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EVOLUTION AND OUTCOMES OF SENTINEL LYMPH NODE MAPPING IN VULVAR CANCER

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Abstract

Objectives: To characterize our institutional experience with sentinel lymph node biopsy in patients with vulvar cancer. We describe the oncologic outcomes of these patients and the utilization of sentinel lymph node detection techniques over time.

Methods: A retrospective analysis of all patients who underwent inguinofemoral sentinel lymph node biopsy as part of their treatment for vulvar cancer at Memorial Sloan Kettering Cancer Center from 1/1/2000–4/1/2019. Patients were included in this analysis if they underwent inguinofemoral sentinel lymph node biopsy for vulvar cancer, irrespective of presenting factors such as histology, tumor size or laterality. An “at-risk groin” was defined as either the right or left groin for which sentinel lymph node biopsy of inguinofemoral lymph nodes was performed.

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AUTHOR CONTRIBUTIONS

Vance A. Broach: Conception and design; analysis and interpretation of data; drafting of manuscript; revising manuscript critically for important intellectual content; final approval of version to be published; agrees to be accountable for all aspects of the work.
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Dr. Jewell is a consultant for Intuitive Surgical and Covidien, outside the submitted work.
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Results: A total of 160 patients were included in our analysis, representing 265 at-risk groins. One hundred and fourteen patients had squamous cell histology representing 195 at-risk groins. Of the 169 negative groins in patients with squamous cell carcinoma, the 2-year isolated groin recurrence rate was 1.2%. Sentinel lymph node detection rate, irrespective of modality, was 96.2%. TC-99 + blue dye detected sentinel lymph nodes in 91.8% of groins; TC-99 + indocyanine green detected sentinel lymph nodes in 100% of groins ($p = 0.157$). Among the 110 groins that underwent mapping with TC-99 and blue dye, 4 patients had failed mapping with blue dye and mapped with TC-99 alone (3.6%). Among the 96 groins that underwent mapping with TC-99 and ICG, 14 patients failed to map with TC-99 and mapped with indocyanine green alone (14.6%).

Conclusions: Sentinel lymph node mapping in vulvar cancer is reliable and oncologically effective. The utilization of indocyanine green for mapping has increased over the past decade and is associated with high rates of sentinel lymph node detection.

INTRODUCTION

Vulvar cancer is a rare malignancy accounting for an estimated 6,070 cases and 1,280 deaths in the United States in 2019 [1]. Globally, 44,235 new cases and 15,222 deaths were attributed to vulvar carcinomas in 2018 [2]. The treatment of early-stage vulvar cancer has traditionally involved radical resection of the primary tumor and full inguinofemoral lymph node dissection. While this treatment was oncologically effective, the surgical morbidity—including wound breakdown, infection, and lymphedema—was considerable. In an effort to reduce surgical morbidity, the operative approach has evolved from the traditional "longhorn" resection, which includes *en-bloc* resection of the primary tumor as well as the inguinofemoral lymphatics, to a "triple incision" approach in which the primary tumor is resected separately from the lymphatics [3-6]. While this reduces surgical morbidity considerably, it does not reduce lymphadenectomy-related complications such as lymphedema.

In an effort to reduce morbidity and improve detection of microscopic metastatic disease in the lymphatics, sentinel lymph node biopsy has been utilized. The safety and oncologic efficacy of this approach was confirmed by two prospective studies, the GOG-173 and the GROINSS-V study. These studies reported a 3.7% false negative predictive value of inguinofemoral sentinel lymph nodes and a groin failure rate of approximately 2% in appropriately selected patients [7, 8].

As utilization of inguinofemoral sentinel lymph node detection increased over time, the methods have evolved. Initially, blue dyes such as lymphazurin and methylene blue, and radiocolloid lymphoscintigraphy were the most commonly utilized means for sentinel lymph node detection [9]. However, since the use of near infrared imaging with indocyanine green injection was first described in 2010, this technique has become more widely adopted as a method for identifying inguinofemoral sentinel lymph nodes [10]. The choice of method for sentinel lymph node detection remains largely dependent on surgeon preference and training.

In this study we describe our institutional experience with sentinel lymph node biopsy in patients with vulvar cancer. We aimed to characterize the oncologic outcomes for these patients, and the utilization of sentinel lymph node detection techniques over time.

