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Survival of Patients with Serous Uterine Carcinoma Undergoing Sentinel Lymph Node Mapping

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Abstract

Objective.—The aim of this study was to determine progression-free survival (PFS) in patients with serous uterine carcinoma undergoing sentinel lymph node (SLN) mapping compared with patients undergoing standard lymphadenectomy.

Methods.—We retrospectively reviewed all uterine cancer patients treated at our institution from 2005 to 2015. Patients were separated into two cohorts: those who underwent SLN mapping at the time of staging (SLN) and those who underwent routine lymphadenectomy (the non-SLN group). SLN mapping was performed according to institutional protocol, incorporating a surgical algorithm and pathologic ultrastaging.

Results.—Overall, 248 patients were identified—153 SLN mappings and 95 routine lymphadenectomies (pelvic and/or paraaortic lymph node dissection). No significant difference in age or body mass index was observed between the groups ($p = 0.08$ and $p = 0.9$, respectively). Minimally invasive surgery was utilized in 117/153 (77%) SLN patients and 30/95 (32%) non-SLN patients ($p = <0.001$). Stage distribution for the SLN and non-SLN cohorts demonstrated 106/153 (69%) and 59/95 (62%) patients with stage I/II disease, respectively, and 47/153 (31%) and 36/95 (38%) patients with stage III/IV disease, respectively ($p = 0.3$). The median number of

nodes removed was 12 (range, 1–50) in the SLN cohort versus 21 (range, 1–75) in the non-SLN cohort ($p = <0.001$). Adjuvant chemotherapy alone or with radiation therapy was administered in 122/153 (80%) SLN patients and 79/95 (83%) non-SLN patients; radiotherapy alone was administered in 12/153 (8%) SLN patients and 7/95 (7%) non-SLN patients ($p = 0.8$). At a median follow-up of 40 months, the 2-year PFS rates were 77% (95% confidence interval [CI], 68–83%) in the SLN group and 71% (95% CI, 61–79%) in the non-SLN group ($p = 0.3$).

Conclusions.—Incorporation of the SLN mapping algorithm into the staging of uterine serous cancer is feasible and does not appear to compromise prognosis. PFS in patients with uterine serous carcinoma undergoing SLN mapping, followed by adjuvant therapy, was similar to PFS in patients undergoing standard lymphadenectomy and adjuvant therapy.

Uterine cancers account for nearly 60% of all gynecologic malignancies, with more than 60,000 new cases diagnosed in 2016.¹ While the vast majority of uterine carcinomas of the endometrium are of endometrioid-type histology, serous-type cancers are more frequently associated with aggressive histology and worse survival outcomes.^{2,3} Despite accounting for approximately 10% of all diagnosed endometrial carcinomas, serous cancers are implicated in nearly 40% of all endometrial cancer-related deaths.² Given the aggressive nature of serous endometrial cancers, despite scant prospective literature specific to this histology, the standard treatment recommendation frequently includes chemotherapy (CT), even in early-stage disease.^{2,4,5}

As with all endometrial cancers, surgical management remains the standard initial approach to diagnosis and treatment for patients with serous carcinomas.⁶ Traditional surgical staging for endometrial cancers includes total hysterectomy, bilateral salpingo-oophorectomy (BSO), evaluation of lymph nodes, and collection of pelvic washings,^{6,7} while routine lymphadenectomy for uterine cancers typically involves the removal of both pelvic and paraaortic lymph nodes to evaluate for metastatic spread.^{2,8} However, more recently, the use of sentinel lymph node (SLN) mapping in endometrial cancer has emerged as a potential alternative to traditional full lymphadenectomy, allowing for the detection of metastatic disease without subjecting the patient to a more extensive operative procedure.^{9–12}

The use of SLN mapping has largely been assessed in the setting of low-grade, endometrioid-type endometrial carcinomas, and it appears safe and feasible in this population.^{9,13} Similarly, in a 2016 analysis of patients with uterine carcinosarcoma undergoing SLN mapping at our institution, progression-free survival (PFS) did not appear significantly different between women treated before and after the incorporation of an SLN algorithm.¹⁴ Given the aggressive tumor biology and poorer survival rates associated with serous endometrial cancers, the current study aimed to determine the role of SLN mapping in these patients, analyzing survival outcomes between those treated before and after the incorporation of an SLN algorithm at our institution.

