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# Impact of incorporating an algorithm that utilizes sentinel lymph node mapping during minimally invasive procedures on the detection of stage IIIC endometrial cancer

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## HIGHLIGHTS

- Incorporation of a modified staging approach utilizing SLN mapping algorithm reduces the need for standard lymphadenectomy.
- This approach does not appear to adversely affect the rate of stage IIIC detection.

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## ABSTRACT

*Objective.* To determine whether the frequency of cases diagnosed with stage IIIC endometrial cancer is affected by the incorporation of a modified surgical lymph node assessment.

*Methods.* Since 2008, we have increasingly utilized a modified nodal assessment using an algorithm that incorporates SLN mapping. For this analysis, we identified all cases of newly diagnosed endometrial cancers undergoing a minimally invasive staging procedure not requiring conversion to laparotomy from 1/1/08 to 12/31/10. Procedures were categorized as standard, modified, and hysterectomy only. Differences were based on time period: 2008 (Y1), 2009 (Y2), and 2010 (Y3). Appropriate statistical tests were used.

*Results.* We identified a total of 507 cases. The distribution of cases was 143 (Y1), 190 (Y2), and 174 (Y3). Tumor grade ($P=0.05$) and high-risk histologies ($P=0.8$) did not differ during the 3 time periods. A standard staging procedure was performed in the following cases: Y1 (93/143; 65%), Y2 (66/166; 35%), and Y3 (40/164; 23%) ($P<0.001$). Median operative times were as follows: Y1 (218 min), Y2 (198 min), and Y3 (176.5 min) ($P<0.001$). The median numbers of total lymph nodes removed among cases with at least 1 node retrieved were: Y1 (20); Y2 (10); Y3 (7) ($P<0.001$). Cases diagnosed as stage IIIC were as follows: Y1 (10/143; 7%), Y2 (15/166; 7.9%), and Y3 (13/164; 7.5%) ($P=1.0$).

*Conclusions.* The incorporation of a modified staging approach utilizing the SLN mapping algorithm reduces the need for standard lymphadenectomy and does not appear to adversely affect the rate of stage IIIC detection.



## Introduction

The role of comprehensive surgical staging for uterine cancers has become an extremely controversial topic. The value of an extended full lymphadenectomy is debatable. Surgical approaches and recommendations range tremendously from no lymphadenectomy for any case to an extensive lymphadenectomy from the pelvis up to the renal vessels. The ASTEC trial demonstrated that a pelvic lymphadenectomy has no therapeutic value [1]. However, without assessing the nodal status, over- or undertreatment becomes a valid concern [2]. Postoperative therapies can be better guided with information regarding nodal status. Other authors strongly advocate a quite extensive lymphadenectomy for high-risk cases based on preoperative biopsy results and intraoperative frozen section results [3]. Unfortunately, this method of determining high risk has not been reproducible at most other institutions. Additionally, there is morbidity as well as increased operative times associated with extensive lymphadenectomy and a clear benefit has yet to be proven [4].

There is likely no therapeutic value in removing normal-sized lymph nodes in patients with uterine cancer. However, these nodes may provide valuable information for accurate stage assessment, and thereby influence decisions regarding the need for adjuvant postoperative treatment. Sentinel lymph node (SLN) mapping has been shown to be feasible and may be the ideal compromise in assessing nodal status while limiting morbidity [5]. Minimally invasive surgery (MIS) already has

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been proven to offer a less morbid overall surgical approach [6,7]. A recent prospective trial seemed to further support continued use and investigation of SLN mapping in uterine cancers [8]. SLN mapping for uterine cancers has been utilized at our institution since 2003 and has become an integral part of nodal assessment during our MIS procedures. In this study, we sought to determine how incorporation of SLN mapping has affected surgical outcomes as well as how it has affected our ability to detect nodal disease (i.e., FIGO stage IIIC).

## Methods and materials

A prospective feasibility trial of SLN mapping in uterine cancer was conducted at our institution from 2003 to 2008. Since completion of that trial, we have been increasingly incorporating a modified nodal assessment using a previously published algorithm [9] that incorporates SLN mapping and reduces the extent of or eliminates a full comprehensive lymphadenectomy. In brief, this SLN algorithm involves the injection of a blue dye (isosulfan blue or methylene blue) into the cervix alone. Any suspicious nodes are removed – irrespective of whether they are blue or not – with a standard lymphadenectomy being performed for any hemipelvis that does not map. A para-aortic nodal dissection is left to the discretion of the attending surgeon.

