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Hyperthermia Combined with Re-Irradiation for Neck Node Metastasis from Head and Neck Cancer

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The effects of hyperthermia combined with re-irradiation were compared with those of re-irradiation alone using retrospectively matched-pair analysis. Between 1984 and 1997, 12 patients were treated with hyperthermia combined with re-irradiation for neck node metastasis from squamous cell carcinoma of the head and neck. During the same period, 12 patients treated with re-irradiation alone were selected retrospectively using the same anatomical diagnosis, nodal site, and nodal size. Recurrent nodes were heated by a 2450MHz microwave or 13MHz radio frequency 4 times on average for 30 to 50 min immediately before radiotherapy. The maximum temperatures were >41℃ in 83% and >42℃ in 58% of patients. Results: The median survival and median recurrence periods were 12 months and 6 months, respectively in both groups. The response rate was 83% in both groups. Nodal size and radiation dose, but not heating temperature, were prognostic factors. Five patients in the hyperthermia group experienced skin ulcers or burns as acute complications. Late complications were observed in one patient in the hyperthermia group and 3 patients in the re-irradiation-alone group. Conclusion: Heating induced acute complications and had no significant effect on the tumors. Further advances in hyperthermic technique are required.

Key words : Hyperthermia, Re-irradiation, Neck node metastasis, Head and neck cancer

INTRODUCTION

We have experienced several cases of re-irradiation of neck node metastases from head and neck cancers. In these cases, radiation doses to the previously irradiated area exceeded the tolerance dose. Recurrent tumors usually have a poor blood supply, and the effect of hyperthermia may be enhanced. Hyperthermia sensitizes the radiation effect, and reduces the dose required to control tumors.

There were many reports on the efficacy of hyperthermia combined with radiation for various tumors in the 1980s. Hyperthermia combined with radiation seems to be effective for previously untreated nodal metastases [1-5]. However, for recurrent nodal disease or previously treated neck node metastases, the efficacy of concomitant hyperthermia is equivocal [6-10].

In this study, the effects of hyperthermia combined with re-irradiation of neck node metastases were compared with those of re-irradiation alone using the retrospective matched pair analysis.

PATIENTS AND METHODS

1. Patient and tumor characteristics

Between October 1984 and September 1997, 12 patients were treated with hyperthermia combined with re-irradiation (combined group) for neck node metastases of squamous cell carcinoma from the head and neck. Thirty-two patients were treated with re-irradiation alone for neck node metastases during the same period. Among them, 12 patients were selected for the control group (radiation-alone group) using anatomical diagnosis, recurrent nodal size, and nodal site adjusted to match those of the combined group (Tables 1 and 2). During selection, the treatment results were blinded. Factors such as sex, age, Karnofsky performance status, previous history of chemotherapy or surgery, previous radiation doses, and time to recurrence after initial treatment did not differ significantly between the two groups (Table

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Table 1 Patient selection

Factors		Hyperthermia + radiation	Radiation alone
Number of patients		12	12
Study period		1985. 12–1996. 1	1984. 10–1997. 9
Re-irradiation	Repeated fields	>4cm²	
	Total dose	>80 Gy	
Diagnosis		Squamous cell carcinoma	
Oral : mesopharynx : larynx : hypopharynx		5 : 3 : 3 : 1	5 : 3 : 3 : 1
Karnofsky performance status		≧70	
Nodes	Submandibular : upper : middle : lower neck	2 : 5 : 3 : 2	2 : 3 : 4 : 1
	Size (cm²) by CT	13.4 ± 9.50	12.4 ± 7.43
	rN2 : rN3	10 : 2	7 : 5

Table 2 Patient data

	Radiation alone group					Concomitant hyperthermia group			
	Diagnosis	Node (mm × mm)		Site		Diagnosis	Node (mm × mm)		Site
1	Oral	36	22	S	1	Oral	31	23	L
2	Oral	40	20	S	2	Oral	33	26	U
3	Oral	40	23	U	3	Oral	42	32	L
4	Oral	65	20	L	4	Oral	45	32	U
5	Oral	73	42	U	5	Oral	70	40	S
6	Meso	23	13	M	6	Meso	35	25	U
7	Meso	31	26	M	7	Meso	45	30	U
8	Meso	40	25	M	8	Meso	59	31	M
9	Larynx	35	35	M	9	Larynx	30	6	M
10	Larynx	50	30	U	10	Larynx	22	16	U
11	Larynx	52	41	U	11	Larynx	48	30	M
12	Hypo	40	25	U	12	Hypo	72	46	S

Meso: Mesopharynx, Hypo: Hypopharynx, Size: nodal size by CT
U: Upper, S: Submandibular, M: Middle, L: Lower neck node

3). Recurrent nodal sites related to previous radiation fields also did not differ.

