Gynecologic Oncology **74,** 416–422 (1999)
Article ID gyno.1999.5487, available online at http://www.idealibrary.com on IDEAL®

Interstitial Brachytherapy for Vaginal Recurrences of Endometrial Carcinoma

Krishnansu Tewari, M.D.,* Fabio Cappuccini, M.D.,* Wendy R. Brewster, M.D.,† Philip J. DiSaia, M.D.,* Michael L. Berman, M.D.,* Alberto Manetta, M.D.,* Ajmel Puthawala, M.D.,‡ A. M. Nisar Syed, M.D.,‡ and Matthew F. Kohler, M.D.*,[1]

**Division of Gynecologic Oncology, University of California, Irvine–Medical Center, 101 The City Drive, Orange, California 92868; †Department of Epidemiology and Biostatistics, University of California, Irvine, Irvine, California 92697; and ‡Department of Radiation Oncology, Long Beach Memorial Medical Center, 2801 Atlantic Avenue, Long Beach, California 90806*

Received January 22, 1999

Objective. **The aim of this study was to evaluate the efficacy of interstitial brachytherapy in the management of vaginal recurrences of endometrial carcinoma.**

Methods. **Thirty patients received interstitial irradiation, with or without external beam radiotherapy. They were followed for a minimum of 5 years or until death.**

Results. **The median age was 66 years at initial diagnosis of endometrial cancer. FIGO stages included Stage I ($n = 18$), Stage II ($n = 7$), and Stage III ($n = 5$). All patients were treated originally by total abdominal hysterectomy and bilateral salpingo-oophorectomy, with or without lymphadenectomy, and 13 (43%) also received postoperative adjuvant whole pelvis radiotherapy as part of their primary treatment. Vaginal recurrences were diagnosed at a mean interval of 29 months after hysterectomy (range, 3–119 months). No patient had clinical evidence of pelvic sidewall extension or of distant metastatic disease. All patients were treated with interstitial brachytherapy; each implant delivered a mean maximal tumor dose of 25.5 Gy. Eighteen patients (60%) also received external beam radiotherapy (mean dose, 48 Gy) as part of their treatment for vaginal recurrence. Twenty-eight patients (93%) experienced a complete clinical response. Ten patients relapsed in the vagina ($n = 5$) or at distant sites ($n = 5$). Eleven patients are dead of disease. From the time of vaginal recurrence, the median overall survival was 60 months and the cause of death adjusted 5-year survival rate was 65%. Major morbidity included radiation proctitis ($n = 2$), fistula ($n = 2$), and radiation stricture ($n = 1$).**

Conclusion. **Interstitial irradiation resulted in favorable local control as well as a 5-year survival rate and morbidity comparable to that reported previously for conventional brachytherapy.** **© 1999 Academic Press**

Key Words: **endometrial cancer; vaginal recurrence; interstitial brachytherapy.**

INTRODUCTION

Although the majority of women with endometrial cancers are diagnosed at an early stage and are thus highly curable, there nonetheless remains a subset of patients who will fail primary therapy and present with recurrent disease. Historically, the vagina has been a common site of recurrence in endometrial carcinoma, with some older series reporting 8–15% vaginal recurrence rates after total abdominal hysterectomy and bilateral salpingo-oophorectomy [1, 2]. Although the selective use of perioperative adjuvant radiation based on a thorough surgical–pathologic evaluation may reduce vaginal recurrence, the problem is not eliminated, as evidenced by an overall 2% rate of isolated vaginal recurrence which persisted in the 1991 Gynecologic Oncology Group evaluation of 895 patients who were prospectively surgically staged [3].

Early investigators suggested both prophylactic treatment for patients at high risk for recurrent disease and various treatment strategies for those who do relapse. In 1929, Joe Vincent Meigs observed a very poor survivorship among patients with vaginal recurrences, despite regression of the vaginal lesion following therapy [4]. In 1958, Felix Noah Rutledge advised prophylactic irradiation of the vagina with a Bloedorn applicator following hysterectomy [5]. Theoretically, this would obliterate potential metastatic channels and sterilize existing microscopic vaginal disease (if present), lowering the risk of vaginal recurrence. In 1961 Alexander Brunschwig described a radical surgical approach to vault recurrences (e.g., pelvic exenteration); however, morbidity was high and only 28% of patients were alive at 5 years [6].

