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Surgical Staging in Endometrial Cancer

Endometrial cancer is the most common gynecologic malignancy in the United States, with nearly 40,000 cases reported annually (approximately 1 in 37 American women).[1] Fortunately, most women present with the onset of symptoms, namely abnormal uterine bleeding or discharge, when disease is limited to the uterine corpus. This early presentation of disease allows for effective management with excellent clinical outcome, leading to only 7,300 deaths per year. Overall 5-year survival for patients with surgical stage I disease is reported at 85% or higher.[2,3]

Recently, endometrial cancer has been categorized into two distinct clinical types. Type I tumors include the more classic endometrial malignancies associated with unopposed estrogenic stimulation of the endometrium from either pharmacologic or physiologic sources. Histologically these lesions are endometrioid in appearance and are clinically associated with obesity, hyperlipidemia, and endometrial hyperplasias. Most type I tumors are early-stage, low-grade tumors and are associated with an excellent prognosis. Type II tumors tend to be more aggressive, both clinically and in histologic appearance. They are associated with high-risk cell types including

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ABSTRACT

Early presentation of endometrial cancer permits effective management with excellent clinical outcome. The addition of hysteroscopy to dilatation and curettage (D&C) in the evaluation of postmenopausal bleeding adds little to the detection of malignancy. Imaging studies such as computed tomography, magnetic resonance imaging, and positron-emission tomography may be of use in determining the presence of extrauterine disease in patients medically unfit for surgical staging. However, these studies are not sufficiently sensitive to replace surgical staging and have little role in routine preoperative evaluation. Clinical staging alone is clearly inadequate, as 23% of preoperative clinical stage I/II patients are upstaged with comprehensive surgical staging. Preoperative tumor grade from D&C or office biopsy may be inaccurate and lead to an underestimate of tumor progression if used to determine which patients should be surgically staged. Clinical estimation of depth of invasion, with or without frozen section, is inaccurate and may lead to underestimation of disease status when surgical staging is not performed. The practice of resecting only clinically suspicious nodes should be discouraged as it is no substitute for comprehensive surgical staging. Comprehensive surgical staging provides proper guidance for postoperative adjuvant therapy, avoiding needless radiation in 85% of clinical stage I/II patients. Finally, resection of occult metastasis with surgical staging may improve survival.

clear cell, uterine papillary serous carcinoma, as well as high-grade endometrioid tumors. Type II tumors tend to occur in thinner, older patients and are typically not hormonally responsive.

Continued controversy surrounds the management of patients thought to have early-stage tumors limited to the uterine corpus (International Fed-

eration of Gynecology and Obstetrics [FIGO] stage I). Specifically, the role of comprehensive surgical staging, including pelvic and para-aortic lymphadenectomy for all patients, has been questioned. Strategies utilizing pre- or postoperative histologic grade and depth of invasion by frozen section or gross inspection have been advocated by some to select only high-

Table 1

FIGO Uterine Cancer Staging Criteria (1988)

Stage	Criteria
I	Limited to uterus
IA	Tumor limited to endometrium
IB	Invasion to less than half of myometrium
IC	Invasion to more than half of myometrium
II	Cervical Involvement
IIA	Endocervical glandular involvement only
IIB	Cervical stromal invasion
III	Pelvic or vaginal involvement
IIIA	Adnexal or serosal involvement, or positive peritoneal cytology
IIIB	Vaginal metastases
IIIC	Metastases to pelvic or para-aortic lymph nodes
IV	Bladder or rectal involvement or distant metastases
IVA	Bowel or bladder mucosal invasion
IVB	Distant metastases- includes omental and inguinal metastases

FIGO = International Federation of Gynecology and Obstetrics.

er-risk patients for complete surgical staging. Cost, survival, and the utilization of adjuvant therapies are also important issues in the management of patients with endometrial cancer.

