Gynecologic Oncology 153 (2019) 574–579

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Uptake of sentinel lymph node procedures in women with vulvar cancer over time in a population based study

Tiffany Zigras [a], Rachel Kupets [a,b], Lisa Barbera [c,d], Allan Covens [a,b], Ying Liu [c], Lilian T. Gien [a,b,c,*]

[a] University of Toronto, Department of Obstetrics and Gynecology, Toronto, Ontario, Canada
[b] Division of Gynecologic Oncology, Odette Cancer Centre, Toronto, Ontario, Canada
[c] Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada
[d] Division of Radiation Oncology, Tom Baker Cancer Centre, Calgary, Alberta, Canada

HIGHLIGHTS

- SLN procedures in vulvar cancer are increasing over time.
- Elderly women with comorbidities are more likely to have groin assessment by SLN.
- SLN uptake is not uniform across centers and barriers to uptake should be explored.

ARTICLE INFO

Article history:
Received 28 December 2018
Received in revised form 5 March 2019
Accepted 6 March 2019
Available online 12 March 2019

Keywords:
Vulvar cancer
Sentinel lymph nodes
Groin node dissection

ABSTRACT

Objectives. To evaluate trends in uptake of sentinel lymph node (SLN) procedures over time and associated factors in women with vulvar cancer.

Methods. A retrospective population-based cohort study identified women with invasive squamous cell carcinoma (SCC) of the vulva using health administrative data for the province of Ontario, Canada, between 2008 and 2016. Patients who underwent SLN procedures were compared to those who had groin node dissection (GND). Multivariable analysis was used to identify factors associated with SLN procedures.

Results. 1385 patients with SCC of the vulva were identified; 1079 had a surgical procedure. Only those with groin node assessment were included in the study cohort (n = 732, 68%). SLN procedures were done in 52%. When comparing SLN versus GND, the rate of SLNs was significantly different by year of diagnosis ($P < 0.001$), associated comorbidity ($P < 0.001$) and institution ($P < 0.0001$). The rates of SLNs by institution with gynecologic oncologist were variable and ranged from 32% to 79% among 9 centers. There were no differences in age, income quintile, and urban/rural residence.

The proportion of SLN procedures increased from 30.1% (CI 18.9–45.6) in 2008 to 65.2% (CI 36.5–107.6) in 2016. On multivariate analysis, factors significantly associated with SLN procedures were more recent year of diagnosis (OR 7.9, CI 2.7–23.5) associated comorbidities (OR 2.7, CI 1.5–5.0) and institution (Site 5, OR 19.6 [CI 3.6–108.3] and Site 6, [OR 6, CI 1.1–33.4]).

Conclusions. The proportion of SLN procedures in women with vulvar cancer has increased over time, but uptake is not uniform across institutions. Barriers to uptake should be explored.

1. Introduction

Vulvar cancer is a rare disease, consisting of 3–5% of all female genital cancers with an incidence of 2.4 in 100,000 cases per year. Median age is 68 years at the time of diagnosis [1,2]. The treatment of vulvar cancer has evolved from invasive and disfiguring en bloc surgery to less radical surgery with resection of vulvar tumor by wide local excision and groin lymphadenectomy through separate incisions [3,4]. Groin node status is an important prognostic factor and guides adjuvant radiation therapy for the treatment of vulvar cancer [5,6].

Sentinel lymph node biopsy (SLN) of groin lymph nodes allows for assessment of groin nodes with a less invasive technique [7]. SLN procedures have the advantage of lower rates of wound breakdown, lower rates of infection, fewer days in hospital, and lower long-term lymphedema rates [8]. The National Comprehensive Cancer Network (NCCN) guidelines on vulvar cancer recommend groin node assessment by

* Corresponding author at: Gynecologic Oncology, Odette Cancer Centre, 2075 Bayview Ave, T2-055, Toronto, ON M4N 3M5, Canada.
E-mail address: Lilian.Gien@sunnybrook.ca (L.T. Gien).

https://doi.org/10.1016/j.ygyno.2019.03.010
0090-8258/

SLN or groin node dissection (GND) for early stage tumors (T1 or T2, ≤4 cm) [9]. Similar guidelines in Ontario, Canada have recommended SLN assessment as the standard of care in women with vulvar cancer since 2014 [7]. SLN programs do require expertise from multidisciplinary teams such as surgeon, pathology, and nuclear medicine. It is recommended that oncology centers demonstrate at least 10 successful SLN followed by completed GND before adopting this practice and maintain a sufficient number of SLN procedures per year [8,10].

