evaluated as event-free. Nutrition-support-free survival denotes the percentage of surviving patients not requiring any nutrition support at the time of treatment start and then 2, 6, 12, 24, 36, 48 and 60 months after registration. The non-hospitalized treatment period during the permissible treatment period is defined as the difference between the duration of actual hospital stays and the permissible treatment period (66 days).

Eligibility Criteria

Inclusion Criteria

For inclusion in the study, the patient must fulfill all of the following criteria:

(1) Histologically proven squamous cell carcinoma in resected specimen.
(2) Primary lesion located in the oral cavity, oropharynx, hypopharynx or larynx.
(3) Pathological Stages III, IVA or IVB (UICC seventh edition).
(4) High risk of locoregional recurrence, defined as fulfilling (i) and/or (ii):
  (i) microscopically positive resection margin;
  (ii) extracapsular nodal extension.
(5) Within 56 days of surgery.
(6) No distant metastasis in head and neck contrast CT or MRI, chest contrast CT or upper abdominal contrast CT within 28 days before registration.
(7) Aged 20–75 years old.
(8) ECOG performance status of 0 or 1.
(9) No prior radiation therapy, chemotherapy or hormonal therapy for target or non-target cancers.
(10) Adequate organ function.
(11) Normal electrocardiogram.
(12) Written informed consent.

Exclusion Criteria

Patients are excluded if they meet any of the following criteria:

(1) Active multiple primary cancers; synchronous or metachronous (within 5 years) double cancers except carcinoma *in situ* or intramucosal tumor.
(2) Infection requiring systemic treatment.
(3) Fever exceeding 38°C at registration.
(4) Women who are or may be pregnant, or who are nursing.
(5) Psychosis or psychiatric symptoms/signs that are judged to make participation in the study difficult.
(6) Long-term use of systemic steroidal treatment (oral/intravenous).
(7) Uncontrolled diabetes mellitus.
(8) Complication with unstable angina, or history of myocardial infarction within the last 6 months.
(9) Uncontrolled hypertension.

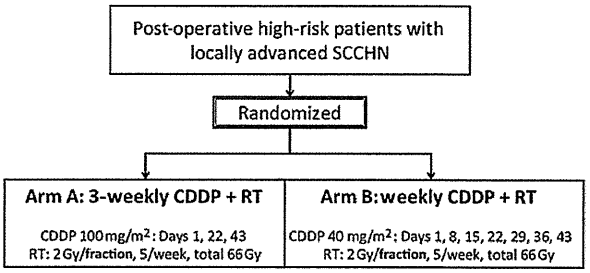

Figure 1. Schema of the study.

(10) Pleural effusion, pericardial effusion or ascites that requires drainage.
(11) Hepatitis B antigen-positive.
(12) Judged to have difficulty in abstaining from smoking or alcohol during the protocol treatment.

Treatment Methods

The protocol treatment consists of 3-weekly CDDP + RT and weekly CDDP + RT (Fig. 1).

Chemotherapy

Patients in the 3-weekly CDDP + RT arm receive concurrent CRT with CDDP at 100 mg/m^2. CDDP is administered on Days 1, 22 and 43, repeated every 3 weeks for three cycles. Patients in the weekly CDDP + RT arm receive concurrent CRT with CDDP at 40 mg/m^2. CDDP is administered on Days 1, 8, 15, 22, 29, 36 and 43, repeated every week for seven cycles.

Radiation Therapy

Radiation therapy is administered with high-energy photons of 4–10 MV X-rays to a total dose of 66 Gy in 33 fractions over 6.5 weeks. The gross tumor volume is not defined in this trial because macroscopic sites of the disease were resected before registration. The clinical target volume (CTV) initial includes locally resected lesion and potential lymph node metastasis area, and CTV boost is defined as a high-risk area with a positive node with extracapsular extension and/or a positive surgical margin with a 1–1.5 cm margin. The planning target volumes (PTV) for CTV initial and CTV boost (PTV initial and PTV boost) are defined as 0.5–1 cm margins around CTV initial and CTV boost to compensate for setup variations and internal organ motion. A total of 46 Gy is delivered to PTV initial, and then an additional 20 Gy is provided to PTV boost.

Follow-up

All enrolled patients are followed up for at least 5 years. The efficacy and the safety are to be evaluated at least every 3 months during the first year, at least every 4 months during

the second year, every 6 months during the third year, and every 12 months during the fourth and fifth years. Data on the use and methods of nutrition support are reported at 2, 6, 12 and then every 12 months until 60 months after registration.

Study Design and Statistical Analysis

This trial is designed to evaluate the non-inferiority of weekly CDDP + RT compared with 3-weekly CDDP + RT for post-operative high-risk patients with locally advanced SCCHN. The planned accrual period is 5 years, and the follow-up period is 5 years after completion of accrual.

In the Phase II part, the planned sample size is 66 patients, which was calculated based on an expected proportion of complete treatment of 80% and a threshold of 50%, with a one-sided alpha of 0.025 and a beta of 0.1.

In the Phase III part, the primary analysis is carried out at 5 years after accrual completion. The hazard ratio between the treatment arms and its confidence interval, estimated by the Cox proportional hazard model stratified by the high-risk factors for recurrence (microscopically positive resection margin and extracapsular nodal extension), is used to test the non-inferiority of the weekly CDDP + RT arm in terms of overall survival. The significance level is set at 0.05 in a one-sided test because of the non-inferiority design of the study. One hundred and sixty-one events would be required to demonstrate, with a statistical power of 75%, that the weekly CDDP + RT arm is not inferior to the 3-weekly CDDP arm in terms of overall survival, with a non-inferiority margin of 10% at 5-year overall survival. Non-inferiority will be concluded if the upper limit of the confidence interval of the hazard ratio does not exceed the limit of 1.32, which is in accord with the non-inferiority margin. According to Schoenfeld and Richter's method (19), a sample size of 260 patients is necessary to observe 161 events, considering the accrual and follow-up periods and that the estimated 5-year overall survival rates of the 3-weekly CDDP + RT arm and the weekly CDDP + RT arm are 49 and 52%, respectively.

Interim Analysis and Monitoring

In this Phase II/III trial, three interim analyses are planned. The first interim analysis is planned at the time of protocol treatment completion of all registered patients in the Phase II part to evaluate the feasibility and safety of both treatment arms and to determine the progression to the Phase III part. The second interim analysis is planned when half of the planned sample size is registered to determine whether the registration of the Phase III part should be continued. The third interim analysis is planned after the registration completion to determine the continuation to the follow-up. The trial will be terminated when the primary objective is accomplished at each interim analysis.

The Data and Safety Monitoring Committee of the JCOG will independently review the interim analysis reports and recommend that the trial either be continued or terminated early. Central monitoring will be performed every 6 months by the JCOG Data Center to evaluate study progress and improve study quality.

Participating Institutions (from North to South)

Hokkaido University Hospital, Miyagi Cancer Center, Tohoku University Hospital, Jichi Medical University Hospital, National Cancer Center Hospital East, Tokyo Jikei Medical University Hospital, National Hospital Organization Tokyo Medical Center, Cancer Institute Hospital, Tokai University, Shizuoka Cancer Center, Aichi Cancer Center, Nagoya University Hospital, Kinki University Hospital, Osaka Prefectural Hospital Organization, Osaka Medical Center for Cancer and Cardiovascular Diseases, Kobe University Hospital, Hyogo Cancer Center, Nara Medical University, Shikoku Cancer Center.

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Conflict of interest statement

None declared.

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Selection of Therapeutic Treatment with Alternating Chemoradiotherapy for Larynx Preservation in Laryngeal Carcinoma Patients

Kei Ijichi[1,*], Nobuhiro Hanai[2], Daisuke Kawakita[1], Taijiro Ozawa[2], Hidenori Suzuki[2], Hitoshi Hirakawa[2], Takeshi Kodaira[3], Shingo Murakami[1] and Yasuhisa Hasegawa[2]

[1]Department of Otolaryngology-Head and Neck Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, [2]Department of Head and Neck Surgery, Aichi Cancer Center Hospital, Nagoya and [3]Department of Radiation Oncology, Aichi Cancer Center Hospital, Nagoya, Japan

*For reprints and all correspondence: Kei Ijichi, Department of Otolaryngology-Head and Neck Surgery, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan. E-mail: ijichi@med.nagoya-cu.ac.jp

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Objective: We analyzed the efficacy of treatments that included alternating chemoradiotherapy in laryngeal cancer patients.
Methods: Alternating chemoradiotherapy consisted of chemotherapy with 5-fluorouracil (600 mg/m^2/day) on Days 1–6 and cisplatin (80 mg/m^2) on Day 7 followed by radiotherapy with 30 Gy. Additional chemoradiotherapy was administered to responders, and laryngectomy was performed in non-responders. The contribution of alternating chemoradiotherapy to laryngeal preservation was compared with that of radiotherapy in patients with T2 disease and with that of laryngectomy in patients with T3/T4 disease.
Results: Analysis of 87 patients was conducted. The 5-year overall survival rate of T2 patients ($n = 46$) was 88.9% for definitive radiotherapy and 82.5% for alternating chemoradiotherapy. The laryngectomy-free rate in T2 patients was 90.5% for definitive radiotherapy and 80.0% for alternating chemoradiotherapy. In patients with T3/T4 disease ($n = 41$), the 5-year overall survival rate was 86.9% for alternating chemoradiotherapy and 67.4% for laryngectomy. The laryngectomy-free rate in T3/T4 patients was 91.7% for alternating chemoradiotherapy and 0.0% for laryngectomy.
Conclusions: In advanced carcinoma of the larynx, alternating chemoradiotherapy treatment might enable larynx preservation.

