The Role of Intraoperative Radiation Therapy (IORT) in the Treatment of Locally Advanced Gynecologic Malignancies

MARCELA G. DEL CARMEN, a JAMES F. MCINTYRE, b ANNEKATHRYN GOODMAN a

a Vincent Gynecologic Oncology Service, b Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts, USA

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ABSTRACT

The prognosis in women with locally advanced primary or recurrent gynecologic malignancies is rather poor. Doses of external beam radiation necessary to treat gross or microscopic recurrence among patients surgically treated or previously irradiated exceed what is tolerated by normal structures. In this group of patients, intraoperative radiation therapy (IORT) can be utilized to maximize local tumor control, minimizing the radiation exposure of dose-limiting surrounding structures. Review of the available literature indicates that IORT may improve long-term local control and overall survival in women with pelvic sidewall and/or para-aortic nodal recurrence. The most encouraging results have been reported in the cases of microscopic residual disease, following surgical debulking. The Oncologist 2000;5:18-25

INTRODUCTION

Women with locally advanced primary or recurrent pelvic malignancies have a rather poor prognosis, especially in the setting of tumor extension to the pelvic sidewall or lymphatic dissemination to the pelvic or para-aortic lymph nodes. Local failure may be the primary cause of death in as many as 60% of patients who die from carcinoma of the cervix or endometrium [1]. Only a selected group of women with locally recurrent disease confined to the central pelvis have a chance of cure with exenterative surgery [1].

External beam irradiation to the pelvis is constrained by dose limitations to normal structures. Radiation doses required to control gross residual or microscopic disease in the pelvis are in excess of those tolerated by normal surrounding structures [2, 3]. Radiation can be safely delivered in doses of 45-54 Gy (in 25-30 fractions of 1.8 Gy) [1]. However, the external beam radiation doses needed to treat residual disease after gross resection would prove to be too morbid [2-4]. This is especially true in advanced local recurrence, where tissue has either been previously irradiated or surgically manipulated [3].

For patients with locally advanced gynecologic malignancies, not previously irradiated, preoperative external beam radiation therapy (EBRT) is also recommended [1]. This treatment may be in conjunction with chemotherapy. In the case of previous irradiation, full-dose EBRT is not an option. If further treatment via this modality is at all possible, re-treatment depends on the radiation dose previously used, the time interval that has elapsed from treatment to recurrence, and the anatomical location of recurrence in relation to normal structures [1].

Intraoperative radiation therapy (IORT) allows direct irradiation of a tumor bed during a planned surgical procedure [2, 5, 6]. Irradiation is utilized to sterilize the remaining tumor nests after debulking of resectable lesions [5]. IORT represents a unique treatment modality since it allows direct visualization of the target volume, which in turn results in a more precise mapping of the field to be irradiated [5]. Secondly, IORT permits removal or shielding of normal structures from the radiation field. In this way, the total dose of radiation that can be delivered safely can be increased, while diminishing...
radiation morbidity in normal tissue [5, 7]. That is, sufficiently high doses of radiation may be delivered via IORT to the high-risk pelvic tissues, while minimizing the exposure to other organs such as the kidneys, bladder, bowel, and rectum [6].

The biologic effectiveness of single-dose IORT is hypothesized to be two to three times that of fractionated radiotherapy. Therefore 15 Gy of IORT is equivalent to giving 30-45 Gy of fractionated external beam irradiation [1].

**PATIENT SELECTION**

Both radiation and gynecologic oncologists should actively participate in the evaluation of the patient who may be a candidate for IORT [1]. The patient’s initial assessment should include a history and physical examination, as well as accurate determination of involvement of the pelvic tumor, which in some instances may necessitate an examination under anesthesia [1]. Laboratory evaluation should include a comprehensive blood count, liver function tests, and blood chemistries [1]. Imaging studies should include a chest x-ray, abdominal/pelvic computed tomography, and pelvic magnetic resonance imaging when indicated to evaluate tumor extent within the pelvis [1].

The Mayo Clinic, through its experience with IORT, has delineated general criteria for the selection of women with gynecologic malignancies for whom IORT may be a treatment option [3, 4]:

- The patient’s medical condition must permit her to tolerate major surgery [1-4].
- Surgery alone would not result in acceptable local control [1-4]. Positive microscopic margins would likely exist if surgery alone was performed [1].
- Patients with distant metastases, including peritoneal seeding, are excluded [1-4].