Given that the morbidity of surgical salvage may be substantial [6, 7] and that chemotherapy in this setting is rarely curative [8, 9], most therapeutic approaches for patients with isolated vaginal recurrences employ one of various radiotherapeutic techniques. Historically, this has consisted of external beam radiotherapy, usually followed by intracavitary brachytherapy in the form of vaginal cylinders or ovoids. Unfortu-

[1] To whom correspondence should be addressed at Department of Obstetrics and Gynecology, Medical University of South Carolina, 171 Ashley Avenue, Charleston, SC 29425-2233. Fax: (843) 792-0533.

0090-8258/99 $30.00

nately, correct placement of these brachytherapy devices, and hence dosimetry, is frequently compromised by tumor volume and the postsurgical absence of the uterus. Using these standard techniques, multiple series in the literature report 5-year salvage rates in patients with vaginal recurrence of 20–60% [4, 10–23]. For those patients who relapse after treatment of their vaginal recurrence, the development of distant metastatic disease remains a stubbornly common feature that awaits the development of effective systemic adjuvant treatment. However, the need for improved brachytherapy techniques is also suggested by the fact that as many as 20 to 40% of patients treated for vaginal recurrence do not achieve local control of their tumor [1].

In recognition of the limitations of conventional brachytherapy, the Department of Radiation Oncology and the Gynecologic Oncology Division at the University of California, Irvine, began employing interstitial irradiation in the treatment of patients with vaginal recurrence of endometrial cancer in 1979. Interstitial brachytherapy may allow for a more precise application of radiation directly to the tumor, resulting in a homogeneous radiation field with potential sparing of the bladder and rectum. This may result in improved dosimetry compared with intracavitary techniques, particularly for deeply infiltrating tumors and bulky recurrences with complex geometries. Interstitial irradiation techniques were reintroduced by Syed and co-workers in the early 1980s for the management of gynecologic cancer [24, 25], but have only rarely been reported in the treatment of vaginal recurrences [26, 27].

The work about to be described is a summary to date of our experience in managing vaginal recurrences of endometrial carcinoma with interstitial irradiation.

MATERIALS AND METHODS

In order to identify patients treated with interstitial brachytherapy for vaginal recurrences of endometrial cancer, we reviewed the tumor registry abstracts and radiation oncology log books of the University of California, Irvine–Medical Center and Long Beach Memorial Medical Center. During the study period between 1979 and 1991, 488 patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy with or without pelvic lymph node sampling for primary endometrial cancer. Twenty-two of these patients (4.5%) experienced a vaginal recurrence in the absence of pelvic sidewall or distant metastatic disease.[2] In addition, 8 patients underwent primary surgical management for endometrial cancer elsewhere and were referred in for treatment of their vaginal recurrence. Thus a total of 30 patients received interstitial brachytherapy for treatment of vaginal recurrences and comprise the clinical material of this retrospective study.

The primary tumor profiles are recorded in Table 1. The median age at the time of primary diagnosis was 66 years, with a range of 45 to 81 years. FIGO surgical stage was retroactively assigned and 40% of the study population had evidence of extrauterine spread at the time of primary diagnosis. This may in fact be an underestimate, since particularly in the early years or in patients who had their hysterectomy in an outside hospital, surgical staging may not have been as rigorous as currently advocated.

TABLE 1
Primary Tumor Characteristics

Number of patients	30
FIGO stage distribution	
IA	3
IB	7
IC	8
IIA	3
IIB	4
IIIA	2
IIIB	2
IIIC	1
Cell type	
Adenocarcinoma	21
Papillary serous	6
Adenosquamous	2
Clear cell	1
Histologic grade	
I	8
II	12
III	10
Surgery	
TAH-BSO, staging	22
TAH-BSO	8
Postoperative external beam radiotherapy	
Yes	13
No	17

Note. TAH-BSO, total abdominal hysterectomy and bilateral salpingo-oophorectomy.

The majority of the lesions were adenocarcinomas ($n = 21$), but uterine papillary serous ($n = 6$), adenosquamous ($n = 2$), and clear cell ($n = 1$) carcinomas were also observed. The grade distribution included grade I ($n = 8$), grade II ($n = 12$), and grade III ($n = 10$). Thirteen patients (43%) had previously received postoperative prophylactic external beam radiation therapy, secondary to high-risk factors.

In addition to biopsy-confirmation of vaginal recurrence, all patients underwent detailed pelvic examination, cystoscopy, proctosigmoidoscopy or barium enema, computed axial tomography of the pelvis and abdomen, and chest radiography.

