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CLINICAL INVESTIGATION **Cervix**

RECTAL DOSE AND SOURCE STRENGTH OF THE HIGH-DOSE-RATE IRIDIUM-192 BOTH AFFECT LATE RECTAL BLEEDING AFTER INTRACAVITARY RADIATION THERAPY FOR UTERINE CERVICAL CARCINOMA

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Purpose: The purpose of this study was to reconfirm our previous findings that the rectal dose and source strength both affect late rectal bleeding after high-dose-rate intracavitary brachytherapy (HDR-ICBT), by using a rectal dose calculated in accordance with the definitions of the International Commission on Radiation Units and Measurements Report 38 ($ICRU_{RP}$) or of dose–volume histogram (DVH) parameters by the Groupe Européen de Curietherapie of the European Society for Therapeutic Radiology and Oncology.

Methods and Materials: Sixty-two patients who underwent HDR-ICBT and were followed up for 1 year or more were studied. The rectal dose for ICBT was calculated by using the $ICRP_{RP}$ based on orthogonal radiographs or the DVH parameters based on computed tomography (CT). The total dose was calculated as the biologically equivalent dose expressed in 2-Gy fractions (EQD_2). The relationship between averaged source strength or the EQD_2 and late rectal bleeding was then analyzed.

Results: When patients were divided into four groups according to rectal EQD_2 ($\geq$ or <median dose) and source strength ($\geq$ or <2.4 $cGy.m^2.h^{-1}$), the group with both a high EQD_2 and a high source strength showed a significantly greater probability of rectal bleeding for $ICRU_{RP}$, D_{2cc}, and D_{1cc}. The patients with a median rectal dose above the threshold level did not show a greater frequency of rectal bleeding unless the source strength exceeded 2.4 $cGy.m^2.h^{-1}$.

Conclusions: Our results obtained with data based on $ICRU_{RP}$ and CT-based DVH parameters indicate that rectal dose and source strength both affect rectal bleeding after HDR-ICBT. © 2010 Elsevier Inc.

High-dose rate, Intracavitary brachytherapy, Late rectal complications, Source strength, ^{192}Ir.

INTRODUCTION

Brachytherapy is essential in radiotherapy for cervical carcinoma and is often combined with external beam radiation therapy (EBRT) for radical treatment. Several studies have suggested that control rates are significantly improved with EBRT and brachytherapy compared with EBRT alone (1, 2). High-dose-rate remote afterloading intracavitary brachytherapy (HDR-ICBT) is widely used throughout Asia and Europe, and its use is steadily increasing in the United States (3). A patterns-of-care study performed in Japan from 1999 to 2001 showed that approximately 90% of patients with cervical cancer who underwent ICBT were treated with HDR and that iridium-192 (^{192}Ir) was used as the ICBT source at almost half of the institutes enrolled in the study (4).

However, rectal complications are a major concern for patients with uterine cervical carcinoma who are treated with a combination of EBRT and ICBT. We previously reported that patients treated not only with a rectal biologically effective dose (BED) $\geq$100 Gy_3 but also with an average source strength of >2.4 $cGy.m^2.h^{-1}$ had a high incidence of rectal bleeding. To our knowledge, this was the first report to demonstrate the effect of source strength and rectal BED on rectal complications after HDR-ICBT in patients with uterine cervical carcinoma (5). However, we were unable to calculate the rectal dose by using the International Commission on Radiation Units and Measurements Report 38 rectal reference point ($ICRU_{RP}$) because we did not start using radiopaque gauze for vaginal packing until 2003. Instead, the rectal point

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dose for ICBT was calculated by inserting a lead wire into the rectal lumen.

Recently, the working group for gynecologic brachytherapy of the Groupe Européen de Curietherapie of the European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) introduced guidelines for contouring the target volumes and organs at risk (OARs) for three-dimensional image-based treatment planning for cervical carcinoma. This group also proposed guidelines for analyzing the dose–volume histogram (DVH) parameters calculated from these volumes (6, 7). A minimum dose for the most irradiated tissue volume of 0.1cc ($D_{0.1cc}$), 1cc (D_{1cc}), and 2cc (D_{2cc}) for, respectively, the rectum, the sigmoid, and the bladder is recommended for routine recording.

Since 2003 we have been using radiopaque gauze for vaginal packing and have obtained computed tomography (CT) during the first session of the HDR-ICBT procedure. The purpose of this study was to reconfirm, by using the retrospectively calculated rectal dose in accordance with the definitions of $ICRU_{RP}$ or GEC-ESTRO DVH parameters obtained by CT, our findings that rectal dose and source strength both affect late rectal bleeding.

