

# Adjuvant High Dose Rate Vaginal Brachytherapy as Treatment of Stage I and II Endometrial Carcinoma

Neil S. Horowitz, MD, William A. Peters, III, MD, Michael R. Smith, MD,  
Charles W. Drescher, MD, Mary Atwood, and Timothy P. Mate, MD

**OBJECTIVE:** To evaluate the efficacy of high dose rate vaginal brachytherapy in the treatment of International Federation of Gynecology and Obstetrics stage IB, IC, and II endometrial carcinoma after surgical staging and complete lymphadenectomy.

**METHODS:** All patients with stage IB, IC, or II adenocarcinoma or adenosquamous carcinoma of the endometrium who received postoperative high dose rate vaginal brachytherapy at our institution between June 1, 1989, and June 1, 1999, were eligible. High dose rate vaginal brachytherapy was delivered in three fractions of 700 cGy. Retrospective chart review was performed. Kaplan-Meier estimates were calculated for disease-free and overall survival.

**RESULTS:** One hundred sixty-four women were identified. Fifty-six percent had stage IB disease, 30% had stage IC disease, and 14% had stage II disease. Approximately one third of patients had high-grade lesions and nearly 40% had deep myometrial invasion. Median follow-up was 65 months (range 6–142 months). To date, 14 patients have had recurrence; 2 at the vaginal apex, 9 at distant sites, 1 at the pelvic sidewall, 1 simultaneously in the pelvis and at a distant site, and 1 at an unknown site. Both patients with vaginal apex recurrences had salvage therapy and are now free of disease. The overall 5-year survival and disease-free survival rates were 87% and 90%, respectively. There were no Radiation Therapy Oncology Group grade 3 or 4 toxicities. High dose rate vaginal brachytherapy was approximately \$1,000 less expensive than external-beam whole-pelvic radiation.

**CONCLUSIONS:** Adjuvant high dose rate vaginal brachytherapy in thoroughly staged patients with intermediate-risk endometrial carcinoma provides excellent overall and disease-free survival with less toxicity and at less cost compared with whole-pelvic radiation. (Obstet Gynecol 2002;99:235–40. © 2002 by The American College of Obstetricians and Gynecologists.)

Endometrial carcinoma is the most common gynecologic malignant disease in the United States, with approxi-

mately 38,000 cases diagnosed annually.<sup>1</sup> Fortunately, disease is confined to the uterus in most patients. Nonetheless, approximately 6,400 patients are estimated to die of endometrial carcinoma in 2001.<sup>1</sup>

Women who have endometrial cancer with high-risk features or documented extrauterine disease require adjuvant therapy. Although irradiation has been the primary choice for adjuvant therapy, the precise mode of delivery is not clear and the role of chemotherapy is not established. There is little agreement on the effectiveness of adjuvant therapy in patients with intermediate-risk disease. However, a Gynecologic Oncology Group study of risk factors and outcome by Morrow et al<sup>2</sup> suggested that adjuvant radiation therapy could improve local and regional failure rates. However, the most appropriate technique for delivery of this adjuvant therapy was not given. With limited additional prospective data to guide physicians, practice opinions and patterns of care are diverse.

Surgically staged patients with disease limited to the uterus are at risk for recurrence, particularly at the vaginal apex. This risk is somewhat predictable by the grade of the tumor, the depth of myometrial invasion, and the presence or absence of lymphovascular space invasion or cervical involvement by tumor.<sup>2,3</sup> Although many vaginal recurrences are cured with secondary radiation therapy, that treatment carries a high rate of complications and few patients are left with a functional vagina. This morbidity could be avoided by a reduction in recurrences.