Diagnosis and Preoperative Evaluation

Most patients with endometrial cancer present with abnormal uterine bleeding or postmenopausal bleeding leading to subsequent evaluation. An endometrial biopsy, D&C, and/or vaginal probe ultrasound may be per-

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formed. Should a diagnosis of atypical hyperplasia be reported, the clinician should be aware that up to 40% of patients with atypical hyperplasias on biopsy or D&C have evidence of an adenocarcinoma on final hysterectomy pathology.[4] Additionally, these tumors are not always early-stage, low-grade tumors. As many as 31% of these patients will have advanced-grade tumors or evidence of myometrial invasion on final pathology.[4] Therefore, it is imperative that these patients be managed by physicians capable of performing comprehensive surgical staging in the event that cancer is found at the time of surgery.

Hysteroscopy

Hysteroscopy has been advocated as an adjunct to D&C. Unguided D&C may have a false-negative rate of 10% to 30% in the evaluation of postmenopausal bleeding.[5] Unfortunately, hysteroscopy combined with D&C may also have false-negative rates of up to 20%. Concern remains that the routine use of hysteroscopy may increase the rate of positive cytology at the time of surgical staging.[6] Therefore, the addition of hysteroscopy to D&C in the evaluation of postmenopausal bleeding seems to add little to current management.

Preoperative Imaging

The initial diagnostic exam should include a complete physical examination, with particular attention paid to possible metastatic sites such as peripheral lymph nodes (supraclavicular, inguinal), the presence of abdominal masses or ascites, vaginal metastases or gross cervical involvement, uterine size and/or parametrial involvement. The role of preoperative imaging in the evaluation of endometrial cancer, particularly as it relates to diagnosing metastatic disease in clinical stage I/II tumors, remains less clear.

A preoperative chest x-ray is noted to be abnormal in 2% of women with endometrial cancer and may serve to diagnose concomitant comorbidities. While other imaging technologies including computed tomography (CT) or magnetic resonance imaging (MRI) have been used

to predict depth of myometrial involvement, these techniques appear to have limited utility in accurately detecting the presence of extrauterine disease. False-positive rates of 10% and false-negative rates of 8% to 35% have been reported.[7] The addition of positron-emission tomography (PET) scanning to CT has proven to be only 60% sensitive with 94% to 98% specificity in accurately detecting extrauterine disease.[8] Therefore, these imaging techniques (CT, MRI, PET) may be more suited for detecting extrauterine disease in patients who are medically unfit for comprehensive surgical staging and not as a replacement for proper surgical assessment of metastatic disease.

FIGO Staging

The surgical staging system as established by FIGO in 1988 is shown in Table 1. Clinical staging for endometrial cancer has largely been abandoned in favor of surgical staging, as clinical staging fails to take into account histopathologic features that more accurately delineate patients who may benefit from adjuvant therapy. Such features include tumor grade, depth of invasion, histologic subtype, lymphovascular space invasion, and nodal metastases.[9] Clinical staging alone is inadequate, as 23% of preoperative clinical stage I/II patients will be upstaged with extensive surgical staging (Table 2).[10]

Staging Procedure

The surgical staging procedure for patients with endometrial cancer should include an examination under adequate anesthesia, followed by adequate surgical exposure and inspection of intra-abdominal structures with biopsy of any suspicious lesions. Lavage peritoneal cytology should be obtained prior to manipulation of the uterus. A complete extrafascial hysterectomy with bilateral salpingo-oophorectomy should be performed. Pelvic and para-aortic retroperitoneal lymph node dissection should be performed. The boundaries of the lymphadenectomy should include the genitofemoral nerve laterally, the hypogastric artery medially, the obturator nerve posteriorly, the circum-

Table 2

Extent of Surgically Determined Extrauterine Disease in Clinical Stage I or II Patients

	Percent of patients
All extrauterine disease (ovary, peritoneum, lymph nodes)	23%
Lymph node metastases only	11%
Pelvic lymph nodes only	6%
Pelvic and para-aortic nodes	3%
Para-aortic nodes only	2%