The anatomical location of disease should be one that is amenable to direct intraoperative treatment of the tumor bed, minimizing the exposure of normal structures [3]. Dose-limiting tissue such as the small bowel can be temporally displaced at the time of radiation so as to maximize the therapeutic ratio between a curative attempt and complications [2].

**TREATMENT TECHNIQUE**

Women suffering from primary locally advanced gynecologic malignancies who are candidates for surgical resection and IORT should be treated preoperatively with EBRT. This approach maximizes the likelihood of attaining a gross total resection [1]. In women with no previous irradiation history, median doses ranging from 45-54 Gy have been given. This dose has been delivered in 1.8 Gy fractions, five days per week, over a five- to six-week course [3, 4, 7].

IORT is delivered at the time of surgery, immediately following surgical resection. The radiation equipment is located within the space of the operating room (Figs. 1 and 2). The dose of IORT delivered depends on the tumor burden after surgical resection, the depth of the target volume, the location of dose-limiting normal structures (such as the small bowel, the rectum, and the bladder), and the degree of previous irradiation in the patient [1, 3, 4].

The IORT dose is generally calculated at the 90% isodose line. Electron energies available range from 6-18 MeV. The target thickness dictates the electron energy chosen [1-4] (Fig. 3). The IORT dose selected varies according to the amount of residual disease and the amount of EBRT the patient has already received or will receive postoperatively [1, 3, 4]. If EBRT in the range of 45-50 Gy has been delivered preoperatively or is planned postoperatively, microscopic residual disease can be irradiated with doses of 10-15 Gy [1, 3, 4]. In the case of gross residual disease, doses of 15-20 Gy are recommended [1, 3, 4]. Higher doses of IORT (≥15 Gy) are usually employed in the treatment of women previously irradiated with high-dose EBRT or who cannot receive full-dose EBRT [3, 4].

**Figure 1. Blueprint layout of the IORT room at the Massachusetts General Hospital.** Set-up during IORT consists of a dedicated operating room where all the radiation equipment is also maintained, allowing for easy conversion into a radiation suite. As the radiation is being delivered, the surgeon, radiation oncologist, anesthesia team, and rest of the staff move to an adjacent shielded room that allows continuous patient monitoring.
RESULTS AFTER CONVENTIONAL TREATMENT

Review of the literature allows for a comparison to be made between patients with advanced recurrent and primary gynecologic malignancies treated with IORT and historic controls.

Recurrent Disease

Local failure has been reported as the principal cause of death in as many as 60% of women with recurrent cervical or endometrial cancer [8]. Most authors cite a five-year survival rate of ≤5% among patients with pelvic recurrences of cervical cancer [9].

Exenterative surgery may present a curative option only among those with local recurrence confined to the central pelvis. This latter treatment modality may lead to fatal complications in as many as 10% of patients and may result in recurrence in another 30% [10]. One series documented a five-year survival of 0% among 143 women with positive margins at the time of anterior exenteration for recurrent cervical cancer [11].
In patients who recur after treatment for endometrial cancer, the prognosis is also poor. The five-year disease-free survival and pelvic control for women with recurrence limited to the vagina have been reported as 40% and 59%, respectively [12]. In this series, if patients had recurrence involving the pelvis, their five-year disease-free survival was noted to be 20% and their pelvic control rate 17% [12].

Primary Disease

Review of the literature also permits comparison between results with IORT and historic controls. For women with stage I cervical cancer treated surgically (via radical hysterectomy) or EBRT plus brachytherapy, the five-year survival rate is >90%. This rate is 75%-90% for those with stage II disease [13]. If the pelvic sidewall is involved (stage III), five-year control rates are much lower, in the order of 50%-65%. Stage IVA disease has an estimated five-year survival of only 25%-35% [13].

Nodal disease in the setting of primary cervical cancer confers a worse prognosis. The Gynecologic Oncology Group documented nodal disease as the most significant prognostic factor associated with recurrence [14]. Women with positive para-aortic lymph nodes had the worst outcome [14]. One series reported a relapse-free survival of 57% and pelvic failure rate of 20% in patients with grossly involved but resectable pelvic lymph nodes [15]. Patients whose pelvic lymph nodes were unresectable exhibited a relapse-free survival of 0% and a pelvic failure rate of 56% [15]. Unfortunately, the control rate mediated by EBRT alone in the setting of grossly involved pelvic lymph nodes is in the order of 50% [16]. Long-term survival among cervical cancer patients with positive para-aortic lymph nodes (microscopic or limited-volume) is reported to be 25%-50% [17, 18]. Unfortunately, the doses necessary to achieve control of macroscopic disease at this level exceed those tolerated by the small intestines [1].