METHODS

This study was approved by the Institutional Review Board at Memorial Sloan Kettering Cancer Center. We performed a retrospective analysis of all patients who underwent inguinofemoral sentinel lymph node biopsy as part of their treatment for vulvar cancer at our institution from January 1, 2000 to April 1, 2019. Patients were included in this analysis if they had undergone inguinofemoral sentinel lymph node biopsy for vulvar cancer, irrespective of presenting factors such as histology, tumor size, or laterality. An “at-risk groin” was defined as either a right or left groin for which inguinofemoral sentinel lymph node biopsy was performed. Patients had subsequent completion lymphadenectomy based on surgeon discretion and clinical factors. Sentinel lymph node detection technique, as well as the success or failure of a specific technique, were determined from operative reports. The decision to utilize a particular method of sentinel lymph node detection was surgeon-dependent after discussion of the risks, benefits and alternatives to each approach with the patient. Pertinent past medical, surgical, demographic, pathologic and treatment data were abstracted from patients’ medical records. Pearson’s Chi-Squared test was used for comparison of categorical variables. All statistical analyses were performed using SPSS software (IBM, Chicago, IL).

RESULTS

Oncologic Outcomes

A total of 160 patients were included in our analysis, representing 265 at-risk groins. The median age was 63 years (range 19-98 years) and median BMI was 27.3 kg/m^2 (range 18.6 – 49.2 kg/m^2). Demographic and pathologic features are summarized Table 1. The SLN was positive for metastasis in 39/265 at-risk groins (14.7%), irrespective of histology. One hundred and fourteen (71.3%) patients had squamous cell histology and 38 patients (23.8%) had mucosal melanoma. The remaining 8 patients (5%) underwent sentinel lymph node mapping for Paget’s disease, sarcoma, basal cell carcinoma and yolk sac tumors.

The 114 patients with squamous cell carcinoma represented 195 at-risk groins. Among patients with squamous cell carcinoma, the median vulvar lesion size was 1.0 cm (range 0.01–11 cm). Of the 195 at-risk groins in this group, 25 (12.8%) were found to have positive sentinel lymph nodes; 17 of these 25 (68%) underwent full lymphadenectomy and 17 (68%) received adjuvant radiation therapy to the groin. Nine of 25 positive groins underwent both radiation therapy and lymphadenectomy (36%). Among positive groins, the 2-year isolated groin recurrence rate was 4%. Among the 169 groins that had negative sentinel lymph nodes, the 2-year isolated groin recurrence rate was 1.2% (2 groin recurrences).

The 38 patients with mucosal melanoma represented 59 at-risk groins. Among patients with mucosal melanoma, the median primary vulvar lesion size was 1 cm (range 0.1 – 2.1 cm). Of the 59 at-risk groins in this group, 9 (15.3%) were found to have positive sentinel lymph

nodes. Two of these 9 (22.2%) underwent full lymphadenectomy. Among the patients with positive sentinel lymph nodes, 2 (22.2%) patients received adjuvant imiquimod to the vulva and 1 patient (11.1%) received adjuvant Nivolumab. No patients received immediate postoperative radiation therapy. Among the 9 groins which were found to have positive sentinel lymph nodes, one (11.1%) experienced a groin-only recurrence at 13 months after surgery. Among the 50 groins with negative sentinel lymph nodes, there were 2 groin-only recurrences (4%) which occurred at 25 and 27 months following initial surgery. Neither of these patients received immediate postoperative therapy and neither of these patients had undergone completion lymphadenectomy.

Sentinel Lymph Node Mapping Techniques

Patients underwent mapping with either Technetium-99 radiocolloid injection (TC-99), blue dye injection, near infrared imaging with indocyanine green injection, or a combination of these modalities. A total of 265 at-risk groins were mapped. Two groins (0.8%) were mapped with TC-99 alone and 3 (1.1%) were mapped with blue dye alone. Twenty-seven groins were mapped with indocyanine green alone (10.2%). One hundred and ten groins (41.5%) were mapped with a combination of blue dye and TC-99. Ninety-six groins (36.2%) were mapped with TC-99 and indocyanine green. Twenty-five groins (9.4%) were mapped with all three modalities. Three groins (1.1%) were mapped with indocyanine green and blue dye without TC-99. The sentinel lymph node detection rate by modality is summarized in Table 2.

Irrespective of modality, the sentinel lymph node detection rate was 96.2%. Two groins were mapped with TC-99 alone and both sentinel lymph nodes were identified. Three groins were mapped with blue dye alone and all 3 sentinel lymph nodes were identified. Of the 110 groins mapped with TC-99 and blue dye, 101 (91.8%) sentinel lymph nodes were identified, compared with 96/96 groins (100%) that were successfully mapped with TC-99 and indocyanine green ($p = 0.157$). The use of indocyanine green alone resulted in 1 groin with failed mapping, with a sentinel lymph node detection rate of 26/27 (96.3%).

