodemographic factors		
Median age (IQR), y	0.99 (0.98–1.00)	.043
Year of diagnosis		
2009–2012	Ref	
2013–2015	0.45 (0.32–0.61)	<.001 ^b
Race		
Non-Hispanic white	Ref	
Black	0.49 (0.29–0.84)	.009 ^b
Hispanic	0.75 (0.39–1.44)	.38
Other	1.38 (0.52–3.62)	.52
Distance from treatment facility		
≤10 miles	Ref	
>10 miles	1.35 (0.98–1.87)	.071
Unknown	0.18 (0.19–1.64)	.13
Pathologic factors		
Extent of primary disease		
T1	Ref	
T2	0.210 (0.15–0.30)	<.001 ^b
T3	0.083 (0.05–0.13)	<.001 ^b
Unknown	0.070 (0.03–0.16)	<.001 ^b
Tumor size		
0–4.0 cm	Ref	
≥4.1 cm	0.75 (0.52–1.08)	.12
Unknown	0.29 (0.18–0.46)	<.001 ^b
Clinical N stage		
N0	Ref	
N1	0.094 (0.05–0.19)	<.001 ^b
N2	0.073 (0.04–0.14)	<.001 ^b
N3	0.030 (0.01–0.07)	<.001 ^b
Unknown	0.480 (0.22–1.07)	.071
Grade		
Well or moderately differentiated	Ref	
Poorly or undifferentiated	1.30 (0.89–1.89)	.18
Unknown	0.28 (0.18–0.42)	<.001 ^b

Abbreviation: IQR, interquartile range.

^aOdds ratio <1: less likely to undergo surgery; odds ratio >1: more likely to undergo surgery.^bStatistically significant.

Cervical cancer with para-aortic lymph node involvement used to be considered M1 disease,¹⁶ but multiple studies have shown good oncologic outcomes with definitive local treatment,^{17–19} resulting in an eventual shift of para-aortic lymph node involvement to be considered regional

Table 3. Multivariable Cox Proportional Hazards Model for Overall Survival in All Patients

	Hazard Ratio (95% CI)	P Value
Sociodemographic factors		
Age	1.03 (1.02–1.04)	<.001 ^a
Charlson/Deyo comorbidity score		
0	Ref	
1	1.26 (1.03–1.54)	.025 ^a
≥2	1.45 (1.06–1.99)	.020 ^a
Insurance status		
Government ^b	Ref	
Private	0.82 (0.66–1.02)	.079
Uninsured	0.52 (0.30–0.88)	.015 ^a
Unknown	0.40 (0.15–1.07)	.068
Median income (residential area)		
<\$38,000	Ref	
\$38,000–\$47,999	0.83 (0.65–1.06)	.140
\$48,000–\$62,999	0.77 (0.60–0.98)	.033 ^a
≥\$63,000	0.91 (0.71–1.15)	.420
Unknown	2.26 (1.03–4.95)	.042
Facility type		
Community/Comprehensive community	Ref	
Academic/Research	0.78 (0.65–0.93)	.006 ^a
Integrated health network	0.87 (0.66–1.14)	.300
Unknown	1.70 (0.91–3.17)	.094
Pathologic factors		
Tumor size		
0–4.0 cm	Ref	
≥4.1 cm	1.62 (1.33–1.96)	<.001 ^a
Unknown	1.15 (0.89–1.49)	.280
Clinical N stage		
N0	Ref	
N1	1.37 (1.04–1.79)	.024 ^a
N2	1.37 (1.04–1.82)	.026 ^a
N3	1.66 (1.13–2.43)	.010 ^a
Unknown	1.25 (0.93–1.69)	.140
Treatment factors		
Radiation therapy		
No	Ref	
Yes	0.75 (0.62–0.92)	.004 ^a
Surgery		
No	Ref	
Yes	0.58 (0.48–0.72)	<.001 ^a

^aStatistically significant.^bIncludes Medicare, Medicaid, and other.

