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CLINICAL INVESTIGATION **Brachytherapy**

TREATMENT OF RECURRENT GYNECOLOGIC MALIGNANCIES WITH IODINE-125 PERMANENT INTERSTITIAL IRRADIATION

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Purpose: To analyze the outcome of permanent ^{125}I interstitial radiotherapy for unresectable retroperitoneal recurrences of gynecologic malignancies.
Methods and Materials: A retrospective review of 20 patients treated between 1979 and 1993 was performed to evaluate survival and morbidity associated with the interstitial ^{125}I technique.
Results: Nineteen tumors were located on the lateral pelvic wall and one in the para-aortic region. Eight patients, not previously irradiated, received external beam radiotherapy (EBRT) along with ^{125}I interstitial implants placed at the time of celiotomy. Nineteen (95%) are dead of disease at 1–69 months of follow-up. The median survival was 7.7 months for patients treated with ^{125}I alone and 25.4 months for those treated with both ^{125}I and EBRT. One patient is alive without evidence of disease 69 months after ^{125}I implantation. Fistulas, bowel obstructions, and fatal complications occurred only among patients previously irradiated.
Conclusions: When used in a previously irradiated field, ^{125}I interstitial radiotherapy has major morbidity and is unlikely to be associated with cure or long-term survival. In radiotherapy-naive patients with unresectable isolated recurrent gynecologic malignancies, ^{125}I implants and EBRT are feasible and occasionally may contribute to long-term disease-free survival. © 2002 Elsevier Science Inc.

Recurrent gynecologic malignancies, Permanent ^{125}I seed brachytherapy.

INTRODUCTION

While many gynecologic neoplasms have the potential for pelvic sidewall recurrence, locally advanced cervical cancer is notorious for this. According to the Annual Report on the Results and Treatment in Gynecological Cancer prepared by the International Federation of Gynecology and Obstetrics (FIGO), by 1988, 85% of cervical cancer patients were receiving definitive or adjuvant radiotherapy as part of their treatment program (1). Forthwith, the vast majority of patients who relapse constitute radiation failures. Ultraradical surgery may be employed to rescue women with central pelvic failures not associated with concomitant distant metastases. Indeed, following Alexander Brunschwig's original report in 1948 (2), several centers have reported 5-year survival rates following pelvic exenteration that have ranged from 20% to 50% (3). For example, Felix Noah Rutledge and colleagues reported a 48.3% 5-year survival rate in a select group of patients with recurrent cervical cancer treated by pelvic exenteration at the M.D. Anderson Hospital and Tumor Institute in Houston (4). The emergence of this specific subpopulation among women with recurrent cervical cancer has enabled us to define a potentially curable high-risk cohort. Of course, careful patient selection is predicated on the constellation of medical, psychological, and oncologic criteria.

Women with retroperitoneal recurrences, specifically those infiltrating the pelvic sidewall or periaortic regions, are a therapeutic challenge. It is mandatory that this group also be studied, as sidewall recurrences after irradiation manifest two to three times more frequently than central failures. Historically, most investigators have considered such recurrences biologically distinct from those occurring in the central pelvis due to the observation that sidewall recurrences are derived predominantly from primary lesions with lymph node metastases, which, by consequence, may indicate systemic dissemination. Furthermore, lymph node negative primary tumors had been noted to recur more frequently in the central pelvis.

External irradiation has been unsuccessful in sterilizing bulky sidewall disease and cure rates of almost zero had been previously documented among patients with sidewall

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recurrences subjected to extirpative surgery (5). For these reasons, locoregional therapy for patients with retroperitoneal recurrences has not been available for tumor control and women with infiltrating pelvic sidewall lesions have been treated with palliative systemic or investigational therapy, irrespective of the presence or absence of demonstrable distant disease. This also holds for patients with perioaortic recurrence.

Over the preceding two decades, innovative strategies of administering interstitial irradiation have been devised, including transperineal interstitial thermoradiation and the combined operative and radiotherapeutic treatment (CORT). Because the distorted geometry and inaccessibility of unresectable high pelvic sidewall and periaortic recurrences can make transperineal and transabdominal interstitial brachytherapy technically impractical in many cases, a third interstitial technique involving permanent interstitial seed implantation has evolved to address the clinical problem of retroperitoneal recurrences in gynecologic cancer. The presence of several long-term cures among recurring patients salvaged with one of these new interstitial irradiation modalities has prompted many to reconsider the prevailing hypothesis that so-called "isolated" sidewall recurrences by definition must reflect subclinical distant disease (3).

We therefore submit that effective locoregional therapy may exist for some women with retroperitoneal recurrences. The purpose of this study is to review and update our experience with permanent ^{125}I seed interstitial endocurietherapy among patients with isolated, unresectable infiltrating disease of the pelvic sidewall or periaortic region following primary therapy with irradiation or surgery.