Data from Morrow et al[9] and Creasman et al.[10]

flex iliac vein inferiorly, and the origin of the inferior mesenteric artery (some claim the superior mesenteric artery) superiorly, as described per the standardized Gynecologic Oncology Group (GOG) protocol.[9]

The appropriate extent of the retroperitoneal lymph node dissection is debated by some, although most agree that numerous sites should be assessed. The argument for complete lymphadenectomy during the staging procedure has its basis in statistical modeling for the detection of positive nodes. In order to have an 80% chance of detecting a single node that is positive (if only 5% of nodes are positive at that particular site) requires that at least 50% of that site's nodes be sampled. Additionally, previous studies have shown that if pelvic nodes are positive, 40% to 50% of patients have para-aortic nodal involvement.

The role of lymph node dissection has been validated in clinical studies, as patients undergoing extended nodal dissection (four or more sites) had a better survival than those who did not undergo nodal sampling (Figure 1).[11] This survival advantage held true for the entire population ($P < .001$), high-risk patients only ($P < .001$), and high-risk patients treated with adjuvant radiotherapy ($P = .01$). These findings were confirmed in a recent publication by Lutman et al, who reported that high-risk subtype patients with at

least 11 lymph nodes evaluated had significantly improved survival.[12] In addition to the above noted surgical approach, in high-risk patients such as those with clear cell or uterine papillary serous carcinoma, infracolic omentectomy should be considered, as these histologic types may be associated with omental metastases similar to ovarian carcinoma.[13]

Intraoperative Staging Decisions

The decision to perform comprehensive surgical staging for patients with endometrial adenocarcinoma should ideally be made prior to surgery. However, some advocates recommend making this decision in a combination of preoperative grade and histology, intraoperative assessment of the presence and depth of myometrial invasion either grossly or with frozen section, and clinical assessment of nodal spread intraoperatively.

Preoperative D&C or biopsy tumor grade is not sufficient to determine which patients should be surgically staged. Daniel et al reported 15% to 20% of cases had their tumor grade upgraded on final pathology, with only a 57% to 68% correlation of tumor grade between D&C and final pathology.[14] In addition, final

cell type is not well correlated with D&C. In a study of biopsy-proven clinical stage I, grade 1, endometrioid tumors (typically low-risk), 19% were upgraded to a higher grade or had a change in preoperative histology compared to final histology.[15] Specifically, 15% of patients were upgraded to grade 2 tumors, 0.5% to grade 3, 2.5% to a serous or clear cell histology, and 1% to a carcinosarcoma histology. Grade and histology migration correspond to an increased risk of nodal metastases and may potentiate the need for adjuvant radiation therapy if the patient is not surgically staged.

Others argue that intraoperative algorithms be used to determine which patients need surgical staging. These algorithms depend on clinical estimation of depth of invasion (DOI) combined with the aforementioned preoperative grade. However, gross estimation of depth of invasion becomes *less* accurate as tumor grade increases.[16] For grade 1 tumors (final pathology grade), clinical estimation of DOI is 87% accurate, whereas for grade 3 tumors, such estimates are only 30% accurate. Using frozen section to improve intraoperative grade or DOI estimation may not be helpful, as frozen section was not shown to be fully predictive of grade (84%

