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A randomized clinical trial of radiation therapy versus thermoradiotherapy in stage IIIB cervical carcinoma

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To clarify the role of thermoradiotherapy for FIGO Stage IIIB cervical carcinomas, both the clinical response and survival of patients treated with radio- or thermoradiotherapy were investigated. Forty patients with Stage IIIB uterine cervix carcinoma were treated with external beam irradiation to the pelvis, combined with iridium 192 high-dose-rate intracavitary brachytherapy. All patients were divided randomly into the following two groups: the radiotherapy (RT) group of 20 patients, who underwent radiotherapy alone; and the thermoradiotherapy (TRT) group of 20 patients, who underwent three sessions of hyperthermia in addition to radiotherapy. The primary endpoint of this study was local complete response and survival. A complete response was achieved in 50% (10 of 20) in the RT group versus 80% (16 of 20) in the TRT group ($p = 0.048$). The 3-year overall survival and disease-free survival of the patients who were treated with TRT (58.2 and 63.6%) were better than those of the patients treated with RT (48.1 and 45%), but these differences were not significant. The 3-year local relapse-free survival of the patients who were treated with TRT (79.7%) was significantly better than that of the patients treated with RT (48.5%) ($p = 0.048$). TRT, as delivered in this trial, was well tolerated and did not significantly add to either the relevant clinical acute or long-term toxicity over radiation alone. TRT resulted in a better treatment response and 3-year local relapse-free survival rate than RT for patients with FIGO Stage IIIB cervical carcinoma.

Key words: Stage IIIB cervical carcinoma, thermoradiotherapy, radiotherapy, prognosis.

1. Introduction

Cervical cancer is one of the most common tumours affecting women worldwide, both in incidence and mortality (Pontén *et al*. 1995), and definitive radiation therapy is widely accepted as the treatment of choice for patients with FIGO Stage IIIB carcinoma of the cervix. Investigators have reported survival rates between 30–50% for patients treated with radiation therapy alone (Lanciano *et al*. 1991, Marcial and Marcial 1993, Barillot *et al*. 1997). While FIGO Stage IIIB carvinomas metastasize to extrapelvic sites more often than earlier stage tumours, pelvic recurrence continues to be a major cause of morbidity and mortality in treated patients. Some clinicians have tried a number of experimental treatments designed to enhance the response of tumours to radiation therapy: neutrons, radiation sensitizers, and chemotherapy

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delivered intra-arterially (Logsdon and Eifel 1999). Most of these approaches have failed to improve the results over treatment with radiation alone (Logsdon and Eifel 1999). Although, combination of radiotherapy with chemotherapy has recently been reported to improve local control of cervical cancer (Morris *et al* 1999, Rose *et al.* 1999).

TRT has been reported to yield higher complete and durable responses compared to radiotherapy alone (RT) in both superficial and deep-seated tumours (Feldman *et al.* 1993, Wust *et al.* 1996, Nagata *et al.* 1997), and it is believed to be another promising treatment modality for the management of advanced cervical cancer (Hornback *et al.* 1986, Datta *et al.* 1987, Sharma *et al.* 1991). However, the late effects of TRT for patients with FIGO Stage IIIB cervical carcinomas has been controversial (Hornback *et al.* 1986, Datta *et al.* 1987, Sharma *et al.* 1991).

This study evaluated the clinical response and survival of patients treated with RT or TRT for FIGO Stage IIIB cervical carcinomas, and compared the findings.

2. Materials and methods

2.1. *Patient characteristics*

The patient eligibility criteria for entry into the study were as follows: (1) histologically proven cervical carcinoma at International Federation of Gynecology and Obstetrics (FIGO) Stage IIIB, (2) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, (3) no prior chemotherapy, radiotherapy, or surgery, (4) adequate bone marrow, liver, and renal function, (5) no concomitant malignancies, and (6) informed consent. In addition, patients with pacemakers or those with subcutaneous fatty layer exceeding 4 cm were considered as not eligible for this study (there were no such patients).