METHODS

We reviewed the records of all patients who underwent surgical staging for uterine serous carcinoma at our institution from January 2005 through July 2015. Surgical staging included total hysterectomy by laparotomy or laparoscopy, with or without the use of the robotic

platform; removal of adnexa; and lymph node evaluation via standard lymphadenectomy or SLN mapping and biopsy. The decision to proceed with systematic lymphadenectomy or the SLN algorithm was made at the discretion of the surgeon.

SLN mapping was performed according to our previously published standard institutional protocol.¹⁵ On examination under anesthesia, patients typically had 4 cc of either blue dye or indocyanine green (ICG) injected into the cervix at the 3 and 9 o'clock positions. Retroperitoneal evaluation involved the localization of dye-filled lymphatic channels extending from the parametria to the primary nodal basins and removal of nodes with uptake of dye/ICG. Pathologic analysis included ultrastaging, utilizing anti-cytokeratin AE1:AE3 (Ventana Medical Systems, Inc., Tucson, AZ, USA) if the initial hematoxylin and eosin (H&E) sections were negative. SLNs could be denoted as positive on the basis of either method of staining. Macro- and micrometastases, as well as isolated tumor cells, constituted a positive SLN.

In addition to routine peritoneal and serosal evaluation and washings followed by retroperitoneal evaluation, with excision, of all mapped SLNs, our institutional SLN algorithm includes the removal of any additional lymph nodes that are suspicious for disease. Completion lymphadenectomy was not performed in all cases unless indicated by the algorithm, and intraoperative assessment of lymph nodes was not routinely performed. In cases in which failure in mapping was noted on a hemipelvis, a side-specific lymphadenectomy was performed, with further paraaortic dissection completed at the discretion of the attending surgeon.

At our institution, a combination of CT and radiation therapy (RT) is typically offered to patients with both early- and advanced-stage disease, although final decisions on adjuvant therapy are made by patients and their primary providers. CT is administered by specialized gynecologic medical oncologists, while RT is administered by specialized gynecologic radiation oncologists. Patients who receive CT or RT are followed by the treating medical or radiation oncologist, as well as the surgeon. Patients are usually seen by an oncologist every 3 months for the first 2–3 years and then every 6 months for the following 2–3 years. It is common practice for our disease management team to follow these patients with cancer antigen 125 (CA125), as well as a computed axial tomography (CAT) scan every 6–12 months for the first 3–5 years of surveillance. In the current study, follow-up for disease recurrence was conducted and documented through routine office visits, surveillance imaging, and monitoring of tumor markers when appropriate. Patterns of recurrence were separated into pure vaginal, pelvic, isolated nodal, and distant/multifocal spread.

Association tests were performed using the Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables. PFS was calculated from the date of surgery to the date of progression, date of death, or date of last follow-up. The 2-year PFS rate was obtained using the Kaplan–Meier method. In univariate PFS analyses, the *p*-values for comparing the estimated PFS rate at 2 years for categorical variables were obtained through Z-test (for binary covariates)/Chi-square testing (for categorical covariates).¹⁶ The *p*-values for continuous variables were obtained using a Cox proportional hazards model. A bivariate

Cox proportional hazards model incorporating lymph node technique and stage was used to evaluate the effect of lymph node technique after controlling for stage.

RESULTS

Two hundred forty-eight patients with uterine serous carcinoma were identified between 2005 and 2015. In our final analysis, 95 patients had routine lymphadenectomy (non-SLN) and 153 were treated using our SLN algorithm (SLN). In the SLN cohort, 108/153 patients (71%) underwent surgery, compared with 13/95 patients (14%) in the non-SLN cohort.

Demographics for the 248 study patients are summarized in Table 1. Median age was 65 and 68 years for the SLN and non-SLN cohorts, respectively ($p = 0.08$), and median body mass index (BMI) was 29.6 and 29.3 kg/m², respectively ($p = 0.9$). A minimally invasive platform was utilized in 117/153 patients (77%) treated with the SLN algorithm versus 30/95 patients (32%) who had standard lymphadenectomy ($p < 0.001$). Stage distribution in the SLN and non-SLN cohorts was as follows: stage I/II, 106 (69.3%) and 59 patients (62.1%), respectively; and stage III/IV, 47 (30.7%) and 36 patients (37.9%), respectively ($p = 0.3$). Myometrial invasion >50% was noted in 34/153 (22.2%) SLN patients and 28/95 (29.5%) non-SLN patients ($p = 0.2$). The presence of lymphovascular space invasion (LVSI) was found in 55 patients (35.9%) in the SLN group and 46 patients (48.4%) in the non-SLN group ($p = 0.6$).

