Intraoperative Electron Beam Radiotherapy (IOERT) in the Management of Recurrent Ovarian Malignancies

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Objective: To investigate disease control, survival outcomes, and tolerance of intraoperative electron beam radiation therapy (IOERT) as a component of treatment for women with recurrent ovarian malignancies.

Methods: From November 1987 to January 2009, 20 patients with recurrent ovarian malignancies received IOERT after maximal surgical cytoreduction. Areas treated included the pelvis (14), para-aortic nodes (6), or inguinal nodes (1). The median IOERT dose was 12.5 Gy (range, 10–22.5 Gy). Sixteen patients also received perioperative external beam radiotherapy as a component of treatment (median, 50 Gy; range, 20–54.3 Gy). All patients were followed prospectively for outcome and toxicity evaluation.

Results: Median follow-up for surviving patients was 76.2 months (range, 1.5–175.8 months). The 5-year Kaplan-Meier estimate of local control was 59%, and central control (within the IOERT field) was 76%. All local relapses occurred in patients who had microscopic margin-positive resections. The 5-year freedom from distant relapse was 37%. The median disease-free interval after IOERT was 14 months. The median survival was 30 months, and the 5-year Kaplan-Meier estimate of survival was 49%. Six patients (29%) experienced grade 3 or higher toxicities, 2 of which (10%) were at least partly attributable to IOERT. Three patients experienced grade 1 or 2 peripheral neuropathy related to IOERT.

Conclusions: Combined modality therapy with external beam radiotherapy, surgery, and IOERT is an option for the treatment of localized recurrent ovarian cancer, with acceptable rates of in-field failure and toxicity. Durable disease control is possible in select women treated with this regimen.

Key Words: Ovarian cancer, Intraoperative radiation therapy, Surgical cytoreduction, Local disease relapse

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In the United States, an estimated 21,880 women will be diagnosed with ovarian cancer in 2010.[1] Approximately 75% of patients present with extrapelvic disease, and despite attempts to optimize surgical cytoreduction and adjuvant systemic therapy, long-term survival remains poor, with 5-year overall survival rates of 40% or less.[2–5] A major challenge in treating ovarian cancer is the propensity for early intraperitoneal (IP) tumoral relapse, even when initial cytoreduction is optimal.[6]

In addition to maximal surgical cytoreduction and adjuvant intravenous platinum-based chemotherapy, various adjuvant therapies have been used to decrease IP relapse and prolong the disease-free interval (DFI). These include IP chemotherapy, interval (second-look) surgical cytoreduction, whole-abdominal radiation therapy (WART), IP instillation of radioisotopes, autologous stem cell transplant, and IP radioimmunotherapy, with mixed results.[4,7–15] The role of radiation therapy remains controversial, despite the inherent radiosensitivity of ovarian cancer.

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Modern chemotherapy has been shown to be equivalent or superior to WART for improving disease-free and overall survival, with less toxicity.[16–19] However, 2 clinical trials have evaluated consolidative WART in combination with pelvic radiotherapy in select high-risk patient populations and have shown improvements in disease-free survival.[11,20] Despite these results, radiotherapy has generally fallen out of favor as front-line adjuvant or consolidative therapy for ovarian malignancies, largely owing to high rates of early and late toxicity associated with WART.[8]

Intraoperative radiotherapy (IORT), which delivers a single high-dose fraction of radiotherapy during surgery directly to the resection bed, has an inherent advantage over standard external beam radiotherapy in that high doses of radiation can be delivered to the areas most at risk for disease recurrence while limiting radiation exposure to surrounding structures, thus minimizing normal tissue toxicities. Since 1981, intraoperative electron radiation therapy (IOERT) has been used routinely at our institution in select patients for a variety of locally advanced malignancies, particularly when resection margins are in doubt.[21–26] The current study evaluates survival, patterns of relapse, DFI, toxicity, and prognostic factors of patients undergoing IOERT for recurrent ovarian malignancies.