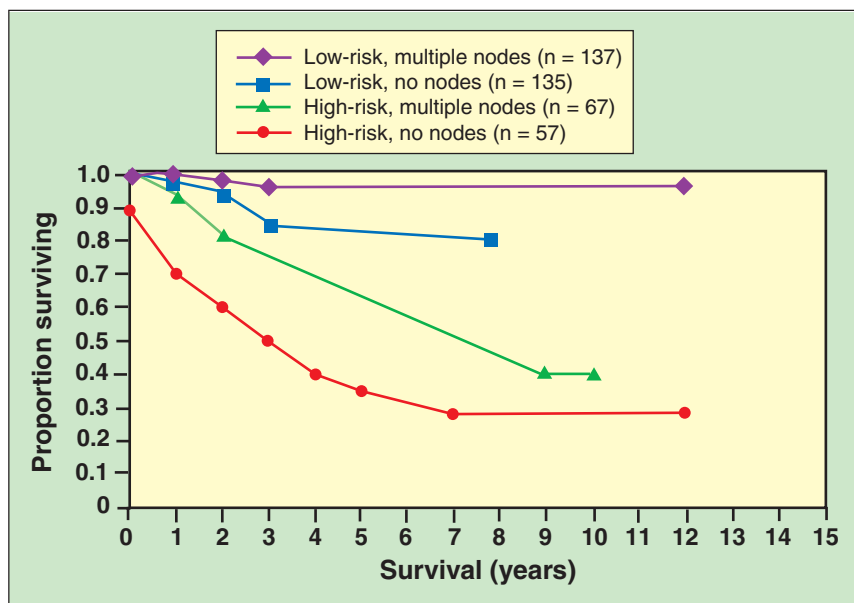


Figure 1: Pelvic Node Sampling and Survival in Women With Endometrial Cancer—Overall survival by extent of surgical staging. Adapted from Kilgore et al.[11]

accuracy) or myometrial invasion (88% accuracy).[17] Additionally, combining clinical estimation of DOI with frozen section or preoperative grade was not predictive of final surgical stage.[18] The practice of resecting only clinically suspicious nodes is also insufficient, as 36% of positive lymph nodes are missed by palpation.[19] Nearly 50% of positive nodes are < 1 cm,[20] and less than 30% of positive nodes are palpably abnormal.[21]

Most advocates of preoperative or intraoperative algorithms to determine which patients should be surgically staged refer to the potential for increased morbidity with the staging procedure. However, multiple authors have found no difference in morbidity (8%) associated with the staging procedure and simple abdominal hysterectomy in this higher-risk and often morbidly obese population.[22,23] Prospective data have demonstrated that the median time for lymphadenectomy is only 24 minutes, with less than 25 mL median blood loss attributed to the lymphadenectomy portion of the procedure.[24] Additionally, the average hospital stay for patients undergoing comprehensive surgical staging in conjunction with their hysterectomy is less than 4 days.[25]

Benefits of Surgical Staging

The demonstration that no disease exists outside the uterus allows one to observe patients otherwise at risk for nodal metastases and recurrence without the use of potentially morbid adjuvant radiation therapy. When patients are managed without complete surgical staging information the clinician may be forced to prescribe adjuvant therapy based merely on clinical assumption and potential risk. Accordingly, nonjudicious use of adjuvant therapy may increase morbidity and cost of care without a proven benefit.

Individual and combined evidence from two prospective randomized studies involving over 1,200 patients failed to demonstrate a survival benefit when pelvic irradiation was administered to the unstaged patient, regardless of the presence of specific uterine risk factors.[3,26] Thus, the

administration of postoperative teletherapy in unstaged patients may subject these women to ineffective treatment and a 3% to 7% risk of severe and 20% risk of mild radiation-associated complications.[27-29]

• **Postoperative Radiation vs Observation**—Recently, the GOG reported final data from a randomized trial of adjuvant radiation therapy for patients with intermediate-risk endometrial cancer following complete surgical staging.[30] Patients with surgical stage IB, IC and occult stage II endometrial carcinoma were randomized to observation or whole-pelvic radiation therapy postoperatively. The study demonstrated that adjuvant radiation therapy decreased pelvic recurrence (12% vs 3%, $P = .007$), but at the cost of increased complications with no improvement in overall survival (86% vs 92%, $P = .557$). Therefore, a strategy maximizing surgical staging while minimizing the use of adjuvant radiation therapy may decrease overall morbidity and cost, at the expense of an increase in the incidence of vaginal metastases.