METHODS AND MATERIALS

Retrospective review of clinical data were approved by the Institutional Review Boards at the University of California, Irvine–Medical Center and at Long Beach Memorial Medical Center, in accordance with assurances filed with and approved by the U.S. Department of Health and Human Services. Tumor registry abstracts and medical records at both institutions were reviewed to identify those patients treated with ^{125}I seed permanent interstitial brachytherapy from January 1979 through December 1993, ensuring at least 5 years of follow-up. Data on demographics, histopathology, primary therapy, sites of recurrence, dosimetry of current radiotherapy, and outcome in terms of survival and complications were recorded.

The criteria for patient selection for therapy prescription included: 1) good physical condition (i.e., Karnofsky Performance Status of 80%) and mental condition with reasonable life expectancy of at least 6 months; 2) recurrence limited to the pelvis or aortic region; 3) entire lesion inaccessible transperineally; 4) limited tumor volume (less than 10 cm in maximal diameter) with no extensive necrosis or fistulas.

A thorough, clinical metastatic workup was carried out in all patients to rule out any distant sites of disease, including a comprehensive physical examination, chest radiography, and computed axial tomography of the abdomen and pelvis (Fig. 1). Patients with distant metastatic disease were excluded and treated with palliative chemotherapy as indicated. Candidates for permanent interstitial seed implantation then underwent exploratory celiotomy for disease assessment. After surgical exposure of the sidewall or periaortic mass, the diagnosis of recurrent carcinoma was established through a mandatory intraoperative frozen section analysis. If regional recurrence was confirmed, maximal organ-sparing cytoreduction was attempted, and permanent ^{125}I interstitial brachytherapy was applied to the unresectable residua.

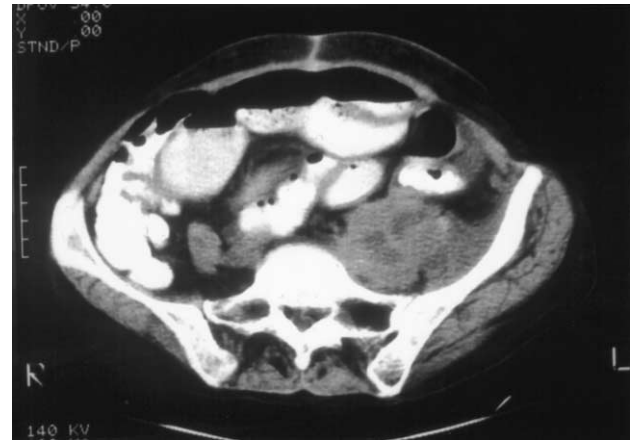

Fig. 1. Computed tomogram demonstrating pelvic sidewall recurrence of cervical cancer in a patient who later underwent exploration with ^{125}I permanent interstitial brachytherapy.

We have previously reported on the technique of transperineal open interstitial brachytherapy (6–8). In the current series, similar operative techniques were employed. In addition to creating the permanent seed interstitial implant under direct vision and palpation, exploratory laparotomy provides several distinct advantages over a closed procedure: 1) disease incompletely amenable to a transperineal approach is made accessible; 2) a histopathologic diagnosis can be obtained and the site and the extent of the recurrent disease can be precisely determined; 3) bowel adhesions can be separated; 4) whenever feasible, tumor reductive, visceral-sparing surgery can be performed which may improve the response to radiation; 5) because distance is an important physical factor for low-energy sources such as iodine-125 in which the dose falls off precipitously, an omental pedicle graft is interposed to separate the small bowel loops from the implanted site; 6) finally, the omentum provides a good absorptive surface and in theory a fresh blood supply can improve circulation to normal tissues destined to be exposed to radiation and enhance tumor cell kill via oxygen fixation.

Technique of the permanent interstitial implant

The permanent implant was created by inserting hollow stainless steel #17 gauge needles, 15 cm in length, parallel

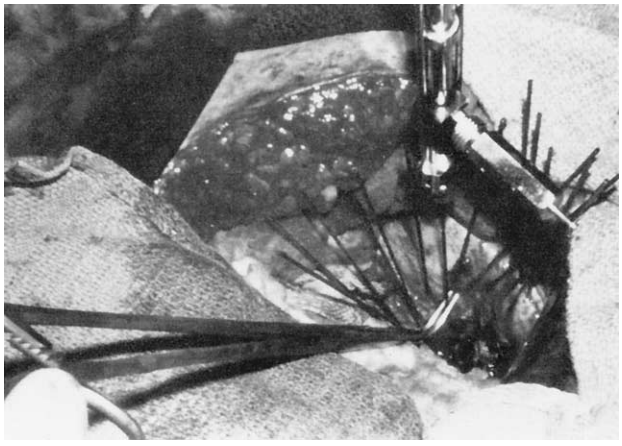

Fig. 2. Real-time intraoperative photograph illustrating the afterloading technique of delivery for ^{125}I seed using the Mick applicator.

to each other, at right angles to the unresectable disease anteroposteriorly. For the implantation of periaortic disease, the needles were directed at 45° to 60° angles to the surface and were spaced 1 cm apart. The radionuclide seeds were implanted into the tumor bed at desired depths using a preloaded Mick's applicator (Mick Radio-Nuclear Instruments, Inc., Bronx, NY). This device withdraws the hollow needle guides in a ratchet-like fashion as seeds are delivered, one by one, at increments of at least 5 mm (Fig. 2). Generally, spacing of the seeds was 1 cm apart.