Key words: laryngeal carcinoma – head and neck carcinoma – chemoradiotherapy – laryngeal preservation

INTRODUCTION

Squamous cell carcinoma of the head and neck is currently treated by a combination of surgery, radiotherapy (RT) and chemotherapy. In cases of carcinoma of the larynx, RT is mainly used for treating early cases and a combination of surgery and RT for advanced cases. In most cases, however, surgery for laryngeal carcinoma results in the loss of vocal function, which is a major disadvantage of this treatment method.

A number of recent reports have discussed treatments that preserve laryngeal function (1–5). Although treatment strategies to date have focused on RT in early cases of cancer (T1-T2), these occasionally fail (particularly in patients with T2 disease), and laryngeal function is then lost due to

subsequent laryngectomy. In cases of advanced carcinoma, laryngectomy is the main treatment option, leading to loss of laryngeal function.

A study by the Veterans Affairs Laryngeal Cancer Study Group in 1991 reported the effectiveness of induction chemotherapy for advanced carcinoma of the larynx (6). Based on this report, we initiated a treatment policy for advanced laryngeal carcinoma in which induction chemotherapy was conducted and then the response evaluated. In responders, chemoradiotherapy was continued to assess whether or not preservation of the larynx was possible, whereas in non-responders, the next step following therapy was surgery.

Here, in order to evaluate the efficacy of induction chemoradiotherapy, we investigated the feasibility of alternating chemoradiotherapy (ACRT) that consisted of one cycle of systemic chemotherapy and RT (30 Gy) followed by either sequential chemoradiotherapy or surgery for T2 or T3 laryngeal carcinoma. We separately investigated patients with T2 or T3/T4 disease: in patients with T2 disease, we compared definitive RT and ACRT; in patients with T3/T4 disease, we compared ACRT and initial laryngectomy. Patients were classified according to the stage of tumor progression and site of primary lesion in the larynx, and survival rate and larynx preservation were investigated.

PATIENTS AND METHODS

Patient Population

A pilot analysis was conducted in 93 patients treated at the Aichi Cancer Center Hospital between 1990 and 2003 with previously untreated invasive squamous cell carcinoma of the larynx, classified as T2 to T4 using the UICC staging system.

Treatment Plan

Induction treatment of ACRT was determined as one cycle of chemotherapy, consisting of 5-fluorouracil and a platinum agent, followed by RT. Chemotherapy in ACRT comprises 5-fluorouracil (600 mg/m^2/day) on Days 1–6 and cisplatin (80 mg/m^2) or nedaplatin (120 mg/m^2) on Day 7 (Fig. 1).

External beam RT was treated with a 6 MV photon using a linear accelerator. All patients received CT images with a fixed thermoplastic mask for CT simulation. Treatment was planned by 3D-conformal radiation therapy and intensity-modulated RT was not used. Typically, initial radiation portals were delivered by bilaterally opposed parallel portals for the upper and middle cervix and an anterior single portal for the lower neck and/or the subclavicular region, if needed. After 40 Gy of radiotherapy, cone-down portals were used to spare the spinal cord. Opposed parallel portals or dynamic conformational rotational arc therapy was often used in boost plan. A daily dose of 1.8–2 Gy was delivered in standard fractionation. Initially, a dose of 36 Gy was delivered to CTVinitial, which included level II to VI in N0 cases. In case of having involved nodal lesion, CTVinitial also expanded to

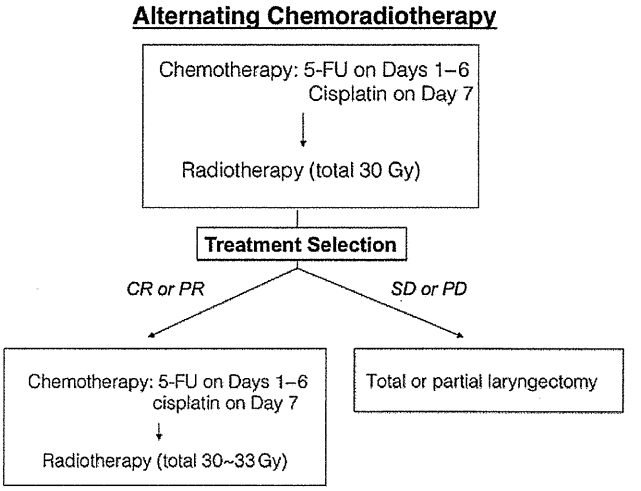

Figure 1. Treatment plan for alternating chemoradiotherapy (ACRT).

retropharyngeal and supraclavicular regions. No prophylactic region is used for patients with glottic cancer with T2N0. Then, an additional 30 Gy was delivered to both the primary lesion and involved node.

After completion of induction chemotherapy with an initial 30 Gy of RT, tumor extension and nodal disease were assessed by laryngoscopy, biopsy and computed tomography (CT) scan of the neck if indicated.

In T2 patients, ACRT was administered to patients with a relatively bulky tumor, for whom the present status is good. In a definitive RT group, the patient with a bulky tumor was indicated of specific concurrent weekly chemoradiotherapy and RT, consisting of cisplatin (70 mg/m^2) and 5-fluorouracil (600 mg/m^2) and RT 1 day per week.

In T3/4 patients, laryngectomy as an initial treatment was performed in patients with a tumor, which extends to the larynx front such as the anterior commissure and ACRT to the remaining patients.

Surgical treatment was performed in cases that were unresponsive to ACRT and in cases of residual disease following other treatments. A proportion of patients, particularly in the early years of this study, received laryngectomy as an initial treatment. Laryngectomy and neck dissection were performed for nearly all T3/T4 patients and for T2 patients with residual neck disease.

Response Assessment of ACRT

ACRT was designed as an index to predict the response to chemoradiotherapy for preservation of the larynx. After completion of ACRT, tumor extension and nodal disease were assessed via laryngoscopy, biopsy and CT scan of the neck ifindicated. Response to treatment was assessed as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) according to the RECIST criteria (7).

In patients receiving ACRT, those with CR and PR received sequential chemoradiotherapy, consisting of an additional one to three cycles of chemotherapy followed by additional 36 Gy of RT. In contrast, patients with SD or PD received laryngectomy (Fig. 1).

Toxicity

Toxicity was analyzed according to the National Cancer Institute Common Toxicity Criteria. Toxic events included leukopenia, thrombopenia, anemia, stomatitis, nausea and vomiting, renal toxicity, diarrhea, infection and hepatic toxicity.

Statistics

This study was designed to also determine the organ preservation rate after treatment including assessment of the response to ACRT. The laryngectomy-free rate was calculated from a set of patients who retained the ability of speech. Survival time was assessed from the first day of treatment until death or last patient contact. Disease-free survival was calculated from the day of initial treatment until first evidence of recurrence. If patients were not operated on, disease-free survival was calculated from the date of CR. Overall survival and disease-free survival rates were calculated according to the Kaplan–Meier method. The JMP 9.0 software was used for statistical analysis (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Patient Characteristics

A total of 94 patients with T2 to T4 operable carcinoma of the larynx were analyzed. Patient characteristics are described in Table 1. Patients were divided into two groups of T2 and T3/T4 disease. The mean age was 61.8 years (range, 41–74 years) at the time of diagnosis of primary tumor. Primary tumor sites included the supraglottis ($n = 34$), the glottis ($n = 42$) and the sub- or transglottis ($n = 11$). A total of 46 patients had T2 disease, while 41 had T3/T4 disease.

Treatment

The type of initial treatment is shown in Table 2. Twenty-one (45.7%) T2 patients received only definitive RT including low-dose chemoradiotherapy. Fourteen T2 patients (24.1%) received low-dose chemoradiotherapy, which included cisplatin and 5-FU in 11 patients and taxotere in 4 patients. Twenty-five (54.3%) patients with T2 disease were treated with ACRT. None of the patients were evaluated as SD following ACRT and underwent laryngectomy. All patients underwent chemoradiotherapy following ACRT, which included one to two cycles of chemotherapy and 36 Gy of RT.