The protocol of this trial was approved by the Kansai Medical University Review Board. Randomization to treatment groups was performed by a computer-generated random number list before the start of treatment. The patients were divided into two groups: the RT group of 20 patients who received radiotherapy alone, and the TRT group of 20 patients treated with RT and hyperthermia once a week for a total of three sessions of up to 30.6 Gy radiation.

The patients' demographics and tumour characteristics between the groups are noted in table 1.

Table 1. Clinical characteristcs.

Characteristic	RT ($n = 20$)	TRT ($n = 20$)
Mean age (years)	61.6	64.9[a]
SD	11.2	9.9
Follow-up time (months)		
Mean	25	36.3[a]
Range	3.5–60.1	5.9–64.3
Histology		
Squamous cell carcinoma	18	17[b]
Adenocarcinoma	2	3
Tumour size (cm)		
Mean	6.1	5.9[a]
SD	1.8	2.2

[a] Two-tailed Students' *t*-test.
[b] Fisher's exact test.

2.2. *Irradiation techniques and doses*

All patients entered in the protocol were treated with external pelvic RT using a 6 MV linear accelerator. A total of 30.6 Gy was targeted to the whole pelvis, with an additional dose to the parametria with central shielding for a total of 52.2 Gy. The fractions were 1.8 Gy daily, given 5 days/week. In addition, iridum 192 high-dose-rate brachytherapy was given in fractions of 7.5 Gy once per week for a total of 30 Gy to point A.

2.3. *Hyperthermia*

Hyperthermia was delivered via a radiofrequency capacitive heating device (Thermotron RF-8, Yamamoto Vinita Co., Osaka, Japan), which uses 8 MHz radiofrequency electromagnetic waves as a source of heat. The output power ranged from 800–1500 W. The heating was performed as previously described (Tanaka *et al.* 1992). The electromagnetic power was applied between two external disk electrodes, 25 and 30 cm in diameter, placed on opposite sides of the pelvic region. The temperature of the tumour was measured in all patients by using a 4-point microthermocouple-sensor, which was inserted in advance into the tumour through a 21-gauge catheter with the aid of ultrasonography, and left until the end of the last hyperthemia session. Hyperthermia was usually applied within 30 min after external radiotherapy, for a total of 60 min, independent of the pattern of temperature elevation, once a week for a total of three sessions. The first heating was usually performed after the third or fifth fraction of external RT.

The maximum tumour temperature (T_{max}) was defined as the maximum temperature obtained in the tumour during the steady state and at the end of treatment. The steady state was defined at 20 min after the start of hyperthermia. The minimum intratumour temperature (T_{min}) was defined as the minimum tumour temperature obtained by the same method. All parameters were determined for each treatment session, and the averages of these parameters were calculated over all treatments for a given tumour (T_{ave}).

2.4. *Evaluation of treatment*

The response of the tumour to the treatment was evaluated as follows: complete response (CR) when no tumour was detected by physical examination or magnetic resonance imaging and cytologic or biopsy studies were negative for malignant cells or at least 1 month after treatment; partial response (PR) when the tumour mass was reduced by $\geq 50\%$; no change (NC) when the reduction in the tumour mass was $< 50\%$.

Toxicities were scored according to a modification of the Radiation Therapy Oncology Group (RTOG) morbidity scale (Trotti *et al.* 2000).

Patients were examined every month for 1 year after treatment and every 2 months thereafter.

2.5. *Sample size and statistical methods*

This trial was designed to address the hypothesis that a complete response rate would be possible in 80% of patients in the TRT group, as compared with an expected rate of 50% in the RT group. A two-group, continuity-corrected χ-square test with a two-sided significance level of 0.05 has 80% accuracy in detecting this difference when the sample size in each group is 20. As a result, 40 patients were required for this trial.

