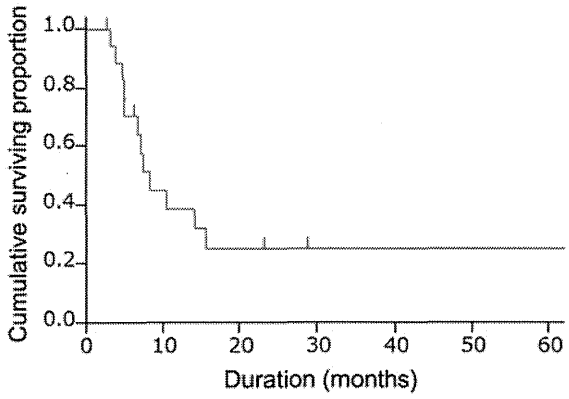

Figure 1. *Overall survival in 17 cases 5-year survival rate was 29.6% (13/17) and the median survival time was 15.2 months.*

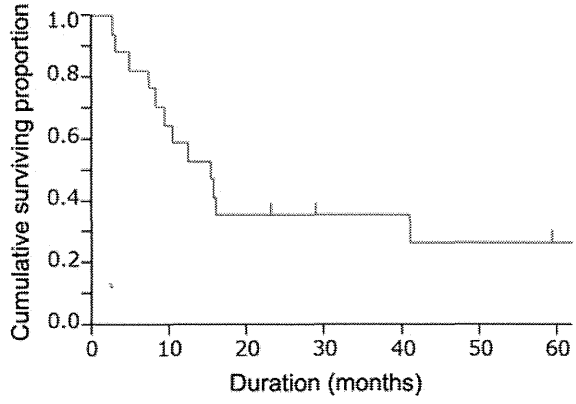

Figure 2. *Progression-free survival in response 14 cases 5-year survival rate was 41.4% (5/14) and the median survival time was 26.8 months.*

There have been some reports of chemoradiation for T4 esophageal cancer using 5-FU plus cisplatin. Ohtsu *et al.* reported in a trial of 21 patients that the 3-years survival rate was 23% and the median survival time was nine months; there were four treatment-related deaths (20). The Japan Clinical Oncology Group (JCOG) reported that the median survival time was 305.5 days, and the 2-year survival rate was 31.5% in a trial with 60 patients. As far as toxicity was concerned, one toxicity-related death occurred. The major form of toxicity exceeding grade 2 was found to be myelosuppression; grade 4 toxicity was observed in five patients (21). In our study, the recurrent cases received second-line chemotherapy with/without salvage surgery. Although our study can not be compared with the study described above, it was a good outcome that five-year overall survival was 29.6%, median survival time was 15.2 months, response rate was 76.4% and disease control rate was 82.4%.

TS-1 has not yet received approval for esophageal cancer by the Ministry of Health, Labor and Welfare in Japan. However, TS-1 has had favorable effects for many kinds of cancers, as mentioned above. A phase I/II study of definitive chemoradiotherapy for esophageal cancer using TS-1 plus cisplatin and concurrent radiation has finished the registration phase and the data have been analyzed by JCOG (22).

When the treatment-related death occurred, the case was valuated by the Safety Review Committee in this trial. The recommendation was that the dose of docetaxel recommended should be reduced from 30 mg/m^2 to 20 mg/m^2, because the response did not differ among each dosage in phase I but there was a possibility that radiation-induced pneumonitis was related to docetaxel (23, 24).

The incidence of severe acute/late radiation-induced pneumonitis was approximately 10% with cisplatin-based second-generation chemotherapy and with radiation (23, 24).

Table II. *Adverse events. (CTCAEv4.0).*

	Grade (n)					
	1	2	3	4	5	Grade 3-5 (%)
Leukocytopenia	0	4	2	1	0	17.6
Neutrophilia	1	4	2	0	0	11.7
Ttronbocytopenia	0	1	1	0	0	5.8
Hemoglobin	0	2	1	0	0	5.8
General fatigue	2	4	0	0	0	0
Esophagitis	2	5	2	0	0	11.7
Fever	1	1	0	0	0	0
Pneumonitis	0	2	0	1	0	5.8
Sepsis	0	0	0	0	1	5.8

Segawa *et al.* reported radiation-induced pneumonitis was severe in the group using docetaxel plus cisplatin with concurrent radiation compared with the group using mitomycin, vindesine and cisplatin in non-small-cell lung cancer (25). Moreover, some studies reported that the incidence of pneumonitis tended to be higher in elderly patients (70 years or older) (26-28). In our study, the treatment-related death was the oldest patient was 79 years - old. Other toxicities including myelosuppression and esophagitis might be reported to increase in elder patients (26, 27), therefore when treating elderly patients, great care should be taken if using this regimen.

TS-1 is the useful anticancer drug which is possible to be administered by oral intake. The response rate in a single-agent for gastric cancer was 44% in phase II study (29). Gimeracil, one component of TS-1, is a dihydropyrimidine dehydrogenase inhibitor used to maintain the concentration

of 5-FU in the blood. This is convenient to be administered and to be effective as same as infusion of 5-FU (10).

Recently, there have been some reports that gimeracil enhanced the efficacy of radiation for cancer by inhibiting rapid repair of X-ray-induced DNA damage in tumors. From this point of view, chemoradiotherapy using TS-1 may be useful in treating patients with locally advanced cancers whose disease progression is difficult to control (12, 13).

In conclusion, chemoradiation using docetaxel plus TS-1 concomitant radiation leads to a high response rate and high local disease control rate. This method has the benefit of no need for high volume hydration and continuous infusion of anti-cancer drug. However, elderly patients must be carefully-monitored to avoid toxicity such as pneumonitis.

Conflicts of Interest

All Authors have nothing to declare.

References

1 Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D: Global cancer statistics. CA Cancer J Clin *61*: 69-90, 2011.

2 Jemal A, Siegel R, Ward E, Hao Y, Xu J and Thun MJ: Cancer statistics. CA Cancer J Clin *59*: 225-249, 2009.

3 Herskovic A, Martz K, Al-Sarraf M, Leichman L, Brindle J, Vaitkevicius V, Cooper J, Byhardt R, Davis L and Emami B: Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med *326*: 1593-1598, 1992.

4 Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA, Al-Sarraf M, Byhardt R, Russell AH, Beitler JJ, Spencer S, Asbell SO, Graham MV and Leichman LL: Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). JAMA *281*: 1623-1627, 1999.

5 Tishler RB, Norris CM Jr, Colevas AD, Lamb CC, Karp D, Busse PM, Nixon A, Frankenthaler R, Lake-Willcutt B, Costello R, Case M and Posner MR: A Phase I/II trial of concurrent docetaxel and radiation after induction chemotherapy in patients with poor prognosis squamous cell carcinoma of the head and neck. Cancer *95*: 1472-1481, 2002.

6 Choy H: Combining taxanes with radiation for solid tumors. Int J Cancer *90*: 113-127, 2000.

7 Mason KA, Hunter NR, Milas M, Abbruzzese JL and Milas L: Docetaxel enhances tumor radioresponse *in vivo*. Clin Cancer Res *3*: 2431-2438, 1997.

8 M Tsukuda, A Kida, M Fujii, N Kono, T Yoshihara, Y Hasegawa, M Sugita and Chemotherapy Study Group of Head and Neck Cancer: Randomized scheduling feasibility study of S-1 for adjuvant chemotherapy in advanced head and neck cancer. British Journal of Cancer *93*: 884-889, 2005.

9 Harada H, Omura K, Tomioka H, Nakayama H, Hiraki A, Shinohara M, Yoshihama Y and Shintani S: Multicenter phase II trial of preoperative chemoradiotherapy with S-1 for locally advanced oral squamous cell carcinoma. Cancer Chemother Pharmacol *71*: 1059-1064, 2013.

10 Maehara Y: S-1 in gastric cancer: a comprehensive review. Gastric Cancer *6*: 2-8, 2003.

11 Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A and Arai K: ACTS-GC Group. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med *357*: 1810-1820, 2007.

12 Fukushima M, Sakuramoto K, Sakata M, Nakagawa F, Saito H and Sakata Y: Gimeracil, a component of S-1, may enhance the antitumor activity of X-ray irradiation in human cancer xenograft models *in vivo*. Oncology Reports *24*: 1307-1313, 2010.

