− Original Article −

Thermochemoradiotherapy for inoperable metastatic cervical lymph nodes of patients with head and neck cancer: Analysis of clinical outcomes and prognostic variables

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頭頸部癌の切除不能頸部リンパ節転移巣に対する温熱化学放射線療法：治療成績および予後因子について

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Key words: hyperthermia, thermochemoradiotherapy, head and neck cancer, metastatic cervical lymph node, prognostic variable

Abstract

The aim of this study is to investigate the important prognostic factors in order to improve the outcomes of thermochemoradiotherapy (TCR) for patients with head and neck cancers.

Materials and methods: We performed TCR for 15 patients with 20 inoperable metastatic cervical lymph nodes. Hyperthermia was done 8.8 sessions on an average by microwave or radiofrequency heating system. Chemotherapy consisted of a combination of cisplatin and pepleomycin or 5-fluorouracil. Additionally, external irradiation was used as radiotherapy.

Results: Among the 20 lesions, 8 (40.0%) had a complete response, 8 (40.0%) had a partial response, and 4 (20.0%) had no change. The total response rate was 80.0%. The overall cumulative local control rate (CLCR) at 5 years was 64.2%. As to the dose of irradiation, the CLCR was 80.2% at 5 years in patients given 50 Gy or more and 0% at 3 months in those given 30 Gy or less. Statistical analysis showed that the total radiation dose was significantly related to the CLCR ($P<0.05$). There were no significant correlations between the CLCR and any other treatment-related factors (hyperthermia system, number of hyperthermia sessions, total dose of cisplatin, drugs given with cisplatin) or tumor-related factors (recurrence or not, tumor size, WHO classification, mode of invasion).

Conclusion: TCR given 50 Gy or more is an effective strategy for inoperable metastatic cervical lymph nodes in patients with head and neck cancer.

抄録：

この研究の目的は頭頸部癌患者対する温熱化学放射線療法の成績向上のための重要な予後因子について検討することである。

対象および方法：15 名の切除不能頸部リンパ節転移 20 病巣に対して温熱化学放射線療法を行なった。温熱療法はマイクロ波または RF 波加温装置を用いて平均で 8.8 回実施した。化学療法はシスプラチンにペプレオマイシンまた

は5Fuを併用し，さらに，外照射を加えた。

結果：20病巣中８例（40％）は著効，８例（40％）は有効であったが，残りの４例（20％）では変化がなかった。奏効率は80％であった。全例の５年累積病巣制御率は64.2％を示し，放射線量別では，50Gy以上の照射例では５年病巣制御率は80.2％に対し，30Gy以下の照射例では３か月で０％であった。統計学的解析により放射線療法の総線量は累積病巣制御率との間に有意差が認められた（P＜0.05）。他の治療に関する因子（温熱療法の方法，回数，シスプラチン投与量，併用薬）および腫瘍に関する因子（再発巣か否か，腫瘍の大きさ，WHO分類，癌浸潤様式）では，病巣制御との間に有意差は認められなかった。

結論：50Gy以上を併用した温熱化学放射線療法は頭頸部癌の切除不能な頸部リンパ節転移巣に対する効果的な治療方法であることが示された。

Introduction

Hyperthermia is generally combined with radiotherapy[1,2] or chemotherapy[3] to control various kinds of malignant tumors. This combination of treatment has been found to be therapeutically useful for cancers of the head and neck[4-9]. Previously, the response to triple-combined therapy with hyperthermia, chemotherapy, and radiotherapy (thermochemoradiotherapy ; TCR) has been evaluated in several studies including patients with head and neck cancer[10-14].

Since 1986, we have performed cisplatin-based TCR to treat primary lesions and/or cervical lymph nodes metastases in patients with inoperable advanced or recurrent cancer of the head and neck[15-20]. The cumulative local control rate after 5 years was 68.2% in patients who received our TCR, as compared with only 22.2% in those who received chemoradiotherapy only before the introduction of hyperthermia. This improved response rate represented a significant increase of 46 percentage points[20].

In this investigation, we performed TCR in order to manage unresectable cervical lymph node metastases from head and neck cancer. We evaluated the tumor-related factors and the treatment-related factors of 20 lesions in 15 patients as clinical characteristics at least 6 years after treatment. The relationships between these factors and the outcomes were analyzed statistically to identify the most important determinants of response.