MATERIALS AND METHODS

The Mayo Clinic Institutional Review Board (IRB) approved this study. We queried the prospective intraoperative radiotherapy database for patients with ovarian malignancies treated with IOERT at Mayo Clinic, Rochester, MN. From November 1987 to January 2009, 20 patients with recurrent ovarian cancer underwent surgical resection and IOERT. All patients had previously undergone surgical debulking at least once at the time of initial cancer diagnosis, subsequently experiencing relapse in the abdomen or pelvis. One patient underwent a re-resection with a second IOERT treatment after recurring in a separate pelvic site 21 months after initial IOERT. No other patient had previously received IOERT.

Patients were selected for this combined modality treatment approach if the pattern of relapse was local rather than disseminated peritoneal relapse and if there was concern that surgical margins would be close or positive. Some patients experienced multiple local relapses treated surgically before IOERT was considered. All patients underwent preoperative evaluation, consisting, at a minimum, of history and physical examination, laboratory studies, and computed tomography (CT) of the abdomen and pelvis. Patients with stable metastatic disease who were considered reasonable surgical candidates were offered combined modality treatment. Patients who had not previously undergone external beam radiotherapy (EBRT) were treated perioperatively (preoperatively or postoperatively) to the tumor bed and regional lymph nodes using megavoltage photons.

Details regarding IOERT delivery at Mayo Clinic have been previously described but are summarized below.[27] Since 1989, IOERT has been delivered in a dedicated operating suite containing a linear accelerator. Previous to this, patients were intraoperatively transferred to the department of radiation oncology under general anesthesia after surgical exploration and debulking. After maximal surgical resection of disease, the primary surgeon and radiation oncologist determined the area of gross or suspected microscopic residual disease. This was done by inspection of both the tumor bed and the resected surgical specimen. Intraoperative electron radiation therapy was delivered using one of a series of custom-made Lucite collimating devices of various lengths, shapes, and diameters selected to best encompass the at-risk field. All patients were treated using electrons with energies ranging from 6 to 12 million electron volts (MeV). The dose was prescribed to the 90% isodose level and was selected based on the amount of residual disease and proximity of critical structures.

Follow-up data including survival, patterns of failure, and toxicity were recorded prospectively in the institutional IOERT database through patients' visits or contact with local physicians. All end points were defined from the date of IOERT. Determination of disease progression was made based on radiographic imaging. Central failure (CF) was defined as recurrence within the IOERT field. Local control was defined as absence of both central failure and failure within the abdomen or pelvis in the region encompassed by the EBRT field. Recurrence outside the abdomen and pelvis was defined as distant failure. Toxicities were initially scored according to criteria developed by the National Cancer Institute intraoperative radiotherapy group[28] then were reclassified using the National Cancer Institute Common Toxicity Criteria (CTCAE) version 4.[29]

The Kaplan-Meier method was used to analyze clinical outcomes.[30] Potential factors associated with local control and overall survival (OS) were examined in a univariate analysis using the log-rank test. Variables examined included age (>60 and ≤60 years), margin status (microscopically or grossly positive and negative margins), tumor grade (high and low), tumor histology (adenocarcinoma and other), tumor size (>5 and ≤5 cm), IOERT dose (>1250 and ≤1250 cGy), and perioperative EBRT (yes or no). $P < 0.05$ was considered significant. The small number of patients in this study did not permit multivariate analysis. All statistical analysis was performed with JMP 8.0 (SAS Institute Inc, Cary, NC).

