MAYO CLINIC

ORIGINAL ARTICLE

Radical Extirpation With Intraoperative Radiotherapy for Locally Recurrent Gynecologic Cancer: An Institutional Review

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Abstract

Objective: To report survival outcomes in patients with locally recurrent gynecologic cancers managed with curative-intent radical extirpation, perioperative external beam radiotherapy, and intraoperative radiotherapy (IORT).

Patients and Methods: We conducted a retrospective cohort analysis of 44 patients with locally recurrent gynecologic cancer treated at a single tertiary-care center (Mayo Clinic in Arizona) over a 15-year period (January 1, 2004, to July 31, 2019). This cohort included patients with uterine (n=21, 47.7%), ovarian (n=3, 6.8%), cervical (n=11, 25.0%), vaginal (n=2, 4.5%), vulvar (n=1, 2.3%), and unknown primary (n=6, 13.6%) cancer. Curative-intent radical extirpation included pelvic exenteration (n=13, 29.5%), laterally extended endopelvic resection (n=22, 50.0%), excision of para-aortic lymph node metastasis (n=8, 18.2%), and radical vaginectomy (n=1, 2.3%). Of the 44 patients in our cohort, 37 (84.1%) received IORT and 7 (15.9%) had intended to receive IORT but did not receive it.

Results: The median follow-up for the 44 patients was 12 months (range, 1 to 161 months). For patients who received IORT, the median progression-free survival (PFS) and overall survival (OS) were 13 and 21 months, respectively, and the 3-year cumulative incidence of central, locoregional, and distant recurrence was 27.0% (10 of 37), 40.5% (15 of 37), and 37.8% (14 of 37), respectively. Surgical margins were classified as negative (28 of 44, 63.6%), microscopic (11 of 44, 25.0%), or macroscopic (5 of 44, 11.4%). Negative, microscopic, and macroscopic surgical margins resulted in 3-year PFS of 51.8%, 20.5%, and 0%, respectively (P=.01) and 3-year OS of 62.9%, 20.0%, and 0%, respectively (P=.035). Progression-free survival (P=.69) and OS (P=.88) were not different between patients with negative surgical margins who received (n=21) and did not receive (n=7) IORT. Ten of 37 patients (27.0%) had development of grade 3 or higher toxicities, with 1 death due to sepsis.

Conclusion: Complete tumor resection at the time of curative-intent radical extirpation achieved higher rates of PFS and OS regardless of IORT administration.

 ■ Mayo Clin Proc Inn Qual Out 2021;5(6):1081-1088

Patients with locally recurrent gynecologic malignancies have a poor prognosis.[1,2] For central recurrence, pelvic exenteration offers the highest potential for cure.[1,3] However, when the disease involves the lateral pelvic sidewall or sacrum, options for cure remain limited because of inability to resect tissue with negative margins.[4-6] In these cases, negative margins can be achieved with a radical surgical procedure such as laterally extended endopelvic resection.[4-6] In our experience, these operations can be technically challenging and are associated with substantial perioperative morbidity. These operations also have a high potential for residual tumor, particularly near bony structures, leading to locoregional recurrence.[4-9]

The use of radiation in this clinical situation is controversial, particularly in patients who have received radiation therapy previously.[10] Dose-limiting structures such as the bowel, bladder, and rectum can make reradiation

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challenging with a high risk for toxicity.[10-12] Intraoperative radiotherapy (IORT) is a modality that allows for additional radiation to be delivered safely, primarily by physically displacing normal tissues such as bladder and bowel away from radiation exposure.[1] The literature suggests that use of IORT for recurrent gynecologic malignancies may improve local control and long-term overall survival (OS).[10,13-15] In this study, we describe our experience with IORT at the time of extirpative surgical treatment in patients with locally recurrent gynecologic malignancies.