To understand uptake rates of SLN procedures in groin node assessment, we conducted a retrospective population based cohort study using linked administrative databases to identify women diagnosed with invasive squamous cell cancer of the vulva. Women with a SLN procedure were compared to those who had a complete GND to evaluate rates over time and factors associated with a SLN procedure.

2. Methods

2.1. Administrative data sources

Four datasets were used for this population-based study between January 1, 2008 and June 20, 2016: The Ontario Cancer Registry (OCR); the Canadian Institute for Health Information (CIHI) discharge abstract database; the Ontario Health Insurance Plan (OHIP) database; and the Registered Persons Database (RPDB). OCR is reported to capture over 95% of the pathology reports relating to cancer cases in Ontario [11]. CIHI Discharge Abstract Database (DAD) lists diagnostic and procedure codes from all inpatient and outpatient hospital admissions for Ontario residents since April 1, 1988. The OHIP database contains medical billing claims by physician in the province. The RPDB contains demographic information on all residents in Ontario who were eligible for OHIP.

In Ontario, universal health care is provided by OHIP, which is a single payor, publically funded health care system estimated to cover 95% of the population [12]. Every Ontario resident is assigned a unique encoded identifier. These datasets were linked using unique encoded identifiers and analyzed at ICES. ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. The use of data in this study was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

2.2. Defining study population

Using electronic data from the OCR, incident cases of squamous cell carcinoma of the vulva were identified using International Classification of Diseases (ICD)-O codes 805-808 and ICD-10 code C51.0-9. Patients included in the study were women over 18 years old, treated for an invasive vulvar squamous cell carcinoma (SCC) that underwent at least a groin node assessment surgically in the defined study time period in Ontario. Patients were excluded if they had any other histology type other than SCC or if they were diagnosed with any malignancy in the antecedent five years prior to the vulvar cancer diagnosis.

2.3. Variable definitions

2.3.1. Outcome variable

To identify type of lymph node procedure, OHIP billing codes and CIHI procedure codes were used. Sentinel lymph node (SLN): patients who had a SLN procedure performed were identified using the OHIP billing code for radionuclide lymphangiogram or the OHIP billing code for SLN biopsy. Patients who had a SLN procedure followed by a complete GND were classified as having a SLN procedure for the purposes of this study to capture the rate of SLN procedures attempted. Radionuclide injection was the standard method for identification of SLN in vulvar cancer in Ontario during the study period. Use of other agents to identify SLN, such as blue dye, may have been used in conjunction but was not captured. Groin node dissection (GND): patients who had a complete GND were identified by CIHI procedure codes and OHIP billing codes for GND/inguinal lymph nodes.

2.3.2. Patient variables

Age: patient age at diagnosis was obtained from OCR. Income Quintile: the income quintile was derived from neighbourhood income per person equivalent (IPPE) which uses a household size-adjusted measure of household income based on postal code of residence at the time of diagnosis and links this to census data [13]. Quintile 1 has the lowest income and quintile 5 has the highest. Comorbidities: comorbidities were obtained from CIHI administrative data over a 5-year period prior to diagnosis of vulvar cancer. The John Hopkins' Aggregated Diagnosis Groups (ADGs) score was used to assign a comorbidity score. Comorbidities at baseline were categorized as low (0–5 ADGs), moderate (6–10 ADGs), or high (≥11 ADGs) [14,15].