Kinney et al. reported on a series of 117 patients undergoing radical hysterectomy and pelvic lymph node dissection for stage IB and IIA cervical carcinoma [19]. Fifty-one of them (44%) had palpably involved pelvic lymph nodes. Of these 51 patients, 29 received adjuvant radiotherapy [19]. Thirty-two of these 51 patients’ nodes had documented disease recurrence. The site of recurrence included an extrapelvic component in 73% of these patients [19]. The authors conclude that since the doses of radiation required to treat large-volume disease often exceed those tolerated by normal structures, resection of macroscopic nodal disease may play a role in improving local control [19].

Similarly, although only 5%-10% of primary endometrial malignancies present with disease extending beyond the uterus, patients with unresectable disease have poor survivals. EBRT and brachytherapy are associated with a high rate of pelvic failure. Five-year survival with disease confined to the pelvis may be in the order of 12% with a local relapse rate of 37% [20]. Pelvic sidewall disease has a reported five-year survival rate of 0% [20].

Women with nodal involvement of their endometrial malignancy, as in the case of those with cervical cancer, have a poor five-year survival. Most survivors have only microscopic disease. After extended-field EBRT in the setting of positive para-aortic lymph nodes, five-year survival has been documented as 40%-60% [1].

RESULTS AFTER TREATMENT WITH IORT

The next section provides a summary of some of the data in the literature regarding the role of IORT in treating advanced gynecologic malignancies. Patients with both primary and recurrent disease have been treated with IORT. The majority of the experience with IORT has been obtained from treating isolated nodal or locally recurrent gynecologic malignancies. The application of IORT in the setting of primary disease has been much more limited.

| Table 1. IORT and disease relapse in recurrent locally advanced gynecologic malignancies |
|-----------------|-----------------|-----------------|-----------------|
| **Site**        | **n of Patients** | **Local Relapse (%)** | **Central Relapse (%)** | **Distant Relapse (%)** |
| Mayo [3, 4, 22]  | All sites        | 55               | 43/5-yr           | 31/5-yr          | 48/5-yr          |
|                 | Cervix           | 36               | 50/5-yr           | 40/5-yr          | 58/5-yr          |
|                 | Endometrium      | 10               | 22/5-yr           | 0               | 33/5-yr          |
|                 | Others           | 9                | 50/5-yr           | 42/5-yr          | 33/5-yr          |
| France [23, 24]  | Cervix           | 70               | 75/3-yr           | —               | 33/3-yr          |
| Univ. Navarre [26, 27] | Cervix (prior ERBT) | 14           | 60/4-yr           | 22/4-yr          | 20/4-yr          |
|                 | Cervix (no prior ERBT) | 24           | 16/4-yr           | 5/4-yr           | 11/4-yr          |
|                 | Others           | 10               | 44/4-yr           | 33/4-yr          | 67/4-yr          |

*Three vagina, four uterine sarcoma, two ovary.

Four endometrium, four ovary, two vulva.
Recurrent Disease

The initial experience at the Massachusetts General Hospital suggested that IORT had applications in the treatment of locally recurrent disease [21]. Five patients with recurrent cervical carcinoma were treated with IORT. Three of these women were also treated with EBRT. A survival of 40% was noted at the time of publication [21]. Tables 1 and 2 summarize a review of the literature regarding rates of relapse and survival data for locally advanced recurrent disease.

The Mayo Clinic has a documented series that includes 55 patients with recurrent gynecologic cancers [3, 4, 22]. Thirty-six of them (65%) were also treated with either preoperative or postoperative EBRT. Re-irradiation, in the dose range of 9-50 Gy, was also used to treat 9 of the 28 (32%) women who had disease recurrence after previous irradiation. Eleven of these 28 patients (39%) also received preoperative chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin. In seven of them (64%), gross total resection was achieved. This chemotherapy regimen preoperatively resulted in a higher disease-free interval. However, the p value did not reach statistical significance. The median IORT dose used in the Mayo series was 15 Gy for microscopic residual disease and 20 Gy for gross residual tumor [3, 4, 22]. At five years, local relapse was seen in 43%, central relapse in 31%, and distant relapse in 48% [1]. Median survival was 20 months. Five-year survival was 29%, with a reported disease-free survival at five years of 21% [1].