^{125}I permanent interstitial implant dosimetry

Iodine-125 seeds were employed for the permanent interstitial implants. This isotope has a half-life of 60.2 days and emits low-energy-level gamma rays of 28 keV. The half-value layer is 2 cm in tissue and 0.025 mL in lead (9). Thus, ^{125}I has high tissue attenuation, such that approximately 80% of the dose is absorbed within 1 cm of implanted tissue. When combined with external beam radiation, the biologically relevant dose can be delivered during the first half-life. ^{125}I encapsulated sources come in several varieties and were first introduced at Memorial Sloan-Kettering in 1964 as a substitute for higher energy radon-222 and gold-198 sources (10).

From 1979 to 1987, the isotope was supplied by Lawrence Soft Ray Corporation (Mountain View, CA), and from 1988 to 1991 the ^{125}I Model 6701 seed (Fig. 3) was obtained from 3M Co. (St. Paul, MN). Radioactive iodine is absorbed in two resin spheres, one on either side of a 24K central gold sphere which provides radiographic visibility.

After 1992, we used the new Model 6711 ^{125}I seed which replaces the gold ball and resin spheres with a single silver rod onto which ^{125}I adsorption occurs (Fig. 4). Two additional low-energy fluorescent X-rays (22.1 keV and 25.2 keV) from the silver rod increase the photon spectrum in the Model 6701 seeds. Furthermore, the increased mass and linear character of the silver rod permit greater radiographic visualization and detection of seed orientation, respectively.

Intraoperatively, Quimby's method was used to distribute the radioactive seeds in the treatment volume (11). The law of average dimension was employed before each procedure to determine the number of ^{125}I seeds required in each situation, making the total activity implanted in millicuries directly proportional to the average of three perpendicular dimensions of the tumor. Specifically, this was accomplished by multiplying the calculated average dimension of the implanted volume by Cevc's empiric value (i.e., a factor of 5). However, an additional 20% activity was added because of the low value of specific dose rate factor for ^{125}I. Henceforth, the total activity of ^{125}I in millicuries required to achieve the desired dose was reached and divided by the activity per seed available (usually, 0.3 mCi to 0.5 mCi). Although this could also be determined using Anderson's nomogram (12), Cevc's formula is a basic and fundamental concept that has remained constant, while the nomogram (which came later) has actually undergone several revisions

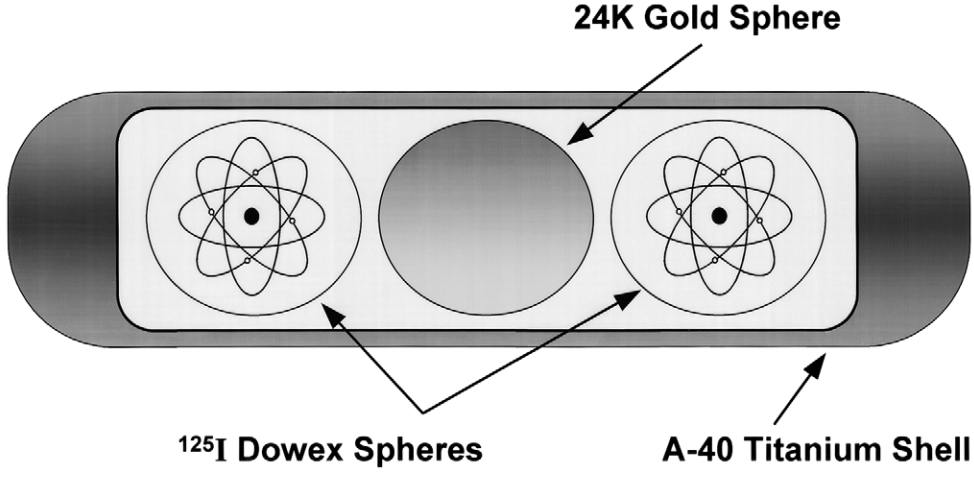

Fig. 3. Schematic for the Model 6701^{125}I seed construction depicting the two Dowex resin spheres and a centrally positioned gold ball (3M Co., St. Paul, MN).