Twenty-four patients with T3/T4 disease received ACRT. Six patients (25.0%) were evaluated as SD following ACRT and underwent laryngectomy (Table 3). The remaining

Table 1. Patient characteristics

	No. of patients
Patients	87
Age, years	
Mean (range)	61.8 (41–74)
Sex	
Male	84
Female	3
Primary tumor site	
Supraglottis	34
Glottis	42
Sub/supraglottis	11
T stage	
T2	46
T3	23
T4	18
N stage	
N0	58
N1	17
N2	
N2a	0
N2b	9
N2c	3
N3	0

Table 2. Initial treatment to all patients with laryngeal cancer

	No. of patients (%)	
	T2	T3/T4
Definitive radiotherapy (including concurrent weekly chemo- and radiotherapy)	21 (24.1)	0 (0.0)
Alternating chemoradiotherapy	25 (54.3)	24 (58.5)
Laryngectomy	0 (0.0)	17 (41.5)
Total	46 (100.0)	41 (100.0)

Table 3. Following therapy after treatment selection in the ACRT arm

	No. of patients (%)	
	T2 ($n = 25$)	T3/4 ($n = 24$)
Chemoradiotherapy	25 (100.0)	18 (75.0)
Laryngectomy	0 (0.0)	6 (25.0)

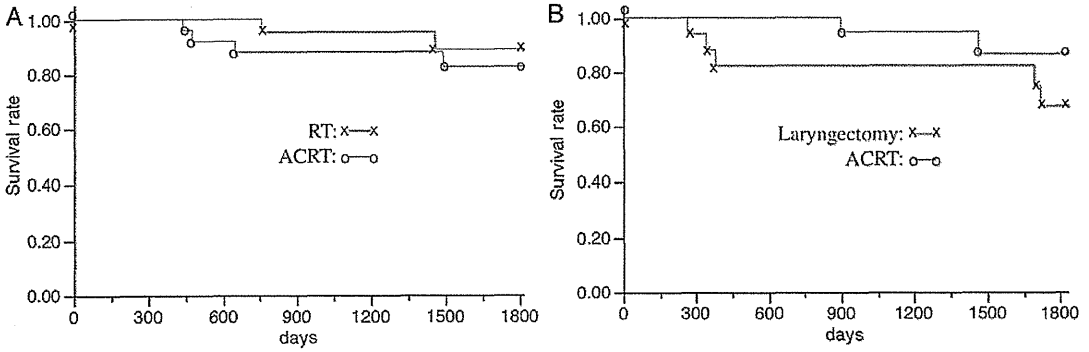

Figure 2. Overall survival rates for each treatment. (A) T2 and (B) T3/T4. ACRT, alternating chemoradiotherapy; LCRT, concurrent low-dose chemo- and radiotherapy; RT, definitive radiotherapy.

patients underwent chemoradiotherapy following ACRT, which consisted of one to three cycles of chemotherapy and 36 Gy of RT. Laryngectomies were performed as an initial treatment for 17 patients with T3/T4 disease.

Overall Survival

The median follow-up was 57.3 months (range: 11.4–137.1 months). The estimated 5-year survival rate was 85.4% for patients with T2 disease and 77.7% for those with T3/T4 disease. The estimated 5-year survival rate for each treatment is shown in Fig. 2. In patients with T2 disease, the survival rate for initial treatment was 82.5% for ACRT and 88.9% for RT (Fig. 2A). In patients with T3/T4 disease, the survival rate for initial treatment with ACRT was 86.9% and with laryngectomy was 67.4% (Fig. 2B).

Cause-specific Survival

Cause-specific survival was analyzed according to the initial treatment. The estimated 5-year survival rate was 100.0% for patients with T2 disease and 92.9% for those with T3/T4 disease. In patients with T3/T4 disease, the survival rate was 100.0% for ACRT and 84.0% for laryngectomy (Fig. 3).

Recurrence

Eight patients (17.4%) with T2 disease experienced recurrence. Four total laryngectomies and four partial laryngectomies were performed for local recurrence. Three total and two partial laryngectomies were performed for salvage treatment of patients receiving ACRT. One total laryngectomy and two partial laryngectomies with definitive RT were performed. One patient had recurrent neck nodes for which neck dissection was performed followed by definitive RT. One patient who underwent ACRT had lung metastasis after 10 months.

Twelve (23.1%) patients with T3/T4 disease experienced disease recurrence. Three additional pharyngotomies were performed for two patients who had received initial

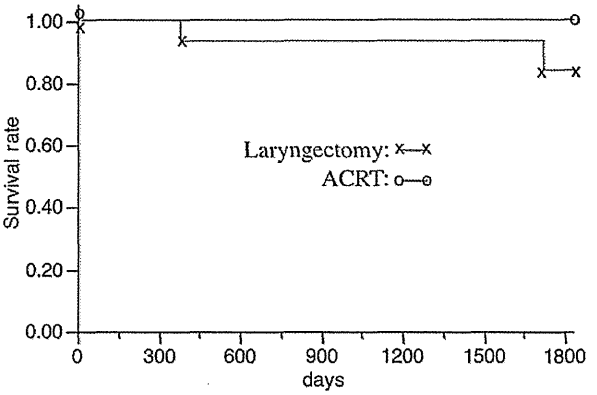

Figure 3. Disease-free survival in T3/4 patients according to treatment. No T2 patient death from primary disease.

laryngectomy and one who received ACRT followed by laryngectomy. Seven patients with recurrent neck disease underwent neck dissection. Of these, three received ACRT and four received laryngectomy as an initial treatment. Two patients had distant metastasis of the lung with ACRT and one had distant metastasis of the skin with initial laryngectomy.

Laryngeal Preservation

Initial laryngectomy was performed in 18 patients (40.5%) with T3/T4 disease, but not in any with T2 disease. The laryngectomy after treatment selection of ACRT was performed for six patients with T3/T4 disease (Table 3). Laryngectomy was performed for residual disease in one T2 patient who received RT and one who received ACRT. In patients with T2 disease, the laryngectomy-free rate was 80.0% for ACRT and 90.5% for RT. In patients with T3/T4 disease, the laryngectomy-free rate was 91.7% for ACRT and 0% for laryngectomy. The laryngectomy-free rate divided by the treatment and tumor site are shown in Table 4.

Toxicity

We analyzed the acute toxicity of RT and ACRT followed by chemoradiotherapy according to the National Cancer Institute

Table 4. Laryngeal preservation according to treatment

	No. of patients (%)							
	T2				T3/T4			
	Supraglottis	Glottis	Sub/transglottis	Total	Supraglottis	Glottis	Sub/transglottis	Total
Definitive radiotherapy (including concurrent weekly chemo- and radiotherapy)	2/3 (66.7)	16/17 (94.1)	1/1 (100.0)	19/21(90.5)	–	–	–	–
Alternating chemoradiotherapy	9/12 (75.0)	10/12 (83.3)	1/1 (100.0)	20/25 (80.0)	15/16 (93.8)	6/6 (100.0)	1/2 (50.0)	22/24 (91.7)
Laryngectomy	–	–	–	–	0/3 (0.0)	0/7 (0.0)	0/7 (0.0)	0/17 (0.0)

Common Terminology Criteria for Adverse Events v4.0 (Table 5). In all events, ACRT showed more severe toxicity than the other treatments. In particular, high frequency of myelosuppression and mucositis were noted. Only one patient with T2 disease received incomplete treatment of ACRT followed by chemoradiotherapy due to severe myelosuppression. The completion rate of ACRT followed by chemoradiotherapy was 97.7% (42/43 patients).

Table 5. Toxicity according to each treatment

	No. of patients								
		Definitive radiotherapy (including concurrent weekly chemo- and radiotherapy) ($n = 21$)				Alternating chemoradiotherapy ($n = 43$)			
Toxicity	Grade	1	2	3	4	1	2	3	4
Leukopenia			2			4	12	14	
Thrombopenia		2	1			6	7	13	1
Anemia		2	1			15	13	3	
Stomatitis		2	13		1	2	29	5	5
Nausea and vomitting		3				7	12	15	2
Renal						9			
Diarrhea						8	2	1	
Infection		1				2	1		
Hepatic						2	2		

DISCUSSION

The present study was an investigation of induction chemoradiotherapy for T2–T4 laryngeal carcinoma. We designed ACRT, which consisted of one cycle of systemic chemotherapy and RT (30 Gy) followed by either sequential chemoradiotherapy or surgery for T2 or T3/T4 laryngeal carcinoma, as an index to predict the response to chemoradiotherapy for preservation of the larynx. We showed the contribution of ACRT to laryngeal preservation.

Over the past 20 years, various trials have been conducted on chemoradiotherapy and RT for head and neck cancers, particularly carcinoma of the larynx. The focus of most trials is preservation of laryngeal function rather than survival. In a trial of the Veterans Affairs Laryngeal Cancer Group (VA), the larynx was preserved in 64% of patients who underwent induction chemoradiotherapy and RT in comparison with total laryngectomy and postoperative RT or induction chemoradiotherapy and radiotherapy (6). Later trials on larynx preservation with induction chemotherapy were conducted not only for laryngeal carcinoma but also for hypopharyngeal carcinoma (8–12).

