Original Contribution

Hyperthermia Combined with Chemoradiotherapy for Treatment of Locally Advanced Head and Neck Cancer with Bulky Lymph Node Metastasis

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Abstract: Local control of metastatic neck nodes is important for treatment in patients with locally advanced head and neck cancer. However, managing inoperable bulky metastatic nodes with necrotic tissue is difficult using ordinary chemoradiotherapy (CRT). Since, hyperthermia (HT) offers complementary and synergistic effects with irradiation and anti-cancer agents, HT combined with CRT was used for treatment in 11 patients with locally advanced head and neck cancer displaying bulky metastatic neck nodes.

The 11 cases included 8 cases with pathological Complete Response (CR), 2 with Partial Response (PR) and 1 with No Change (NC). The response rate was 90.9%. Overall survival rate (OS) at 1 and 2 years was 90.9% and 42.4%, respectively, and median survival time was 22.0 months. Local control rate (LCR) was 61.4% at both 1 and 2 years.

These clinical results indicate the effectiveness of thermochemoradiotherapy in patients with head and neck cancer displaying bulky lymph node metastasis.

Key Words: bulky lymph node, head and neck cancer, hyperthermia

Introduction

For patients with head and neck cancer, control of metastatic neck nodes is important. However, managing patients with inoperable bulky lymph nodes is difficult using chemoradiotherapy (CRT), as such nodes often include massive necrotic/hypoxic components that display varying degrees of radioresistance. A total dose of $\geq$ 85 Gy is needed to achieve > 50% local control rate for tumors > 5 cm in diameter[1]. In clinical practice, a total dose of 85 Gy is unreasonable, given the tolerated doses in normal head and neck tissue (e.g., temporomandibular joint: 60-65 Gy; skin (10 cm^2): 70 Gy; larynx: 70-79 Gy as TD5/5 (prediction radiation-dose of normal tissue complication probability at 5%

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within 5 years after radiotherapy))[2].

Hyperthermia (HT) itself has anti-cancer effects. When cells are exposed to elevated temperatures (> 41.0°C), lethal damage is inflicted, predominantly to proteins[3][4]. Radioresistant cells such as hypoxic cells, low pH cells[5] and cells in late S phase are thermosensitive. Moreover, radiotherapy (RT) and numerous chemotherapeutic agents display complementary effects with HT that lead to synergism[3].

HT may thus prove very beneficial in the management of bulky and/or necrotic nodes with metastatic disease. We performed HT with CRT for the treatment of head and neck cancer with bulky lymph nodes, and retrospectively analyzed clinical data for 11 patients to confirm the effectiveness of thermochemoradiotherapy in patients with head and neck cancer displaying bulky lymph node metastasis.

Patients & Method of Treatment

Patient characteristics

From July 2001 to July 2004, we treated 11 patients (8 men, 3 women) with head and neck cancer displaying bulky lymph node metastasis by using HT combined with CRT for the first treatment at Yokohama City University Center Hospital. Patient characteristics are shown in Table I.

Median follow-up period was 15.5 months (range, 8.5-35.5 months). Median age was 60 years (range, 49-68 years). Primary tumor locations were the nasopharynx (n=2), oropharynx (n=5) and hypoharynx (n=4). All patients were diagnosed histologically as squamous cell carcinoma except for 1 case with basaloid carcinoma. Pretreatment clinical stage was stage III (n=1), stage IVa (n=5) or stage IVb (n=5). The size of metastatic lymph nodes was ranged from 40 to 70 mm (median 45 mm). The location of metastatic lymph node was level II (n=8) and level III (n=3).

Table I. Patient's Characteristics.

Case	Age	Sex	Primary site	Stage	T	N	LNsize (mm)	LN level	Patho.	Hb (mg/dl)
1	60	M	naso	III	2a	2	45	II	p	12.6
2	54	M	naso	IVb	2a	3	60	II	m	11.6
3	52	F	oro	IVa	2	2c	45	II	m	13.7
4	62	M	oro	IVa	2	2b	45	III	ba	10.9
5	49	F	oro	IVb	2	3	60	II	m	12.7
6	62	F	oro	IVb	4	3	65	II	m	13.6
7	48	M	oro	IVb	4	3	70	III	m	15.1
8	68	M	hypo	IVa	2	2c	40	III	p	14.3
9	61	M	hypo	IVa	2	2c	45	II	m	13.9
10	52	M	hypo	IVa	4	2b	40	II	p	14.7
11	67	M	hypo	IVb	4	3	60	II	p	14.4
Median	60						45			13.7

M: male, F: female

Patho.: pathology, naso: nasopharynx, oro: oropharynx, hypo: hypopharynx

p: poorly differentiated squamous cell carcinoma, m: moderately differentiated squamous cell carcinoma, ba: basaloid carcinoma

Method of treatment

Treatment protocol is shown in Table II. HT was administered to the neck with the patient 1-2 times a week during the period of CRT.

