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SENTINEL LYMPH NODE MAPPING ALONE COMPARED TO MORE EXTENSIVE LYMPHADENECTOMY IN PATIENTS WITH UTERINE SEROUS CARCINOMA

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Abstract

Objectives—The objective of our study was to assess survival among patients with uterine serous carcinoma (USC) undergoing sentinel lymph node (SLN) mapping alone versus patients undergoing systematic lymphadenectomy (LND).

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Methods—We retrospectively reviewed patients undergoing primary surgical treatment for newly diagnosed USC at our institution from 1/1/1996–12/31/2017. Patients were assigned to either SLN mapping alone (SLN cohort) or systematic LND without SLN mapping (LND cohort). Progression-free (PFS) and overall survival (OS) were estimated using Kaplan-Meier method, compared using Logrank test.

Results—245 patients were available for analysis: 79 (32.2%) underwent SLN, 166 (67.7%) LND. 132 (79.5%) in the LND cohort had paraaortic LND (PALND) versus none in the SLN cohort. Median age: 66 and 68 years in the SLN and LND cohorts, respectively ($p>0.05$). Proportion of stage I/II disease: 67.1% ($n=53$) and 64.5% ($n=107$) in the SLN and LND cohorts, respectively ($p>0.05$). Median follow-up: 23 (range, 1–96) and 66 months (range, 4–265) in the SLN and LND cohorts, respectively ($p<0.001$). Two-year OS in stage I/II disease ($n=160$, 60.1%): 96.6% ($SE\pm 3.4$) and 89.6% ($SE\pm 2.2$) in the SLN and LND cohorts, respectively ($p=0.8$). Two-year OS in stage III disease ($n=77$): 73.6% ($SE\pm 10.2$) and 77.3% ($SE\pm 5.8$) in the SLN and LND cohorts, respectively ($p=0.8$).

Conclusions—SLN mapping alone and systematic LND yielded similar survival outcomes in stage I–III USC. In our practice, the SLN algorithm has replaced systematic LND as the primary staging modality in this setting.

Keywords

Endometrial cancer; Sentinel lymph node; Uterine serous carcinoma; Lymphadenectomy

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy. Uterine serous carcinoma (USC) is an aggressive histologic subtype of this disease [1]. USCs comprise approximately 10% of all new cases of endometrial cancers diagnosed annually, but account for 40% of endometrial cancer deaths [2]. USC tends to spread beyond the uterus. Because of this tumor's aggressive behavior, adjuvant treatment and primary surgical staging are required for most patients [2].

As with other endometrial cancers, the initial staging surgery for USC includes retroperitoneal lymph node assessment, to ascertain disease prognosis and examine the factors associated with oncologic outcomes [3]. Although randomized trials have failed to show any survival benefit associated with systematic nodal dissection in endometrial cancer, detection of nodal disease does affect staging, prognosis and possibly postoperative treatment decisions. However, because of its low histologic prevalence, USC is under-represented in randomized studies. The morbidity associated with nodal dissection—including lymphedema, lymphocyst formation, and other potential organ injuries—is considerable [4–7]; therefore, questions have been raised regarding the necessity for extensive lymphadenectomy (LND) in every case.

Sentinel lymph node (SLN) mapping has been proposed as an alternative method for detecting nodal metastases in endometrial cancer. Use of the Memorial Sloan Kettering

Cancer Center SLN algorithm results in a very low (<0.5%) false-negative predictive value (FNPV) in the detection of nodal metastases [3, 8].

The published studies to date that have addressed the use of SLN mapping in USCs have primarily included other histologic subtypes of endometrial cancer, such as grade 3 endometrioid tumors, clear cell carcinomas and carcinosarcomas, and the applicability of those results to a purely USC population is limited. In other studies, patients who underwent SLN and full lymphadenectomy (LND) are combined [9–12]. The impact of the SLN algorithm on oncologic outcomes in USC is, therefore, less well-established. In the current study, we evaluated SLN mapping in patients with USC by comparing the outcomes of those who underwent SLN mapping alone (i.e., with no additional non-SLN nodes removed) to those who underwent pelvic +/- paraaortic LND without SLN mapping.