The efforts to reduce risk of vaginal or pelvic recurrences in patients with International Federation of Gynecology and Obstetrics (FIGO) stage I and II disease have included postoperative whole-pelvic irradiation. The Gynecologic Oncology Group performed a randomized clinical trial of whole-pelvic irradiation versus observation in this intermediate-risk group of patients.<sup>4</sup> Although the study has not yet been presented in final form, early analysis showed that recurrence was limited to the vagina in most patients who had recurrence in the

*From the Swedish Medical Center, Seattle, Washington, and Washington University Medical Center, St. Louis, Missouri.*

pelvis.<sup>4</sup> In an attempt to obtain better local and regional control without incurring the same morbidity as whole-pelvic irradiation, several authors have advocated the use of vaginal brachytherapy.<sup>5–10</sup> Given the potential benefits of this adjuvant therapy, it has been the practice at our institution to treat women with intermediate-risk endometrial carcinoma with high dose rate vaginal brachytherapy. To help clarify the proper treatment strategy for intermediate-risk endometrial carcinoma and to compare the efficacy of this approach with that of whole-pelvic irradiation, we report our experience with high dose rate vaginal brachytherapy.

## MATERIALS AND METHODS

After obtaining approval by the internal review board, we used the Swedish Medical Center Tumor Institute cancer registry to identify 397 women with endometrial carcinoma who underwent surgical staging and radiation therapy between June 1, 1989, and June 1, 1999. Surgical staging was defined as exploratory laparotomy, pelvic washings, total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy. Pelvic lymphadenectomy included bilateral removal of all nodal tissue and skeletonization of all vessels from the mid-portion of the common iliac artery to the circumflex vein, and from the psoas muscle laterally to the ureter medially to include the hypogastric artery and vein and the obturator fossa anterior to the obturator nerve. The para-aortic lymphadenectomy included removal of nodal tissue over the distal vena cava and aorta from the level of the inferior mesenteric artery to the mid-right and left common iliac artery, respectively. An adequate lymphadenectomy was defined as procurement of 12 or more lymph nodes. Pathology samples were evaluated in a routine manner by the Department of Surgical Pathology at Swedish Medical Center. A gynecologic pathologist reviewed the samples only when the diagnosis was controversial. The FIGO grading and staging systems were used to determine the grade and stage of disease. Patients were eligible if they had FIGO stage IB, IC, or II disease, a histologic subtype of adenocarcinoma, adenocarcinoma with squamous metaplasia, or adenosquamous carcinoma, and if they received high dose rate vaginal brachytherapy as their only adjuvant treatment.

High dose rate vaginal brachytherapy was given as three biweekly outpatient treatments using a vaginal applicator 2.0 to 3.0 cm in diameter and Ir<sup>192</sup>. Treatments began by the fourth postoperative week. A dose of 700 cGy given to a depth of 0.5 cm into the vaginal mucosa was administered with each treatment, for a total

**Table 1.** Demographic Characteristics of Study Patients

Characteristic	Patients (N = 164), n (%)
Age* (y)	
<51	19 (11.6)
51–60	41 (25.0)
61–70	60 (36.6)
≥71	44 (26.8)
Race	
White	154 (93)
Japanese	3 (2)
Black	2 (1.5)
Native American	2 (1.5)
Asian, not otherwise specified	3 (2)
Body weight† (lb)	
<150	68 (42)
150–199	56 (34)
200–299	24 (14)
≥300	2 (2)
Unknown	14 (8)
Pregnancy history	
Nulliparous	18 (11)
Multiparous	132 (80)
Unknown	14 (9)
Comorbid illness	
Hypertension	52 (32)
Diabetes	18 (11)

\* Median, 64 years (range 34–89 years).

† Median, 165 lb (range 102–341 lb).

dose of 2100 cGy. The proximal 5 cm of the vagina was treated.

For women who met the inclusion criteria, clinical charts were abstracted and disease status determined through the cancer registry or through correspondence with the patient's primary care physician. Kaplan–Meier estimates were calculated for overall survival and disease-free survival.

