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Does intra-operative radiation at the time of pelvic exenteration improve survival for patients with recurrent, previously irradiated cervical, vaginal, or vulvar cancer?

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HIGHLIGHTS

- We found no evidence that IORT changes survival outcomes and recurrence.
- Indications for IORT at PE confer worse prognosis, perhaps due to tumor laterality.
- Careful patient selection is critical as IORT is unlikely to overcome sidewall extension.

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ABSTRACT

Objective. To determine whether intra-operative radiation therapy (IORT) at the time of pelvic exenteration (PE) or laterally extended endopelvic resection (LEER) improves progression-free survival (PFS) in patients with recurrent, previously irradiated gynecologic cancers.

Methods. We conducted a single institution retrospective review of patients who had undergone a complete PE for locally recurrent gynecologic cancer. Demographic and clinicopathologic data were collected.

Results. 32 patients were identified (2000–2012); 21 (66%) cervical cancer, 8 (25%) vaginal, and 3 (9%) vulvar cancer. All patients were previously irradiated. Twenty-one (66%) received IORT. Mean age was 51. Eight patients had a LEER, all with IORT. Median PFS and OS, respectively, for those with PE alone was 33 and 41 vs. 10 and 10 months for PE + IORT compared to 9 and 17 months for LEER + IORT ($P = .04$). Increasing tumor size negatively impacted PFS (hazard ratio 1.3; 95%CI 1.12–1.52). Margin status was not associated with survival. No patients undergoing LEER + IORT recurred only locally whereas 62% recurred with a distant component (+/− local). Patients with PE alone had mainly local (36%) and few (9%) distant recurrences compared to 31% local and 38% distant (+/− local) recurrences for those with PE + IORT.

Conclusions. We failed to demonstrate that IORT changes survival and recurrence outcomes. However, patients with clinical indications for IORT at the time of PE have worse prognosis compared to those who do not require IORT. If the need for IORT is anticipated, the surgeon may consider performing a LEER to decrease local recurrence if cure is the goal or consider palliative treatment options.

Introduction

Pelvic exenteration (PE) is an ultra-radical procedure that is indicated for a select population of patients with locally recurrent gynecologic malignancies. In those patients in whom cure is the goal of the procedure, and have disease that is truly limited to the pelvis, five-year survival rates are approximately 30–60% [1–11]. Those who are candidates for a curative procedure are almost always radiated with full dose radiation to the pelvis, and may even need a laterally extended endopelvic resection (LEER) to render them free of disease [12,13]. Patients with disease extending to the pelvic sidewall, or those with microscopically positive margins, however, may not be curable with radical surgery alone [14].

In addition to distant recurrence, local failure is often a site for recurrent disease, despite radical surgery [15]. In patients undergoing salvage surgery for recurrent gynecologic malignancies, the microscopic

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residual disease that remains is difficult to treat with external beam radiation (EBRT) due to location, and is often found within a previously irradiated field.

Intraoperative radiation therapy (IORT) may provide adjuvant treatment that potentially can improve survival in the appropriately selected patient [16–20]. IORT is a unique modality that allows the sterilization of microscopic disease. The ability to mobilize normal tissues away from the treatment field, as well as the opportunity for selective shielding of adjacent tissues allows for protection of vital organs during IORT. This allows for a single fraction, high dose radiation to be delivered with minimal risk to surrounding tissues [21]. IORT can be delivered via two techniques; electron beam technique and HDR brachytherapy. In the electron beam technique, radiation is delivered by a linear accelerator, and directed to the tumor bed with a cone [14]. In HDR brachytherapy, catheters within a 1 cm thick tissue equivalent material are placed along the tumor bed and a high dose Iridium 192 source is used to deliver the localized radiation. There is data to support that the application of IORT in patients undergoing surgery for recurrent gynecologic malignancies may result in improved long term local control and overall survival [14,16–20,22–27].

The objective of this study is to determine the effect of intraoperative radiation therapy at the time of pelvic exenteration or LEER on survival in patients with recurrent, previously irradiated gynecologic cancers.

Methods

The Ohio State University and James Cancer Hospital institutional review board approved this study. A single institution retrospective chart review was conducted of all patients who underwent a PE or LEER procedure with curative intent between 2000 and 2012.

Patients with cervical, vaginal, or vulvar cancer without evidence of distant disease at the time of surgery were included. Patients who received IORT at the time of secondary cytoreduction were excluded. Hospital and office charts were reviewed and data were collected for demographic, clinicopathologic factors, recurrence and survival data.

