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Open Interstitial Brachytherapy for the Treatment of Local-Regional Recurrences of Uterine Corpus and Cervix Cancer after Primary Surgery

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Patients who develop locally recurrent uterine corpus or uterine cervix cancer after primary surgery are usually treated with radiotherapy. The optimal radiotherapeutic approach, however, has not been defined. We report the use of exploratory laparotomy, omental pedicle grafting, and intraoperative transperineal interstitial brachytherapy in the treatment of 28 such patients (10 with recurrent corpus and 18 with recurrent cervix cancer). In addition, 22 patients also received perioperative whole pelvic teletherapy while 21 also received a second closed interstitial application. Local control was achieved in 20 patients (71%), but only 10 (36%) continue to be alive without disease after a median of 44 months. Eighteen patients have died (17 of disease) a median of 13 months after open implant. Patients treated with a single implant ($n = 7$), with side wall involvement ($n = 5$), with tumors greater than 6 cm in size ($n = 4$), with a history of previous pelvic irradiation ($n = 8$), or with persistent disease after open interstitial therapy ($n = 8$), were not salvaged. Ten patients suffered acute morbidity which included deep venous thrombosis ($n = 1$), wound separation ($n = 1$), urinary infection ($n = 2$), wound infection ($n = 2$), pneumonia ($n = 1$), and fever ($n = 3$). Two other patients experienced chronic non-tumor-related comorbidities. These included a vesicovaginal fistula with a rectovaginal fistula in 1 patient and a small bowel obstruction with a ureteral stricture in another. A single individual suffered from both acute and chronic complications (fever, ureterointestinal fistula). Although associated with modest morbidity, open interstitial brachytherapy allows for surgical exploration of the abdomen and more complete evaluation of the extent of disease as well as precise needle placement for those

with locally recurrent uterine malignancies. Whether these results are superior to those after intracavitary techniques in improving local tumor control and survival awaits prospective randomized study. © 1994 Academic Press, Inc.

INTRODUCTION

Although only 15% of women in the United States with uterine corpus cancer and 30% of women with uterine cervix cancer die from their disease, as many as 50% of these cases represent patients who develop recurrent cancer after definitive therapy for early-stage tumors [1-3]. The proportion of women with early-stage lesions is expected to increase as widespread cytologic screening for cervical cancer and frequent endometrial sampling for corpus cancer become more common, thus creating more individuals who are at risk for a recurrent malignancy. The optimal therapy for recurrent lesions after potentially curative therapy for early-stage disease has not been completely defined, but depends on such factors as the method of primary treatment, the site of recurrence, and the extent of disease. Patients who develop pelvic recurrences after primary surgical therapy are usually treated with radiation, while patients who develop local-regional recurrences after primary radiotherapy are usually treated with radical surgery. Interestingly, a few patients have also been salvaged after primary radiotherapy using re-irradiation with interstitial implants since this technique allows more precise dose localization and irradiation of smaller volumes thus theoretically improving disease control and decreasing radiation toxicity to normal tissue [4].

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Interstitial brachytherapy using transvaginal radium needles was first introduced by Abbe in 1913 as a method to treat carcinoma of the cervix [5]. This technique was later refined by Waterman [6] and then reintroduced by Syed and colleagues using a transperineal application in the late 1970's [7]. Syed developed a template to guide the insertion of the hollow needles into and around the lesion to deliver maximal doses to the tumor and minimal radiation to the surrounding normal tissue. He also described a method of after-loading the radioactive sources, thereby greatly decreasing radiation exposure to hospital personnel [7, 8]. Similar techniques have also been utilized in the treatment of vaginal malignancies. In 1983 Puthawala *et al.* reported on 27 patients with primary vaginal carcinoma who were treated with Syed's technique of interstitial brachytherapy. Local control was observed in 85% (23 of 27) with long-term disease-free survival of 50% [9].

The success achieved with cervical and vaginal cancers prompted our group to investigate whether interstitial radiotherapy may be effective in treating vaginal recurrences after primary surgery for uterine corpus and cervical cancer. This was thought to be particularly appropriate since the vaginal apex is often distorted by surgical changes or recurrent disease, resulting in poor geometry for intracavitary techniques. Furthermore, patients with extensive submucosal disease including those with paravaginal and pelvic extension are poor candidates for intracavitary therapy since adequate radiation doses cannot be delivered to the periphery of the tumor without excessive morbidity.