SLNs were identified in 124/153 patients (81%) who underwent SLN mapping. Eighty-two patients (66%) were mapped bilaterally, and 42 patients (34%) had unilateral mapping only. Ninety-nine patients received blue-dye injection for the purpose of SLN detection, and 54 were mapped with ICG. Metastatic disease was found in 28/124 (23%) SLNs, of which 4 were noted to be micrometastases and 12 were isolated tumor cells. Of the 153 patients in the SLN cohort, the median number of SLNs removed was 3 (range, 0–15). The median total number of lymph nodes evaluated in the SLN cohort was 12 (range, 1–50) compared with 21 (range, 1–75) in the non-SLN group ($p = 0.001$).

Postoperative therapy was used in 134/153 patients (88%) who underwent SLN mapping and 86/95 patients (91%) who did not (Table 2; $p = 0.8$). CT was used in 122/134 patients (91%) in the SLN cohort and 79/86 patients (92%) in the non-SLN group. In the SLN group, this included 72 patients who received CT with intravaginal RT (IVRT) and 12 who received CT with external beam RT (EBRT). Thirty-eight of 122 patients received CT alone, and 12 of 122 received RT alone. In the non-SLN group, 44 patients received CT with IVRT and 9 received CT with EBRT. Twenty-six patients received CT alone, and 7 patients received RT alone. A breakdown of adjuvant therapy by stage of disease is demonstrated in Table 2.

Sixty-four patients with uterine serous carcinoma recurred, which included 31 patients who had undergone SLN mapping and 33 who had undergone routine lymphadenectomy. Distant/multifocal disease recurrence was predominant in both groups, noted in 23/31 (74%) SLN patients and 22/33 (67%) non-SLN patients. Local disease in the form of either vaginal or pelvic recurrence was noted in 9.7% of SLN patients and 9.1% of non-SLN patients.

Patients who experienced pure nodal recurrence of disease accounted for 16.1% of the SLN group and 24.2% of the non-SLN group.

At the time of analysis, 85 of the 248 study patients had suffered progression of disease or had died, including 40 in the SLN cohort and 45 in the non-SLN cohort. Median follow-up of patients who did not progress was 31.5 months in the SLN group, compared with 76.8 months in the non-SLN group. The 2-year PFS rates were 77% (95% confidence interval [CI] 68–83%) in the SLN group and 71% (95% CI 61–79%) in the non-SLN group ($p = 0.3$) [Fig. 1]. Patients who were noted to have stage III/IV disease, >50% myometrial invasion, LVSI, or positive washings had a significantly lower 2-year PFS rate (Table 3). In a bivariate model, only stage III/IV disease remained a statistically significant predictor of worse PFS (compared with stage I/II; hazard ratio [HR] 3.64; $p = 0.001$) [Table 4].

DISCUSSION

Uterine serous carcinomas are an aggressive subset of endometrial cancers associated with significant mortality. Standard management of these tumors has traditionally involved surgical staging with lymphadenectomy for the purposes of stage classification and prognosis. The utility of lymph node dissection for therapeutic purposes has more recently been called into question. In a 2008 study by Benedetti Panici et al., 514 patients with stage I endometrial carcinoma were randomized to undergo systematic pelvic lymphadenectomy or no lymphadenectomy.¹⁷ While it was noted that patients in the lymphadenectomy arm benefited from increased detection of lymph node metastasis, and thus improved surgical staging, the 5-year disease-free and overall survival (OS) rates remained similar in both cohorts (81 and 86% in the lymphadenectomy arm, and 82 and 90% in the no lymphadenectomy arm, $p = 0.7$ and 0.5 , respectively). Similarly, the 2009 MRC ASTEC trial of 1408 women with presumed uterine-confined endometrial cancer randomized patients to surgical staging with or without lymphadenectomy.¹⁸ In their final analysis, the hazard ratio for recurrence-free survival was 1.35 (95% CI 1.06–1.73, $p = 0.017$) in favor of the non-lymphadenectomy arm, with no difference in OS noted between groups (HR 1.16, 95% CI 0.87–1.54, $p = 0.31$). The concern over unnecessary lymphadenectomy is particularly relevant in light of the known morbidity associated with extensive removal of lymphatic tissue. In a 2006 retrospective report on the incidence of symptomatic lower extremity lymphedema in patients treated for uterine malignancies, a statistically significant difference was noted in the rates of lymphedema between patients who had lymph nodes removed at the time of surgery compared with those who did not (2.4 vs. 0%, respectively; $p = 0.0001$).¹⁹

