
Endometrial Cancer: Part 2— Prognostic Factors and Treatment

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The most common malignancy of the female genital tract is carcinoma of the endometrium. Prognosis is determined primarily by histologic subtype, grade of differentiation and stage at presentation. Treatment is usually surgical and includes TAH BSO with abdominal cytology evaluation.

In Part 1 of this article (May/June, pp. 19-21), Dr. Rodriguez outlined research findings related to the epidemiology of endometrial cancer and discussed the basics of diagnosis and work-up. In Part 2 he examines factors related to metastatic disease and prognosis, as they relate to treatment.

Prognostic Factors

Histologic subtype, grade of differentiation and stage at presentation are the most important surgical-pathologic features associated with metastatic disease and prognosis.

Various histologic subtypes of endometrial carcinomas exist, with significant differences in biologic behavior. High-risk types include clear cell and papillary serous carcinomas; these occur in approximately 5% and 6% of cases, respectively, and are considered poorly differentiated, by definition.

Adenocarcinoma, with its subtypes (papillary serous carcinoma, clear cell carcinoma and endometrioid adenocarcinoma), occurs in approximately 80% of cases. (Once determined to be clinically equivalent to one another, the subtypes adenocarcinoma with squamous differentiation and adenocarcinoma with squa-

mous metaplasia were then classified primarily as endometrioid adenocarcinoma.)

Because of differences in biologic behavior, the three subtypes of adenocarcinoma need to be distinguished from one another. Papillary serous carcinoma is a highly malignant epithelial cancer that tends to occur in older patients and is associated with metastatic disease at the time of diagnosis. Only 25% of patients with papillary serous carcinoma present at stage I, with 5-year survivals of 35-40% despite surgery and radiation therapy.

Classification of grade of endometrioid adenocarcinoma is based on architectural changes. Grades 1, 2 and 3 are classified by percent of solid growth patterns, with 0-5%, 5-50%, and >50%, respectively. A large Gynecologic Oncology Group (GOG) surgical-pathology trial¹ showed that grade is highly predictive of the presence of extrauterine disease, including adnexal and nodal involvement; pelvic nodes were positive in 3% of patients with grade 1 disease, in 9% of patients with grade 2 disease and in 18% of those with grade 3. Para-aortic nodes were positive in 2%, 9% and 11% of patients, respectively. Lymph node metastasis correlates with 5-year survival, which is ap-

proximately 70% for patients with pelvic metastasis and 35% for those with para-aortic metastasis.¹

The International Federation of Gynecology and Obstetrics' staging classification for endometrial cancer has changed from a clinical to a surgical staging system, based on the large discrepancy between clinical findings and extrauterine disease surgically present in apparent early-stage clinical disease (Table 1). Surgical stage is highly predictive of survival, with estimated survivals of 83%, 73%, 52% and 27% for patients with stage I, II, III and IV, respectively.²

Surgical staging with regional node assessment enables identification of extrauterine disease and allows postoperative adjuvant radiation therapy to be individualized. Pathology findings that correlate with prognosis and have been incorporated into surgical staging include myometrial invasion, cervical involvement, uterine serosal, adnexal or nodal involvement, and the presence of malignant cells in peritoneal cytologic fluid washings. Though not incorporated into staging, lymph-vascular space involvement is predictive of prognosis and is highly predictive of nodal metastasis. While the presence of malignant cytol-

ogy is generally felt to be associated with a poor prognosis and is indicative of stage IIIA disease, controversy exists about whether this is truly a poor prognostic factor. Further study of this subgroup of patients is needed.

Treatment

Endometrial cancer treatment is closely tied to an understanding of prognostic factors that translate into incidence of lymph node metastasis and poor outcome. Surgery is the most common primary treatment in 95% of cases. Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH BSO) with collection of peritoneal cytology is the most common surgical procedure performed. While the need for regional nodal sampling in all cases of endometrial cancer is a source of controversy, pathology data collected by the GOG establish criteria for identification of patients at significant risk of metastasis who should, therefore, undergo nodal sampling¹ (Table 2). Nodal metastases are present in fewer than 5% of patients with grade 1 and 2 lesions with less than one-third depth myometrial invasion. The American College of Obstetricians and Gynecologists (ACOG) recommends against node sampling in these low-risk lesions, and survival rates exceed 95% in patients with such lesions, who are at low risk for metastasis.

