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Prospective assessment of lymphatic dissemination in endometrial cancer: A paradigm shift in surgical staging

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Abstract

Objective—To prospectively assess pelvic and para-aortic lymph node metastases in endometrial cancer with lymphatic dissemination, emphasizing the examination of para-aortic metastases relative to the inferior mesenteric artery (IMA).

Methods—Over 36 months, 422 consecutive patients were managed by predefined surgical guidelines differentiating low-risk patients from patients at risk for dissemination requiring systematic lymphadenectomy. Low risk was defined as grade 1 or 2 endometrioid type with myometrial invasion (MI) ≤50% and primary tumor diameter (PTD) ≤2 cm. Pelvic and para-aortic lymph nodes were submitted separately, with nodes identified from all 8 pelvic and 4 para-aortic node-bearing basins. Surgical quality assessments examined median node counts (primary surrogate for quality) and nodes harvested above and below the IMA and excised gonadal veins (secondary surrogates).

Results—Lymphadenectomy was not required in 27% of patients (all low risk) and in 33% (n=112) of endometrioid cases. However, 22 patients (20%) of this latter cohort had lymphadenectomy and all lymph nodes were negative. Sixty-three (22%) of 281 patients undergoing lymphadenectomy had lymph node metastases: both pelvic and para-aortic in 51%, only pelvic in 33%, and isolated to the para-aortic area in 16%. Therefore, 67% of patients with lymphatic dissemination had para-aortic lymph node metastases. Furthermore, 77% of patients with para-aortic node involvement had metastases above the IMA, whereas nodes in the ipsilateral para-aortic area below the IMA and ipsilateral common iliac basin were declared negative in 60% and 71%, respectively. Gonadal veins were excised in 25 patients with para-aortic node metastases; 7 patients (28%) had documented metastatic involvement of gonadal veins or surrounding soft tissue.

Conclusions—The high rate of lymphatic metastasis above the IMA indicates the need for systematic pelvic and para-aortic lymphadenectomy (vs sampling) up to the renal vessels. The latter should include consideration of excision of the gonadal veins. Conversely, lymphadenectomy does not benefit patients with grade 1 and 2 endometrioid lesions with MI ≤50% and PTD ≤2 cm.

Keywords

Endometrial neoplasms; Lymph node excision; Lymphatic metastasis; Outcomes assessment

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Introduction

In many Western countries, endometrial cancer is the most common malignancy of the female reproductive tract. This disease generally manifests early in its natural history and is amenable to surgical management when confined to the corpus. In 1988, the International Federation of Gynecology and Obstetrics (FIGO) recognized the limitations of clinical assessment of disease extent and recommended a surgical staging process [1]. However, definitive guidelines were not established for assessment of lymphatic dissemination. Hence, 2 decades later, the various staging and treatment algorithms still reflect institutional or physician philosophies. The most controversial management issue relates to the requirement for, and the extent and therapeutic value of, lymphadenectomy concomitant with hysterectomy. Assessment of regional node-bearing basins varies from elective omission to sampling (selective assessment) to systematic pelvic and para-aortic lymphadenectomy [2–7]. Furthermore, the anatomic extent and level of dissection remain ill defined for patients undergoing para-aortic node sampling or systematic dissection [5,7–9].

Comparisons of prospective trials in which lymphadenectomy was either not performed (Postoperative Radiation Therapy for Endometrial Carcinoma [PORTEC]) [2] or was required but not standardized (Gynecological Oncology Group trial 99 [GOG-99]) [3] have produced little evidence for incorporating the histologic evaluation of lymph nodes in the treatment of early-stage endometrial cancer [10,11]. By contrast, multiple retrospective series have suggested that lymphadenectomy may modulate or eliminate the need for adjuvant therapy [12–15] and possibly provide therapeutic value for patients with positive lymph nodes (gross or occult) [7,16,17]. For optimal clinical outcomes, dedicated efforts must be redirected at identifying patients with endometrial cancer who will not benefit from either lymphadenectomy or radiotherapy, thereby minimizing over-treatment. The corollary is the identification of patients who might derive therapeutic value from either or both treatments, thereby minimizing undertreatment.

On the basis of detailed outcomes analyses of 915 patients treated at our institution between 1984 and 1996 [6,16,18–28], we initiated a new paradigm on January 1, 2004, for surgical management of endometrial cancer. Lymphadenectomy was no longer deemed necessary for the subset of patients in whom no node metastasis (type I, grades 1 and 2; myometrial invasion [MI], ≤50%; primary tumor diameter [PTD], ≤2 cm) was encountered [6]. By contrast, all other patients were candidates for systematic lymphadenectomy up to the renal vessels [28]. Nodes were to be submitted separately from each of the 10 node-bearing basins, including a division of the para-aortic nodes by location below or above the inferior mesenteric artery (IMA). In addition, interval quality assessments of the surgical performance of each gynecologic oncologist were conducted to assure uniform node harvesting. This prospective single-institutional surgical series illustrates the prevalence of pelvic node metastases by histologic subtype, the high prevalence of para-aortic node metastasis among patients with documented lymphatic dissemination, and the para-aortic metastatic site frequency relative to the IMA.