Retrospective data[2,23] support an observation-only strategy in intermediate risk patients, which includes all grade 3 tumors, stage IB grade 2 or 3 tumors, and all stage IC patients when surgically staged. Recent studies support this approach for endometrial cancer patients, documenting a salvage rate for vaginal recurrences of 63% and no difference in overall survival when compared to patients receiving adjuvant radiation therapy.[30,31]

• **Further Support for Surgical Staging**—Routine performance of comprehensive surgical staging is cost-effective and may result in a 31% decrease in costs compared to intraoperative decision algorithms.[31,32] In recognition of the importance of surgical staging, GOG Protocol 210, a prospective study with the goal of developing a molecular disease classification system to complement FIGO staging, now requires full surgical staging including para-aortic and high para-aortic lymphadenectomy. Additionally, the American College of Obstetricians and Gynecologists

(ACOG) endorsed the importance of surgical staging in a practice bulletin issued September 15, 2004, stating:

Every patient undergoing surgery for the treatment of endometrial cancer should be counseled preoperatively as to the possible need and benefit of staging and should be offered the option at the time of their initial surgical procedure.

• **Role of Gynecologic Oncologist**—The preferred strategy to employ comprehensive surgical staging for all patients with endometrial cancer requires all patients to undergo surgery conducted by a gynecologic oncologist (or gynecologist with general surgery backup). Unfortunately, only 32% of women with endometrial cancer in the United States currently have surgery performed by a gynecologic oncologist. An additional 11% have a gynecologic oncologist on standby.[33]

In a patterns-of-care study, Roland et al reported only a 26% histologically confirmed lymph node assessment in patients operated by a non-gynecologic oncologist compared to 83% of patients when surgery was performed by a gynecologic oncologist.[34] Additionally, this study demonstrated that complete tumor-node-metastasis (TNM) staging was successfully performed by gynecologic oncologists 94% of the time, as compared to 45.2% by non-gynecologic oncologists. More importantly, only 6 patients (8.6%) with intermediate-risk disease deemed at risk for extrauterine spread received radiation when managed by gynecologic-oncologists vs 15 patients (21.7%) managed by non-gynecologic oncologists secondary to adequate surgical staging.

Laparoscopy in the Management of Endometrial Cancer

Recently, laparoscopic surgery in the management of endometrial cancer has come to the forefront with the intent to reduce complications and recovery time in this difficult, obese, surgical population. Despite the difficulties of laparoscopy in these pa-

tients, studies have shown that the procedure is feasible 85% to 95% of the time.[35,36] The technique is similar to abdominal staging in that the abdomen is inspected, washings are obtained, and a complete para-aortic and pelvic lymphadenectomy is performed. Variations exist as to completion of the hysterectomy either vaginally or totally laparoscopically (the specimen may be extracted from the vagina after amputation).

Several studies[35,37-41] have demonstrated safety in terms of postoperative complications, with some finding that complications were higher with open abdominal surgery. Long-term prospective outcomes, as well as safety data, are still pending from the prospective evaluation of exploratory laparotomy with staging vs laparoscopic hysterectomy and staging (GOG Protocol LAP2). However, retrospective studies have demonstrated no difference in survival.[39,40]

One would expect that overall survival should be similar because most studies report at least equal (if not improved) nodal counts with laparoscopy compared to laparotomy. The purported benefits of the laparoscopic approach include an average 2-day shorter hospital stay. Despite an initial increase in hospital charges secondary to laparoscopy costs,[36] cost savings may be realized, as out-of-hospital expenses such as wound care, income loss, and lack of productivity in society tend to favor laparoscopy.

Conclusions

In conclusion, comprehensive surgical staging for endometrial cancer clearly is more advantageous than clinical staging. Surgical staging allows for determination of disease extent and detection and/or resection of occult metastases. Staging can be safely performed at the time of hysterectomy without added morbidity, and

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provides proper guidance with respect to postoperative adjuvant therapy, avoiding needless radiation therapy in 85% of clinical stage I/II patients. Finally, it appears to be the most cost-effective strategy in this setting.