Among all modalities, sentinel lymph node mapping failed in 10 of 265 (3.8%) at-risk groins. Among the 110 groins mapped with TC-99 and blue dye, 4 patients had failed mapping with blue dye and mapped with TC-99 alone (3.6%). Among the 96 groins mapped with TC-99 and indocyanine green, 14 patients had failed mapping with TC-99 and mapped with indocyanine green alone (14.6%) (Table 2). Among the 148 groins that mapped with indocyanine green, either alone or in combination with another modality, indocyanine green failed to identify the sentinel lymph node in 2 groins (1.4%).

Over a 10-year period (January 1, 2000 to December 31, 2009) a total of 41 patients underwent sentinel lymph node mapping with a combination of TC-99 and blue dye. Indocyanine green dye was first used at our institution for inguinofemoral sentinel lymph node mapping in 2012, when it was utilized in 12.5% of cases. By 2014, 100% of inguinofemoral sentinel lymph node mapping involved indocyanine green; since that time, indocyanine green has been utilized in 85-100% of cases. The utilization of blue dye has decreased over that time: from 100% of cases in 2011 to 16.7% of cases in 2019. The

utilization of TC-99 has also dropped over the past 8 years: from 100% of cases in 2012 to 66.7% of cases in 2019.

DISCUSSION

Sentinel lymph node mapping of vulvar cancer has become the standard for evaluating lymph node metastasis in appropriately selected patients. Other studies have demonstrated that this technique reduces the morbidity of lymph node dissection while maintaining oncologic safety and efficacy [11]. In our study, we demonstrated oncologic safety similar to that of previous prospective studies. Specifically, among patients with squamous cell carcinoma, we found a 2-year isolated groin failure rate of 1.2% in patients with negative sentinel lymph nodes. This is comparable to the 2% groin failure rate reported in the GROINSS-V study [8].

Initially, the use of blue dye and radiocolloid lymphoscintigraphy was the dominant technique in sentinel lymph node mapping for vulvar cancer. Among patients who participated in GOG-173, all had sentinel lymph node mapping with a combination of blue dye and radiocolloid lymphoscintigraphy. Similarly, in our cohort, 100% of patients were mapped with blue dye and TC-99 in the early part of the study. In GOG-173, 92.5% of patients had at least 1 sentinel lymph node identified at surgery; 61% of these patients had nodes that were both blue and TC-99 positive. False negative rates were 7.8% for radiocolloid alone, 2.0% for blue dye alone and 1.6% for radiocolloid plus blue dye. This is consistent with our findings; in our cohort, 91.8% of groins were successfully mapped with blue dye and T-99. A meta-analysis in 2014 by Meads and colleagues reviewed mapping techniques with radiocolloid lymphoscintigraphy as well as blue dye, reporting sentinel lymph node detection rates of 94.0% (95% confidence interval, 90%-96%) for radiocolloid lymphoscintigraphy alone and 68.7% (95% confidence interval, 63-74%) for blue dye alone.

Sentinel lymph node biopsy in vulvar cancer is associated with very high rates of mapping, irrespective of the mapping modality. However, preoperative lymphoscintigraphy along with intraoperative radiolocalization requires multiple procedures that often need to be performed a day in advance of surgery. Additionally, intraoperative detection with TC-99 is cumbersome and relies on audial rather than visual cues, necessitating a pause in the procedure at frequent intervals so that TC-99 uptake can be measured with a Geiger counter. The use of blue dye does facilitate visual cues regarding the location of the sentinel lymph node, but this localization is only useful when the lymphatics and lymph node are identified.

Indocyanine green with near infrared imaging eliminates these drawbacks by providing visual cues that can be appreciated in real time during the procedure. In 2010, Crane et al described the use of a bespoke near infrared light source and camera for intraoperative indocyanine green-labeled inguinofemoral sentinel lymph nodes [10]. They subsequently reported their experience mapping sentinel lymph nodes for vulvar cancer in 16 groins using TC-99, blue dye, and indocyanine green with near infrared imaging. In this study, 29 sentinel lymph nodes were identified with TC-99, 26 with indocyanine green, and 21 with blue dye [12]. More recently, in 2017 Soergel and colleagues reported their experience with indocyanine green in 27 patients with vulvar cancer, representing 52 at-risk groins.

Importantly, they found 8 sentinel lymph nodes that were not identified by TC-99 but were identified by indocyanine green alone [13]. In our study, we also found that indocyanine green performed favorably and reliably identified the sentinel lymph node when used either alone or in combination with another technique.

Drawbacks of this study include its relatively small sample size and its retrospective nature. Retrospective surgical trials may be particularly problematic as they are uniquely susceptible to selection bias, in this case patient and surgical technique selection. Additionally, this study does not address possible advantages of the use of radiocolloid lymphoscintigraphy. Potential advantages include the localization of the sentinel lymph node in obese patients, where transdermal visualization of indocyanine green may be challenging. Some surgeons also utilize lymphoscintigraphy to aid in determining the size and location of their incision in all patients. The retrospective nature of this study limits our ability to determine to what extent radiocolloid localization was utilized for this purpose in these patients.

