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Interstitial preoperative high-dose-rate brachytherapy for early stage cervical cancer: Dose–volume histogram parameters, pathologic response and early clinical outcome

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ABSTRACT

PURPOSE: To analyze dose–volume histogram parameters and pathologic response after preoperative high-dose-rate brachytherapy (HDRB) for high-risk early stage cervical cancers (ESCCs).
METHODS AND MATERIALS: From June 2007 to December 2011, 32 patients with a histologically proven invasive cervical cancer with high risk of local recurrence (size >2 cm, adenocarcinoma type, perineural and/or lymphovascular invasion) underwent a preoperative HDRB, which delivered a total dose of 39 Gy in nine fractions over 5 days. All the patients underwent hysterectomy after HDRB.
RESULTS: With a median clinical target volume of 50 cc (minimum–maximum, 42–74), the median V_{100} was 49 cc (minimum–maximum, 42–50). Median D_{90} was 45 Gy (equivalent dose at 2 Gy per fraction, 56 $Gy_{\alpha\beta10}$). Median D_{2cc} was 34 Gy, 31 Gy, 28 Gy, and 38 $Gy_{\alpha\beta3}$ for bladder, rectum, sigmoid, and vagina, respectively. Twenty-eight patients (88.5%) achieved a complete histologic response after surgery, whereas for the 4 remaining patients, residual tumor cells (3 patients) and gross residual disease (1 patient) were observed in the pathologic specimen. With a median followup of 24 months (minimum–maximum, 5–48), no local recurrence was observed; 1 patient died of intercurrent cause. Early toxicity occurred within the 30 days after HDRB (Common Terminology Criteria for Adverse Events v3.0) was G1 diarrhea for 15 patients (47%) and G1 urinary frequency or urgency for 13 patients (40.6%). No G2–G3 toxicities were noticed.
CONCLUSIONS: Preoperative HDRB for high-risk ESCCs represents a well-tolerated procedure, which leads to a high rate of postoperative pathologic response. Dose–volume histogram parameters were at least equivalent to those obtained with a low-dose-rate procedure. Long-term results will help to analyze the place of preoperative brachytherapy in the management of high-risk ESCCs.

Keywords: Cervical cancer; Brachytherapy; High-dose-rate; Early stage; Pathologic response

Introduction

Brachytherapy is considered as an essential therapeutic component for cervical cancer. The dose rate debate has been extensively analyzed, and randomized prospective and retrospective studies have suggested overall statistically equivalent local control, overall survival (OS), and complication rates for high-dose rate (HDR) and low-dose rate (LDR) (1). Although the patterns of failure and survival were similar in patients treated by LDR or HDR, an image-guided HDR planning led to a large decrease in late radiation effects in patients treated by high-dose-rate brachytherapy (HDRB) (2). Therefore, the use of HDRB is becoming increasingly common (3). In the United States, the most recent Quality Research in Radiation Oncology survey from 2007 to 2009 shows that 62% of surveyed facilities use HDR compared with 13% in the 1996–1999 survey (4). Compared with new radiation techniques for cervical cancer, such as

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Conflict of interest: Nucletron Company (Nucletron BV, Veenendaal, The Netherlands).

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intensity-modulated radiation therapy (RT), HDRB remains the best technique regarding conformal dose delivery (5). Although for locally advanced tumors, the use of brachytherapy is considered as the standard of care for increasing the dose to the clinical target volume (CTV) and decreasing the dose to the organs at risk (OAR) after a first course of concomitant chemoradiation therapy, the place of preoperative brachytherapy for early stage cervical cancer (ESCC) remains under debate. Surgery as sole therapy achieves a high rate of local control; however, tumor size (>2 cm) (6, 7), adenocarcinoma histologic type (8), and the presence of lymphovascular space invasion (LVI) (9, 10) or perineural invasion (PNI) (11) on the preoperative biopsy have been presented as risk factors for local recurrence after definitive surgery. Since the advent of chemoradiation, the use of preoperative treatment has fallen out of favor to give the high survival rates with chemoradiation (12). The results of LDR brachytherapy performed before surgery were already reported (13–17). The present study reports dose–volume histogram (DVH) parameters, pathologic response, and early clinical outcome after HDRB performed in a preoperative intent for ESCCs presenting with at least one of the previously described high-risk prognostic factors of local recurrence.