## RESULTS

Of the 397 women identified in the cancer registry, 164 met the study criteria. The remaining 233 patients were excluded for the following reasons: high-risk histology ( $n = 21$ ); inadequate lymphadenectomy ( $n = 23$ ); FIGO stage other than IB, IC, or II ( $n = 98$ ); and treatment other than vaginal brachytherapy ( $n = 91$ ). Of the 91 patients who received treatment other than vaginal brachytherapy, only 15 had stage IB to IIB disease. Table 1 shows demographic characteristics of the 164 women included in the study. As expected, adenocarcinoma was the most common histologic subtype in this patient group, accounting for 88% of all cases. Seventeen patients (10%) had adenocarcinoma with squamous metaplasia and 3 (2%) had adenosquamous carcinoma. Fifty-six percent of patients had FIGO stage IB disease,

**Table 2.** International Federation of Gynecology and Obstetrics Stages and Tumor Grades

Disease stage	Tumor grade ( <i>n</i> )			Total, <i>n</i> (%)
	1	2	3	
IB	15	47	31	93 (56)
IC	20	21	9	50 (30)
IIA	4	8	5	17 (10)
IIB	1	2	1	4 (4)
Total, <i>n</i> (%)	40 (24)	78 (47)	46 (29)	164

30% had stage IC disease, and 14% had stage II disease. Approximately one third of patients had a high-grade tumor, with 29% (*n* = 46) having grade 3 tumors (Table 2). Few women had lower uterine segment involvement (36%) or lymph vascular space invasion (14%) (Table 3).

Perioperative complications were limited to 14 patients (8%). Complications included minor vein injuries (*n* = 6), postoperative small-bowel obstruction (*n* = 3), superficial wound cellulitis or disruptions (*n* = 2), deep vein thrombosis (*n* = 1), pulmonary embolus (*n* = 1), and a minor bladder injury (*n* = 1), that was repaired at the time of surgery. Patient with a small-bowel obstruction required a repeated operation. Only one patient received a blood transfusion.

One hundred sixty-one patients (98%) received all three courses of high dose rate vaginal brachytherapy, and 3 patients received two of the three intended courses. The final application of high dose rate vaginal brachytherapy was withheld in two patients because of profuse watery vaginal discharge with irritation to the perianal skin. In the third patient, a severe bladder infection prevented completion of the full course of radiation. One patient had transient suprapubic deep pelvic pain with each treatment course, but no cause for this was discovered. No grade 3 or 4 cutaneous, gastrointestinal, or genitourinary toxicities occurred.

The median follow-up was 65 months (range 6–142 months). To date, 14 patients (8.5%) have had relapse. The median time to recurrence was 12 months (range 3–45 months). Of the 14 recurrences, 2 were found at the vaginal apex, 9 at a distant site only, 1 at the pelvic sidewall, 1 in both the pelvis and at a distant site simultaneously, and 1 at an unknown site (Table 4). Both patients who had recurrence at the vaginal apex had salvage therapy and they are alive without evidence of disease at 60 and 68 months from their recurrence (Table 5). The projected 5-year disease-free survival rate is 90% (Figure 1).

Fifteen patients died during the study, for an overall survival rate of 87% at 60 months (Figure 2). Seven patients died of recurrent endometrial carcinoma, and 8 died of intercurrent illness. The median time from recur-

rence to death was 6 months (range 0–31 months). No patient died of complications of therapy. When corrected for intercurrent deaths, the projected 5-year survival rate is 95%.

## DISCUSSION

There is consensus that patients with low-grade, noninvasive endometrial cancer should receive no further therapy, whereas those with extrauterine disease should receive external-beam irradiation or chemotherapy. However, in patients with intermediate-risk carcinoma, the ideal adjuvant therapy is not clear. To accurately determine risk category, patients must undergo thorough surgical staging, including complete lymphadenectomy.