Figure 2. Kaplan-Meier overall survival curve, stratified by receipt of surgery, for patients with ≥ 60 days of follow up.

nodal disease.² Similar findings have been shown in node-positive^{20–22} and distant metastatic prostate cancer.²³

The role for definitive RT, generally with chemotherapy, in the management of unresectable vulvar cancer is well documented from multiple prospective studies,^{15,24} with contemporary series showing feasibility of using advanced techniques with good oncologic outcomes in well-selected patients.^{25–27} Standard

limitations of retrospective analysis and database studies apply. We attempted to mitigate as much bias as possible by adjusting for measured confounders through MVA. However, given the NCDB limitations and potential for ascertainment bias, we believed that there was too extreme a difference in baseline characteristics between patients undergoing surgery and those not undergoing surgery. Even with potentially conducting propensity score matching, we were not confident that we would be able to control sufficiently for other confounding variables that may not be as well-captured within the NCDB, such as more sensitive markers of morbidity, surgeon's assessment of resectability, and nature of lymph node disease, among others. Given that pelvic lymph node status did not seem to be regularly coded until 2009, the sample size was somewhat limited, given the clinical rarity of this disease stage and that $>70\%$ of patients with vulvar cancer captured in the NCDB have an unknown pelvic lymph node status. Missing data were an issue for certain examined variables, such as primary tumor size and grade, which were both unknown in approximately 30% of patients not undergoing surgery. The NCDB does not capture which lymph node basins are covered by RT, nor does it reliably capture whether the primary tumor was treated. Given these significant concerns, to suggest a causative relationship or comparative effectiveness of up-front surgery versus up-front RT is beyond the ability of the database and the scope of this paper. However, some form of definitive locoregional treatment, either RT or surgery (with consideration of adjuvant RT), rather than treating with palliative chemotherapy alone, seems to benefit patients in this clinical scenario.

Figure 3. Kaplan-Meier overall survival curve, stratified by receipt of RT, in patients (A) undergoing surgery and (B) not undergoing surgery. Abbreviation: RT, radiation therapy.

However, because this is the largest series to evaluate this relevant endpoint and given the lethality of node-positive vulvar cancer, we believe that these findings are interesting enough to consider future prospective clinical trials in this clinical scenario. In the absence of randomized data, we believe that the 9th edition of the AJCC Cancer Staging Manual should consider whether pelvic lymph node metastases remain classified as a metastatic disease site, given that survival numbers among these patients are much closer to those of patients with regionally node-positive disease rather than known metastatic disease.

Conclusions

Patients with vulvar cancer metastatic to pelvic lymph nodes should be strongly considered for aggressive, definitive treatment similar to those with inguinal lymph

node-positive disease. Patients with surgically resectable disease should be considered for surgery and adjuvant RT, without strong evidence to support use of concurrent chemotherapy. Patients with either technically or medically unresectable disease should be treated with definitive RT, with consideration of concurrent chemotherapy.

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Supplemental online content for:

Role of Locoregional Treatment in Vulvar Cancer With Pelvic Lymph Node Metastases: Time to Reconsider FIGO Staging?

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eTable 1: Multivariate Analysis of Use of RT in Patients Who Underwent Surgery

eTable 2: Multivariable Cox Proportional Hazards Model for Overall Survival in Patients Who Underwent Surgery

eTable 3: Multivariable Cox Proportional Hazard Models for Overall Survival in Patients Who Did Not Undergo Surgery

eTable 1. Multivariate Analysis of Use of RT in Patients Who Underwent Surgery (N=810)