Table II. Treatment Protocol.

Eligibility criteria
Age between 40 and 75
Performance Status : 0-1
No previous chemotherapy and/or radiotherapy
WBC ≧ 2,500, Plt ≧ 100,000
No severe hepatic nor renal dysfunction
No severe infection nor heart disease that precludes this treatment
Treatment Schedule
Concurrent thermo-chemo-radiotherapy
Radiotherapy for neck 1.8 to 2.0 Gy/fr by 6MV photon beam
Chemotherapy
Ccr ≧ 60 ml/min.
CDDP (60 mg/m²)+5FU (600 mg/m²)+MTX (20 mg/m²)+LV (30 mg/m²)
Ccr < 60 ml/min.
CBDCA+UFT (2001～2002) or TS-1 alone (2003～2004)
Hyperthermia (RF Capacitive heating)
LR-RL technique, duration 45-60 min, once or twice a week during radiotherapy

Hyperthermia

HT was administered after radiotherapy using a RF-capacitive heating apparatus (Thermotron RF-8). Median heating time for HT was 55 min (range, 40-60 min) and median power output was 290 W (range, 250-500 W). Median number of HT applications was 6 (range, 3-9). Electrodes were placed on the right and left sides of the neck. Electrodes ranged from 7 cm to 14 cm in diameter. Thermometry was performed by inserting thermocouples directly into the metastatic neck node for 8 patients, and onto the skin for 3 patients.

Radiotherapy

Conventional RT was performed just before HT using 6-MV photon beams generated by a linear accelerator. All cases received RT as the radical treatment field using a parallel-opposed lateral field and matched anterior portal field covering the primary tumor, metastatic nodes and possible lymph node pathways of spread with sufficient margins. Median total dose was 68.0 Gy (range, 66.6-70.2 Gy) for primary tumor, and 70.0 Gy (range, 68.0-77.4 Gy) for metastatic neck nodes. Fraction size was 1.8 or 2.0 Gy/day, 5 fractions/week.

Chemotherapy

Systemic chemotherapy was administered during the period of radiotherapy to all 11 patients. The

combination of chemotherapeutic agents was determined based on renal function according to creatinine clearance (Ccr) values. Cisplatin (CDDP) 60 mg/m^2+5-fluorouracil (5FU) 600 mg/m^2+levofolinate (LV) 20 mg/m^2+methotrexate (MTX) 30 mg/m^2 was administered for 6 patients with Ccr $\geq$ 60 ml/min. Carboplatin (CBDCA) and UFT (n=3) or TS-1 alone (n=2) was administered for 5 patients with Ccr $<$ 60 ml/min.

Data analysis

Data were analyzed in July 2005. After treatment, both primary tumor and metastatic neck lymph nodes were pathologically assessed by biopsy in all 11 patients.

Response evaluation was defined as follows: CR, pathologically complete response in both primary site and metastatic node; PR, $\geq$ 50% regression in tumor volume on CT and/or MRI; and NC, $<$ 50% regression in tumor volume on CT and/or MRI.

OS and LCR were calculated using Kaplan-Meier methods. As for LCR, the dead cases without local recurrence were included in censored cases. For univariate analysis, log-rank testing was used. Values of $p < 0.05$ were considered statistically significant.

Results

Results are shown in Table III. The 11 cases included 8 cases with CR, 2 cases with PR and 1 case with NC. Initial response rate was 90.9% and CR rate was 72.7%.

Table III. Treatment Results.

Case	Radiotherapy		Hyperthermia				Chemo-thepapy	Initial effect	Survival period (months)
	Total dose (Gy) /fraction	OTT (days)	No. of times	Time (min)	Power (W)	T_{max} (°C)			
1	68.0/34	52	3	60	380	44.0t	4agents	CR	19.5/a
2	69.2/37	63	9	55	420	43.8t	4agents	CR	35.5/a
3	72.0/36	54	5	40	250	46.9t	4agents	CR	15.5/a
4	68.0/34	47	6	55	250	45.0t	4agents	CR	13.0/a
5	69.0/37	51	5	55	280	43.6t	TS-1	CR	25.5/a
6	70.0/35	50	6	55	250	41.6s	4agents	CR	17.5/a
7	74.6/41	59	7	60	460	41.9s	Cb+UFT	NC	11.5/a
8	74.6/41	50	9	55	360	44.0t	TS-1	PR	22.0/d
9	76.0/38	55	8	60	500	44.4t	Cb+UFT	PR	13.0/d
10	77.4/43	58	6	50	300	42.0s	Cb+UFT	CR	8.5/d
11	68.0/34	50	3	45	250	42.5t	4agents	CR	12.5/d
Median	70.0/37	54	6	55	290	44.0	response rate: 90.9%		MST 22.0

OTT: overall treatment time
t: tumor, s: skin
MST: median survival time
4agents: CDDP+5FU+LV+MTX
Cb+UFT: CBDCA+UFT
a: alive, d: dead

Among the 8 cases of CR, 6 patients received TS-1, and another 2 patients received UFT for adjuvant therapy. Local recurrence developed within 1 year for 2 patients, and as of the time of writing 1 patient was alive and the another patient died 12.5 months after with renal failure by hypercalcemia.