2.3.3. Procedure and health system variables

Procedure: Procedures completed were obtained from CIHI. Procedure codes for vulvectomy were used to identify those who underwent a vulvectomy at the time of groin node assessment. Year: the year of the procedure was obtained from CIHI. Surgeon type: Surgeon type was classified as gynecologic oncologist vs non-gynecologic oncologist. Hospital volume: Institutional volume of gynecologic cancer cases was estimated through CIHI by determining the number of gynecologic surgical procedures done at each institution per year from 2007 to 2015. The median number of gynecologic cancer procedures per year ranged from 22 to 404. Therefore a high volume center was defined as an intuition that performed greater than or equal to 100 gynecologic cancer surgeries per year. Rural Location: rural location was determined using the Rural Index for Ontario that is linked to Canadian census data and obtained from the RPDB. Institution: institutions were de-identified. Within Ontario, cancer care is centralized to regional centers. Regional cancer centers were given numerical assignments (Site 1–6). Centers with low number of cases were combined. Three community hospitals where gynecologic oncologists were identified to be working were combined and labeled as “community hospital with gynecologic oncologist”. Six community hospitals in the province without gynecologic oncologists were combined and labeled “community hospital without a gynecologic oncologist”.

2.4. Statistical analysis

Descriptive statistics were used to compare the two groups. Student *t*-test was used for continuous data and Chi-square test was used for categorical data to compare the frequency distributions. Multivariate analysis was used to determine factors that were significantly associated with having a SLN procedure and included clinically relevant predictor variables selected a priori: patient age, year of procedure, comorbidities (using the ADG score), income quintile, and institution. Trends in the proportion of SLN procedures were evaluated over the study period for all patients and for women over 70 years old. Statistical significance of trends was tested using the Cochrane-Armitage test. Statistical significance was defined as P-value<0.05. Statistically analyses were performed using SAS 9.4© (SAS Institute Inc., Cary, NC, USA).

3. Results

During the study period of January 1, 2008 to June 20, 2016 there were 1385 patients with SCC of the vulva identified (see Fig. 1). Of these women, 1079 patients had a surgical procedure. Among those who had a surgical procedure for vulvar cancer, the overall rate of groin node assessment was 68% (n = 732). Of all the groin node assessments, SLN was done in 52% (n = 380) and GND in 48% (n = 352).

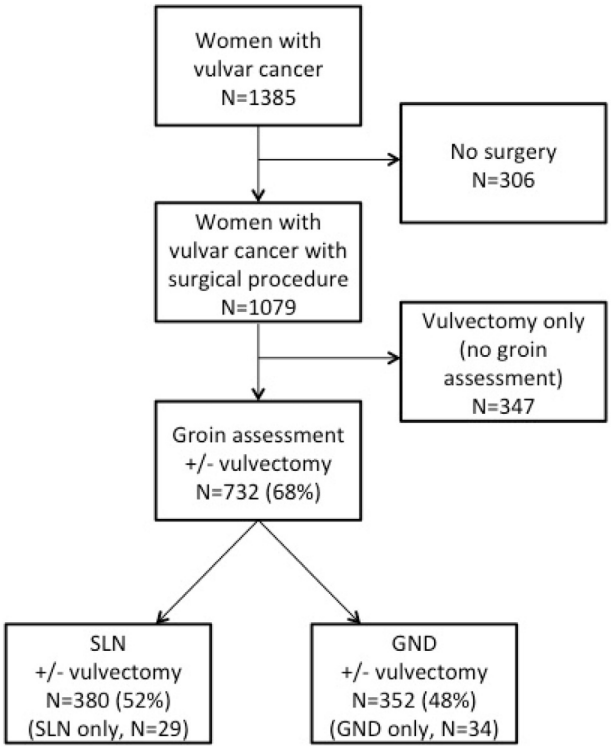

Fig. 1. Diagram of patient selection for inclusion. SLN: sentinel lymph node. GND: groin node dissection.

Table 1 outlines the demographics of the patients who underwent groin assessment. For those who had a SLN procedure, the mean age was 65.5 years (SD ± 14.6), 57% had a high ADG comorbidity score, 91% had their procedures by gynecologic oncologists (GYNONC), 83% were performed at high volume gynecologic centers, and 87.9% were performed in a non-rural location.