External beam radiotherapy was first administered via a linear accelerator to 17 previously unirradiated patients and to 1 patient who had received radiotherapy 10 years earlier but showed minimal evidence of radiation change. Using anterior and posterior parallel opposed pelvic portals, radiation was generally delivered over a 28-day period at a dose of 1.8 Gy per day, 5 days per week, for a mean dose of 48 Gy.

[2] During the study period, three patients were diagnosed with vaginal recurrences in conjunction with distant metastases and did not receive interstitial irradiation. Thus, they have been excluded from the present series.

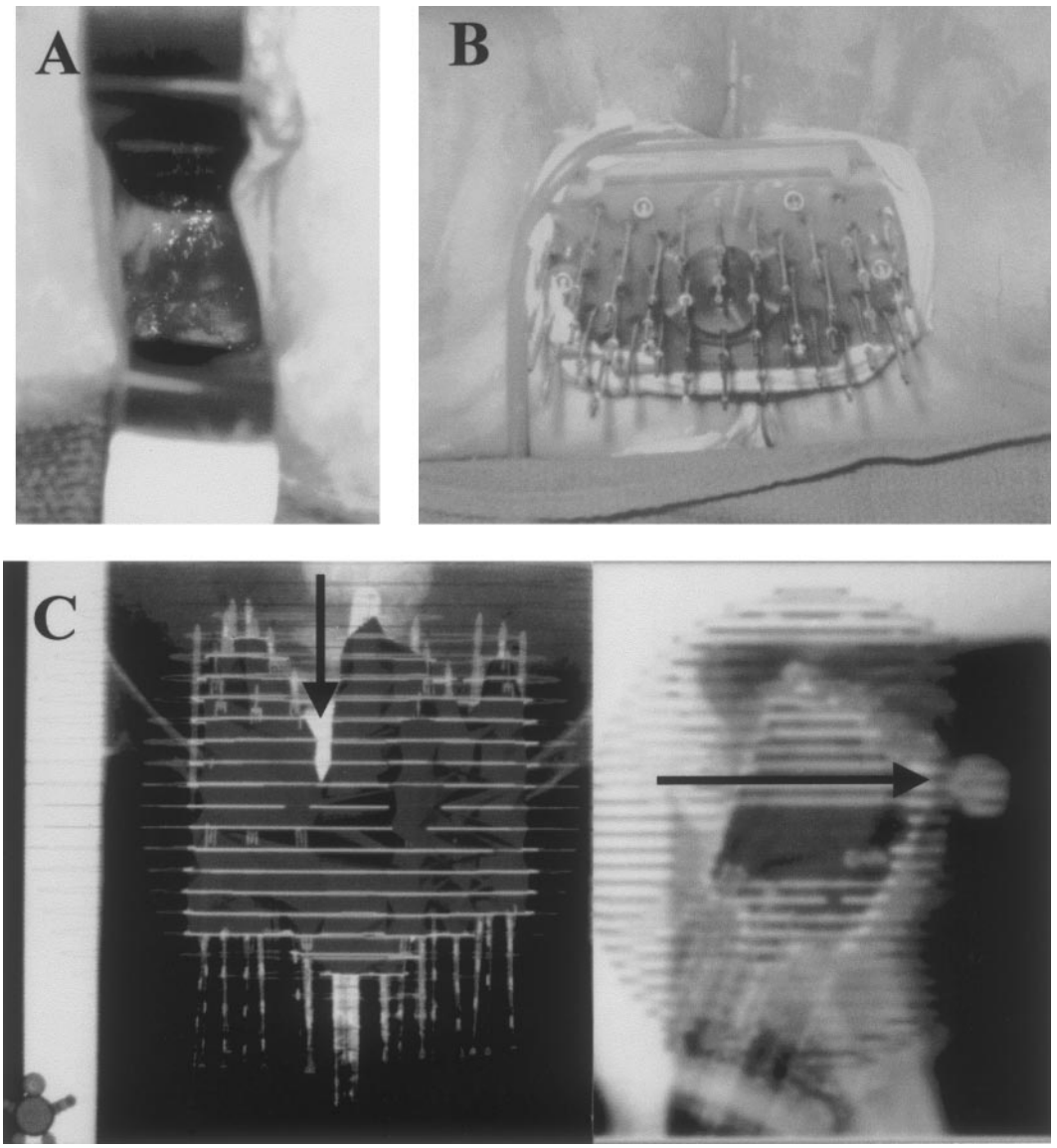

FIG. 1. A. Vaginal vault recurrence, measuring 3 × 2 cm, occurring 4 years after hysterectomy for a Stage I adenocarcinoma of the endometrium. B. Interstitial implant created with the Syed–Neblett dedicated vaginal template and 17-gauge stainless steel hollow guide needles. C. Anterior and lateral localization films demonstrating the position of the needles, with overlay of the computer-generated isodose curve (ROC Program Module). Arrows delineate the rectum (anterior view) and Foley catheter balloon (lateral view), which are filled with radio-opaque contrast material.