Current standard practice includes the use of radiocolloid tracer as well, with or without blue dye or indocyanine green, for identification of the inguinofemoral sentinel lymph node in appropriately selected patients with vulvar cancer. While the results of this retrospective series specifically pertaining to the performance of near infrared imaging are quire promising, prospective studies examining the efficacy of indocyanine green and near infrared imaging are needed to clarify the role of SLN mapping in this disease.

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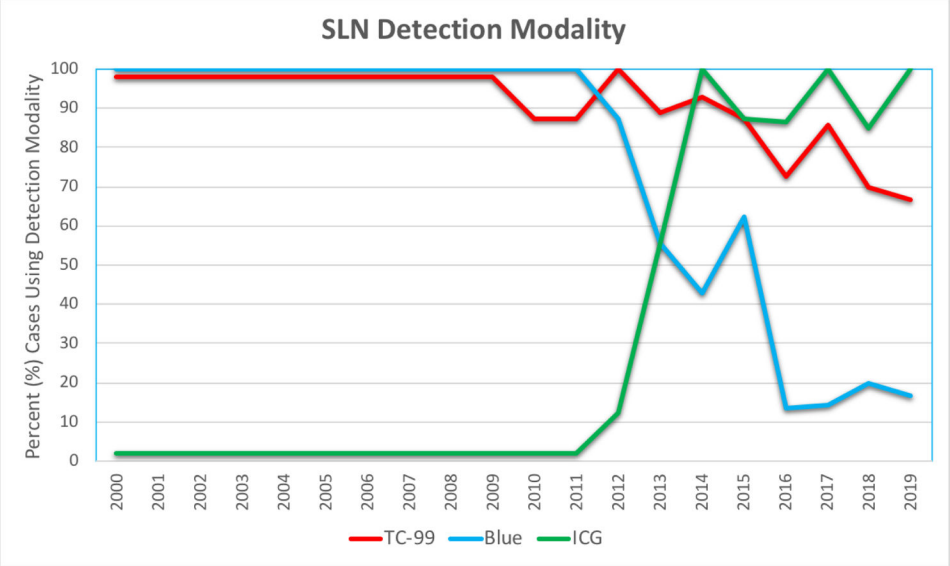

Figure 1.

Utilization of sentinel lymph node mapping techniques over time

SLN, sentinel lymph node; ICG, indocyanine green; TC-99, technetium-99

Table 1.

Patient demographics

		Number of Patients (Total = 160)	Number of at-risk groins (Total = 265)	*P*
Race	Black	10 (6.3%)	17 (6.4%)	< 0.001
	White	140 (87.5%)	234 (88.3%)	
	Asian	4 (2.5%)	5 (1.9%)	
	Declined to Answer	6 (3.8 %)	9 (3.4%)	
Histology	Squamous Cell	114 (71.3%)	195 (73.6%)	< 0.001
	Melanoma	38 (23.8%)	60 (22.6%)	
	Paget's Disease (Adenocarcinoma)	4 (2.5%)	6 (2.3%)	
	Yolk Sac Tumor	1 (0.6%)	1(0.4%)	
	Sarcoma	2 (1.3%)	2 (0.8%)	
	Basal Cell Carcinoma	1 (0.6%)	1 (0.4%)	

Table 2.

Sentinel lymph node detection modalities

		Number of Patients (Total = 160)	Number of at-risk groins (Total = 265)	*P*
SLN Modality	TC-99 alone	2 (1.3%)	2 (0.8%)	< 0.001
	Blue dye alone	2 (1.3%)	3 (1.1%)	
	ICG Alone	18 (11.3%)	27 (10.2%)	
	TC-99 + Blue Dye	71 (44.4%)	110 (41.5%)	
	TC-99 + ICG	51 (31.9%)	96 (36.2%)	
	TC-99 + Blue Dye + ICG	14 (8.8%)	25 (9.4%)	
	ICG + Blue	2 (1.3%)	3 (1.1%)	
SLN Detection Rate	TC-99 alone		2 (100%)	0.134
	Blue dye alone		3 (100%)	
	ICG Alone		26 (96.3%)	
	TC-99 + Blue Dye		101 (91.8%)	
	TC-99 + ICG		96 (100%)	
	TC-99 + Blue Dye + ICG		24 (96%)	
	ICG + Blue		3 (100%)	

SLN, sentinel lymph node; ICG, indocyanine green; TC-99, technetium-99