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Staging Laparotomy for Endometrial Carcinoma: Assessment of Peritoneal Spread

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To evaluate surgical staging procedures in women with endometrial carcinoma, we examined the techniques used to assess the peritoneal cavity in 295 clinical stage I patients treated between 1985 and 1993. These patients were felt to be at increased risk for extrauterine disease because of significant myometrial invasion, high-grade (2 or 3), or variant histology (papillary serous, clear cell, or mixed). Patients had a mean of two intraperitoneal samples taken: 224 patients (76%) had at least an omental biopsy and peritoneal cytology. Additional peritoneal biopsy sites included pericolic gutters (50), pelvic peritoneum (45), bowel serosa/mesentery (24), diaphragm (22), appendix (11), and adhesions (7). At the time of staging laparotomy, 22 patients (7.5%) had gross evidence of peritoneal spread, which was readily confirmed by directed biopsy. In the 273 women without gross peritoneal disease, 3 (1%) had occult metastases detected by routine biopsy, 3 (1%) had microscopic metastases in palpably abnormal biopsies, and 22 had positive cytology as the only evidence of peritoneal disease. Only three operative complications were potentially attributable to peritoneal assessment: cystotomy (1), partial small bowel obstruction (1), and ileus (1). Peritoneal failures have been noted in 12 patients over a mean follow-up interval of 39 months. Seven of these patients had obvious peritoneal disease at laparotomy. Two of the remaining 5 had optimal peritoneal sampling and represent false-negative cases. A staging laparotomy that included total abdominal hysterectomy with adnexal resection, cytology, omental biopsy, and biopsy of grossly abnormal sites would have potentially identified all patients with known peritoneal disease. Routine biopsy of other grossly normal peritoneal sites is associated with extremely low yield and is not recommended. © 1995 Academic Press, Inc.

Most women with endometrial carcinoma experience abnormal bleeding and are diagnosed early in the course of their disease when the tumor is still confined to the uterus. While histologic grade, depth of myometrial invasion, and extension to the cervix are important prognostic features associated with the primary uterine tumor [1], endometrial cancers that have spread to retroperitoneal lymph nodes or to sites within the peritoneal cavity are at especially high risk for recurrence. Survival rates for patients with extrauterine disease are less than 50% [2].

Endometrial carcinomas that have invaded through the full myometrial thickness can access the peritoneal cavity by direct extension into adjacent tissues or by release and implantation of cells at any intraabdominal site. Cells from intrauterine tumors may also traverse the fallopian tube to gain direct access to the peritoneal cavity. In contrast, tumor embolization via lymph–vascular spaces results in spread to retroperitoneal nodes or distant organs such as lung, bone, and brain. When the International Federation of Gynecology and Obstetrics (FIGO) adopted its surgical staging scheme for uterine corpus cancers in 1988, it assigned patients with peritoneal disease to stage IVB [3]. This acknowledges the prognostic importance of intraperitoneal spread; however, specifically defined guidelines as to what constitutes an adequate staging assessment of the peritoneal cavity are not addressed by this staging system.

We undertook this study to examine the value of various staging procedures in identifying tumor spread within the peritoneal cavity. The impact of retroperitoneal lymph node assessment is the subject of a separate study. Our purpose was to define which operative sampling procedures or combination of procedures proved most important in detecting occult extrauterine disease. These could then be incorporated into a standardized staging approach recommended for all high-risk patients. An equally significant goal was to identify those procedures

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shown to be of limited value so that their routine use could then be abandoned with a potential reduction in operative risk and cost.

MATERIALS AND METHODS

Between January 1985 and March 1993, 612 patients with uterine corpus cancers underwent primary surgical therapy at The University of Texas M.D. Anderson Cancer Center. Patients analyzed for this review were those with clinical stage I carcinomas felt to be at risk for extrauterine disease. These included those with histologic grade 2 or 3 typical adenocarcinoma, variant cell types (papillary serous, clear cell, or mixed), or grade 1 tumors with greater than 50% myometrial invasion. Because grade 1 tumors with superficial invasion have a small recurrence risk, we do not routinely perform an aggressive staging operation in these cases. These were excluded, as were all uterine sarcomas. A total of 295 patients met the eligibility guidelines. Data for cases prior to September 1988 were collected by retrospective record review. Surgical pathologic data and follow-up information for other cases were prospectively entered on a departmental database as part of an ongoing project to evaluate surgical staging efforts.