Subjects and Methods

For twelve years, from 1986 to 1998, we treated 20 lesions in 15 patients with advanced or recurrent cancer around the oral region that had inoperable cervical lymph node metastasis with use of TCR. The clinical characteristics of the patients and lesions are shown in Table 1. The subjects ranged from 33 to 83 years of age with a mean of 60.4 years and consisted of 10 men and five women. Each primary lesion consisted of oral cancer in 8 patients, maxillary sinus cancer in 4, oropharyngeal cancer in 2, and nasopharyngeal cancer in 1. Eleven lesions in 6 patients were primary carcinomas in the head and neck region, and 9 lesions in 9 patients were recurrent. The stages of these lesions at both first visit and recurrence were at stage IV in all patients. Five patients required treatment for bilateral or unilateral multiple cervical lymph node metastases. The longest diameter of the metastatic lesions ranged from 21 to 76 mm (mean, 43.8 mm). All lesions were histologically diagnosed as squamous cell carcinoma. We used the World Health Organization grade and the mode of invasion according to Yamamoto et al.[21] as histological characteristics of lymph nodes. The clinical characteristics of patients are summarized in Table 1.

Prior to TCR, the patients initially received 2 to 4 Gy of irradiation. They were then given hyperthermia while receiving intravenous analgesics plus cisplatin-based combined chemotherapy, administered either intravenously or intra-arterially. These combined therapies were basically performed once or twice a week. The details of treatment and responses are shown in Table 2. Local hyperthermia was applied externally. Initially, a radiofrequency capacitive hyperthermia system (Novatherm-IH®, InterNova Co. Ltd., Tokyo, Japan) was used at a frequency of 13.56 MHz. In these days, we mainly used a 2,450-MHz microwave hyperthermia system (HMS-020A®, Aloka Co. Ltd., Tokyo, Japan) (Fig. 1). Hyperthermia was applied 5 to 15 times (mean, 8.8 times) per lesion. The cumulative number of applications was 176. Of these applications, 142 (80.7%) could be continued for at least

Table 1. Clinical characteristics of subjects

Case No	Lesion No	Age (yrs)	Sex	Primary site	Treatment site	Previous therapy	T N	Stage	Maximum size(mm)	WHO grade	Mode of invasion *
1	1	51	F	buccal mucosa	r-SIJLN	/	T4N2c	Ⅳ A	35	3	3
	2				l-SIJLN				21	3	3
2	3	61	F	oropharynx	r-SIJLN	/	T4N2c	Ⅳ A	40	2	3
	4				l-SIJLN				35	2	3
3	5	56	M	maxillary sinus	r-SIJLN	/	T4N2c	Ⅳ A	40	3	3
	6				l-SIJLN				21	3	3
4	7	72	M	buccal mucosa	r-SIJLN	/	T3N3	Ⅳ B	70	1	4c
	8				r-SMLN				76	1	4c
5	9	65	M	oropharynx	r-SIJLN	/	T4N2c	Ⅳ A	42	2	3
	10				l-SIJLN				35	2	3
6	11	55	F	tongue	SMLN	/	T3N3	Ⅳ B	65	2	4c
7	12	62	M	tongue	MIJLN	Ope	rT0N2a	r Ⅳ A	50	2	4d
8	13	40	M	tongue	SIJLN	Ope	rT0N2b	r Ⅳ A	55	2	4c
9	14	74	F	maxillary sinus	SIJLN	Ope	rT0N2a	r Ⅳ A	40	3	4c
10	15	64	F	upper gingiva	Parotid LN	Ope Rad	rT0N1M1	r Ⅳ C	30	1	3
11	16	83	M	upper gingiva	SIJLN	Rad	rT0N2b	r Ⅳ A	33	2	3
12	17	33	M	maxillary sinus	SIJLN	Ope Rad	rT0N3	r Ⅳ B	66	3	4d
13	18	58	F	nasopharynx	MIJLN	Ope Rad	rT0N2a	r Ⅳ A	31	2	3
14	19	70	M	maxillary sinus	SIJLN	Rad	rT0N2a	r Ⅳ A	48	2	4d
15	20	62	M	upper gingiva	SIJLN	Ope Rad	rT0N2a	r Ⅳ A	43	1	3