In the present study, after one course of induction chemotherapy (combination of cisplatin and 5-FU), patients were administered 30 Gy of radiation, and the effects of chemoradiotherapy and RT was assessed. Additional chemotherapy was then administered to CR or PR patients with RT of 30–36 Gy. Laryngectomy was performed for SD and PD patients. In the VA trial, two courses of chemotherapy as induction therapy were conducted, after which the effect of treatment was assessed. Similarly, EORTC and GETTEC studies analyzed that the trial that of patients was divided two groups: (i) surgery followed by RT or (ii) PF followed by RT in good responders otherwise by surgery and postoperative RT (9,10). Thus, an investigation for larynx preservation was required in laryngeal carcinoma treatment. To obtain both CR and larynx preservation, many trials including chemoselection have been investigated.

In our study, however, induction therapy consisted of RT of 30 Gy following one course of chemotherapy, after which the efficacy of treatment was assessed.

With induction therapy as chemoradiotherapy, not only the chemosensitivity of the tumor but also its radiosensitivity was evaluated, which we consider a more practical assessment of response to treatment aimed at preserving the laryngeal function than that of the VA study. As a treatment, the effect of ACRT is judged. CR or PR was achieved in 100% of patients with T2 disease and 75% of those with T3/T4 disease. The subsequent treatment was chemoradiotherapy (Table 3), suggesting that ACRT is more effective for relatively small tumors.

In the present study, the CR rate following the completion of definitive therapy for patients who underwent chemoradiotherapy after ACRT was 97.7% in patients with T2 disease and 100% in those with T3/T4 disease. Given this result, we consider selection based on ACRT to be an accurate method of evaluation. No treatment-related deaths occurred in the present study. As above, the method of evaluation by ACRT followed by additional chemoradiotherapy in responders is believed to be a feasible treatment method.

Laryngeal preservation was investigated in terms of treatment method and tumor subsite (Table 4). In T2 patients, no marked differences were observed in laryngeal preservation between treatments other than surgery, nor were any differences observed between tumor subsites. In patients with T3/T4 disease, the laryngectomy-free rate was high in patients who underwent ACRT, particularly those with supraglottic carcinoma, indicating a somewhat larger percentage of advanced supraglottic carcinoma patients with high sensitivity to chemoradiotherapy.

The overall survival of patients receiving surgery was somewhat lower than that of other treatments, which is consistent with the VA and Radiation Therapy Oncology Group (RTOG) 91-11 trials (1,6). This finding indicates that the survival rates of treatments other than surgery investigated in this study were not low and that these are promising treatments for laryngeal preservation.

In the VA study, a laryngeal preservation rate of 64% was obtained in comparison with 0% for surgery with chemotherapy and radiation following induction chemotherapy in Stage III and IV glottic or supraglottic laryngeal cancer patients. No significant differences were observed in overall- or disease-free survival rates.

When investigating induction chemotherapy in the RTOG 91-11 trial, although no differences were noted in the laryngeal preservation rate or local-regional control rate in comparison with RT alone, laryngectomy-free survival and disease-free survival rates were significantly higher than RT alone. Thus, induction chemotherapy is considered to be significantly more effective in laryngeal preservation than surgery or radiation. On comparing the laryngeal preservation rate and local-regional control rate in patients receiving concurrent cisplatin and radiation therapy, rates in patients who underwent induction chemotherapy tended to be significantly higher (1). However, in a follow-up report, no significant differences were noted between the two groups in laryngectomy-free survival in long-term analysis (13). In addition, the result of severe side effect was greater in the chemotherapy groups. Laryngectomy-free survival showed no difference between the induction chemotherapy followed by RT group and concurrent cisplatin and RT group. We conclude that induction chemotherapy is needed as a strategy in the hope of both preserving the larynx and improving the survival rate.

In other reports, the addition of docetaxel to induction chemotherapy of cisplatin and 5-FU (TPF) resulted in a significantly higher overall survival rate (2,14,15). These trials were concluded that the TPF regimen improves laryngeal preservation compared with PF. Chemotherapy consisting of cetuximab has recently been used as an induction therapy for head and neck cancer patients (16). Further, induction chemotherapy combined with intensity-modulated RT (IMRT) to laryngeal cancer has been reported (3,4,17). With further modification, we thought ACRT including docetaxel or cetuximab and IMRT might be a promising candidate for future treatments.

In the present study, the laryngectomy-free rate was highest in the ACRT group with T3/T4, particularly in patients with glottic carcinoma. In a previous report, a high laryngectomy-free rate was achieved with the selection of responders by induction chemotherapy (5). Due to diversification of treatment methodologies with consideration of individual differences in sensitivity to chemo-radiation, delaying treatment selection until after induction chemotherapy is becoming more readily acceptable than definitive therapy. In the present study, selection of surgery or chemoradiotherapy based on induction chemoradiotherapy did not lower the survival rate and allowed for potential laryngeal preservation. This treatment method might be particularly useful against advanced laryngeal carcinoma. Further studies on induction chemotherapy with the aim of laryngeal preservation are warranted.

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Conflict of interest statement

None declared.

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Original Article

Stereotactic body radiotherapy for patients with small hepatocellular carcinoma ineligible for resection or ablation therapies

Tomoki Kimura,[1] Hiroshi Aikata,[2] Shigeo Takahashi,[1,3] Ippei Takahashi,[1] Ikuno Nishibuchi,[1] Yoshiko Doi,[1] Masahiro Kenjo,[1] Yuji Murakami,[1] Yohji Honda,[2] Hideaki Kakizawa,[4] Kazuo Awai,[4] Kazuaki Chayama[2] and Yasushi Nagata[1]

[2]Department of Medicine and Molecular Science, Division of Frontier Medical Science, Programs for Biomedical Research, Departments of [1]Radiation Oncology and [4]Diagnostic Radiology, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, and [3]Department of Radiation Oncology, Kagawa University Hospital, Kagawa, Japan

Aim: To evaluate the efficacy and safety of stereotactic body radiotherapy (SBRT) in patients with small hepatocellular carcinoma (HCC) who were ineligible for resection or ablation therapies.

Methods: Overall, 65 patients with 74 HCC (median tumor size, 16 mm) were enrolled. They were treated at the prescribed dose of 48 Gy in four fractions at the isocenter. Child–Turcotte–Pugh (CTP) scoring was used to classify 56 and nine patients into classes A and B, respectively. Local progression was defined as irradiated tumor growth on a dynamic computed tomography follow up. The median follow-up period was 26 months. Tumor responses were assessed according to the modified Response Evaluation Criteria in Solid Tumors. Treatment-related toxicities were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0.

Results: The 2-year overall survival, progression-free survival and local control rates were 76.0% (95% confidence interval [CI], 65.4–86.7%), 40.0% (95% CI, 27.6–52.3%) and 100% (95% CI, 100%), respectively. At 6–12 months after SBRT, grade 3 or higher toxicities was observed in 15 (23.1%) patients. The incidence of grade 3 or higher toxicities was higher in CTP class B than in class A ($P = 0.0127$).

Conclusion: SBRT was effective and relatively safe for patients with small HCC who were ineligible for resection or ablation therapies.

Key words: hepatocellular carcinoma, stereotactic body radiotherapy, transarterial chemoembolization

INTRODUCTION

ACCORDING TO THE latest Japanese survey in 2009, hepatocellular carcinoma (HCC) was the third most common cause of cancer-related death.[1] HCC is closely associated with hepatitis B or C viral infections and the increasing prevalence of viral infections has led to an increased incidence of HCC. Curative therapy for small HCC involves resection or transplantation surgery.[2–4] However, because of liver dysfunction, underlying cirrhosis or the presence of multifocal tumors arising from viral infection, only 10–30% of patients who initially present with HCC are eligible for surgery.[5] For such patients, locoregional therapies such as ablative therapies or transarterial chemoembolization (TACE) are recommended.[2–4] Ablative therapies, such as radiofrequency ablation (RFA) and percutaneous ethanol injection are considered to be safe, effective and reliable treatments for small HCC,[6,7] however, they are limited by ultrasonographically invisible HCC or tumors located near large vessels and in deep liver layers. TACE has been used widely and is reported to be effective in patients with any type of

Correspondence: Dr Tomoki Kimura, Department of Radiation Oncology, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima City, 734-8551, Japan. Email: tkkimura@hiroshima-u.ac.jp

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HCC, regardless of tumor size, location or number.[8,9] However, TACE is not the first-line treatment option for small HCC in several guidelines.[2–4,10]

Radiotherapy, a locoregional therapy, can be considered as an alternative to ablation and TACE when these therapies have failed.[1] Stereotactic body radiotherapy (SBRT), which delivers high radiation doses to focal HCC, has particularly helped to avoid radiation-induced liver damage. Several studies have reported good treatment outcomes with SBRT for HCC with or without TACE,[11–15] and radiation therapy experiences with HCC have rapidly increased during the past decade.[16] However, according to the European Association for the Study of the Liver/European Organization for Research and Treatment of Cancer Clinical Practice Guidelines, detailed radiation therapy data, including SBRT for HCC, is insufficient to determine efficacy and safety.[4] Our single institution study aimed to evaluate the efficacy and safety of SBRT for HCC patients who were ineligible for resection or ablation therapies.