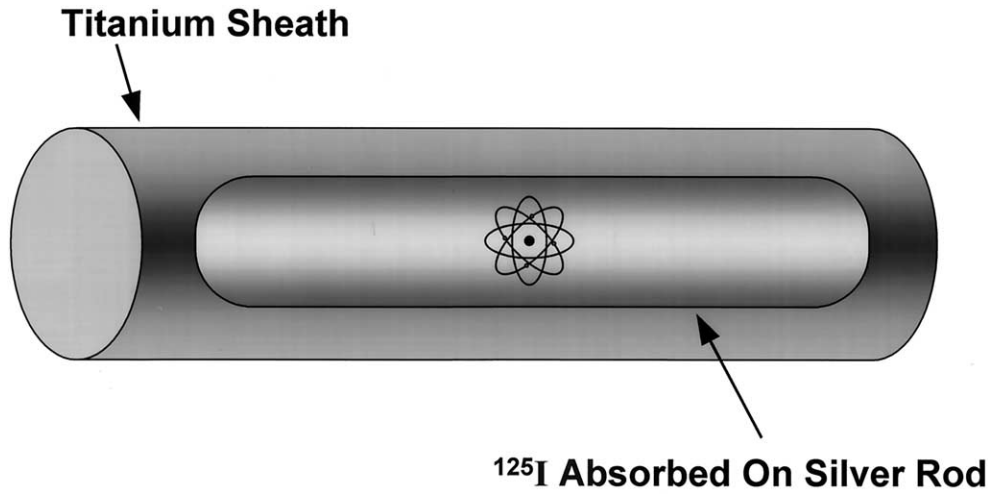

Fig. 4. Schematic for the Model 6711 ^{125}I seed construction depicting the silver rod (3M Co., St. Paul, MN).

during the past 20 years. Thus, the Cevc equation, as depicted below, was used to derive the total number of seeds for tumor implantation (13):

$$\left[\frac{(\text{length} + \text{width} + \text{thickness})}{3} \times 5 \div \text{activity per seed} = \text{number of seeds}\right] \quad (1)$$

Anteroposterior and lateral orthogonal localization X-rays were obtained for computerized dose calculations. Isodose distribution plots at every 0.5 cm distance in the implanted volume were obtained for the determination of minimum and maximum dose rates in the implanted volume. The total dose delivered by the ^{125}I implant was calculated for total decay (i.e., 1 year) and ranged from 12,000 to 16,000 cGy. The intended minimum surface dose delivered in the first half-life of 60 days was between 6000 cGy and 8000 cGy.

Statistical analysis

The relationship between the number of seeds, total activity in millicuries per implant, and tumor volume was analyzed by Spearman rank correlation. Survival was determined from the date of ^{125}I seed permanent interstitial brachytherapy. Survival curves were estimated using the Kaplan–Meier method, with differences between groups estimated by the log–rank test; subjects alive at the time of last follow-up were censored in survival analysis. Perioperative complications were defined as those occurring within 30 days of permanent open interstitial brachytherapy, with other complications considered delayed.

RESULTS

Between 1979 and 1993, 41 patients with recurrent gynecologic malignancies involving the pelvic sidewall (n = 36) or the periaortic region (n = 5) were evaluated for open interstitial permanent seed brachytherapy. Of these, 17 were excluded secondary to the presence of concomitant distant metastases, 3 patients refused to undergo laparotomy, and one was in such poor health that surgical intervention was contraindicated. Thus, the study population consisted of 19 patients with recurrent squamous cell cancers (uterine cervix, n = 18; primary invasive vaginal carcinoma, n = 1) and one with recurrent endometrioid adenocarcinoma of the ovary. The median age of those treated was 42 years (range 25–70 years).

For the entire study group, the time interval between completion of primary treatment and the clinical manifestation of pelvic failure ranged from 6 to 40 months (median, 15 months). Tumors ranged from 4 to 9 cm in maximal diameter and were located on the lateral pelvic wall (n = 19) or in the periaortic region (n = 1), and were not amenable to surgical resection. Previous therapy consisted of radical surgery in the majority (n = 13) of patients. However, 12 also received external beam radiation therapy (EBRT) to the pelvis to doses between 4500 and 5500 cGy in 5–6 weeks; EBRT had been administered to five women as adjuvant postoperative treatment and to seven as a component of primary radiotherapy, in either case limiting the delivery of EBRT in combination with interstitial implants at the time of recurrence (Table 1). The seven women treated with primary EBRT also had intracavitary irradiation with doses varying from 4000 to 5000 mg/hr.

All 8 patients not previously irradiated received EBRT to doses between 3950 and 5040 cGy along with ^{125}I interstitial implants. Megavoltage irradiation was administered through parallel and opposed portals employing a 4–6-MeV linear accelerator. Specifically, anterior and posterior fields measured approximately 16 cm by 18 cm and lateral fields measured approximately 10 cm by 18 cm. Four of the 20 patients were also treated with ^{192}Ir transperineal interstitial implants for disease extending into the central pelvis and three received chemotherapy consisting of either cisplatin

Table 1. Distribution of tumor histopathology and FIGO stage stratified by previous radiotherapy

Primary site, histology	FIGO Stage	Radiation-naive (*n*)	Prior radiotherapy (*n*)
Cervix, squamous carcinoma	IB	7	6
	IIA	0	1
	IIB	0	1
	IIIB	0	3
Vagina, squamous carcinoma	III	0	1
Ovary, endometrioid carcinoma	III	1	0
Total		8	12

and 5-fluorouracil ($n = 2$) or hydroxyurea ($n = 1$) as a radiosensitizer.