All 30 patients with vaginal recurrence were treated with interstitial brachytherapy. Using a Syed–Neblett dedicated vaginal template (Figs. 1A and 1B), implants were placed transperineally, most employing epidural analgesia. Multiple 17-gauge stainless steel guide needles were inserted through the template, into the tumor-bearing regions of the vaginal vault. The implants were individualized with respect to the number of guide needles and depth of insertion.

X-ray localization films with inactive dummy sources were next obtained, followed by computerized dose distribution plotting and volume analysis using the ROC Program Module (Fig. 1C). The placement of radio-opaque contrast material in the rectum and Foley catheter balloon permitted calculation of the radiation dose that would be received by the rectum and bladder. Radioactive iridium-192 seeds, spaced 1 cm apart in plastic ribbons, were afterloaded into the guide needles and left in place for a mean interval of 42 h. The prescription dose of minimum radiation was delivered to the perimetry of the radiated field. Regions encompassed by the isodose curves received a higher dose of radiation.

Ten patients received interstitial brachytherapy in conjunction with laparotomy, which permitted the size and extent of recurrent disease to be more precisely determined. There were no cases of extensive disease discovered at the time of lapa-

rotomy which would have necessitated aborting the "open" implant procedure in patients treated by this technique for vaginal recurrence. Bowel and bladder adhesions to the tumor were separated surgically and the guide needles were placed through the perineal template into the entire lesion under direct vision and palpation. An omental pedicle graft was always interposed between the tumor and the bladder and rectum, thereby preventing small bowel loops from adhering to the implant site and providing a new blood supply to the area to be irradiated. In addition, marker seeds were used to facilitate dosimetry planning and optimal needle placement of a second implant procedure when required (see below). This open implant approach was adopted in the later years of the study period [28, 29].

In order to deliver an optimal total dose of interstitial radiation, a second implant procedure was planned for patients with lesions larger than 2 cm in diameter ($n = 16$). In addition, six women with vaginal recurrences less than 2 cm in diameter also received a second interstitial implant secondary to the presence of significant macroscopic residual disease following the first procedure. This second application was performed 3 weeks after the first implant using the "closed" transperineal approach described above.

The mean maximal tumor dose delivered by each brachytherapy application was 25.5 Gy. The mean maximal total tumor dose was 85.8 Gy for 18 patients who received teletherapy plus interstitial brachytherapy for vaginal recurrence. The mean maximal total tumor dose was 98.5 Gy for 12 previously irradiated patients (mean dose, 47.7 Gy) who received interstitial irradiation only (mean dose, 50.8 Gy) for treatment of vaginal recurrence. The mean radiation dosages per implant received by the bladder and the rectum was 12.5 and 12.1 Gy, respectively. The mean total radiation dosages to the bladder were 60.5 Gy (teletherapy plus one implant) and 69.8 Gy (teletherapy plus two implants); the mean total radiation dosages to the rectum were 60.1 Gy (teletherapy plus one implant) and 69.2 Gy (teletherapy plus two implants).

Statistical methods employed for survival analysis included Kaplan–Meier Lifetable analysis and nonparametric univariate linear rank statistics using the Statistical Analysis Systems. A P value <0.05 was considered statistically significant. The survival rate was adjusted for cause of death from endometrial cancer and calculated at 5 years.

RESULTS

Vaginal Recurrences

Table 2 summarizes the characteristics of the vaginal recurrences. Vaginal relapses were diagnosed at a mean interval of 28.7 months following primary diagnosis, but an extraordinary range from 3 months to 10 years (i.e., 119 months) to recurrence was observed. The histologic grade distribution was not radically different from that of the primary uterine tumors.