METHODS

Patient eligibility

FROM DECEMBER 2008 to April 2013, 77 patients with 93 tumors underwent SBRT at Hiroshima University Hospital. The following inclusion criteria for curative SBRT were used: (i) over 20 years old; (ii) an Eastern Cooperative Oncology Group Performance Status (PS) of 0–2; (iii) Child–Turcotte–Pugh (CTP) class A or B; (iv) less than three HCC nodules, each up to 50 mm in diameter without portal venous thrombosis or extrahepatic metastases; (v) inoperability because of poor general condition or surgery refusal; and (vi) unsuitability for RFA because of tumor location (on the liver surface, particularly high risk of pneumothorax, and near the porta hepatis), tumor invisibility on ultrasonography or bleeding tendencies (platelet count, ≤50 000/mL; prothrombin activity, ≤50%). The study protocol was approved by the Human Ethics Review Committee of Hiroshima University and a signed consent form was obtained from each subject.

Hepatocellular carcinoma was diagnosed by its characteristic appearance of early arterial phase enhancement and portal venous phase hypodensity, which were revealed in most patients by dynamic computed tomography (CT) or combined angiography CT. However, HCC was histologically diagnosed in eight patients in whom these CT appearances were not observed.

Treatment procedure

Stereotactic body radiotherapy was performed according to a 3-D conformal method in which a single high dose was delivered to the tumor. Respiratory motion was coordinated by voluntary breath-holding at the end-inspiratory phase with Abches (APEX Medical, Tokyo, Japan), a device that allows patients to control their chest and abdomen respiratory motion. For simulations, dynamic CT scans (Lightspeed QX/I; GE Medical Systems, Waukesha, WI, USA), including the non-contrast enhancement, arterial, portal and venous phases, were performed by giving a bolus injection of non-ionic iodinated contrast material (100 mL at a rate of 3 mL/s). Arterial phase CT volume data were transferred to a 3-D treatment planning system (Pinnacle^3 ver. 9.0; Phillips Medical Systems, Fitchburg, WI, USA). Gross tumor volume (GTV) was defined as the tumor volume containing the remains of iodized oil from TACE and early enhancement in the arterial phase of dynamic CT. The clinical target volume margin was usually defined as 0–5 mm around the GTV. A planning target volume (PTV) margin of 5–8 mm, including the respiratory motion reproducibility and setup error, was usually added. Eight non-coplanar ports were selected in all patients, including beam direction that avoided the critical organs, if possible. The prescribed doses and fractionations were evaluated at the isocenter.

The SBRT dose and fractionation schedule was selected depending on tumor location. A total dose of 48 Gy in four fractions was selected for peripherally located HCC, and that of 60 Gy in eight fractions was selected for centrally located HCC that was located within 5 mm of the major vessels, such as the aorta, portal vein and inferior vena cava. For HCC that was close to the gastrointestinal tract, decreased dose/fractionations were selected to maintain dose constraints of the gastrointestinal tract (30 Gy in four fractions of ≤1 cc).

Beams of 6–10 MV photons were delivered from a linear accelerator (CLINAC 2300 C/D or iX; Varian Medical Systems, Palo Alto, CA, USA).

Before SBRT, patients underwent TACE with iodized oil (Lipodol; Guerbet Japan, Tokyo, Japan), if they agreed. A coaxial microcatheter was selectively inserted into the hepatic feeding artery of a segment or subsegments containing the target tumor. Anticancer chemotherapies, such as cisplatin (Randa; Nippon Kayaku, Tokyo, Japan; 7–70 mg/body at a concentration of 10 mg/mL) or miriplatin (Miriplatin Hydrate; Dainippon Sumitomo Pharma, Tokyo, Japan;

20–80 mg/body at a concentration of 20 mg/mL) were mixed with iodized oil and administrated by injecting the drug into the hepatic artery that fed a target tumor segment or subsegments. A small amount of gelatin sponge particles was used to induce embolization until the feeding artery flow was markedly decreased.

Evaluation

All patients were examined monthly, and follow-up dynamic CT or magnetic resonance imaging (MRI) was performed every 3 months after SBRT completion. In addition, serum HCC-specific tumor markers were investigated every 2 months. If the tumor marker levels were significantly increased, additional dynamic CT or MRI was performed. Tumor responses were assessed according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST), with accounting of tumor necrosis recognized by non-enhanced areas.[17] The target lesion response was only evaluated by these criteria in this study. Local tumor progression was defined as progressive disease in mRECIST and local control was defined as free of local progression. Treatment-related toxicities were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0.

Statistical methods

Univariate analyses using the Mantel–Haenszel χ^2-test or Student's *t*-test and multivariate analyses using the logistic regression were performed to determine statistical significance of differences in responses. The Kaplan–Meier method was used to calculate the overall survival, progression-free survival and local control rates. StatMate for Windows (version 4.01; ATMS, Tokyo, Japan) was used to perform all statistical analyses. Statistical significance was defined as $P < 0.05$.

RESULTS

Patient characteristics

OF 77 PATIENTS with 93 tumors who underwent SBRT, 65 patients with 74 lesions who received 48 Gy in four fractions were analyzed. Twelve patients with 19 lesions, including nine patients with 11 centrally located HCC who were administrated 60 Gy in eight fractions, and three patients with eight lesions who had dose constraints for gastrointestinal tract exposure, were excluded from analysis (Fig. 1). The patients' clinical characteristics are summarized in Table 1. The majority of patients previously underwent surgery or ablation therapies, and SBRT was recommended when these options were limited by technical difficulties or if the patient was inoperable or refused resection. The reasons behind contraindications for resection and ablation therapy are summarized in Table 2. Before SBRT, 60 patients with 68 HCC had undergone TACE with iodized oil. The median time interval between TACE and SBRT was 1 month (range, 1–31). The interval was 1–2 months in most patients. However, in two patients it was 7 and 31 months; these patients were initially treated with TACE because one patient was elderly with complications and the other initially wanted TACE treatment alone. We defined "untreated patients" as patients

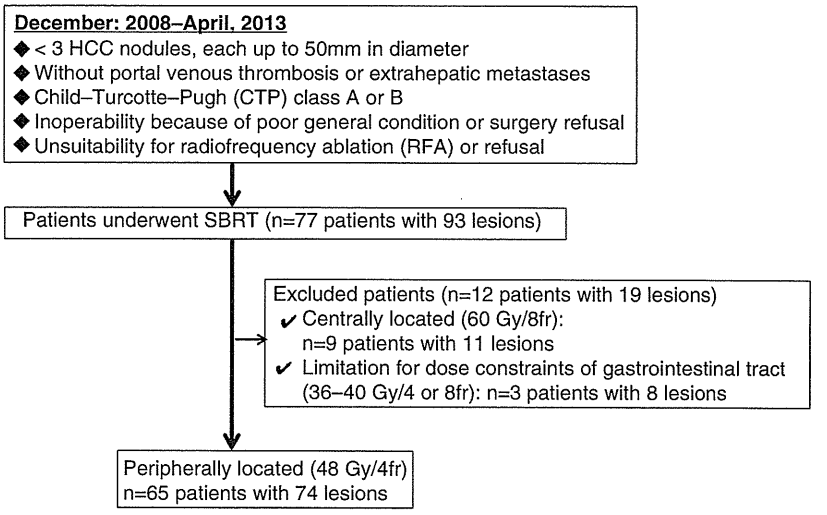

Figure 1 Treatment selection. Of 77 patients with 93 tumors who underwent stereotactic body radiotherapy, 12 patients with 19 lesions were excluded from analysis, including nine patients with 11 centrally located hepatocellular carcinomas who received 60 Gy in eight fractions and three patients with eight lesions who had dose constraints for the gastrointestinal tract.

