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HDR brachytherapy for the reirradiation of cervical and vaginal cancer: Analysis of efficacy and dosage delivered to organs at risk

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HIGHLIGHTS

- Evaluation of the efficacy of HDR brachytherapy (BT) for the reirradiation of cervical cancer
- Evaluation of the toxicity of HDR BT for the reirradiation of cancer arising within a previously irradiated area
- A cumulative EQD2 of approximately 100 Gy can be safely delivered to 2 cm^3 of the bladder and rectum.

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ABSTRACT

Objective. To evaluate the efficacy and toxicity of HDR brachytherapy (BT) for the reirradiation of cervical or vaginal cancer arising within a previously irradiated area with a special focus on dosage delivery to organs at risk.

Methods. Twenty consecutive patients with cervical (N = 19) or vaginal (N = 1) cancer were reirradiated with curative intent using BT with or without external beam irradiation and hyperthermia. The median biologically equivalent dose in 2 Gy fractions (EQD2), assuming $\alpha/\beta = 10$, for reirradiation was 48.8 Gy (range: 16.0–91.0 Gy), and the median cumulative EQD2 (for primary treatment and reirradiation) was 133.5 Gy (range: 96.8–164.2 Gy). The median follow-up after retreatment was 31 months (range: 6–86 months).

Results. The 3-year overall survival (OS) rate was 68% (95% confidence interval [CI]: 44%–91%). The 3-year disease-free survival (DFS) rate was 42% (95% CI: 19%–65%). The 3-year local control (LC) rate was 45% (95% CI: 22%–69%). For nine patients who received 3D treatment planning, the median cumulative EQD2 to 2 cm^3 of rectum was 94.4 Gy (range: 67.1–118.8 Gy) and to 2 cm^3 of bladder was 99.3 Gy (range: 70.4–122.3 Gy). Grade 3 late toxicity was observed in 3 patients (15%). An interval between primary RT and reirradiation of ≤12 months and a tumor diameter >3 cm were significant prognostic factors adversely affecting OS, DFS and LC.

Conclusions. HDR BT is a valuable method for the reirradiation of cervical cancer. A cumulative EQD2 of approximately 100 Gy was safely delivered to 2 cm^3 of the bladder and the rectum.

Introduction

Radiochemotherapy combined with BT is the standard curative treatment for advanced stage cervical cancer. Local recurrences are observed in 5–18% of patients [1–4].

Despite a number of improvements in surgical technique [5] and the reduction of operative mortality to 5%, the 5-year survival rate after recurrence is still approximately 40% [6–9]. A curative (R0) resection significantly impacts treatment outcomes [10,11]. Patients with R1 resection, especially with tumors close to the pelvic sidewalls, can be treated with intraoperative RT [12,13]. Exenteration is the treatment of choice in younger patients with good performance status and small recurrent tumors located centrally in the pelvis [14].

However, the majority of patients with local recurrence (LR) after radical RT are older and have serious co-morbidities. Acceptance of surgical procedures is also low, given the potential for severe complications and the risk of operative mortality. Thus, the only curative treatment option available to these patients is reirradiation. Reports of reirradiation in patients with cervical cancer are few [14–18]. BT has long been used for the reirradiation due to the conformal dose distribution. However, there are no data in the literature concerning the dose that should be prescribed for reirradiation with this technique, whether as the sole treatment or in combination with external beam radiotherapy (EBRT) for curative purposes. The aim of this retrospective study was to evaluate the efficacy and toxicity of

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HDR BT as a retreatment with a special focus on dose delivery to organs at risk (OAR) to generate guidelines for clinical practice.

Material and methods

A review of the database from the Brachytherapy Department at our institution identified 20 consecutive patients who received HDR BT reirradiation between 1997 and 2011 for a local recurrence or second cancer occurring within a previously treated volume, following radical RT for cervical (19) or vaginal (1) cancer. Eighteen patients were deemed inoperable (N = 11) or refused surgery because of co-morbidities (N = 7). Two had intraoperative HDR. The median age was 62 years (range: 26–77 years). Three patients had adenocarcinoma, 16 had squamous cell carcinoma and one had undifferentiated carcinoma. The Karnofsky performance status scores ranged from 80 to 100.

The initial treatment for 14 patients with cervical cancer consisted of definitive external beam radiotherapy (EBRT) alone (N = 5) or with concomitant chemotherapy (N = 9) and BT (N = 9). The other five patients were treated surgically, with an adjuvant EBRT combined with BT (N = 3), BT alone or EBRT alone. One patient with vaginal cancer after hysterectomy was treated using BT (radium). The patients were treated by linear accelerator (N = 14), Cobalt 60 (N = 3) or 300 kV orthovoltage radiotherapy (N = 1). For BT, the dose delivered by the 2-dimensional (2D) treatment plan was calculated at point A and at the rectum and bladder reference points, based on ICRU 38 report [19]. BT was also planned in computed tomography (CT). 3D plans were reported in high risk clinical target volumes (HR-CTV), defined as the cervix and the involved parametrium or the vaginal tumor and the paravaginal tissue (if involved) with a 1 cm margin in the longitudinal direction. The maximum dose delivered to 2 cm^3 of rectum and bladder was reported. 100% of the prescribed dose of EBRT was taken into account while calculating doses delivered to the tumor and the OAR. The total doses (EBRT and HDR BT) were recalculated as the biologically equivalent doses to 2 Gy fractions (EQD2) using the following equation: $EQD2 = nd\ (d + \alpha/\beta/2\ Gy + \alpha/\beta)$, where n = the number of fractions, d = dose (Gy) per fraction (assuming $\alpha/\beta = 10$ Gy for tumor control, $\alpha/\beta = 3$ Gy for late normal tissue damage). The doses were not corrected for overall treatment time. It should be emphasized that with 2D treatment planning BT and 300 kV orthovoltage RT, the calculated doses represent only a rough estimate of the doses actually received.