Histological diagnosis was squamous cell carcinoma in all patients.
SMLN, SIJLN, MIJLN: submandibular, superior, middle internal jugular lymph nodes
Ope: operation　Rad: radiation　　*: according to Yamamoto et al [28)]

Table 2. Treatments and results

Case No	Lesion No	Hyperthermia system	Session ＜42℃	Session ≧42℃	Radiation dose (Gy)	Cisplatin (mg)	Drug combined	Tumor response	Nodal recurrence	Time	Patient outcome	Survival
1	1	Microwave	1	10	65	60	Pep	PR	(+)	3m	Dp	8m
	2	Microwave	1	14	65	60	Pep	PR	(+)	3m		
2	3	Microwave	1	9	70	130	5-FU	CR	(−)	6y 5m	Do	6y 5m
	4	Microwave	0	10	70	130	5-FU	CR	(−)	6y 5m		
3	5	Microwave	1	5	70	260	5-FU	PR	(+)	5m	Dn	9m
	6	Microwave	0	7	60	260	5-FU	PR	(−)	9m		
4	7	Microwave	0	5	70	50	5-FU	PR	(−)	4m	Dlm	4m
	8	Microwave	3	2	70	50	5-FU	CR	(−)	4m		
5	9	Microwave	0	8	70	60	5-FU	CR	(−)	1y10m	Do	1y10m
	10	Microwave	0	8	70	60	5-FU	CR	(−)	1y10m		
6	11	Radiofrequency	3	10	59	40	Pep 5-FU	CR	(−)	1y10m	Dn＊	2y 8m
7	12	Radiofrequency	5	5	50	100	Pep	PR	(−)	5m	Dlm	5m
8	13	Microwave	4	6	78	120	Pep	CR	(−)	10y0m	NED	10y0m
9	14	Microwave	3	5	56	60	5-FU	CR	(−)	3y 1m	Do	3y 1m
10	15	Microwave	0	6	50	60	Pep 5-FU	PR	(−)	7m	Dlm	7m
11	16	Microwave	1	7	56	80	UFT	PR	(−)	9m	Do	9m
12	17	Radiofrequency	2	5	15	/	UFT	NC	(+)	2m	Dn	4m
13	18	Radiofrequency	0	12	21	120	Pep	NC	(+)	3m	Dn	8m
14	19	Radiofrequency	7	0	21	120	5-FU	NC	(+)	2m	Dn	2m
15	20	Microwave	2	8	30	60	Pep	NC	(+)	3m	Dn	6m

Pep: Peplomycin　CR: complete response　NED: no evidence of disease　Do: died of other disease
PR: partial response　Dp: died of primary lesion　Dn: died of neck lesion
NC: no change　Dlm:died of lung metastasis　＊: recurrence in a nonheated region