In an attempt to clarify the value of adjuvant therapy in intermediate-risk endometrial carcinoma, the Gynecologic Oncology Group performed a phase III randomized study of surgery versus surgery plus adjuvant whole-pelvic radiation therapy given to a dose of 5040 cGy.<sup>4</sup> Patients with FIGO stage I or occult stage II disease who had undergone a complete surgical staging were eligible. The preliminary results suggested that adjuvant radiation significantly decreased the rate of pelvic recurrences but did not significantly affect survival. Treatment improved the disease-free interval but was associated with more frequent and more severe toxicities. Ten patients (5%) had grade 3 or 4 gastrointestinal toxicities, 6 (3%) had grade 3 or 4 gastrointestinal obstructions, and 6 (3%) had grade 3 or 4 cutaneous toxicities.<sup>4</sup> Although two patients in the treatment group

**Table 3.** Histopathologic Tumor Assessment

Finding	Patients ( <i>N</i> = 164), <i>n</i> (%)
Histologic examination	
Adenocarcinoma	144 (88)
Adenocarcinoma with squamous metaplasia	17 (10)
Adenosquamous carcinoma	3 (2)
Depth of invasion	
None	3 (2)
Inner one third	99 (61)
Middle one third	32 (19)
Outer one third	30 (18)
Lower uterine segment involvement	59 (36)
Lymph vascular space invasion	
Positive	23 (14)
Negative	131 (80)
Suspicious	6 (4)
Unknown	4 (2)

**Table 4.** Site and Frequency of Recurrence in the Current Study and Gynecologic Oncology Group Protocol 99

Recurrence site	Current study: high dose rate vaginal brachytherapy (N = 164), n (%)	Gynecologic Oncology Group Protocol 99	
		Surgery only (n = 202), n (%)	Surgery + whole-pelvic radiation (n = 190), n (%)
Vagina	2 (1)	13 (9)	2 (1)
Pelvis	1 (<1)	5 (2)	1 (<1)
Distant	9 (5.5)	9 (4.4)	10 (5)
Pelvis and distant	1 (<1)	4 (2)	0 (0)
Unknown	1 (<1)	0 (0)	0 (0)
Total	14 (8)	31 (15)	13 (6.8)

died, neither patient received radiation therapy; they were included on an intention-to-treat basis.

In light of the toxicities associated with adjuvant therapy and its questionable survival benefits, the role of adjuvant therapy for patients with intermediate-risk disease remained unclear, a fact that a recent survey of the members of the Society of Gynecologic Oncologists highlighted.<sup>11</sup> Of the members familiar with the results of Gynecologic Oncology Group protocol 99, approximately 20% were more likely and 27% less likely to use adjuvant radiation therapy on the basis of the results of the study. The type of adjuvant therapy used by the members varied depending on the grade and stage of the disease and whether the patient had had complete staging. For patients with stage IB or IC disease of any grade, approximately 15% to 25% of respondents used adjuvant vaginal brachytherapy. Whole-pelvic radiation was reserved primarily for patients with stage IB grade 3 or stage IC disease; roughly 30% to 45% of members used this adjuvant therapy. Of note, 20% to 30% of members offered combination vaginal brachytherapy and whole-pelvic radiation to treat intermediate-risk patients. When patients had not undergone a thorough surgical staging, the percentage of members recommending adjuvant ra-

diation increased to approximately 60%. Similarly, in the National Comprehensive Cancer Network practice guidelines for endometrial carcinoma, treatment options for intermediate-risk endometrial carcinoma included observation, vaginal brachytherapy, or pelvic radiation with or without vaginal brachytherapy.<sup>12</sup>

In our study, in which use of adjuvant therapy was limited to high dose rate vaginal brachytherapy, overall survival and disease-free survival rates were similar to those reported in Gynecologic Oncology Group protocol 99. Overall, the patients in our study and those in Gynecologic Oncology Group protocol 99 are similar; equal percentages of patients with FIGO stage IB (56% vs 57.9%) and IC (30% vs 32.6%) disease were included. However, our study included more patients with FIGO stage II (14% vs 9.5%), and more with grade 2 (47% vs 38.9%) and grade 3 (29% vs 15.3%) tumors. Although we used only adjuvant vaginal brachytherapy in our equally "at risk" group, we achieved a similar recurrence rate as Gynecologic Oncology Group protocol 99 (Table 4). Most recurrences in both studies occurred at distant sites, raising the question of whether systemic therapy is needed to ultimately improve overall survival.