Materials and methods

Between January 1, 2004, and December 31, 2006, a total of 441 patients with endometrial cancer was referred for surgical management by 1 of 7 gynecologic oncologists at Mayo Clinic, Rochester, Minnesota. This report details the surgical treatment of 422 patients managed with hysterectomy and removal of adnexal structures. Exclusion criteria for 19 patients included referral after hysterectomy elsewhere, advanced disease usually involving the vagina and parametrium with synchronous lung or liver lesions, multiple medical

comorbid conditions, and young age of patients who wanted to be managed conservatively to retain their fertility.

Hysterectomy (type I) was usually performed by laparotomy. At the surgeon's discretion, a wide extrafascial hysterectomy (either type II or type III in 34 patients [8%]) with unroofing of the ureters was chosen when invasion of the cervix was suspected or documented. Likewise, patients with low-grade tumors identified by endometrial sampling or patients selected for laparoscopic lymphadenectomy were also considered to be candidates for vaginal hysterectomy and adnexal excision. Frozen-section histologic assessment of the uterus and adnexa was performed in all cases. On the basis of existing guidelines (Table 1), pelvic and para-aortic lymphadenectomy was omitted in patients considered to be at low risk for lymphatic dissemination [28]. In the absence of extrauterine macroscopic disease, frozen-section review dictated the need for systematic pelvic and para-aortic lymphadenectomy and cytologic assessment when there was an unfavorable PTD (>2 cm), nonendometrioid histologic subtype, grade 3 histology, or depth of MI greater than 50%. With documented macroscopic extrauterine disease, systematic lymphadenectomy was routinely performed when optimal cytoreduction was anticipated.

According to the surgical algorithm, bilateral pelvic lymphadenectomies routinely included complete skeletonization of the common, external, and internal iliac vessels and the harvesting of all fatty and lymphatic tissues above and below the obturator nerve. The superior surgical margin of dissection for the iliac nodes was the bifurcation of the aorta and, for the obturator nodes, the origin of the obturator nerve as it entered the pelvis. The latter dissection was facilitated by displacing the common iliac vessels medially and by retracting the psoas muscle laterally. This approach allowed removal of the fatty and lymphatic tissue, affording visualization of the superior gluteal vein and the lumbosacral trunk deep to the obturator nerve. The distal extent of the lymphadenectomy was the circumflex iliac vein anteriorly and the obturator internus and lateral aspect of the levator ani below the obturator foramen posteriorly. The venous plexus in the posterior floor of the obturator fossa underwent routine skeletonization.

The para-aortic lymphadenectomy was facilitated by mobilizing the ascending and descending colon sufficient for bilateral visualization of the superior borders of the renal veins. All lymphatic and adipose tissue was harvested from the lateral, anterior, and medial aspects of the vena cava and aorta and, when indicated, from the retrocaval areas. To facilitate the latter, the medial border of the vena cava was retracted laterally and all palpable or visualized adipose and nodal tissue was removed with care to minimize trauma to the lumbar veins. The surgical algorithm was for surgeons to submit para-aortic node-bearing tissue separately according to the level of the IMA and the side of origin; tissue removed between the renal vein and the IMA was identified separately from that removed between the IMA and the bifurcation of the aorta. Surgical discretion was used to determine excision of the right and left gonadal veins at their insertions into the vena cava and the left renal vein, respectively.

Systematic pelvic and para-aortic lymphadenectomies were performed predominantly by laparotomy. Laparoscopic para-aortic lymphadenectomy was performed by a single surgeon (S.C.D.) using a retroperitoneal approach to access the left and right para-aortic node basins through the left flank area [29,30]. This method was chosen for the consistency with which it allows removal of lymph nodes up to the level of the renal veins, even in obese patients with a body mass index (weight in kg divided by height in m^2) greater than 40. This was followed by a transperitoneal pelvic lymph node dissection. The node-bearing basins in the pelvis and para-aortic regions were assessed by site of origin; 4 basins (common, external,

and internal iliac; and obturator) per pelvic sidewall and 4 para-aortic basins (right and left; above and below the IMA).

To assure a uniform approach to the predetermined surgical guidelines, we assessed the adherence of each surgeon to the algorithm for optimal surgical quality of care. With all surgeries performed and all pathologic findings interpreted in a single institution, the number of nodes removed from the pelvis and para-aortic basins was the surrogate for quality assessment of the extent and thoroughness of the lymphadenectomy. The initial analysis was performed 10 months after initiation of patient accrual. The median number of nodes harvested by each surgeon was compared with the median number of nodes removed by the group of surgeons in a given period. Results were masked for sharing among the staff, and the surgeons received individualized assessments of their efforts. A second quality assessment was conducted 21 months after initiation of enrollment. Subset analysis was available for the separate periods as a function of quality of surgical care by group and by individual surgeon.