	No RT (n=238)	RT (n=572)	Odds Ratio	95% CI	P Value
Sociodemographic factors					
Year of diagnosis					
2009–2012	148 (62.2)	316 (55.2)		Ref	
2013–2015	90 (37.8)	256 (44.8)	1.52	1.06–2.17	.022 ^a
Distance from treatment facility					
≤10 miles	86 (36.1)	271 (47.4)		Ref	
>10 miles	152 (63.9)	299 (52.3)	0.65	0.45–0.93	.019 ^a
Facility type					
Community/Comprehensive community	104 (43.5)	273 (49.7)		Ref	
Academic/Research	106 (45.2)	198 (36.7)	0.66	0.45–0.96	.032 ^a
Integrated health network	27 (11.3)	75 (13.6)	0.96	0.55–1.68	.84
Unknown	1 (0.4)	26 (4.5)	9.90	1.21–80.8	.032
Pathologic factors					
Positive regional lymph nodes					
Not examined	17 (7.1)	50 (8.7)		Ref	
0	7 (2.9)	9 (1.6)	0.50	0.13–1.93	.32
1	110 (46.2)	213 (37.2)	1.53	0.75–3.10	.24
2–3	56 (23.5)	186 (32.5)	2.27	1.09–4.75	.029 ^a
≥4	37 (15.5)	90 (15.7)	1.15	0.52–2.55	.73
Unknown	11 (4.6)	24 (4.2)	1.01	0.35–2.91	.98
Treatment factors					
Chemotherapy					
No	209 (87.8)	228 (39.9)		Ref	
Yes	29 (12.2)	344 (60.1)	12.93	8.20–20.4	<.001 ^a

Abbreviation: RT, radiation therapy.

^aStatistically significant.

eTable 2. Multivariable Cox Proportional Hazards Model for Overall Survival in Patients Who Underwent Surgery

	Hazard Ratio (95% CI)	P Value
Sociodemographic factors		
Age	1.04 (1.03–1.05)	<.001 ^a
Charlson/Deyo comorbidity score		
0	Ref	
1	1.41 (1.10–1.81)	.007 ^a
≥2	1.82 (1.26–2.62)	.001 ^a
Facility type		
Community/Comprehensive community	Ref	
Academic/Research	0.79 (0.62–1.00)	.050
Integrated health network	0.78 (0.54–1.12)	.18
Pathologic factors		
Tumor size		
0–4.0 cm	Ref	
≥4.1 cm	1.60 (1.27–2.02)	<.001 ^a
Unknown	0.88 (0.57–1.34)	.54
Positive regional lymph nodes		
Not examined	Ref	
0	0.24 (0.05–1.26)	.092 ^a
1	0.94 (0.37–2.36)	.891
2–3	1.64 (0.66–4.11)	.29
≥4	2.84 (1.11–7.27)	.030 ^a
Unknown	1.43 (0.77–2.67)	.26
Treatment factors		
Radiation therapy		
No	Ref	
Yes	0.78 (0.61–0.99)	.048 ^a

^aStatistically significant.**eTable 3. Multivariable Cox Proportional Hazard Models for Overall Survival in Patients Who Did Not Undergo Surgery**

	Hazard Ratio (95% CI)	P Value
Sociodemographic factors		
Age	1.03 (1.01–1.04)	<.001 ^a
Insurance status		
Government	Ref	
Private	0.52 (0.36–0.76)	.001 ^a
Uninsured	0.48 (0.24–0.97)	.041 ^a
Unknown	0.30 (0.07–1.21)	.089
Median income (residential area)		
<\$38,000	Ref	
\$38,000–\$47,999	0.60 (0.41–0.90)	.013 ^a
\$48,000–\$62,999	0.74 (0.50–1.08)	.12
≥\$63,000	0.70 (0.48–1.01)	.057
Unknown	1.65 (0.64–4.28)	.30
Pathologic factors		
Tumor size		
0–4.0 cm	Ref	
≥4.1 cm	1.50 (1.04–2.15)	.029 ^a
Unknown	1.37 (0.94–2.00)	.099
Treatment factors		
Radiation therapy		
No	Ref	
Yes	0.66 (0.47–0.94)	.019 ^a

^aStatistically significant.