For this analysis, we identified all consecutive cases of newly diagnosed endometrial cancers undergoing a planned MIS procedure and not requiring conversion to laparotomy from 1/1/08 to 12/31/10. We chose 2008 as the starting point because our pilot feasibility protocol completed accrual early that year. Procedures were categorized as follows: 1) Hysterectomy only (HYST): neither SLN mapping nor any other nodal assessment is performed; 2) MODIFIED: SLN algorithm is used; and 3) STANDARD: pelvic and aortic nodal dissection to the inferior mesenteric artery is performed. All of the SLN mapping procedures were performed using a cervical injection on the day of surgery with blue dye only.

Operating room time was determined from time of patient entry into the operating room until departure from the operating room, while operative time was determined from the start of skin incision to the completion of skin closure. FIGO grade and histologies were recorded from the final pathologic assessment of the uterus after hysterectomy. The preoperative grade and histology were used if no residual tumor was found in the hysterectomy specimen. Serous, clear cell, and undifferentiated carcinomas, and carcinosarcomas were considered high-risk histologies. The time periods analyzed were 2008 (Y1), 2009 (Y2), and 2010 (Y3). SLNs with cytokeratin-positive (i.e., IHC+) cells only were not considered as positive nodes for this analysis. Nominal data were analyzed using chi-square test or Fisher exact test as appropriate. Continuous data were analyzed using Kruskal–Wallis test. SPSS statistical software was used to perform statistical tests.

## Results

We identified 507 consecutive cases undergoing a MIS procedure without conversion to laparotomy during the 3-year study period. The clinical characteristics of our cohort are described in Table 1. The median age and BMI did not differ across the 3 time periods. The majority of cases (385/423; 91%) in which final FIGO grade was assessed were grade 1 or 2. The distribution of grade was the same in all 3 time periods. The majority of cases were low-risk histology and the distribution also did not significantly change over time. The robotic platform was used more frequently over time, with 43% of the cases being performed robotically in Y1 compared with 72% in Y3 ($P<0.001$).

The surgical procedures performed during the time periods are depicted in Fig. 1. Incorporation of the SLN mapping algorithm increased significantly from 23% (Y1) to 52% (Y2) and to 71% (Y3) ($P<0.001$). Subsequently, the number of cases undergoing a comprehensive pelvic and aortic nodal dissection significantly decreased from 65% (Y1) to 35% (Y2) and to 23% (Y3) ($P<0.001$). In Y3, the rate of comprehensive pelvic and aortic nodal dissection varied by surgeon and ranged from 0% to 67% ($P<0.001$) based on individual surgeon experience with SLN mapping. Beyond the surgeon variability in Y3, a comprehensive nodal dissection was more often performed in higher risk histologies and higher grade based on preoperative diagnoses. Comprehensive staging in Y3 for each preoperative histology diagnosis was as follows: endometrioid (18%), serous (53%), carcinosarcoma (33%), and other (0%) ($P=0.01$). Comprehensive staging for each preoperative grade diagnosis was 8% in grade 1, 30% in grade 2, and 50% in grade 3 ($P<0.001$). Fig. 2 depicts the median operating room and operative times over the 3 time periods. The median operating room time in Y1 was 297 min (range, 135–613 min) compared with 247 min (range, 128–493 min) in Y3 ($P<0.001$). The median operative time in Y1 was 218 min (range, 80–533 min), compared with 176.5 min (range, 85–402 min) in Y3 ($P<0.001$). The overall median node counts were 19 (range, 0–43) in Y1, 6 (range, 0–57) in Y2, and 6 (range, 0–44) in Y3 ($P<0.001$). The median node counts including only cases with at least 1 node retrieved were 20 (range, 3–43) in Y1, 10 (range, 1–57) in Y2, and 7 (range,

**Table 1**
Clinical characteristics of cases based on time period.

| Variable | 2008 (Y1) | 2009 (Y2) | 2010 (Y3) | P-value |
|---|---|---|---|---|
| N | 143 | 190 | 174 | |
| Age (years) | | | | |
| Median (range) | 61 (27–85) | 59 (32–86) | 61 (31–88) | 0.4 |
| BMI (kg/m$^2$) | | | | |
| Median (range) | 28.1 (17.6–57.2) | 28 (18.6–60.6) | 29.5 (18.7–66) | 0.1 |
| MIS approach — N (%) | | | | |
| STD | 81 (56.6) | 74 (38.9) | 48 (27.6) | <0.001 |
| RBT | 62 (43.4) | 116 (61.1) | 126 (72.4) | |
| Uterine weight (g) | | | | |
| Median (range) | 107.5 (20–407) | 115 (35–349) | 105.5 (30–547) | <0.001 |
| Final tumor grade — N (%)[a] | | | | |
| 1 | 82 (68.3) | 109 (69) | 90 (62.1) | 0.05 |
| 2 | 30 (25) | 29 (18.4) | 45 (31) | |
| 3 | 8 (6.7) | 20 (12.7) | 10 (6.9) | |
| Final histology — N (%) | | | | |
| Endometrioid | 114 (79.7) | 156 (82.1) | 140 (80.5) | – |
| Other | 29 (20.3) | 34 (17.9) | 34 (19.5) | |
| Histology risk group — N (%)[b] | | | | |
| Low | 121 (85.6) | 159 (83.7) | 143 (82.2) | 0.8 |
| High | 22 (15.4) | 31 (16.3) | 31 (17.8) | |