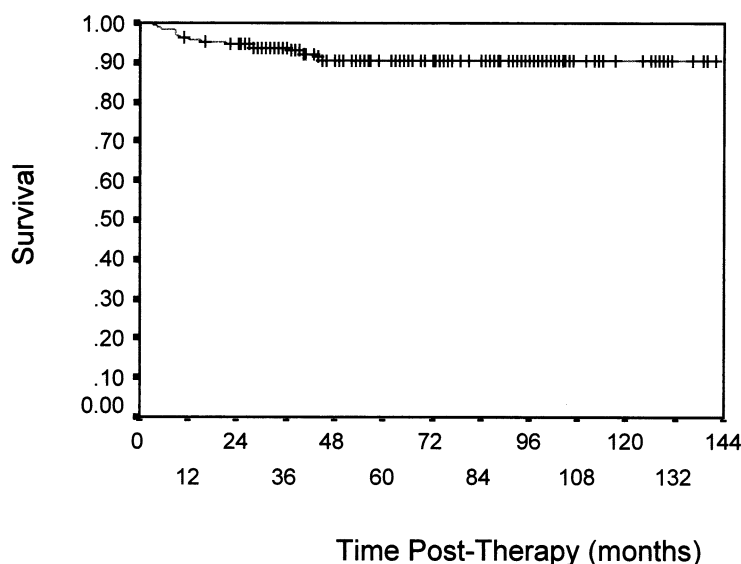
The favorable results that we obtained with vaginal

**Table 5.** Stage of Disease Groups, Grade, Depth of Invasion, Site of Recurrence, and Outcome in Patients With Recurrence After High Dose Rate Vaginal Brachytherapy

Stage	Grade	Depth of invasion	Site of recurrence	Outcome
IB	1	Inner one third	Bilateral inguinal lymph nodes	Died of disease
IB	3	Inner one third	Omentum, terminal ileum	Died of disease
IB	2	Middle one third	Carcinomatosis	Died of disease
IB	2	Inner one third	Suburethral	Alive, no evidence of disease
IC	3	Outer one third	Liver, peritoneum	Alive with disease
IC	2	Outer one third	Vagina	Alive, no evidence of disease
IC	3	Outer one third	Lung	Alive with disease
IC	3	Middle one third	Spine T5 level, bone	Died of disease
IC	2	Outer one third	Pelvic sidewall	Died of disease
IC	1	Middle one third	Pelvic sidewall, lung	Died of disease
IC	1	Middle one third	Unknown	Died of disease
IC	2	Outer one third	Left tibia, lung	Alive with disease
IC	3	Middle one third	Lung	Died of disease
IIIB	3	Inner one third	Vaginal cuff	Alive, no evidence of disease

**Figure 1.** Rates of disease-free survival in patients with intermediate-risk endometrial carcinoma treated with high dose rate vaginal brachytherapy.

Horowitz. *Adjuvant Vaginal Brachytherapy*. *Obstet Gynecol* 2002.