In the European literature, the French have one of the largest series. They have reported their experience with IORT in 70 patients with recurrent cervical carcinoma [23, 24]. Thirty of the women also received EBRT. Additional chemotherapy in the form of 5-fluorouracil (5-FU) and cisplatin or a cisplatin-containing regimen was given to 20 of the patients. The mean IORT dose administered was 18 Gy. With a mean follow-up of 15 months, the French Intraoperative Group found median survival to be 11 months and local control to be 21%. The reported overall survival (at three years) was 8%. One and two-year survivals were 47% and 17%, respectively. Local relapse was seen in 50 (75%) of the 70 patients. Distant relapse was noted in 33% of the women [23]. It is important to note that 40 of these women did not receive EBRT and 37 of them had gross residual tumor [23]. The poor results documented in this study may be a reflection of inclusion of all patients without selecting for tumor volume and site of recurrence [25].

A series from the University of Navarre, Spain, included 31 patients with locally advanced or recurrent cervical carcinoma [26, 27]. These patients were treated with both chemotherapy (cisplatin and 5-FU) and EBRT (40-46 Gy) followed by surgery with or without IORT to high-risk areas for recurrence [26]. Complete and quasi-complete response was documented pathologically in 74% of the surgical specimens [26]. A partial response was noted in 26% [26]. Median follow-up was 27 months, with an actuarial disease-free survival of 80% and a locoregional control rate of 93.4% [26].

Primary Disease

Although there has been rather limited experience with IORT in the treatment of primary locally advanced gynecologic malignancies, patients who have disease extending to the pelvic sidewall or locally advanced nodal metastases are ideal candidates for IORT. Table 3 summarizes the survival data from some of the available series.

In one series, 16 patients who had locally advanced cervical cancer were treated with IORT to the para-aortic region.
Eleven of them (69%) had involvement of the para-aortic nodes. Two patients (12%) received para-aortic EBRT. IORT doses ranged from 15-20 Gy. In the 10 to 36 months following IORT, 4 of the 11 women with positive nodes (36%) were alive, 2 of them (36%) with no evidence of disease [6].

The experience at the Mayo Clinic includes treatment with IORT in eight patients with primary locally advanced cancers [3, 4, 22]. Seven of them (88%) were also treated with either preoperative or postoperative EBRT. The pattern of failure noted in this group of patients was as follows: 62% had local relapse at five years; 43% relapsed centrally at five years; and 36% demonstrated distant relapse at five years [1]. Among these women, median survival time was 12 months. Fourteen percent of them survived at five years, while the same percentage demonstrated disease-free survival at five years [1].

It is important to recognize the improvement in survival and local control when maximal tumor resection is achieved surgically. A five-year survival of 42% was documented in the Mayo Clinic series in cases of microscopic residual tumor [1]. In contrast, only 11% of patients with gross residual disease survived this same time interval [1]. These patients were also more likely to demonstrate distant metastases. Seventy-eight percent of women with gross residual disease had evidence of distant metastases at the five-year interval (in contrast with only 31% among those with microscopic residual disease) [1]. Median survival in the group with gross residual disease was 19 months, while it was reported as 36 months for those with only microscopic tumor [1].

<table>
<thead>
<tr>
<th>Series [Ref.]</th>
<th>n of Patients</th>
<th>Median Survival (months)</th>
<th>Survival (%)</th>
<th>Disease-Free Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo [3, 4, 22]</td>
<td>8</td>
<td>12</td>
<td>14/5-yr</td>
<td>14/5-yr</td>
</tr>
<tr>
<td>Konski a [28]</td>
<td>8</td>
<td>27</td>
<td>63/2-yr</td>
<td>—</td>
</tr>
<tr>
<td>Lyon b [29]</td>
<td>20</td>
<td>18</td>
<td>75/1-3 yrs</td>
<td>—</td>
</tr>
</tbody>
</table>

a Four cervix, two vagina, one endometrium, one uterine sarcoma.

b Eight cervix.

c Twenty cervix.