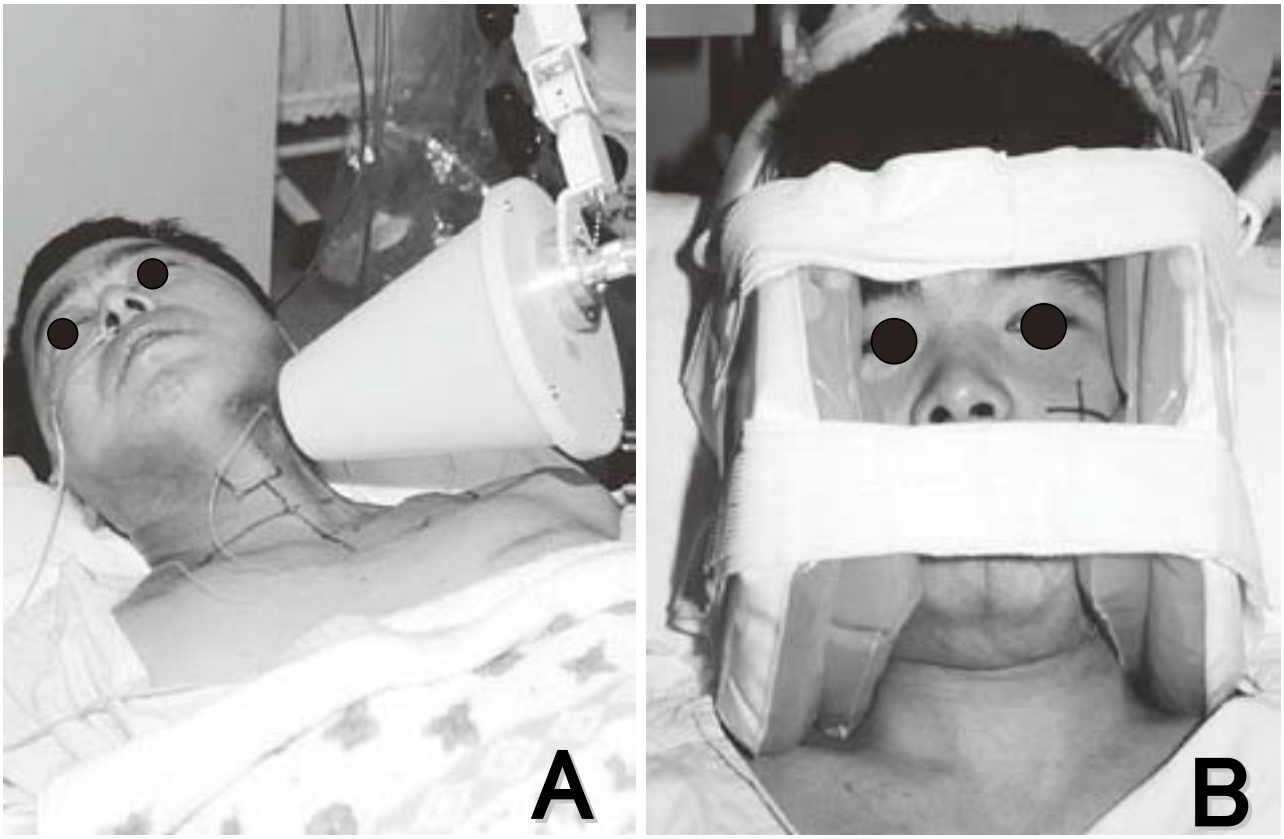

Fig 1. (A) microwave hyperthermia system (B) radiofrequancy hyperthermia system

30 min at the designated effective temperature of 42℃ or higher. Fourteen patients received cisplatin-based chemotherapy. Cisplatin was administered in doses ranging from 50 to 260 mg (mean, 98.9 mg) and was combined with peplomycin, 5-fluorouracil, or both anticancer agents. Eleven patients received radical radiotherapy with a total dose of 50 Gy or higher (mean, 64.3 Gy). Four patients who had recurrent lesions after prior irradiation were given palliative radiotherapy with a total dose of 30 Gy or less.

Treatment outcome was evaluated on the basis of primary response as assessed by tumor shrinkage as well as by cause specific factors such as cumulative local control rate and cumulative survival rate. Tumor response was evaluated on the basis of macroscopic, MR imaging, and computed tomographic findings as complete response (CR), partial response (PR), or no change (NC) according WHO criteria . The local control rate and survival rate , especially, progression-free survival according RECIST criteria, was calculated by the method of Kaplan and Meier. Toxicity was also assessed.

We also examined tumor-related factors (primary or recurrent lesion, metastatic lesion size), histological malignancy of biopsy specimens (WHO grade, mode of invasion), and treatment-related factors (hyperthermia system, number of heating sessions, total radiation dose, total cisplatin dose, and additional anticancer agents combined with cisplatin). The relations between these factors and local control rate were studied by univariate analysis. A generalized Wilcoxon test was used to determine statistical significance. The simultaneous prognostic effect of various factors was determined in a multivariate analysis with a proportional-hazards model. P values of less than 0.05 were considered to indicate statistical significance. The HALWIN® statistical software package (Gendai Sugaku Co. Ltd., Kyoto Japan) was used for data analysis.

Results

Treatment Outcomes

The primary response to treatment is shown in Table 2. Of the 20 lesions, the response was CR in 8 lesions (40.0%), PR in 8 (40.0%), and NC in 4 (20.0%).

Fig 2. T2-weighted fat-saturated MR image of a case resulting in CR (case 5)[19]

Metastatic adenopathy of bilateral superior internal jugular (arrows) and left retropharyngeal (arrow head) lymph nodes were seen before treatment.