The relationship between the patients in both groups and the histology was analysed with Fisher's exact test. The tumour size and age were analysed with the two-tailed Student's *t*-test. Thermal parameters including T_{min}, T_{max}, and T_{ave} were obtained as described above, and presented here as mean $\pm$ SD. Incidence rates of Grade 3 or higher toxicity were compared between patients in both groups using Fisher's exact test. Survival was measured in days from the start of treatment. The survival proportion was estimated by using the Kaplan–Meier method (Kaplan and Meier 1958), and differences in survival were analysed with the log-rank test (Mantel 1966). The statistical analysis was performed using Stata 4.0 Software (Stata Corp., Stata Statistical Software: Release 4.0, College Station, TX). *p*-values <0.05 were considered significant.

3. Results

Between October 1994 and February 1999, 40 patients with FIGO Stage IIIB carcinoma of the uterine cervix were enrolled in this study at Kansai Medical University. All randomized patients were evaluated for clinical response and survival. As shown in table 1, there was no significant difference in the patients' demographics or in the tumour characteristics between the two groups.

3.1. *Treatment response and long-term clinical outcome*

The number of patients with CR was significantly larger in the TRT (16 of 20 patients, or 80%) than in the RT group (10 of 20 patients, or 50%) ($p = 0.048$, Fisher's exact test). The respective number of patients who had a partial response (PR) or no response to treatment (NC) was 25% (5 of 20) and 25% (5 of 20) in the RT group versus 15% (3 of 20) and 5% (1 of 20) in the TRT group ($p = 0.3$ and $p = 0.09$, Fisher's exact test).

At present, in the RT group, nine patients (45%) are alive and well, six have had a local recurruence, one has had multiple distant metastases, and four have had both local recurrence and multiple distant metastases. One patient is alive with cancer. Ten patients (50%) have died from recurrent disease.

In the TRT group, 13 patients (65%) are alive and well, two have had a local recurrence, three have had distant metastases (one with multiple metastases, two with lung), and two have had both local recurrence and distant metastases (one with multiple metastases, one with lung). Six patients (30%) have died from recurrent disease. One patient had died from cerebral haemorrhage, in spite of no cancer recurrence after 21.3 months completion of treatment.

3.2. *Survival*

The 3-year overall survival and disease-free survival of patients treated with TRT (58.2 and 63.6%) were better than those of patients treated with RT (48.1 and 45%), but the difference was not significant (log-rank test, figures 1 and 2). The 3-year local relapse-free survival of patients treated with TRT (79.7%) was significantly better than that of patients treated with RT (48.5%) ($p = 0.048$, log-rank test, figure 3).

3.3. *Thermometry results*

The thermometry results for FIGO Stage IIIB cervical cancer cases demonstrated a maximum tumour temperature (T_{max}) of $41.8 \pm 1.1^{\circ}$C, an average temperature (T_{ave}) of $40.6 \pm 1^{\circ}$C, and a minimum temperature (T_{min}) of $39.6 \pm 0.9^{\circ}$C.

