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The prognostic significance of tumor volume regression during radiotherapy and concurrent chemoradiotherapy for cervical cancer using MRI ☆

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Abstract

Objective. The purpose of this study was to determine the prognostic significance of tumor volume regression rate during radiotherapy (RT) measured by three serial magnetic resonance imaging (MRIs) studies performed in patients treated with RT alone and compare the results with patients treated with concurrent chemoradiotherapy (CCRT).

Methods. We evaluated 81 patients with uterine cervical cancer who underwent three serial MR examinations, i.e., at the start of RT, at 36–45 Gy of external RT and 1 month after the end of RT. Forty-three patients were treated with RT alone and 38 patients were treated with CCRT. Pre-RT tumor volume (V1), the tumor volume regression rate measured during the fourth week of RT and residual tumor volume at 1 month after the end of RT (V3) were determined for each patient. The cut-off value used for the three parameters studied was the one that made the largest outcome difference. These volume parameters were analyzed to determine a difference in the treatment outcome.

Results. In the patients treated with CCRT, the mean value of the V1 was larger and the mean value of the V3 was smaller than in patients treated with RT alone. The mean value of the mid-RT regression rate was somewhat higher in patients treated with CCRT than in patients treated with RT alone; however, this difference was not statistically significant (79% vs. 69%). In both the RT alone and the CCRT group, the patients with a mid-RT regression $\geq 75\%$ had 100% 5-year local control rates and a better disease free survival than the patients with mid-RT regression $<75\%$. The patients with V3 = 0 cm^3 also had a better 5-year local control rate than the patients with a V3 > 0 cm^3, but statistical significance was found only in the patients treated with CCRT.

Conclusions. The mid-RT tumor volume regression rate, at 36–45 Gy of external RT, was a predictor of local control rate in both RT and CCRT patient groups. However, in the patients who were treated with CCRT, the local control rate difference was even larger by post-RT residual volume than by the mid-RT tumor regression rate. Further studies on appropriate evaluation timing for mid-RT response in patients receiving CCRT are needed.

Keywords: Cervical cancer; Magnetic resonance imaging; Tumor regression; Concurrent chemoradiotherapy

Introduction

Radiotherapy (RT) is a major treatment modality for patients with cervical cancer. The response to RT is known to affect an individual's treatment outcome. There are ranges of response and evaluation times using methods that predict treatment failure after RT; for those patients that fail RT salvage therapy is then started [1–5]. Although the response after completion of RT is important, determination of prognostic factors early during RT has been reported to be valuable [6–11]. The tumor volume regression rate, measured during RT, appears to have greater prognostic value than either the pretreatment tumor volume or the residual tumor volume after RT has been completed [9].

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To date, tumor responsiveness measured during RT has been based on results from patients treated with RT alone [6,7,9–11]. However, it seems inappropriate to use the same radioresponse evaluation timing in patients treated with concurrent chemoradiotherapy (CCRT). In a randomized trial on CCRT conducted by Keys et al., the rate of residual disease on hysterectomy specimens was lower in patients who received CCRT compared with those treated with RT alone (48% vs. 59%; $P=0.04$) [12]. It has been shown that the radioresponsiveness is heightened [13] and the complete remission rates are increased in patients receiving combined treatment compared to RT alone.

Patients with cervical cancer treated with the intent to cure at our institution had magnetic resonance imaging (MRIs) obtained at 36–45 Gy of external RT to evaluate the pelvic geometry following tumor shrinkage before commencing brachytherapy. The purpose of this study was to determine the prognostic significance of tumor volume regression during RT measured by three serial MRIs in patients treated with RT alone and to determine whether the significance of this parameter could be applied to patients treated with CCRT.

Materials and methods

Patients

From March 1997 to November 2003, 323 uterine cervical cancer patients were treated with curative RT at Samsung Medical Center; among these cases, we retrospectively reviewed 81 patients who had three serial pelvic MRIs. We excluded patients with histology other than squamous cell carcinoma of the cervix, those who had recurrent cancer or cancer on the cervical stump, those who had no measurable tumor on pretreatment MRI due to extensive biopsy and those who were treated with neoadjuvant chemotherapy or had incomplete treatment.