A 2010 report by Soliman et al. examining the practice patterns of Society of Gynecologic Oncology (SGO) members noted that 66% of respondents performed a full lymphadenectomy for grade 2 cancers, and 90% did so for grade 3 malignancies; however, when performing paraaortic lymphadenectomy, 50% of respondents used the inferior mesenteric artery (IMA) as the upper border, and only 11% extended the dissection to the renal vessels.²⁰ Similarly, in the SGO review of uterine serous cancers, comprehensive surgical staging including pelvic and paraaortic lymphadenectomy is recommended for all women diagnosed with these tumors based on the belief that the removal of lymph nodes

may be of particular therapeutic value in this high-grade, high-risk population.^{2,21} One of the largest studies, utilizing published data from the Surveillance, Epidemiology, and End Results (SEER) Program, demonstrated an improvement in 5-year disease-specific survival among all patients with intermediate-/high-risk disease (including those with grade 3 tumors) who underwent a more extensive lymph node resection, compared with patients with low-risk disease (including grade 1/2 tumors) who showed no such improvement ($p = <0.001$ and $p = 0.23$, respectively).²² Notably, however, this study included only endometrioid-type endometrial carcinomas, and even the extent of removal of benign lymph nodes was associated with improved survival ($p = <0.001$). Furthermore, SEER data lack information regarding adjuvant CT, making these results difficult to interpret.

More recently, a number of published studies have specifically examined the role of SLN mapping in women with uterine serous carcinoma. In a 2015 Canadian study, 19/39 patients (49%) with disease of serous histology underwent SLN mapping. Of these, 79% had an SLN detected; the calculated negative predictive value (NPV) of detected nodes was 100%.²³ A 2015 French analysis also focused on SLN mapping in patients with high-risk endometrial cancers; of 180 patients, 34 (19%) were initially categorized as 'high-risk', including 18 (53%) with type 2 carcinomas.²⁴ The false negative rate (FNR) in this population was 20%, compared with 2.3% in the low-/intermediate-risk group ($p = 0.0008$). However, it is worth noting that despite initial pathologic categorization based on biopsy results, only 26 (14%) carcinomas were definitively found to be type 2 on final pathology, of which the total number of serous tumors was not specified. More recently, a retrospective review at Duke University of 36 cases of high-risk uterine cancers demonstrated an FNR of 0% and an NPV of 100% after the application of an SLN algorithm.²⁵

Our study on SLN mapping exclusively in patients with serous endometrial carcinomas included 248 patients, the largest of any series in the literature, and utilized a comparative cohort of patients who had undergone systematic lymphadenectomy in order to assess survival outcomes between these groups. No statistically significant difference was noted in 2-year PFS rates amongst these clinically similar groups. These findings are similar to those previously published by our institution on survival outcomes in patients with uterine carcinosarcoma (another high-grade endometrial cancer) undergoing SLN mapping.¹⁴ Potential criticism of these findings is based on the concern that a less extensive lymphadenectomy risks retention of metastatic disease in non-removed lymph nodes. This is of particular concern in the setting of serous uterine carcinomas as SEER data have described rates of pelvic and paraaortic lymph node metastases of 27 and 21%, respectively, in stage III/IV disease.²⁶ However, at the SGO 2015 Annual Meeting on Women's Cancer, a multicenter analysis of intermediate- and high-risk endometrial cancers demonstrated that staging via the SLN mapping algorithm resulted in fewer lymph nodes removed but demonstrated a similar or higher detection rate of stage IIIC disease.²⁷ Furthermore, as the majority of women diagnosed with uterine serous carcinomas receive adjuvant systemic therapy of some type, even for stage I disease, the therapeutic role of systematic lymphadenectomy in these patients continues to be debated. Particularly in light of our data showing similar survival outcomes in cohorts with fewer nodes removed, clinicians must balance the risk of morbidity with the unknown benefit of an extensive lymph node dissection.