PATIENTS AND METHODS

The Mayo Clinic Institutional Review Board approved this retrospective medical record review (IRB #18-009261). The medical records of 44 patients treated at Mayo Clinic in Arizona from January 1, 2004 ,to July 31, 2019, were reviewed. All patients with locally recurrent gynecologic cancer underwent radical extirpation with intention for IORT. Radical extirpative procedures included pelvic exenteration, laterally extended endopelvic resection, excision of para-aortic lymph node metastases, and radical vaginectomy. Candidates for IORT were medically fit patients with locally recurrent gynecologic cancer not amenable to surgical resection alone and without evidence of distant metastasis.[1]

Pretreatment evaluation included a complete history and physical examination, routine laboratory studies, and imaging to assess the extent of local disease and to rule out distant metastasis (computed tomography, magnetic resonance imaging, and positron emission tomography at the discretion of the treating physician). A multidisciplinary tumor board of physicians from gynecologic oncology, medical oncology, radiation oncology, and surgical pathology determined appropriate treatment plans. If a patient had a history of radiation therapy, outside records were reviewed to determine if additional preoperative irradiation was feasible. Radiation dose was based on the time interval from prior radiation therapy, the prior radiation therapy dose, and the location of the radiation therapy field. Systemic chemotherapy was added as indicated based on tumor histology and characteristics.

Surgical resection was performed, and the abdomen was fully explored to ensure that there was no evidence of other sites of metastases. Surgical specimens were oriented and sent for frozen section to confirm margin status. Surgical margins were classified as negative, microscopic, or macroscopic residual tumor. Exenteration and the ability to achieve complete tumor resection were not prerequisites for administration of IORT. The final decision to administer IORT was made intraoperatively by both the gynecologic oncologist and the radiation oncologist. Intraoperative radiotherapy techniques used at Mayo Clinic have been described previously.[16] A dedicated linear accelerator (Mobetron, IntraOp Medical, Inc) was used in specialized operating suites for delivery of IORT. Intraoperative radiotherapy was prescribed at appropriate doses (range, 10 to 18 Gy) to the 90% isodose level and took into account the amount of residual tumor and its proximity to critical structures. The size of the IORT applicator encompassed the tumor bed plus a 2- to 3-cm margin. The thickness of the tumor bed was estimated by direct measurement or by preoperative imaging. The appropriate energy (range, 6 to 15 MeV) of IORT was selected to ensure adequate dose coverage to the full thickness of the tumor bed.

Progression-free survival (PFS) was defined as the time from radical surgical treatment to disease recurrence or progression. Overall survival was defined as the time from radical surgical treatment to death from all causes. After surgical treatment, surveillance was scheduled in 3-month intervals for the first 2 years and then in 6-month intervals until 5 years after treatment. Disease progression was determined using physical examination findings and/or imaging ordered at the discretion of the treating physician. Disease recurrence was classified as central, locoregional, or distant relapse. Central recurrence was defined as disease appearing within the IORT field. Locoregional recurrence was defined as disease within the IORT field in addition to local lymph nodes. Distant recurrence was defined as disease outside the pelvis. Patients who were alive and disease-free at last follow-up were treated as censored observations. Toxicity was scored using the National Cancer Institute's Common Terminology

Criteria for Adverse Events (formerly, Common Toxicity Criteria).

The Mann-Whitney *U* test was used to analyze continuous variables as appropriate. Frequency distributions were compared using the χ^2 test and Fisher exact test for categorical variables. Progression-free survival and OS were estimated using the Kaplan-Meier method and log-rank test. Progression-free survival and OS were compared between patients who received and did not receive IORT. Univariate analysis was performed to assess the clinical and pathologic risk factors for survival including residual tumor, tumor pathology, site of recurrence, tumor size, history of external beam radiotherapy (EBRT) at initial diagnosis, perioperative EBRT at recurrence, and IORT. Risk factors with statistical significance were selected for further analysis with the multivariate Cox proportional hazards regression model. In all cases, $P<.05$ was considered statistically significant. SPSS Statistics for Windows, version 23.0 (IBM Corp) and Prism 6.0c (GraphPad Software) statistical software were used for statistical analyses.