Among the 2 patients in PR, 1 patient received radical neck resection, but died at 22.0 months due to lymphangitis, the another patient declined therapy and died at 13.0 months with multiple metastases.

One patient displayed NC of a metastatic node despite CR of the primary site. This patient could not receive neck dissection due to adhesion to the carotid artery, but received UFT as adjuvant therapy. The patient died of the disease at 12.5 months.

OS rate was 90.9% at 1 year and 42.4% at 2 years. Median survival was 22.0 months (Fig. 1), and LCR was 61.4% at both 1 and 2 years (Fig. 2). In univariate analysis, size of metastatic lymph nodes (between < 6 cm and ≥ 6 cm) did not represent a prognostic factor for OS ($p=0.643$; Fig. 3) nor LCR ($p=0.941$; Fig. 4).

Acute complications included grade 3 leukopenia in 7 cases and grade 3 thrombocytopenia in 3 cases. No severe chronic toxicity was observed.

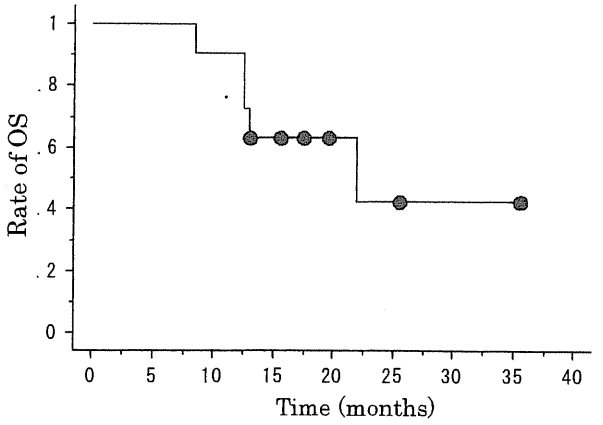

Fig. 1. Overall Survival rate of All Eleven Patients.

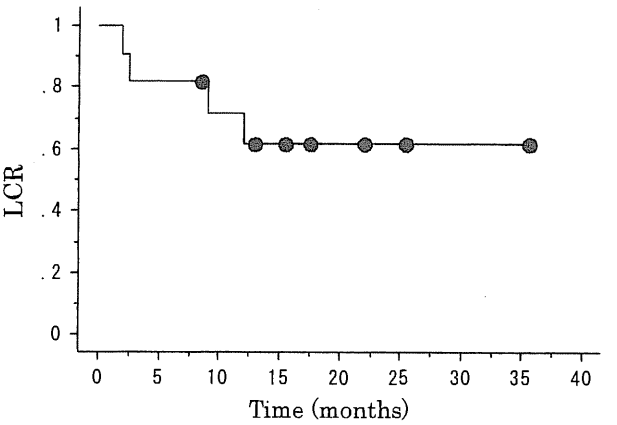

Fig. 2. Local Control Rate of All Eleven Patients.

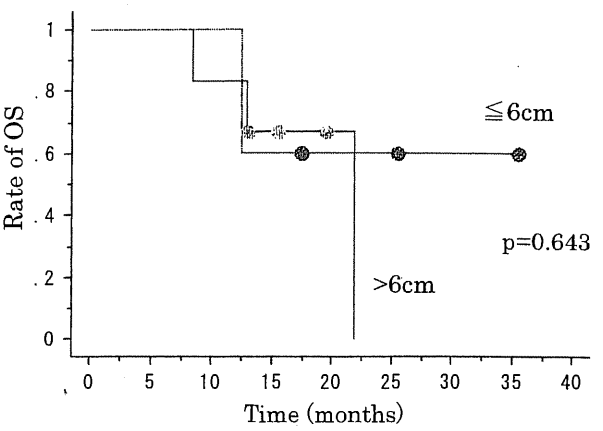

Fig. 3. Overall Survival by Lymph Node Size.