Table 1 Patients background

Sex		Tumor location	
Male	44 patients	S1	0 lesions
Female	21 patients	S2	1 lesion
Age, years	49–90 (median, 73)	S3	5 lesions
Tumor size	5–54 mm (median, 16 mm)	S4	12 lesions
Performance status		S5	8 lesions
0	61 patients	S6	10 lesions
1	4 patients	S7	17 lesions
Type of viral infection		S8	21 lesions
HBV	5 patients	UICC stage (7th)	
HCV	54 patients	T1N0M0	51 patients
Alcoholic	4 patients	T2N0M0	14 patients
Others	2 patients	BCLC stage	
Child–Pugh class		Stage 0	37 patients
A	56 patients	Stage A	28 patients
B	9 patients	Previous treatment	
Child–Pugh score		Resection	29 patients
5	43 patients	Radiofrequency ablation; RFA	16 patients
6	13 patients	Percutaneous ethanol injection; PEI	7 patients
7	5 patients	Transarterial chemoembolization; TACE	60 patients
≥8	4 patients	TACE alone	24 patients
		Untreated patients†	13 patients

BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization; UICC, International Union Against Cancer.
†Untreated patients were patients who underwent TACE following stereotactic body radiotherapy within 1–3 months without no other previous therapies.

who underwent TACE following SBRT within 1–3 months without no other previous therapies, such as surgery or ablative therapies. Thirteen patients (13/65: 20%) were included in this definition.

The median follow-up period at the time of evaluation was 26 months (range, 3–60).

Dosimetric factors

The median mean PTV dose was 47.5 Gy (range, 45.9–51.8), which is considered to be a good dose coverage to the PTV.

The median mean liver dose (MLD) was 7.1 Gy (range, 2.8–13.1), and the percentages of uninvolved liver volume (total liver minus PTV) exceeding 10 Gy (V10), 20 Gy (V20) and 30 Gy (V30) were 25.1% (range, 8.0–52.1%), 9.3% (range, 3.5–23.9%) and 4.8% (range, 1.3–10.8%), respectively.

Treatment outcomes

Tumor response rates according to mRECIST were evaluated at 0 to less than 3 months, 3 to less than 6 months, and 6 to less than 12 months after SBRT

Table 2 Reasons of contraindication for resection and ablation therapy

Contraindications for resection	
Insufficient postoperative liver function	27
Other comorbidities (heart failure, renal failure, brain infarction, COPD)	15
Old age (≥75)	12
Rejection	11
Contraindications for ablation therapy	
HCC adjacent to or invading main vessel or biliary system	18
HCC adjacent to intestine	1
HCC abutting the diaphragm	23
US invisible	7
Insufficient liver function of post-ablation therapy	5
Other comorbidities (heart failure, renal failure, brain infarction, COPD†)	6
Rejection	5

†One patient with severe COPD may develop pulmonary failure if pneumothorax was observed after RFA because of HCC abutting the diaphragm.
COPD, chronic obstructive pulmonary disease; HCC, hepatocellular carcinoma; US, ultrasonography.

Table 3 Target tumor response

	0–3 months	3–6 months	6–12 months
CR	31	55	72
PR	40	17	1
SD	3	2	1
PD	0	0	0
Total	74	74	74

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

completion. Table 3 shows the complete response (CR), partial response, stable disease and progressive disease numbers. The CR rate increased during longer follow-up periods. Figure 2 shows the dynamic CT appearance of a tumor response. Early arterial enhancement was more evident after 6 months, than that before SBRT; however, it gradually disappeared after 11 months.

Figure 3 shows the overall survival, progression-free survival and local control. During the follow-up period, 24 of the 65 patients died. The cause of death was cancer progression in 15, hepatic failure in two, upper gastrointestinal bleeding in one and liver-unrelated causes in six. The median overall survival period was 41 months, and the 1- and 2-year overall survival rates were 92.3% (95% confidence interval [CI], 85.8–99.7%) and 76.0% (95% CI, 65.4–86.7%), respectively. The 1- and 2-year progression-free survival rates were 63.6% (95% CI, 51.7–75.5%) and 40.0% (95% CI, 27.6–52.3%), respectively. The 1- and 2-year local control rates were both 100% (95% CI, 100%).

Treatment-related toxicities

Sixty patients underwent TACE before SBRT, and 17 patients (28.3%) experienced new grade 3 acute hematological toxicities after TACE. These spontaneous toxicities were cured before SBRT.

Table 4 shows the baseline and post-SBRT (0–3, 3–6 and 6–12 months after SBRT completion) liver toxicities that exceeded those of grade 3. A grade 4 decreased platelet count was observed in one patient. Grade 3 or 4 toxicities at the baseline and 0–3, 3–6 and 6–12 months after SBRT completion were observed in five (7.7%), 11 (16.9%), 13 (20.0%) and 15 (23.1%) patients, respectively. The incidence of grade 3 or higher toxicities was higher in class B than that in class A ($P = 0.0127$); however, there were no significant dosimetric factors (MLD, ≥5 Gy vs <5 Gy, $P = 0.7471$; liver V20, ≥15 Gy vs <15 Gy, $P = 0.1673$).

No patient experienced gastrointestinal toxicity.

Prognostic factors

Table 5 shows the univariate and multivariate analyses of overall and progression-free survival. CTP (class A), tumor–node–metastasis (TNM) stage (T1N0M0), adverse effects (≤grade 2) were significant prognostic factors of longer overall survival in the univariate analysis. These factors were also significant prognostic factors of longer overall survival in the multivariate analysis. In addition, Barcelona Clinic Liver Cancer (BCLC) stage (stage 0), TNM stage (T1N0M0) and greatest tumor dimensions (<20 mm) were significant prognostic factors of progression-free survival in the univariate analysis, although significant factors were not identified in the multivariate analysis.

DISCUSSION

THIS STUDY DEMONSTRATED excellent local control for patients with small HCC (median diameter, 16 mm) who were ineligible for resection or

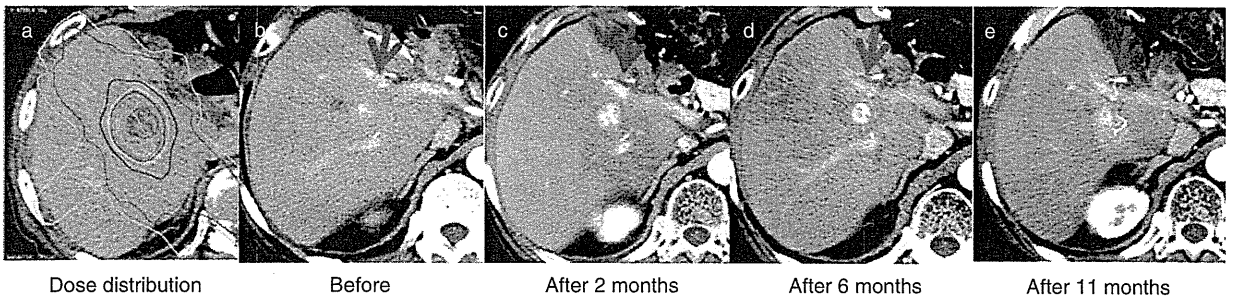

Figure 2 Dynamic computed tomographic appearance of tumor responses (arterial phase). (a) Dose distribution (48 Gy/4 fractions). (b) Before stereotactic body radiotherapy (SBRT), early arterial enhancement is visible (red arrow). (c) After two and (d) after 6 months, early arterial enhancement is more evident than before stereotactic body radiotherapy (red arrow). (e) After 11 months, enhancement remains, although the tumor is shrinking (red arrow).

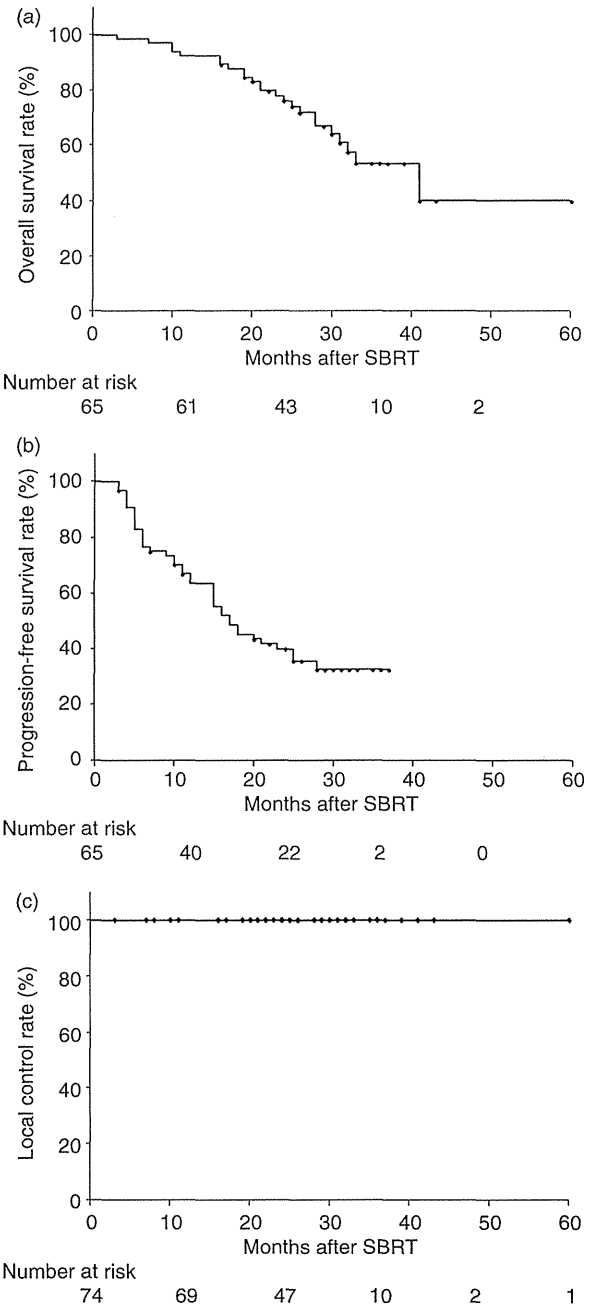

Figure 3 Treatment results of stereotactic body radiotherapy (SBRT) for hepatocellular carcinoma. (a) Overall survival rates. The 1- and 2-year overall survival rates were 92.3% and 76.0%, respectively. (b) Progression-free survival rates. The 1- and 2-year progression-free survival rates were 63.6% and 40.0%, respectively. (c) Local control rates. The 1- and 2-year local control survival rates were both 100%.