METHODS

After obtaining approval from the Institutional Review Board at Memorial Sloan Kettering Cancer Center (MSK), we retrospectively reviewed the records of all patients who underwent surgical staging for USC at MSK from January 1, 1996 through December 31, 2017. Surgical staging included total hysterectomy (irrespective of surgical/anatomic route), removal of adnexa, and lymph node evaluation using systematic LND and/or the SLN algorithm. The decision to proceed with systematic LND or SLN mapping was made by the surgeon. Expert gynecologic pathology review was performed on all cases.

SLN mapping was performed according to our previously published institutional protocol [8]. Patients typically had 4 mL 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 subsequent removal of nodes with uptake of dye/ICG. Pathologic analysis included ultrastaging of all SLNs in 5-micrometer (μ m) sections at each of two levels, 50- μ m apart. Anti-cytokeratin AE1:AE3 (Ventana Medical Systems Inc., Tucson, AZ) was used if the initial hematoxylin and eosin (H&E) sections were negative. Nodal disease was classified as macro-metastases, micro-metastases, or isolated tumor cells.

Our institutional SLN algorithm includes routine peritoneal and serosal evaluation and peritoneal washings. This is followed by retroperitoneal evaluation, removal of all mapped SLNs and any additional lymph nodes suspicious for disease, without performing routine intra-operative frozen section consultation. In the current study, completion LND was not performed unless indicated by the algorithm. In cases where failure in mapping was noted in a hemipelvis, a side-specific LND was performed. Further para-aortic dissection was completed at the discretion of the attending surgeon, with the guidance of preoperative imaging.

At our institution a combination of chemotherapy and radiation therapy (RT) is typically offered to patients who have both early myoinvasive and advanced stage USC. Decisions for adjuvant therapy were not changed nor modified based on whether LND or SLN mapping alone was done. However, the final decision regarding adjuvant therapy is made through

consultation between patients and their primary providers at MSK. Follow-up visits are scheduled every 3 months for the first 2–3 years, and then every 6 months for the next 2–3 years. Surveillance via computerized axial tomography scans is typically performed every 3–6 months during the first 2 years, and then every 6–12 months for the next 2–3 years. Patterns of recurrence are categorized as local/regional (including disease recurrence at the vaginal cuff and/or pelvis), isolated nodal, and distant/multifocal spread.

Clinical, pathologic and follow-up data were reviewed for each patient. Descriptive statistics and association tests were performed using SPSS software (v. 23; SPSS Inc., Chicago, IL). The Kruskal-Wallis test was used to compare continuous variables, and Fisher's exact test or the Chi-squared test used to compare categorical variables. Progression-free survival (PFS) was calculated from the date of surgery to the date of progression, date of death, or date of last follow-up. Overall survival (OS) was calculated from the date of surgery to the date of death or date of last follow-up. OS and PFS estimates were obtained using the Kaplan-Meier method, and the Logrank test was used to compare cohorts. A Cox proportional hazards model was used to determine independent prognostic factors for survival. All calculated p-values were two-sided, and p-values <0.05 were considered statistically significant.

RESULTS

Four-hundred two patients with USC who received treatment at our institution between January 1, 1996 and December 31, 2017 were identified. After excluding 5 patients (1 who had neoadjuvant CT prior to surgery, 3 with history of multiple primary malignancies, and 1 for serous endometrial intraepithelial carcinoma but no invasive disease), 397 patients were available for the final analysis. Thirty-seven of these patients were excluded because they had failed SLN mapping on one side of the pelvis and had undergone unilateral side-specific completion LND; 114 were excluded because they had had SLN mapping and additional non-SLNs removed. Seventy-nine (32.2%) patients underwent SLN mapping with no additional lymph node dissection (SLN cohort) and 280 (67.8%) patients underwent bilateral lymph node dissection (LND cohort).

