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Original research article

Tolerance of the vaginal vault to high-dose rate brachytherapy and concomitant chemo-pelvic irradiation: Long-term perspective☆

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ABSTRACT

Aim/background: We sought to determine the tolerance level and complication rates of the vaginal vault to combined high-dose-rate intra-cavitary brachytherapy with concomitant chemo-radiotherapy.

Patients and methods: A retrospective review of medical records of all the patients who received definitive chemo-radiotherapy for cervical cancer between 1998 and 2002 was undertaken. The records were reviewed for doses and for radiation-associated early and late sequelae of the vagina, rectum and bladder. Cumulative biological effective dose was calculated for two reference vaginal surface points.

Results: Fifty patients were included. Average age at diagnosis was 54 years. Median follow-up was 59 months. There were no recorded instances of acute grade IV toxicity. Maximal high-dose-rate vaginal surface dose (upper central point) was 103 Gy, and maximal brachytherapy lateral surface dose was 70 Gy. Maximal cumulative biological effective dose for the lateral surface reference point was 465.5 Gy_3, and the maximal cumulative biological effective dose for the superior reference point was 878.6 Gy_3. There were no cases of vaginal necrosis or fistulas, and no cases of grade IV late vaginal, rectal or bladder toxicity. No correlation was found between the maximal vaginal surface dose and vaginal, rectal or bladder toxicity.

Conclusions: The maximal surface HDR brachytherapy dose of 103 Gy and the maximal cBED of 878.6 Gy_3 were not associated with fistula or necrosis or other grade 3–4 vaginal complications. Concomitant chemo-radiotherapy, including pelvic radiotherapy and high-dose-rate intracavitary brachytherapy, is relatively safe for cervical cancer patients.

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1. Background

The treatment of locally advanced uterine-cervix cancer includes concomitant chemo-radiotherapy and intracavitary brachytherapy as definitive treatment. Radiotherapy doses should be optimized to achieve maximal tumor control but great caution needs to be taken to avoid life-threatening or disabling early and late complications. Brachytherapy allows for creating dose escalation which is possible since the tolerance dose of the proximal vagina (vault), uterine-cervix and uterus is high.[1,2]

Numerous factors need to be taken into account when planning the treatment, apart from the patient's habitus and tumor configuration. Procedural factors associated with source placement are often important factors affecting outcome. Vaginal shortening can occur during treatment; therefore, doses to more distal areas of the vagina, which are considered to be less tolerant than the proximal vagina, may increase during treatment.[3] These factors may prevent the use of optimal brachytherapy, smaller applicators and mini ovoids, which might cause the vaginal vault mucosa tolerance dose to become a dose-limiting factor.[1] Moreover, the shift from intracavitary low-dose rate (LDR) brachytherapy to intracavitary high-dose-rate (HDR) brachytherapy has led to some uncertainty. As opposed to LDR brachytherapy, there is no standardized way to deliver HDR brachytherapy, and treatments vary considerably between institutions. Dwell time patterns change from patient to patient, to allow optimization of dose distributions according to tumor geometry.[4] Fractionation of HDR with four to six fractions can be applied to achieve nominal complication rates similar to LDR. However, HDR complication rates are likely to be susceptible to minor changes of dose and biological parameters, due to the amplified biological effects.[1]

The development of complications is multifactorial and includes medical comorbidities, total dose of radiation, dose per fraction, number of fractions, dose rate, radiation field, radiation technique, and whether surgery was performed prior to radiotherapy.[1] There are only a few reports of vaginal necrosis secondary to radiotherapy, most reported in patients treated with adjuvant concomitant chemoradiotherapy.[5–7] Publications often lack important components of treatment planning, doses, vaginal surface dose, complications, treatment failure, and other vital clinical data.[4] Since the advent of 3D planning, the rectum and bladder have been given new restrictions according to volume, while the vaginal vault tolerance dose is still in the dark. Moreover, definitive treatment for cervical cancer includes concomitant chemotherapy and external beam radiotherapy (EBRT) together with HDR brachytherapy, and all should be taken into account when calculating the exposed doses of the mucosa (vagina, rectum, and bladder). The addition of chemotherapy is expected to narrow the therapeutic window when combined treatment is applied. More studies are needed to evaluate the outcome of definitive treatment for uterine-cervix cancer, encompassing both detailed dosimetric and clinical aspects of treatment, to serve as a guide for non-compromising treatment of this potentially curable disease.[1]

Severe complications after radiotherapy for cervical cancer may occur decades after treatment completion.[6] There is a paucity of information regarding late toxicity after chemoradiation for locally advanced cervical cancer, while total vaginal necrosis after treatment is rarely reported.[8] The purpose of the current study was to determine the tolerance levels and late complication rates of the vaginal vault to combined concomitant chemotherapy with external pelvic irradiation and intracavitary HDR brachytherapy, mostly late occurring vaginal necrosis. Complications of adjacent organs were also recorded, as well as survival, recurrences and other clinical data.

2. Patients and methods

A single center, retrospective study of the medical records of all consecutive patients with carcinoma of the uterine cervix treated between May 1998 and May 2002 with concomitant external beam radiotherapy, weekly chemotherapy, and intracavitary HDR brachytherapy was conducted. All the patients were treated with curative intent.

The medical records of 50 consecutive locally advanced patients were reviewed for radiotherapy doses and radiation-associated late sequelae of the proximal vagina (vault) with an emphasis on late-occurring vaginal necrosis. Complications of the rectum and bladder were also recorded. Vaginal patency was graded according to vaginal examination recorded in the medical files. The recorded examinations were reviewed and scored by an onco-gynecologist into four levels (level 0 – no toxicity; 1 – mild; 2 – moderately obliterated and shortened vagina; level 3 – complete vaginal obliteration). Vaginal, rectal and bladder toxicity were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (September 2009). Data collected included demographics, follow-up, time and site of recurrence, mortality, sexual activity, and the presence and site of other malignancies.

The HDR planning process was based on 2D planning. In order to evaluate the doses received by the vaginal mucosa, two sets of points were defined for each ovoid: 5 points on the uppermost and 5 points on the lateral surface of the ovoid opposite the five active dwell positions at a distance equal to the radius of the ovoid. For each patient, the total vaginal dose for the whole HDR treatment was calculated on the surface of the ovoids at the lateral and the upper central point according to the method in our previous publication by Nevelsky et al.[9]

$$cBED = BED_{EBRT} + BED_{HDR} = nd_{EBRT}\,[1 + (d_{EBRT}/3)] + nd_{HDR}\,[1 + (d_{HDR}/3)]$$

Fig. 1 – Equation used for calculation of cumulative biological effective dose (cBED). HDR: high-dose-rate brachytherapy; EBRT: external beam radiotherapy. The α/β ratio used was 3 for late responding tissue.