ablation therapies. Several studies have reported good treatment outcomes with SBRT for HCC with or without TACE using several doses/fractionations.[11–15] Table 6 summarizes several reports providing SBRT for HCC treatment results. The doses/fractionations ranged 24–60 Gy per three to six fractions. In addition, most patients received previous treatment including resection, ablative therapies and TACE. Bujold *et al.* reported a phase I/II trial of SBRT (median dose, 36 Gy in six fractions) and the 1-year local control rate was 87% (95% CI, 78%–93%) in 102 patients with locally advanced HCC that were BCLC stages A–C (stage C, 65.7%).[11] In the other studies, for small HCC with tumor size of between 20–30 mm, the local control rate was approximately 90% at 2 years and 65–90% at 3 years, which were also excellent results. These results indicate the possibility of achieving local control for HCC, including advanced cases. In these studies, some patients underwent TACE before SBRT. TACE is the standard therapy in patients who are ineligible for resection or ablation therapies; however, the treatment results are unsatisfactory because of several limitations such as incomplete necrosis due to hypovascularity, dual blood supply around the HCC capsule, multiple collateral feeding circulation and others.[8] According to a Japanese nationwide survey during 2004 and 2005, the 3-year overall survival rate of patients with solitary HCC was 54.6%.[18] On the other hand, Takayasu *et al.* reported excellent 1- and 3-year overall survival rates of 93% and 72% among 836 patients with T1N0M0, and 90% and 60% of 2070 patients with T2N0M0 who underwent TACE as an initial treatment, respectively.[9] However, this study may have been influenced by selection bias because these patients were selected from the following specific criteria applied to 60 773 patients who underwent TACE from 2000 to 2005 in Japan: initial treatment was TACE. Kang *et al.* reported an excellent local control rate (2-year, 94.6%) with SBRT for inoperable HCC as a local salvage treatment after incomplete TACE and concluded that SBRT plus TACE was promising.[14] They suggested several theoretical advantages of combined SBRT and TACE, such as tumor shrinkage, the remaining lipiodol as a target for image-guided radiotherapy and enhanced sensitivity to irradiation. In the present study, most patients underwent TACE before SBRT and excellent local control was achieved. However, whether this combined therapy is superior to TACE alone is unknown because of the lack of a phase III study.

Although most patients were ineligible for resection or RFA because of poor liver function, complications

Table 4 Grade 3 or 4 treatment-related toxicities

Toxicity (*n*)	Baseline (*n* = 65)	0–3 months (*n* = 65)	3–6 months (*n* = 64)	6–12 months (*n* = 64)
Elevated total bilirubin	0	1	2	2
Elevated AST/ALT	0	2	2	2
Decreased platelet count	5	8	9	10†
Ascites	0	1	2	4
Other toxicity‡	0	1	2	5
Total	5	11	13	15

†Includes one patient of grade 4.
‡Includes elevated γ-glutamyltransferase, hepatic encephalopathy and portal vein thrombosis.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

and advanced age, the overall survival rate was relatively good. CTP (class A), TNM stage (T1N0M0) and adverse effects (≤grade 2) were significant prognostic factors of longer overall survival in the univariate and multivariate analyses. From these results, SBRT may improve overall survival in a limited number of patients, such as those with early-stage disease and those who belong to CTP class A. However, the progression-free survival rate was not good (2-year, 40.0%). Factors such as BCLC stage (stage 0), TNM stage (T1N0M0) and greatest tumor dimensions (<20 mm) were significant in the univariate analysis, which indicated that the incidence of intrahepatic recurrence increased with tumor size. Compared with

Table 5 Prognostic factors; univariate analysis and multivariate analysis

Prognostic factor		2-year OS (%)	UVA *P*	MVA *P*	2-year PFS (%)	UVA *P*	MVA *P*
Sex	Male	76.6	0.9750	–	31.9	0.3643	–
	Female	75.1			55.9		
Age, years	≥70	79.5	0.1351	–	41.4	0.8251	–
	<70	70.0			37.7		
CTP class	A	81.5	0.0217	0.00164	42.4	0.2847	–
	B	44.4			25.0		
Viral infection	HBV or HCV	79.1	0.2402	–	39.2	0.4363	–
	NBNC	33.3			33.3		
BCLC stage	0	76.1	0.4083	–	51.2	0.0114	0.5964
	A	74.5			24.9		
TNM stage	T1N0M0	79.7	0.0285	0.0293	48.2	0.0005	0.0802
	T2 or 3bN0M0	61.9			9.5		
Greatest tumor dimensions	≥20 mm	75.0	0.3281	–	24.0	0.0225	0.1527
	<20 mm	77.1			51.6		
GTV	≥10 cc	83.3	0.7911	–	16.7	0.1040	–
	<10 cc	75.3			42.4		
Adverse effects	≥Grade 3	51.3	0.0003	0.0132	31.8	0.6116	–
	≤Grade 2	83.4			42.1		
Diagnosis history	Initial	75.5	0.7874	–	61.5	0.1690	–
	Recurrence	76.2			34.4		
Previous treatment (TACE alone)	Yes	72.1	0.7262	–	44.4	0.3488	–
	No	78.5			36.7		

BCLC, Barcelona Clinic Liver Cancer; CTP, Child–Turcotte–Pugh; GTV, gross tumor volume; HBV, hepatitis B virus; HCV, hepatitis C virus; MVA, multivariate analysis; NBNC, non-hepatitis B/non-hepatitis C; OS, overall survival; PFS, progression-free survival; TACE, transcatheter arterial chemoembolization; UVA, univariate analysis.

Table 6 Other reports

Author/year	*n*	Median tumor size (mm)	BCLC stage C (%)	Previous treatment (%)	Dose/fraction (Gy/fr)	Prescription	Local control rate	Overall survival rate	Toxicity ≥ grade 3 (%)
Bujold, 2013, Canada[11]	102	72	65.7	52	24–54 Gy/6 fr	N.A.	87.0% (1 y)	34.0% (2 y)	30
Andolino, 2011, USA[12]	60	31	N.A.	N.A.	24–48 Gy/3–5 fr	80% isodose	90% (2 y)	67% (2 y)	35
Kwon, 2010, Korea[13]	42	N.A.	0	81	30–39 Gy/3 fr	70–85% isodose	67.5% (3 y)	58.6% (3 y)	2.4
Kang, 2012, Korea[14]	47	29	17	100	42–60 Gy/3 fr	70–80% isodose	94.6% (2 y)	68.7% (2 y)	10.7
Sanuki, 2013, Japan[15]	185	26	N.A.	68.1	40 or 35 Gy/5 fr	70–80% isodose	91.0% (3 y)	70.0% (3 y)	13
Current study, Japan	65	16	0	98.4	48 Gy/4 fr	Isocenter	100% (2 y)	76.0% (2 y)	23.1

BCLC, Barcelona Clinic Liver Cancer; N.A., not available; y, years.

other modalities, such as RFA, the intrahepatic recurrence rate in this study was relatively high, despite excellent local control. Tateishi *et al.* reported the treatment results of RFA in 664 patients (319 naïve patients, 345 non-naïve patients) with HCC, in which the 2-year cumulative tumor recurrence rate was 43.4%, including a 2-year local recurrence rate of 2.4%.[9] The results of Tateishi *et al.*'s study indicated that approximately 40% of patients, even though approximately half of the population consisted of naïve patients, developed intrahepatic recurrence within 2 years after RFA. In our study, most patients (80%) were non-naïve and the median duration between initial treatment to SBRT was 23 months (range, 0–144), which we considered as one of the reasons of the high intrahepatic recurrence rate. As another reason, the long-term existence of early arterial enhancement after SBRT may indicate the potential of metastatic lesions, although no enlarged area was noted on CT. Liver toxicities exceeding grade 3 were observed in 21 patients (23.1%) at 6–12 months after SBRT, despite including five patients with decreased platelet counts before SBRT. The frequency of liver toxicities exceeding grade 3 was similar to those in other reports, as shown in Table 6. In our study, the grade 3 or higher toxicity incidence was also higher in CTP class B compared with that in class A ($P = 0.0127$). Lee *et al.* in their experience of 131 patients with HCC who received 3-D conformal radiotherapy, reported that the incidence of liver complications significantly increased in patients with CTP class B ($P = 0.044$), and indicated that the CTP class may be a useful parameter to predict toxicity.[19] On the other hand, there were no significant dosimetric factors such as MLD or liver V20 in our results. To avoid hepatic toxicity, the dose-volume limits guidelines recommended by the Quantitative Analyses of Normal Tissue Effects in the Clinic for normal liver dose constraints of 3–6 fractions of SBRT have been offered. For example, the MLD (liver – GTV) should receive less than 13–18 Gy, or that an MLD of 700 mL or higher of the normal liver should receive 15 Gy or lower.[20] One of the reasons that no significant dosimetric factors were observed in our study was that the MLD in our study was lower than that of the above recommendations (7.1 Gy; range, 2.8–13.1).