METHODS AND MATERIALS

Patient characteristics

A total of 87 patients with histologically proven carcinoma of the uterine cervix were treated at the Department of Radiation Oncology, Osaka University Hospital, Osaka, Japan between February 2003 and May 2007. Patients were staged according to the International Federation of Gynecology and Obstetrics criteria and clinically examined without general anesthesia by a gynecologic oncologist and a radiation oncologist using palpation, cystoscopy, and sigmoidoscopy. Abdominal CT and pelvic magnetic resonance imaging (MRI) were performed to help with appropriate staging. Complete blood counts and liver and renal function tests were also performed. Twenty-five patients were excluded from the study because 3 had received interstitial brachytherapy, 11 were lost to follow-up, 5 died or showed local recurrence within 1 year after radiotherapy, and 6 had for various reasons not undergone CT during the first session of HDR-ICBT. We analyzed the remaining 62 patients, who had been treated with ^{192}Ir HDR-ICBT using a tandem-ovoid or tandem-cylinder applicator and followed up for 1 year or more (median, 42 months; range, 12–62 months). The stage distribution of the patients was as follows: 10 with Stage I disease (16%), 27 with Stage II (44%), 21 with Stage III (34%), and 4 with Stage IV (6%). The median age of the study cohort was 69 years (range, 35–86 years).

Radiotherapy

Both EBRT and HDR-ICBT were performed as previously described (5), with some modifications. The treatment schedules for EBRT and HDR-ICBT are listed in Table 1. A set of Fletcher-type (Fletcher-Williamson Asian-Pacific) metal applicators (Nucletron International B.V., Veenendaal, The Netherlands) was mainly used for ICBT. For patients with vaginal infiltration or with a narrow vagina, a tandem with a vaginal cylinder was used. Anterior and posterior vaginal packing with radiopaque gauze was used to maximize the distance from the source to the bladder wall and the rectal wall. Calculation of the dose profiles was based on orthogonal radiographs taken during each individual application, and the $ICRU_{RP}$ dose was estimated from these films with a treatment planning system (Plato, Nucletron). A series of transverse CT images of the pelvis with the applicators inserted was also obtained in 2.5- or 5-mm steps during the first HDR-ICBT. Concurrent chemoradiotherapy was administered to 25 of the patients (40%). Nedaplatin, an analog of cisplatin developed in Japan, was administered 5 times weekly at 35 mg/m^2 with a concurrent EBRT and ICBT.

Table 1. Treatment schedule for uterine cervical carcinomas

Tumor stage	WP (Gy)	CS (Gy)	ICBT
T1a	0	0	7.2 Gy × 4
T1b	0	40	7.2 Gy × 4
T2	20	30	7.2 Gy × 4
T3	30	20	6.8 Gy × 4
T4	40	10	6.8 Gy × 3

Abbreviations: WP = whole-pelvic irradiation; CS = pelvic irradiation with midline block; ICBT = intracavitary brachytherapy.

Calculation of rectal dose

Cumulative DVH was analyzed according to the recommendations of the GEC-ESTRO Working Group (7). The rectum was contoured from the bottom of the ischial tuberosity to the sigmoid flexure by using the external wall contour. The minimal dose received by the 0.1-cc, 1-cc, and 2-cc volumes with the highest irradiation ($D_{0.1cc}$, D_{1cc}, and $D_{2cc,}$ respectively) was determined. To determine the dose from the combined EBRT (whole pelvic irradiation dose, excluding the fractions with central shielding) and ICBT, the total dose (EBRT + ICRT) was calculated as the biologically equivalent dose in 2-Gy fractions (EQD_2) using the linear quadratic model for incomplete sublethal damage repair (8). The equation used to calculate the EQD_2 was as follows:

$$EQD_{2total} = EQD_{2EBRT} + EQD_{2ICBT} = Nd(d + \alpha/\beta)/(2 + \alpha/\beta) + N_B d_B(d_B + \alpha/\beta)/(2 + \alpha/\beta)$$

where N is the fraction number of EBRT (before central shielding), d is the fractional dose of EBRT, N_B is the fraction number of HDR-ICBT, and d_B is the fractional dose of HDR-ICBT. The values used for late effects on OARs (*i.e.* bladder, rectum, and sigmoid colon) were α/β =3 Gy. For the first HDR-ICRT session, EQD_2 for $ICRU_{RP}$ was estimated from the orthogonal radiographs, and EQD_2 for the respective DVH parameters was estimated from CT images with the applicators inserted. For subsequent HDR-ICRT sessions, only EQD_2 for $ICRU_{RP}$ was estimated each time, whereas the DVH parameters obtained in the first session were reused because no CT scan was performed.

Follow-up and evaluation of late rectal complications

The patients were followed up by gynecologic and radiation oncologists on an outpatient basis every month in the first year, every 2 months in the second year, every 3 months in the third year, every 4 months in the fourth year, every 6 months in the fifth year, and annually thereafter until 10 years after treatment. Each follow-up examination included collection of clinical history; a physical examination comprising abdominal, pelvic bimanual and speculum examinations; and a Pap smear from the vaginal vault or uterine cervix. The method for the grading of rectal complications has been described previously (5). Grade 1 toxicity refers to minor