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Reirradiation using high-dose-rate brachytherapy in recurrent carcinoma of uterine cervix

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ABSTRACT

PURPOSE: To assess the feasibility of reirradiation with image-based high-dose-rate brachytherapy in previously irradiated patients with recurrent carcinoma of uterine cervix.

METHODS AND MATERIALS: Thirty previously irradiated patients diagnosed with central recurrence were treated with reirradiation. Martinez Universal Perineal Implant Template was used in 24 patients and Vienna applicator in 6 patients. Median interval between two radiation schedules was 25 months. Median delivered dose was 42 Gy equivalent dose at 2 Gy (EQD2; interquartile range, 37−46 Gy EQD2).

RESULTS: All 30 patients tolerated reirradiation well. Complete response was seen in 23 (76%) patients. With a median followup of 25 months, 2-year local control, disease-free survival, and overall survival were 44%, 42%, and 52%, respectively. Fifteen patients developed local recurrences; Local control rate was significantly higher with doses >40 Gy EQD2 (52% vs. 34%; $p = 0.05$). Disease-free survival was better for patients with longer interval (>25 months) between two radiotherapy schedules. Grade III radiation proctitis and cystitis was seen in 3 patients each, and Grade II small bowel toxicity was seen in 3 patients.

CONCLUSIONS: Reirradiation using high-dose-rate brachytherapy is feasible with acceptable outcomes in isolated local recurrence deemed unsuitable for surgery. The outcome is better with higher doses.

Keywords: Reirradiation; High-dose-rate brachytherapy; Carcinoma of uterine cervix

Introduction

The current standard of care for treatment of locally advanced carcinoma of uterine cervix is radical radiotherapy (RT) comprising external beam and brachytherapy (BT) with or without chemotherapy. The reported 5-year disease-free survival (DFS) and overall survival (OS) range between 40% and 70%. Isolated local recurrence is seen in about 30% of failures, which are treated with surgical exenteration whenever feasible with a variable outcome of 10−56% at 5 years reported in limited series (1−4). However, such surgery is feasible only in a select group of patients and is associated with significant morbidity and mortality (4, 5). Other salvage treatment modalities like reirradiation, chemotherapy, and so forth has also been attempted with dismal outcomes (6, 7). Few series with reirradiation have reported encouraging outcomes with acceptable toxicities (8).

Salvage reirradiation series with external beam RT (EBRT), BT, or combination of both are limited and report high complication rates. Moreover, the techniques used for reirradiation used poor techniques by current standards. In the recent past, there have been significant advances in radiation technology that have been successfully implemented in the clinical practice. One such advance is image-guided adaptive BT (IGABT) with the use of CT/MR imaging. IGABT in cervical cancers has shown better outcome both in terms of local control rates and lesser toxicities (9). The major advantage of MR IGABT approach is soft tissue visualization including the tumor extent and accurate delineation of target with applicator in place. With an aim to report feasibility and clinical outcome of patients

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treated with reirradiation using image-based BT for isolated locally recurrent cervical cancers, we undertook this analysis.

Methods and materials

Between January 2002 to May 2012, 30 patients of post-radical radiation isolated locally recurrent cervical cancers who were treated with reirradiation using high-dose-rate (HDR) BT with ^{192}Ir at our institution were analyzed. They were deemed inoperable/unwilling for surgery and were suitable for BT. All patients had received some form of RT before recurrence either EBRT or both EBRT and BT. Prior (first) RT was given at our institution for some patients whereas few had received RT at other centers.

All patients had histologic proven diagnosis of recurrence. A clinical examination was done for all patients for mapping of central and parametrial disease. A metastatic work-up (CT scan, positron emission tomography [PET]-CT scan, and/or x-ray chest) was done to rule out any pelvic nodal metastasis or distant metastatic disease at time of reirradiation. All patients were treated with HDR BT alone. Twenty-four patients were treated using Martinez Universal Perineal Implant Template (MUPIT) based interstitial BT, whereas 6 patients using Vienna applicator (ring with additional needles). None of these patients received any EBRT or chemotherapy.