Clinical and pathologic features of the study patients are presented in Table 1. Median age was 66 years (range, 51–89) in the SLN cohort and 68 years (range, 44–87) in the LND cohort ($p>0.05$). There was no difference in median body mass index (BMI) between the cohorts. Both cohorts had similar stage distribution, with stage I/II disease being the most common. The rates of deep myometrial invasion, lymphovascular space invasion (LVSI), and positive peritoneal washings were similar in both patient cohorts ($p>0.05$ for all observations). The median number of excised lymph nodes was 18.5 (range:1–75) in the LND cohort and 3 (range:1–11) in the SLN cohort ($p<0.001$). Para-aortic lymph node dissection was performed in 132 (79.5%) patients in the LND cohort and no patients in the SLN cohort ($P<0.001$). Rates of nodal metastasis were 26.5% and 29.5% in the SLN and LND cohorts, respectively ($p=0.6$).

The majority of patients received postoperative adjuvant treatment (84.8% and 89.8% in the SLN and LND cohorts, respectively; $p=0.9$). Chemotherapy alone or combined with RT was

the most common adjuvant treatment in both cohorts. Carboplatin plus paclitaxel was the most commonly administered chemotherapeutic agent.

The median follow-up time was 23 months (range, 1–96) for patients in the SLN cohort, and 66 months (range, 4–265) for patients in the LND cohort ($p<0.001$). Recurrence was observed in 97 (39.5%) patients, and recurrence rates were similar in both of the study cohorts ($p=0.5$). Distant/multifocal disease recurrence was predominant in both of the study cohorts. Patterns of disease recurrence are described in Table 2. The 2-year PFS rates were 58.8% (SE ± 6.5) and 64.9% (SE ± 3.8) in the SLN and LND cohorts, respectively ($p=0.478$) (Figure 1). On univariate analysis, patients with advanced stage disease, deep myometrial invasion, LVSI, positive washings, and those who did not undergo para-aortic nodal dissection had significantly shorter PFS. On multivariate analysis, deep myometrial invasion, positive washings, LVSI, and advanced stage disease were independent prognostic factors for worse PFS (Table 3).

At the time of analysis, 78 (31.8 %) of 245 study patients were deceased. The 2-year OS rates were 89.1% (SE ± 4.3) in the SLN cohort and 83.9% (SE ± 2.9) in the LND cohort ($p=0.9$) (Figure 2). Univariate analysis showed that stage III disease, 50% myometrial invasion, LVSI, or positive washings were associated with significantly lower 2-year OS ($p<0.001$). On multivariate analysis, positive peritoneal cytology (HR: 2.11; 95% CI [1.24–3.61]; $p=0.006$), $>50\%$ myometrial invasion (HR: 1.82; 95% CI [1.02–3.22]) and LVSI (HR: 2.04; 95% CI [1.18–3.51]; $p=0.01$) were independent prognostic factors for diminished OS (Table 4).

Patients who underwent para-aortic nodal dissection had higher 2-year PFS rates (69.7% [SE ± 4.1] vs. 55.4.3% [SE ± 5.2]; $p=0.015$) on univariate analysis, but multivariate analysis failed to show any significant association between para-aortic nodal dissection and 2- year PFS (HR 1.19; 95% CI [0.97–2.29], $p=0.06$). Additionally, para-aortic nodal dissection did not demonstrate an effect on 2-year OS in patients with USC (86.8% [± 2.4] vs. 83.2 [± 2.7], $p=0.12$).

DISCUSSION

In 1988, the International Federation of Gynecology and Obstetrics (FIGO) changed the staging system for endometrial cancer from clinical staging to surgical staging, following publication of the seminal paper by Creasman *et al.* [13, 14]. Two large randomized European trials failed to demonstrate any survival benefit for routine pelvic lymph node dissection, but showed higher rates of lymphedema in the LND arms [4, 5]. SLN mapping in patients with endometrial cancer started in the early 2000s and has become increasingly utilized over the past decade [3]. MSK's institutional SLN mapping algorithm (which indicates side-specific pelvic LND when an SLN is not detected during mapping) significantly decreased the false-negative detection rate from 15% to 2%. Most importantly, it decreased the FNPV to 0.4% in women with low-risk endometrial cancer [8]. The multicenter, prospective FIRES trial provided robust data regarding the accuracy of SLN mapping in patients with endometrial cancer, suggesting that SLN mapping has a high

degree of diagnostic accuracy in detecting endometrial cancer metastases and can safely replace LND in the staging of endometrial cancer. [10].