RESULTS

Of the 44 patients with recurrent disease who underwent radical surgical treatment with intention for IORT, 37 (84.1%) received IORT and 7 (15.9%) ultimately did not receive IORT due to complete tumor resection.

The median time from initial diagnosis to first recurrence or disease progression was 36 months (range, 3 to 360). Patients were divided to 2 groups according to the time of initial treatment to recurrence: 12 or more months vs less than 12 months. There were no survival differences in PFS (hazard ratio, 1.236; 95% CI, 0.4845 to 3.155; $P=.66$) and OS (hazard ratio, 1.188; 95% CI, 0.4611 to 3.060; $P=.73$) after IORT.

Extirpation With IORT

The 37 patients who underwent extirpation with IORT were diagnosed as having the following cancers: uterine, 20 (54.1%); ovarian, 2 (5.4%); cervical, 8 (21.6%); vaginal, 2 (5.4%); vulvar, 1 (2.7%); and unknown primary, 4 (10.8%). Tumor characteristics including histologic subtypes are listed in Table 1, with endometrioid endometrial adenocarcinoma being most common (n=11, 29.7%). The median age of this cohort was 62 years (range, 29 to 89 years). Sites of recurrence (Table 2) occurred centrally (n=5, 13.5%), at the pelvic sidewall (n=16, 43.2%), lymph nodes (n=8, 21.6%), or multiple sites (n=8, 21.6%). The median tumor size was 5 cm (range, 1 to 12 cm).

Treatments received at initial diagnosis and at recurrence are listed in Table 2. At recurrence, 35 patients (94.6%) received preoperative radiation therapy prior to planned extirpation, with a median dose of 45 Gy (range, 19.8 to 57 Gy); 23 patients (62.2%) received both EBRT at the time of initial diagnosis and radiation therapy prior to extirpation, receiving a median cumulative dose of 95.4 Gy (range, 75.2 to 110 Gy); and 10

TABLE 1. Tumor Characteristics Stratified by Histology in the IORT Cohort

Cancer type	No. (%) of patients (N=37)
Uterine	
Endometrioid	11 (29.7)
UPSC	2 (5.4)
Leiomyosarcoma	3 (8.1)
Clear cell adenocarcinoma	1 (2.7)
ESS	2 (5.4)
Mullerian sarcoma	1 (2.7)
Ovarian	
Serous adenocarcinoma	1 (2.7)
Undifferentiated adenocarcinoma	1 (2.7)
Cervical	
Squamous	7 (18.9)
Adenocarcinoma	1 (2.7)
Vaginal	
Squamous	1 (2.7)
Adenocarcinoma	1 (2.7)
Vulvar	
Squamous	1 (2.7)
PUO	
Squamous	1 (2.7)
Adenocarcinoma	1 (2.7)
Mullerian adenocarcinoma	1 (2.7)
Spindle cell	1 (2.7)

ESS, endometrial stromal sarcoma; IORT, intraoperative radiotherapy; PUO, pelvic of unknown origin; UPSC, uterine papillary serous carcinoma).

TABLE 2. Treatments and Disease Status at Recurrence and at Initial Diagnosis in the IORT Cohort[a]

Variable	Median dose (Gy)	No. (%) of patients (N=37)
Recurrence		
RT		
Prior EBRT (at initial diagnosis)	50 (35-70)	25 (67.6)
Preoperative RT (prior to extirpation)	45 (19.8-57)	35 (94.6)
Both	95.4 (75.2-110)	23 (62.2)
Site of recurrence or disease progression prior to extirpation		
Central	NA	5 (13.5)
Pelvic wall		16 (43.2)
Lymph node		8 (21.6)
Multisite		8 (21.6)
Type of surgery	NA	
LEER		18 (48.6)
PE		10 (27.0)
Tumor debulking + LND		8 (21.6)
Radical vaginectomy		1 (2.7)
Residual tumor	NA	
No viable tumor		4 (10.8)
Negative		21 (56.8)
Microscopic		11 (29.7)
Macroscopic		5 (13.5)
Site of recurrence or disease progression after IORT	NA	
Central		10 (27.0)
Locoregional		15 (40.5)
Distant		14 (37.8)
Initial diagnosis	NA	
Treatments received		
Surgery		7 (18.9)
Primary RT[b]		9 (24.3)
Surgery + R		10 (27.0)
Surgery + CT		1 (2.7)
Surgery + RT + CT		10 (27.0)