Treatment

Hyperthermia was performed 2 to 7 times (mean 4 times) one or two times per week using 2443 MHz microwaves for superficial tumors or 13 MHz radio frequency for large tumors. Three thermistors were inserted in the tumor core, tumor margin, and subcutaneous tissue, respectively. The target temperature was above 42.5℃, but most patients could not tolerate such a high temperature. Maximum temperatures of >41℃ and >42℃

Table 3 Patient characteristics

Factors	Hyperthermia + radiation	Radiation alone	P values
Sex male : female	6 : 6	10 : 2	0.193
Age (years)	63.0 ± 10.8	60.4 ± 14.6	ns
Karnofsky index 70 : 80 : 90	1 : 4 : 7	2 : 4 : 6	ns
Previous operation −:+	8 : 4	6 : 6	ns
Previous chemotherapy −:+	7 : 5	9 : 3	ns
Previous radiation dose (Gy)	59.5 ± 11.4	59.5 ± 11.8	ns
Interval (months)	25.8 ± 34.8	12.6 ± 12.5	0.235
Re-irradiation dose (Gy)	60.4 ± 9.49	57.7 ± 10.5	ns
Re-irradiation field (cm^2)	37.1 ± 26.0	41.7 ± 37.3	ns

ns: not significant

were obtained in 83% and 58% of patients, respectively. The duration of heating was 30 to 50 min. One patient underwent mild heating (<40℃) 11 times. All patients were irradiated immediately after hyperthermia. The radiation doses and field sizes did not differ significantly between the groups (Table 3). Chemotherapeutics cisplatin and/or 5FU were administered intravenously to 3 patients in the combined group and 3 patients in the radiation-alone group. Four patients in the combined group were given intratumor injections of interleukin 2, OK432, or bleomycin before hyperthermia.

Analysis

All patients were followed up monthly for the first year and bimonthly for the next year up to 78 months (median 15 months) after re-irradiation. Tumor response was classified as complete response (CR), partial response (PR: >50% reduction in tumor volume), or no change (NC: <50% reduction). The difference in tumor response was analyzed by the Chi-square test or Fisher's exact test. The cumulative survival rates were estimated by the Kaplan Meier method, and compared using the Log-rank and Breslow's tests. The SPSS program (SPSS Co. Japan) was used for data processing. A p value of 0.05 was considered as significant.

RESULTS

The overall 5-year survival rate was 6%. There were no significant differences between the two groups in both overall survival and recurrence-free survival (Figures 1 and 2). The median survival time and median recurrence time were 12 months and 6 months, respectively. The response rates to the treatment did not differ significantly (Table 4). Complete and partial responses were obtained in 4 and 6 patients in the combined group, and in 5 and 5 patients in the radiation-alone group, respectively. The prognostic factors for recurrence-free survival were tumor response to treatment, anatomical diagnosis, recurrent nodal stage or size, and radiation dose (Table 5). Responses did not differ significantly by temperature or chemotherapy (Table 6).

Five patients in the combined group experienced moderate acute complications including 2 thermal blisters, 2 skin ulcers, and 1 case of skin necrosis (Table 7). One patient had a persistent ulcer, but no other patients had late complications in the combined group. In the radiation-alone group, 3 patients developed syncope, myelitis, or laryngeal edema requiring laryngostomy as late complications.

DISCUSSION

This study was a retrospectively matched pair-analysis using strictly adjusted prognostic factors. Most studies show that the prognostic factors for loco-regional control are anatomical diagnosis, tumor volume, and radiation dose [1, 11−13]. For recurrent tumors, the interval from the first irradia-

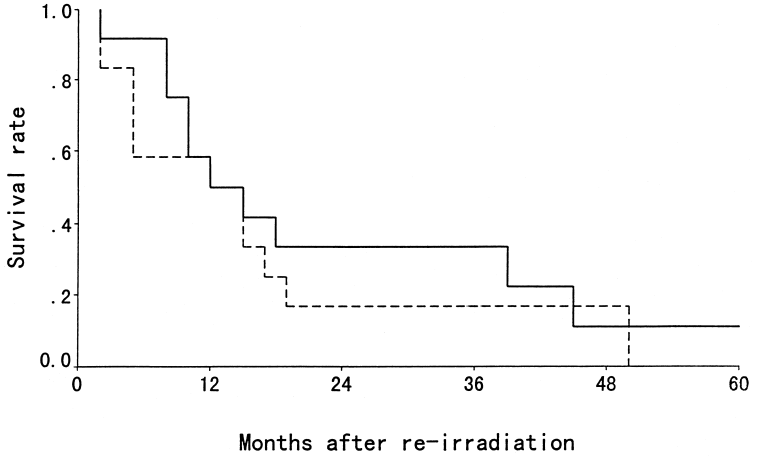

Fig. 1 Survival after re-irradiation with (solid line) or without hyperthermia (dotted line).

