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Perioperative high-dose-rate brachytherapy in locally advanced and recurrent gynecological cancer: Final results of a Phase II trial

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ABSTRACT

PURPOSE: To determine the long-term results of a Phase II trial of perioperative high-dose-rate brachytherapy (PHDRB) in primary advanced or recurrent gynecological cancer.

METHODS AND MATERIALS: Fifty patients with locally advanced and recurrent gynecological cancer suitable for salvage surgery were included. Unirradiated patients (n = 25) received preoperative chemoradiation followed by surgery and PHDRB (16−24 Gy). Previously irradiated patients (n = 25) received surgery and PHDRB alone (32−40 Gy).

RESULTS: Median followup was 11.5 years. Eight unirradiated patients (32%) developed Grade ≥3 toxic events including two fatal events. Local and locoregional control rates at 16 years were 87.3% and 78.9%, respectively. Sixteen-year disease-free and overall survival rates were 42.9% and 46.4%, respectively. Ten previously irradiated patients (40.0%) developed Grade ≥3 adverse events, including four fatal events. Local and locoregional control rates at 14 years were 59.6% and 42.6%, respectively. Fourteen-year disease-free and overall survival rates were 16.0% and 19.2%, respectively.

CONCLUSIONS: PHDRB allows effective salvage of a subset of unfavorable gynecological tumors with high-risk surgical margins. Toxicity was unacceptable at the initial dose levels but deescalation resulted in the absence of severe toxicity without a negative impact on locoregional control. A substantial percentage of patients remain alive and controlled at >10 years including a few previously irradiated cases with positive margins.

Keywords: Gynecological cancer; Recurrence; Perioperative; High-dose-rate; Brachytherapy; External beam radiation therapy

Introduction

Locally recurrent gynecologic cancer has a poor prognosis, especially if radiotherapy was used in the primary management (1, 2). Most of large central or lateral pelvic relapses cannot be salvaged because tumor-free margins cannot be obtained. The presence of microscopic positive margins or close (≤5 mm) margins has been largely considered a selection failure because they present a risk of subsequent local failure higher than 40% (3−5). Although some of these cases require additional therapy, further external beam radiation therapy (EBRT) at meaningful doses is usually avoided due to the risk of toxicity. The same is true for patients with locally advanced gynecological cancer, who are referred for completion surgery at the end of the chemoradiation program due to extensive disease inappropriate for definitive brachytherapy. These patients are at high risk of local failure due to the presence of close or positive margins at the pelvic boundaries.

Furthermore irradiation in high-risk patients with perioperative high-dose-rate brachytherapy (PHDRB) has been used only occasionally in gynecological cancer (4, 6) but presents several theoretical advantages that include CT-based treatment planning, pathology-adjusted dose selection, and fractionation.

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The present report updates our former publication (6) with extended followup and inclusion of additional cases. It also describes the results obtained after the implementation of technical and methodological changes aimed at decreasing the toxicity observed in the former report.

Patients and methods

Eligibility criteria

From February 2000 to November 2015, 50 patients with recurrent (n = 43) or locally advanced (n = 7) gynecological cancer were treated with surgical resection and PHDRB. Furthermore details of the treatment program can be found elsewhere (6). Patients were not candidates for salvage or adjuvant interstitial brachytherapy due to extensive disease that could not be encompassed by an interstitial implant or tumor location in an anatomical area not accessible through percutaneous brachytherapy.

Treatment protocol

Twenty-five unirradiated patients with a median age of 55 years (range, 37−72) were included. Seven cases presented primary advanced disease (IIIb or IVa), eight cases paraaortic node metastases, and 15 patients locally recurrent disease after prior surgery (Table 1). Patients were treated with preoperative cisplatin-based chemoradiation to a median dose of 45 Gy in 25 daily treatments followed by surgical resection and PHDRB 4−6 weeks later. The brachytherapy dose was 16 Gy in 4 b.i.d. treatments for negative margins and 24 Gy in 6 b.i.d. treatments for close (<10 mm) or positive margins. Surgical margins were negative in 11 cases (44%), close (average = 1.5 mm) in 4 cases (16%), and positive in 10 cases (40%). As per protocol guidelines, the maximal dose of 24 Gy was reduced to 16 Gy in 4 b.i.d. treatments when the first Grade ≥ 3 event was recorded (November 2009). The median PHDRB dose was 24 Gy (range, 16−24 Gy) and the overall 2-Gy equivalent dose values with the addition of the EBRT component for patients with negative and close/positive margins were 64.4 Gy and 71.9 Gy, respectively.