In 1990, DiSaia in collaboration with Drs. Syed and Puthawala described in detail a technique of "open implant" for recurrent cancer in the upper vagina following previous hysterectomy. Exploratory laparotomy at the time of the first implant was added to previously described techniques of interstitial brachytherapy [10].

The rationale for this treatment approach was based on four assumptions: (1) The size and extent of the recurrent disease could be more precisely determined at the time of laparotomy. (2) Bowel and bladder adhesions to the tumor could be separated surgically. (3) The after-loading ^{192}Ir implant guides could be precisely placed intraoperatively to the entire lesion utilizing direct vision and palpation. At times, the surgeon placing the needles could even avail himself of the advantage of having a hand in the pelvis while implanting the needles via the perineal template. (4) Finally, an omental pedicle graft could be interposed to separate the bladder and rectum from the tumor, thus functioning as bolus to prevent small bowel loops from adhering to the implant site. In addition, omental lengthening provided a new blood supply to the irradiated area in the anticipation that it would decrease complications.

We report the results of our first 28 patients treated with this technique of open interstitial brachytherapy.

MATERIALS AND METHODS

From 1984 through 1989, 28 patients were treated with open interstitial brachytherapy at UCI Medical Center and Long Beach Memorial Center. The median age was 60 years (range, 31–84). Ten patients had locally recurrent uterine corpus cancer and 18 recurrent uterine cervix cancer. All tumors were diagnosed by physical exam and vaginal biopsy during routine surveillance after primary surgical therapy. Computerized axial tomography or magnetic resonance imaging demonstrated all tumors to be limited to the pelvis. Patients with radiographic evidence of extrapelvic disease were excluded. Patients had been treated a median of 15 months (range, 2–300) previously with extrafascial or radical hysterectomy with ($n = 8$) or without ($n = 20$) postoperative radiation. Sixty-four percent (18 of 28) of the recurrences occurred in the first 2 years after surgery. Review of the primary lesions revealed that 16 of 18 patients with cervical cancer had squamous cell tumors, while one each had an adenocarcinoma of the endocervix and another neurosecretory small cell cancer. Fifteen of the patients with cervical cancer had previously undergone radical hysterectomy and pelvic lymphadenectomy (14 FIGO [2] Stage IB, 1 Stage IA₂). Two had previously been treated with extrafascial hysterectomy for microinvasive cancer (Stage IA₂) and another had unsuspected cervical cancer (Stage IB) diagnosed after abdominal extrafascial hysterectomy. All 10 patients with corpus cancer had disease limited to the uterus at surgical staging (1 FIGO [1] Stage IA, 4 Stage IB, 1 Stage IC, 1 Stage IIA, 3 Stage IIB). All uterine corpus malignancies were endometrioid adenocarcinomas except 2. A single patient had a clear cell cancer (Stage IA) and another a mixed mullerian carcinosarcoma (Stage IIB). All biopsies of recurrent disease were similar to the histology of the primary specimen. Eight of the 28 patients (29%), 4 with cervical cancer and 4 with corpus cancer, received adjunctive radiotherapy (7 whole-pelvic teletherapy, 1 intracavitary brachytherapy) in conjunction with primary hysterectomy.

The technique of open interstitial brachytherapy was according to DiSaia with only minor modifications [10]. Briefly, patients who had not previously received adjunctive radiation following surgery were treated with external radiation to the whole pelvis to 50 Gy with a midline block at 40 Gy prior to ($n = 10$) or after ($n = 12$) interstitial therapy. Anterior and posterior parallel opposed pelvic portals or the four-field box technique were used with 1.8 to 2.0 Gy per fraction, five radiotherapy fractions per week. Individuals with small lesions

FIG. 1. Transperineal interstitial brachytherapy at the time of laparotomy to recurrent cancer at the vaginal apex (from DiSaia *et al.* *Endocr. Hyper. Oncol.* 6, 251-256 (1990)).

received exploratory laparotomy and an interstitial implant before any external beam therapy as a preferred approach which allowed lysis of bowel adhesions in the pelvis while patients who had previously received radiotherapy usually did not receive teletherapy as part of their treatment ($n = 6$). However, upon review of the adjunctive radiation doses given after hysterectomy at other institutions, it was decided that two patients could be safely treated with 40 and 34 Gy of additional external beam radiation prior to or after interstitial brachytherapy, respectively.