LEER, laterally extended endopelvic resection; LND, lymph node dissection; NA, not applicable; PE, pelvic exenteration; RT, radiation therapy.
[a]CT, chemotherapy; EBRT, external beam RT; IORT, intraoperative radiotherapy;
[b]Primary RT included treatment with EBRT, brachytherapy, or both.

patients received chemotherapy (27.0%) prior to surgery.

Ten patients (27.0%) underwent pelvic exenteration, 18 (48.6%) had laterally extended endopelvic resection, 8 (21.6%) underwent excision of para-aortic lymph node metastasis, and 1 (2.7%) had radical vaginectomy. Thirty-five of the cases (94.6%) were performed via laparotomy (1 conversion from laparoscopy to laparotomy) and 2 as minimally invasive with robotic assistance. Two patients underwent *en bloc* vessel resection as a result of tumor attachment or invasion.

Tumor specimens were submitted to surgical pathology for frozen section to confirm margin status. Twenty-one patients (56.8%) had negative surgical margins, with 4 of whom (10.8%) having no viable tumor. Eleven patients (29.7%) had microscopic and 5 (13.5%) had macroscopic margin involvement. Thirty-three patients (89.2%) had a single IORT field while 4 (10.8%) had multiple IORT fields, with a median dose of 12.5 Gy (range, 10 to 18 Gy) and median energy of 9 MeV (range, 6 to 15 MeV).

At the end of this study period, median follow-up was 12 months (range, 1 to 161 months). Fourteen patients (37.8%) experienced complete remission without relapse, and 1 patient is alive with subsequent disease recurrence. Twenty-two patients (59.5%) died, all due to disease progression except for 1 patient who died of perioperative complications. There were 10 central recurrences (27.0%), 15 locoregional recurrences (40.5%), and 14 distant recurrences (37.8%) after IORT.

There were 16 occurrences of toxicity or complications in 10 patients (27.0%). The 16 occurrences included 2 gastrointestinal fistulas, 5 pelvic abscesses, 2 pulmonary embolisms, 2 perioperative hemorrhages, 1 gastrointestinal obstruction, 1 peripheral neuropathy, 1 ureteral stenosis, and 2 other events. The 2 other events were upper extremity compartment syndrome and postoperative atrial fibrillation in one patient each. There was one grade 5 complication with patient death 4 days postoperatively due to gastrointestinal anastomotic leak leading to septic shock.

The overall median PFS of 13 months (3-year PFS, 33.5%) and median OS of 21 months (3-year OS, 38.3%) are depicted in the Figure using Kaplan-Meier survival curves. On univariate analysis, 3-year PFS for patients with negative, microscopic, and macroscopic margins was 51.8%, 20.5%, and 0%, respectively (P=.006), and 3-year OS was 62.9%, 20.0%, and 0%, respectively (P=.035). Patients with small tumors were more likely to have complete surgical resection, with a median tumor diameter of 4.4 cm in patients

Mayo Clin Proc Inn Qual Out ■ December 2021;5(6):1081-1088 ■ https://doi.org/10.1016/j.mayocpiqo.2021.10.004
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with negative surgical margins compared with 6.5 cm in patients with microscopic or macroscopic residual tumor (P=.037). Perioperative EBRT (P=.20), dose of EBRT (P=.78), administration of concurrent chemoradiotherapy or chemotherapy alone (P=.54), site of recurrence (P=.83), and administration of IORT (P=.53) were not associated with achievement of complete surgical resection.