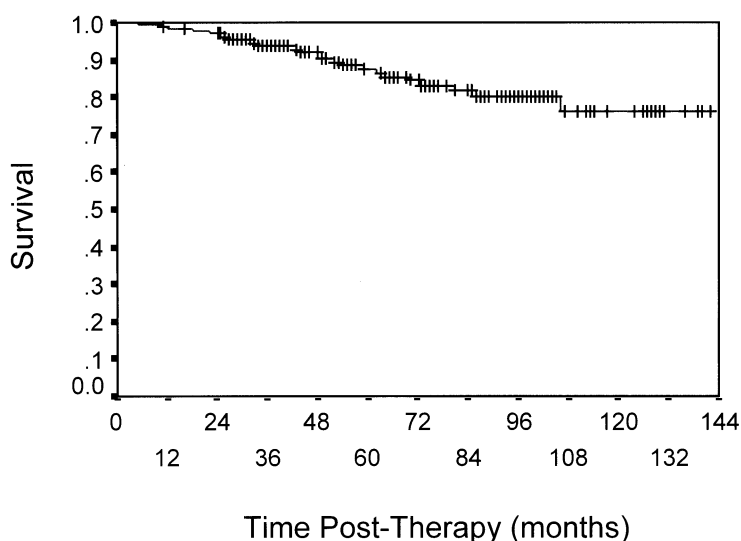
vault brachytherapy are similar to those in other recent reports. In a series of approximately 160 patients with stage IA, IB, and IC endometrial adenocarcinoma treated with total abdominal hysterectomy, bilateral salpingo-oophorectomy, full pelvic lymphadenectomy, and adjuvant vaginal brachytherapy, Mohan et al<sup>13</sup> found 15-year overall and disease-free survival rates of 98% and 94%, respectively. This treatment was associated with a 13% rate of moderate to severe morbidity and a 4.4% recurrence rate. Although these findings are slightly better than our results, the differences may be related to the number of grade 1, stage IA patients and lack of stage II patients in the study by Mohan et al. Chadha et al<sup>8</sup> and Ng et al<sup>14</sup> also reported success with vaginal brachytherapy; overall and disease-free survival

rates were 93% and 94% and 87% and 82%, respectively, for patients with FIGO stage IB grade 3 and IC endometrial carcinoma treated with postoperative high-dose and low-dose vaginal vault brachytherapy. Chadha et al observed no vaginal or pelvic recurrences, whereas Ng et al observed eight local or regional recurrences (five in the lower two thirds of the vagina outside of the radiation field). Seven of these eight recurrences were treated with salvage therapy, consisting of additional radiation therapy or surgery. Our study, in conjunction with others, adds to the growing body of literature suggesting that vaginal vault brachytherapy is equivalent to whole-pelvic radiation in reducing local recurrences and increasing disease-free survival.

We found that high dose rate vaginal brachytherapy is

**Figure 2.** Overall survival rate in patients with intermediate-risk endometrial carcinoma treated with high dose rate vaginal brachytherapy.

Horowitz. *Adjuvant Vaginal Brachytherapy*. *Obstet Gynecol* 2002.



well tolerated. The three patients who did not complete therapy did not do so because of grade 3 or 4 gastrointestinal, genitourinary, or cutaneous toxicities. In contrast, the whole-pelvic radiation therapy used in Gynecology Oncology Group protocol 99 was associated with more frequent and more severe toxicities. In addition, because high dose rate vaginal brachytherapy can be delivered over a very short time (approximately 10 minutes per treatment) and only three treatments are required, it is convenient. We did not formally address sexual function after high dose rate vaginal brachytherapy; however, follow-up examinations did not indicate compromised vaginal length or pliability that would have resulted in decreased function.

Using Medicare relative value units (RVU) as a means of comparison, a standard treatment regimen of external-beam whole-pelvic radiation to a dose of 5040 cGy given over 28 cycles is roughly 95 RVUs. The high dose rate vaginal brachytherapy regimen in our study was 71.4 RVUs. Reimbursement per RVU varies across the United States; in our area, reimbursement is approximately \$38 to \$42 per RVU. Thus, the cost of external beam therapy (\$3600–\$4000) is approximately \$1000 more than high dose rate vaginal brachytherapy (\$2700–\$3000).