In only 3 patients was an attempt made at resection of the recurrent tumor, with the residual tumor volume implanted. The median number of seeds implanted was 58 (range 20–127) with a median total activity of 19 mCi (range 8–43 mCi). The wide range of seed numbers and total activity in implants were proportional to tumor volumes calculated intraoperatively (Spearman correlation coefficients 0.56 and 0.74, $p = 0.02$ and 0.002, respectively).

Follow-up was determined from the time of open interstitial implant. At the time of this review, all but 1 patient (95%) were dead of disease. Special mention must be made of this patient who had undergone primary radical hysterectomy and subsequently relapsed at the pelvic wall with a 7-cm-diameter lesion; she was rescued with the permanent ^{125}I seed interstitial implant and remains without evidence of disease 69 months after salvage therapy. The median survival in the 12 patients ineligible for concomitant EBRT with their open implant was 7.7 months (range 0.7–20.1 months), all of whom failed and progressed in the pelvis. The median survival in the 8 individuals without prior radiotherapy was 25.4 months (range 2.2–68.7 months), including two with survival greater than 4 years (Fig. 5, log–rank $p = 0.03$); of the seven women who died in this group, five failed in the pelvis alone and two suffered locoregional and distant recurrences after ^{125}I irradiation and EBRT.

^{125}I permanent open interstitial brachytherapy was associated with 12 major complications in 11 patients. Eight of these occurred in the 12 patients who had received previous radiation therapy and included perioperative hemorrhage ($n = 2$, one fatal); delayed radiation proctitis with fatal lower gastrointestinal bleeding ($n = 1$); perioperative adult respiratory distress syndrome (ARDS, $n = 1$); small bowel obstruction ($n = 2$); and enteric fistula ($n = 2$, one enterovaginal, the other enterocutaneous), the latter four conditions requiring exploratory celiotomy and surgical correction. A delayed pelvic hemorrhage occurred in a patient not previously irradiated and was presumably due to radiation necrosis. Other complications occurring in those who had not previously received radiotherapy included delayed hemorrhagic cystitis requiring bladder irrigation only ($n = 1$), delayed hemorrhagic proctitis stabilized with local care and red cell transfusions ($n = 1$), and ureteral ligation at the time of exploration for ^{125}I open interstitial brachytherapy ($n =$

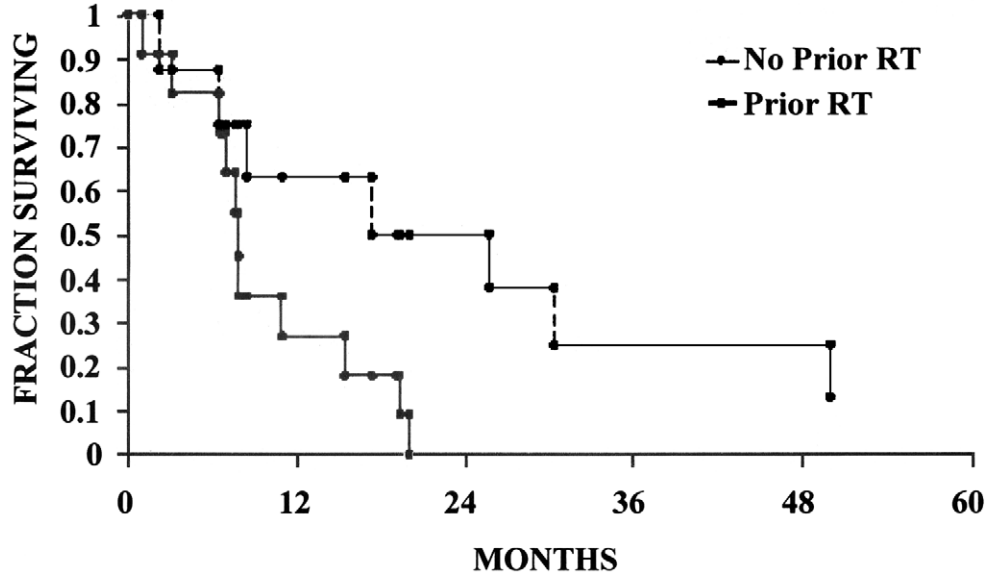

Fig. 5. Survival curves based on the use of EBRT in combination with ^{125}I permanent interstitial brachytherapy.

1). All six complications requiring operative intervention or resulting in mortality occurred in previously irradiated individuals.

DISCUSSION

The overall incidence of recurrent cancer from most sites is 50%, of which 20% to 30% are localized without evidence of dissemination (14, 15). At least 20% of female genital tract tumors treated for cure in North America and in Europe will relapse in the pelvis without detectable distant metastases (16). Webb, Munnell, and Figge have independently examined the critical points of failure in the treatment of gynecologic cancer (17–19), and concluded that the majority of localized pelvic recurrences are cervical in origin. The remaining arise from endometrial, vaginal, and vulvar primaries; ovarian carcinomas of low malignant potential and sarcomas contribute only a minority.