Extirpation Without IORT

In the group that did not receive IORT, 1 patient had uterine cancer, 1 had ovarian cancer, 3 had cervical cancer, and 2 had unknown primary cancers (Table 3). Of the 7 patients, 3 underwent pelvic exenteration and 4 underwent laterally extended endopelvic resection. All patients had negative margins at intraoperative pathologic assessment. One patient underwent *en bloc* vessel resection with subsequent vessel replacement graft. Three patients experienced major perioperative complications related to abscess formation.

There were 4 (57.1%) recurrences after extirpative surgical treatment, which were all distant recurrences. Three patients (42.9%) achieved complete remission with 46 to 56 months of PFS at the end of the study period (Figure).

TABLE 3. Treatments and Disease Status at Recurrence in the Cohort.

Variable	No. (%) of patients (N=7)
Tumor type	
Cervical	3 (42.9)
Ovarian	1 (14.3)
Uterine	1 (14.3)
PUO	2 (28.6)
Type of surgery	
LEER	4 (57.1)
PE	3 (42.9)
Residual tumor	
Negative	7 (100.0)
Microscopic	0 (0.0)
Macroscopic	0 (0.0)
Site of recurrence or disease progression after IORT	
Central	0 (0.0)
Locoregional	0 (0.0)
Distant	4 (57.1)

IORT, intraoperative radiotherapy; LEER, laterally extended endopelvic resection; PE, pelvic exenteration; PUO (pelvic of unknown origin).