TABLE 2
Vaginal Recurrence Characteristics

	Number of patients
Interval to recurrence	
0–12 months	10
13–24 months	10
25–36 months	3
37–60 months	2
>5 years	5
Size (largest diameter)	
>2 cm	14
2–3 cm	7
>3 cm	9
Location	
Apex alone	18
Apex and other vagina	12
Extent	
Vagina only	22
Vagina + parametria	8

Although there was a trend toward an inverse relationship between time to recurrence and histologic grade, with mean intervals to relapse of 45 months for Grade I (range, 9–119 months), 25 months for Grade II (range, 5–84 months) and 19 months for Grade III (range, 3–43 months), respectively, this was not statistically significant ($P = 0.149$). The cell types of the recurrent lesions were identical to those of the primary uterine malignancy.

Sixteen patients (53%) were symptomatic, presenting with vaginal bleeding or pain, while 14 patients (47%) were asymptomatic. Sixteen patients (53%) had lesions greater than 2 cm in diameter, and in 9 patients (30%), the lesions were larger than 3 cm in diameter. The majority of the lesions were confined to the vaginal apex, although 12 patients (40%) had extension of disease from the apex to more distal sites along the vaginal cylinder. There were no patients with *isolated* distal or suburethral vaginal recurrence.

Twenty-two patients (73%) had disease limited to the vaginal mucosa or submucosa only, while 8 patients (27%) had clinical evidence of parametrial involvement. No patient had evidence of pelvic sidewall disease or distant metastases.

Local Control

Twenty-eight patients (93%) experienced complete clinical resolution of the vaginal vault recurrence, i.e., a complete clinical response. Twenty-three of these patients maintained local control for a minimum of 5 years, while 5 patients suffered a second relapse within the vagina, at a median interval of 16 months (range, 7–48 months) following interstitial brachytherapy. Two patients experienced only a partial response to radiation therapy. Thus the 5-year local control rate for the study population was 77%.

Distant Metastases

Five patients who achieved and maintained a complete response in the vagina and pelvis failed at distant sites, relapsing at a median interval of 11 months (range, 2–54 months) following interstitial brachytherapy.

Survival

All patients have been followed for a minimum of 5 years or until death. A total of 11 patients are dead of disease, including the 2 patients who experienced only partial responses to interstitial brachytherapy, 4 of the 5 patients who developed a second vaginal recurrence, and all 5 patients who failed at distant sites. The 1 survivor of a second vaginal relapse was salvaged by an abdominal radical upper vaginectomy followed by treatment with a progestational agent (Megace) and remains disease free 96 months later.

The cause of death adjusted 5-year disease-free survival rate is 65% for the study population, with a median overall survival of 60 months following treatment with interstitial irradiation. This includes 10 of 16 patients (62%) with vaginal vault recurrences greater than 2 cm in diameter and 7 of 13 patients (54%) who had received prior radiotherapy. Two of 6 women with recurrent papillary serous endometrial carcinoma have been salvaged. Eight patients are dead of intercurrent disease, with mortality occurring beyond 5 years in each case.

Nonparametric univariate analyses were performed because of the small sample size. There was not a significant difference in median survival after vault recurrence as a function of previous radiotherapy, tumor grade (I vs II/III), interval to recurrence ($\leq$12 months vs $>$12 months), size of the recurrence ($\leq$3 cm vs $>$3 cm), or the use of the open implant technique. Kaplan–Meier Lifetable analysis was performed to evaluate differences in survival adjusting for cause of death from endometrial cancer and did not demonstrate a survival advantage based on the variables analyzed by univariate analysis.

TABLE 3
Radiotherapy for Vaginal Recurrences

Author	Year	*N*	F/U (years)	% Survival
Meigs [4]	1929	23	5	22
Javert [10]	1956	40	5	20
Rubin [11]	1963	15	5	20
Price [12]	1965	14	1–6	28
Brown [13]	1968	24	5	50
Badib [14]	1969	63	5	38
Ingersol [15]	1971	44	5	48
Phillips [16]	1982	54	5	33
Aalders [17]	1984	42	3–19	26
Greven [18]	1987	18	3–10	33
Curran [19]	1988	46	5	42
Poulsen [20]	1988	21	10	47
Kuten [21]	1989	17	4.8	40
Morgan [22]	1993	34	5	60
Pai [23]	1997	20	10	46

Sequelae of Therapy

All interstitial implants were well tolerated. The most common acute morbidities observed were urinary tract infection and transient fever. None of the patients who received interstitial brachytherapy in conjunction with a laparotomy experienced any significant acute morbidity (e.g., prolonged ileus, blood transfusion).

