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Comparison of a sentinel lymph node and a selective lymphadenectomy algorithm in patients with endometrioid endometrial carcinoma and limited myometrial invasion

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HIGHLIGHTS

- SLN algorithm in low-risk endometrial carcinoma allows for lymph node assessment in more patients.
- Fewer lymph nodes are removed in patients undergoing an SLN approach vs selective lymphadenectomy.
- Oncologic outcomes are similar for SLN algorithm compared to selective lymphadenectomy.

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ABSTRACT

Objectives. To assess clinicopathologic outcomes between two nodal assessment approaches in patients with endometrioid endometrial carcinoma and limited myoinvasion.

Methods. Patients with endometrial cancer at two institutions were reviewed. At one institution, a complete pelvic and para-aortic lymphadenectomy to the renal veins was performed in select cases deemed at risk for nodal metastasis due to grade 3 cancer and/or primary tumor diameter > 2 cm (LND cohort). This is a historic approach at this institution. At the other institution, a sentinel lymph node mapping algorithm was used per institutional protocol (SLN cohort). Low risk was defined as endometrioid adenocarcinoma with myometrial invasion <50%. Macrometastasis, micrometastasis, and isolated tumor cells were all considered node-positive.

Results. Of 1135 cases identified, 642 (57%) were managed with an SLN approach and 493 (43%) with an LND approach. Pelvic nodes (PLNs) were removed in 93% and 58% of patients, respectively ($P < 0.001$); para-aortic nodes (PANs) were removed in 14.5% and 50% of patients, respectively ($P < 0.001$). Median number of PLNs removed was 6 and 34, respectively; median number of PANs removed was 5 and 16, respectively (both $P < 0.001$). Metastasis to PLNs was detected in 5.1% and 2.6% of patients, respectively ($P = 0.03$), and to PANs in 0.8% and 1.0%, respectively ($P = 0.75$). The 3-year disease-free survival rates were 94.9% (95% CI, 92.4–97.5) and 96.8% (95% CI, 95.2–98.5), respectively.

Conclusions. Our findings support the use of either strategy for endometrial cancer staging, with no apparent detriment in adhering to the SLN algorithm. The clinical significance of disease detected on ultrastaging and the role of adjuvant therapy is yet to be determined.

1. Introduction

The value of surgical staging in endometrial carcinoma is a subject of debate; as such, there is no uniform approach to lymph node assessment in clinically uterine-confined disease. Staging strategies range from no lymphadenectomy, with the use of preoperative imaging or

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intraoperative frozen section to guide management, to comprehensive lymphadenectomy. The results of two randomized trials showed no improvement in disease-free or overall survival for patients with early-stage endometrial carcinoma who had undergone systematic pelvic lymphadenectomy [1,2]. However, in a recent Classification and Regression Tree (CART) analysis, surgical staging, but not the total number of lymph nodes removed, was found to be the most important prognostic factor for overall survival in endometrial cancer [3]. Uterine factors have been shown to be less accurate predictors of recurrence than lymph node status [4,5]. Taken together, assessing nodal status at the time of initial staging in these patients is imperative.

In the landmark study by Creasman et al., pelvic nodal metastasis was found in 5% of patients with superficial myometrial invasion [6]. When taking into consideration the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system, Chi et al. found that 5.5% of patients with disease of endometrioid histology, all grades and myometrial invasion <50%, had nodal metastasis [7]. Despite the low incidence of nodal disease in these low-risk patients, omitting lymphadenectomy from their surgical management would result in inadequate staging, and consequently either preclude administration of adjuvant therapy when warranted or lead to the overtreatment of certain patients. Comprehensive lymphadenectomy is associated with intraoperative complications, such as increased operating time, nerve and vessel injury, higher blood loss, and postoperative morbidity [8]. The rate of long-term lymphedema directly attributed to lymphadenectomy was recently reported to be 23% [9]. The morbidity associated with comprehensive lymphadenectomy is of particular concern in the low-risk population.

Sentinel lymph node (SLN) mapping is emerging as an acceptable approach for nodal assessment in endometrial carcinoma. This is reflected by the inclusion of an SLN algorithm in the 2014 National Comprehensive Cancer Network (NCCN) guidelines for the management of endometrial cancer [10]. However, when introducing a novel management strategy, we must take great care not to compromise oncologic outcome or inflict harm on our patients. With this in mind, we conducted the following study, in which we sought to assess and compare the clinicopathologic outcomes between two nodal assessment approaches in patients with "low-risk" endometrial carcinoma as defined by endometrioid histology and limited myoinvasion.

2. Materials and methods

Patients with low-risk endometrial cancer at two institutions were identified using the uterine cancer institutional databases at the Mayo Clinic (Mayo) and Memorial Sloan Kettering Cancer Center (MSK). Low risk was defined as endometrioid adenocarcinoma of any grade with myometrial invasion <50%. At one of the institutions, tumor size is not routinely assessed intra- or postoperatively. Therefore, tumor size was not included in our risk classification. From the Mayo Clinic, the historic lymph node dissection (LND) cohort encompassed the years 2004 through 2008. The SLN cohort from MSK encompassed the years 2006 through 2013.