Following approval of this study by the institutional review board, all candidates for primary surgical management of endometrial cancer whose care was managed at our institution were identified using the institutional surgical index and the gynecologic surgery database. Clinicopathologic characteristics were abstracted from the surgery and pathology reports. The FIGO surgical staging system was used for staging [1]. Histologic subtyping followed the World Health Organization classification [31]. In accordance with FIGO guidelines, architectural grading was by degree of glandular differentiation [1].

For statistical purposes, we categorized as endometrioid any tumors that were endometrioid, endometrioid with squamous differentiation, adenosquamous, or mucinous. Grade 1 and 2 lesions were combined and compared with grade 3 lesions. Statistical analysis was performed with the Fisher exact test and with χ^2 analysis to test for relationships between pairs of categorical variables. The Student *t* test was used to compare continuous variables. Differences were considered statistically significant at $P<.05$. A commercially available statistical program (JMP for Windows—version 6.0.0, 2005; SAS Institute, Inc, Cary, North Carolina) was used for analysis.

Results

After the implementation of specific surgical guidelines (Table 1) on January 1, 2004, a total of 422 patients with endometrial cancer was treated surgically at Mayo Clinic, Rochester, Minnesota, through December 31, 2006. For benchmarking the quality of lymph node dissection, the number of patients managed during 3 intervals of about 1 year each was 113, 139, and 170 for 10, 11, and 15 months, respectively. The mean±SD age of the population was 64.2±11.7 years (median, 63 years; range, 31–92 years). The mean±SD body mass index was 34.2±10.3 (median, 32; range, 16.4–76.8). Additional characteristics of patients are detailed in Table 2.

Surgical management

According to the institutional guidelines, lymphadenectomy was deemed not necessary in 112 (27%) patients, whereas 310 (73%) were deemed candidates for systematic lymph node dissection (Fig. 1). All 82 patients with nonendometrioid histologic findings were included in the latter group. However, as described in the materials and methods section, lymphadenectomy was not considered necessary in 112 (33%) of 340 patients (Table 2) with endometrioid carcinoma or the equivalent who were deemed at low risk for lymphatic dissemination on the basis of frozen-section analysis.

Of all 422 patients with endometrial cancer, 303 (72%) had lymphadenectomy. Twenty-two (20%) of 112 patients not requiring lymph node assessment nonetheless underwent lymphadenectomy. The most common reasons for node harvesting in this favorable group included the presence of palpable adenopathy, initiation of dissection before receipt of the frozen-section report, and prior physician preferences that persisted during the early phase of the study.

Conversely, 29 (9%) of 310 candidates for lymphadenectomy did not undergo dissection (Fig. 1). Reasons for omitting lymphadenectomy included disseminated disease either within or beyond the abdominal cavity, extreme comorbid conditions, and advanced age (>90 years). The only patient with apparent early-stage endometrial cancer and deep MI who did not undergo lymphadenectomy was an 89-year-old woman with multiple episodes of intraoperative hypotension.

Lymphadenectomy limited only to the para-aortic area and only to the pelvis was performed in 1 and 15 patients, respectively. The reason for the former was the “presence of concomitant advanced breast cancer and palpable para-aortic lymph nodes.” The varied reasons for the latter were predominantly related to excessive obesity with low-grade disease and advanced age (>90 years). The remaining 265 patients had systematic pelvic and para-aortic lymphadenectomy as per the guidelines. Minor protocol deviations were considered acceptable for inclusion, such as not harvesting nodes separately or not properly labeling nodes from each node-bearing basin in the pelvic or para-aortic areas.

Owing to the surgical complexity, an analysis was conducted to determine the estimated blood loss per procedure and the length of hospital stay. The median estimated blood loss was 300 mL (range, 20–2500 mL) and the median length of hospital stay was 4 days (range, 2–56 days). An additional complication related to the lymphadenectomy was the transection of an obturator nerve that was repaired intraoperatively.

Surgical quality assessment

Initiatives for assessment of surgical quality were conducted after the first 10 months to determine compliance with the predefined guidelines and again after a subsequent 11-month interval to ascertain the extent of quality improvement. Parts a and b of Fig. 2 illustrate that for 6 of the 7 surgeons, the 95% confidence interval for the mean number of dissected nodes was either above or intersected with the group mean for the pelvic and para-aortic areas. A single outlier had a confidence interval below the group mean for the mean number of nodes harvested from both areas. Masked results were shared among the staff, and all 7 surgeons received an individualized assessment of their efforts. The second interim analysis at a 21-month interval (Fig. 2, parts c and d) documented improvement in this quality metric, with the confidence interval for all surgeons intersecting the mean number of nodes for both areas.

