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Prevalence of and factors contributing to missing lymph tissue in uterine cancer staging surgery

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HIGHLIGHTS

- About half of the study patients did not have a complete set of lymph node samples.
- Incomplete lymph nodes did not seem to affect patient survival.

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ABSTRACT

Objective. We wished to investigate the prevalence of missing lymph nodes (MLN), factors contributing to MLN, and the effect of MLN on progression free survival (PFS).

Methods. Patients with uterine cancer undergoing abdominal hysterectomy and lymphadenectomy were recruited. All surgeries adhered to the Gynecologic Oncology Group protocol in collecting all the lymph node tissues in paraaortic, common iliac, obturator fossa, and external and internal iliac bilaterally. Data regarding race, age, body mass index (BMI), lymph node counts, staging, location of missing lymph nodes, length of surgery, and estimated blood loss were collected and analyzed in reference to missing lymph nodes. The definition of missing lymph node was an incomplete nodal specimen obtained without actual lymph node tissue.

Results. Between April 2003 and January 2010, 235 consecutive patients were enrolled prospectively; 108 patients had missing lymph nodes post-operatively (46%), and 127 patients had complete lymph nodes. We found no correlation between MLN relative to race ($P = 0.97$), age ($P = 0.25$), BMI ($P = 0.09$), estimated blood loss ($P = 0.38$), American Society of Anaesthesiologist physical status classification system ($P = 0.18$), surgery time ($P = 0.22$), hospital stay ($P = 0.05$), nodes without cancer ($P = 0.12$), nodes with cancer ($P = 0.99$), stage ($P = 0.90$), grade ($P = 0.17$), or PFS ($P = 0.29$).

Conclusion. In our study, although prevalence of missing lymph nodes seems relatively high, none of the perioperative variables studied appeared to contribute to missing lymph nodes. Finally, missing lymph nodes did not affect progression free survival.

Introduction

Uterine cancer is the most common cancer of the female genital tract and the fourth most common cancer after breast, lung, and colorectal cancers in North America and Europe. Approximately 40,000 American women are diagnosed with endometrial cancer annually [1]. Accurate staging of endometrial cancer allows for customization of postoperative adjuvant therapy, and lymphadenectomy itself may also provide a therapeutic benefit [1–3]. Lymphadenectomy during hysterectomy has been useful in providing an accurate assessment of the cancer stage [1].

Studies of lung [4], colorectal; [5], esophageal [6,7], and bladder [8] cancers showed that the number of lymph nodes found in the surgical specimen correlates with more accurate staging. In uterine cancer, pelvic lymph node counts equal to or greater than 12 are an important prognostic variable in patients with International Federation of Gynecology and Obstetrics (FIGO) stage I and II endometrial cancer. The association between survival rate and lymph node counts is the result of improved staging in patients with higher pelvic lymph node samples [9].

Therefore, obtaining a high number of lymph nodes during uterine cancer surgical staging seems to be desirable. However, our experience showed that the lymph node count may vary among patients [10]. Although the lymph nodes are sampled from the standard locations recommended by the Gynecologic Oncology Group (GOG) surgical

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manual [18], many postoperative pathology reports show that not all specimens contain lymph node tissues [5]. In this study, we evaluated the prevalence of missing lymph nodes, factors contributing to missing lymph nodes during endometrial cancer staging, and the effect of the missing lymph nodes on progression free survival (PFS) in these patients.

Methods

Our oncology practice consists of four gynecologic oncologists, but all of the study patients came from one surgeon who maintained a prospective patient database. The Institutional Review Board of Methodist University Hospital approved this study. Patients were entered prospectively into the database. Inclusion criteria were patients with endometrial cancer who underwent open abdominal hysterectomy with pelvic and aortic lymphadenectomy from April 2003 through January 2010. All incisions were midline abdominal incisions. The technique for uterine cancer surgical staging followed the Gynecology Oncology Group surgical protocol [18]. After abdominal hysterectomy and bilateral salpingo-oophorectomy, pelvic lymphadenectomy was done by removing all the lymph tissues from four locations on each side of the pelvis: 1) common iliac, 2) external iliac, 3) internal iliac, and 4) obturator fossa. The borders of the pelvic lymphadenectomy were the circumflex iliac vein distally, the midcommon iliac proximally, the ureter medially, and the genitofemoral nerve laterally. The paraaortic nodes were removed from the midcommon iliac to the level of the inferior mesenteric artery bilaterally. In our institution, lymphadenectomy is performed in all patients with uterine cancer and undergoing hysterectomy.