13 Takahi M, Sakata K, Someya M, Tauchi H, Iijima K, Matsumoto Y, Torigoe T, Takahashi A, Hareyama M and Fukushima M: Gimeracil sensitizes cells to radiation via inhibition of homologous recombination. Radiotherapy and Oncology *96*: 259-266, 2010.

14 Wada Y, Yoshida K, Suzuki T, Mizuiri H, Konishi K, Ukon K, Tanabe K, Sakata Y and Fukushima M: Synergistic effects of docetaxel and S-1 by modulating the expression of metabolic enzymes of 5-fluorouracil in human gastric cancer cell lines. Int J Cancer *119*: 783-791, 2006.

15 Hihra J, Yoshida K, Hamai K, Emi M, Yamaguchi Y and Wadasaki K: Phase I Study of Docetaxel (TXT) and 5-Fluorouracil (5-FU) with Concurent Radiotherapy in Patients with Advanced Esophageal Cancer. Anticancer Res *27*: 2597-2604, 2007.

16 Matsumoto H, Hirai T, Hirabayashi Y, Murakami H, Higashida M, Kawabe Y, Urakami A, Yamashita K, Hiratsuka J, Imajyo Y and Tsunoda T: A phase I/II study of docetaxel/TS-1 with radiation for esophageal cancer patients – step 1. Gan To Kagaku Ryoho *33*: 2021-2026, 2006 (Japanese).

17 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer *45*: 228-247, 2009.

18 National Cancer Institute. Common Terminology Criteria for Adverse Events v.3.0and v.4.0 (CTCAE). Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

19 Matsumoto H, Hirabayashi Y, Kubota H, Murakami H, Higashida M, Haruma K, Hiratsuka J, Nakamura M and Hirai T: A combined therapy with docetaxel and nedaplatin for relapsed and metastatic esophageal carcinoma. Anticancer Res *32*: 1827-1831, 2012.

20 Ohtsu A, Boku N, Muro K, Chin K, Muto M, Yoshida S, Satake M, Ishikura S, Ogino T, Miyata Y, Seki S, Kaneko K and Nakamura A: Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. J Clin Oncol *17*: 2915-2921, 1999.

21 Ishida K, Ando N, Yamamoto S, Ide H and Shinoda M: Phase II study of cisplatin and 5-fluorouracil with concurrent radiotherapy in advanced squamous cell carcinoma of the esophagus: a Japan Esophageal Oncology Group (JEOG)/Japan Clinical Oncology Group trial (JCOG9516). Jpn J Clin Oncol *34*: 615-619, 2004.

22 Shitara K and Muro K: Chemoradiotherapy for treatment of Esophageal Cancer in Japan: Current status and perspectives. Gastrointest Cancer Res *3*: 66-72, 2009.

23 Karasawa K, Katsui K, Seki K, Kohno M, Hanyu N, Nasu S, Muramatsu H, Maebayashi K, Mitsuhashi N, Haga S, Kimura T and Takahashi I: Radiotherapy with concurrent docetaxel for advanced and recurrent breast cancer. Breast Cancer *10*: 268-274, 2003.
24 Segawa Y, Kiura K, Takigawa N, Kamei H, Harita S, Hiraki S, Watanabe Y, Sugimoto K, Shibayama T, Yonei T, Ueoka H, Takemoto M, Kanazawa S, Takata I, Nogami N, Hotta K, Hiraki A, Tabata M, Matsuo K and Tanimoto M: Phase III trial comparing docetaxel and cisplatin combination chemotherapy with mitomycin, vindesine, and cisplatin combination chemotherapy with concurrent thoracic radiotherapy in locally advanced non-small-cell lung cancer: OLCSG 0007. J Clin Oncol *28*: 3299-3306, 2010.
25 Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, Katagami N and Ariyoshi Y: Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol *17*: 2692-2699, 1999.
26 Gridelli C, Langer C, Maione P, Rossi A and Schild SE: Lung cancer in the elderly. J Clin Oncol *10*: 1898-1907, 2007.
27 Rocha Lima CM, Herndon JE 2nd, Kosty M, Clamon G and Green MR: Therapy choices among older patients with lung carcinoma: an evaluation of two trials of the Cancer and Leukemia Group B. Cancer *94*: 181-187, 2002.
28 Takigawa N, Kiura K, Segawa Y, Hotta K, Tamaoki A, Tokuda Y, Nagata T, Watanabe K, Gemba K, Moritaka T, Horita N, Takeda H, Okimoto N, Takemoto M, Matsuo K, Shinkai T, Tabata M, Ueoka H, Kanazawa S and Tanimoto M: Benefits and adverse events among elderly patients receiving concurrent chemoradiotherapy for locally advanced non-small cell lung cancer: analysis of the Okayama Lung Cancer Study Group trial 0007. J Thorac Oncol *6*: 1087-1091, 2011.
29 Koizumi W, Kurihara M, Nakano S and Hasegawa K: Phase II study of S-1, a novel oral derivative of 5-fluorouracil, in advanced gastric cancer. For the S-1 Cooperative Gastric Cancer Study Group. Oncology *58*: 191-197, 2000.

Received March 12, 2014
Revised May 12, 2014
Accepted May 14, 2014

Int J Clin Oncol (2014) 19:437–444
DOI 10.1007/s10147-013-0580-3

ORIGINAL ARTICLE

Boron neutron capture therapy for advanced salivary gland carcinoma in head and neck

Teruhito Aihara · Norimasa Morita · Nobuhiko Kamitani · Hiroaki Kumada · Koji Ono · Junichi Hiratsuka · Tamotu Harada

Received: 6 March 2013 / Accepted: 29 May 2013 / Published online: 25 June 2013

Abstract
Purpose Boron neutron capture therapy (BNCT) is among the radiation treatments known to have a selective lethal effect on tumor cells. This study summarizes the tumor responses and the acute and late adverse effects of BNCT in the treatment of patients with both recurrent and newly diagnosed T4 salivary gland carcinoma.
Methods Two patients with recurrent cancer and 3 with newly diagnosed T4 advanced malignancy were registered between October 2003 and September 2007, with the approval of the medical ethics committees of Kawasaki Medical School and Kyoto University. BNCT was performed, in a single fraction using an epithermal beam, at Japan Research Reactor 4.
Results All patients achieved a complete response within 6 months of treatment. The median duration of the complete response was 24.0 months; the median overall survival time was 32.0 months. Three of the 5 patients are still alive; the other 2 died of distant metastatic disease. Open biopsy of the parotid gland after BNCT was performed in 1 patient and revealed no residual viable cancer cells and no serious damage to the normal glandular system. Although mild alopecia, xerostomia, and fatigue occurred in all patients, there were no severe adverse effects of grade 3 or greater.
Conclusions Our preliminary results demonstrate that BNCT is a potential curative therapy for patients with salivary gland carcinoma. The treatment does not cause any serious adverse effects, and may be used regardless of whether the primary tumor has been previously treated.

Keywords BNCT · Paraboronophenylalanine · 18F-BPA PET · Salivary gland carcinoma · Radio-resistant cancers

Introduction

Head and neck cancers (HNCs) account for approximately 10 % of all malignancies, and about 90 % of HNCs consist of squamous cell carcinoma. Salivary gland carcinomas are among the non-squamous cell carcinomas and may consist of either adenocarcinoma, mucoepidermoid carcinoma, or adenoid cystic carcinoma. These rare malignant epithelioid tumors account for less than 5 % of HNCs [1, 2].

Surgery represents the mainstay of treatment for small, well-localized, low-grade salivary gland carcinoma. The main drawback of surgery, especially for patients with advanced tumor stage (T-stage) malignancy (T3/T4), is the resultant deterioration in quality of life, given the many important physiological functions of the tissues involved and the cosmetic issues related to surgery. Patients with locally advanced cancer are often deemed

T. Aihara (✉) · N. Morita · T. Harada
Department of Otolaryngology Head and Neck Surgery, Kawasaki Medical School, Matsushima 577, Kurashiki 701-0192, Japan
e-mail: aiteru@med.email.ne.jp

T. Aihara · H. Kumada
Proton Medical Research Centre, University of Tsukuba, Tsukuba, Japan

N. Kamitani · J. Hiratsuka
Department of Radiation Oncology, Kawasaki Medical School, Kurashiki, Japan

K. Ono
Radiation Oncology Research Laboratory, Research Reactor Institute, Kyoto University, Osaka, Japan

inoperable because of technical issues related to the tumor extent and location. Patients with serious medical comorbidities may also be considered inoperable. Patients may refuse surgery because of the potential deterioration in quality of life or for other, personal reasons. These non-surgical patients are candidates for radiation therapy. Several authors have reported that a dose–response relationship may exist with radiotherapy and have described relatively favorable results with the sole use of radiation at a dose greater than 66 Grey (Gy) for the definitive treatment of T1–3 disease [3–5]. However, the results in patients with T4 disease are reportedly less favorable for both local control and overall survival [6]. Therefore, alternatives to surgery and to conventional radiation therapy are required for the primary treatment of locally advanced salivary gland cancer.