Table 1
Tumor characteristics

	Prior irradiation (n = 25)	Unirradiated (n = 25)
Diagnosis		
Cervical cancer	15 (60%)	13 (52%)
Endometrial cancer	3 (12%)	9 (36%)
Vulvovaginal cancer	7 (28%)	3 (12%)
Tumor size		
At presentation (mean ± SD)	n/a	4.8 ± 2.3
At PHDRB (mean ± SD)	3.6 ± 1.8	2.1 ± 1.9
Stage at PHDRB		
Primary	0 (0%)	7 (28%)
Recurrent	25 (100%)	18 (72%)
Histology type		
Adenocarcinoma nos	10 (40%)	9 (36%)
Squamous cell carcinoma	12 (48%)	12 (48%)
Clear cell/papillary serous carcinoma	2 (8%)	3 (12%)
Other	1 (4%)	1 (4%)
High risk features		
Lymphovascular space involvement	4 (16%)	5 (20%)
Perineural involvement	5 (20%)	0 (0%)
Nodal status		
Negative	12 (48%)	7 (28%)
Positive	10 (40%)	13 (52%)
Extracapsular spread	5 (20%)	7 (28%)
Not explored	3 (12%)	5 (20%)

PHDRB = perioperative high-dose-rate brachytherapy; SD = standard deviation.

Twenty-five previously irradiated patients with a median age of 57 years (range, 28−73) were treated with surgical resection and PHDRB. Patients had previously received external irradiation (n = 25, 100%) to a median dose of 46 Gy (range, 45−70 Gy), brachytherapy (n = 9, 36%) to a median dose of 10 Gy in two fractions, surgery (n = 16, 64%) and chemotherapy (n = 11, 44%) during the primary management. The brachytherapy dose was 32 Gy in 8 b.i.d. treatments for negative margins and 40 Gy in 10 b.i.d. treatments for close/positive margins. Further EBRT was not administered. Surgical margins were categorized as negative in one case (4%), close (average = 1.7 mm) in 12 cases (48%), and positive in 12 cases (48%). As per protocol guidelines, the maximal dose of 40 Gy was reduced to 32 Gy in 8 b.i.d. treatments when the first Grade ≥ 3 event was recorded (May 2002); this dose was further reduced to 24 Gy in 6 b.i.d. treatments when the first Grade ≥ 3 event attributable to the dose of 32 Gy of PHDRB was recorded (November 2004). The median PHDRB dose was 32 Gy in 8 b.i.d. treatments (range, 24−40 Gy), and the overall 2-Gy equivalent dose values for patients with negative and close/positive margins were 37.3 Gy and 38.1 Gy, respectively.

PHDRB methodology

Complete details of the treatment program can be found elsewhere (6). In brief, the clinical target volume was determined intraoperatively under direct vision during open laparotomy by the surgical and radiation oncology teams and was delineated with four gold markers placed at the cardinal points. The clinical target volume was covered with a single-plane implant of 6Fr catheters with a margin of 1 cm in all directions (Fig. 1) following the abdominal route or more recently, the perineal route. Once the implant was completed, a radioprotective flap was created with the greater omentum.

Unirradiated patients were implanted with a median of four catheters (range, 2−8) with a median time to loading of 4 days (range, 1−8) and a median treatment duration of 3 days (range, 2−5). The average treated volume $(TV)_{100}$ and TV_{150} values were 101.2 cm^3 and 34.6 cm^3, respectively (dose homogeneity index = 0.65). Previously irradiated patients were implanted with a median of five catheters (range, 2−7) with a median time to loading of