Among the 81 patients, 38 patients were treated with CCRT (Table 1). Forty-three patients treated with RT alone had a significantly higher median age and longer overall treatment time than patients treated with CCRT. The reasons for radiotherapy alone were as follows: patients who were more than 65 years old and whose general condition was not good to be treated with concurrent chemoradiotherapy in 12 patients, physicians preference in 12, medical comorbidities in 11, and patient's refusal of chemotherapy in 8. The pelvic or para-aortic lymph nodes that exceeded 1.5 cm in diameter on CT or MRI and/or that had significant F^{18}-FDG (Fluoro-deoxy-glucose) uptake on Positron Emission Tomography (PET) were considered positive for tumor involvement. The median follow-up duration was 39 months (range, 9–97 months) in patients treated with RT and 36 months (range, 5–58 months) in patients treated with CCRT.

Table 1
Patient characteristics

		RT ($n=43$)	CCRT ($n=38$)
Age, median (range)		66 years (35–83)	55 years (29–79)
FIGO[a] stage	IB_1–IIA	13 (30.2%)	8 (21.1%)
	IIB	20 (46.5%)	17 (44.7%)
	III–IVA	10 (23.3%)	13 (34.2%)
Pelvic node Involvement		14 (32.6%)	19 (50.0%)
Para-aortic node involvement		0	6 (15.8%)
Overall treatment time, median (range)		53 days (43–76)	58 days (43–90)

[a] Federation of International Gynecology and Obstetrics.

Table 2
Tumor volume and volume regression rate measured by MRIs

	RT alone ($n=43$)	CCRT ($n=38$)	p
Pre-RT tumor volume, cm^3, mean (95% CI)	45 (33–57)	65 (50–81)	0.03
Mid-RT volume regression rate, %, mean (95% CI)	69 (62–76)	79 (73–85)	n.s[a]
Post-RT tumor volume, cm^3, mean (95% CI)	5 (0–10)	3 (0–8)	<0.01

[a] Not significant.

Treatment

All patients were given a combination of external beam RT (EBRT) and then intra-cavitary brachytherapy (ICR), which was initiated after an EBRT dose of 41.4 to 45 Gy (median dose: 45 Gy). EBRT was performed with 15-MV photons to the entire pelvis and the dose ranged from 41.4 to 55.8 Gy (median dose: 50.4 Gy). The extended pelvic field, including para-aortic lymph nodes, was used in six patients with para-aortic node involvement, with a dose up to 45 Gy. ICR using a high dose rate (HDR) source was carried out with a reference point A prescription of 24 Gy, twice a week in six fractions. The regimen for CCRT consisted of three cycles of 5-fluorouracil (1000 mg/m^2 in a continuous infusion over 96 h) and cisplatin (60 mg/m^2) at three-week intervals in 29 patients or six cycles of weekly cisplatin (30 mg/m^2) alone in nine patients.

Tumor volume measurement

Three serial MRIs were performed at the start of RT (pre-RT), at the fourth week of RT (mid-RT) and 1 month after completion of RT (post-RT). In each of the three MR examinations, based on the T2-weighted images, two radiation oncologists defined the tumor areas in each slice. The tumor volume was calculated for each of the MRIs by a summation of all of the areas of tumor and multiplied by the slice profile. Three tumor volumes for each patient were obtained: pre-RT tumor volume (V1), mid-RT tumor volume (V2) and post-RT residual tumor volume (V3). The mid-RT volume regression rates were expressed as the percent (%) reduction of tumor volumes measured on mid-RT MRIs relative to the initial tumor volumes (V1–V2/V1).

Cut-off values for each parameter were identified stepwise by 5 cm^3 and 10% increments. The volume thresholds and tumor regression thresholds were correlated with the outcome endpoints. The most discriminating threshold values for V1, mid-RT tumor regression rate and V3 were the same for both treatment groups 44 cm^3, 75% and 0 cm^3, respectively.

Outcome analysis

Local failure was defined as the identification of recurrent or progressive tumor within the pelvis during the follow-up period. The initial recurrence site was used to determine local recurrence and/or distant metastasis. Comparison of the mean value of the measured tumor volumes and regression rates was evaluated using the Wilcoxon Rank-sum test. The failure rates according to the variables studied were analyzed using the Fisher's exact test or Cochran Mantel–Haenszel Test. Kaplan–Meier life table analysis and the log–rank test were used to assess the survival rate and differences according to prognostic factors. A p-value of <0.05 was considered significant.

Results

Tumor volume and regression rate

Measured tumor volume and volume regression rate according to treatment groups were presented in Table 2. In patients treated with CCRT, the mean value of the V1 was larger (65 cm^3 vs.