**This article is reviewed
on pages 50 and 54.**

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The Kirby/Leath/Kilgore Article Reviewed

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Kirby et al are correct in their statement that continued controversy surrounds the comprehensive surgical staging of all patients with clinical stage I endometrial adenocarcinoma. Such is the case because lymph node metastasis is found in only 10% of these patients. The proportion of patients found to have lymph node metastasis is even lower among those with grade 1 and 2 tumors with minimal or no invasion. A high proportion of patients with endometrial adenocarcinoma fall into this group.

In the classic paper by Creasman et al,^[1] of the 621 women with endometrial adenocarcinoma who underwent surgical staging, 468 had

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grade 1 or 2 tumors and the tumor invaded to less than one-third of the myometrial thickness or not at all in 367. The incidence of pelvic lymph node metastasis in patients with grade 1 tumors that invaded to less than one-third of the myometrial thickness was 3%. Among women with grade 2 tumors with less than one-third myometrial invasion, the proportion with pelvic lymph node metastasis was 5%. The incidence of periaortic lymph node metastasis was 1% and 4%, respectively.

These numbers were obtained from analysis of the final pathology diagnosis. Kirby et al argue that there is no accurate way of knowing the tumor grade and depth of invasion until the permanent tissue sections from the hysterectomy specimen are studied. Therefore, they suggest that every patient with a biopsy or curettage diagnosis of grade 1 endometrial adenocarcinoma and a frozen section evaluation that confirms the histologic grade and shows minimal or no myometrial invasion should undergo a comprehensive lymphadenectomy, to benefit the few who, on final analysis, may be found to have a poorly differentiated or deeply invasive tumor. They use selected studies from the literature to support their recommendation.

Evaluation Methods, Morbidity, and Survival

Is the predictive value of a preoperative and intraoperative tumor evaluation as poor as suggested by Kirby et al? Will the final pathology diagnosis cause a significant change in therapy, and more importantly, will not performing a lymphadenectomy in selected cases have an impact on survival? Is a comprehensive lymphadenectomy always a safe procedure with no associated morbidity, as Kirby et al would like us to believe?

I will approach the last question first. Kirby et al tell us that the morbidity associated with a total abdominal hysterectomy and a pelvic and periaortic lymphadenectomy is no different from that associated with hysterectomy alone. If the lymphadenectomy is such a safe and simple procedure, we should be training our gynecology residents—who will diagnose the majority of the 40,000 new cases of endometrial cancer each year—to do them. They may do a better job than the general surgeons, who do not have adequate training or experience in performing pelvic or periaortic lymphadenectomies. Perhaps we gynecologic oncologists, as a group, are gifted technicians who

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are able to do these procedures fast and safely. However, data from other centers suggest otherwise.

The gynecologic oncology group from Duke University showed that women who underwent pelvic lymph node sampling sustained increased blood loss and transfusions, longer operative time, and increased morbidity compared to those who only underwent a hysterectomy.[2] In addition, Lewandowski et al[3] showed that 11% of patients who received whole-pelvic irradiation after total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic and periaortic lymph node dissection developed severe intestinal complications compared to none of those who did not undergo a lymphadenectomy.

It is likely that the reported differences in morbidity associated with the lymphadenectomy could be explained in part by the composition of the population studied. It has been shown that the success of completing a periaortic lymphadenectomy in patients with endometrial carcinoma steadily decreases as the patients' body mass index increases and with the presence of oth-

er severe comorbid conditions. This is true whether the procedure is done via laparotomy or laparoscopy.[4]

Omitting the Lymphadenectomy

Several studies suggest that omitting the lymphadenectomy in selected cases of endometrial adenocarcinoma has no negative impact on survival. Larson et al[5] reported on 102 women with grade 1 endometrial adenocarcinoma confined to the endometrium or that did not invade deeper than the inner half of the myometrium. These patients did not undergo lymphadenectomy and did not receive adjuvant therapy. Their cumulative 5-year survival was 87%. Belinson et al[6] reported on 216 women with clinical stage I endometrial adenocarcinoma who did not undergo pelvic lymphadenectomy. Adjuvant radiation therapy and periaortic lymph node dissection was performed in those who had deep myometrial invasion, grossly positive pelvic lymph nodes, or cervical involvement. With a median follow-up of 61 months, only 21 (10%) recurrences were encountered. Only two

(1%) of the recurrences occurred in the pelvis.