Boron neutron capture therapy (BNCT) is a form of high linear energy transfer (LET) radiation therapy. With this type of treatment, high radiation doses can be selectively delivered to tumor cells without causing serious damage to the normal surrounding tissue, utilizing the high boron 10 (10B) accumulation that occurs in the tumor. Clinical trials on the treatment of recurrent HNC, including recurrent salivary gland carcinoma, have been conducted using L-10B-para-boronophenylalanine (L-BPA) as a boron delivery agent for BNCT [7–9]. The median overall survival in these studies ranged from 12.0 to 13.5 months, and the 3-year overall survival rate was 31–39 %. BNCT was especially effective for patients with recurrent salivary gland carcinomas; their 3-year overall survival rate was 78 %. Therefore, BNCT has the potential to be a curative therapy for patients with locally advanced salivary gland carcinoma, both as secondary treatment and as initial treatment. This preliminary study summarizes the tumor responses and the acute and late phase reactions of normal tissue with BNCT in patients with recurrent and newly diagnosed T4 salivary gland carcinoma.

Methods and materials

Patient and tumor characteristics

The indications for the use of BNCT at our institution were as follows: (1) newly diagnosed or recurrent locally advanced (T3 and T4) cancers; (2) deepest part of the tumor within 5 cm of the skin surface; (3) a tumor/normal tissue (T/N) boron concentration ratio, obtained from fluorine-18-labeled fluoroboronophenylalanine positron emission tomography (FBPA-PET), greater than 2.5 [10]; (4) consent to perform BNCT from the patient and the patient's family; and (5) World Health Organization performance status 2 or less.

All study patients had proven salivary gland carcinoma by histopathological and/or cytological examination. Pretreatment evaluation consisted of a history and physical examination, complete blood count, biochemical analysis, chest radiography, computed tomography (CT) and/or magnetic resonance imaging of the head and neck, and [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET).

Patient and tumor characteristics, including tumor node metastasis (TNM) stage and time until recurrence, are summarized in Table 1. Two patients with recurrent cancer (Patients 1 and 2, recurrence group) and 3 with newly diagnosed T4 advanced malignancy (Patients 3–5, initial treatment group) were enrolled between October 2003 and September 2007 with the approval of the medical ethics committees of Kawasaki Medical School and Kyoto University and of the Nuclear Safety Bureau of the Japanese government. The T-stage in the recurrence group was considered to be the original, pretreatment stage. The mean patient age was 56.0 years (range 44–74 years) at the time of study entry. The median follow-up period was 30.4 months (range 22–38 months). The most predominant histology was adenoid cystic carcinoma. No patients showed evidence of neck disease or distant metastasis. Patient 1 had previously

Table 1 Patient and tumor characteristics

Patient	Tumor site	Age/sex	WHO PS	Histology	TNM	GTV (cm^3)	Previous treatment
1	Submandibular gland	54/F	1	ACC	rT4aN0M0	32.5	Submandibulectomy radiation (66 Gy, 2 Gy/Fx)*
2	Maxillary sinus	44/M	1	ACC	rT4bN0M0	115.0	Palliative surgery radiation (60 Gy, 2 Gy/Fx + 50 Gy, 10 Gy/Fx)**
3	Parotid gland	74/F	1	AC	T4aN0M0	42.1	None
4	Lachrymal sac	58/M	0	ACC	T4N0M0	23.1	None
5	Maxillary sinus	50/F	0	ACC	T4aN0M0	88.4	None

ACC adenoid cystic carcinoma, *AC* acinic cell carcinoma, *GTV* gross target volume, *TNM* tumor node metastasis, *WHO PS* World Health Organisation performance status

* This case recurred 10 years after initial treatment (T2N0M0 Stage II ACC)

** This case recurred 3 years after initial treatment (T4N0M0 Stage IV ACC)

received conventional radiation therapy (total dose, 66 Gy) after radical surgery. Patient 2 had previously received conventional radiation therapy (60 Gy), stereotactic radiotherapy (50 Gy), and palliative surgery. All patients in the initial treatment group refused surgery.

Treatment procedures and dose calculation

L-BPA in fructose solution was used as a boron delivery agent at a total dose of 500 mg/kg. An intravenous BPA drip infusion of 200 mg/kg per hour was started 2 h before neutron irradiation, with the flow reduced to 100 mg/kg per hour during treatment [11]. Patients were placed on the treatment table in a sitting or supine position, and their head position was fixed after confirming appropriate placement with positioning lasers. A neutron collimator, 10–15 cm in diameter, was constructed to shield normal tissue. Thermoluminescence dosimeters were attached to the skin surface involved in the irradiation field, and gold wires were placed inside the collimators for dosimetry. Venous blood samples were obtained every hour, between the start of BPA administration and the completion of treatment, in order to measure boron concentration by prompt γ-ray spectrometry. Neutron flux (neutron/cm^2/s) was measured 10 min after the start of irradiation by gold-foil activation analysis. Neutron irradiation was performed in a single fraction, using an epithermal beam, at a reactor power of 3.5 MW. All patients were treated in Japan Research Reactor 4 of the Japan Atomic Energy Agency (JAEA).

The radiation dose calculation before treatment completion, and the evaluation after treatment, were made using a computer work station equipped with the JAEA computational dosimetry system (JCDS), a dose-planning software program [12]. Serial CT images were entered into the JCDS, and the gross target volume (GTV) was defined using the 3-dimensional images of the head and neck reconstructed from the CT data (Fig. 1). The tumor and normal-tissue doses were expressed as the photon-equivalent dose (Gy-Eq), calculated as the weighted dose adjusted for relative biological effectiveness (RBE) and compound biological effectiveness (CBE) factors [13]. The RBE factor was 3.0 for fast-neutron and thermal-neutron dose components, and 1.0 for the γ-ray dose component. The CBE factor for L-BPA in tumor, normal skin, normal mucosa, and eye was 3.8, 2.5, 4.9, and 2.5, respectively.

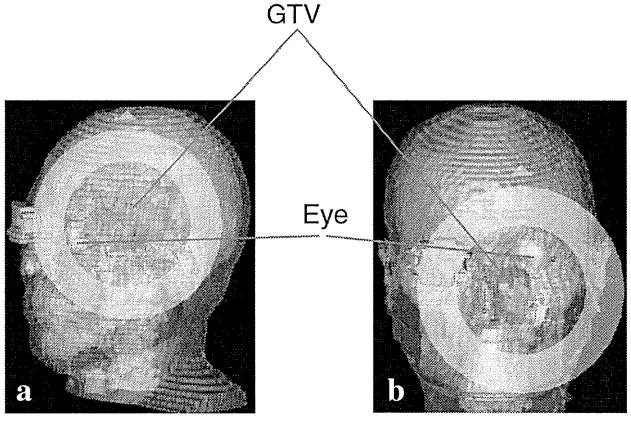

Fig. 1 Radiation field of Patient 2 (**a**) and Patient 5 (**b**). The eyes of tumor side for Patient 2 and Patient 5 were included in radiation field by *yellow circle* (JCDS)

The minimum planned dose at the GTV was 20 Gy-Eq; the maximum dose for normal skin and mucosa within the irradiated field was limited to 15 Gy-Eq in the recurrence-group patients and 18 Gy-Eq in the initial treatment-group patients. The maximum dose for the contralateral eye was 10 Gy-Eq. The neutron irradiation time was estimated by the JCDS, based on the blood boron concentration during treatment and the neutron flux. FBPA-PET was used to estimate the tumor/blood ratio and normal tissue/blood ratio for boron; the boron concentrations in the tumor and in the normal tissues (to give the T/N ratio upon which dosing was based) were estimated by multiplying the blood concentration by the FBPA-PET data for each patient.