Data on race, age, body mass index (BMI), lymph node counts, staging, estimated blood loss (EBL), American Society of Anesthesiologists (ASA) Physical Status classification system, length of surgery, and length of hospital stay were retrieved from the database. Length of surgery was defined as time measured from skin incision to closure. Lymph node count was defined as number of lymph nodes counted by the pathologist and reported in the final pathology report. Complete lymph node sampling was defined as having at least one lymph node tissue/count for each surgical lymphadenectomy site. In other words, a complete (not missing) lymph node specimen had the minimum of one lymph node tissue from the external and internal common iliac, obturator and aortic lymph node locations. Thus, in a typical uterine cancer staging, a complete lymph node specimen must have at least 10 lymph nodes (minimum 5 nodes per right and left side) and at least one nodal tissue per surgical site location. Missing or incomplete lymph node specimen was defined as a specimen in which no lymph node tissue was found by the pathologist after the specimen had been removed by the surgeon during the staging surgery. Locations of missing nodes were identified. Various perioperative variables were correlated with the presence or absence of lymph node tissue in the surgical specimens.

A minimum of 48 patients from each group of missing and complete lymph nodes were necessary to detect a 15% relative change between the two groups to be statistically significant (alpha = 0.05, two-tailed) with 80% power. Two-sample t-test was done for interval variables. Pearson chi-square test was done for nominal variables. Mantel–Haenszel chi-square test was done for ordinal variables. A binomial test was used to compare the proportion of missing nodes between right and left sides. Kaplan–Meier procedure was used to generate the survival curves for complete and missing nodes followed by log-rank test to compare the two survival curves. $P < 0.05$ was considered statistically significant.

Results

Between April 2003 and January 2010, 235 consecutive patients who underwent uterine cancer surgical staging were entered prospectively into the database. The complete demographic data are presented in Table 1. Most of the patients (74%) had stage I cancer. The prevalence of missing lymph nodes was 46%: 108 patients had missing lymph nodes and 127 had complete lymph nodes (aortic, common/internal external iliac and obturator nodes bilaterally). The missing lymph nodes did not correlate with age, race, stage, BMI, length of surgery, estimated blood loss, or ASA status (Tables 2 and 3). No variables were significantly correlated except BMI and surgery-time, which showed a trend close to statistical significance. Missing lymph nodes did not seem to affect progression free survival (Table 4, Fig. 1).

Among the 38 patients with lymph nodes containing cancer cells, the average total lymph node count was 17.1 ± 11.9. Among the 197 patients with lymph nodes without cancer, the average total lymph node count was 15.7 ± 7.1. The difference between these two average counts was not statistically significant ($P = 0.46$).

Conclusions

The role of uterine cancer lymphadenectomy remains controversial despite the fact that the main route of uterine cancer metastases is lymphatic. We recommend routine, systematic lymphadenectomy, because predicting tumor grade and depth of invasion based on pre- or intraoperative factors is difficult at best [11–13]. Other surgeons recommend selective nodal biopsy based on pre- and intraoperative clinical information [3]. The Mayo Clinic reported the effectiveness of frozen biopsy in determining the need for lymphadenectomy [14]. However, the quality and availability of frozen biopsies as in the Mayo Clinic may not be present in all geographic areas. With the added risk of postoperative adjuvant treatment, some clinicians have recommended that only lymphadenectomy can provide important diagnostic information that may help avoid adjuvant treatment for patients [15]. The purpose of this study was not to address this controversy. Our goal was to look for the role of missing lymph nodes in a clinical practice where lymphadenectomy is done routinely. We also did not include patients with minimally invasive surgical (MIS) staging since MIS added more confounding variables (open abdominal versus MIS).

Accuracy in endometrial cancer staging requires information from the surrounding lymph nodes. The Gynecologic Oncology Group (GOG) surgical manual recommends removing lymph nodes among the specified locations [18]. As surgeons remove these lymphatic substances to sample lymph tissues, it is not always known whether the specimens

Table 1
Demographic data.

	N	Mean	Range
Age (years)	235	60.9	30–92
Race			
African American	78		
Caucasian	153		
Others	4		
Cancer stage			
I	175		
II	17		
III	41		
IV	2		
Cancer grade			
I	115		
II	59		
III	61		
Estimated blood loss (mL)		280	20–1800
Length of surgery (minutes)		106.7	55–270
Hospital stay (days)		3.3	1–14
Total number of lymph nodes		15.9	4–48
Nodes without tumors		15.1	4–48
Nodes with tumors		0.8	0–9
ASA			
I	12		
II	122		
III	95		
V	0		