Although not specifically required to do so, the surgeons were encouraged to stratify para-aortic lymph nodes by their location referable to the IMA. This information was reported for 185 (70%) of the 266 patients who underwent para-aortic lymphadenectomy. This parameter was likewise included in the quality assessment of the patients, with a dramatic improvement in the separation of the nodes by location above or below the IMA, from 19 (26%) of 73 patients during the initial 10 months, to 70 (83%) of 84 patients during the subsequent 11 months, and 96 (88%) of 109 patients during the final 15 months of accrual.

Over the 3-year study period, the mean±SD number of pelvic nodes removed by lymphadenectomy in 280 patients at risk for lymphatic dissemination was 36.5±13.4

(median, 35; range, 4–95). The mean±SD number of para-aortic nodes harvested from 266 at-risk patients who had para-aortic node dissection was 17.4±8.1 (median, 17; range, 1–35).

Lymph node metastasis by histologic subtype

According to the guidelines, 112 patients were of sufficiently low risk to warrant no lymphadenectomy. These patients accounted for 33% of the 340 endometrioid patients and 27% of the entire population of 422 patients. However, 22 (20%) of the 112 patients had lymph node dissection with all nodes declared free of metastases.

Of the 281 at-risk patients who underwent lymphadenectomy, 63 (22%) had lymphatic dissemination to the regional nodes (Table 3). Of the 228 patients with endometrioid carcinoma who were candidates for lymphadenectomy, 209 (92%) had nodes removed and 34 (16%) of those 209 had documented lymphatic involvement, which represented 10% of the entire endometrioid population of 340 patients.

Nonendometrioid carcinoma was identified in 82 (19%) of 422 patients, with macroscopic and microscopic extrauterine disease detected in 37% (n=30) and 21% (n=17), respectively. Node metastasis was documented in 40% of 72 patients who had assessment of regional nodes (Table 3).

Pelvic and para-aortic node metastasis in patients with lymphatic dissemination

Assessment of the sites of lymphatic spread in the 63 patients with lymph node metastasis showed that 53 patients (84%) had positive pelvic nodes and that 39 (62%) had positive para-aortic nodes (46% right para-aortic only, 16% left only, and 38% bilateral). Specifically, 29 patients (46%) had involvement of both pelvic and para-aortic nodes, 24 (38%) had involvement of pelvic nodes only, and 10 (16%) had isolated para-aortic lymph node metastasis. For a more reliable assessment of the frequency of distribution of lymph node metastasis, we examined only the 57 patients with documented nodal involvement who had both a formal pelvic and a formal para-aortic lymphadenectomy. Lymph node metastasis was documented in both the pelvic and para-aortic node-bearing basins in 29 (51%) of these patients (Table 4). Pelvic lymph node involvement without para-aortic spread was identified in 19 (33%) of the 57 patients, and isolated para-aortic metastasis was documented in 9 patients (16%). Therefore, in the 57 patients with lymphatic dissemination, 48 (84%) had pelvic metastasis and 38 (67%) had para-aortic lymph node metastasis.

Stratification of the 57 patients with lymph node metastases by histologic type (Table 4) showed a similar regional distribution for endometrioid (n=32) and nonendometrioid (n=25) carcinomas. Pelvic lymph node involvement in patients with lymphatic dissemination was detected in 81% and 88% of patients with endometrioid and nonendometrioid histologic findings, respectively. Para-aortic node involvement with lymphatic spread was documented in 63% and 72% of patients with endometrioid or nonendometrioid cancers, respectively.

Para-aortic lymph node metastasis as a function of the IMA

The sites of metastatic involvement of the para-aortic lymph nodes relative to the IMA were known in 26 of the 39 patients with positive para-aortic nodes. Para-aortic nodes above the IMA were involved in 77% of these patients (Table 5). Site distribution as a function of the IMA included 6 (23%) of the 26 patients with involved lymph nodes only below the IMA, 8 (31%) with positive nodes above and below the IMA, and 12 (46%) with positive nodes above and ipsilateral negative nodes below the IMA. The group with positive nodes above and ipsilateral negative nodes below the IMA included 2 patients with bilateral involvement above and unilateral involvement below the IMA. Therefore, ipsilateral nodes below the IMA were declared free of metastatic involvement in 60% of patients with documented

lymphatic spread to nodes above the IMA (Table 5). In juxtaposition to the para-aortic region, the common iliac pelvic node-bearing basin was analyzed separately for patients with known para-aortic spread. The status of the common iliac node basins was reported separately in 35 of the 39 patients with documented para-aortic lymph node involvement. The common iliac nodes ipsilateral to the site of the para-aortic lymph node metastasis were declared free of metastatic involvement in 71% of patients (Table 5).