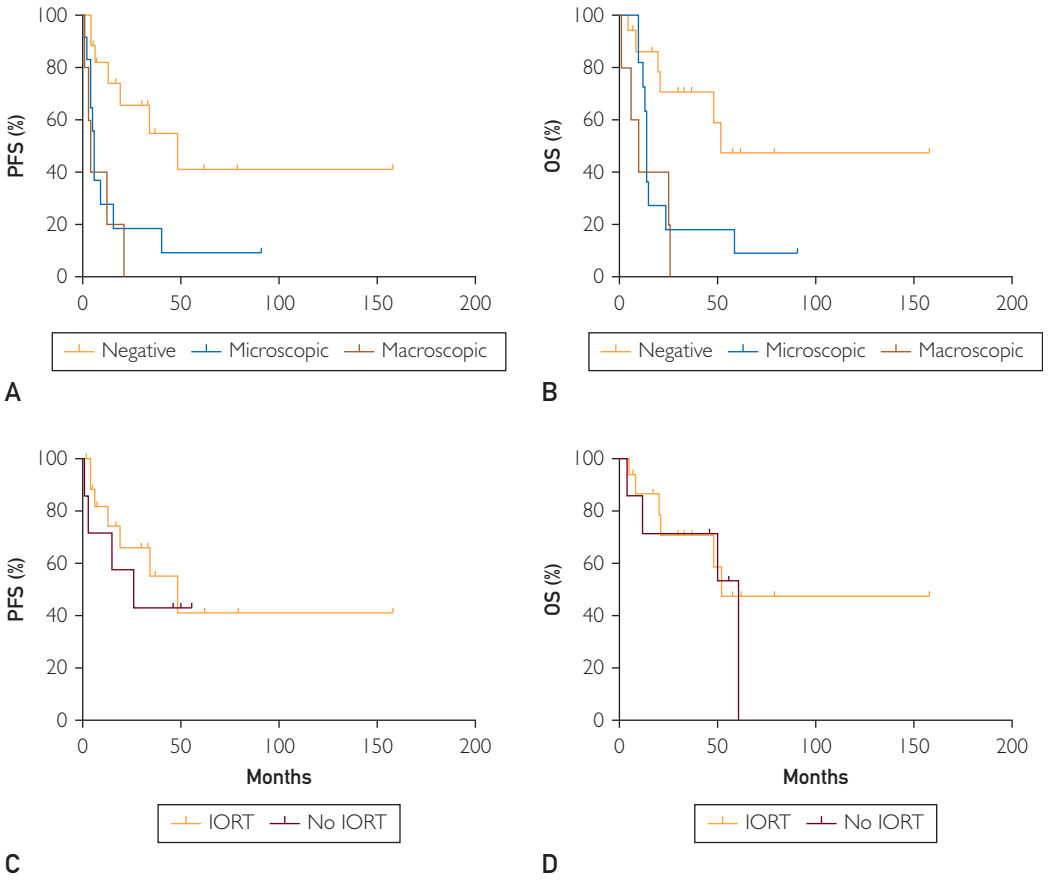
IORT vs No IORT

In patients who had complete tumor resection, there was no difference in PFS (P=.69) and OS (P=.88) between those who received IORT and those who did not. Additionally, in this same group of patients with complete tumor resection, there was no difference in locoregional control (P=.29) or distant control (P=.21) between those who received IORT and those who did not.

DISCUSSION

In this study, we reviewed outcomes of patients with locally recurrent gynecologic malignancies who received extirpative surgical treatment with or without IORT. Patients who underwent extirpative operations with complete tumor resection had improved PFS and OS compared with patients who had suboptimal resection regardless of IORT administration.

The primary goal of curative-intent extirpative operations should be complete tumor resection. The role of IORT at the time of radical surgical treatment in patients with locally recurrent gynecologic malignancies is promising, but data are limited to only small retrospective studies.[10,13,17] The most encouraging results are seen in cases with no or microscopic residual tumor after debulking procedures, suggesting variable but improved disease control and survival with use of IORT.[10,13,17] In a retrospective analysis of 39 patients with locally recurrent gynecologic cancer, microscopic or macroscopic residual tumor after radical surgical treatment with IORT produced central and locoregional control rates of 81% and 67.4%, respectively.[10] The cohort had a 5-year PFS and OS of 55% and 50%, respectively.[10] In another study of 86 patients with locally recurrent cervical cancer treated with radical surgical treatment and IORT, negative, microscopic, and macroscopic resection margins produced significant differences in distant control (61%, 45%, and 25%, respectively) and PFS (45%, 27%, and 14%, respectively).[15] Most recently, a



		Median PFS	3-year PFS (%)	*P*	Median OS	3-year OS (%)	*P*
No IORT	Negative	26	54.8	.69	61	70.8	.88
IORT	Negative	48	51.8	.006	52	62.9	.035
	Microscopic	6	20.5		14	20.0	
	Macroscopic	4	0		10	0	

FIGURE. Kaplan-Meier survival curves. A, Progression-free survival (PFS) of patients with negative, microscopic, or macroscopic residual tumor in the intraoperative radiotherapy (IORT) cohort. B, Overall survival (OS) of patients with negative, microscopic, or macroscopic residual tumor in the IORT cohort. C, Progression-free survival of patients with negative residual tumor with or without IORT. D, Overall survival of patients with negative residual tumor with or without IORT.

retrospective study of 32 patients who received radical surgical treatment with IORT, 5-year PFS was 40.9% in patients with microscopic residual tumor in contrast to 9.1% with macroscopic residual tumor, and 5-year OS was 77.3% for microscopic and 54.5% for macroscopic residual tumor.[3]

Prognosis for patients with locally recurrent or persistent gynecologic malignancies is poor overall, and often central recurrence is the primary site.[3] In patients with distant metastasis, survival rates are dismal.[2,4] The literature supports central and locoregional control to decrease risk of distant metastasis.[2] In concordance with prior retrospective studies, our results suggest that complete tumor resection is imperative for central control, PFS, and OS. In patients who received IORT, sites of recurrence were more likely to be locoregional (n=15, 40.5%) or distant (n=14, 37.8%). Central recurrence was more common in patients with microscopic (n=4,

Mayo Clin Proc Inn Qual Out ■ December 2021;5(6):1081-1088 ■ https://doi.org/10.1016/j.mayocpiqo.2021.10.004
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40.0%) and macroscopic (n=4, 40.0%) residual tumor. In the cohort that received IORT, there was improved 3-year PFS with negative surgical margins, in contrast to microscopic or macroscopic, of 51.8%, 20.5%, and 0.0%, respectively (*P*=.006) and 3-year OS of 62.9%, 20.0%, and 0.0%, respectively (*P*=.035). In patients who did not receive IORT, sites of recurrence were all distant (n=4, 100.0%). Our study also found that small tumors were more likely to have complete tumor resection (*P*=.037), with a median tumor diameter of 4.4 cm. These data suggest that patients who would have the most survival benefit from curative-intent extirpative operations are those with small tumors amenable to complete resection.

