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De-escalation of the cumulative central radiation dose according to the tumor response can reduce rectal toxicity without compromising the treatment outcome in patients with uterine cervical cancer☆

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HIGHLIGHTS

- A retrospective study was conducted to determine the efficacy of midline block.
- The midline block decreased rectal and bladder dose and reduced late toxicity.
- The lowered central dose did not compromise the patients' oncologic outcome.

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ABSTRACT

Objective. To assess the treatment outcome and toxicity of a low cumulative central dose using a midline block (MLB) during external beam radiotherapy (EBRT).

Methods. Between January 1988 and December 2010, 1559 patients with FIGO stage IB–IIB uterine cervical cancer that underwent EBRT and high-dose-rate intracavitary brachytherapy (HDR-ICBT) were retrospectively analyzed. During EBRT, MLB was performed (n = 1195, MLB group) when a sufficient response was achieved to insert the tandem through the cervical canal and place ovoids in the vaginal cavity. MLB was not applied for patients with a slow tumor response (n = 364, non-MLB group). The doses were estimated according to the International Commission on Radiation Units and Measurements (ICRU) points. The biologically equivalent dose in 2-Gy fractions (EQD2) was calculated to estimate the cumulative dose from EBRT and ICBT.

Results. $EQD2_{pointA}$, $EQD2_{rectum}$, and $EQD2_{bladder}$ were all significantly lower in the MLB group (all $P < 0.05$). The 10-year grade ≥ 2 late rectal toxicity rate was significantly lower in the MLB group ($P = 0.012$), while there was no significant difference in late genitourinary and small bowel toxicity. ICRU rectal and bladder doses showed significant predictability on late rectal and bladder toxicities. After propensity score matching, all patient and tumor characteristics were well matched and the survival and recurrence rates between the two groups were similar (all $P > 0.05$), despite the lower $EQD2_{pointA}$ in the MLB group ($P < 0.001$).

Conclusions. Applying MLB according to tumor response during EBRT lowered the cumulative central dose and reduced late rectal toxicity without compromising treatment outcome.

1. Introduction

Uterine cervical cancer is the fourth most common female cancer and the fourth leading cause of female cancer mortality worldwide [1]. However, it is the second most common and third leading cause of cancer mortality in developing countries [1]. Definitive radiotherapy (RT) or concurrent chemoradiotherapy (CRT) are the standard treatments for early stage and locally advanced uterine cervical cancer [2,3]. Standard RT for uterine cervical cancer consists of external beam RT (EBRT) and intracavitary brachytherapy (ICBT).

ICBT plays a major role in definitive treatment of patients with uterine cervical cancer. The impact of ICBT on survival was reported in two population-based studies, which showed significantly higher overall survival (OS) in patients who received ICBT compared to those who

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did not [4,5]. High-dose-rate ICBT (HDR-ICBT) has begun to replace low-dose-rate ICBT [6–8]. One of the concerns in utilizing HDR-ICBT is its association with late toxicity. The late toxicity rate of the rectum and bladder is radiation dose-dependent. A previous report suggested that, keeping the biological effective dose of point A at ≤90 Gy was associated with fewer late rectal and bladder complications [9]. Moreover, recent studies showed that the dose volume parameters of the rectum and bladder were associated with the rate of late toxicity [10,11]. Therefore, doses to the rectum and bladder should be kept to a minimum while administering a sufficient tumoricidal dose to enhance the therapeutic ratio.

In an attempt to reduce the central dose, the use of a midline block (MLB) during EBRT was evaluated in a prospective multi-institutional study in Japan that delivered a biologically equivalent dose in 2-Gy fractions (EQD2) of 52–65 Gy to point A [12,13]. They reported a comparable outcome and lower incidence of late toxicity compared to other studies that used higher point A doses. However, the median follow-up period was relatively short in both studies. In our institution, we have adopted MLB during EBRT over the last 3 decades. MLB was applied according to the tumor response. Here, we present the long-term follow-up data on treatment and toxicity outcomes of using MLB during EBRT in conjunction with HDR-ICBT.

2. Patients and methods

2.1. Patients

The study included 1559 patients with histologically confirmed International Federation of Gynecologic and Obstetrics (FIGO) stage IB–IIB uterine cervical carcinoma who underwent definitive RT or CRT using EBRT and HDR-ICBT between January 1988 and December 2010. Approval for this study was obtained from the Institutional Review Board. All patients were clinically staged, and computed tomography (CT) (n = 1234) or magnetic resonance imaging (MRI) (n = 409) were performed to evaluate lymph node involvement. Since 2004, 158 patients underwent 18F-fluorodeoxyglucose positron emission tomography.