How many patients in whom the frozen section evaluation of the hysterectomy specimen shows a grade 1 tumor with no invasion will be at significant risk of having lymph node metastasis? In a recent study from the M. D. Anderson Cancer Center, of 36 patients with stage IA, grade 1 adenocarcinoma on frozen section, 4 were found to have grade 1 tumors with positive peritoneal cytology.[7] Of the remaining 32 patients, 9 had a grade 1 tumor and three had a grade 2 tumor with less than 50% myometrial invasion. The authors estimated that for patients with a frozen section diagnosis of stage IA, grade 1 endometrial adenocarcinoma, the probability of nodal metastasis is only 1% to 2%. They also studied patients with a pre-hysterectomy biopsy diagnosis of grade 1 endometrial adenocarcinoma and an intraoperative gross assessment of no myometrial invasion.[8] Of these patients with presumed stage IA, grade 1 endometrial adenocarcinoma, only 1 (4%) was significantly upstaged. Others have shown that com-

bining the histologic grade obtained on the presurgery endometrial biopsy and the frozen section evaluation of the hysterectomy specimen could further improve the correlation with the final pathology diagnosis.[9,10]

Extent of Excision

Kirby et al are also correct in that the appropriate extent of the lymphadenectomy varies. They describe a complete retroperitoneal lymph node dissection that extends from the origin of the inferior mesenteric artery (or the superior mesenteric artery) down to the entry of the superficial circumflex iliac vein into the external iliac vein. If this procedure was indeed associated with no increased morbidity, then it may be justified to perform it in women with comorbid conditions who have a small chance of lymph node metastasis (2 cm or

less, grade 1 tumors with no invasion or minimal invasion on pre- and intraoperative evaluation). I suggest that it will be impossible to show that the benefit (ie, survival) outweighs the risk (ie, morbidity) in these patients.

—*Enrique Hernandez, MD, FACOG, FACS*

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The Kirby/Leath/Kilgore Article Reviewed

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Endometrial cancer is the most common gynecologic malignancy affecting women in the United States. In 1988, the International Federation of Gynecology and Obstetrics shifted from a clinical staging protocol to one based on surgical factors, making surgical staging the accepted treatment approach to endometrial cancers, with excellent survival compared to other gynecologic malignancies. The manuscript by Kirby et al brings to light the controversies surrounding the surgical evalu-

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ation of endometrial cancers. Although surgical staging has been shown to have both prognostic and therapeutic benefit, major problems in the United States continue to result in suboptimal treatment of patients with endometrial cancer. These problems include the lack of an accepted surgical protocol (in terms of adequacy of lymph node sampling) and incomplete surgical staging secondary to patient factors or the lack of referral to specialty-trained gynecologic oncologists.

Diagnosis and Preoperative Evaluation

Radiographic assistance in determining preoperative disease extent in patients with endometrial cancers has been shown to be of limited value. Sonographic measurement of endometrial thickness has not been shown to correlate well with tumor grade or stage at final surgery.[1] Other imaging techniques such as com-

puted tomography (CT) or magnetic resonance imaging (MRI) have been shown to predict local-regional staging but remain limited when used to predict lymph node involvement and, therefore, are not useful when predicting extent of indicated surgery.[2] F-18-fluorodeoxyglucose-positron-emission tomography (FDG-PET) also has been shown to have only moderate sensitivity in predicting lymph node metastases preoperatively in women with endometrial cancer.[3] As emphasized by Kirby et al, these modalities should not replace lymphadenectomy but may be helpful in patients where lymphadenectomy cannot be adequately performed or was not performed during the initial surgery.

