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Utilization and Outcomes of Sentinel Lymph Node Biopsy for Vulvar Cancer

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Abstract

Objective—To examine the use and predictors of sentinel node biopsy in women with vulvar cancer.

Methods—The Perspective database, an all-payer database that collects data from over 500 hospitals, was used to perform a retrospective cohort study of women with vulvar cancer who underwent vulvectomy and lymph node assessment from 2006 to 2015. Multivariable models were used to determine factors associated with sentinel node biopsy. Length of stay and cost were compared between women who underwent sentinel node biopsy and lymphadenectomy.

Results—Among 2,273 women, sentinel node biopsy was utilized in 618 (27.2%), while 1655 (72.8%) underwent inguinofemoral lymphadenectomy. Performance of sentinel node biopsy increased from 17.0% (95% CI, 12.0–22.0%) in 2006 to 39.1% (95% CI, 27.1–51.0%) in 2015. In a multivariable model, women treated more recently were more likely to undergo sentinel node biopsy while women with more comorbidities and those treated at rural hospitals were less likely to undergo the procedure. The median length of stay was shorter for those undergoing sentinel node biopsy (median 2 days; IQR 1–3) compared to women who underwent inguinofemoral lymphadenectomy (median 3 days, IQR 2–4). The cost of sentinel node biopsy was \$7599 (IQR, \$5739–\$9922) versus \$8095 (IQR, \$5917–\$11,281) for lymphadenectomy.

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The authors did not report any potential conflicts of interest.

Conclusion—The use of sentinel node biopsy for vulvar cancer has more than doubled since 2006. Sentinel lymph node biopsy is associated with a shorter hospital stay and decreased cost compared to inguinofemoral lymphadenectomy.

Introduction

In 2014, there were an estimated 4,850 new cases of vulvar cancer and 1,030 deaths in the US.¹ At diagnosis 30% of women have lymph node metastases. Vulvar cancer is most commonly treated with radical local excision and inguinofemoral lymphadenectomy.² However, inguinofemoral lymphadenectomy is associated with significant complications, including lymphedema (14-49%), lymphocyst formation (11-40%), and wound complications.³

To reduce surgical morbidity from lymphadenectomy, studies have examined the feasibility of sentinel lymph node biopsy. Several prospective trials and systematic reviews have suggested that sentinel node biopsy is associated with a high sensitivity and low false negative rate for the detection of metastatic disease.⁴⁻¹⁰ In a Cochrane review of the procedure, the pooled sensitivity was 91-95% depending on the modality of sentinel node detection.⁷

Currently the National Comprehensive Cancer Network and the Society of Gynecologic Oncology recommend sentinel lymph node biopsy in patients with a primary, unifocal vulvar tumor <4cm in diameter and no gross evidence of nodal involvement.¹¹ A variety of radiotracers (technetium-99m sulfur) and dyes (indocyanine green and blue dyes) have been used for node detection. Increased sensitivity has been observed in studies when both a radiocolloid and an intradermal dye (most commonly technetium-99m sulfur and isosulfan blue 1%) are used together intraoperatively, and combining both is recommended.^{4,6,8,11}

To date, little is known about the patterns of groin node evaluation in women with vulvar cancer. We examined the use and predictors of sentinel lymph node biopsy in women with vulvar cancer and explored the outcomes and costs of the procedure.

Materials and Methods

We performed a retrospective cohort study using data from the Perspective database (Premier, Inc., Charlotte, North Carolina). Perspective is an all-payer database developed to examine the patterns of care and outcomes of patients from across the U.S. This voluntary database contains data from over 500 hospitals, including data source demographic information, data on diagnoses and procedures collected through billing codes, medication and device use, and cost. Within participating hospitals all patients are captured. Data within the database is transmitted to Premier by participating hospitals and undergoes a multistep quality control process to verify the accuracy and completeness of the data. All data was de-identified and the Columbia University Institutional Review Board deemed the study exempt.