Reirradiation BT procedure

MUPIT implant procedure was done under spinal or general anesthesia. A thorough pelvic examination under anesthesia was performed to define and map the disease clinically. Depending on the disease profile, appropriate BT applicator to suit the disease extent was used. Before the advent of Vienna applicator, MUPIT applicator with stainless needles was used routinely. Wherever possible, silver markers (1−2 mm) were implanted submucosally to mark the superior and inferior extent of recurrent disease. After determining vaginal length with help of obturator, 18 gage stainless steel needles (18−20 cm) were inserted through the perineum and MUPIT into the desired target volume. The number and position of needles were determined based on desired target and per rectal examination (at times transrectal ultrasound guidance) during needle insertion. Precaution was taken to keep all the needles adequately away from rectal wall. The detail description of the MUPIT based procedure has been described in earlier (10). With the successful implementation of MR IGABT at our center (11), we used Vienna applicator with needles in recent patients for reirradiation. BT planning was done on the same day using PLATO (V.14. 3, Nucletron B.V, an Elekta company, Elekta AB, Stockholm, Sweden) planning system. For BT planning, CT scan with axial slices was used for MUPIT patients whereas T2-weighted (T2W) axial, sagittal, and coronal MRI sequences were used for Vienna applicator patients. For Vienna applicator patients, target volume delineation (high-risk clinical target volume—HRCTV) and organ at risk (OAR) delineation were done as per Groupe Europeen de Curietherapie European Society for Therapeutic Radiology and Oncology (GEC ESTRO) guidelines (12). The dose volume parameters were obtained for HRCTV, bladder, and bowel. Target volume and OAR delineation were not done for patients treated with MUPIT in the pre-GEC-ESTRO guidelines period. Hence, dose volume parameters are not available for this group of patients. For MUPIT patients, catheter reconstruction was done using CT scan images. After reconstruction, dose points were defined in midplane at center of square geometry. The prescribed dose was normalized at these dose points. After normalization, optimization was done to improve target coverage and reduce dose to normal tissue. Plan evaluation was done depending on the needles implanted and 85−100% isodose lines coverage and 50−85% isodose lines for rectum and bladder doses. For MUPIT patients, treatment was delivered in 6−13 fractions in single application, using 3−4 Gy/fraction, two fractions per day, 6 h apart over 1 week, whereas for Vienna applicator patients; treatment was delivered in four or five fractions in two applications, 1 week apart. The number of fractions and total dose were decided after considering volume of implant, dosimetry, previous RT doses, and gap between two RT schedules. The radiation doses were converted into equivalent dose at 2 Gy (EQD2), with alpha/beta values of 10 and 3 for tumor and OARs (rectum/bladder/sigmoid), respectively, to evaluate and correlate the outcomes.

After completion of treatment, patients were followed up at 3 months for response assessment, then every 3−4 months till 2 years, and 6 months thereafter. Radiological investigations were done as deemed necessary by treating physician. In case of suspected recurrence, biopsy confirmation was done. Late toxicities were recorded as per Radiation Therapy Oncology Group grading system.

All statistical analysis was done using Statistical Package for the Social Sciences (SPSS 17, SPSS Inc., Chicago, IL) software. Survival analysis was done using Kaplan−Meier methods and curves were plotted. The prognostic factors were compared using log-rank test for statistical significance, and a p-value of less than 0.05 was taken as significant.

Results

Table 1 shows the patient and tumor characteristics. With a median age of 56 years (interquartile range, 49−57 years), all patients had Karnofsky performance status of 80−90. Twenty-six patients had squamous carcinoma, whereas remaining four had adenocarcinoma at recurrence. Twenty patients had postoperative, postradiation vaginal vault recurrence whereas the rest of them had postradical radiation central cervical recurrence. Majority of patients had recurrent disease of <4 cm in maximum diameters. Vagina was either free or only upper third involved in 28 (93%) of patients.

Table 2 shows RT details and response rates after reirradiation. The median gap between two irradiation schedules was