Kirby et al discuss the limited value and potential adverse effects of adding hysteroscopy to traditional endometrial sampling techniques. Given that the procedure increases cost

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and potential surgical morbidities, as well as some evidence that suggests a higher incidence of positive peritoneal cytology, hysteroscopy is not endorsed as a significant addition to the preoperative evaluation in patients with abnormal bleeding.

Other authors have attempted to correlate phenotypic and molecular markers (ploidy, proliferating cell nuclear antigen, p53, HER2/*neu*, bcl-2, estrogen receptor, progesterone receptor) in preoperative endometrial samples with morphologic data and disease stage at hysterectomy in an attempt to better identify patients at risk of lymph node metastases.[4] Larger studies need to be performed to fully assess the clinical utility of these potential associations before dictating surgical management decisions. The majority patients will still benefit from complete surgical staging where indicated.

Staging Procedure

Kirby et al remind us that the decision to perform comprehensive surgical staging should ideally be made prior to entering the operating room. Significant data highlight the limitations of using preoperative tumor grade, cell type, and depth of myometrial invasion to assess risk of lymph node metastases.[5] As Kirby et al review, many of these intraoperative algorithms become less accurate as tumor grade increases, and they are significantly limited by the experience of the surgeon and reading pathologist.

Advocates for the use of intraoperative algorithms to dictate extent of surgical dissection refer to the idea that increased surgical dissection equals increased surgical morbidity. Available data, however, suggest that when performed by a trained, experienced surgeon, hysterectomy and lymph node dissections can be performed safely with minimal or no increase in morbidity as measured by blood loss, operative time, infections, thromboembolic phenomena, and hospital stay, as detailed by Kirby et al.[6-7]

As Kirby et al report, several studies have demonstrated that a laparoscopy-assisted staging procedure

can be safely performed in these patients and is associated with shorter hospital stays and blood loss despite higher operative costs. What is important to highlight, however, is the quality-of-life benefit of laparoscopic staging, including shorter time to return to normal activity and potentially shorter time to commence adjuvant radiation therapy if indicated. Problems such as port site recurrences and the surgeon's lack of education or experience with the laparoscopic technique need to be further addressed.

Benefits of Surgical Staging

Kirby et al note that women undergoing definitive surgery for endometrial cancer should undergo thorough surgical staging, even when low-grade disease is found on preoperative biopsy, irrespective of gross or frozen assessment of depth of myometrial invasion. Up to 30% of grade I cancers will demonstrate postoperative histologic factors that highlight the need for surgical staging to address whether adjuvant radiation therapy would be of benefit.[8]

If patients are adequately staged, surgical documentation of lack of extrauterine disease can allow selected patients to forgo costly and potentially morbid adjuvant radiation therapy. As Kirby et al point out, the recent report from the Gynecologic Oncology Group on adjuvant radiation therapy in intermediate-risk, early-stage endometrial cancer patients did show a decreased risk of pelvic recurrence. However, this result came at the price of increased complications, and overall survival was not improved.

Other authors highlight the need for further study about the role of adjuvant radiation therapy for intermediate-risk endometrial cancer. The definition of who is truly at high risk and would benefit from adjuvant therapy as well as the comparison of potentially less morbid radiation techniques (such as vaginal brachytherapy) in this group of patients needs to be better delineated in larger studies.[9] If the true surgical stage is not known, the interpretation of survival impact for these different patient categories and

adjuvant modalities becomes difficult if not impossible.

Conclusions

Kirby et al highlight the importance of adequate surgical staging in endometrial cancer patients and the clinical and economic impact the process can have on the treatment of this generally curable disease. Patients managed by gynecologic oncologists are more likely to undergo comprehensive staging and are, therefore, less likely to receive potentially morbid radiation therapy. Emphasizing public education regarding the benefits of having an adequate surgical procedure as well as professional education regarding the need for subspecialty referral will hopefully continue to improve the delivery of gynecologic care to women facing endometrial cancer in the United States.

—Karen A. Moller, MD

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