Gonadal vein involvement with para-aortic metastasis

Surgeons were encouraged to remove the gonadal vessels during para-aortic lymphadenectomy. Gonadal veins were harvested in 195 (73%) of the 266 patients whose surgical management included removal of para-aortic lymph nodes. Histologic information for gonadal veins was available in 25 patients with para-aortic nodal disease. Metastatic involvement of the gonadal vein or surrounding soft tissue was documented in 7 (28%) of 25 patients with documented para-aortic lymph node metastases. Conversely, in the absence of para-aortic node involvement, no metastatic disease was detected in the gonadal veins or surrounding soft tissues.

Discussion

Although surgical staging of endometrial cancer was recommended by FIGO 2 decades ago, controversy continues to focus on its diagnostic and therapeutic value [3,7,11,12,32,33]. Central to the divergence of opinion is the role of lymphadenectomy. Proponents maintain and cite literature supporting the diagnostic and therapeutic value of surgical assessment of pelvic and para-aortic lymph nodes [4,13–16,19]. This approach provides a rationale for the type and extent of adjuvant therapy [12,19,28]. However, major criticisms include a lack of standardization for the staging procedure (sampling vs systematic dissection, no minimal node count, and varying degrees of dissection), a lack of quality assessment, and the assertion that all patients are candidates for full staging. Opponents contend that lymphadenectomy increases morbidity and that its therapeutic benefit has not been demonstrated through randomized clinical trials [11]. Although limiting surgery to hysterectomy and oophorectomy is a perceived virtue, the inherent deficiency of this approach is that a large percentage of patients require external beam radiotherapy to traditional fields but the extent of disease is unknown and thus many patients receive unnecessary radiotherapy [2,33]. Both approaches are methods based, reflect individual biases, and perhaps attest to the limited progress in outcomes for this disease during the past 2 decades [34,35].

An extensive retrospective review of 915 consecutively treated patients has suggested the need for several modifications in the surgical management of patients with endometrial cancer [6,16,18–28]. In particular, a subgroup of 123 patients derived no benefit from lymphadenectomy based on readily assessable pathologic parameters [6]. No patient who had a grade 1 or 2 endometrioid tumor with a PTD of 2 cmor less and an MI of 50% or less had detectable lymphatic dissemination found on lymphadenectomy. Furthermore, the 5-year cancer-specific survival was 100%. Therefore, the practice guidelines initiated in January 2004 by institutional consensus (Table 1) suggested that patients with these favorable determinants identified on the basis of intraoperative frozen-section analysis could forego lymphadenectomy. In the ensuing 3 years, 112 (33%) of 340 endometrioid cases (27% of the entire population of 422 patients) did not require lymphadenectomy (Fig. 1). In an acceptable deviation from the guidelines, 22 patients in this cohort had lymphadenectomy; all nodes were declared free of disease, further validating the retrospective outcomes assessment. Minimizing overtreatment is paramount, particularly in patients who generally present with multiple medical comorbid conditions such as excessive obesity and diabetes.

We previously reported retrospective outcomes analyses that likewise demonstrated a higher than anticipated frequency of lymph node involvement, particularly within the para-aortic node-bearing regions [27]. We previously reported that 47% of patients with pelvic node metastasis had para-aortic lymph node involvement detected either at surgical staging or during subsequent recurrence [27]. These observations were consistent with previous estimates of 40% to 57% [5,8,21,36–38]. In light of the high frequency of para-aortic involvement with lymphatic dissemination and the limitations of retrospective analyses, we sought to assess the prevalence of pelvic and para-aortic node involvement in at-risk patients. Findings of this study were strengthened by periodic review of the quality of surgical staging overall and of the individual surgeons. In patients identified at risk for lymphatic spread, lymph node metastases were detected in 22% of those who had a lymphadenectomy, including 16% of patients with endometrioid cancers. Although 84% of patients with lymphatic dissemination had documented involvement of the pelvic nodes, 67% had metastases in the para-aortic nodes. These findings suggest a higher prevalence of para-aortic involvement in endometrial cancer than that reported either by our group previously [21,27,39] or by other contemporary authors [5,8,21,36–38], which authenticates the importance of para-aortic lymphadenectomy in defining both the extent of disease and the strategies for adjuvant therapies. In addition, a therapeutic approach that omits lymphadenectomy in favor of hysterectomy with oophorectomy followed by pelvic radiotherapy would undertreat most of the patients who have lymphatic metastases because of the high frequency of simultaneous involvement in the para-aortic area.

Reports that address the routes of lymphatic dissemination in endometrial cancer have suggested that the principal connections are between the uterine corpus and the external iliac and obturator basins [36,37,40]. A direct route may exist from the corpus to the para-aortic node-bearing basins by the lymphatic channels adjacent to the gonadal vessels within the infundibulopelvic ligament [37,40]. Previous reports have also suggested a potential direct lymphatic communication between the external iliac and obturator basins and the para-aortic node-bearing tissue [8,21]. Therefore, an a priori assertion exists that the para-aortic node-bearing tissue in the region of the origin and insertion of the gonadal arteries and veins, respectively, would be favored sites for nodal involvement. Our present findings support such involvement, particularly in the area above the IMA, which was involved in 77%of patients with para-aortic lymphatic spread. In a limited series, Hirahatake et al. [36] similarly observed that 7 (64%) of 11 patients had positive nodes above the IMA. In our series, equally cogent was the observation that ipsilateral nodes below the IMA were not involved in 60% of patients and that the ipsilateral common iliac nodes were not involved in 71% of patients with positive nodes above the IMA. Of those patients with lymphatic dissemination, 16% presented with isolated para-aortic nodal involvement. In addition, carcinoma was detected in the tissues submitted with the gonadal vessels in 28% of patients with para-aortic nodal involvement.