Significant long-term morbidity occurred in five patients (17%). Two patients who had received a total dose of 83.0 and 80.4 Gy to the rectum developed severe radiation proctitis. Both received a permanent descending end colostomy. An additional two previously irradiated patients who had received 49 and 39 Gy for vaginal recurrence by interstitial irradiation suffered a colovaginal fistula and a rectovaginal fistula, respectively. Neither patient was a candidate for colonic diversion as they experienced a second vaginal recurrence during the period of fistula diagnosis and subsequently expired from progressive disease; it is uncertain as to whether the fistulas resulted from radiotoxicity, tumor progression, or both. Finally, one patient who had received an open interstitial implant was subsequently explored for a large bowel obstruction; a radiation stricture of the sigmoid colon was discovered and treated without colonic diversion.

DISCUSSION

Although the prognosis for patients with endometrial cancer is generally good, there nonetheless exists a subset of patients who are at risk for treatment failure, recurrence, and death. In 1991, Lurain and co-workers from Northwestern Prentice Women's Hospital in Chicago studied 264 consecutive patients with clinical stage I endometrial carcinoma and identified several prognostic factors which may influence the risk of recurrence; these included advancing patient age, histopathology, tumor grade, lymph node status, nonnodal extrauterine disease spread, peritoneal cytology, and tumor size $>$2 cm [30]. However, the precise selection of patients for prophylactic postoperative radiation is frustrated by the fact that 30 to 50% of the vaginal recurrences in this and other studies originate in patients who should be considered "low risk" by virtue of superficial myometrial invasion, low histologic grade, and/or no extrauterine disease at the time of primary hysterectomy.

A number of theories have been advanced over the years to explain the pathogenesis of vaginal recurrence [31]. It has been speculated that neoplastic seeding (i.e., "spillage") at the time of hysterectomy may account for the development of vaginal apical recurrences, while retrograde spread via the rich network of lymphatics could account in particular for suburethral and distal vaginal recurrences. Still other investigators favor

TABLE 4
Vaginal Recurrences—Interstitial Series

Author	Year	*N*	F/U (years)	% Survival
Nag [26]	1997	15	5	65
Charra [27]	1998	34	5	56
Present	1999	30	5	65

venous dissemination over lymphatic spread as a mechanism of vaginal recurrence in endometrial cancer, since vaginal metastases are relatively uncommon in other cancers where lymphatic spread is common, such as carcinoma of the cervix. Indeed, other malignant neoplasms notorious for hematogenous metastases, such as choriocarcinoma and hypernephroma, often seed the vaginal wall.

An extensive literature has previously reported the salvage of patients with vaginal recurrence of endometrial cancer using external beam radiotherapy and conventional intracavitary brachytherapy and is listed in Table 3 [4, 10–23]. Survival rates at 5 or more years have ranged from 20 to 60%, with an average of approximately 37%. Morgan and colleagues have reported the only series with a 5-year survival in excess of 50%; one possible explanation may lie in the fact that nearly two-thirds of their patients had vaginal recurrences of less than 2 cm in diameter [22].

In contrast, only two institutions have previously reported the use of interstitial irradiation, either alone or in combination with external beam radiotherapy, in the management of isolated vaginal relapses of endometrial carcinoma. Nag and co-workers from the Arthur G. James Cancer Hospital in Ohio and Charra and colleagues from the Centre Hospitalier Lyon-Sud in France have reported 5-year survival rates of 68 and 56%, respectively [26, 27]. The present series updates this interstitial experience with a 5-year survival rate of 65% (Table 4). Comparisons of survival rates between Tables 3 and 4 must be made cautiously, as patient selection bias may have profoundly influenced the results in many of the series, including our own. In addition, it would appear that survival rates have increased with time (see Table 3), possibly reflecting a more detailed clinical and surgical evaluation both at initial diagnosis of endometrial carcinoma and at the time of vaginal recurrence.

The treatment-related complication rate of 17% which appears in the present analysis is comparable with complication rates previously reported for vaginal recurrences treated with external beam radiotherapy and conventional intracavitary brachytherapy. Series published from 1987 to 1993 which have contained 18 to 51 patients have documented severe complications in 10–16% of patients following treatment [18, 21, 22]. Although Pai and co-workers rescued fewer than 50% of patients utilizing modern high-dose-rate intracavitary brachytherapy, they observed a 25% acute complication rate and only one severe late complication attributable to radiotherapy in their series of 20 patients with vaginal recurrence [23]. As in the present series, there is a predominance of rectal and colonic toxicities distributed throughout these literatures.