All patients underwent a standard preoperative evaluation to assess clinical extent of disease and operative risk. This consisted of history and physical examination, Papanicolaou smear, review of endometrial biopsy specimen, laboratory studies, chest radiograph, electrocardiogram, and assignment of an American Society of Anesthesiologists (ASA) score. Additional laboratory and diagnostic studies, as well as medical consultation, were done as indicated by the clinical situation.

Total abdominal hysterectomy with removal of the adnexae was performed in all patients. The extent of the peritoneal sampling was determined by the individual attending staff member and ranged from exploration only to a systematic evaluation of the abdominal cavity with cytology and multiple biopsies similar to that employed in the surgical staging of epithelial ovarian malignancies. After September 1988, a more extensive sampling approach was recommended for those patients who did not present exceptional technical or anesthetic risks for additional procedures. Pathologic and cytologic findings were presented and reviewed at a multidisciplinary planning conference where recommendations for adjuvant and adjunctive therapy were made. For this study, the number, location, appearance, and pathologic interpretation of all peritoneal sampling sites were abstracted with careful documentation of the gross appearance of each biopsy site.

Patients were followed postoperatively on a regular schedule that included examinations every 3–4 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Follow-up status and duration were recorded. Special attention was focused on the location (intraperitoneal vs retroperitoneal vs other site) of recurrence.

Demographic and staging data were collated and are presented descriptively. All descriptive statistics and their comparisons were carried out using SPSS software.

RESULTS

The mean age of the 295 patients was 63 years (range 32–88). The group's racial makeup was white, 77%; black, 11%; Hispanic, 11%; and Asian, 1%. Ninety-five percent of the patients were peri- or postmenopausal. Median parity was 2. Patient weights ranged from 35 to 159 kg, with 47% of patients weighing within 10% of their ideal body weight (IBW). The remaining patients exceeded IBW by more than 10%: 13% weighed between 10 and 20% above IBW, 22% weighed between 20 and 50% above, and 18% weighed more than 50% above. An ASA risk score was assigned in all but 2 patients: 1 woman was category I, 91 were category II, 187 were category III, and 14 were category IV.

The uterus and adnexae were removed in all cases. The extent of peritoneal sampling by technique varied: 21 (7%) had no evaluation of the peritoneum, 38 (13%) had peritoneal cytology only, 10 (3%) had omental biopsy only, 147 (50%) had both cytology and omental biopsy, and 79 (27%) had additional peritoneal sites biopsied. In patients who had peritoneal tissue biopsies of some type, the mean number of sites sampled was 2. The extent of sampling by number of biopsy sites was as follows: none, 59 patients; one site, 157; two sites, 30; three sites, 15; four or more sites, 34.

The median duration of staging laparotomy (including hysterectomy) was 145 min. Median blood loss was 300 ml. Three complications were potentially attributable to peritoneal sampling. One cystotomy occurred during biopsy of bladder peritoneum. Postoperative bowel complications were seen in two cases: one prolonged ileus and one partial small bowel obstruction. Both resolved with bowel rest and conservative management.

All patients were considered to have clinical stage I tumors prior to laparotomy. For patients with adequate sampling to allow assignment of surgical stage, 103 of 244 cases (42%) were assigned to a higher stage based upon surgical findings. Most patients (76%) had typical endometrioid adenocarcinomas. Variant histologic types were seen in 69 cases (23%). Surgical stage, histologic grade, and cell type are summarized in Table 1.

We reviewed operative and pathology reports in detail

TABLE 1
Surgical Stage, Grade, and Histology for All Cases

Surgical stage	Endometrial			Variant histology			
	G1	G2	G3	UPSC	CC	AS	Mixed
Ia	0	12	3	7	0	0	1
Ib	0	57	20	4	1	2	1
Ic	4	10	6	2	1	2	2
IIa	1	4	0	0	0	0	0
IIb	2	6	1	1	0	0	1
IIIa	2	11	4	4	1	1	2
IIIb	0	0	1	1	1	2	0
IIIc	3	6	11	7	1	1	2
IV	0	6	5	11	2	2	0
Unstaged	2	43	6	4	1	1	0
Total	14	155	57	41	8	11	9