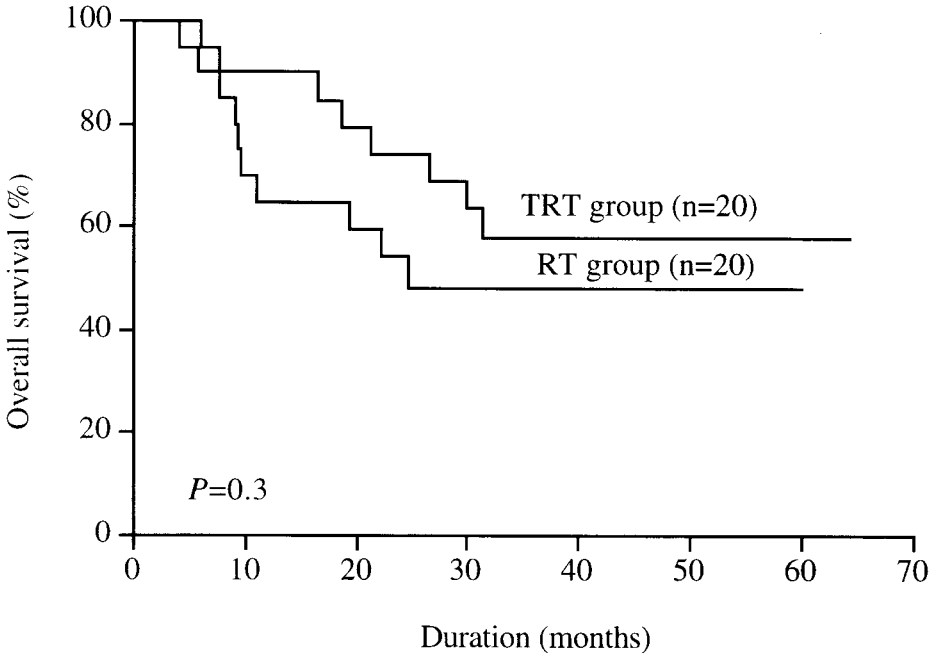

Figure 1. Overall survival of patients in the RT group compared to that of patients in the RT group using the Kaplan–Meier method and analysed with the log-rank test. The survival of patients treated with TRT was better than that of patients treated with RT, although not significantly ($p = 0.3$).

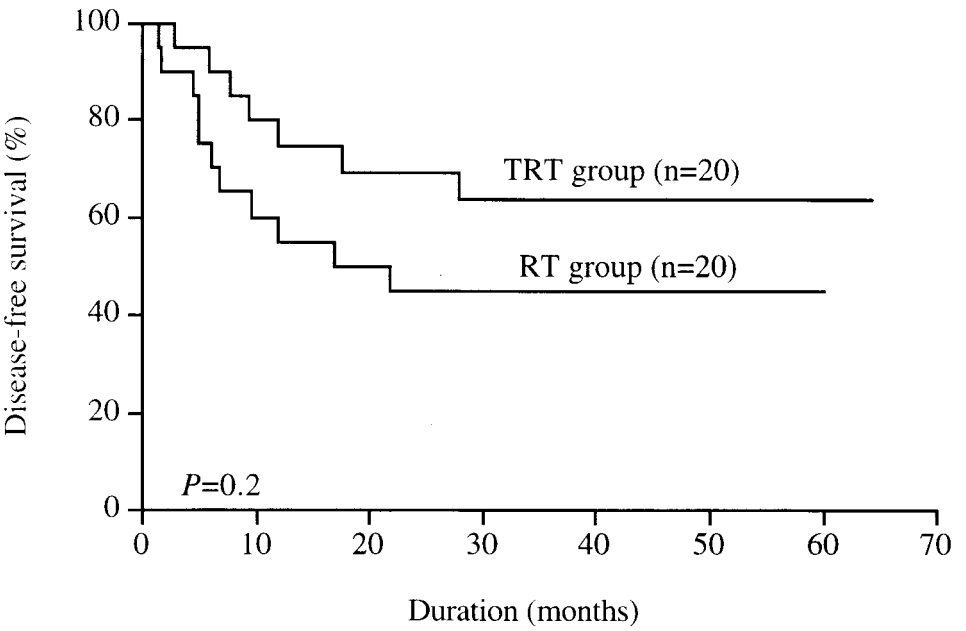

Figure 2. Disease-free survival of patients in the RT group compared to that of patients in the RT group using the Kaplan–Meier method and analysed with the log-rank test. The survival of patients treated with TRT was better than that of patients treated with RT, although not significantly ($p = 0.2$).