When comparing those who underwent SLN to those who had a GND, age, income quintile, hospital volume for gynecologic malignancies, surgeon type, center type (teaching versus community) and rural location were not significantly different between the groups. There was a significant difference for ADG comorbidity score ($P < 0.001$) and between institutions ($P < 0.001$) when comparing SLN to GND. Those with a higher comorbidity score had a higher proportion of SLN compared to GND. With respect to institutions, the rate of SLN by institution ranged from 11% in community hospitals with no gynecologic oncologist to 79.4% at Site 5. Among the regional cancer centers, rates of SLNs ranged from 32 to 79.4%.

Over the course of the study period, the proportion of SLN procedures increased from 30.1% (95% CI 18.9–45.6) in 2008 to 65.2% (95% CI 36.5–107.6) in 2016. The Cochrane-Armitage test for trend did show a significant difference, $P < 0.001$ (Fig. 2). When evaluating patients over 70 years old, there was an even higher rate of SLN uptake from 24.3% (95% CI 11.1–46.2) in 2008 to 81.8% (95% CI 37.4–155.3) in 2016. The Cochrane-Armitage test for trend again showed a significant difference, $P < 0.001$ (Fig. 3).

A multivariate logistic regression analysis was performed to determine factors significantly associated with having a SLN procedure. Clinically important variables were selected a priori, and included age, year of procedure, ADG, income quintile and institution (Table 2). Factors that were significantly associated with a SLN procedure were more recent year of diagnosis (OR 7.9, 95% CI 2.7–23.5), higher comorbidity score (OR 2.7, 95% CI 1.5–5.0) and institution. Age and income quintile were not significant factors in predicting SLN procedure. Community hospital without gynecologic oncologist was selected as the referent group for institution. After adjusting for covariates, two regional cancer centers were significantly associated with an increased odds of having a SLN procedure. Site 5 had an OR of 19.6 (95% CI 3.6–108.3) and Site 6 had an OR of 6 (95% CI 1.1–33.9). The remaining sites were not significantly associated with an increased OR of having a SLN procedure.

Table 1
Demographics & clinical characteristics.

Variable		GND N = 352 (%)	SLN N = 380 (%)	P value
Age	Mean ± SD	65.90 ± 14.68	65.45 ± 14.62	0.68
ADG group[a]	Low (0–5)	44 (12.5)	24 (6.3)	<0.001
	Moderate (6–10)	159 (45.2)	139 (36.6)	
	High (≥11)	149 (42.3)	217 (57.1)	
Income quintile[b]	1 (lowest)	98 (27.8)	80 (21.1)	0.05
	2	76 (21.6)	67 (17.6)	
	3	64 (18.2)	79 (20.8)	
	4	60 (17.0)	69 (18.2)	
	5 (highest)	54 (15.3)	84 (22.1)	
Rural location	Yes	60 (17.0)	46 (12.1)	0.058
	No	292 (83.0)	334 (87.9)	
Hospital type	Community	33 (9.4)	29 (7.6)	0.4
	Teaching	319 (90.6)	351 (92.4)	
Surgeon type	Gyn oncologist	325 (92.3)	346 (91.1)	0.53
	Non gyn oncologist	27 (7.7)	34 (8.9)	
Gynecology volume[c]	High	295 (83.8)	314 (82.6)	0.67
	Low	57 (16.2)	66 (17.4)	
Year of diagnosis	2008	51 (69.9)	22 (30.1)	<0.001
	2009	38 (59.4)	26 (40.6)	
	2010	57 (74)	20 (26)	
	2011	38 (50)	38 (50)	
	2012	45 (50.6)	44 (49.4)	
	2013	46 (42.2)	63 (57.8)	
	2014	33 (29.5)	79 (70.5)	
	2015	36 (33)	73 (67)	
	2016	8 (34.8)	15 (65.2)	
Institution[d]	Community hospital without gyn oncologist	8	≤5	<0.001
	Community hospital with gyn oncologist	22 (45.8)	26 (54.2)	
	SITE 1	76 (51)	73 (49)	
	SITE 2	44 (62.9)	26 (37.1)	
	SITE 3	97 (66.9)	48 (33.1)	
	SITE 4	34 (68)	16 (32)	
	SITE 5	35 (20.6)	135 (79.4)	
	SITE 6	29 (37.2)	49 (62.8)	
	Missing	7 (53.8)	6 (46.2)	