Our study shares the limitations inherent in retrospective research, particularly the possibility that differences between the groups attributable to changing disease management over time could preferentially benefit one cohort over another, although no specific evidence of this was noted in this study. Another potential limitation is the unequal median follow-up times between cohorts, although this is predominantly attributed to the time frame during which SLN mapping became the standard of care at our institution. It is also worth noting that patients in the SLN cohort had a median node removal count of 12, compared with 21 in the non-SLN group, which is likely attributable to the additional nodes removed as part of the SLN algorithm, either as completion lymphadenectomy on an unmapped hemipelvis, and/or removal of additional suspicious-appearing nodes. This is supported by the finding that median node removal counts decreased from 16 during the years 2005–2010 to 10 between 2011 and 2015, likely due to improved proficiency in the SLN technique.

CONCLUSION

Our study demonstrates that the incorporation of an SLN mapping algorithm into the staging of uterine serous cancers is feasible and does not appear to compromise prognosis. Further confirmation of these data in additional studies is necessary.

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FIG. 1.
Progression-free survival in patients undergoing SLN mapping versus standard lymphadenectomy. *SLN* sentinel lymph node

TABLE 1Characteristics of all patients with uterine serous carcinoma ($n = 248$)

	SLN cohort ($n = 153$)	Non-SLN cohort ($n = 95$)	<i>p</i> value
Age, years [median (range)]	65 (45–89)	68 (45–85)	0.077
BMI [median (range)]	29.6 (17.6–53.4)	29.3 (17.2–60.3)	0.916
Procedure			
Laparotomy	36 (23.5)	65 (68.4)	<0.001
MIS	117 (76.5)	30 (31.6)	
Stage			
I/II	106 (69.3)	59 (62.1)	0.269
III/IV	47 (30.7)	36 (37.9)	
Myometrial invasion (%)			
<50	119 (77.8)	67 (70.5)	0.228
>50	34 (22.2)	28 (29.5)	
LVSI			
Yes	55 (35.9)	46 (48.4)	0.063
No	98 (64.1)	49 (51.6)	
Adjuvant therapy			
Any CT	122 (79.7)	79 (83.2)	0.801
CT alone	38	26	
CT+IVRT	72	44	
CT+EBRT	12	9	
Radiation therapy	12 (7.8)	7 (7.4)	
IVRT	10	7	
EBRT	2	0	
None	19 (12.4)	9 (9.5)	

Data are expressed as n (%) unless otherwise specified

SLN sentinel lymph node, BMI body mass index, MIS minimally invasive surgery, LVSI lymphovascular space invasion, CT chemotherapy, IVRT intravaginal radiation therapy, EBRT external beam radiation therapy

TABLE 2

Adjuvant therapy by stage in the SLN versus non-SLN cohorts

	Stage I		Stage II		Stage III		Stage IV	
	SLN (n = 99)	Non-SLN (n = 48)	SLN (n = 7)	Non-SLN (n = 11)	SLN (n = 38)	Non-SLN (n = 36)	SLN (n = 9)	Non-SLN (n = 0)
Chemotherapy ± RT	71	38	6	9	37	32	8	NA
RT alone	11	6	1	1	0	0	0	NA
None	17	4	0	1	1	4	1	NA

SLN sentinel lymph node, *RT* radiation therapy, *NA* not applicable

TABLE 3

Univariate progression-free survival analysis

Variables	No. of patients	No. of progressions/deaths	2-year PFS rate (%) (95% CI)	<i>p</i> value
All	248	85	74.5 (68.2–79.7)	
SLN status				
No	95	40	70.9 (60.5–79.1)	0.345
Yes	153	45	76.6 (68.2–83.1)	
Stage				
I/II	165	36	84.9 (77.9–89.8)	<0.001
III/IV	83	49	54 (42.1–64.5)	
Myometrial invasion (%)				
<50	186	45	82.6 (75.9–87.6)	<0.001
>50	62	40	50.6 (36.9–62.8)	
LVSI				
No	147	27	85.3 (77.9–90.4)	<0.001
Yes	101	58	59.4 (48.7–68.6)	
Washings				
Negative	198	54	80.3 (73.6–85.5)	<0.001
Positive	41	24	51 (33.8–65.9)	

.SLN sentinel lymph node, LVSI lymphovascular space invasion, PFS progression-free survival, CI confidence interval

TABLE 4

Bivariate progression-free survival model

Variable	Levels	HR (95% CI)	<i>p</i> value
SLN	Yes versus no	0.97 (0.62–1.51)	0.894
Stage	III/IV versus I/II	3.64 (2.36–5.61)	<0.001

SLN sentinel lymph node, *HR* hazard ratio, *CI* confidence interval