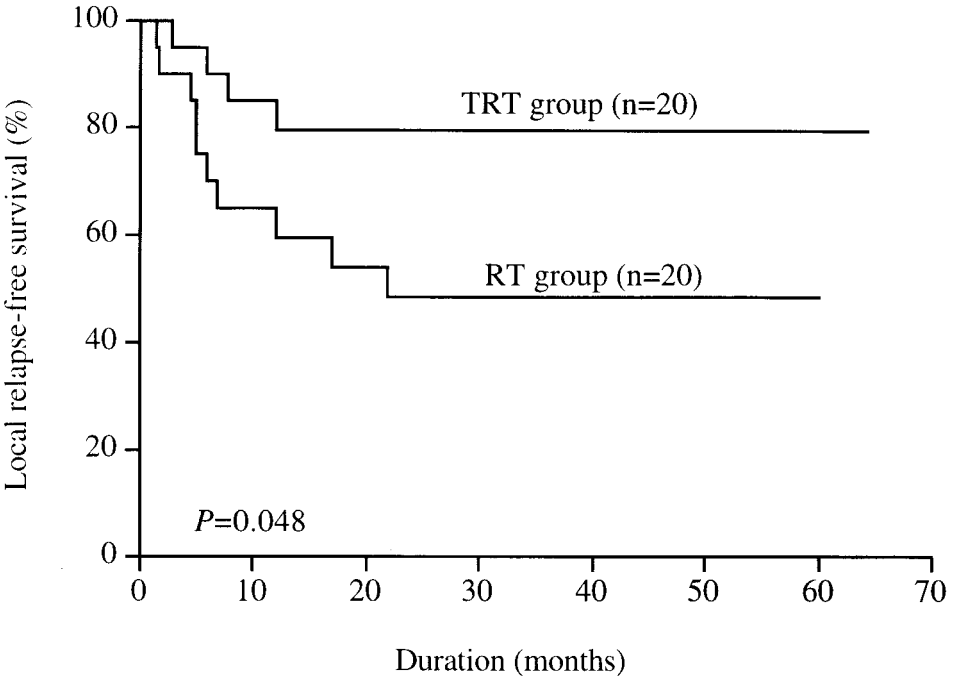

Figure 3. Local relapse-free survival of patients in the RT group compared to that of patients in the RT group using the Kaplan–Meier method and analysed with the log-rank test. The survival of patients treated with TRT was significantly better than that of patients treated with RT ($p = 0.048$).

3.4. *Toxicity*

The findings in all patients were evaluated for evidence of toxicity. In the RT group, no patients showed acute or late toxicity either during or after treatment. In the TRT group, however, five of 20 patients (25%) showed either acute and/or late toxicities. Among early toxicities, there were Grade 1 subcutaneous fatty tissue necrosis, which had occurred in two patients, and Grade 1 colitis in one patient. In addition, one patient had both acute and late Grade 3 toxicity, such as Grade 3 diarrhoea during treatment, followed by sigmoid-ileum fistula 2 years after completion of treatment. Another patient had developed Grade 3 obstructive ileus of the colon 1.5 years after the completion of treatment. Both cases were treated without surgery. None of the patients had Grade 4 toxicity.

Thus, TRT, as delivered in this trial, was well tolerated and did not significantly add to either the relevant clinical acute or late toxicity over radiation alone. However, because of the relatively short follow-up period of this study, caution should be taken with the late toxicity associated with TRT.

4. Discussion

In this clinical study, TRT for patients with FIGO Stage IIIB cervical carcinoma proved to be a promising treatment with respect to the local control rate ($p = 0.048$) and the 3-year local relapse-free survival ($p = 0.048$). The effects of TRT on late results in these patients have been controversial, however, as is evident from earlier clinical trials (Datta *et al.* 1987, Sharma *et al.* 1991). The results are in agreement

with those reported by Sharma *et al.* (1991), who have shown improved local tumour control for Stage II and III cervical carcinoma with the help of regional hyperthermia in a randomized trial. However, one did not observe an increased rate of distant metastases (five patients in both RT and TRT groups), in contrast to data being reported by Sharma *et al.* (1991). Improvement by adjuvant hyperthermia of a local control and survival in patients with Stage IIIB uterine cervix carcinoma was also reported earlier by Datta *et al.* (1987). More recently, the results of a trial by a Dutch group (Van der Zee *et al.* 2000) have also demonstrated an increase in 3-year overall survival, from 27 to 51%, by adding hyperthermia to radiotherapy for cervical carcinoma patients. In contrast to both findings reported in this paper and above mentioned others, Hornback *et al.* (1986) reported that, although tumour control was superior when patients underwent regional hyperthermia, 5-year survival was not statistically affected by hyperthermia. Notably, this former study was not randomized.