Although the landmark GOG staging study reported extending the para-aortic dissection to the proximity of the renal vessels [32], most published reports addressing the patterns of lymphatic spread to the para-aortic area neither describe distribution relative to the IMA nor limit the lymphadenectomy to the lower para-aortic nodes [3,7,8,41]. Routinely performing lymphadenectomies only up to the IMA will potentially miss 38% to 46% of patients with positive para-aortic nodes because of the high rate of isolated involvement above the IMA. Furthermore, 63% of patients in this series with positive lymph nodes below the IMA also had positive nodes above the IMA that would have escaped detection if the dissection had been limited to the lower node basins. Thus, the node-bearing tissue between the IMA and the renal vessels is important for assessment of the extent of disease and for determination of overall treatment dispositions.

An anticipated criticism of this study is that the surgical strategy was predicated on the availability of reliable intraoperative frozen-section histologic assessment. The 4 tumor characteristics that identify patients who can safely forgo lymphadenectomy include 2 simple measurements (depth of MI and macroscopic PTD) and 2 readily discriminated parameters, namely, low or moderate grade and endometrioid histologic findings. Each element is within the purview of—and readily distinguishable by—a surgical pathologist. Use of this paradigm would eliminate the need for lymphadenectomy in 1 of 3 patients with endometrioid cancer, which is the cohort with the highest prevalence of obesity and insulin resistance; both conditions are associated with the highest surgical risk.

Adopting a treatment paradigm for endometrial cancer that is disease based and predicated on anticipated patterns of failure must be considered. The defining objectives should be to minimize overtreatment by identifying patients who do not require lymphadenectomy or radiotherapy while minimizing under-treatment by identifying patients who might benefit from one or more methods. We have previously identified a subgroup not requiring definitive staging or radiotherapy [6], and this report provides additional support for such a practice. Definitive validation must await longer follow-up to address disease-free survival. Continuous outcomes assessment will perhaps also allow expansion of the inclusion criteria within the subgroup not requiring staging. Conversely, candidates for definitive surgical staging deserve a systematic pelvic and para-aortic lymphadenectomy (vs sampling) of all lymph node basins in the pelvic and para-aortic areas up to the renal veins. This approach will facilitate the accurate determination of the type and extent of adjuvant therapy. Finally, appropriately designed clinical trials that include a standardized and comprehensive staging process are needed to provide data that will definitively determine whether lymphadenectomy has therapeutic value.

Acknowledgments

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Abbreviations

FIGO	International Federation of Gynecology and Obstetrics
GOG-99	Gynecological Oncology Group trial 99
IMA	inferior mesenteric artery
MI	myometrial invasion
PORTEC	Postoperative Radiation Therapy for Endometrial Carcinoma
PTD	primary tumor diameter