We examined women with invasive vulvar cancer (ICD9 184.1-184.4) who underwent surgery from January 2006 to March 2015. Surgery included any resection of the vulva

(ICD9 71.4, 71.5, 71.6, 71.61, 71.62 and CPT 56630, 56631, 56632, 56633, 56634, 56637, 56640, 56620, 56625). Performance of lymphadenectomy was determined using ICD9 (40.1, 40.11, 40.24, 40.29, 40.3, 40.5, 40.50, 40.54) and CPT (38500, 38760, 38765, 56631, 56632, 56634, 56637, and 56640) codes. Sentinel lymph node biopsy was defined as either the presence of a CPT for radiopharmaceutical mapping (38792, 38900, 78195, 78800, 78801) or of a billing code for a substance used for sentinel lymph node biopsy (technetium-99, isosulfan blue, patent blue, sulphan blue, methylene blue, indocyanine green). Patients with codes for both a lymphadenectomy and sentinel lymph node biopsy were classified as having undergone sentinel lymph node biopsy. Patients with codes for neither lymphadenectomy nor sentinel lymph node biopsy were classified as not having undergone nodal evaluation.

Clinical characteristics and demographics included age at the time of surgery (<40, 40-49, 50-59, 60-69, 70), year of surgery (2006-2015), marital status (married, single, other/unknown), race (white, black, other/unknown) and insurance type (commercial, Medicare, Medicaid, uninsured, unknown). Risk adjustment for comorbid medical conditions was performed using the Elixhauser comorbidity index with patients categorized as 0, 1, 2 comorbidities.¹²

Hospital characteristics included hospital location (urban vs rural), teaching status (non-teaching vs teaching), hospital bed size (<400, 400-600, >600 beds), and region (Northwest, Midwest, South, West). Annualized hospital volume was calculated for each hospital and estimated as the total number of procedures performed divided by the number of years in which a hospital performed at least one procedure. Hospital volume was then classified into three approximately equal tertiles.

Outcomes analyzed included length of stay and cost. Length of stay was defined as the number of hospital days from the procedure until discharge to home or another facility.¹³ Cost was captured based on facility-specific cost data reported by hospitals to the database. Perspective captures cost data through a log of all items that are billed to a patient during the facility stay.¹⁴ Approximately 75% of hospitals report direct cost based on procedural accounting, while the other quarter of hospitals report cost based on Medicare cost-to-charge ratios.^{15,16} The total cost of the hospitalization was recorded and adjusted for inflation using the Consumer Price Index and reported in 2015 U.S. dollars.¹⁷ Extreme costs were winsorized to the 3rd and 97th percentiles. Separate analyses are also reported for fixed and variable costs.¹⁴

Frequency distributions between categorical variables were compared using χ^2 tests. The trends in use of sentinel lymph node biopsy over time are reported using Cochran-Armitage trend tests. Cost data and length of stay are reported as medians with interquartile ranges and compared using Wilcoxon tests. The association between the clinical, demographic, and hospital characteristics and use of sentinel lymph node biopsy were examined using multivariable random-intercept Poisson regression models. These models included a hospital-specific intercept to account for hospital-level clustering. Results are reported as risk ratios (RR) and 95% confidence intervals. All analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, North Carolina). All statistical tests were two-sided.

Results

A total of 2,273 women were identified. Within the cohort, 618 (27.2%) women underwent sentinel lymph node biopsy while 1655 (72.8%) had an inguinofemoral lymphadenectomy (Table 1, Figure 1). The rate of use sentinel lymph node biopsy was 17.0% (95% CI, 12.0-22.0%) in 2006, remained relatively stable until 2009 when it was 18.2% (95% CI, 13.2-23.3%), and then increased annually to 39.1% (95% CI, 27.1-51.0%) in 2015 ($P<0.001$) (Figure 2). Among women who underwent sentinel lymph node biopsy, 45.3% of procedures used isosulfan blue, 69.3% technetium-99, and 21.5% methylene blue (Table 2). Two or more agents were used in 62.5% of the cases.

The clinical and demographic characteristics of the cohort are displayed in Table 1. sentinel lymph node biopsy was more often performed in married women ($P=0.04$) and Medicare recipients ($P=0.02$). Women treated in teaching hospitals (versus non-teaching) ($P<0.001$) and urban centers (versus rural) ($P<0.001$) were more likely to undergo sentinel lymph node biopsy. Similarly, those women treated at high volume centers were more likely to undergo a sentinel lymph node biopsy ($P<0.001$).