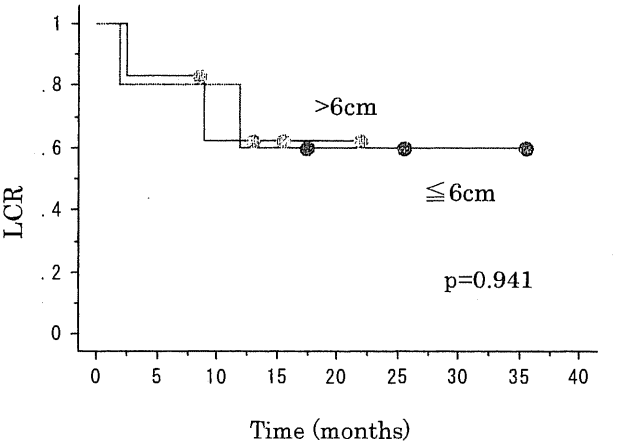

Fig. 4. Local Control Rate by Lymph Node Size.

Discussion

In general, HT exerts synergistic effects with other therapies on cells under hypoxia, low pH, late S phase, all of which normally represent disadvantageous conditions for RT. Since huge masses usually display poor perfusion, resulting in central hypoxic conditions driving anaerobic glycolysis and inducing low pH, combination with HT may improve clinical outcomes from RT. HT offers complementary and synergistic effects with irradiation and anti-cancer agents, and displays few adverse effects other than burn injury. Superficial metastatic neck nodes are suitable for HT, since temperature in the lesion is easily controlled and measured.

In patients with bulky metastatic lymph nodes of head and neck cancer, radical neck dissection is considered curative. However, many patients are considered inoperable due to adhesions between metastatic node and surrounding tissue. CRT is selected in such cases, but prognosis is usually poor due to difficulties with tumor control, particularly for bulky metastatic lymph nodes.

We have conducted HT combined with CRT in 11 patients with inoperable bulky metastatic lymph nodes of head and neck cancer since July 2001. We could perform standard concurrent CRT in 11 patients. We interrupted HT with CRT for 10 days in Case 2 due to grade 3 leukopenia. It prolonged overall treatment time for 63 days, but CR was confirmed in this patient and disease-free survival has reached 35.5 months as of the time of writing.

As for HT, 11 patients were treated with standard total number of fractions and heating time. Concerning T_{max}, thermometry was performed in 8 patients by inserting thermocouples directly into the metastatic neck node and confirming the relevant temperature ($\geq$ 42.5°C). In another 3 patients with tumor involving the carotid artery, relevant temperature could not be confirmed in the metastatic neck node. However, superficial temperature on the skin was confirmed (range, 41.6～42.0°C) and seemed sufficiently high.

Arcangeli studied a total of 81 neck nodes in 38 patients treated with either thermoradiotherapy or RT alone[6]. Patients with thermoradiotherapy showed greater CR rates and LCR for 2 years than with RT alone (CR, 79% vs. 42%; LCR, 58% vs. 14%, respectively). CR rates and LCR at 2 years in the present study were equivalent to those results.

Valdagni et al. reported a randomized trial comparing RT plus HT with RT alone for metastatic lymph nodes in patients with stage IV head and neck[7]. In that trial, a significant difference in treatment results was identified. Initial effective rate (83.3% vs. 40.9%, respectively; $p=0.016$), 5-year LCR (68.6% vs. 24.2%, respectively; $p=0.015$) and 5-year survival rate (53% vs. 0%, respectively; $p=0.02$) were all significantly better with RT plus HT. Although we have not observed 5-year survival, the initial effective rate of our study seems equivalent to that result.

Urano et al. reported that bigger tumor volume decreases the treatment time to achieve tumor control by about 50% (in vivo)[8]. This means that tumors with larger diameter display higher thermosensitivity. In the present study, no significant difference in OS or LCR were noted between groups classified according to size of metastatic lymph nodes.

Recently, there are many reports with good results for the treatment of locally advanced head and neck cancer with concurrent CRT. But, managing patients with bulky lymph nodes is still difficult. Our results back up the benefits of HT combined CRT.

In conclusion, we confirmed the effectiveness of HT combined with CRT in patients with head and neck cancer displaying bulky lymph node metastasis. However, long-term survival and prognostic factors still need to be examined in larger clinical trials.

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巨大な頸部リンパ節転移を有する局所進行頭頸部癌に対する温熱併用放射線化学療法

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要　　旨: 局所進行頭頸部癌において，頸部転移リンパ節の局所制御が重要である．しかし，手術不能で巨大な頸部転移リンパ節は，通常の放射線化学療法によるコントロールが困難であるため，我々は巨大な頸部転移リンパ節を有する局所進行頭頸部癌に対し，温熱併用放射線化学療法を施行してきた．2001 年 7 月から 2004 年 7 月までの間に治療した 11 例を対象として治療効果を検討したところ，CR8 例・PR2 例・NC1 例で，奏効率は 90.9%であった．1 年および 2 年生存率がそれぞれ 90.9%・42.4%，中央生存期間が 22.0ヶ月，1 年および 2 年局所制御率ともに 61.4%であった．巨大な頸部転移リンパ節を有する局所進行頭頸部癌に対する温熱併用放射線化学療法の有用性が示唆された．