Unfortunately, the relatively favorable long-term survival rates among many women treated by exenteration for central recurrences in the postirradiated pelvis have not been enjoyed by those with multifocal disease or with postirradiation relapses infiltrating the pelvic wall. Five-year survival rates in these latter groups have been under 10%, with a median life expectancy of only 8 months (16). The quality of life among such patients is extremely poor as their recurrences represent lymphatic metastases or inadequately treated primary disease, commonly leading to sciatica, lower extremity lymphedema, and hydronephrosis (20).

Postsurgical failures at the pelvic sidewall may be treated with external irradiation with the intent to palliate; however, occasional long-term local control and even cure have been observed (6). Most women with recurrent gynecologic cancer, however, will have already received prior adequate radiation therapy by virtue of their high risk for relapse, and therefore reirradiation by external beam is rarely used because of significant morbidity.

Reirradiation with interstitial implants using various isotopes has a distinct advantage over external irradiation because interstitial brachytherapy can deliver a cancericidal dose directly to the tumor mass with differential sparing of surrounding normal tissues (e.g., the bladder and the rectum). However, like EBRT, reirradiation with interstitial implants can still be associated with significant morbidity as demonstrated by the current report. Interstitial irradiation using radon seeds and radium needle implants was used as early as 1940 in recurrent pelvic cancers but was abandoned by radiotherapists due to the hazards of radiation exposure from high-intensity radioisotopes and poor dosimetry leading to discouraging results (21). With the advent of low-intensity sources such as ^{125}I and afterloading ^{192}Ir techniques, these problems have been minimized and interest has been renewed.

Traditionally, interstitial brachytherapy for recurrent tumors has employed the intraoperative placement of temporary ^{192}Ir implants using transperineal (8) or transabdominal (16) templates. Intraoperative brachytherapy is accomplished through the precise application of radioactive sources directly into the tumor volume, allowing for dose intensification. Such an approach may make reirradiation feasible in selected patients with recurrent pelvic malignancies (6).

Interstitial hyperthermia is a novel approach for managing postirradiation relapses which do not lend themselves to surgical resection. The rationale is based on a spectrum of biologic and physical research which predicts that hyperthermia, known to be cytotoxic at temperatures above 41°C, may be selectively lethal to cancer cells (22). S phase cells and hypoxic cells which exist at a subnormal pH are relatively radioresistant; hyperthermia may be selectively lethal to such cells, synergizing with radiation through inhibition of cellular repair mechanisms. Hyperthermia may be localized in a similar manner to ionizing radiation; its tissue-specific actions are predicated on specific thermal and electrical properties which may be exploited in its clinical application as an adjuvant to radiotherapy (23). Surwit and colleagues from the University of Arizona conducted a Phase I trail of interstitial thermoradiation in 21 women with transperineally accessible gynecologic cancer (12 with recurrent cervical cancer) (24). There were seven complete and 10 partial responses and 4 patients developed fistulas. Notwithstanding, a defined role for hyperthermia in the clinical problem under discussion has never been established.

Höckel and colleagues have pioneered the combined operative and radiotherapeutic treatment (CORT) for recurrent gynecologic malignancies infiltrating the pelvic sidewall (3, 16, 25). Introduced at the University of Mainz Medical School in Germany, CORT was a new concept developed by their group in 1989 to manage unifocal tumors recurring in an irradiated pelvis with pelvic wall infiltration (25). The three phases of CORT include ablative therapy to resect the tumor, destroyed organs, and inner pelvic wall muscles; pelvic wall plasty; and postoperative tumor bed irradiation. The Mainz radiotherapists use a Microselectron ^{192}Ir high-dose-rate brachytherapy unit with PLATO planning system (Nucletron, Veenendaal, The Netherlands) (16).

Höckel's group treated 48 women with CORT from 1989 to 1994. At a median observation period of 33 months (range, 3 to 71 months), the 3-year and 5-year survival probabilities calculated using the Kaplan-Meier method were 50% and 44%, respectively (16). The overall local control rate was 68% at 5 years, and the censored severe complication rate was 33%. No patient died as a consequence of treatment with CORT.

Many isolated pelvic recurrences are not accessible transperineally, or are either too high in the pelvic sidewall for CORT or located in the periaortic regions. During the late 1970s and early 1980s, the Division of Gynecologic Oncology together with the Department of Radiation Oncology at the University of California, Irvine became interested in using permanent interstitial irradiation for unifocal pelvic sidewall and periaortic recurrences. We have refined our

technique over the past two decades to treat recurrent gynecologic malignancies not amenable to exenterative surgery.