RESULTS

Patients' and Treatment Characteristics

Patients' clinical characteristics are summarized in Table 1. The median age at the time of IOERT was 60 years (range, 33–78 years). The mean time from initial cancer diagnosis to first recurrence was 55 months, and the mean time from initial diagnosis to surgery with IOERT was 80 months. Most of the patients (70%) had epithelial ovarian carcinomas, and most tumors were high grade. Other histological classifications represented included granulosa cell, malignant teratoma, adenosarcoma, and squamous cell carcinoma. Fourteen patients underwent IOERT for pelvic relapses, whereas 1 patient was treated for inguinal lymph node relapse, and the remaining 6 were treated for para-aortic nodal relapses. Four patients had previously undergone external

TABLE 1. Patients' characteristics at the time of recurrence

Characteristic	Value
Age, yrs	
Median	59.8
Range	32.7–77.7
Tumor histology, n	
Epithelial ovarian carcinoma*	13
Granulosa cell	3
Other†	4
Tumor grade, n	
Low	3
High	14
Unknown	3
Prior EBRT, n	
Yes	4
No	15
Prior chemotherapy, n	
Yes	19
No	1

*Epithelial ovarian carcinoma histologies: 6 unclassified adenocarcinomas, 4 papillary serous tumors, 2 transitional cell tumors, and 1 clear cell tumor.

†One each of adenosarcoma, malignant teratoma, stromal tumor, and squamous cell histology.

radiation and were not treated perioperatively with EBRT. All but one patient had received systemic therapy at some point before combined modality therapy with IOERT, usually in the immediate postoperative period after the first diagnosis.

Treatment characteristics are summarized in Table 2. The median at-risk area treated with IOERT was 5 cm (range, 2.2–15.3 cm), and treatment was accomplished using a single IOERT field in all but 2 patients. The median IOERT dose was 1250 cGy (range, 1000–2250 cGy), and most of the patients were treated with either 9 or 12 MeV electrons. Final pathology after surgery revealed negative surgical margins in 9 patients, whereas 11 had microscopically positive margins. In one patient, unresectable macroscopic tumor was visualized in the tumor bed. Most patients treated with perioperative EBRT were treated preoperatively. The median EBRT dose in all patients was 5000 cGy (range, 2000–5430 cGy). Three patients were treated with WART only, one received WART with a boost to the tumor bed and locoregional lymph nodes, and all others underwent locoregional irradiation only.

Survival

Six patients were alive at the time of last follow-up at a median of 6.3 years (range, 0.1–14.6 years). Survival estimates for all patients are shown in Figure 1. Median survival was 30 months. The 5- and 10- year Kaplan-Meier estimates of survival were 49% and 18%, respectively. Variables associated with improved survival on univariate analysis included low tumor grade ($P = 0.03$) and administration of perioperative EBRT (trend for significance, $P = 0.06$).

Patterns of Relapse

The cumulative incidence of central, local, and distant disease relapse is shown in Figure 2. The median DFI after IOERT for the entire cohort was 14 months (range, 2.6–175.8 months). Excluding patients with less than 6 months follow-up, 3 (18%) of 17 patients were free of recurrence of any kind (central, local, or distant) at a mean follow-up of 11.2 years. The histological findings for these patients were malignant teratoma, adenosarcoma, and unspecified adenocarcinoma.

Central relapse was uncommon and occurred in only 3 patients (14%) at a mean of 2 years from IOERT. The

TABLE 2. Treatment characteristics

Characteristic	Value
Surgical margin, n	
Negative	9
Microscopic positive	11
Macroscopic positive	1
IOERT	
Maximum field at risk size, cm	
Median	5
Range	2.2–15.3
IOERT Dose, cGy	
Median	1250
Range	1000–2250
IOERT Field, n	
Pelvis	14
Para-aortic	6
Inguinal	1
Energy, n	
12 MeV	8
9 MeV	12
6 MeV	1
Total fields, n	
1	19
2	2
Perioperative EBRT	
Timing, n	
Preoperative	10
Postoperative	6
None	4
Dose, cGy	
Median	5000
Range	2000–5430