Follow-up

All patients were analyzed at 4-week intervals after BNCT. Follow-up CT was performed at 1, 3, 6, and 12 months, and FDG-PET was performed every 3 months for the first year after BNCT. For the second year, patients underwent CT and FDG-PET every 4–6 months. The treatment response was evaluated using the Response Evaluation Criteria in Solid Tumor guidelines [14]. Adverse effects were defined by the Common Terminology Criteria for Adverse Events, version 3.0 [15].

Results

T/N ratios and boron concentrations

The T/N boron ratios before BNCT ranged from 2.5 to 5.0 (Table 2). The median blood boron concentration at the time of neutron irradiation was 25.3 μg/g (range 22.6–29.3 μg/g). As previously stated, the boron concentrations in the tumor and normal tissue were estimated by multiplying the blood concentration by the FBPA-PET data for each patient.

Radiation doses by BNCT

The minimum GTV dose of 20 Gy-Eq was achieved in all patients (Table 2), with the mean dose ranging from 32.9 to 82.3 Gy-Eq. The maximum dose delivered to normal tissue, such as the skin of the head and neck, the oropharyngeal

Table 2 Dose evaluation after BNCT

Patient	T/N ratio	Blood boron concentration	Irradiation time (min)	Radiation dose to the tumor (Gy-Eq)		Radiation dose to the organs at risk (Gy-Eq)			
				Average	Minimum	Skin	Mucosa	Eye	
1	3.8	24.4	45	52.4	30.4	14.1	14.0	7.3 (I)	3.1 (C)
2	2.5	25.6	38	38.9	21.2	9.3	9.9	10.8 (I)	3.3 (C)
3	5.0	29.3	25	82.3	44.2	9.0	8.1	1.8 (I)	
4	3.5	22.6	35	63.6	34.4	16.6	15.8	14.1 (I)	10.2 (C)
5	2.5	25.3	51	48.8	20.0	17.3	14.1	18.4 (I)	4.9 (C)

I ipsilateral, *C* contralateral

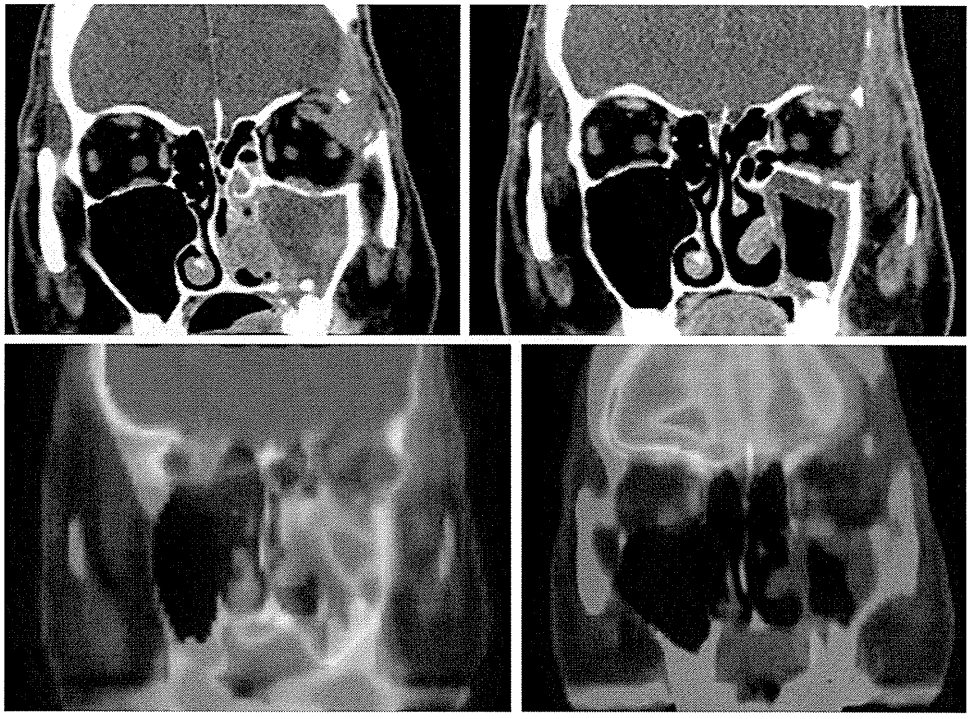

Fig. 2 Case presentation (Patient 2). *Top left image* CT findings before BNCT. The tumor recurred in maxillary sinus and the temporal region. *Top right*, 3 months later, the tumor size reduced on CT. *Bottom left image* FDG-PET findings before BNCT. The recurrent tumor showed uptake FDG for both lesions. *Bottom right*, 9 months later, the FDG-PET showed substantial decrease in tumor uptake

mucosa, and the contralateral eye, were within the planned dose range. The mean dose for the skin and the mucosa in the recurrence group was 14.1 and 9.3 Gy-Eq and 14.0 and 9.9 Gy-Eq, respectively. The dose for the skin and the mucosa in the initial treatment group ranged from 9.0 to 16.6 Gy-Eq and 8.1 to 15.8 Gy-Eq, respectively. The ipsilateral eye in Patients 2, 4, and 5 was included in the radiation field (Fig. 1a, b), with eye doses exceeding the planned dose (10.8, 14.1, and 18.4 Gy-Eq, respectively).

Tumor response and adverse effects

All patients achieved a complete response within 6 months of BNCT (Figs. 2, 3, 4). The median duration of this complete response was 24.0 months (range 22–32 months). One of the 2 patients in the recurrence group experienced local recurrence 24 months after BNCT, and 1 patient in each group developed distant metastasis between 12 and 19 months after BNCT (Table 3). Patient 3 (initial treatment group) developed an enlarged regional neck lymph node, beyond the irradiation field, 17 months after BNCT. Selective neck dissection was performed; no evidence of disease was found after this lymph node was removed. We were able to evaluate the histological changes caused by BNCT in this patient, who gave written consent for this investigation. Open biopsy of the parotid gland was performed at the time of selective neck dissection, with pathological examination revealing no residual viable cancer cells in the parotid gland and no serious damage to the normal glandular system (Fig. 5).

The median overall survival time was 32.0 months (range 22–38 months). Three of 5 patients were still alive at the conclusion of the study period; the others died of distant metastatic disease.

All patients developed grade 1–2 acute adverse effects in the irradiated field (Table 3), with the most frequently seen complication being grade 1 dermatitis. Dermatitis

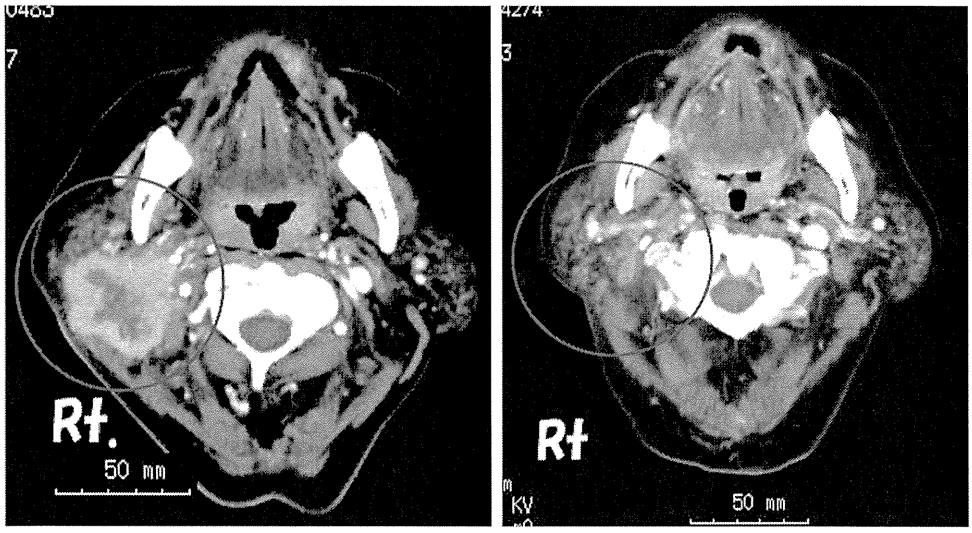

Fig. 3 Case presentation (Patient 3). *Left* prior to irradiation, *right* 2 months after irradiation. Before irradiation (*left*), the right parotid gland region was tumor, shown by *circle*. Two months after BNCT (*right*), the CT showed that the tumor almost disappeared and looked like scart 3