MIS = minimally invasive surgery; STD = standard laparoscopy; RBT = robotically assisted laparoscopy.
[a] Grade not assessed for serous, clear cell, and undifferentiated carcinomas, carcinosarcoma, adenosarcoma, and endometrial stromal sarcoma.
[b] High risk = serous, clear cell, and undifferentiated carcinomas, and carcinosarcoma.

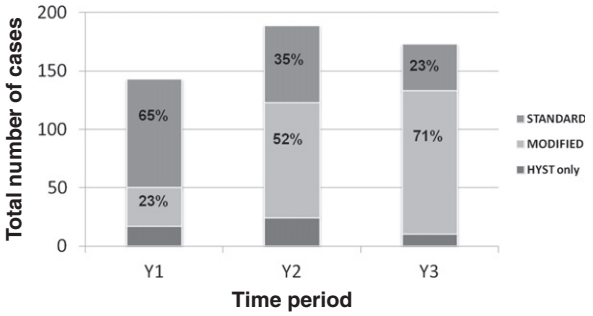


**Fig. 1.** Change in nodal assessment procedures across the 3 time periods (P<0.001).

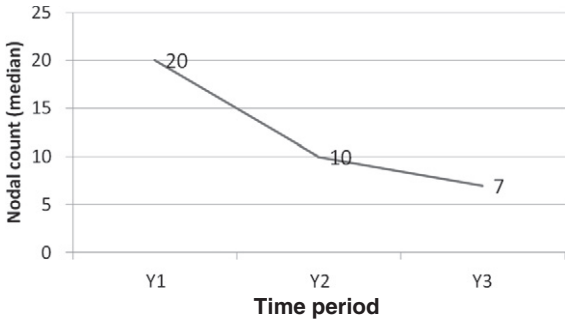


**Fig. 3.** Median nodal counts including only cases with at least 1 node retrieved across the 3 time periods (P<0.001).

1–44) in Y3 (P<0.001) (Fig. 3). Perioperative complications up to 30 days postoperatively occurred in 25 (18%) cases in Y1, 18 (10%) cases in Y2, and 14 (8%) cases in Y3 (P=0.02). The rate of identifying stage IIIC cases over time is depicted in Fig. 4; there was no difference noted over the 3 time periods. The rates of identifying stage IIIC cases limiting to only the high-risk histologies based on final pathologic interpretation (n=84) were 9% in Y1, 13% in Y2, and 16% in Y3 (P=0.8). The rates limiting to final pathologic grade 3 cases were 0% in Y1, 5% in Y2, and 10% in Y3 (P=0.6).

## Discussion

Total hysterectomy is the primary treatment for the vast majority of patients initially diagnosed with endometrial cancers [2]. GOG LAP2 confirmed the findings of multiple prior reports that a laparoscopic (MIS) approach results in improved perioperative outcomes, and quality-of-life, without compromising oncologic outcomes [6,7,10]. Therefore, a MIS approach is widely accepted as preferred over a laparotomy. Currently the most controversial aspect of surgical management of endometrial cancer is the lymph node assessment. Recommendations vary from no lymphadenectomy for any patient, to selected "sampling" in all or some patients, to comprehensive lymphadenectomy based on risk factors, and to comprehensive lymphadenectomy up to the renal vessels for all cases [2].

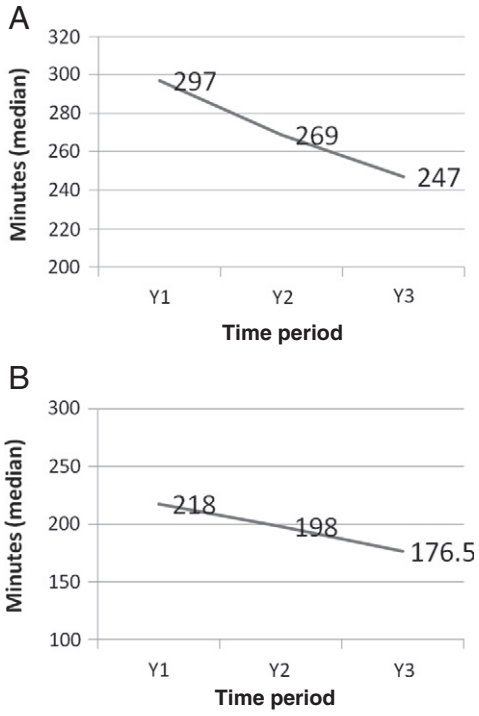


**Fig. 2.** Median operating room (A) and operative (B) times across the 3 time periods (P<0.001). Operating room time was determined from the time of patient entry into the operating room until departure from the operating room. Operative time was determined from the start of skin incision to the completion of skin closure.