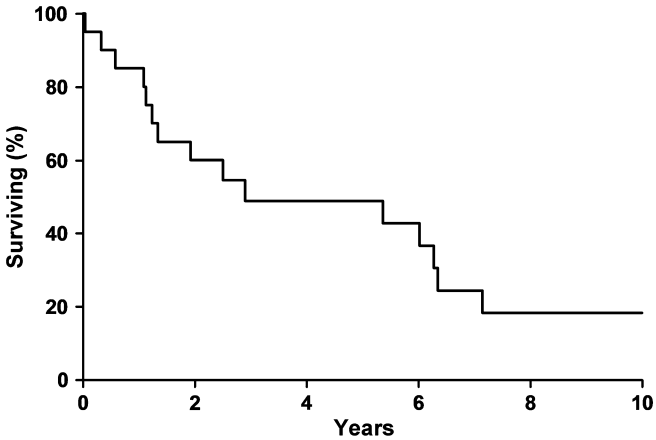

FIGURE 1. Kaplan-Meier survival curve.

5-year Kaplan-Meier estimate of central control was 76%. All patients who experienced a central relapse had microscopic residual disease at the time of IOERT. The one patient with macroscopic residual disease did not experience central relapse. One of the 3 patients with central failure experienced a simultaneous distant failure, whereas the other 2 patients (10%) had central-only failures.

Local relapse occurred in a total of 6 patients (29%) at a mean of 1.6 years from IOERT. The 5-year actuarial local control was 59%. Isolated local relapse (nondistant relapse) occurred in 4 patients (19%). Five of the 6 patients who experienced local relapse had high grade tumors. Five local relapses occurred in the pelvis, whereas the other occurred in the para-aortic region. All local relapses occurred in the patients who did not receive EBRT as part of their combined modality therapy, in patients who received WART only without treatment of nodal basins, or in areas outside the volume receiving the highest EBRT dose. On univariate analysis, an association with improved local control was noted in the patients with negative pathologic margins ($P = 0.05$)

Distant relapse was the most common pattern of recurrence, with a total of 9 patients (43%) developing distant metastasis at a mean of 1.6 years from IOERT. The 5-year actuarial freedom from distant relapse was 37%. Only one patient, with granulosa cell histology, was alive with distant disease at the time of last follow-up, having developed metastasis 19 months after IOERT.

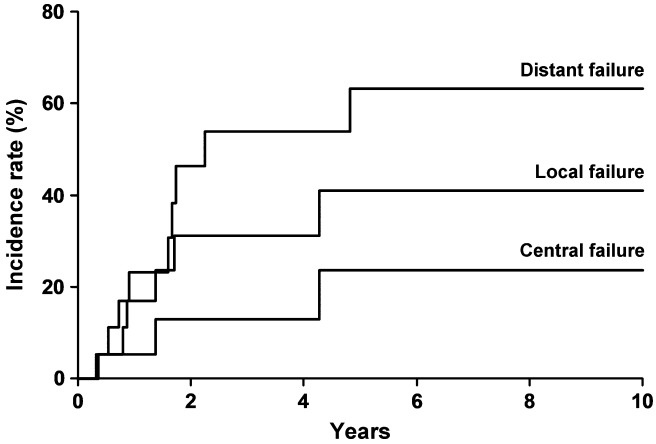

FIGURE 2. Cumulative incidence of relapse.

TABLE 3. Toxicity

	CTCAE Toxicity Grade (n [n Related to IOERT])			
	2	**3**	**4**	**5**
Connective tissues				
Abscess	1 (0)		1 (1)	
Bone fracture	1 (0)			
Lymphedema	1 (1)			
Gastrointestinal				
Obstruction	1 (0)	3 (0)		
Chronic diarrhea	1 (0)			
Fistula	1 (1)			
Neurologic				
Peripheral neuropathy	3 (3)			
Urinary				
Ureteral obstruction			1 (1)	
Chronic cystitis	1 (1)			
Vascular				
Deep vein thrombosis	1 (0)			
Hemorrhage				
Totals	11 (6)	3 (0)	2 (2)	1 (0)