The exploratory laparotomy was performed in the following manner. Small and large bowel adhesions within the pelvis were lysed so as to empty the pelvic basin of adherent loops of bowel. The apex of the vagina was then identified and the bladder and rectosigmoid dissected free from the usually adherent vaginal vault. The retroperitoneal lymph node bearing spaces were then examined for metastasis and selective pelvic and para-aortic node sampling performed at the discretion of the surgeon. Then using a Syed-Neblett Applicator, 17-gauge hollow guides, 20 cm in length were inserted by a second team of radiotherapists using a transperineal approach (Fig. 1). With direct vision and palpation, the needles were placed to encompass the full extent of the lesion with no more than 5 mm of the tip of each needle exposed beyond the level of the intraperitoneal tissue edge. The template was then secured and an omental pedicle ("carpet") placed to cover the operative site (Fig. 2) [11]. Following pelvic placement of the omental tissue, interrupted sutures were utilized to fix the pedicle in place. In a similar fashion,

the redundant rectosigmoid was sutured so as to fill the pelvic basin (Fig. 3). Postoperative computerized dose distribution plotting and volume analysis were obtained using localization X-ray films. Each of the perineal guides was then after-loaded with an appropriate number of ^{192}Ir seeds (5 to 10) spaced 1 cm apart in plastic ribbons. Depending on the thickness of the tumor, the central six guide needles usually had only 3 to 5 seeds placed to avoid rectal or bladder injury. The activity of each ^{192}Ir seed usually ranged from 0.25 to 0.35 mg Ra eq. After an optimal dose (2000 to 2500 cGy minimum tumor dose) was delivered, the sources and needles were removed and the patient was discharged after complete surgical recovery. Most commonly a second application was deemed necessary and thus was performed 3 weeks after the first implant ($n = 21$). Laparotomy was not necessary for the second application. Routinely two-thirds of the planned interstitial dose was delivered with the first application since needle placement was optimal.

RESULTS

At the time of exploratory laparotomy all patients had intraperitoneal adhesions. Three patients had inadvertent

FIG. 2. Development of omental carpet with transection of right gastroepiploic artery and placement along the descending colon into the pelvis (from DiSaia *et al.* *Endocr. Hyper. Oncol.* 6, 251-256 (1990)).

FIG. 3. Fixation of redundant rectosigmoid into the pelvis at the completion of open interstitial needle placement to prevent pelvic small bowel adhesions (from DiSaia, *Cancer* 48, 548-559 (1981)).

enterotomies during adhesion lysis which required repair without incident. No patient was noted to have gross intraperitoneal disease. Twenty-four patients (86%) in the study group had tumor with maximal dimensions less than 6 cm. Five patients (four of which with tumors greater than 6 cm) had disease adherent to the pelvic side wall. Two of these five patients underwent *en bloc* sigmoid resection with ^{125}I seeds placed into the tumor bed. A single patient with bulky disease adherent to the pelvic side wall also underwent a palliative colostomy for impending sigmoid obstruction secondary to extrinsic tumor compression while another patient was treated with intra-arterial cisplatin following the open implant. The fifth patient with side wall disease was treated with interstitial and external radiation alone. Finally, two patients had isolated para-aortic lymph node metastases. One of these patients received postoperative extended field radiation and the other patient with nodal metastases died 3 months after surgery from a rapidly progressive tumor. Seven others had lymph node sampling which was benign on histopathologic review. All patients underwent omental

lengthening with the formation of an omental carpet (Fig. 2) except one where it was not technically feasible. The median blood loss and operating time were 300 ml (range, 100-1200) and 2 hr and 40 min (range, 1:35-5:00), respectively, while the median hospital stay was 7 days (range, 5-27).

Ten patients (29%) suffered acute postoperative complications (Table 1) which included deep venous thrombosis ($n = 1$), superficial wound dehiscence ($n = 1$), and infectious morbidities ($n = 8$). Sources of infection included urine ($n = 2$), wound ($n = 2$), pneumonia ($n = 1$), and unknown ($n = 3$). All acute complications responded to appropriate therapy and were self-limited.