These lymph nodes were disappeared after treatment.

The total response rate calculated on the basis of CR plus PR was 80.0%. The MR image of a case resulting in CR after treatment were shown in Fig. 2[19]. Among the 16 lesions receiving a radiation dose of at least 50 Gy, 8 (50.0%) had a CR and 8 (50.0%) had a PR; the response rate was 100.0%.

Pain decreased in all patients. Adverse reactions due to hyperthermia (skin ulceration) occurred in only 1 lesion (5.0%). Treatment was not discontinued in any patient.

As follow-up treatment, upper neck dissection was done in only one patient. Disappearance of tumor cells was confirmed histopathologically.

The cumulative local control rate of all lesions at 1,3, 5 years was 64.2%. Analysis of the data according to the radiation dose showed that patients given a radiation dose of 50 Gy or higher had a cumulative local control rate of 80.2% at 5 years, as compared with 0% at 3 months in patients given a radiation dose of 30 Gy or less. The cumulative local control rate at 5 years according to primary tumor response was 100% for lesions with a CR, 60.0% for those with a PR, and 0% for those with NC.

The progression-free survival rate is shown in Fig. 3. The progression-free survival rate at 1, 3,5 years was

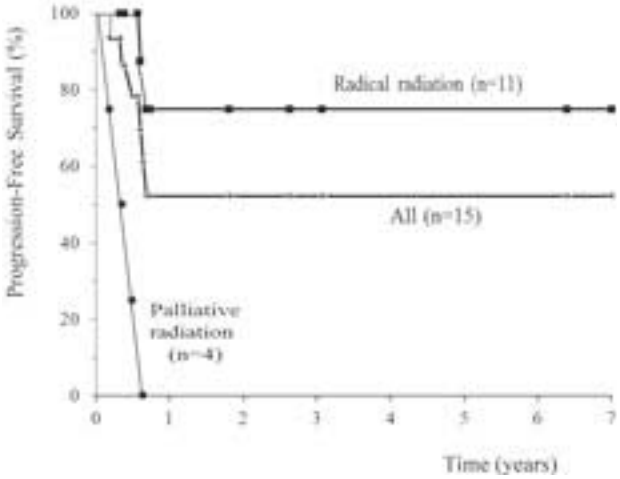

Fig 3. Progression-Free Survival (Kaplan-Meier method)

52.2% overall, 75.0% in patients given a radiation dose of 50 Gy or higher, and 0% in patients given a radiation dose of 30 Gy or lower.

As for outcome, 1 patient is alive with no evidence of disease, 4 died of other diseases, and 10 died of their cancers. In this latter group, 1 patients died of their primary lesions, 5 died of cervical recurrence in the treated area, 1 died of cervical metastasis and recurrence in a nonheated area, and 3 died of lung metastasis.

The cause-specific cumulative survival rate at 5 years was 30.0% overall, 40.9% in patients given a radiation dose of 50 Gy or higher, and 0% in patients given a radiation dose of 30 Gy or lower.

Results of Statistical Analysis

Univariate analysis

The results of univariate analysis of the relations between the 5-year cumulative local control rate and various clinical variables are shown in Table 3. There was no significant correlation between the local control rate and any tumor-related factor (primary or recurrent lesion, tumor size, WHO grade, mode of invasion).

Univariate analysis of treatment-related factors revealed a significant correlation between the local control rate and total radiation dose ($p = 0.0009$). No other treatment-related factor (hyperthermia system, number of heating sessions, total cisplatin dose, drugs combined with cisplatin) was significantly related to the local control rate.