Toxicity

Table 3 shows all grades 2 to grade 5 toxicities, scored by CTCAE version 4, identified in this patient cohort. The most common toxicities were gastrointestinal and neurologic. Only one gastrointestinal toxicity, the formation of a small rectovaginal fistula, which subsequently closed spontaneously, was partly attributable to IOERT. Three patients experienced grade 2 peripheral neuropathy in the form of sciatic-type pain requiring daily medication use as a result of IOERT. One other patient experienced transient peripheral neuropathy (grade 1), which subsequently resolved. Two patients experienced life-threatening grade 4 toxicities, both potentially related to IOERT. One patient developed an abscess postoperatively, causing transient bacteremia, which ultimately required surgical evacuation. Another patient developed ureteral stenosis in the ureter, draining urine from her only intact kidney, 9 years after IOERT. Finally, there was a single perioperative mortality, occurring on postoperative day 16 after a massive left pelvic sidewall resection secondary to a surgical vascular injury. In all, 12 (60%) of 20 patients experienced any grade 2 or higher toxicity, and 6 (30%) of 20 patients experienced a grade 3 or higher toxicity.

DISCUSSION

This trial reports on the clinical outcomes for a series of consecutively treated patients at a single institution with

a combined modality approach that included IOERT for locally recurrent ovarian cancer. Multiple prospective trials, including 2 meta-analyses, have shown that volume of residual disease remaining after initial cytoreductive surgery for ovarian cancer is inversely correlated with DFI and OS.[31–38] The Gynecologic Oncology Group defines optimal cytoreduction as residual disease less than 1 cm in maximum diameter, although mounting evidence suggests that survival outcomes may improve even further if cytoreduction beyond less than 1 cm is possible.[33,39–42]

The optimal treatment for patients who experience local recurrence after initial therapy is unknown, and the benefit of secondary cytoreduction in this setting is unclear.[43] Based on the information available, patients most likely to benefit from secondary cytoreduction have the following characteristics: an initial progression-free interval of more than 1 year, a response to first-line therapy, a good performance status, and locally-only recurrent disease, which is technically amenable to gross total resection.[44–49] For patients meeting the aforementioned criteria, secondary cytoreduction has generally been shown to be effective for prolonging survival outcomes, although this is yet to be validated in a large prospective, randomized, controlled trial. Both the Gynecologic Oncology Group and the European Organization for Research and Treatment of Cancer (EORTC) are actively enrolling patients on trials designed to answer this question.[43] It stands to reason that strategies to optimize local eradication of tumor may contribute to improvements in survival outcomes, especially in patients with localized relapse.

Intraoperative electron beam radiation therapy has a distinct advantage over conventionally fractionated EBRT because it can be given in a single large fraction to the areas most at risk for disease recurrence while potentially avoiding nearby critical structures such as the ureters, bowels, kidneys, and bladder. In the present study, maximal surgical resection, IOERT, and perioperative EBRT was associated with durable local control in most patients. The failure rate within the IOERT field was estimated to be 24% at 5 years, and most patients who had disease recurrence relapsed distantly. Although there was no control group in this study, these results compare favorably with those from other series in which a combined modality approach for locally recurrent ovarian cancer was not used. A review of published institutional series in which patients were treated with maximal surgical cytoreduction at the time of cancer recurrence shows a wide range of median survival times, ranging from 16 to 56 months in patients treated with optimal debulking versus 8 to 27 months if optimal debulking was not possible.[47] In a recently published institutional series, OS at 2 and 5 years was found to be 58% and 26%, respectively, in women with ovarian malignancies who underwent maximum surgical cytoreduction at the time of first disease recurrence.[43] Another alternative to surgical cytoreduction for recurrent ovarian cancer is chemotherapy. Response rates to second-line chemotherapy vary but are typically in the 25% to 30% range.[50,51] The median survival from the time of IOERT in the current series was 30 months and the 5-year OS was 49%.