The results of the study show significantly better local control and local relapse-free survival in the TRT group as compared to those undergoing conventional RT. The biological basis for combining hyperthermia and radiation includes two types of interaction, namely, direct hyperthermic cytotoxicity ($\geq 42.5^{\circ}$C) and hyperthermic radiosensitization ($<43^{\circ}$C). It was shown by others that only 10–20% of the tumour volume could be heated to cytotoxic levels with regional hyperthermic techniques. Most of the tumour volume could be heated to radiosensitizing temperatures in the range of 40–42°C (Feldman *et al.* 1995). In this study, the average temperature was $40.6 \pm 1^{\circ}$C being in the radiosensitizing range. The mechanism of tumour response to TRT at this range of temperature seems to involve the development of apoptosis through the activation of one of the *bax* pathways that were reported previously (Harima *et al.* 2000).

On the other hand, there was no significant difference in either overall survival or disease-free survival between the patients treated with TRT (58.2 and 63.6%) and those treated with RT (48.1 and 45%). At first, relatively low numbers of patients can explain the lack of evidence for a significant improvement in overall or disease-free survival. Moreover, there was a non-cancer related incidence of death in the TRT group. In fact, one patient in the TRT group has died from cerebral haemorrhage, in spite of no cancer recurrence after 21.3 months completion of treatment. Thus, disease-free survival rate of patients treated with TRT was better than overall survival rate. Secondly, it was found out that the main factor affecting the survival rate was related to distant metastases in both groups.

A way to improve the treatment outcome by combining radiation therapy with chemotherapy has been reported by Wong *et al.* (1999). In that report, patients undergoing chemoradiation had significantly rare distant metastases compared to those who received radiation alone ($p = 0.012$), although there was no difference in long-term local tumour control ($p = 0.99$). It is possible, therefore, that adding chemotherapy to the protocol used for this study might reduce the probability of distant metastases. On the other hand, the Gynecologic Oncology group (Morris *et al.* 1999) has explored the role of radiation therapy and concurrent chemotherapy with hydroxyurea, cisplatin and 5-fluorouracil. In their study, the rate of local recurrences was significantly lower with cisplatin-based regimen, whereas the rate of distant recurrences was only slightly reduced. These results suggested that the principal effect of cisplatin is radiosensitization. In this series, the patients with local recurrence might be influenced or further improved by addition of chemotherapy.

Hyperthermia-induced toxicity was previously reported by Nishimura *et al.* (1992), who suggested that radiation-induced intestinal damage was enhanced by regional hyperthermia in patients with locally advanced colorectal cancer. In addition, small bowel obstruction, intestinal fistula, and intestinal perforation developed in 2–19% of the patients with deep-seated malignant tumours treated with radiotherapy and regional hyperthermia (Feldmann *et al.* 1995). In this series, two patients treated with TRT had Grade 3 toxicity. One patient had diarrhoea during treatment and developed a sigmoid-ileum fistula 2 years after completing treatment. The second patient developed a colon obstruction 1.5 years after treatment. Both complications were managed without surgery. However, caution should be taken for late toxicity associated with TRT, because the follow-up period of this study is relatively short.

5. Conclusions

TRT was shown to be more effective in treating patients with FIGO Stage IIIB cervical carcinoma as compared to conventional RT. In addition, TRT was well tolerated and had acceptable toxicity.

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