Note. G1, grade 1; G2, grade 2; G3, grade 3; UPSC, uterine papillary serous carcinoma; CC, clear cell; AS, adenosquamous.

to correlate the surgeon's clinical impression of the biopsy specimen with the final pathologic interpretation. Random biopsies of grossly normal peritoneal sites were labeled "normal," while biopsies of sites described as adhesion, thickening, nodules, or irregularity were labeled as "abnormal." Biopsies of sites felt to represent obvious cancer, noted in 22 women (7.5%), were called "gross tumor." These data are summarized in Table 2. While all biopsies thought to contain gross tumor were pathologically positive, only six specimens (1.7%) categorized as normal or abnormal contained occult carcinoma. These included four omental biopsies, one sample from the pelvic cul-de-sac, and one biopsy from small bowel serosa. The latter two biopsies came from areas described as palpably "irregular." The pathologic positivity rates were 3/302 (1%) for random biopsy of clinically normal sites, 3/44 (7%) for biopsy of clinically abnormal sites, and 35/35 (100%) for sites felt to represent gross tumor. No random biopsy of a clinically normal area outside the omentum demonstrated occult tumor. The 3 women with occult omental metastases had no other positive biopsy sites.

Peritoneal cytology results are also summarized in Table 2. A total of 35 patients had positive cytologies, 13 of whom had palpable abnormalities or obvious tumor identified at exploration. In the other 22 cases, a positive cytology was the only indication of extrauterine disease.

Patients have been followed for a median of 39 months. Sixty-one of the total 295 women (21%) have developed clinical recurrence. Most recurrences were outside the peritoneal cavity in retroperitoneal or distant sites. However, 12 women had a recurrence which included a peritoneal component. These cases were examined individually because they represent potential peritoneal staging failures. In 4, gross tumor had been identified at staging laparotomy, and 3 had positive peritoneal cytology specimens. Five women with "negative" peritoneal staging operations subsequently presented with intraperitoneal failure. The clinical information summarizing these cases is seen in Table 3. Overall, peritoneal recurrences were seen in 4 of 22 patients (18%) with gross tumor, 3 of 22 (13.6%) with positive cytology only, and 5 of 251 (2%) with no evidence of disease at the primary laparotomy.

DISCUSSION

We have taken an individualized approach to the surgical staging of patients with endometrial carcinoma. Because virtually all such patients have their disease diagnosed by endometrial biopsy or dilatation and curettage, histologic type and cytologic grade are generally known prior to the staging operation. While sampling errors do occur [6], there is reasonable correlation between biopsy diagnoses and hysterectomy diagnoses in most cases. We limit an extended surgical staging effort to patients with grade 2 or 3 adenocarcinomas and those with high-risk variant cell types, such as papillary serous and clear cell carcinoma, because these are the women most likely to have extrauterine disease [1].

Most patients with superficially invasive, grade 1 adenocarcinomas are unlikely to have extrauterine disease and are cured by hysterectomy alone [2,4]. Our approach in these cases has been to perform total abdominal hysterectomy and bilateral salpingo-oophorectomy with peritoneal cytology and abdominal exploration. A small percentage of patients with grade 1 adenocarcinomas will demonstrate significant myometrial invasion and, therefore, be at risk for tumor recurrence [5]. These patients may benefit from a more extensive staging effort. We identify these cases by estimating depth of myometrial invasion intraoperatively using a combination of gross

TABLE 2
Pathologic Result by Clinical Impression of Biopsy Site

Site	Normal		Abnormal		Gross Tumor	
	−	+	−	+	−	+
Omentum	199	3	9	1	0	16
Peritoneum (abdomen)	40	0	4	0	0	6
Peritoneum (pelvis)	26	0	11	1	0	7
Bowel serosa	7	0	11	1	0	5
Diaphragm	21	0	0	0	0	1
Appendix	9	0	2	0	0	0
Adhesions	—	—	7	0	0	0
Cytology	206	22	0	4	0	9

Note. (−), no pathologic evidence of tumor; (+), tumor present.