Chi–square test used for categorical variables. Age is normally distributed. GND: groin node dissection. SLN: sentinel lymph node.
[a] ADG: Johns Hopkins Aggregated Diagnosis Group.
[b] N = 731.
[c] Gyn volume: high volume defined as >100 gynecologic oncology cases per year.
[d] ICES prohibits reporting of cells ≤5, therefore row percentages have also been omitted to protect from possible re-identification.

4. Discussion

In this population-based cohort, the rate of SLN significantly increased over the study period from 30% in 2008 to 65% in 2016. The rate increased even more in women >70 years old from 24% in 2008 to 82% in 2016. The sharp increase in SLN likely reflects the acceptance of the SLN procedure as a means of groin lymph node assessment by surgeons, in particular for elderly patients. In the past when GND was the only option available, surgeons may have elected to omit a groin node assessment in elderly patients with vulvar cancer with multiple comorbidities to minimize morbidity, whereas in more recent years, there is a lower threshold to attempt a SLN biopsy where the morbidity is low yet important clinical information can be gained.

For women who had a surgical procedure, overall groin node assessment either by SLN or GND between 2008 and 2016 was 68% in our study. Previous work by our group has shown a groin node assessment rate of 62% between 1998 and 2007 [16]. We expected the overall groin node assessment to be higher after 2007 with the increased uptake of SLN, yet there was only a 6% increase in proportion of groin nodes

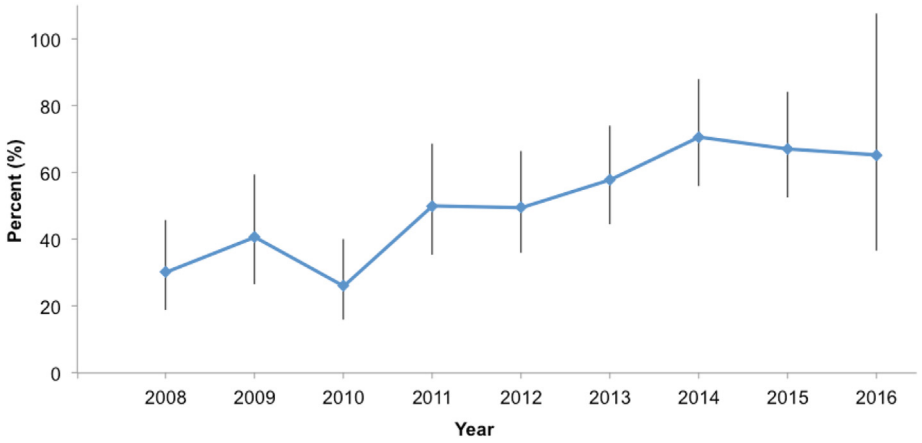

Fig. 2. Trends in SLN procedure in women with vulvar cancer who underwent groin lymph node procedure with 95% CI. Cochrane-Armitage Trend Test P-value <0.001.

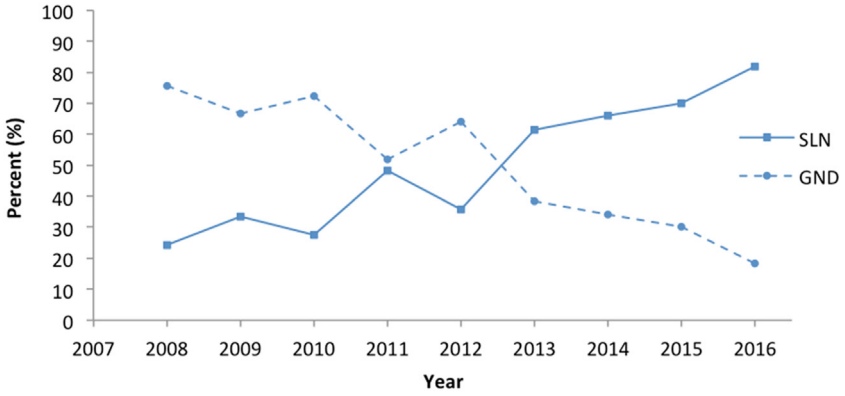

Fig. 3. Trends in SLN procedure in women over 70 years old with vulvar cancer who underwent groin lymph node procedure. Cochrane-Armitage Trend Test P-value <0.001 for SLN and P-value <0.001 for GND. SLN: sentinel lymph node. GND: groin node dissection.