Table 3. Univariate analysis of the relations between clinical characteristics and local control rate

Clinical characteristic			No.	5 year local control rate (%)	*p* value
Tumor factors	Primary lesion		(n=11)	70.1	
	Recurrent lesion		(n= 9)	55.6	0.276
	Tumor size (diameter)	20-39 mm	(n= 8)	62.5	
		40-49 mm	(n= 6)	50	
		50-76 mm	(n= 6)	83.3	0.552
	WHO grade	grade 1	(n= 4)	75	
		grade 2	(n=10)	80	
		grade 3	(n= 6)	33.3	0.104
	Mode of invasion	grade 1,2	(n= 0)	/	
		grade 3	(n=12)	58.3	
		grade4c,d	(n= 8)	75	0.89
Treatment factors	Hyperthermia system	microwave	(n=15)	72	
		radiofrequency	(n= 5)	40	0.085
	Heating sessions	≦ 5 session	(n= 7)	47.6	
		≧ 6 session	(n=13)	69.2	0.507
	Radiation dose	15-30 Gy	(n= 4)	0	
		50-78 Gy	(n=16)	80.2	0.0009
	Cisplatin dose	＜ 100 mg	(n=11)	72.7	
		≧ 100 mg	(n= 8)	62.5	0.759
	Drug combined	5-FU	(n=11)	72.9	
		Pep(+5-FU)	(n= 8)	50	0.167

p: by generalized Wilcoxon test

Table 4. Multivariate analysis of relations between clinical characteristics and local control (n=20)

Clinical characteristic	Regression coefficient	Relative risk	95% CI	*p* value
Tumor size	0.139	1.149	(0.106- 12.503)	0.909
WHO grade	3.004	20.161	(0.646-629.673)	0.087
Hyperthermia system	0.382	1.465	(0.049- 44.070)	0.826
Heating session	0.138	1.148	(0.050- 26.340)	0.931
Radiation dose	0.098	0.907	(0.830- 0.990)	0.029
CDDP dose	0.241	0.786	(0.075- 8.181)	0.84

95% CI: 95% Confidence interval

Multivariate analysis

The results of multivariate analysis are shown in Table 4. The total radiation dose was significantly related to the local control (p = 0.029), whereas other factors were not.

Discussion

Few studies have assessed the response of head and neck cancers to triple therapy with hyperthermia, cisplatin-based chemotherapy, and radiotherapy over the course of 2 or more years[11,13]. To our knowledge, no previous study has examined tumor- and treatment-related factors and statistically analyzed their relations to the response to TCR.

This study was designed to clarify the characteristics most closely related to a response to TCR in patients with head and neck cancer. Patients with unresectable lymph node metastasis from head and neck cancer were given TCR and followed up for at least 6 years. The clinical characteristics (tumor- and treatment-related factors) of 20 lesions in 15 patients were

examined. The data were statistically analyzed to determine the characteristics most closely related to treatment response. We discuss our results and contrast them with the findings of previous studies of both thermoradiotherapy only and TCR.

Treatment Response

In our study, the primary response rate with TCR was 80.0% for all lesions and 100.0% for lesions treated with a radiation dose of 50 Gy or higher. The characteristics of our study group differ from those of previous studies, precluding a direct comparison of results. However, our response rates were similar to those of prior studies reporting rates of 79.0%, 88.2%, and 100%[5,7,8]. The rate of CR in our study was 40.0% for all lesions and 50.0% for lesions that received a radiation dose of 50 Gy or greater. The rate of CR was higher in some previous studies, ranging from 60.0% to 82.3%[5,7-9].

The cumulative local control rate at 5-years was 64.2% for all lesions and 80.2% for lesions receiving a radiation dose of 50 Gy or greater. Although few studies have previously examined the relation between radiation dose and local control, the local control rate of lesions irradiated with a dose of 50 Gy or higher has been reported to be 58.0% at 2 years[5] and 62.5%[8], 64.5%[9], and 68.6%[7] at 5 years. Our results compare favorably with these findings.

The cause-specific cumulative survival rate at 5 years was 30.0% overall and 40.9% in patients given a radiation dose of 50 Gy or greater. In previous studies, the 5-year cumulative survival rate in patients given a similar dose of radiation has been reported to be 29.0%[9] and 53.3%[7].

Statistical Analysis of Clinical Characteristics

Tumor-related factors

Comparison of primary lesions with recurrent lesions revealed no significant difference in the local control rate after 5 years. This finding is consistent with the results of previous studies, which found that multidisciplinary treatment including hyperthermia was effective even against recurrent disease[1,4,8,11,15,16,18,20]. We found no significant correlation between tumor size and treatment response, and TCR was also effective against large tumors, which are often difficult to control. This finding agrees with the results of many previous investigations showing that even large tumors respond to multidisciplinary treatment including hyperthermia[1-8,12]. In contrast, tumor size correlates with the response to radiotherapy[5,7]. The microenvironment of large tumors is characterized by poor blood flow and low partial oxygen pressure and pH. Tumors with these characteristics are most sensitive to hyperthermia[1,24]. Large tumors exceeding 7 cm in diameter have been found to respond poorly to hyperthermia[1,2,4].