TABLE 3
Clinical Information for Five Patients Who Developed Intraperitoneal Recurrence Following a Laparotomy with "Negative" Peritoneal Assessment

Patient	Stage	Histology	Depth[a]	Peritoneal sampling			Time to recur (months)	Recurrence site
				Cytology	Omentum	Peritoneum		
1	Unstaged	G3 Adeno	0 mm	No	No	Adhesions	37	Diffuse[b]
2	Ib	G3 Adeno	5/15 mm	No	No	Nodule	18	Diffuse
3	Ib	G2 Adeno	1/22 mm	Yes	Yes	None	21	Diffuse
4	Ia	UPSC	0 mm	Yes	Yes	None	28	Diffuse
5	IIIc	G2 Adeno	12/20 mm	Yes	No	None	12	Pelvis

Note. G2, grade 2; G3, grade 3; Adeno, endometrial adenocarcinoma; UPSC, uterine papillary serous carcinoma.
[a] Depth, mm invasion/mm myometrial thickness.
[b] Diffuse, multiple simultaneous peritoneal sites ± ascites.

visual inspection and frozen-section study. Several studies have established the accuracy of these techniques [7,8]. During our study interval, 14 of 110 grade 1 cases (13%) were found to have significant myometrial invasion and so underwent surgical staging.

By combining the use of preoperative biopsy information with intraoperative estimates of myometrial invasion we hope to limit additional surgical procedures to those patients who are truly at risk for having more advanced disease. Employing these selection criteria, 42% of patients explored in this series had a higher surgical stage than was predicted by clinical evaluation. This would seem to confirm that our preoperative criteria did, indeed, identify the high-risk subgroup. We are now analyzing our grade 1 cases as a separate subset to assess the potential impact of surgical staging in low-risk patients.

Efforts to define the components of surgical staging operations and target them toward at-risk subgroups are important for several reasons. First, most women with endometrial carcinoma are postmenopausal; many have additional surgical risks associated with obesity, diabetes mellitus, and other concomitant medical illnesses. Additionally, patients in the highest risk groups (grade 3, papillary serous, clear cell) tend to be older than those with grade 1 cancers [4]. Two-thirds of our cases were categorized as ASA 3 or higher. A short and less-complicated operation would be desirable for these women.

Second, while staging techniques to evaluate the peritoneal cavity are easily performed by most experienced surgeons, staging in the elderly, obese patient can occasionally present technical challenges related to operative exposure that make some procedures difficult or impossible to perform. Third, operative complications related to peritoneal sampling procedures are rare, but they occur. We noted complications that were potentially attributable to staging procedures in 1% of cases. This number may be greater if a large percentage of patients are treated with both surgery and postoperative external beam irradiation [9].

And last, a therapeutic benefit to operative staging has not yet been definitively established. Although important prognostic information may be obtained, additional treatment undertaken in response to this information may not strongly influence long-term survival rates [10,11].

Our original concept was that peritoneal assessment for endometrial carcinoma should be similar to that used in the staging of patients with early epithelial tumors of the ovary. We considered obtaining cytologic specimens, multiple peritoneal biopsies, diaphragm biopsy, omental biopsy, and biopsy of any other clinically abnormal area. However, on the basis of our data analysis, this approach is excessive. Only 3 of 302 random biopsies of grossly normal sites demonstrated microscopic cancer; all 3 were from the omentum. All other histologically confirmed metastatic sites were from areas that were grossly identified as abnormal or obvious cancer. Consequently, our recommendation for peritoneal assessment is to obtain cytology specimens, and then, to perform a detailed exploration with biopsies targeted only to abnormal sites and the omentum. This approach would have identified all cases with known peritoneal disease at the time of initial operation.

We then looked at patients who subsequently developed disease failure within the peritoneal cavity. Five patients with "negative" staging operations developed peritoneal failure. While all five had normal explorations, only two had optimal sampling, which included both a cytologic specimen and an omental biopsy. Peritoneal disease might have been detected in the other three cases had these additional samples been obtained. Consequently, the estimated false-negative rate for our recommended peritoneal staging approach would be less than 2%.

Clearly, concepts regarding the operative staging of endometrial carcinoma are evolving. We have presented

here guidelines for peritoneal assessment that were shown to be quite accurate in identifying patients with extrauterine disease. The procedures recommended also have the advantage of being simple to perform, even in the technically difficult case.

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