Another series from the Mayo Clinic noted treatment-related (surgery, IORT, EBRT, chemotherapy) grade 3 or higher toxicity in 36% of the patients [4]. Twelve patients suffered from complications in the gastrointestinal tract, six from soft tissue toxicity, four from hematological ones, one from bone, one from vascular tissue, and two from peripheral nerve toxicity [4]. The cumulative data gathered from the experience at the Mayo Clinic indicate a 17% risk of grade 3 or higher toxicity (11 of 63 women) [22]. Gastrointestinal obstruction or fistula formation occurred in 8% of patients, soft-tissue injury was reported in 3%, while ureteral obstruction was seen in 3% [22]. Some recommend that a ureteral stent should be placed in the IORT field either as prophylaxis or with the development of ureteral obstruction whenever tumor is adherent to the ureter prior to surgical resection [1].

**Table 3. IORT and survival results in primary gynecologic malignancies**

<table>
<thead>
<tr>
<th>Site of Toxicity</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral nerves</td>
<td>5%-30%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>8%-16%</td>
</tr>
<tr>
<td>Ureteral obstruction</td>
<td>3%</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>1%-2%</td>
</tr>
<tr>
<td>Hematologic</td>
<td>1%-2%</td>
</tr>
<tr>
<td>Vascular tissue</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Bone</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

**TOXICITY**

There has not been an increased morbidity to the surgical procedure performed when IORT is added. Complications were noted in 35% of patients receiving preoperative EBRT only. This was comparable to a 32% associated risk in those women receiving EBRT and IORT [7]. Table 4 lists the most common toxicities of IORT. The dose-limiting structures for IORT in both the pelvis and the para-aortic regions seem to be peripheral nerves [1, 6]. Reports of painful neuropathy range from 5%-30% [1]. One of the Mayo Clinic series quotes a rate of 48% of treatment-related toxicities (surgery, IORT, EBRT) [3]. In 29% of them (6 of 21 patients), IORT was directly responsible for the toxicity suffered. One patient suffered from vascular tissue toxicity, two from gastrointestinal tract toxicity, one from soft tissue, two from ureteral toxicity, and two from peripheral neuropathy [3].

Another series from the Mayo Clinic noted treatment-related (surgery, IORT, EBRT, chemotherapy) grade 3 or higher toxicity in 36% of the patients [4]. Twelve patients suffered from complications in the gastrointestinal tract, six from soft tissue toxicity, four from hematological ones, one from bone, one from vascular tissue, and two from peripheral nerve toxicity [4]. The cumulative data gathered from the experience at the Mayo Clinic indicate a 17% risk of grade 3 or higher toxicity (11 of 63 women) [22]. Gastrointestinal obstruction or fistula formation occurred in 8% of patients, soft-tissue injury was reported in 3%, while ureteral obstruction was seen in 3% [22]. Some recommend that a ureteral stent should be placed in the IORT field either as prophylaxis or with the development of ureteral obstruction whenever tumor is adherent to the ureter prior to surgical resection [1].

**CONCLUSIONS**

Patients diagnosed with locally advanced primary or recurrent gynecologic malignancies have a rather poor prognosis. The doses of external beam radiation necessary to treat either gross or microscopic recurrence in those who have been surgically treated or previously irradiated exceed what is tolerated by normal structures [1-4]. IORT has been added to the treatment armamentarium in this group of patients. This treatment modality allows maximizing local tumor control achievable with radiation, while minimizing...
the radiation exposure of dose-limiting surrounding structures. IORT has demonstrated the potential for improving both the long-term local control and the overall survival in women with pelvic sidewall and/or para-aortic nodal recurrence [1, 3, 4]. Perhaps the most encouraging results can be seen in the cases of microscopic residual disease, following surgical debulking [3].

The experience with IORT has served to further document the importance of optimal surgical resection. Higher five-year disease-free and overall survival rates are seen in women with microscopic residual disease, when compared to those with gross residual disease [1, 4]. Review of institutional experiences with IORT, especially among those institutions with the most experience, may serve to establish guidelines for patient selection. These criteria may in turn be utilized in the design of future clinical trials. The construction, execution, and evaluation of clinical trials are desperately needed in order to adequately assess the role of IORT in the treatment of patients with advanced primary and recurrent gynecologic malignancies.

**REFERENCES**