Histopathologically, grade 3 undifferentiated squamous cell carcinoma according to the WHO classification had a slightly but not significantly poorer response compared with grade 1 and 2 tumors. Kitamura et al.[22] found no significant relation between the histological response to TCR and the degree of tumor differentiation in patients with squamous cell carcinoma of the esophagus. Few studies have reported no distinct difference in the response to TCR according to histopathological daignosis, including sarcoma , in patients with cancer arising in various organs[1,2] , but this point remains to be fully investigated. There was no significant difference in treatment response between tumors with a grade 3 mode of invasion and those with grades 4c or 4d modes of invasion. The response of even these latter tumors, generally associated with a poor prognosis [21] , was good. To our knowledge, a good response of tumors with a grade 4 invasion pattern to TCR has not been reported previously.

The relation between histopathological malignancy grade and treatment response is affected by complex interactions among thermosensitive, radiosensitive, and chemosensitive factors, functioning in a microenvironment influenced by tissue blood flow, oxygen partial pressure, pH including tumor parenchyma, interstitial tissue, and normal tissue. These factors are considered to underlie the response to multidisciplinary therapy, but the details remain unclear.

Treatment-related factors

We found no significant difference in treatment response between microwave heating and radiofrequency heating. Our results are in accord with those of Masunaga et al.[4] , who also found that treatment response did not differ between microwave

and radiofrequency hyperthermia. However, other studies comparing these types of hyperthermia are lacking. To achieve an effective tumor temperature, the heating system has to be carefully selected and the applicator modified[23,24]. Heat-induced pain and injury to normal tissue should be avoided[15-18,23-26]. The heating temperature may sometimes be reduced by the cooling effect of blood flow. To prevent this phenomenon, we previously evaluated the use of a balloon catheter to temporarily block blood flow to tumor supply arteries[15]. We also assessed the usefulness of injecting a local anesthetic containing a vasoconstrictor substance around the tumors[16]. The present study, however, found no significant correlation between the number of heating sessions and treatment response. This finding is in accordance with the results of previous studies[1,3,7] . In particular, Valdagni et al.[7] found no difference in treatment response between 2 sessions and 6 sessions of hyperthermia. Other studies have also found no correlation between heating variables and treatment response[9].

Comparison of patients who received a radiation dose of 50 Gy or greater with those who received a radiation dose of 30 Gy or less revealed a significant correlation between the radiation dose and treatment response, as well as a significant difference in response between these doses of radiation. These results are similar to those reported by Masunaga et al.[4] and suggest that radical radiation is an important determinant of treatment response. These findings are not supported by the results of Egawa et al.[2], who found no significant difference in response between a radiation dose of 40 Gy or greater and a dose of less than 40 Gy.

As for chemotherapy, there was no significant correlation between treatment response and the total dose of cisplatin or the specific anticancer agents combined with cisplatin. This finding conflicts with the results of a study done by Herman et al.[10], which showed a significant correlation between the dose of cisplatin and the response rate in patients given TCR including cisplatin alone. To our knowledge, however, ours was the first study to assess response to thermoradiotherapy combined with multiple-anticancer chemotherapy including cisplatin in patients with head and neck cancer. To confirm our results, studies using larger groups of patients are necessary.

Good local control of advanced head and neck cancer does not eliminate the risks of metastasis from non-irradiated regions, recurrence, and distant metastasis. We used cisplatin-based chemotherapy because of its synergism with thermoradiotherapy[10-13,22,27]. Future studies should evaluate the types, doses, and treatment schedules for combined chemotherapy designed to suppress distant metastasis as well as local disease. We previously reported that hyperthermia alone and thermochemotherapy inhibit metastasis in an experimental models of cervical lymph node metastasis from oral squamous cell carcinoma in hamsters[24,28,29]. Further investigation may be warranted that operation including neck dissection following TCR become an effective strategy in patients with advanced head and neck cancer[13,30].

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