Four patients have suffered from chronic morbidity of which three were thought to be treatment related (Table 1). Two of these patients each suffered from two simultaneous long-term complications. One experienced a ureteral stricture and small bowel obstruction requiring bowel resection while another experienced both a vesicovaginal and a rectovaginal fistula. The former patient was treated with permanent ^{125}I seeds in addition to the temporary ^{192}Ir interstitial implant and has subsequently died of recurrent disease while the latter received two implants plus teletherapy and is alive without disease 45 months after surgery. A third patient had a ureterointestinal fistula after a single implant and postoperative teletherapy and has also died of disease. Finally, a single woman developed a vesicovaginal fistula related to a fatal pelvic recurrence.

Local control was achieved in 20 (71%) patients. All 8 patients with persistent disease at the completion of salvage therapy died of disease after a median of 7 months (range, 2-19). Nine patients (36%) developed a second recurrence after salvage open interstitial therapy either

TABLE 1
Acute and Chronic Non-Tumor-Related Morbidity of Open Interstitial Brachytherapy Stratified According to the Amount of Adjuvant Radiation

Morbidity	Second closed implant only	External beam only	External and second implant
Acute			
Infection	3 ^a	2 ^b , 1 ^a	2
Deep venous thrombosis		1 ^b	
Wound seroma		1 ^a	
Chronic			
Ureteral and small bowel obstruction		1	
Vesicovaginal and rectovaginal fistula			1
Ureterointestinal fistula	1 ^a		

^a Previous history of radiation as part of primary therapy.

^b Received external beam radiation before open implant.

TABLE 2

Radiation Used in Combination with Open Interstitial Brachytherapy for the Treatment of Local-Regional Recurrences of Uterine Corpus and Cervix Cancer Based on Size of Pelvic Recurrence (Disease Free/Total Treated)

Size of recurrent tumor	Second closed implant only	External beam only	External and second implant
<6 cm	0/5 ^a	0/6 ^b	10/13 ^c
>6 cm	0/1	0/1	0/2

^a Three endometrial, one cervical, one mixed mullerian.

^b Five cervical, one endometrial.

^c Eight cervical, five endometrial.

in the pelvis ($n = 5$) or at distant sites ($n = 4$). All patients who developed a second recurrence died a median of 19 months (range, 7–42) after exploratory laparotomy and open interstitial brachytherapy. Seven patients received only a single implant and 4 of these achieved local control (Table 2). However, all 7 patients died of disease with local failure in the pelvis. Reasons for not receiving a second implant included history of previous posthysterectomy radiation, distant disease identified outside of the pelvis, and morbidity related to the first application (i.e., small bowel obstruction). Moreover, none of the 8 patients who were treated with previous pelvic irradiation received both a second closed interstitial implant and external beam teletherapy in combination with an open implant and all have died of disease (Table 3).

Tumor size was a strong predictor of response and subsequent survival. Patients with maximal tumor dimensions exceeding 6 cm were not salvaged ($n = 4$), while 10 of 24 (42%) patients with tumors less than 6 cm are alive without evidence of disease a median of 44 months (range, 22–74) after open implant (Table 2). Dose intensity was also predictive of long-term survival (Table 3). All long-term disease-free survivors received a total dose of approximately 80 to 90 Gy to their recurrent tumor after teletherapy, open implant, and a second closed application. Patients treated with less intensity (a second implant alone or teletherapy alone in addition to open implant) were not successfully treated. Four patients with uterine malignancy (40%) and 6 patients with cervical cancer (33%) remain disease free. Thus, among those with small lesions (less than 6 cm) who were treated with full-dose radiotherapy (two implants and teletherapy), the durable response rate was 77% (10 of 13). It is noteworthy, however, that a single patient remained disease free until she died of a cerebral vascular accident 19 months after two implants without external radiation therapy. Finally, the patient who received intra-arterial chemotherapy died of disease at 15 months, while the patient

who was treated with extended radiotherapy is alive at 55 months without evidence of disease.