The Mayo Clinic historical surgical algorithm for the study period was to perform a hysterectomy, bilateral salpingo-oophorectomy (BSO), peritoneal cytology, and bilateral pelvic and para-aortic lymphadenectomy. A gynecologic oncology pathologist performed frozen section of the uterine specimen to determine tumor size and depth of myometrial invasion. Lymphadenectomy was omitted in patients with disease of endometrioid histology with any grade or tumor size if there was no myometrial invasion, and in patients with disease of endometrioid histology, grade 1 or 2, with <50% myometrial invasion and tumor diameter ≤ 2 cm (Supplementary Fig. 1) [11]. At MSK, a previously published SLN algorithm was used per institutional protocol (Supplementary Fig. 2) [12]. Lymphatic mapping was performed by injecting blue dye or indocyanine green (ICG) into the cervical stroma at superficial and deep levels at the 3- and 9-o'clock positions for a total of 4 mL. Identified SLNs were excised and evaluated by the institutional SLN Pathologic Processing Protocol [13]. Any suspicious nodes were removed regardless of mapping. In cases with no mapping on a hemi-pelvis, a side-specific LND was performed. Para-aortic LND was performed at the surgeon's discretion.

Macrometastasis, micrometastasis, and isolated tumor cells (ITCs) were all considered node-positive for this analysis. ITCs were defined as cells measuring ≤0.2 mm, as seen on corresponding hematoxylin and eosin (H&E) sections and not just immunohistochemical (IHC) staining. Micrometastasis was defined as tumor within a lymph node larger than 0.2 mm but less than 2.0 mm in greatest diameter. Notably, when the tumor measurement was not delineated in the pathology report and the terms "isolated tumor cells" and "micrometastasis" were not used, a determination was made based on the pathology report, with clarification from a gynecologic pathologist when needed. For example, "rare scattered tumor cells" were classified as ITCs, whereas "diffuse clusters of cells" were defined as micrometastases. Lymph nodes with a tumor burden ≥2.0 mm were reported as metastatic lymph nodes without further delineation of number or cells or the size of the metastasis. Cytokeratin-positive cells not seen on H&E were considered node-negative. Adjuvant therapy was administered per recommended institutional guidelines.

We compared patient-, treatment-, and disease-specific parameters between cohorts using the chi square or Fisher exact test for categorical variables, the two-sample *t* test for age and body mass index (BMI), and the Wilcoxon rank-sum test for number of nodes removed and number of positive nodes. Disease-free survival, disease-specific survival, and overall survival were evaluated within the first 3 years after surgery. Survivorship was estimated using the Kaplan-Meier method and compared between the cohorts using the log-rank test. All calculated P values were two-sided, and P values <0.05 were considered statistically significant.

3. Results

A total of 1135 cases were identified: 642 in the SLN cohort and 493 in the selective LND cohort. Patient and tumor characteristics are shown in Table 1. Patients in the SLN cohort were significantly younger (mean age, 59.6 vs 63.1 years), had an overall lower mean BMI (31.7 vs 35.4 kg/m^2), and more likely to not have myometrial invasion (57.0% vs 29.4%) compared with patients in the LND cohort ($P < 0.001$ for each characteristic). The distribution of FIGO grade was similar in the two cohorts. In the SLN cohort, 15.2% of patients had lymphovascular space invasion (LVI) compared with 3.0% in the LND cohort ($P < 0.001$). There are institutional differences in the diagnostic criteria for the presence of LVI.

Pelvic lymph nodes were excised in 92.8% of the patients in the SLN cohort compared with 57.8% in the LND cohort ($P < 0.001$; Table 2). Among those who underwent pelvic nodal assessment, the median number of pelvic lymph nodes excised per patient was 6 (interquartile range [IQR]: 3,11) in the SLN cohort versus 34 (IQR: 26,45) in the LND cohort ($P < 0.001$). Positive pelvic lymph nodes were detected in 5.1% (33/642; 95% CI, 3.4–6.9%) and 2.6% (13/493; 95% CI, 1.2–4.1%) of patients, respectively ($P = 0.03$). These last percentages are not identical to the detection rate of stage IIIC1 since some patients with positive pelvic lymph nodes also had positive para-aortic lymph nodes and belong in stage IIIC2. The median number of positive pelvic nodes per patient among those patients with positive pelvic nodes was 1 (IQR: 1,2) for both groups.

Para-aortic nodes were excised in 14.5% of the patients in the SLN cohort compared with 49.7% in the LND cohort ($P < 0.001$). Among those who underwent para-aortic nodal assessment, the median number of para-aortic lymph nodes excised was 5 (IQR: 3,8) in the SLN cohort versus 16 (IQR: 11,23) in the LND cohort ($P < 0.001$). Positive para-aortic lymph nodes were detected in 0.8% (5/642; 95% CI, 0.1–1.5%) and 1.0% (5/493; 95% CI, 0.1–1.9%) of patients, respectively ($P = 0.75$). Among the patients with positive para-aortic nodes (5 in each cohort), 4 in