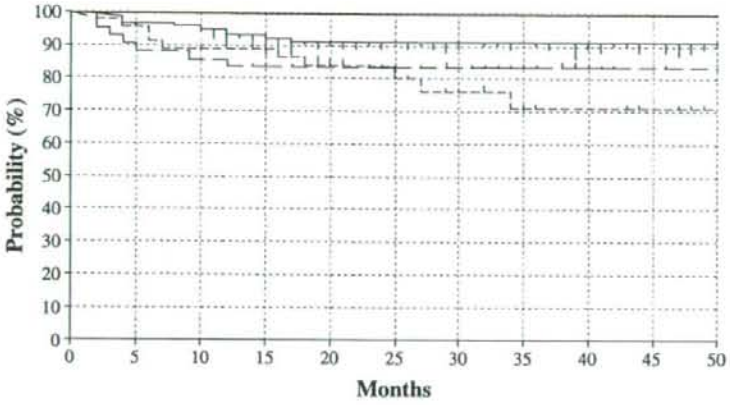

Figure 2. Locoregional failure-free survival rates in CT-RT and R alone; solid thick line (Stage Ib, II, CT-RT), solid thin line (Stage Ib, II, RT alone), dotted thick line (Stage III, IV, CT-RT), dotted thin line (Stage III, IV, RT-alone).

in R alone. There was the significant difference between CR-RT and R alone ($p < 0.05$).

We compared late complications (rectum) free survival rates between CR-RT and R alone. Late complications-free survival rate at 50 months in rectum was 87% in CR-RT and 90% in R alone. The difference between CR-RT and R alone was not significant ($p = 0.73$).

We compared late complications (bladder) free survival rates between CR-RT and R alone. Late complications-free survival rate at 50 months in bladder was 93% in CR-RT and 96% in R alone. There was the significant difference between CR-RT and R alone ($p < 0.05$).

Discussion

Here we reported results the treatment results of CT-RT in cervical cancer, focusing especially on acute and late complications conducted by the JROSG. In this study, CT-RT was employed more in patients who had the larger tumor diameter and more positive pelvic lymph nodes, as compared with RT alone. However, locoregional failure-free survival in patients treated with CT-RT was significantly better than in patients with R alone in Stage Ib or II, indicating that CT-RT overcame disadvantages for local control such as larger tumor diameter and more positive pelvic lymph nodes. These results concurred with randomized trials [4,7,9,10] which reported that local failures were significantly decreased in the cisplatin arms of these studies, suggesting that chemotherapy was acting as a radiation sensitizer [19].

There were no significant differences in overall survival and disease-free survival rates between CT-RT and R alone in our study. These results did not agree with the randomized trials [4,7,9,10]. The

Table III. Survival Rates at 50 months.

	Radiotherapy and Chemotherapy (N = 63)		Radiotherapy alone (N = 163)		
	%	95% CI	%	95% CI	*P*
Overall survival					
Stage Ib, II	82%	24% to 100%	81%	72% to 90%	n.s
Stage III, IV	66%	49% to 83%	43%	23% to 63%	n.s
Disease-free survival					
Stage Ib, II	74%	54% to 94%	76%	70% to 82%	n.s
Stage III, IV	59%	44% to 74%	52%	34% to 70%	n.s
Locoregional failure-free survival					
Stage Ib, II	100%	100%	91%	86% to 96%	<0.01
Stage III, IV	83%	72% to 94%	71%	55% to 87%	n.s
Distant metastasis-free survival					
Stage Ib, II	74%	54% to 94%	87%	80% to 94%	n.s
Stage III, IV	65%	50% to 80%	65%	47% to 83%	n.s

* Abbreviation: n.s., not significant.

Table IV. Acute complications.

	Radiotherapy and Chemotherapy (N = 63)					Radiotherapy alone (N = 163)				
	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Leukocytes	10	5	11	33	4	135	11	14	4	0
Platelets	48	2	4	9	0	159	2	1	1	0
Diarrhea	28	27	8	0	0	96	41	24	1	0
Urinary frequency	56	6	1	0	0	150	11	2	0	0

prevalence of larger tumor diameters and more positive pelvic lymph nodes in CT-RT patients may have influenced our results.

Concomitant chemotherapy did not decrease distant metastasis in our study. The prevalence of disadavantageous factors working against systemic control in CT-RT patients, such as larger tumor diameters and more positive pelvic lymph nodes were perhaps too great for the chemotherapy to produce systemic benefit.