Table 2
Multivariate logistic model on predictors of SLN.

Covariate		OR (95% CI)	P value
Age (continuous)		1 (0.98, 1.01)	0.37
Procedure year	2008	Referent	
	2009	1.34 (0.59, 3.05)	0.48
	2010	0.84 (0.37, 1.92)	0.68
	2011	3.12 (1.43, 6.84)	0.004
	2012	3.61 (1.69, 7.74)	0.001
	2013	5.43 (2.6, 11.3)	<0.0001
	2014	9.31 (4.4, 19.7)	<0.0001
	2015	8.24 (3.88, 17.5)	<0.0001
	2016	7.91 (2.66, 23.5)	0.0002
ADG[a]	Low (0–5)	Referent	
	Moderate (6–10)	1.74 (0.93, 3.26)	0.085
	High (>11)	2.7 (1.45, 5.01)	0.0017
Income quintile	1 (lowest)	Referent	
	2	0.86 (0.52, 1.45)	0.58
	3	1.41 (0.84, 2.38)	0.2
	4	1.3 (0.76, 2.23)	0.34
	5 (highest)	1.45 (0.85, 2.46)	0.17
Institution	Community hospital without gyn oncologist	Referent	
	Community hospital with gyn oncologist	2.33 (0.39, 13.9)	0.35
	SITE 1	3.09 (0.57, 16.8)	0.19
	SITE 2	2.06 (0.36, 11.7)	0.42
	SITE 3	1.48 (0.27, 8.13)	0.65
	SITE 4	1.6 (0.27, 9.53)	0.6
	SITE 5	19.6 (3.56, 108.3)	0.0006
	SITE 6	5.99 (1.06, 33.9)	0.043

[a] ADG: Johns Hopkins Aggregated Diagnosis Group.

assessed between the two study periods. The SLN rate in our study cohort was 52%. Cham et al. found that in the USA, the overall groin node assessment rate for patients undergoing surgery was only 39% between the study period of 2006–2015 [17]. The SLN rate in this group of patients was only 27.2% with the remainder of the patients having a GND. A survey performed in Germany found that in 2010 only 20% of the hospitals adhered to the international consensus guidelines on SLN in vulvar cancer appropriately [18]. Furthermore, 24% of the hospitals were routinely performing SLN followed by GND. A possible explanation for why Canada may have higher rates of SLNs compared to the USA may be related to health care delivery models. In Ontario, gynecologic cancer treatment is performed at regional cancer centers. This centralized care allows centers to generally see higher clinical volumes of rare tumors and quickly gain experience of new procedures, as opposed to diluting experience across multiple institutions.

Despite centralization of gynecologic cancer care, there is still variability among institutions in the rate of SLN procedures. On multivariate analysis, institution where the procedure was performed was found to be predictive of SLN uptake. There were two centers that were significantly associated with uptake of SLN procedures, Site 5 with an OR of 19.6 (3.56–108.3) and Site 6 with an OR of 6 (1.06–33.9). These two sites make up roughly one third of the study cohort and are the sites with the highest rates of SLN procedures. The two sites appear to be driving the overall rate of SLN procedures up for the study population.

While surgeons do have a learning curve when adopting a SLN program, uptake is not solely dependent on surgeon skill set [19]. Surgeons, pathologists, and hospital support staff must all be of the same mindset with respect to the importance and development of hospital protocol and procedures. This study was not designed to look at the specific factors associated with low uptake of SLN within particular institutions, but should be explored to identify the barriers institutions are facing in adopting SLN programs. Furthermore, given that vulvar cancer is more rare among the gynecologic malignancies, even regional cancer centers may have low surgical volumes that may affect expertise in the SLN procedure.