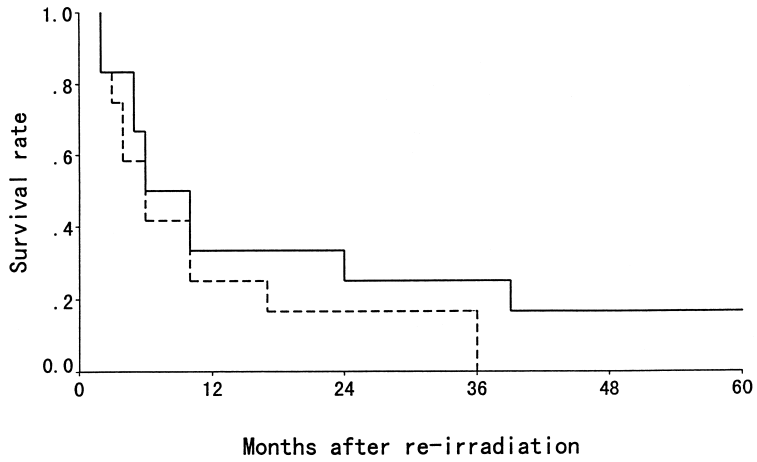

Fig. 2 Relapse-free survival after re-irradiation with (solid line) or without hyperthermia (dotted line).

Table 4 Tumor response according to treatment

	Response			
Treatment	CR	PR	rate (%)	NC
Concomitant group	4	6	(83)	2
Radiation alone	5	5	(83)	2

CR: complete response, PR: partial response, NC: no change
Figures represent number of patients.

Table 5 Prognostic factors for recurrence-free survival

Factors	(Number)	Median months	Log-rank (Breslow)
Response	CR (9)	21	
	PR (4)	6	0.0003
	NC (11)	2	
Diagnosis	Larynx (6)	19	
	Mesopharynx & oral (16)	4	0.0034
	Hypopharynx (2)	2	
Nodal stage	rN2 (17)	16	0.0156
	rN3 (7)	7	(0.0354)
Nodal size	＜40mm (9)	17	0.0667
	≧40mm (15)	8	(0.0162)
Radiation dose	＜60Gy (10)	8	0.0416
	≧60Gy (14)	17	(0.0650)

Table 6 Response by treatment

Factors		Response			Total
		CR	PR	NC	
Radiation dose	＜60Gy	3	5	2	10
	≧60Gy	6	6	2	14
Temperature	＜40℃	5	5	2	12
	≧40℃	4	6	2	12
	≧42.5℃	2	3	1	6
Chemotherapy	−	4	9	2	15
	+	5	2	2	9
Intratumor injection		2	1	1	4

Figures represent number of patients.
CR: complete response, PR: partial response, NC: no change

Table 7 Complications

Treatment	Acute complications	Late complications
Hyperthermia + re-irradiation	5 (2 thermal blisters, 2 ulcers, 1 necrosis)	1 (persistent ulcer)
Re-irradiation alone	0	3 (syncope, myelitis, laryngeal edema)

tion to recurrence is also a prognostic factor [14–15]. These factors did not differ among the groups in this study.

Hyperthermia combined with re-irradiation for neck node metastases had no advantages over re-irradiation alone with respect to survival, local control, and response rates in this study. There have been many reports suggesting the usefulness of hyperthermia in previously untreated neck node metastases with complete response rates of 50 to 85% [1, 2, 4, 16, 17]. However, the benefits of hyperthermia for recurrent nodal disease are questionable [6–8, 10, 13]. The results of combined therapy were definitely different between persistent tumors and recurrent tumors [10, 11, 18]. Recurrent patients are in a deteriorated condition and usually have large tumors.

Among many prognostic factors for local control, tumor volume is one of the most important [1, 7, 8, 11–13]. In this study, the nodal size or stage was significant. The second important factor is usually the radiation dose. We prescribed lower doses than those for previously untreated tumors so as not to exceed the tolerance of normal tissue. Therefore, the radiation dose may have been marginally significant in this study. Heating temperature was not significant. One of the reasons was probably a lower temperature than the effective temperature of 42.5℃ because the heating technique was difficult to apply in the head and neck regions. Another reason was that the tumors were too large to obtain significant effects. Randomized studies showed no effects of hyperthermia on large recurrent lymph nodes [8], and no benefits for well-heated recurrent tumors using interstitial thermoradiotherapy [10].

Recent studies on trimodal therapy (chemotherapy, hyperthermia, and radiation) showed high control rates for previously untreated nodal metastases [16–18], but not for previously treated tumors in this study. To enhance the hyperthermic effects, we added intratumor chemotherapy in 4 patients. The effects were marked in experiments on mice [19]. Some tumors may respond to the aggressive treatment, but acute complications also increased. Complication rates of 10 to 30% have been reported for concomitant hyperthermia [1, 7–13, 16, 18]. The 20% rate in this study was about the same, but the temperature measured was not very high. Ulcers or necrosis seemed to be caused by the intratumor injection of anticancer drugs. However, late complications consisted of only one persistent ulcer, compared to 3 complications in the radiation-alone group. No increase in late complications was reported by other authors [8, 10, 12].

In conclusion, hyperthermia combined with re-irradiation had no significant advantages over re-irradiation alone with respect to survival, local control, and response in recurrent neck node metastases of head and neck cancer. Nodal size and radiation dose were prognostic factors for recurrent neck nodes. Heating also induced acute complications in patients. Further advances in hyperthermic techniques are required.

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