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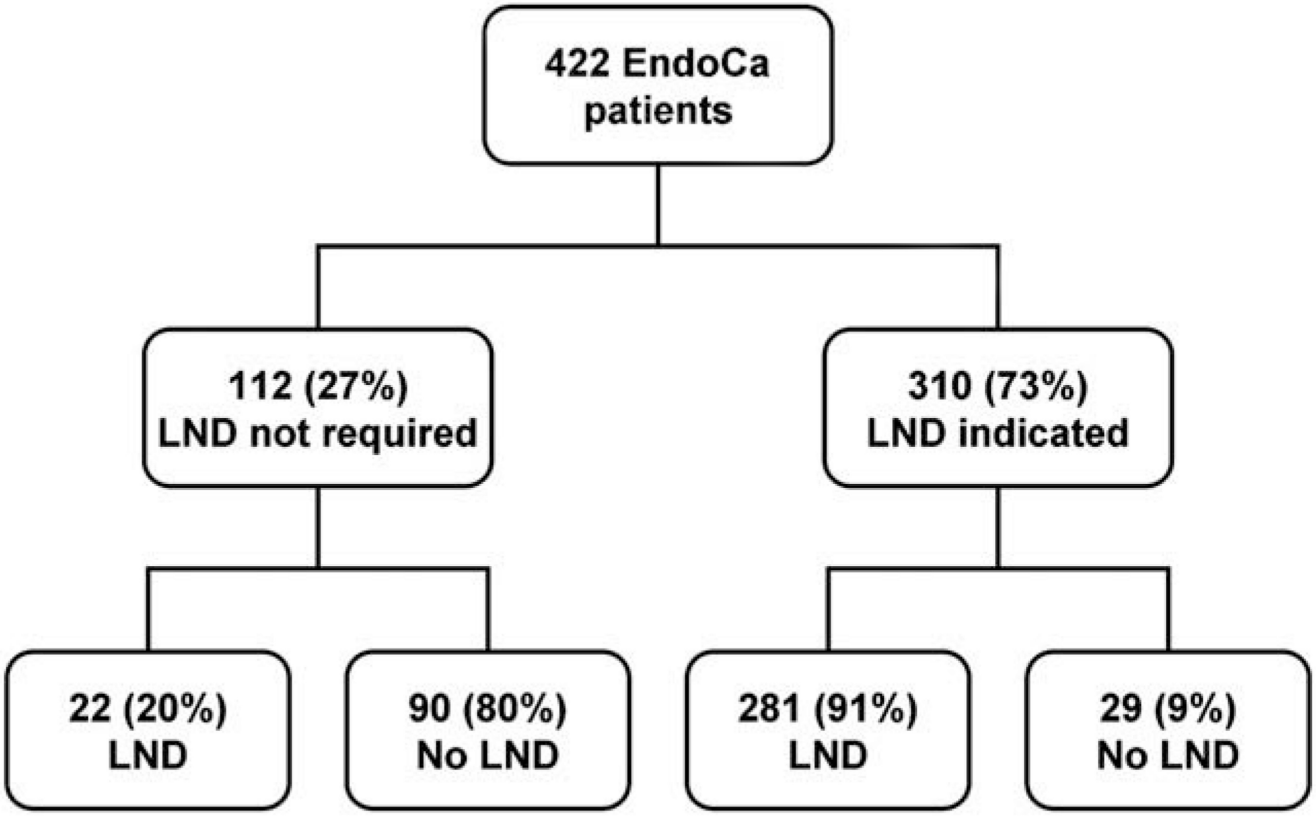

Fig. 1.

Treatment distribution by defined surgical guidelines as detailed in Table 1 for patients with endometrial cancer (EndoCa) managed during the 36-month period between 2004 and 2006. LND indicates lymph node dissection (either pelvic, para-aortic, or both).