Other institutional series have been published detailing the use of IORT with maximal surgical resection for recurrent ovarian malignancies. Table 4 summarizes clinical outcomes from these studies and includes data from the current study.[52–57] Our report increases the number of patients whose outcomes have been documented in the medical literature from 46 to 64. The 2005 publication from Stanford University by Yap et al,[57] accounting for 22 of these patients, is comparable to the current series in study size, treatment approach, and clinical outcomes. They report a mean DFI from initial diagnosis to intraoperative radiotherapy of 48.2 months. In this series, the mean time from initial diagnosis to first recurrence was 55.4 months, and the mean time from diagnosis to surgery with IOERT was 79.9 months. The median DFI in the Stanford study was 11 months compared to 14 months in this study. They report a median survival after IORT of 26 months compared to 30 months in this study. The 5-year survival in the current series is significantly longer than that in the Yap series (49% vs 22%); however, this may be the result of selection bias. The longer interval between initial diagnosis and IOERT in our series

TABLE 4. Literature review

Series	Date	No. Patients	IORT Modality	IORT Dose (Gy)	Median DFI (mos)	Local Failures* (n)	Median Survival (mos)	5-Year OS (%)
Yordan et al[52]	1988	4	Electron beam	—	6	—	—	—
Konski et al[53]	1990	5	Electron beam	20	—	2/5	14	—
Hicks et al[54]	1993	5	Orthovoltage	15	—	4/5	5	—
Martinez-Monge et al[55]	1993	4	Electron beam	15	—	—	19	30†
del Carmen et al[56]	2003	4	Electron beam	12.5	17	2/4	—	—
Yap et al[57]	2005	22	Orthovoltage	12	11	7/22	26	22
Current series	2010	20	Electron beam	12.5	14	6/21	30	49

*Failure within the external beam field or within the pelvis for non–EBRT-treated patients.
†Survival reported is at 4 years.

may indicate that the patients we selected for combined modality therapy would have performed better regardless of treatment.

In our series, the rate of grade 3 or higher toxicity with combined modality therapy was significant (30%) although not inconsistent with other series. Yap et al[57] reported a 41% incidence of grade 3 or higher toxicity. Surgery-alone series report perioperative complication rates of 9% to 26%, with overall complication rates ranging from 26% to 36%. The perioperative mortality rate reported in the surgical literature is typically in the 1% to 3% range.[43,46,49] There was one perioperative death in the current study.

As a retrospective single-institution review, this study is subject to biases, confounding factors, and applicability issues as are all reports of this nature. First, the study reports on 20 patients treated over a period of more than 20 years, representing a treatment rate of less than one patient treated per year. However, most of the patients in the study were treated by one of 2 radiation oncologists (M.G.H. and I.A.P.) whose experience with IOERT in other disease sites has been well documented.[21–25] Another weakness of the study is the heterogeneous nature of the study population, in particular, the varied tumor histologies. In addition, not all patients were treated with a combined modality approach at the time of first recurrence; in fact, one patient with a granulosa cell tumor had already undergone 4 surgeries for disease recurrence before undergoing IOERT. This emphasizes the importance of patient selection when considering IOERT. In general, the patients on this study met the previously mentioned criteria indicative of the patients most likely to benefit from secondary cytoreduction at the time of recurrence. Finally, all patients in this series received IOERT and surgery, thus preventing a direct analysis of any additional benefit that surgery with IOERT may have provided relative to surgery alone.

This study documents outcomes with a combined modality approach including IOERT for the treatment of recurrent ovarian cancer. Our institutional experience suggests that in a carefully selected cohort of patients, IOERT can be safely combined with surgery and perioperative EBRT for the treatment of these recurrences. Using this approach, local control was achieved in most of the women, and some were able to experience long-term freedom from disease recurrence. Whereas no definitive statement can be made regarding the contribution of IOERT to the local control of disease in this cohort of patients, our results compare favorably with other series. Until level I evidence is available to guide therapy in this spectrum of disease, treatment should continue to be individualized, and consideration should be given to a combined modality approach, including IOERT, for locally recurrent ovarian cancer, particularly when the likelihood of microscopic residual disease is high.

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