The interval between the primary treatment and reirradiation ranged from 3 to 76 months (median 23 months).

Before reirradiation, work-up for all patients included a clinical examination, abdominal and pelvic CTs, a chest X-ray, blood count and biochemistry. An MRI was performed in four patients. All but one patient had pathologically proven recurrence.

The reirradiated cancers were located within the cervix (N = 8), cervix and parametrium (N = 2), vagina (N = 8), vagina and para-vaginal tissue (N = 1), and the parametrium (N = 1).

Tumors, measured by CT, MRI or clinical examination, with a diameter of more than 3 cm were recorded in eight patients, and tumors equal to or less than 3 cm in diameter were found in 12 patients. There were two secondary cancers developed after 11 and 12 years of follow up, and 18 recurrences, including five cases in which a suboptimal dose was delivered during primary RT (50–64 Gy) and one geographical miss.

Three patients were reirradiated with HDR BT combined with EBRT (in one patient, combined with 5 cycles of cisplatin [40 mg/m^2]). Seventeen patients received HDR BT alone. The following techniques were used to administer HDR BT: eleven interstitial, six vaginal cylinders, one Harrison–Anderson–Mick applicator HAM for R1 resection after exenteration, one interstitial for R1 resection and one intraoperative interstitial application for an inoperable tumor. Patients were treated mostly with interstitial BT (N = 11), one after R1 resection and nine with concomitant hyperthermia (HT). Once a week, interstitial HT, at a temperature between 42.5 and 49 °C, was administered for 45 min before and during the interstitial HDR BT, for 4–5 times. Conformal EBRT was delivered to pelvic lymph nodes and the tumors with a 0.5 cm margin using high energy 6–15 MV photons with 1.8–2 Gy fractions to total doses of 38.0–52.2 Gy. HDR BT was planned using the PLATO treatment planning system, Nucletron and Oncentra Master Plan Version 3.3 SP1, and delivered using an Ir-192 (10 Ci nominal activity) source from Nucletron Microselectron. HR-CTV was defined above. MRI was used for the contouring process without fusion in 4 cases. Dose Volume Histogram (DVH) parameters were analyzed, as follows: D100 (minimum dose delivered to 100% of the target volume), and dose delivered to 2 cm^3 of rectum and bladder in 12 patients who received 3D treatment planning. For eight patients, dose delivery was reported at ICRU points in OAR (rectum and bladder). All doses were normalized to EQD2, except for a single 20 Gy fraction and 1.5 Gy fractions delivered twice a day, with minimum 6 hour break. During primary treatment HDR BT was delivered in 4 fractions of 7.5 Gy given once a week for inoperable patients, after EBRT, in 2 fractions of 7.5 Gy after the hysterectomy, in combination with EBRT or in 3 fractions of 7.5 Gy, after the hysterectomy, when EBRT was not performed. During reirradiation, HDR BT was delivered in 10–15 fractions of 3 Gy given every day or in 4–6 fractions of 5–7.5 Gy given once a week. The treatment characteristics are detailed in Table 1.

Patients were followed-up for 6 weeks post treatment, then every 3 months for the first 2 years and twice per year thereafter. A biopsy was taken in one patient to confirm consecutive recurrence, and in seven other patients the diagnosis was based on clinical examination with a CT or MRI and detection of elevated tumor markers. Complications of the bladder and rectum were scored using the Radiation Oncology Group Early and Late Radiation Morbidity Scoring System [20]. Late complications of the vagina were scored using the SOMA evaluation scoring system [21]. Failures were defined as local recurrence, distant metastases, or both.

All time intervals were calculated from the final day of treatment. The events recorded for disease-free survival (DFS) were disease progression or death from any cause. Local control (LC) was defined as the length of time from the end of treatment to local recurrence (LR). Patients alive without a LR were censored at the last observation. LR was diagnosed regardless of the occurrence of distant metastasis. The following variables were included in the analysis of prognostic factors: time from the primary RT to reirradiation (≤12 months vs. >12 months), tumor diameter before reirradiation (≤3 cm vs. >3 cm), age (≤55 years vs. >55 years), primary treatment with surgery and irradiation or irradiation alone, the location of the tumor (cervix vs. vagina vs. parametrium/paravaginal tissue involvement) and the EQD2 of reirradiation. LC, DFS and overall survival (OS) curves were derived from Kaplan–Meier estimates and compared using the log-rank test.

P-values of <0.05 were considered statistically significant. The influence of potential prognostic factors on the risk of failure was assessed using a Cox model.

Results

The median follow-up time was 31 months (range: 6–86 months). Nineteen patients exhibited complete tumor response after reirradiation. Seven patients are free of disease, from 19 to 86 months post treatment (median: 55 months). LR alone were observed in 4 patients, from 0 to 40 months post-treatment. LR and distant metastasis was observed in 5 patients, and distant metastasis in 4 patients. Seven patients died. Six patients are alive with disease, receiving chemotherapy or supportive care. No patients were lost to follow-up.

The median EQD2 (assuming $\alpha/\beta = 10$ Gy for tumor control) calculated for reirradiation was 48.8 Gy (range: 16–91 Gy), and the median EQD2 calculated for primary RT and reirradiation was