In a multivariable model, patients treated more recently were more likely to undergo sentinel lymph node biopsy. Compared to women treated in 2006, the adjusted risk ratio (aRR) for undergoing sentinel lymph node biopsy for those operated on in 2010 was 1.56 (95% CI 1.00-2.45) and 2.34 (95% CI 1.36-4.03) in 2015 (Table 3). Women treated in rural compared to urban hospitals were less likely to undergo sentinel lymph node biopsy (aRR 0.24, 95% CI 0.06-0.96). Similarly, women with 2 or more comorbid medical conditions were less likely to undergo sentinel lymph node biopsy (aRR 0.67, 95% CI 0.47-0.94).

The median length of stay was shorter for those undergoing sentinel lymph node biopsy (median 2; IQR 1-3) compared to women who underwent inguinofemoral lymphadenectomy (median 3, interquartile range [IQR] 2-4, $P<0.001$) (Table 4). The total cost of sentinel lymph node biopsy was \$7599 (IQR, \$5739-\$9922) versus \$8095 (IQR, \$5917-\$11,281) for inguinofemoral lymphadenectomy ($P<0.001$). Similar trends were noted in the analyses of fixed and variable costs.

Discussion

Our data suggest that the use of sentinel node biopsy for vulvar was relatively constant from 2006 to 2009 and then increased steadily since 2010. Compared to inguinofemoral lymphadenectomy, sentinel lymph node biopsy is associated with a shorter hospital stay and a modest decrease in cost.

The performance characteristics of sentinel node biopsy have been examined in a number of prospective trials.⁴⁻⁶ In 2008, the Groningen International Study on Sentinel nodes in Vulvar cancer (GROINSS-V) reported that sentinel node biopsy had a sensitivity of 94%, and false negative predictive value (FNPV) of 2.9%.⁴ In 2012, Gynecologic Oncology Group protocol 173 reported that sentinel node biopsy had a sensitivity of 92% and FNPV of 3.7% among patients with a tumor size ≤ 2 cm and ≤ 6 cm.⁶ Subsequent meta-analyses and a

Cochrane review in 2014 have indicated similar safety and efficacy and recommended its use for early-stage tumors.⁷⁻¹⁰

While sentinel node biopsy has only recently been examined for vulvar cancer, the technology has been utilized for several years for breast cancer and melanoma. In breast cancer, sentinel node biopsy was introduced in the late 1990s as an alternative to axillary lymphadenectomy. Sentinel node biopsy use increased rapidly from approximately 27% of cases in 1998 to 66% by 2005.¹⁸ Comparatively, use of sentinel node biopsy for vulvar cancer has remained modest.

A number of factors have likely contributed to the slow dissemination of sentinel node biopsy for vulvar cancer. Perhaps most importantly, vulvar cancer is rare and thus the number of cases performed by individual surgeons is often low, limiting the potential to develop the technical skills for a new procedure.. Currently the American Society of Breast Surgeons recommends surgeons record their experiences and outcomes with a goal of a detection rate of 85% and a false negative rate of 5%. A minimum of 20 sentinel lymph node biopsy procedures in conjunction with axillary lymph node dissection or with supervision from an experienced surgeon is required.^{19,20} At the present, there is no required number of procedures for competency in vulvar sentinel lymph node biopsy.

We found sentinel lymph node biopsy was more likely to be performed at urban compared to rural hospitals. This may be due to the limited number of providers who are comfortable performing sentinel lymph node biopsy for vulvar cancer, particularly at rural facilities. Access to high-quality care is often a concern for women with gynecologic tumors in rural and underserved areas.^{21,22}

Prior studies in vulvar cancer have noted a number of racial and socioeconomic disparities in treatment and outcomes.²³⁻²⁵

Our data are in accord with prior work that suggests that sentinel node biopsy is cost effective for vulvar cancer. A cost effectiveness analysis demonstrated that the cost of initial treatment and three-year follow-up was \$22,415 for sentinel lymph node biopsy compared to \$26,344 for inguinofemoral lymph node dissection.²⁶ A second cost utility analysis also suggested that sentinel lymph node biopsy was superior to lymph node dissection in terms of both cost (\$13,499 vs \$14,621) and quality adjusted life years (4.16 vs 4.00).²⁷

While our study benefits from the inclusion of a large number of patients, we acknowledge several important limitations. First, there may have been under capture of sentinel node biopsy in a small number of women. Second, we lack data on tumor characteristics, including stage, histology, size and location of the primary lesion. A priori, the goal of our study was simply to examine the use of sentinel node biopsy and not to analyze the impact of its use on survival. Third, we cannot distinguish women who underwent sentinel node biopsy followed by lymphadenectomy and those who underwent sentinel node biopsy alone. Fourth, while the database has been used in a number of economic studies, our estimates of costs represent direct hospital costs and do not capture societal costs. Fifth, while the database captures women from a large number of hospitals, the included hospitals varied over time and may not be generalizable to the entire population.