We previously compared the efficacy and oncologic outcomes of SLN mapping and selective lymph node dissection for determining lymphatic spread in patients with low-risk and high-risk endometrioid tumors, including those with high-risk histology (including USC) [15–17]. The largest published series on SLN mapping in patients with USC included 248 cases from our institution [12]. We noted 2-year PFS rates of 77% (95% CI, 68–83%) in the SLN group and 71% (95% CI, 61–79%) in the LND group ($p = 0.3$). However, in that analysis, our objective was to examine how incorporation of SLN mapping affected oncologic outcomes. In that analysis, the criteria for inclusion in the SLN cohort was significantly broader, as many patients in the “SLN cohort” also underwent either planned backup or selective LND due to failed SLN mapping. The current study was designed to evaluate the oncologic outcomes of patients with USC who only had SLNs removed and did not undergo additional LND. In the current study, therefore, the median total number of removed nodes was only 3 in the SLN cohort, compared to 12 in our previous analysis.

Several investigators have described their experience with SLN mapping in terms of nodal disease detection and survival in patients with high-risk endometrial cancer [9, 11, 12, 18, 19]. Soliman *et al.* reported the results of a prospective trial of 123 patients with high-risk endometrial cancer (grade 3 endometrioid, clear cell, USC) who underwent SLN mapping followed by complete LND [11]. The bilateral SLN detection rate was only 58%, but 95% of 23 (23%) node-positive women were correctly identified as having disease in the SLN, resulting in a false-negative rate of 5% and a FNPV of 0.8%. (In our study, the bilateral mapping rate in the SLN cohort was 89.9%, with nodal metastasis identified in 21 (26.5%) patients.) Another retrospective study by Touhami *et al.* of 128 patients with high-risk endometrial cancer reported an SLN mapping sensitivity of 95.8% and NPV of 98.2% [19]. Both the prospective and retrospective studies mentioned above added routine lymph node dissection after SLN mapping, but each of these studies included fewer than 50 cases of USC. A recent European multi-institutional retrospective analysis compared the SLN algorithm versus SLN with selective LND in high-risk, early-stage endometrial cancer. This study showed that 5-year DFS rates were similar in both groups: 79.2% (CI 95%: 56–91) for patients in the SLN algorithm group, and 81.6% (CI 95%: 67–90) for patients in the SLN with LND group ($p = 0.831$) [9]. Although this study has a methodology very similar to ours, most of the patients had high-risk endometrioid endometrial cancer and there were a limited number of patients with USC. Thus, as would be expected, the study reported better DFS rates than were found in our patient cohort.

Some retrospective data suggest that patients with high-risk endometrial cancer may benefit from para-aortic nodal dissection, despite randomized trials in all risk categories demonstrating no survival advantage [4, 5, 20, 21]. The SEPAL study suggested that pelvic and para-aortic LND was associated with better oncologic outcomes in high-risk patients compared with pelvic LND alone; however, as in most studies, the number of patients with non-endometrioid histology was very small ($n=55$, 8%), which limits our ability to gather true value in USC specifically [20]. Most recently, Venigalla *et al.* used the National Cancer Database (NCDB) to analyze 7250 patients with clinical stage I serous carcinoma, clear cell