The application of permanent ^{125}I seeds for open interstitial brachytherapy in the management of limited retroperitoneal recurrences has several dosimetric advantages when compared to the use of other isotopes. When the low-energy ^{125}I is implanted, the gamma rays are concentrated in the immediate surrounding tissues, sparing adjacent normal structures as well as medical personnel. Additionally, the relatively long half-life (60.2 days) leads to prolonged radiation exposure to the implanted tumor volume. Furthermore, the therapeutic benefit is theoretically boosted by natural increases in local dose after radiation-induced tumor shrinkage brings the ^{125}I seeds closer together (26). Finally, by providing continuous low-dose radiation, ^{125}I may decrease the oxygen enhancement ratio, improving efficacy in hypoxic portions of the tumor (27).

Unfortunately, the application of ^{125}I interstitial implants has been limited by dose heterogeneity due to both intrinsic radiobiological factors such as scatter and anisotropy, and technical factors such as inaccurate seed distribution. The philosophical and clinical approach to performing interstitial brachytherapy is grounded in the concept of dose nonuniformity (28). Sources with uniform linear density are used in both the Quimby system and the Paris system of interstitial implants, but for any multisource implant, the dose nonuniformity is altered depending on the selection of the reference dose rate (28). The dose nonuniformity ratio (DNR) is based on volumetric data and is defined as the ratio of the high dose volume relative to the reference volume. Thus, interstitial implants are *volume implants* and the potential shortcomings of dose heterogeneity may be anticipated by studying preexisting interstitial programs. The most common application of ^{125}I permanent interstitial irradiation has been in the treatment of prostatic malignancies (29–31), although therapy for other sites of disease, such as central nervous system, head-and-neck tumors, and pancreatic cancer has also been described (32–35).

The treatment of clinically localized prostate carcinoma with interstitial iodine-125 radiation therapy has served as our spatial model for retroperitoneal pelvic recurrences of gynecologic malignancies. Ragde and coworkers from the Pacific Northwest Cancer Foundation in Seattle have reported their experience with 126 consecutive patients treated with iodine-125 irradiation employing a Bruel & Kjaer ultrasound unit (31). The seminal vesicles were not included in the treatment plans and a Quimby (uniform loading) implantation technique was used. The overall 7-year survival was 77% with no deaths from prostate carcinoma in the cohort. Clearly, although the relatively favorable tumor biology of prostatic lesions cannot be compared to that of aggressive gynecologic recurrences, the principles of the Quimby technique and dosimetric planning in the true pelvis provides a satisfactory template on which to model volumetric treatment for gynecologic pelvic sidewall relapses.

In the present series, we have presented 1 patient with a periaortic recurrence. As noted above, periaortic metastases are contraindicated in CORT. The spatial model for periaortic ^{125}I irradiation has evolved from our own experience in managing unresectable pancreatic carcinoma. From 1975 to 1980, we treated 18 patients with locally advanced adenocarcinoma of the head, body, and tail of the pancreas using a combination of biliary bypass, external irradiation of 30–50 Gy to the pancreas and regional lymph nodes, and 10–15 Gy to the region using permanent ^{125}I implants (35). A median survival of 14 months was observed with excellent palliation of pain, jaundice, and vomiting.

The prostate cancer and unresectable pancreatic cancer ^{125}I irradiation programs have provided a framework for the development of our current practice in using ^{125}I permanent implants for recurrent gynecologic cancers. In 1982 we presented a case series of subjects from our ancestral Radiation Oncology and Gynecologic Oncology Divisions at the California Hospital Medical Center and Southern California Cancer Center in Los Angeles (6). From 1975 to 1978, a total of 40 previously irradiated patients with recurrent pelvic malignancies (e.g., rectosigmoid, uterine cervix, vagina, endometrium, ovary, urinary bladder, prostate) were reirradiated with either removable afterloading ^{192}Ir sources or permanent ^{125}I seeds with or without exploratory laparotomy. A complete local control of implanted pelvic tumors was achieved in 67% ($n = 27$) patients, with 33% ($n = 13$) remaining alive and disease-free for a minimum follow-up period of 2 years. Severe morbidity, including soft tissue necrosis and fistulas, occurred in 15% of the patients.

Nori and colleagues from the Memorial Sloan-Kettering Cancer Center in New York prepared an encouraging report in 1981 (36). In an analysis of 96 women with recurrent gynecologic cancer treated by interstitial implants with or without external irradiation and debulking surgery, 85 received permanent implants using ^{222}Rn, ^{198}Au, ^{125}I, and ^{192}Ir (36). Although long-term survival was not extraordinary (10% at 5 years for women with recurrent cervical cancer and 5% at 5 years for patients with other recurrent gynecologic cancers), sustained symptomatic relief was obtained in 70% of patients.