The low rate of sentinel node biopsy in women with vulvar cancer offers an opportunity to improve the quality of care for vulvar cancer. While our analysis did not directly examine outcomes, prior work has shown that sentinel node biopsy is safe and effective in this setting. Further comparative effectiveness studies to examine the effectiveness of sentinel lymph node biopsy in real world settings would be of great utility. Targeted initiatives to promote sentinel lymph node biopsy in women with early-stage vulvar cancer could potentially lower costs as well as perioperative morbidity.

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Precis

Vulvar sentinel lymph node biopsy has increased since 2010 and is associated with a shorter hospital stay and decreased cost compared to inguinofemoral lymphadenectomy.

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Figure 1.
Flowchart of patient selection.

Figure 2.

Trends in sentinel lymph node biopsy among women with vulvar cancer who had lymph node dissection ($P < 0.001$). Trends in performance of sentinel lymph node dissection versus lymphadenectomy were compared using Cochran-Armitage trend tests. Error bars represent 95% confidence intervals.

Table 1

Demographic and clinical characteristics of the cohort stratified by performance of sentinel lymph node biopsy.

Characteristics	No Sentinel Lymph Node Biopsy		Sentinel Lymph Node Biopsy		<i>P-value</i>
	N	%	N	%	
<i>All</i>	1,655	(72.8)	618	(27.2)	
<i>Age (years)</i>					0.97
<40	60	(3.6)	24	(3.9)	
40-49	169	(10.2)	63	(10.2)	
50-59	324	(19.6)	122	(19.7)	
60-69	369	(22.3)	144	(23.3)	
70	733	(44.3)	265	(42.9)	
<i>Year</i>					<0.001
2006	181	(10.9)	37	(6.0)	
2007	160	(9.7)	47	(7.6)	
2008	178	(10.8)	37	(6.0)	
2009	184	(11.1)	41	(6.6)	
2010	167	(10.1)	49	(7.9)	
2011	189	(11.4)	97	(15.7)	
2012	204	(12.3)	82	(13.3)	
2013	178	(10.8)	98	(15.9)	
2014	175	(10.6)	105	(17.0)	
2015	39	(2.4)	25	(4.1)	
<i>Marital status</i>					0.04
Married	581	(35.1)	236	(38.2)	
Single	896	(54.1)	300	(48.5)	
Other/unknown	178	(10.8)	82	(13.3)	
<i>Race</i>					0.20
White	1,288	(77.8)	497	(80.4)	
Black	119	(7.2)	32	(5.2)	
Other/unknown	248	(15.0)	89	(14.4)	
<i>Insurance status</i>					0.02
Commercial	508	(30.7)	175	(28.3)	
Medicare	917	(55.4)	354	(57.3)	
Medicaid	121	(7.3)	44	(7.1)	
Uninsured	83	(5.0)	23	(3.7)	
Unknown	26	(1.6)	22	(3.6)	
<i>Hospital location</i>					<0.001
Urban	1,596	(96.4)	615	(99.5)	
Rural	59	(3.6)	3	(0.5)	
<i>Hospital teaching status</i>					<0.001
Teaching	1,066	(64.4)	467	(75.6)	

Characteristics	No Sentinel Lymph Node Biopsy		Sentinel Lymph Node Biopsy		<i>P-value</i>
	N	%	N	%	
Non-teaching	589	(35.6)	151	(24.4)	
<i>Hospital bed size</i>					0.52
<400	496	(30.0)	170	(27.5)	
400-600	531	(32.1)	205	(33.2)	
>600	628	(38.0)	243	(39.3)	
<i>Hospital region</i>					0.02
Northeastern	287	(17.3)	75	(12.1)	
Midwest	269	(16.3)	113	(18.3)	
South	884	(53.4)	352	(57.0)	
West	215	(13.0)	78	(12.6)	
<i>Comorbidity (Elixhauser)</i>					0.48
0	103	(6.2)	47	(7.6)	
1	281	(17.0)	106	(17.2)	
2	1,271	(76.8)	465	(75.2)	
<i>Annualized hospital volume</i> ^{<i>I</i>}					<0.001
Low	228	(13.8)	52	(8.4)	
Medium	267	(16.1)	53	(8.6)	
High	1,160	(70.1)	513	(83.0)	

P-value based on χ^2 tests.