Prior retrospective studies suggested that there is a potential therapeutic value to lymphadenectomy, mostly for high-risk early-stage endometrial cancers and possibly for advanced stage cases [11,12]. In contrast, a prospective randomized trial, MRC-ASTEC, showed no survival advantage in patients who underwent a pelvic lymphadenectomy compared with those who did not [1]. There are drawbacks to routinely adopting either a "no lymphadenectomy" strategy or a "complete lymphadenectomy" strategy for all patients. A "middle ground" alternative that provides the needed prognostic and treatment-influencing information while limiting morbidity is needed.

Many now feel that lymphadenectomy is likely not therapeutic in itself based on the results of ASTEC [2]. However, there are 2 major points to consider. The first is that a para-aortic lymphadenectomy was not required in this trial. The second is that the nodal status was not used to inform the decisions regarding postoperative therapy and many of the node-positive patients did not receive any postoperative therapy. Chemotherapy has been shown to improve overall survival in patients with FIGO stage III/IV disease [13]. Some argue that uterine factors should be used to decide whether to administer postoperative chemotherapy and not perform lymphadenectomy. However, some authors have reported excellent survival in patients with confirmed node-negative stage I endometrial cancers who do not receive adjuvant chemotherapy [14,15]. If the lymph node status is unknown, there is a risk that some patients may be inappropriately over- or undertreated [2]. Furthermore, a lymphadenectomy increases operative time and increases the risk of developing symptomatic lower extremity lymphedema [4].

There is an obvious need for an alternate method that will accurately identify nodal disease while minimizing morbidity. SLN mapping may be the necessary and important alternative [5]. Multiple retrospective reports have demonstrated the feasibility of SLN mapping and suggested that it may be reasonable to omit a full lymphadenectomy in cases that map well [4,9]. Ballester and colleagues recently published the results of a prospective study demonstrating a very low false-negative rate using SLN mapping, mostly in the low and intermediate risk cases [8]. These findings need to be validated in a larger prospective series and the accuracy, especially in higher risk cases, is yet to be determined.

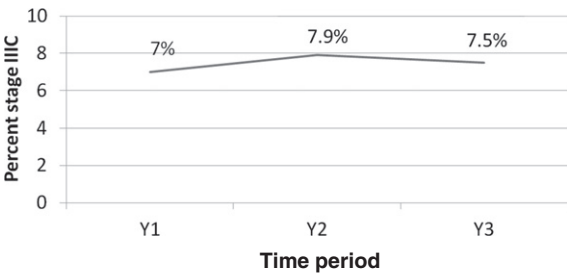


**Fig. 4.** Rate of identification of FIGO stage IIIC disease across the 3 time periods (P=1.0).

Our data provide retrospective insights that suggest that the number of patients that undergo full lymphadenectomy may be safely reduced by incorporating a SLN mapping algorithm. Within 3 years, the percentage of patients subjected to full lymphadenectomy decreased significantly from 65% to 23% at our institution. This led to significant decreases in median operating room time by nearly 1 h. Similarly, the median operative time was significantly reduced by approximately 40 min. The median number of nodes removed also significantly decreased by 13, from a median of 20 to a median of 7. It is reassuring that the incorporation of this SLN assessment strategy did not compromise the ability to detect nodal disease. Lymph node involvement was found in the same percentage of cases across the 3 years, despite the reduction in use of comprehensive lymphadenectomy and the decrease in the total number of lymph nodes removed.

Longer follow-up is needed in our cohort to determine how the increased use of the SLN strategy impacts long-term complications, specifically lymphedema, as well as overall survival. The importance of "ultra-staging" of the sentinel lymph nodes, which detects immunohistochemical (IHC)-only positive SLNs and micrometastases, also requires further investigation. The optimal SLN mapping technique also needs to be further elucidated. Our experience has been that a simple cervical injection with dye alone seems to be convenient, least costly, and most reproducible. However, we recognize that there is still controversy regarding the site of injection (cervix and/or endometrium), use of radiotracer, and use of hysteroscopy [16]. Our data provide further support to the concept of incorporating SLN mapping in the surgical management of patients with newly diagnosed endometrial cancers. These data provide a strong rationale for conducting a large, well-designed prospective trial comparing SLN assessment to lymphadenectomy.

**Conflict of interest statement**

The authors have no conflicts of interest to disclose.

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