Although the correct adjuvant treatment regimen for patients with intermediate-risk endometrial carcinoma remains controversial, we believe that high dose rate vaginal brachytherapy provides equivalent overall survival and disease-free survival with less toxicity and less cost compared with whole-pelvic radiation therapy. This treatment strategy is only applicable if a patient has had complete staging, including complete lymphadenectomy. On the basis of these results, future randomized trials assessing the role of adjuvant therapy should include a treatment arm of high dose rate vaginal brachytherapy.

## REFERENCES

- Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. *CA Cancer J Clin* 2001;51:15–36.
- Morrow CP, Bundy BN, Kurman RJ, Creasman WT, Heller P, Homesley HD, Graham JE. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: A Gynecologic Oncology Group study. *Gynecol Oncol* 1991;40:55–65.
- Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer (a Gynecologic Oncology Group Study). *Cancer* 1987;60(8 Suppl):2033–41.
- Roberts JA, Brunetto VL, Keys HM, Zaino R, Spirtos NM, Bloss JD, et al. A phase III randomized study of surgery versus surgery plus adjuvant radiation therapy in intermediate-risk endometrial adenocarcinoma (GOG 99) [abstract]. In: Abstracts of the 29th Annual Meeting of the Society of Gynecologic Oncologists 1998;35:70.
- Macleod C, Fowler A, Duval P, et al. High dose rate brachytherapy alone post-hysterectomy for endometrial carcinoma. *Int J Radiation Oncology Biol Phys* 1998;42:1033–9.
- Anderson JM, Stea B, Hallum AV, Rogoff E, Childers J. High dose rate postoperative vaginal cuff irradiation alone for Stage IB and IC endometrial cancer. *Int J Radiation Oncology Biol Phys* 2000;46:417–25.
- Weiss E, Hirnle P, Arnold-Bofinger H, Hess CF, Bamberg M. Adjuvant vaginal high dose rate afterloading alone in endometrial carcinoma: Patterns of relapse and side effects following low dose therapy. *Gynecol Oncol* 1998;71:72–6.
- Chadha M, Nanavati PJ, Liu P, Fanning J, Jacobs A. Patterns of failure in endometrial carcinoma stage IB grade 3 and IC patients treated with postoperative vaginal vault brachytherapy. *Gynecol Oncol* 1999;75:103–7.
- Marchetti DC, Piver MS, Tsukada Y, Reese P. Prevention of vaginal recurrence of stage I endometrial adenocarcinoma with postoperative vaginal radiation. *Obstet Gynecol* 1986;67:399–402.
- Moss WT, Brand WN, Battifora H, eds. *Radiation oncology—Rationale, technique, results*. 5th ed. St. Louis: Mosby, 1979.
- Naumann RW, Higgins RV, Hall JB. The use of adjuvant radiation therapy by members of the Society of Gynecologic Oncologists. *Gynecol Oncol* 1999;75:4–9.
- Teng N, Greer B, Kapp D, Kavanagh J, Koh WJ. National Comprehensive Cancer Network Practice Guidelines for Endometrial Carcinoma. *NCCN Proceedings. Oncology* 1999;13:45–67.
- Mohan DS, Samuels MA, Selim MA, Shalodi AD, Ellis RJ, Samuels JR, et al. Long-term outcomes of therapeutic pelvic lymphadenectomy for stage I endometrial adenocarcinoma. *Gynecol Oncol* 1998;70:165–71.
- Ng TY, Perrin LC, Nicklin JL, Cheuk R, Crandon AJ. Local recurrence in high-risk node-negative stage I endometrial carcinoma treated with postoperative vaginal vault brachytherapy. *Gynecol Oncol* 2000;79:490–4.

Address reprint requests to: Neil S. Horowitz, MD, Washington University Medical Center, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, 4911 Barnes Jewish Hospital Plaza, St. Louis, MO 63110; E-mail: horowitzn@msnotes.wustl.edu.

Received May 15, 2001. Received in revised form September 18, 2001. Accepted September 24, 2001.