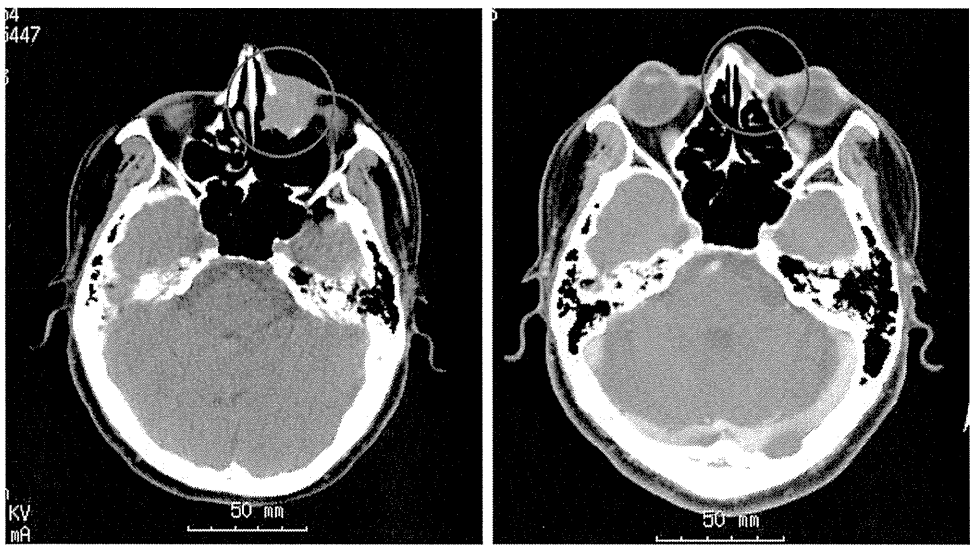

Fig. 4 Case presentation (Patient 4). Before irradiation (*left*), left orbital tumor on CT shown by *red circle*. Six months later (*right*), the tumor disappeared

developed on the first day of BNCT in all patients who experienced this side effect, and lasted for 3 weeks. Mucositis was also frequently observed within 1 week of treatment, disappearing within 3–5 weeks. A late adverse effect was defined as developing at an interval of longer than 3 months after BNCT. Although mild alopecia, xerostomia, and fatigue occurred in all patients except 1, no severe late adverse effects of grade 3 or higher were observed. Despite the inclusion of the ipsilateral eye in the radiation field, there was no evidence of visual disturbances or cataracts in Patients 2, 4, and 5.

Discussion

Three patients in the present series were newly diagnosed with T4 disease, and their first treatment experience was with BNCT. To the best of our knowledge, BNCT as primary treatment has not been performed elsewhere. All patients showed a complete response within 6 months of treatment. Although most patients experienced at least 1 adverse effect, either acute or late phase, the symptoms were mild and generally tolerable. Our results demonstrate that BNCT is feasible and safe for patients with salivary gland carcinoma. The treatment does not cause any serious adverse effects, and may be used regardless of whether the primary tumor has already been treated.

Carcinomas originating from the salivary glands were once thought to be radioresistant, and surgery was considered the primary treatment. Recent reports, however, disproved this notion by demonstrating that postoperative radiotherapy improves locoregional control for patients with close or incomplete resection, perineural invasion, and advanced-stage salivary gland carcinoma [21–23]. Chen et al. [3]

Table 3 Clinical results of all patients

Patient	Tumor response	Acute adverse effects (Grade)	Late adverse effects (Grade)	Loco-regional control (months)	Distant metastasis (months) and sites	Survival (months)
1	CR	Dermatitis (G1) Oral pain (G1) Mucositis (G1)	None	24	None	36, alive
2	CR	Dermatitis (G1) Alopecia (G1)	Alopecia (G2)	22	12, lung	22, DOC
3	CR	Dermatitis (G1) Mucositis (G1) Oral pain (G1)	Alopecia (G1)	38	None	38, alive
4	CR	Dermatitis (G1)	None	32	None	32, alive
5	CR	Dermatitis (G2) Mucositis (G1) Nausea/vomiting (G1) Dry eye (G2)	Fatigue (G1) Taste alteration (G1) Alopecia (G2)	24	19, bone	24, DOC

DOC died of cause

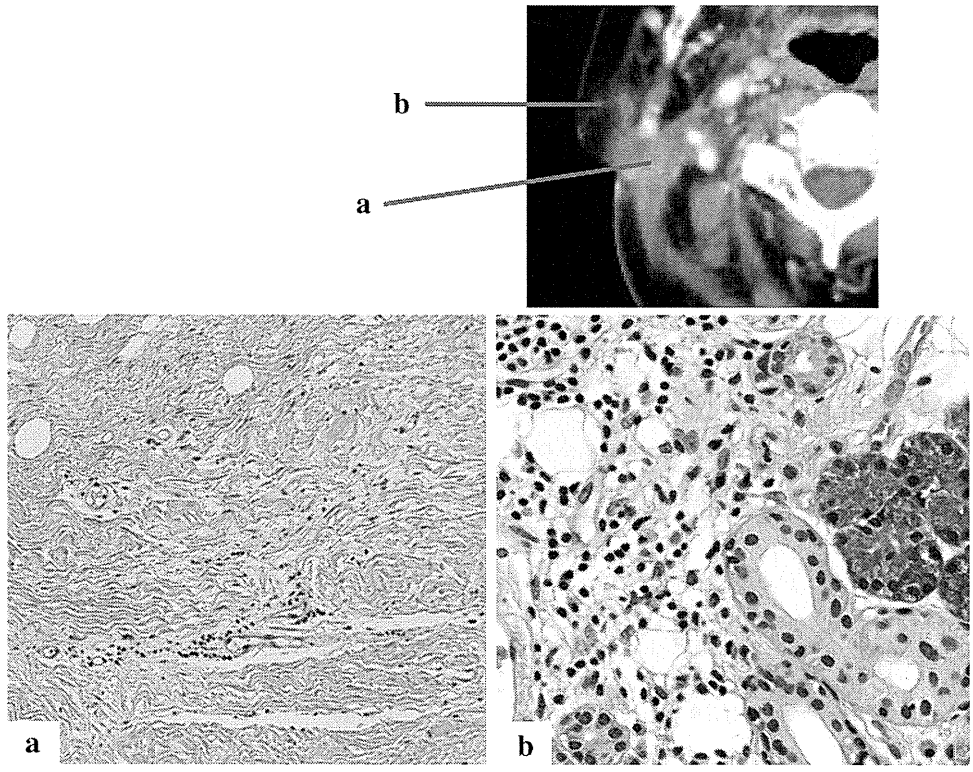

Fig. 5 Histological examination of Patient 3. The tumor lesion scarred in a CT image 5 months after the BNCT. Five months after BNCT, CT showed no tumor with scar formation. This case underwent open biopsy to check the residual viable cancer cells. The pathological examination revealed that no malignant tumor cells were observed in the scar tissue (**a**), and that the parotid tissue showed almost no damage by radiation (**b**)

reported that radiation therapy alone can also achieve long-term local control and improve survival in a significant percentage of patients treated. However, local control in patients with advanced T-stages in Chen's study was much worse than in those with early-stage disease: 8 of 12 patients with T4 disease developed a local recurrence, and the 10-year local control rate was 30 % in these patients, compared with 81 % in patients with T1/T2 disease. An advanced T-stage was also identified as a significant independent predictor of local recurrence in other retrospective studies [20, 21, 24]. All patients in our series showed a complete response after BNCT, in spite of having advanced T-stages, and only 1 patient in the recurrence group experienced a locoregional recurrence. This finding suggests that BNCT has a theoretical advantage over conventional low LET radiation for the treatment of advanced T-stage salivary gland carcinoma, with its superiority of dose distribution and the biological differences in cellular response.

Re-irradiation has been accepted as an alternative to surgery for patients with recurrent disease. Several authors have reported the importance of re-irradiation, with or without concomitant chemotherapy, in improving survival in patients with recurrent HNCs [16–19]. In these reports, the median overall survival was 8.5–15.0 months, and the median progression-free survival was 5.7–6.1 months. In our study, the overall and progression-free survival in Patient 1 was 36 and 24 months, respectively, and in Patient 2 was 22 and 12 months, respectively.

None of our study patients experienced Grade 3 or higher adverse effects after BNCT, whereas previous studies have reported severe acute and late toxicities of Grade 3–4 or higher in 10–20 % of patients who receive irradiation or re-irradiation using conventional photon therapy [16–20, 25]. Although direct comparison of our series with previous studies is impossible because of our small study sample, the results of BNCT are seemingly more favorable.