The small number of patients in our study and many other published works often confounds the determination of important clinicopathologic features which influence survival following vaginal recurrence. However, some investigators have made noteworthy observations. In 1992, Podczaski and coworkers from Hershey Medical Center reported that the site of recurrence, time interval of surgery to recurrence, and use of postoperative pelvic radiotherapy were statistically related to patient prognosis [32]. In 1988, Curran and colleagues from the Fox Chase Cancer Center in Philadelphia applied a primary vaginal carcinoma staging system to vaginal recurrences of endometrial carcinoma and observed that a higher rate of pelvic control was observed for apical than for suburethral recurrences [19]. In many of the vaginal recurrence series previously cited, survival analyses often combined patients with both upper and distal vaginal relapses. Indeed, adjusting Ingersoll's data to consider only the 25 patients with apical vaginal recurrences, the 5-year survival rate increases from 48 to 64% [15]. Perhaps apical vaginal disease truly represents a different tumor biology than distal/suburethral vaginal recurrence.

It must be acknowledged that the patient population in our study is composed of a very select group. Specifically, all 30 patients underwent a thorough clinical and radiographic evaluation, which included a laparotomy in 10 patients. Thus, our group consisted of cases where disease was known with some certainty to be confined to the vagina or adjacent parametria. Patients with unrecognized extravaginal disease (e.g., pelvic sidewall disease, intra-abdominal metastases) may have contributed significantly to the relatively poor salvage rates reported in prior studies in the literature. Moreover, perhaps some failures of local radiotherapy for apparent isolated vaginal recurrences may relate to theories of vaginal recurrence which emphasize retrograde lymphatic and venous metastasis. In such cases, vaginal recurrence may represent just an external manifestation of a more ominous pelvic recurrence, because lymphatic spread and venous dissemination will probably not be restricted to the vagina.

Our data show that interstitial brachytherapy alone, or in combination with external beam radiation therapy, can effect long-term local control and cure in many patients who suffer vaginal recurrence of endometrial cancer. Whether such a treatment modality is superior to that of conventional intracavitary techniques is difficult to ascertain given the paucity of interstitial series in the literature and the highly selected nature of the present study's patient population. However, despite the fact that nearly half of the patients in our series were retreatments (i.e., 13 patients had previously received radiation therapy as part of adjunctive primary treatment), the cause of death adjusted survival rate of 65% reported here in this study of interstitial therapy was achieved with acceptable morbidity and

compares favorably with that of prior published series. This should prompt further study of this treatment modality.