^{*I*}Low volume 4 cases/year, intermediate volume 4.3-5.2 cases per year, high-volume 5.3 cases per year. IQR: interquartile range.

Table 2

Modality of sentinel lymph node detection in women who underwent the procedure.

Method of sentinel node detection	Modality	
	N	(%)
<i>Localization agent *</i>		
Technetium-99	428	(69.3)
Isosulfan blue	289	(45.3)
Methylene blue	133	(21.5)
Not otherwise specified	5	(0.8)
<i>Number of agents used</i>		
1	227	(36.7)
2	386	(62.5)
Unknown	5	(0.8)

* Not mutually exclusive

Table 3

Multivariable model of predictors of sentinel lymph node biopsy.

Covariate	aRR
<i>Age (years)</i>	
<40	Referent
40-49	0.89 (0.54-1.46)
50-59	0.91 (0.57-1.45)
60-69	0.90 (0.56-1.44)
70	0.81 (0.49-1.32)
<i>Year</i>	
2006	Referent
2007	1.27 (0.82-1.96)
2008	1.10 (0.69-1.77)
2009	1.31 (0.82-2.09)
2010	1.56 (1.00-2.45) *
2011	1.95 (1.31-2.91) *
2012	1.94 (1.28-2.94) *
2013	2.41 (1.60-3.62) *
2014	2.53 (1.68-3.79) *
2015	2.34 (1.36-4.03) *
<i>Marital status</i>	
Married	Referent
Single	0.85 (0.71-1.02)
Other/unknown	1.22 (0.82-1.81)
<i>Race</i>	
White	Referent
Black	0.83 (0.57-1.20)
Other/unknown	0.84 (0.64-1.12)
<i>Insurance status</i>	
Commercial	Referent
Medicare	1.26 (0.97-1.63)
Medicaid	1.04 (0.73-1.47)
Uninsured	0.78 (0.49-1.22)
Unknown	1.56 (0.97-2.50)
<i>Hospital location</i>	
Urban	Referent
Rural	0.24 (0.06-0.96) *
<i>Hospital teaching status</i>	
Teaching	Referent
Non-teaching	0.72 (0.43-1.20)
<i>Hospital bed size</i>	

Covariate	aRR
<400	Referent
400-600	1.01 (0.59-1.71)
>600	1.03 (0.58-1.82)
<i>Hospital region</i>	
Northeastern	Referent
Midwest	0.92 (0.46-1.84)
South	1.20 (0.67-2.16)
West	1.30 (0.63-2.67)
<i>Comorbidity (Elixhauser)</i>	
0	Referent
1	0.80 (0.55-1.15)
2	0.67 (0.47-0.94) *
<i>Annualized hospital volume^I</i>	
Low	Referent
Medium	0.82 (0.44-1.51)
High	1.19 (0.73-1.96)

Mixed-effect model was fitted accounting for hospital-level clustering. The covariates included age, year, marital status, race, insurance status, hospital location, teaching status, bed size, region, comorbidity and annualized hospital volume.

* P-value <0.05

^I Low volume 4 cases/year, intermediate volume 4.3-5.2 cases per year, high-volume 5.3 cases per year. aRR: adjusted risk ratio

Table 4

Outcomes stratified by performance of sentinel lymph node biopsy.

Outcome	No Sentinel Lymph Node Biopsy		Sentinel Lymph Node Biopsy		<i>P-value</i>
	Median	IQR	Median	IQR	
Length of stay	3	(2-4)	2	(1-3)	<0.001
Total cost	8,095.32	(5,917.04-11280.69)	7,599.01	(5,738.73-9,922.66)	<0.001
Fixed cost	4,132.02	(2,815.69-5,918.68)	3,798.16	(2,609.42-5,289.17)	<0.001
Variable cost	3,836.33	(2,696.67-5,646.02)	3,566.21	(2,728.25-4,929.32)	0.01

* Cost expressed as 2015 US dollars. Length of stay presented as days. Data presented as medians with interquartile range (IQR) and compared using Wilcoxon tests.