carcinoma, or carcinosarcoma who underwent hysterectomy from 2010 to 2013 [21]. Pelvic LND was associated with decreased risk of death compared with no LND, in all histologic subtypes (HR = 0.65, 95% CI: 0.59–0.71). The addition of para-aortic LND was associated with a decreased risk of death (HR = 0.85, 95% CI: 0.79–0.91) compared to pelvic LND alone for patients with USC. It is unclear from the NCDB analyses whether LND was done only in the setting of microscopic nodal disease, or whether nodal status impacted postoperative therapy decisions; furthermore, as the NCDB has no central pathology review, we cannot ascertain the accuracy of pathologic assessments. In our study, none of the patients in the SLN cohort had a para-aortic LND. However, we observed similar 2-year OS rates for the patients in the LND cohort, most of whom underwent para-aortic LND. Our results do not appear to support the theory that the removal of microscopic nodal disease results in a survival benefit, as the randomized trials had suggested. The lymphatic channels do not end at either the inferior mesenteric or the renal veins. It is highly likely that one would encounter nodal disease in the lymphatics above the renal vein in cases with infrarenal nodal metastasis. Therefore, LND to remove microscopic disease would have to be carried above the renal veins, and likely to the scalene nodal basins, in order to be truly therapeutic.

The current study has limitations common to all retrospective studies. In addition, the median follow-up time was shorter in our SLN cohort than LND cohort (23 months vs. 66 months), and this impacted the outcome analysis as we chose to report 2-year outcomes. Our study included patients treated at our institution during a long period of time, but it is important to note that patient management has changed over time. Additional follow-up on the outcomes of SLN mapping is required. Nevertheless, our findings suggest that SLN mapping alone is safe in patients with USC. Furthermore, SLN mapping alone can be utilized to evaluate nodal spread while avoiding the morbidity associated with systematic nodal dissection.

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Highlights

- Systematic LND showed no survival benefit vs SLN mapping alone in patients with USC
- Detection of nodal metastasis is the same in SLN mapping alone vs systematic LND
- Advanced disease and LVSI were the most significant factors in oncologic outcomes

Figure 1.
Progression-free survival for all patients with USC

Figure 2.
Overall survival for all patients with USC

Table 1.

Demographics and clinical features of patients with uterine serous carcinoma (n=245)

	Exclusive SLN cohort (n=79)	Systematic LND (n=166)	p value
Age, years [Median (range)]	66 (51–89)	68(44–87)	0.979
BMI [Median (range)]	30.6(18.2–53.4)	29.2(17.2–60.3)	0.286
Procedure			
Laparotomy	8(10.1)	118(71.1)	<0.001
MIS	71(89.9)	48(28.9)	
Stage			
I/II	53(67.1)	107(64.5)	0.837
III	23(29.1)	54(32.5)	
IV	3(3.8)	5(3.0)	
Myometrial invasion (%)			0.158
<50	62 (78.5)	116(69.9)	
50	17 (21.5)	50(30.1)	
LVI			0.126
Yes	28(35.4)	76(45.8)	
No	51(64.6)	90(54.2)	
Peritoneal washings			0.813
Positive	14(18.2)	30(19.5)	
Negative	63(81.8)	124(80.5)	
Total node counts [Median (range)]	3(1–11)	18.5(1–75)	<0.001
Bilateral SLN mapping on pathologic exam	71(89.9)	0(0)	<0.001
Paraortic dissection			
Yes	0(0)	132(79.5)	
No	79(100)	34(20.5)	
Nodal metastasis rate	21(26.5)	49(29.5)	0.634
Macrometastasis	15(71.4)	49(100)	
Micrometastasis	1(4.8)	0(0)	
ITC	5(23.8)	0(0)	

Data are expressed as n (%) unless otherwise specified

Table 2.

Adjuvant treatment regimens, recurrence patterns and survival outcomes of patients with uterine serous cancer (n=245)

	Exclusive SLN cohort (n=79)	Systematic LND (n=166)	p value
Adjuvant therapy	67(84.8)	149(89.8)	0.92
Any CT	51(64.5)	117(70.4)	0.698
CT alone	9	29	
CT+IVRT	35	65	
CT+EBRT	7	22	
CT+IVRT+EBRT	0	1	
Radiation Therapy	16(20.2)	31(18.6)	
IVRT	14 (17.7)	17 (10.2)	
EBRT	2 (2.5)	14 (8.4)	
Hormone	0	1	
None	8	17	
Recurrence rates	29(36.7)	68(40.9)	0.524
Locoregional	1(3.4)	7(4.2)	
Nodal only	4(5.0)	19(11.4)	
Peritoneal/distant	24(30.3)	42(25.3)	
Follow-up time, months [Median (range)]	23(1–96)	66(4–265)	<0.001
2-year PFS(±SE) rates	58.8(±6.5)	64.9(±3.8)	0.478
Stage I/II	70.9(±7.7)	80.1(±3.9)	
Stage III	34.6(±10.8)	42.0(±6.9)	
2-year OS(±SE) rates	89.1(±4.3)	83.9(±2.9)	0.846
Stage I/II	96.6(±3.4)	89.6(±3.0)	
Stage III	73.6(±10.2)	77.3(±5.8)	