REFERENCES

1. Moller LA, Engelholm SA: Treatment of vaginal recurrence in endometrial cancer: a review. Acta Obstet Gynecol Scand 75:1–7, 1996
2. Rotman M, Aziz H, Kuruvilla A: Vaginal recurrences in endometrial cancer. Int J Radiation Oncol Biol Phys 15:1043–1044, 1988
3. 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 40:55–65, 1991
4. Meigs JV: Adenocarcinoma of the fundus of the uterus: a report concerning the vaginal metastses of this tumor. N Engl J Med 201:155–160, 1929
5. Rutledge FN, Tan SK, Fletcher GH: Vaginal metastases from adenocarcinoma of the corpus uteri. Am J Obstet Gynecol 75:167–174, 1958
6. Brunschwig A: Surgical treatment of recurrent endometrial cancer. Obstet Gynecol 18:272–276, 1961
7. Barber HRK, Brunschwig A: Treatment and results of recurrent cancer of corpus uteri in patients receiving anterior and total pelvic exenteration: 1947–1963. Cancer 22:949–955, 1968
8. Burke TW, Stringer CA, Morris M, Freedman RS, Gershenson DM, Kavanagh JJ, Edwards CL: Prospective treatment of advanced or recurrent endometrial carcinoma with cisplatin, doxorubicin and cyclophosphamide. Gynecol Oncol 40:264–267, 1991
9. Pinelli DM, Fiorica JV, Roberts WS, Hoffman MS, Nicosia SV, Cavanagh D: Chemotherapy plus sequential hormonal therapy for advanced and recurrent endometrial carcinoma: a Phase II study. Gynecol Oncol 60: 462–467, 1996
10. Javert CT, Douglas RG: Treatment of endometrial adenocarcinoma; study of 381 cases at New York Hospital. Am J Roentgenol 75:508–515, 1956
11. Rubin P, Gerle RD, Quick RS, Greenlaw RH: Significance of vaginal recurrence in endometrial carcinoma. Am J Roentgenol 89:91–100, 1963
12. Price JJ, Hahn GA, Rominger CJ: Vaginal involvement in endometrial carcinoma. Am J Obstet Gynecol 91:1060–1065, 1965
13. Brown JB, Dockerty MB, Symmonds RE, Banner EA: Vaginal recurrence of endometrial carcinoma. Am J Obstet Gynecol 100:544–549, 1968
14. Badib AO, Kurohara SS, Beitia AA, Webster JH: Recurrent cancer of the corpus uteri: Techniques and results of treatment. Radiology 105:596–602, 1969
15. Ingersol FM: Vaginal recurrence of carcinoma of the corpus: management and prevention. Am J Surg 121:473–477, 1971
16. Phillips GL, Prem KA, Adcock LL, Twiggs LB: Vaginal recurrence of adenocarcinoma of the endometrium. Gynecol Oncol 13:323–328, 1982
17. Aalders JG, Abeler V, Kolstad P: Recurrent adenocarcinoma of the endometrium: a clinical and histopathological study of 379 patients. Gynecol Oncol 17:85–103, 1984
18. Greven K, Olds W: Isolated vaginal recurrences of endometrial adenocarcinoma and their management. Cancer 60:419–421, 1987
19. Curran WJ, Whittington R, Peters AJ, Fanning J: Vaginal recurrences of endometrial carcinoma: the prognostic value of staging by a primary vaginal carcinoma system. Int J Radiat Oncol Biol Phys 15:803–808, 1988
20. Poulsen MG, Roberts SJ: The salvage of recurrent endometrial carcinoma in the vagina and pelvis. Int J Radiat Oncol Biol Phys 15:809–813, 1988
21. Kuten A, Grigsby PW, Perez CA, Fineberg B, Garcia DM, Simpson JR: Results of radiotherapy in recurrent endometrial carcinoma: a retrospective analysis of 51 patients. Int J Radiat Oncol Biol Phys 17:29–34, 1989
22. Morgan JD, Reddy S, Sarin P, Yordan E, Degeest K, Hendrickson FR: Isolated vaginal recurrences of endometrial carcinoma. Radiology 189: 609–613, 1993
23. Pai HH, Souhami L, Clark BG, Roman T: Isolated vaginal recurrences in endometrial carcinoma: treatment results using high-dose-rate intracavitary brachytherapy and external beam radiotherapy. Gynecol Oncol 66: 300–307, 1997
24. Fleming P, Syed AMN, Neblett D, Puthawala A, George III FW, Townsend D: Description of an afterloading ^{192}Ir interstitial-intracavitary technique in the treatment of carcinoma of the vagina. Obstet Gynecol 55:525–530, 1980
25. Puthawala A, Syed AMN, Nalick R, McNamara C, DiSaia PJ: Integrated external and interstitial radiation therapy for primary carcinoma of the vagina. Obstet Gynecol 62:367–372, 1983
26. Nag S, Martinez-Monge R, Copeland LJ, Vacarello L, Lewandowski GS: Perineal template interstitial brachytherapy salvage for recurrent endometrial adenocarcinoma metastatic to the vagina. Gynecol Oncol 66:16–19, 1997
27. Charra C, Roy P, Coquard R, Romestaing P, Ardiet JM, Gerard JP: Outcome of treatment of upper third vaginal recurrences of cervical and endometrial carcinomas with interstitial brachytherapy. Int J Radiat Oncol Biol Phys 40:421–426, 1998
28. DiSaia PJ, Syed AMN, Puthawala AA: Malignant neoplasia of the upper vagina. Endocurie Hypertherm Oncol 6:251–256, 1990
29. Monk BJ, Walker JL, Tewari K, Ramsinghani NS, Syed AMN, DiSaia PJ: Open interstitial brachytherapy for the treatment of local–regional recurrences of uterine corpus and cervix cancer after primary surgery. Gynecol Oncol 52:222–228, 1994
30. Lurain JR, Rice BL, Rademaker AW, Poggensee LE, Schink JC, Miller DS: Prognostic factors associated with recurrence in clinical stage I adenocarcinoma of the endometrium. Obstet Gynecol 78:63–69, 1991
31. Way S: Vaginal metastases of carcinoma of the body of the uterus. J Obstet Gynecol Br Empire 58:558–572, 1951
32. Podczaski E, Kaminski P, Gurski K, MacNeill C, Stryker JA, Singapuri K, Hackett TE, Sorosky J, Zaino R: Detection and patterns of treatment failure in 300 consecutive cases of “early” endometrial cancer after primary surgery. Gynecol Oncol 47:323–327, 1992