Pathological examination in Patient 3 revealed no detectable cancer cells in the post-treatment surgical specimen, and very little damage to the normal part of the parotid gland. If this patient had received the same dosage in the form of conventional photon therapy, normal glandular cells in proximity to the parotid tumor would not have survived. This provides evidence that BNCT can achieve complete response on the cellular level without severe damage to the surrounding normal tissue, resulting in prominent local control and minimal adverse effects.

A high rate of distant metastasis has been reported in patients with advanced T-stage disease, with a significant association observed between advancing T-stage and the presence of these metastases [3, 21, 25]. Although all patients in the present study had advanced T-stage disease, not all patients showed clinically recognizable distant metastases. The 2 patients (Patients 2 and 5) who developed distant metastases had tumors of relatively large volume (Table 1), suggesting that the chance of microscopic dissemination becomes higher with a larger tumor volume at presentation. The development of effective systemic therapy strategies that can be used concomitantly with BNCT is needed to reduce the risk of distant metastasis.

Because a nuclear reactor is required to obtain sufficient numbers of epithermal neutrons, BNCT is performed in only a few institutes at the present time. In addition, BNCT is also limited by appropriate 10B dose distribution, with treatment not possible with low tumor accumulation (T/N ratio less than 2.5). However, with the development of accelerator-based neutron sources, and of other kinds of boron-delivery agents and systems for improving 10B accumulation in tumors, it is expected that BNCT may become widespread as an alternative to surgery or conventional photon radiotherapy for patients with advanced salivary gland carcinoma.

Conclusion

Our preliminary results demonstrate that BNCT is a potential curative therapy for patients with salivary gland carcinoma. The treatment does not appear to cause serious adverse effects, and may be used as treatment for either primary or recurrent disease. Although these excellent clinical results will have a major impact on future strategies for treatment of salivary gland carcinoma, this study was limited by a short follow-up period and a small number of patients. A longer duration of follow-up and a larger prospective study are needed to verify these initial results.

Acknowledgments This work was supported by JSPS Grant-in-Aid for Scientific Research (C) Number 24592611.

Conflict of interest The authors declare that they have no conflict of interest. Teruhito Aihara have no personal or financial interests to declare and receive no financial support from an industry source related to the current manuscript.

References

1. Satou T (2000) Head and neck tumor. In: Nomura AKK, Honjyou I, Inuyama A (eds) Clinical textbook of the ear, nose and throat regions 21, edn, vol 17. Nakayama-syoten, Tokyo, pp 17–28
2. Ridge JA, Glisson BS, Lango MN et al (2008) Head and neck tumors. In Pazdur R, Wagman LD, Camphausen KA, Hoskins WJ (eds) Cancer management: a multidisciplinary approach, 11 edn. CMPMedica, Lawrence
3. Chen AM, Bucci MK, Quivey JM, Garcia J, Eisele DW, Fu KK (2006) Long-term outcome of patients treated by radiation therapy alone for salivary gland carcinomas. Int J Radiat Oncol Biol Phys 66:1044–1050
4. Parsons JT, Mendenhall WM, Stringer SP, Cassisi NJ, Million RR (1996) Management of minor salivary gland carcinomas. Int J Radiat Oncol Biol Phys 35:443–454
5. Terhaard CH, Lubsen H, Rasch CR, Levendag PC, Kaanders HH, Tjho-Heslinga RE, van Den Ende PL, Burlage F, Dutch Head and Neck Oncology Cooperative Group (2005) The role of radiotherapy in the treatment of malignant salivary gland tumors. Int J Radiat Oncol Biol Phys 61:103–111
6. Mendenhall WM, Morris CG, Amdur RJ, Mendenhall NP, Siemann DW (2005) Radiotherapy alone or combined with carbogen breathing for squamous cell carcinoma of the head and neck: a prospective, randomized trial. Cancer 104:332–337
7. Kato I, Ono K, Sakurai Y, Ohmae M, Maruhashi A, Imahori Y, Kirihata M, Nakazawa M, Yura Y (2004) Effectiveness of BNCT for recurrent head and neck malignancies. Appl Radiat Isot 61:1069–1073
8. Aihara T, Hiratuka J, Morita N, Uno M, Sakurai Y, Maruhashi A, Ono K, Harada T (2006) First clinical case of boron neutron capture therapy for head and neck malignancies using 18F-BPA PET. Head Neck 28:850–855

9. Kankaanranta L, Seppälä T, Koivunoro H, Saarilahti K, Atula T, Collan J, Salli E, Kortesniemi M, Uusi-Simola J, Mäkitie A, Seppänen M, Minn H, Kotiluoto P, Auterinen I, Savolainen S, Kouri M, Joensuu H (2007) Boron neutron capture therapy in the treatment of locally recurred head and neck cancer. Int J Radiat Oncol Biol Phys 69:475–482
10. Imahori Y, Ueda S, Ohmori Y, Sakae K, Kusuki T, Kobayashi T, Takagaki M, Ono K, Ido T, Fujii R (1998) Positron emission tomography-based boron neutron capture therapy using boron-ophenylalanine for high-grade gliomas: part II. Clin Cancer Res 4:1833–1841
11. Ono K, Masunaga S, Kinashi Y et al (2006) Neutron irradiation under continuous BPA injection for solving the problem of heterogenous distribution of BPA. In: Advances in neutron capture therapy. Takamatsu, pp 27–30
12. Kumada H, Yamamoto K, Yamamoto T, Nakai K, Nakagawa Y, Kageji T, Matsumura A (2004) Improvement of dose calculation accuracy for BNCT dosimetry by the multi-voxel method in JCDS. Appl Radiat Isot 61:1045–1050
13. Coderre JA, Morris GM (1999) The radiation biology of boron neutron capture therapy. Radiant Res 151:1–18
14. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
15. Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, Langer C, Murphy B, Cumberlin R, Coleman CN, Rubin P (2003) CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 13:176–181
16. Haraf DJ, Weichselbaum RR, Vokes EE (1996) Re-irradiation with concomitant chemotherapy of unresectable recurrent head and neck cancer: a potentially curable disease. Ann Oncol 7:913–918
17. Lee N, Chan K, Bekelman JE, Zhung J, Mechalakos J, Narayana A, Wolden S, Venkatraman ES, Pfister D, Kraus D, Shah J, Zelefsky MJ (2007) Salvage re-irradiation for recurrent head and neck cancer. Int J Radiat Oncol Biol Phys 68:731–740
18. Goldstein DP, Karnell LH, Yao M, Chamberlin GP, Nguyen TX, Funk GF (2008) Outcomes following reirradiation of patients with head and neck cancer. Head Neck 30:765–770
19. Unger KR, Lominska CE, Deeken JF, Davidson BJ, Newkirk KA, Gagnon GJ, Hwang J, Slack RS, Noone AM, Harter KW (2010) Fractionated stereotactic radiosurgery for reirradiation of head-and-neck cancer. Int J Radiat Oncol Biol Phys (Epub ahead of print)
20. Gomez DR, Hoppe BS, Wolden SL, Zhung JE, Patel SG, Kraus DH, Shah JP, Ghossein RA, Lee NY (2008) Outcomes and prognostic variables in adenoid cystic carcinoma of the head and neck: a recent experience. Int J Radiat Oncol Biol Phys 70:1365–1372
21. Renehan AG, Gleave EN, Slevin NJ, McGurk M (1999) Clinicopathological and treatment-related factors influencing survival in parotid cancer. Br J Cancer 80:1296–1300
22. Terhaard CH, Lubsen H, Rasch CR, Levendag PC, Kaanders HH, Tjho-Heslinga RE, van Den Ende PL, Burlage F (2005) The role of radiotherapy in the treatment of malignant salivary gland tumors. Int J Radiat Oncol Biol Phys 61:103–111
23. Chen AM, Granchi PJ, Garcia J, Bucci MK, Fu KK, Eisele DW (2007) Local-regional recurrence after surgery without postoperative irradiation for carcinomas of the major salivary glands: implications for adjuvant therapy. Int J Radiat Oncol Biol Phys 67:982–987
24. Bhide SA, Miah A, Barbachano Y, Harrington KJ, Newbold K, Nutting CM (2009) Radical radiotherapy for treatment of malignant parotid tumours: a single centre experience 1995–2005. Br J Oral Maxillofac Surg 47:284–289
25. Mendenhall WM, Morris CG, Amdur RJ, Werning JW, Villaret DB (2005) Radiotherapy alone or combined with surgery for salivary gland carcinoma. Cancer 103:2544–2550