CT-RT significantly increased late complications in rectum, small or large bowel, and bladder in our study. Actually, 31% of patients treated with CT-RT suffered complications higher than Grade 2 in rectum, small or large bowel, and bladder at 50 months after treatment. However, CT-RT was no prognostic factor in multivariate analysis, indicating that the interpretation of results obtained by non-randomized trials should be careful due to bias. CT-RT was employed more in patients who had the larger tumor diameter and more positive pelvic lymph nodes in this study. Besides, the heterogeneity of the schedules used for concurrent chemotherapy and the wide spread use of combination chemotherapy should be recognized as a problem in analyzing the influence on late complications.

HDR was used in all patients in this study. It is not clear if it is safe to give chemotherapy concurrently with HDR. In the randomized trial conducted by Canadian institutions, low dose rate, medium dose rate, and high dose rate techniques were all allowed. Only 38 of the 253 patients treated had HDR, with a schedule of 8 Gy times 3 fractions. There was no subset analysis done to determine any difference in toxicity between LDR, MDR, and HDR [20]. There are only a few reports in which HDR was used in CT-RT [21–24]. Besides, the number of patients in their reports was small and their results are conflicting. Souhami et al. reported an increased incidence of GI toxicity (26% with cisplatin versus 7.5% without) in patients receiving cisplatin-based chemotherapy along with external beam and HDR, which occurred rather early at a median follow-up of 11 months [24]. Sood et al. reported increased acute toxicities with chemotherapy and radiation using HDR techniques, but no increase in late

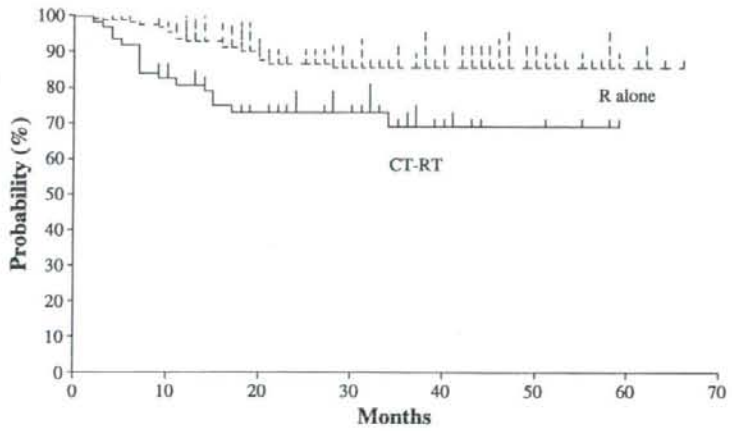

Figure 3. Late complications-free survival rates in CT-RT and R alone. Patients who had late complications Grade 2 or higher in rectum, small or large bowel, and bladder were analyzed.

complications [23]. It is unclear if the use of HDR in this study was related to increased late complications because CT-RT and R alone showed no differences in late complications in rectum or bladder, which are influenced to a greater degree than small or large bowel by the intracavitary irradiation.

Mature analysis confirms that the addition of fluorouracil and cisplatin to radiotherapy using LDR significantly improved the survival rate of women with locally advanced cervical cancer without increasing the rate of late treatment-related side effects [4].We are planning the randomized trials to elucidate optimal radiation doses when HDR is used. Recently, Potter et al. reported that combined intracavitary and interstitial MRI-based brachytherapy in patients with significant residual disease after external-beam therapy is feasible and allows excellent local control and a low rate of morbidity [5]. Dimopoulos et al. reported that MRI-based MRI-based 3D conformal HDR and cisplatin appeared to be safe and effective [25]. We are also considering to use these high quality HDRs.

In summary, CT-RT significantly improved local control of patients with Stage Ib and II in univariate analysis. CT-RT caused significantly more acute complications such as leukopenia, thrombocytopenia, and diarrhea. Late complications (rectum, small or large bowel, and bladder) in CT-RT increased significantly, as compared with R alone in univariate analysis. These results were obtained by using non-randomized data and the interpretation of these results should be careful due to bias in data. However, our results indicate that the optimal radiation doses for CT-RT remain to be resolved. Further randomized trials in which strict dose guidelines are provided in these protocols are necessary to elucidate optimal radiation doses for CT-RT.

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