DISCUSSION

Most patients in the United States are treated surgically for early uterine corpus and early uterine cervical malignancies [1,2]. This allows radiotherapy to be used with curative intent should local recurrences occur. Among patients treated with radical hysterectomy for invasive cervical cancer, approximately 15% will relapse, with the majority of recurrences being in the pelvis where radiation may be effective [12]. Interstitial brachytherapy is ideal for such lesions since dose distribution can be optimized despite distorted anatomic geometry. We report the use of exploratory laparotomy and omental pedicle grafting with concomitant interstitial brachytherapy as a method to deliver maximal radiation to recurrent cancer at the apex of the vagina with minimal long-term morbidity.

The need for brachytherapy in treating patients with recurrent endometrial and recurrent cervical cancer has not been firmly established. Indeed patients have been salvaged with external irradiation alone [13–15]. Nevertheless, brachytherapy is currently recommended for vaginal recurrences since more favorable radiation doses can be delivered, thereby potentially increasing local control and survival [15–17]. The current study confirms the significance of dose intensity since only individuals receiving two implants in combination with teletherapy were salvaged. Whether interstitial implants improve survival over intracavity techniques, however, has not yet been studied in a prospective randomized fashion. The addition of exploratory laparotomy to interstitial implantation can potentially further improve salvage therapy but any benefit must be weighed against the added morbidity and expense of surgery.

The most significant advantage to open interstitial brachytherapy over more traditional intracavity brachytherapy in the treatment of locally recurrent uterine can-

TABLE 3

Radiation Used in Combination with Open Interstitial Brachytherapy Based on Previous History of Radiation Therapy (Disease Free/Total Treated)

Previous pelvic radiation	Second closed implant only	External beam only	External and second implant
Yes	0/6 ^a	0/2 ^b	0/0
No	0/0	0/5 ^c	10/15 ^d

^a Three endometrial, two cervical, one mixed mullerian.

^b Two cervical

^c Four cervical, one endometrial.

^d Ten cervical, five endometrial.

cer would be increased local control and theoretically prolonged survival. This may be achievable since the radioactive sources can be more precisely placed at the time of exploratory laparotomy in an attempt to optimize dosimetry; particularly when used for recurrent tumors extending into parametrial tissue. Furthermore, individuals found to have disease outside the pelvis at the time of surgical exploration (para-aortic nodes) may then have their therapy modified appropriately (i.e., extended field radiation or palliative care alone). Another theoretical advantage to this technique over the closed interstitial method would be a lower complication rate. This would be a result of more precise intraoperative needle placement and omental pedicle grafting, thus assuring that the bladder and bowel are not injured by needle insertion and subsequent interstitial irradiation.

It is difficult to compare the results of the current report to previously published series since sites of recurrence, tumor volume, and radiotherapeutic techniques vary greatly in the literature [13–20]. Indeed, one of the strengths of our case series is the uniformity with which patients were selected for treatment and the standardized treatment regimen. Despite these differences, our overall long-term cure rate of 36% compares favorably to the 15 to 50% disease-free survival of similar patients treated with other methods of salvage radiotherapy [13–20]. The results of the present review using open interstitial brachytherapy to treat recurrent cervix or corpus cancer may, however, be underrepresentative of the true efficacy of this technique since low-risk patients (less than 6 cm with no previous radiotherapy) have a long-term disease-free survival rate of 77%.

Complication rates are even more difficult to compare since many reports are incomplete and/or do not report long-term morbidity [13–16, 18]. Nevertheless, our long-term complication rate of 11% (three patients) is unfortunate but compares favorably to the 10% [17–19] and 16% [20] reported elsewhere. Although none of the patients in our series experienced a fatal complication of radiotherapy, this has also been reported by other investigators [20].

Our findings substantiate those of others. Size is an important risk factor, with small-volume disease being easier to control and cure [20]. We also confirm that patients who have received previous pelvic irradiation as part of primary adjunctive therapy are very difficult to cure [13]. None of our eight patients so treated achieved long-term disease-free intervals presumably due to the presence of radiation-resistant clones previously unresponsive to therapy. Finally, the fact that none of the patients who received a single interstitial implant achieved long-term disease-free survival awaits further confirmation.

Open interstitial brachytherapy allows for surgical exploration of the abdomen and pelvis and the theoretical benefit of improved dosimetry with fewer related complications. However, until prospective, randomized studies compare intracavitary, interstitial, and open interstitial techniques, the optimal brachytherapy for recurrent uterine corpus and uterine cervical cancer will remain uncertain.

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