Pelvic and para-aortic node sampling is recommended in all patients with grade 3 or poorer histologic subtypes, and in all those with more than one-third myometrial invasion or cervical/adnexal involvement with any grade.³ Kilgore and colleagues reported nodal metastasis rates that ranged from 9 to 34% in such intermediate-risk patients.⁴

Study findings have suggested that surgical staging, including lymphadenectomy, improves survival.⁴ Though controversial, lymphadenectomy certainly adds important prognostic information that can be used to individualize postoperative therapy. In a recent GOG study⁵ stage I and occult stage II endometrial carcinoma patients treated with TAH BSO and complete surgical staging were

Stage	Grade	Characteristics
IA	1, 2, 3	Tumor limited to endometrium
IB	1, 2, 3	Invasion to < half myometrium
IC	1, 2, 3	Invasion to > half myometrium
IIA	1, 2, 3	Endocervical glandular involvement only
IIB	1, 2, 3	Cervical stromal invasion
IIIA	1, 2, 3	Tumor invades serosa or adnexae or positive peritoneal cytology
IIIB	1, 2, 3	Vaginal metastases
IIIC	1, 2, 3	Metastases to pelvic or para-aortic lymph nodes
IVA	1, 2, 3	Tumor-invaded bladder and/or bowel mucosa
IVB		Distant metastases including intra-abdominal and/or inguinal lymph node

Grade 1	5% or less of a nonsquamous or nonmorular solid growth pattern
Grade 2	6-50% of a nonsquamous or nonmorular solid growth pattern
Grade 3	More than 50% of a nonsquamous or nonmorular solid growth pattern

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Treatment Factors	Low Risk	Intermediate Risk	High Risk
Stage	IA, G1 & 2	IA, G3 IB, IC (all grades) IIA, IIB (all grades) IIIA (+ cytology)	IIIA, IIIB, IIIC (all grades) IVA, IVB (all grades)
Postoperative treatment	None	Vaginal cuff rad Pelvic rad (questionable)	Vaginal cuff rad Pelvic rad Para-aortic rad (+ aortic nodes) Abdominal rad (intra-abdominal spread)

G = grade; rad = irradiation.
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randomized to postoperative observation or adjuvant pelvic radiation. In patients with grade 2 or 3 carcinomas, deep myometrial invasion or lymph-vascular space involvement, there was improved local control but no improvement in survival with whole pelvic external radiation versus observation alone; the preponderance of recurrences were at the vaginal apex

and could, therefore, be treated successfully with radiation at the time of recurrence. This suggests that early-stage, intermediate-risk endometrial cancer can be treated with TAH BSO and pelvic and para-aortic lymphadenectomy with intracavitary vaginal brachytherapy if the lymph nodes and adnexa are negative. Several authors have already published

data showing excellent results with this approach,^{6,7} thereby averting the morbidity of whole pelvic radiation when the nodes are negative. If no lymphadenectomy is performed, radiation is recommended for these intermediate-risk patients.

Patients with occult endocervical involvement can be treated with hysterectomy and complete surgical staging. Many of these patients will be found to have other high-risk factors and will require adjuvant pelvic or vaginal radiation. Patients with gross cervical involvement should be treated with radical hysterectomy or preoperative radiation followed by extrafascial hysterectomy and para-aortic lymphadenectomy.

Summary and Conclusions

As discussed in Part 1 of this article, endometrial carcinoma occurs primarily in postmenopausal women; patients generally present with abnormal uterine bleeding. Factors related to chronic estrogen exposure, including estrogen replacement

therapy (ERT), are associated with a higher incidence of the disease. Progestins given in combination with estrogens are protective against endometrial cancer, and the importance of complying with a hormone replacement therapy (HRT) regimen, as prescribed, should be stressed to patients. Because of apparent increased efficacy and compliance, clinicians should consider favoring the continuous combined progestin regimens over the cyclic regimens when the goal is reducing endometrial cancer risk.

Treatment is usually surgical and includes TAH BSO with evaluation of abdominal cytology. Pelvic and para-aortic lymph node sampling allows for individualized treatment in patients with intermediate risk factors, with either adjuvant whole pelvic irradiation or vaginal cuff brachytherapy. ■

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References

1. Creasman W, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer: A Gynecologic Oncology Group study. *Cancer* 1987; 60(Suppl 8):2035-41.
2. Abeler VM, Kjørstad KE. Endometrial adenocarcinoma in Norway: A study of a total population. *Cancer* 1991;67:3093-103.
3. American College of Obstetricians and Gynecologists. Endometrial cancer. ACOG technical bulletin no. 162. Washington, DC: American College of Obstetricians and Gynecologists, December 1991.
4. Kilgore LC, Partridge EE, Alvarez RD, et al. Adenocarcinoma of the endometrium: Survival comparisons of patients with and without pelvic node sampling. *Gynecol Oncol* 1995;56:29-33.
5. Roberts JA, Zaino R, Keys H, et al. A Phase III study of surgery vs. surgery plus adjuvant radiation therapy in intermediate risk endometrial adenocarcinoma. *Gynecol Oncol* 1998;68:135.
6. Anderson JM, Stea B, Hallum AV, et al. High-dose rate postoperative vaginal cuff irradiation alone for stage IB and IC endometrial cancer. *Int J Radiation Oncol Biol Phys* 2000;46(2):417-25.
7. Chadha M, Nanavati PJ, Liu P, et al. Patterns of failure in endometrial carcinoma stages IB grade 3 and IC patients with postoperative vaginal vault brachytherapy. *Gynecol Oncol* 1999;75(1):103-7.