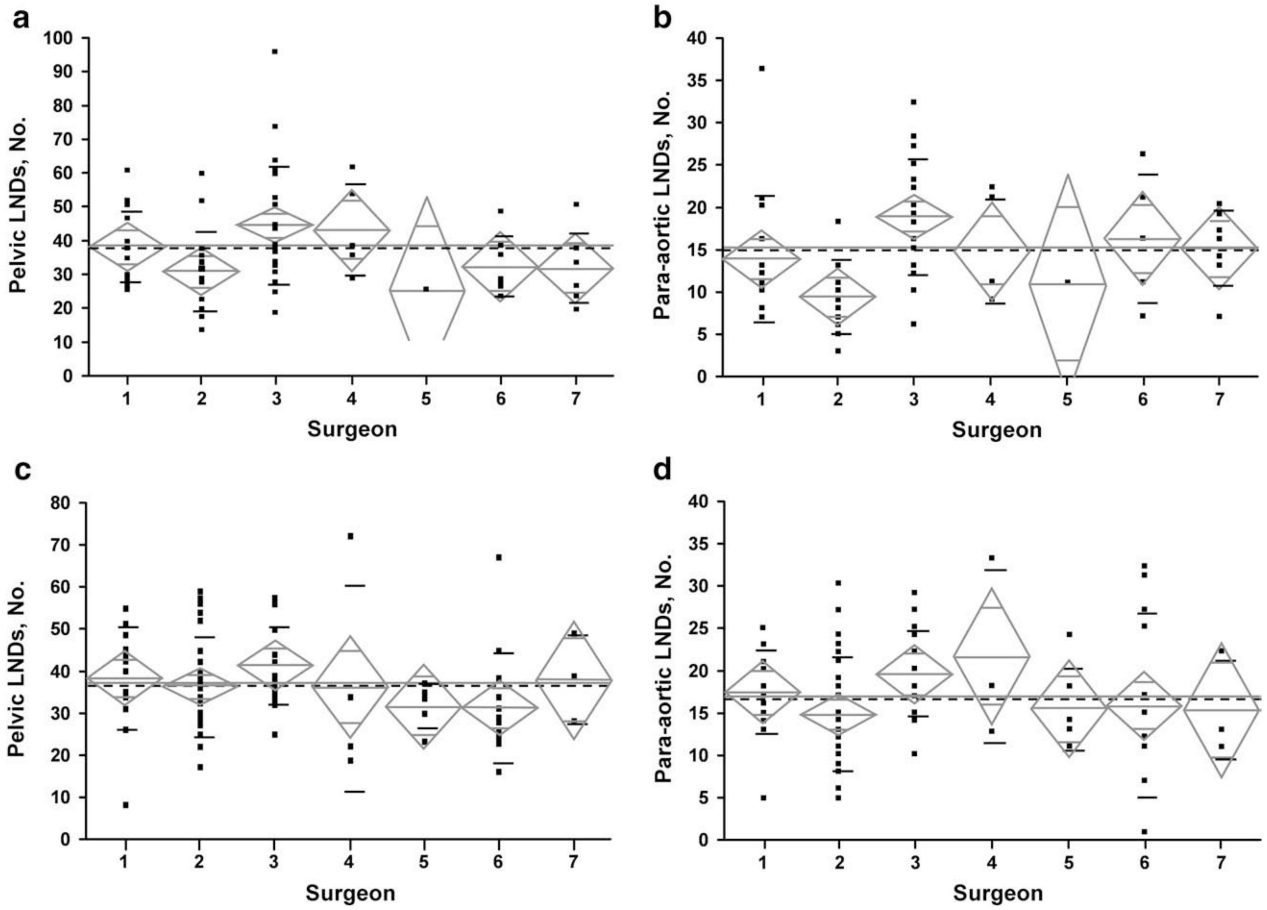

Fig. 2.

Surgical quality assessments detailed the mean number and 95% confidence intervals (diamonds) and 1 SD (horizontal lines) from group mean of lymph nodes removed per site and surgeon from 2 successive interim analyses. First interim analysis (after 10 months) of the efficiency of harvesting pelvic (a) and para-aortic (b) nodes denoting the mean, 95% confidence interval, and 1 SD per surgeon relative to the group mean. Second interim analysis (after 21 months) to assess quality improvement for pelvic (c) and para-aortic (d) lymphadenectomy performed by each surgeon. LND indicates lymph node dissection.

Table 1

Guidelines for surgical management of endometrial cancer at Mayo Clinic, Rochester, Minnesota (2004–2006)

Hysterectomy
Bilateral salpingo-oophorectomy
Peritoneal cytology
Bilateral pelvic and para-aortic lymphadenectomy
Para-aortic dissection up to renal vessels
Excision of gonadal vessels at insertions (optional)
Omit lymphadenectomy if no disease beyond corpus and
(1) Endometrioid (grade 1 or 2), MI ≤50%, and PTD ≤2 cm; or
(2) Endometrioid and no MI (independent of grade and PTD)
Omentectomy, staging biopsies, or cytoreduction for nonendometrioid or advanced disease

Abbreviations: MI, myometrial invasion; PTD, primary tumor diameter. Data from Mariani et al. [28].

Table 2

Characteristics of 422 patients with endometrial cancer managed surgically at Mayo Clinic, Rochester, Minnesota (2004–2006)

Characteristic	Number (%) [a]
Age, mean±SD, y	64.2±11.7
BMI, mean±SD	34.2±10.3
Stage	
I–II	314 (74)
III–IV	108 (26)
Depth of myometrial invasion	
≤50%	327 (77)
>50%	95 (23)
Histologic grade	
1–2	304 (72)
3	118 (28)
Lymphadenectomy[b]	
Yes	303 (72)
No	119 (28)
Histologic subtype	
Endometrioid [c]	340 (81)
Nonendometrioid [d]	82 (19)

Abbreviation: BMI, body mass index (kg/m^2).

[a] Values are number (percentage) unless indicated otherwise.

[b] Pelvic or para-aortic or both.

[c] Includes mucinous.

[d] Serous, clear cell, and undifferentiated.

Table 3

Prevalence of lymphatic dissemination in patients with lymphadenectomy stratified by histologic subtype

Histologic subtype	Number of patients		
	Total (*n*=281)	Node-positive (*n*=63)	Prevalence,%
Endometrioid [a]	209	34	16
Nonendometrioid [b]	72	29	40

[a] Includes mucinous.

[b] Serous, clear cell, and undifferentiated.

Table 4

Frequency of observed metastases to pelvic or para-aortic or both node-bearing regions[a]

Node site	Endometrioid, number (%) (*n*=32)	Nonendometrioid, number (%) (*n*=25)	Total, number (%) (*n*=57)
Pelvic only	12 (37)	7 (28)	19 (33)
Pelvic plus para-aortic	14 (44)	15 (60)	29 (51)
Para-aortic only	6 (19)	3 (12)	9 (16)

[a] In patients with lymphatic dissemination who underwent systematic pelvic and para-aortic lymphadenopathy.

Table 5

Metastatic site frequency in patients with documented para-aortic node involvement relative to the inferior mesenteric artery

Node site	Node status	%
Para-aortic above IMA	Positive	77
Para-aortic below IMA Ipsilateral [a]	Negative	60
Common iliac Ipsilateral [b]	Negative	71

Abbreviation: IMA, inferior mesenteric artery.

[a] At least 1 side declared negative below positive ipsilateral nodes above the inferior mesenteric artery.

[b] At least 1 side declared negative below positive ipsilateral para-aortic nodes.