Breast Cancer (2014) 21:40–46
DOI 10.1007/s12282-012-0345-2

ORIGINAL ARTICLE

Long-term outcome of hypofractionated radiotherapy to the whole breast of Japanese women after breast-conserving surgery

Takeaki Ishihara · Eisaku Yoden · Kei Konishi · Naomi Nagase · Kenji Yoshida · Junichi Kurebayashi · Hiroshi Sonoo · Nobutaka Murashima · Ryohei Sasaki · Junichi Hiratsuka

Received: 29 November 2011 / Accepted: 30 January 2012 / Published online: 22 February 2012

Abstract
Background In Japan, there are still no reports of long-term outcome for hypofractionated radiotherapy to the whole breast after breast-conserving surgery (BCS). We report our institution's results from evaluation of the efficacy and safety of hypofractionated radiotherapy for Japanese women.
Methods Data in the medical records of 327 patients were retrospectively reviewed. The patients were treated with hypofractionated radiotherapy between January 2003 and December 2006 at the Kawasaki Medical School Hospital and were followed for more than 3 years. The median age was 54 years old (the age range was 28–80 years). The whole breast was irradiated with a total dose of 42.56 Gy/16 fx with boost irradiation to positive margins. Adjuvant therapy consisted of chemotherapy and/or hormone therapy and was administered to 300 patients, based on their stage or pathological findings.
Results Follow-up periods ranged from 21 to 92 months; the median follow-up period was 60 months. At 5-year follow-up, overall survival, cause-specific survival, relapse-free survival, and local control were 96.0, 97.5, 95.3, and 99.7% respectively. Grade 2 radiation pneumonitis occurred in five patients. Grade 2 radiation dermatitis occurred in 17 patients. Severe late complications were not observed.
Conclusions In our study, hypofractionated radiotherapy led to good results without severe toxicity. We believe hypofractionated radiotherapy after BCS is safe and efficient treatment for Japanese women.

Keywords Breast cancer · Breast-conserving surgery · Hypofractionated radiotherapy

T. Ishihara (✉) · E. Yoden · K. Konishi · N. Nagase · J. Hiratsuka
Department of Radiation Oncology, Kawasaki Medical School, 577, Matsushima, Kurashiki, Okayama 701-0192, Japan
e-mail: spz694w9@onyx.ocn.ne.jp; takeaki@med.kobe-u.ac.jp

T. Ishihara · K. Yoshida · R. Sasaki
Department of Radiation Oncology, Kobe University Graduate School of Medicine, Hyogo, Japan

J. Kurebayashi · H. Sonoo
Department of Breast and Thyroid Surgery, Kawasaki Medical School, Okayama, Japan

N. Murashima
Department of Surgery, Kurashiki Medical Center, Okayama, Japan

Introduction

Breast-conserving therapy, consisting of breast-conserving surgery (BCS) followed by whole breast irradiation, is an established standard treatment for patients with early breast cancer [1–10]. In Japan, a fraction dose of 1.8–2 Gy and a total dose of 45–50 Gy are usually applied in the postoperative setting with or without additional boost irradiation of the excision site. In late years, alternative hypofractionated radiotherapy (e.g., 42.56 Gy/16 fx, 41.6 Gy/13 fx, 40 Gy/15 fx) has been reported to be feasible and acceptable [11–17] and is becoming popular as a convenient regimen. There are few reports of long-term results of hypofractionated radiotherapy for Japanese women. Morbidity of breast cancer is lower in Japan than in Europe and the United States. In addition, large breasts are more common in Europe and the United States than in Japan. Therefore, an original survey is needed to investigate the

efficacy and safety of hypofractionated radiotherapy for Japanese women. We introduced hypofractionated radiotherapy after BCS as practical clinical treatment in 2003. We retrospectively investigate and describe the long-term results in this article.

Patients and methods

Patient selection

In our institution, since January 2003, all patients planned to receive postoperative radiotherapy after BCS were informed about the merits and demerits of two regimens, 50 Gy/25 fx (conventional regimen) and 42.56 Gy/16 fx (hypofractionated regimen), on the basis of published data [14]. The choice was entrusted to each patient, and more than 95% of patients selected the hypofractionated regimen, and gave written informed consent. Therefore, 910 patients were treated with the hypofractionated regimen from January 2003 to September 2010. Patient data in the medical records were retrospectively reviewed. Eligibility criteria for this analysis were:

1 treated with BCS followed by whole-breast hypofractionated radiotherapy consisting of 42.56 Gy in 16 fractions with or without boost irradiation to the tumor bed;
2 patients with early-stage breast cancer of pStage0-IIB; and
3 follow-up period of more than 3 years after the completion of radiotherapy.

To avoid statistical complexity, exclusion criteria were:

1 lost to follow-up within 3 years ($n = 16$);
2 died of other disease within 3 years without recurrence of breast cancer ($n = 3$);
3 simultaneous bilateral breast cancer ($n = 7$);
4 history of breast cancer ($n = 13$);
5 induction chemotherapy ($n = 5$); and
6 incomplete radiotherapy ($n = 2$).

As a result, 327 patients were included in this retrospective analysis. Patient characteristics are summarized in Table 1.

Table 1 Clinical, tumor, and treatment characteristics

Clinicopathologic characteristic	*n*
Age	28–80 (median 54)
<50/≥50	115/212
PS	
0-1/2/3≥	325/2/0
Surgery	
Bp or Bq only/SNB/Ax	29/117/181
Bp/Bq/Tm	185/142/0
Chemotherapy	
Yes/no	109/218
Hormone therapy	
Yes/no	261/66
pT stage	
is/1/2/3	29/206/91/1
pN stage	
0/1	261/66
pStage	
Stage 0	29
Stage I	164
Stage II A	107
Stage II B	27
Histology	
DCIS	28
IDC	268
Special types	29
Unclassified or NA	2
Margins	
Positive/negative	66/261
ER and/or PgR*	
Positive/negative/NA	253/38/36
HER2	
Positive/negative/NA	30/252/45

Ax axillary dissection; *Bp* wide excision; *Bq* quadrantectomy; *CR* complete response; *DCIS* ductal carcinoma in situ; *ER* estrogen receptor; *IDC* invasive ductal carcinoma; *NA* not available; *PgR* progesterone receptor; *SNB* sentinel node biopsy; *Tm* tumorectomy

* The definition of hormone-receptor positive is that one or both of ER or PgR receptor is positive

Surgery

All patients received BCS: wide excision (Bp) in 185 patients and quadrantectomy (Bq) in the other 142. No patient received tumorectomy (Tm). If cancer cells remained within 5 mm from the surgical margin, the specimen was defined as "stump-positive." In this study, 66 patients had positive margins at final pathological examination. 181 patients underwent level I/II axillary lymph nodes dissection. 117 patients underwent sentinel node biopsy (SNB) alone. Twenty-nine patients received no axillary surgery.

Radiotherapy

Techniques of radiotherapy, except for dose fractionation, were as same as for traditional methods. Patients were treated with external beam radiotherapy to the whole breast, using tangential fields with 4–6 MV photons. The field border was determined in the following way: the inferior border was located 1–2 cm below the

inframammary fold; the superior border, at the height of the suprasternal notch; the medial border, at the midsternal line; and the lateral border, at the mid-posterior axillary line. The anterior margin was located at least 2 cm from the surface of the breast and the posterior margin was maintained with a gantry-tilting technique to limit the maximum lung depth included in the field to 3 cm or less. A total dose of 42.56 Gy/16 fr was prescribed generally at the isocenter and, when necessary, wedge filters and/or the field-in-field technique were used to optimize dose homogeneity. The objective of optimization was to keep the minimum dose in the deep part of the breast no less than 95% and to limit the maximum dose within the breast to no more than 107% of the prescribed dose. For positive margins, additional boost irradiation of 10–13.3 Gy/4–5 fractions (using 4–11 MeV electrons) was administered to the excision site.