Randall and coworkers from Bowman Gray School of Medicine managed 13 women with recurrent gynecologic malignancies with interstitial reirradiation (37). A Syed-Neblett Interstitial Template No. 2 (Rad-Irid, Forestville, MD) was used to facilitate six temporary interstitial ^{192}Ir implants, while seven permanent interstitial implants were created with ^{198}Au ($n = 5$) and ^{103}Pd ($n = 2$). Isotopic gold was used in preference to ^{125}I because its half-life of 2.7 days results in a higher and more favorable initial dose rate compared to ^{125}I. A downside to the use of radioactive gold, however, is that its predominant gamma energy, 0.41 MeV, makes some exposure of hospital personnel inevitable. Four of seven women (57%) treated with permanent isotopes

Table 2. Management strategies for recurrent gynecologic cancer

Distant metastases:	Investigational or palliative systemic therapy
Abdominal intraperitoneal metastastes:	Palliative surgery; Investigational or systemic therapy
Central pelvic recurrences: (Radiation failure)	Pelvic exenteration Total/anterior/posterior; Supralevator/infralevator
Pelvic-perineal recurrence: (Nonsurgical candidate)	Iridium-192 interstitial thermoradiotherapy Transperineal temporary implants with hyperthermia
Pelvic sidewall recurrence: (Radiation failure)	Combined operative and radiotherapeutic treatment Transabdominal ^{192}Ir interstitial brachytherapy
Pelvic sidewall or periaortic recurrence: (Radiation-naive)	Iodine-125 interstitial implants + EBRT Permanent seed implants

achieved local control as compared with two of six (33%) treated with temporary implants.

During the preceding decade, Sharma and coworkers from Loyola University Medical Center provided a further testament to the efficacy of ^{125}I interstitial implants in the management of recurrent gynecologic cancer (38). The investigators treated 21 women with pelvic recurrences with ^{125}I interstitial implants to a total dose of 4600 cGy to 25,900 cGy. All but 1 patient had previously received 4000–6140 cGy to the pelvis via external irradiation. The complete response rate was noteworthy at 75%. There were eight survivors at 36 months to 103 months follow-up, including two who were alive with distant disease. It should be noted that seven survivors were among patients with recurrences apparently confined to the vagina ($n = 5$), suburethral region ($n = 1$), or cervical stump ($n = 1$). One patient with a pelvic sidewall recurrence was alive at 50 months. Seven patients (33%) suffered severe complications including vesicovaginal fistula ($n = 4$), rectovaginal fistula ($n = 2$), and rectal fibrosis ($n = 1$).

Unlike Sharma's report, not all patients in the current series (8 of 20) received pelvic radiation as part of their initial therapy. Most of these patients (7 of 20) had originally presented with Stage I cervical tumors clinically confined to the cervix and treated primarily with radical hysterectomy and pelvic lymphadenectomy (39). Consequently, in our radiation-naive patients EBRT was added to open ^{125}I brachytherapy as an adjunct to the pelvic side wall recurrence.

The most important observation of this small series is that the use of ^{125}I in the treatment of retroperitoneal recurrences is ineffective and associated with a high complication rate if EBRT was a component of primary treatment. Indeed, the very low dose-rate of interstitial ^{125}I-based brachytherapy may favor tumor cell repopulation during the same irradiation period as reflected in the decreased median survival observed in the previously irradiated group of patients for whom ^{125}I seed irradiation could not be combined with EBRT. The degree to which radiation vs. prior surgery contributed to the risk of complications and poor prognosis is unknown, but since almost all patients had undergone radical surgery as part of their primary therapy, the contribution of prior radiation therapy seems significant. However, those with prior radiation tended to be patients with more advanced lesions at the time of diagnosis, and recurrence in a previously irradiated field implies a more aggressive tumor biology. We would expect such lesions to be less likely to respond to any type of regional or systemic therapy. Furthermore, it is not surprising that the differences in complication rates observed (between previously irradiated and radiation-naive patients) reflect the increased likelihood of encountering distorted anatomy and intense fibrosis when operating in a previously irradiated field.

Among previously unirradiated individuals, ^{125}I and EBRT can be effective in long-term palliation and prolonging survival and can even rarely cure individuals with limited morbidity. Among 8 patients treated according to this regimen, the median survival was over 25.4 months with complications such as fistula or bowel obstruction requiring surgical intervention being absent.

Locoregional pelvic recurrence represents a true failure of primary therapy. Noncentral pelvic recurrences not associated with distant metastases may be separated into three groups: 1) low volume relapse accessible transperineally; 2) transperineally inaccessible postirradiated pelvic failure; 3) transperineally inaccessible postsurgical pelvic failure.

Our management strategy for recurrent gynecologic cancer is depicted in Table 2. We believe that the accessible lesions of the vagina, vulva, urethra, and perineum can be more adequately implanted with removable ^{192}Ir implant techniques using both interstitial hyperthermia and a stable, dedicated Syed-Neblett transperineal template in an effort to deliver a more uniform dose distribution and optimize local control.

For previously irradiated patients with large volume sidewall recurrences, the CORT concept employing high-dose-rate ^{192}Ir irradiation is ideal. Finally, for periaortic or postsurgical sidewall relapses, a strong consideration should be given to the creation of a permanent ^{125}I implant which may possibly have a favorable impact on survival. Unfortunately, only 15% of patients with pelvic recurrences have not been previously irradiated and are thus candidates for permanent seed irradiation with EBRT (40–45). This technique is contraindicated in the previously irradiated field where it is associated with both significant morbidity and absolutely no benefit.

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