Intraoperative radiation therapy was given at the discretion of the attending surgeon, and depended on margin status or clinical suspicion of positive margins. Six to ten centimeter, 0–30° beveled cones were positioned along the tumor bed. If the geometry of the tumor bed did not allow the use of the electron cone technique, intraoperative HDR catheter treatment was delivered. The IORT doses ranged from 10 to 20 Gy (median 17.5 Gy). Electron energies ranged from 6 to 12 MeV and the dose was prescribed to the 90% isodose line. For HDR treatment, the dose was prescribed at 0.5 cm from the surface of the applicator. One patient also received iodine-125 seed implants.

Categorical variables were compared with chi-square test, continuous variables with Student's T-test if data had normal distribution and with nonparametric Wilcoxon rank sum tests if the data were not normally distributed. JMP 9.0 software (SAS Institute Inc., Cary, NC) was used for data analysis. Kaplan–Meier curves were generated and compared with log rank tests. PFS and OS were calculated from the day of surgery to progression or all-cause mortality. Cox proportional hazards ratios were calculated. *P* values <0.05 were considered statistically significant.

Results

Thirty-two patients were identified between 2000 and 2012 that met the inclusion criteria. The majority of patients had recurrent cervical cancer (66%), followed by recurrent vaginal (25%) and recurrent vulvar cancer (9%) (Table 1). All patients had previously received full dose pelvic radiation. Patients with a uterus in place received intracavitary or interstitial brachytherapy in addition to external beam radiation for primary treatment. Patients with a recurrence in the vagina were treated with vaginal brachytherapy and pelvic radiation if they had not received this previously.

Table 1
Patient characteristics.

Variable	No.	%
Age (y)		
Mean, SD	51 (12)	
Range	28–72	
Primary site		
Cervix	21	66
Vagina	8	25
Vulva	3	9
Histologic type		
Squamous cell carcinoma	24	75
Adenocarcinoma	4	13
Endometrioid	1	3
Sarcomatoid	1	3
Serous	1	3
Clear cell	1	3
Prior EBRT		
Yes	32	100
No	0	0
Treatment		
LEER (yes)	8	25
IORT (yes)	21	66

EBRT: external beam radiation therapy; *LEER*: laterally extended endopelvic resection; *IORT*: intra-operative electron radiation therapy.

Twenty-one patients (66%) received IORT at the time of PE/LEER. The mean age was 51; patients who received IORT were younger than those without IORT (48 vs 59, $P = .007$). IORT was given to the pelvic sidewall (one or both) and once also to the sacral hollow, wherever the suspicion and/or documentation of a close margin was the highest. The median IORT dose was 17.5 Gy (range 10–17.5) in the LEER/IORT group versus 15 Gy (range 15–20) in the PE/IORT group ($P = 0.7$). Beveled cones were used for 11 patients and catheters in 8 patients, while 2 patients received both electron cone IORT and HDR IORT. Six patients received radiation therapy after pelvic exenteration ranging from 10 to 40 Gy (mean 26 Gy); 25% of LEER/IORT, 23% of PE/IORT, and 9% of PE/no IORT patients. Postoperative radiation did not significantly decrease the risk of recurrence in the entire population (HR 1.13, 95%CI 0.37–2.29, $P = 0.82$) or in the patients who received IORT (HR 0.77, 95% CI 0.21–2.24, $P = 0.65$).

Eleven patients (34.4%) underwent a PE, none of whom underwent IORT (PE only). Eight patients (25%) had a LEER, all whom underwent IORT (LEER + IORT). The remaining 13 patients (40.6%) had a PE with IORT (PE + IORT) (Table 2). There was no significant difference in the mean tumor size among the three treatment modality groups. The patients undergoing a PE only (no IORT) had fewer patients (27%) with a treatment free interval (TFI: between primary diagnosis and pelvic exenteration) of less than 24 months compared to 71% of those who received IORT ($P = .03$). Fifty percent of patients undergoing the

Table 2
Prognostic factors and outcomes after exenterative procedure by treatment modality.

Variable N (%)	PE only (−)IORT N = 11	PE(+)IORT N = 13	LEER(+)IORT N = 8
Treatment-free interval <24 months	3 (27)	11 (85)	4 (50)
Positive margin	4 (36)	5 (38)	1 (13)
LVSI	4 (57)	7 (78)	4 (50)
Maximum tumor diameter (median, range)	5.8 (0–13.3)	6.5 (0–10.3)	5 (2.2–11)
Site of recurrence (after PE or LEER)			
None	6 (55)	4 (31)	3 (38)
Local only	4 (36)	4 (31)	0
Distant only	0	3 (23)	2 (25)
Local + distant	1 (9)	2 (15)	3 (38)

PE: pelvic exenteration; *IORT*: intra-operative electron radiation therapy; *LEER*: laterally extended endopelvic resection; *LVSI*: lymphovascular space invasion.