In a survey of breast surgeons in Canada regarding adoption of SLN procedures, barriers identified were associated with cost of acquiring equipment needed rather than a lack of belief in the procedure [20]. This survey identified that low volume centers may not feel able to provide SLN given the learning curve and multidisciplinary nature of the procedure. Needs across institutions may vary; some centers may need mentorship and training on surgical or pathologic techniques such as ultrastaging of sentinel lymph node, while other centers may need access to specific equipment or services, such as nuclear medicine. Individual sites must perform needs assessments to determine what is required to have a successful SLN program and can look to larger regional cancer centers for mentorship in establishing their own programs.

As institutions move toward the use of indocyanine green (ICG) for identification of SLN in cervical and endometrial cancer, this may also be used for vulvar cancers. Studies have reported on the technical feasibility of using ICG for the assessment of SLN in vulvar cancer [21,22]. While ICG was not being used for identification of vulvar cancer SLN during the study time period, it is being adopted and moving forward may evade the need for radionuclide injection by nuclear medicine. There will still be a need for institutions to commit to a SLN program and invest in specialized equipment such as a near-infrared fluorescence-imaging device to identify the SLN after ICG injection. Surgeons may also still encounter a learning curve with the move to ICG alone, such as identifying the correct incision location in the groin without the assistance of the gamma probe to help with SLN detection.

Strengths of our study include the large cohort of patients with squamous cell carcinoma of the vulva available for inclusion. The administrative database from which the cases were collected is comprehensive and reliable for the evaluation and monitoring of practice trends in the province. In addition, given that the population-based database captures all patients across the province, the risk of selection bias is reduced.

Despite our ability to capture all patients with vulvar cancer in the population of Ontario in the provincial database, our study does have certain limitations that accompany the use of administrative data. There is a risk of misclassification bias. Patients with SLN procedures were identified using billing codes used by nuclear medicine and for SLN biopsy. This has the potential to miss patients who had SLN identified using a blue dye technique alone where the surgeon did not bill for a SLN procedure. In addition, the reason for not completing a SLN procedure could not be extracted from the database. If a patient was not eligible for a SLN procedure and underwent a GND because of clinically suspicious nodes, bulky nodes, or for large tumor size (e.g. ≥4 cm) this detail could not be captured in the database and the inability to make this distinction could make the rate of SLN uptake appear artificially lower. Likewise, superficially invasive lesions with ≤1 mm depth of invasion where groin assessment would be omitted could not be captured. Based on previous work by Gien et al., we estimate this to be approximately 11% of the vulvar cancer cohort [16]. FIGO stage and tumor grade was also not available from the database and therefore could not be taken into account as possible predictors for SLN uptake. The cohort for inclusion, however, was made up of patients who had a surgical procedure for groin node assessment and therefore presumed to have at least surgically resectable disease. Lastly, certain demographic information such as BMI, smoking status, race, marital status could not be obtained.

5. Conclusion

Our findings show that the proportion of SLN procedures in women with vulvar cancer has increased over time. Factors significantly associated with having a SLN procedure include the year of diagnosis, associated comorbidities, and institution where the procedure occurred. The implementation of SLN procedures appears to have increased groin node assessment in older patients with comorbidities, where previously nodal assessment would have likely been omitted. The uptake of SLN procedures, however, has not been uniform as demonstrated by the wide variability in SLN rates across institutions. The reasons for this variation among institutions must be explored to understand and address the barriers being faced. Referral to expert centers is one strategy to improve access for patients. Institutions should consider what their individual needs are to have a successful SLN program and seek support for centers where SLN for groins assessment is standard practice.

Conflict of interest

None of the authors have any conflict of interest to declare.

Acknowledgements

This study was supported by the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the MOHLTC is intended or should be inferred.

Author contribution

TZ: Study design and analysis, writing of original draft. RK, LB, AC: Contributed to study design. YL: Collected data and performed data analysis. LG: Conceptualized project, study design and analysis. All authors contributed to editing and reviewing manuscript.

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