2.2. Treatment

EBRT was performed in all patients, and the field border differed according to the extent of nodal involvement. Patients most commonly received EBRT to the whole pelvis. In cases with paraaortic lymph node involvement, extended-field RT to T11/12 or T12/L1 was performed [14]. In patients with pelvic lymph node involvement near the aortic bifurcation, semi-extended field RT with the superior border extending to the upper margin of L2 was performed for prophylaxis of paraaortic lymph node recurrence. EBRT was delivered to a total dose of 45–50.4 Gy in 1.8 Gy per fraction. A weekly pelvic examination was performed to evaluate tumor response. Once sufficient tumor regression was achieved to enable ICBT applicator insertion, MLB was placed (MLB group, n = 1195). The MLB was 4-cm wide; it as high as the upper boundary of the prescribed HDR-ICBT isodose line and as low as the inferior field border. Patients with an insufficient response to place the ICBT applicators received full dose EBRT without MLB (non-MLB group, n = 364). The portal arrangement was changed to the anteroposterior–posteroanterior (AP–PA) technique after MLB insertion (Supplemental Fig. S1). Usually, HDR-ICBT was initiated after 27–36 Gy of EBRT. After completion of HDR-ICBT, EBRT with MLB was delivered to the patients. After completion of HDR-ICBT, EBRT with MLB was delivered. Conventional 2-dimensional ICBT was used, and the position of point A, the bladder point, and the rectal point were defined according to the International Commission on Radiation Units and Measurements (ICRU) 38 recommendation. For HDR-ICBT planning, both orthogonal AP–PA and lateral images were generated, with dummy sources inserted into the applicator. The reference points of the bladder and rectum were identified on films by insertion of a Foley catheter balloon filled with 7 mL of contrast media and by filling the rectum with 100 mL of barium [9]. Tandem and ovoids were consistently used for HDR-ICBT throughout the study period. The median HDR-ICBT dose was 30 Gy (range, 15–57 Gy) administered at a median of 5 Gy (range, 3–6 Gy) per fraction at point A. HDR-ICBT was performed 3 times a week when the fraction dose was 3 Gy, and 2 times a week when the fraction dose was larger. A lymph node boost of 5.4–14.4 Gy in 1.8 Gy per fraction was performed in cases with lymph node metastases. The total biological effective dose was calculated as EQD2 (α/β value of 3 for normal tissue [Gy_3] and 10 for tumor [Gy_{10}]) at point A ($EQD2_{pointA}$), the bladder point ($EQD2_{bladder}$), and the rectal point ($EQD2_{rectum}$) [15].

Concurrent chemotherapy was administered to 505 patients, and most of them received platinum-based chemotherapy (n = 484). During brachytherapy, chemotherapy was continued but not on the same day as HDR-ICBT insertion. The commonly applied regimens were a combination of carboplatin or cisplatin with 5-fluorouracil administered on the first, fourth, and seventh weeks of RT, or weekly administration of cisplatin during RT. For patients with adenocarcinoma, a combination of cisplatin, cyclophosphamide, and adriamycin was administered prior to the declaration of National Cancer Institute for cisplatin-based CRT [16].

2.3. Follow-up, toxicity evaluation, and management

Follow-up examinations were performed every 3 months for the first 2 years, every 6 months for the next 3 years, and then once per year every year thereafter. The patients were instructed to visit the clinic as soon as they experienced rectal bleeding, hematuria, vaginal bleeding, or any other symptoms. Recurrences involving the cervix, vagina, or parametrial tissue were classified as local, and lymph node failures within the RT field were defined as regional. Recurrence outside the RT field was defined as distant. Late toxicities were defined as those occurring 3 months after treatment and were graded according to the Radiation Therapy Oncology Group late radiation morbidity scoring scheme [17]. Late distal ureteral strictures caused by RT were considered late genitourinary (GU) toxicity and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Although conservative care was the treatment of choice in less severe cases, some patients received active intervention due to more severe complications. For treatment of patients with late rectal toxicities, transfusion (n = 32), colonoscopy with cauterization (n = 29), and surgical procedures such as colostomy (n = 37) were performed. For treatment of patients with late GU toxicities, transfusion (n = 9), ureteral stent or percutaneous nephrolithotomy (n = 19), cystoscopy with cauterization (n = 9), and surgical intervention such as cystectomy or cystostomy (n = 5) were performed. For treatment of patients with late small bowel toxicities, surgical interventions such as small bowel resection or ileostomy were performed (n = 17).

2.4. Statistical analyses

Categorical data were analyzed using Fisher's exact test or χ^2 analyses, and continuous data were compared between groups using the Mann–Whitney U test. The Kaplan–Meier method and log-rank test were used to estimate and compare rates of OS and progression-free survival (PFS). Rates of local recurrence (LR), regional recurrence (RR), and toxicity were estimated by means of the cumulative incidence method and were compared between the two groups using Gray's test [18]. OS, PFS, LR, and RR rates were measured from the date of treatment start to the date of death from any cause, date of recurrence or death, date of local recurrence, and date of regional recurrence, respectively. Only death was considered a competing risk for local recurrence, regional recurrence, and toxicity. The predictive values of ICRU doses for late toxicity were evaluated using receiver operating characteristic

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