Because of its retrospective nature, we are aware that this study has certain limitations, such as the single institutional design and short follow-up periods. Moreover, SBRT still can be considered as an alternative to surgery, ablation and TACE when these therapies fail. Most of our patients previously underwent these

therapies, which could have influenced the SBRT treatment results.

In conclusion, SBRT appeared to be effective and relatively safe for patients with small HCC who were ineligible for resection or ablation therapies.

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CASE REPORT

Radiation-induced pyogenic vertebral osteomyelitis after re-irradiation for para-aortic lymph node metastases in a patient with cervical cancer

Ippei Takahashi · Yuko Kaneyasu · Yasuko Yamamoto · Takuro Okumura · Masahiro Kenjo · Tomoki Kimura · Yuji Murakami · Yasushi Nagata

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Abstract This article describes a case of radiation-induced pyogenic vertebral osteomyelitis (PVO) after re-irradiation for para-aortic lymph node metastases in a patient with cervical cancer. A 62-year-old woman was admitted to our hospital with fever and severe back pain 4 months after re-irradiation (initially 56 Gy plus a secondary 50 Gy) of the para-aortic lymph nodes at the level of the fourth lumbar vertebra. *Streptococcus* group G was detected in a vertebral biopsy specimen and blood cultures. The patient was diagnosed with radiation-induced PVO, and intravenous antibiotic therapy was initiated. Symptoms improved significantly 2 weeks later. The patient was healthy with no evidence of relapse 5 years after the second course of radiotherapy.

Keywords Pyogenic vertebral osteomyelitis · Radiation-induced · Re-irradiation · Cervical cancer · Radiotherapy

Introduction

Pyogenic vertebral osteomyelitis (PVO; also called pyogenic spondylitis or vertebral osteomyelitis) refers to an infection of the vertebral body. PVO after radiation therapy is extremely rare. Several studies have reported osteoradionecrosis and osteomyelitis of the cervical spine resulting from radiotherapy (RT) for primary head and neck cancers. However, to the best of our knowledge, there are no reports of PVO after radiation for malignancies in the abdomen and pelvis. Here, we report a case of PVO associated with re-irradiation for para-aortic lymph node metastases in a patient with cervical cancer.

I. Takahashi (✉) · Y. Kaneyasu · T. Okumura · M. Kenjo · T. Kimura · Y. Murakami · Y. Nagata
Department of Radiation Oncology, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima City 734-8551, Japan
e-mail: ippei@hiroshima-u.ac.jp

Y. Yamamoto
Department of Obstetrics and Gynecology, Chuden Hospital, Hiroshima, Japan

Case report

The patient was a 62-year-old woman (gravida 4, para 2) with squamous cell carcinoma of the uterine cervix. Pelvic examination revealed a mass greater than 6 cm on the posterior wall of the cervix, with obvious parametrial involvement but no pelvic sidewall involvement. The tumor had expanded to less than 1/3 of the vagina. Enlarged left supraclavicular lymph nodes measuring between 1 and 2 cm were palpable. Computed tomography (CT) revealed multiple para-aortic and supraclavicular lymph node metastases (Fig. 1a); hence, the FIGO stage was initially determined as IVB. The patient's performance status (PS) was 1, body weight was 48 kg, height was 165 cm, and body mass index (BMI) was 17.6. Her medical history was uneventful. On the basis of PS and BMI, the patient was not suitable for concurrent chemoradiotherapy (CCRT); therefore, she received RT alone.

In August 2006, the patient received external beam radiotherapy (EBRT) to the entire pelvis and para-aortic lymph node chain (56 Gy/28 fractions) (Fig. 1b) and supraclavicular lymph nodes (57.5 Gy/23 fractions). In this case, a "gap calculation" between the pelvic and para-aortic fields was performed to avoid overlap and excessive dose to the small intestines. High-dose intracavitary

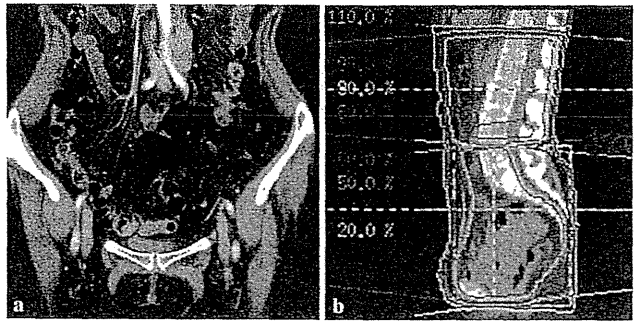

Fig. 1 a Contrast-enhanced computed tomography image before treatment. *Arrows* indicate the swollen para-aortic lymph nodes. b Dose–distribution chart for the initial external beam radiotherapy (EBRT) plan. The gap between the entire pelvic and para-aortic fields was unchanged during the initial EBRT (*arrow*)

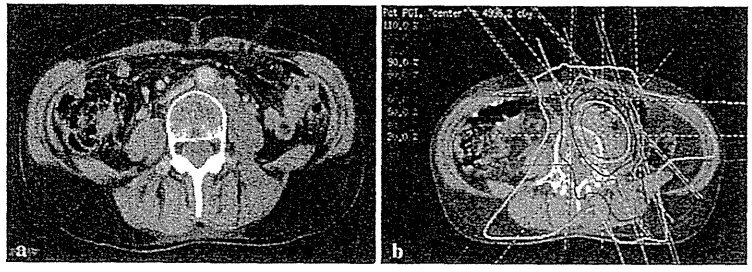

Fig. 2 a Contrast-enhanced computed tomography image before the second external beam radiotherapy (EBRT) treatment. The *arrow* indicates the regrowing para-aortic lymph node. b Dose–distribution chart for the second EBRT plan

brachytherapy combined with EBRT was administered at 18 Gy/3 fractions. Three adjuvant chemotherapy courses of weekly paclitaxel (60 mg/m^2, day 1, 8, 15, 3 courses) were administered after RT. A complete response was obtained at 1 month after RT by internal examination of the primary lesion and supraclavicular lymph nodes. A CT scan 6 months after the initial treatment also showed a complete response of the primary tumor and metastatic supraclavicular lesions, but one para-aortic lymph node at the level of the fourth lumbar vertebra (L4) remained (Fig. 2a). In March 2007, she received a second treatment of EBRT (50 Gy/25 fractions) (Fig. 2b).

In July 2007, she consulted us because of fever and severe back pain. On examination, her temperature was 37.8 °C and tenderness of the spine on percussion was detected at the fourth and fifth lumbar vertebra. A blood test revealed an inflammatory response with a C-reactive protein (CRP) level of 18.8 mg/dL, white blood cell count of 7,800/μL, and an elevated erythrocyte sedimentation rate (ESR). She was immediately hospitalized and was administered pain management with codeine phosphate. Tests for infection, such as blood culture, sputum culture, and viral tests, were all negative on admission. Similarly, imaging studies presented no significant findings. Thereafter, the fever and back pain continued intermittently for 1 month.

Magnetic resonance imaging (MRI) re-examination was performed in August 2007, 2 months after the onset of symptoms (Fig. 3). As shown in Fig. 3, the high-dose region almost corresponded to the signal intensity-changed areas on the MRI scan. Because infection of the vertebral body was suspected, she received CT-guided biopsy at the L4 level (Fig. 4). As a result, *Streptococcus* group G was detected in the biopsy specimen and blood cultures collected the same day.

The patient was diagnosed with radiation-induced PVO, and intravenous antibiotic therapy (ampicillin/sulbactam, 3 g/day) was initiated. Her symptoms, fever, and back pain improved significantly 2 weeks after treatment. Her CRP level had decreased to within the normal range, and no