Data are expressed as n (%) unless otherwise specified

CT, chemotherapy; IVRT, intravaginal radiation therapy; EBRT, external beam radiation therapy

Table 3.

Univariate and multivariate analysis for PFS in patients with uterine serous carcinoma (n=245)

	No. of Patients	No. of events	2-year PFS(±SE) rate	p value*	Adjusted HR (95% CI)	p value**
All	245	97	63.7(±3.2)			
Procedure						
Laparotomy	126	53	60.9(±3.9)	0.895		
MIS	119	44	66.6(±4.7)			
Stage						
I/II	160	42	77.2(±3.5)	<0.001		
III	77	49	39.9(±5.9)		1.5 (1.01–2.25)	0.047
Myometrial invasion (%)						
<50	178	54	72.8(±3.5)	<0.001		
50	67	43	40.4(±6.2)		1.685 (1.01–2.80)	0.045
LVSI						
No	141	36	76.0(±3.8)	<0.001		
Yes	104	61	47.7(±5.1)		1.77(1.07–2.91)	0.025
Peritoneal washings						
Negative	187	62	70.1(±3.5)	<0.001		
Positive	44	30	38.1 (±7.1)		2.11(1.31–3.41)	0.002
Paraaortic dissection						
Yes	132	48	69.7(±4.1)	0.015		
No	113	49	55.4(±5.2)		1.49(0.977– 2.296)	0.06
SLN mapping						
Exclusive	79	29	58.8(±6.5)	0.478		
Systematic LND	166	68	64.9(±3.8)			

Data are expressed as n (%) unless otherwise specified

SLN, sentinel lymph node; MIS, minimally invasive surgery; LVSI, lymphovascular space invasion; LND, lymph node dissection

* univariate analysis

** multivariate analysis

Table 4.

Univariate and multivariate analysis for OS in patients with uterine serous carcinoma (n=245)

	No. of Patients	No. of deaths	2-year OS($\pm$ SE) rate	p value	HR(95% CI)	p value
All	245	78	85.4($\pm$ 2.4)			
Procedure						
Laparotomy	126	50	82.0($\pm$ 3.5)	0.668		
MIS	119	28	89.6($\pm$ 3.1)			
Stage						
I/II	160	35	89.8($\pm$ 2.6)	<0.001		
III	77	41	76.5($\pm$ 5.0)		1.19(0.74–1.91)	0.475
Myometrial invasion (%)						
<50	178	43	89.6($\pm$ 2.5)	<0.001		
50	67	35	74.8($\pm$ 5.5)		1.82(1.02–3.22)	0.40
LVSI						
No	141	26	93.1($\pm$ 2.4)	<0.001		
Yes	104	52	75.8($\pm$ 4.3)		2.04(1.18–3.51)	0.01
Peritoneal washings						
Negative	187	50	88.4($\pm$ 2.5)	<0.001		
Positive	44	24	76.1($\pm$ 6.6)		2.11(1.24–3.61)	0.006
Paraaortic dissection						
Yes	132	48	86.8($\pm$ 3.0)	0.123		
No	113	30	83.2($\pm$ 4.0)			
SLN mapping						
Exclusive	80	14	89.1($\pm$ 4.3)	0.935		
Systematic LND	166	64	83.9($\pm$ 2.9)			

Data are expressed as n (%) unless otherwise specified

SLN, sentinel lymph node; MIS, minimally invasive surgery; LVSI, lymphovascular space invasion; LND, lymph node dissection