Methods and materials

Patient features

From June 2007 to December 2011, 103 patients presenting with a cervical cancer underwent HDRB either after a first course of radiochemotherapy for Stages 1B2–IVA or lymph node–positive disease (71 patients, 69%) or in a preoperative intent for Stages 1B1–2A1 disease (32 patients, 31%). This study focused on the 32 patients treated preoperatively because of the presence of at least one of the following risk factors of local recurrence: tumor size >2 cm, adenocarcinoma histologic type, and the presence of PNI or LVI. All the patients were presented with a proven invasive squamous cell carcinoma (28 patients, 87.5%) or adenocarcinoma (4 patients, 12.5%) of the cervix, whereas LVI and/or PNI were observed in 14 patients (43.8%). The tumors were classified (2009 International Federation of Gynecology and Obstetrics classification) as Stage 1B1 in 94% (30 patients) and Stage 2A1 in 8% (2 patients) with 18 patients (56.3%) with a tumor size of >2 cm (Table 1). All the patients were considered eligible for HDRB. According to our local policy, MRI and 18 fluoro-deoxy-glucose positron emission tomography scan were carried out followed by a laparoscopic pelvic lymph node dissection. Patients presenting with lymph node involvement were not considered eligible for this analysis and underwent radiochemotherapy followed by HDRB.

Table 1
Patient, tumor, and treatment features

Data	Median	Minimum–maximum
Age (y)	51	28–73
Followup (mo)	24	2–57
Performance status	0	0–2
BMI	23	19–31
Median tumor size (mm)	18	12–25
Number of patients with tumor size >2 cm	18	56.3%
Histologic features		
Squamous cell carcinoma, no.	28	88.4%
Adenocarcinoma, no.	4	11.6%
PNI or LVI, no.	14	43.8%
Total delivered dose (Gy)	39	38–40
Fraction number	9	9–9
Overall HDRB time (d)	5	5–5
Implant time (mn)	37	20–45
Hospitalization time (d)	5	5–6
Break HDRB and/or surgery (d)	42	36–63

BMI = body mass index; PNI = perineural invasion; LVI = lymphovascular space invasion; HDRB = high-dose-rate brachytherapy.

Interstitial HDRB procedure and treatment planning

HDRB used a novel applicator that is not commercially available named Nice Gynecologic Applicator (NGA) based on (Figs. 1a–1c) (*1*) a uterine tandem; (*2*) a vaginal cylinder including eight equidistant channels allowing the placement of eight plastic needles (240 mm *Sharp Needles*; Nucletron BV, Veenendaal, The Netherlands); (*3*) a skin suture template that is fixed on the vaginal cylinder and sutured to the skin; (*4*) a blocking needle template that is fixed to the vaginal cylinder, fixing uterine tandem in the center, and needles in the circumference. This new NGA prototype was initially proposed by the Antoine Lacassagne Cancer Center to the Nucletron Company in April 2006. The related patent was officially published by the World Intellectual Property Organization on April 1, 2010 (Publication Number: WO/2010/036103). The full description of the NGA prototype is available on the World Intellectual Property Organization Web site (18). Because new technique and dose protocol were applied, this analysis was approved by local institutional review boards.

HDRB was performed under general anesthesia. The procedure started by the insertion of three silver seeds 1 cm into the cervix for guiding delineation of the CTV on the postimplant CT scan. After cervical canal dilatation, the uterine tandem was inserted; the vaginal cylinder was placed into the vagina. The skin suture template and blocking needle template were positioned. Eight needles were pushed inside the vaginal cylinder. The proximal part of the needles was in an endocavitary position, whereas the distal part was in an interstitial position. The length of the intracervical part (interstitial part) of the needles and uterine tandem was 40 mm. The procedure ended by the fixation of the needles and suture of the prototype to the skin. One hour after the end of the procedure, a postimplant CT scan was performed. Although a postimplant CT scan (and not MRI) was used for the planification, we nevertheless considered the GYN GEC-ESTRO Working Group recommendations for the definition of the CTV (19). We considered the