Additionally, our results suggest that IORT may improve disease control and survival outcomes if optimal surgical resection is achieved and multimodality treatment comprising perioperative EBRT and IORT is employed. Our results are in agreement with another retrospective study by Calvo et al[4] indicating benefit of EBRT integrated with radical surgical treatment and IORT in cases of locally recurrent gynecologic malignancies. The administration of EBRT preoperatively or postoperatively should be considered because the addition of EBRT delivers a higher cumulative radiation dose than IORT alone.[1] At our institution, we administer EBRT preoperatively because it optimizes delivery of radiation therapy without delay in the event of postoperative complications.[1] However, our study did not find that preoperative EBRT led to complete tumor resection (*P*=.20) and that only tumor size was related to complete resection (*P*=.037). Further study is needed to determine if preoperative EBRT aids in tumor volume reduction.

Intraoperative radiotherapy is beneficial for its ability to deliver high-dose radiation therapy to the site of recurrence, decreasing risk of radiation to surrounding critical structures.[1] These cases are not without their complications, however, and it is challenging to distinguish if complications are related to radiation therapy or to radical surgical treatment.[1] In our study, multimodality treatment with perioperative EBRT, optimal surgical resection, and IORT had acceptable toxicity, congruent with toxicity rates presented in the literature.[15] Grade 3 or higher toxicities developed in 10 patients (27.0%), and 1 patient died 4 days postoperatively due to gastrointestinal anastomotic leak resulting in septic shock. The 5-year PFS for locally recurrent gynecologic cancer without treatment is 10%.[6] It is important to counsel patients on the natural history of the disease and its poor survival outcomes without treatment. The discussion on curative-intent radical surgical treatment with both EBRT and IORT should include lack of prospective data on associated toxicities and the limited retrospective data on survival outcomes.

One of the strengths of this study was the radicality of the operations performed, almost half (48.6%) being laterally extended endopelvic resection procedures. Three patients underwent *en bloc* vessel resection as a result of tumor attachment or invasion (2 patients who received IORT and 1 who did not). All 3 patients had complete remission at the end of this study period, suggesting that radicality may be warranted if long-term survival in patients with locally recurrent or persistent gynecologic malignancies can be achieved.

One of the limitations of this study was its retrospective nature. This study also included a small sample size from a single institution, and statistical significance may have been difficult to achieve. Our cohort included a heterogeneous sample pathology, and thus the results may not be generalizable. Administration of IORT was an intraoperative decision based on surgical resection margins, risk of residual tumor, and potential for local recurrence. The case may be that there were no survival differences between those who received and did not receive IORT because of inherent selection bias to not administer IORT in cases of complete tumor resection, cancers with low risk for local recurrence, and patients with favorable long-term prognosis. Long-term prospective data are needed to determine the survival benefit of IORT in patients with suboptimal resection.

CONCLUSION

While the role of IORT in the treatment of recurrent or persistent disease remains controversial, our study documents the importance of complete tumor resection at the time of extirpative surgical treatment in optimizing survival benefit. It may behoove physicians

to select appropriate candidates with the highest probability of complete tumor resection and ability to tolerate radical surgical treatment with high-dose radiation therapy to maximize the chance for cure and minimize overall patient morbidity.

Abbreviations and Acronyms: **EBRT,** external beam radiotherapy; **IORT,** intraoperative radiotherapy; **OS,** overall survival; **PFS,** progression-free survival

Potential Competing Interests: The authors report no competing interests.

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