Adjuvant therapy

Any limitation of adjuvant therapy was not made in association with the hypofractionated radiotherapy. Adoption of adjuvant therapy depended on attending surgeon, and chemotherapy and/or hormone therapy were selected according to commonly-accepted criteria based on pathological stage or histological findings. 300 patients received adjuvant systemic therapy. Chemotherapy involved various combinations of the following drugs: cyclophosphamide, adriamycin, 5-fluorouracil, methotrexate, epirubicin, paclitaxel, docetaxel, tegaful-uracil, and doxifluridine. Chemotherapy was administered sequentially (not concurrently) with radiotherapy. Hormone therapy involved the following drugs: anastrozole, exemestane, tamoxifen, toremifene citrate, leuprorelin, goserelin, and letrozole. Hormone therapy was generally maintained from 2 to 5 years after the completion of radiotherapy.

Follow-up and patient evaluation

Patients were seen at least once a week during radiotherapy and at 1 month after completing radiotherapy. They were then seen every 3 months for 3 years. After 3 years, they were seen annually. At each visit, physicians recorded a history and performed a physical examination (mainly skin reaction and respiratory symptoms related to radiotherapy). A chest X-ray was taken before a radiotherapy session, and then at each follow-up visit during the first year. From the second year they had a routine chest X-ray semi-annually. When X-ray films or physical symptoms suggested radiation pneumonitis, more frequent X-ray tests or computed tomography (CT) were considered. Bilateral mammography, bone scan, and abdominal ultrasonography were performed annually. Radiation dermatitis and radiation pneumonitis were evaluated by use of the Radiation Therapy Oncology Group (RTOG)-acute radiation morbidity scale scoring criteria and the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) late radiation morbidity scoring scheme [18].

Statistical analysis

The survival time was calculated from the date of surgery. Survival curves and actuarial rates of recurrence were calculated using Kaplan–Meier method, and the significance of prognostic factors was assessed by log rank test [19]. Multivariate analysis was performed using stepwise Cox proportional hazard regression models [20]. A $P < 0.05$ between groups was considered significant. Stat View (version 5.0) software was used for all statistical analysis.

Results

Median follow-up period was 60 months. Of 327 patients, 14 patients died; 9 died of breast cancer and 5 died of other causes. Recurrence was observed in 15 patients. Of these patients, 14 developed distant metastases (bone, brain, lung, liver). Local recurrence in the ipsilateral breast was observed in one patient only, who was salvaged by mastectomy. Metachronous contralateral breast cancer occurred in four patients (one patient also had distant metastases).

Figure 1 shows overall survival (OS), cause-specific survival (CSS), relapse-free survival (RFS), and the local control (LC). Actuarial 5-year OS, CSS, RFS and LC were 96.0, 97.5, 95.3 and 99.7%, respectively. Figure 2 shows

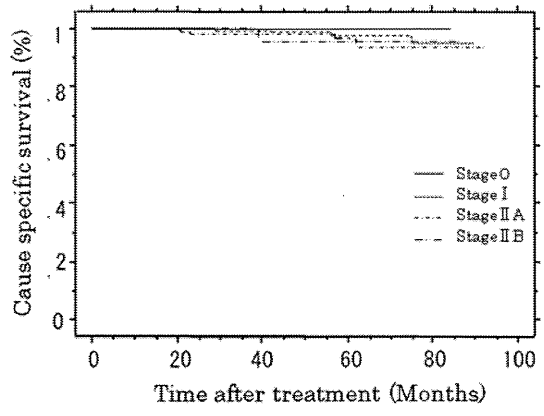

Fig. 1 Survival graphs showing overall survival, cause-specific survival, relapse-free survival, and local control ($n = 327$)

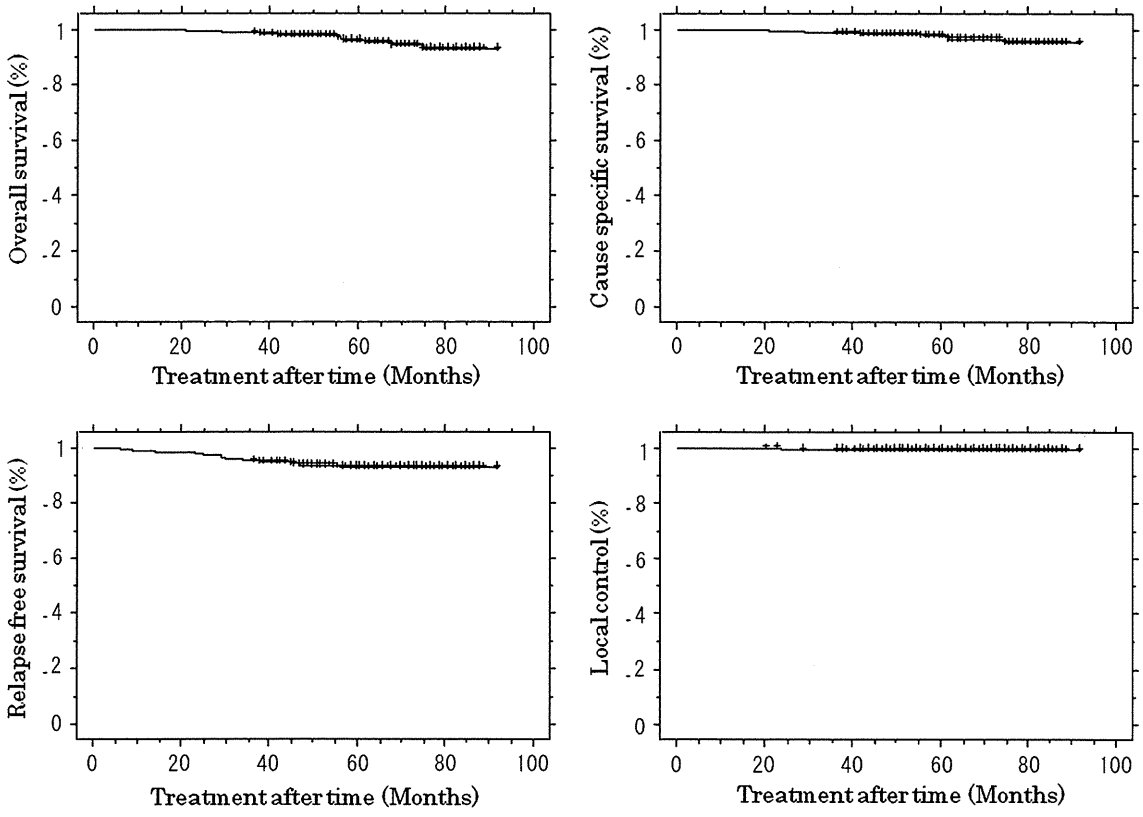

Fig. 2 Cause-specific survival of 327 patients at each pStage. The patients were divided by stage, as follows: stage 0, 29 patients; stage I, 164 patients; stage IIA, 107 patients; and stage IIB, 27 patients

5-year CSS for each stage. Actuarial 5-year CSS for each stage were: stage 0, 100%; stage I, 97.7%; stage IIA, 96.7%; and stage IIB, 96.3%.

Table 2 summarizes the relationship between RFS and other variables. Univariate analysis indicated that hormone therapy ($P = 0.0009$; HR 4.75; CI 1.72–13.10) was a significant prognostic factor for RFS. Multivariate analysis, using stepwise selection, similarly showed that hormone therapy ($P = 0.0027$; HR 4.71; CI 1.71–13.01) was a significant prognostic factor for RFS in this study.

Radiotherapy-induced dermatitis was observed for 268 patients (251 patients with grade 1, 17 with grade 2). Most patients did not need treatment for their dermatitis, but some were given appropriate drugs (e.g., an ointment or a steroid-containing cream). Two to six months after the completion of radiotherapy, 16 patients developed radiation pneumonitis (11 patients with grade 1, five with grade 2). No patients had radiation pneumonitis of grade 3 or higher. In addition, two patients were diagnosed with bronchiolitis obliterans organizing pneumonia (BOOP). They received treatment with prednisolone and the symptoms improved. Concerning late toxicity, we observed no patients with grade 2 or higher toxicity.

Discussion

Hypofractionated radiotherapy to the whole breast after BCS is an alternative to radiotherapy with conventional fractionation. In Japan, however, there are no studies that report the long-term outcome of hypofractionated radiotherapy, and in fact, it is still less common. We previously reported preliminary results of the hypofractionated regimen [21]. At a median follow-up of 26 months, we obtained good results for OS, CSS, DFS, and LC. The objective of this study was to update our previous findings, after long-term observation.

Our current study shows acceptable results (with regard to OS, CSS, RFS, and LC); in Table 3 these are compared with those from other studies that used a hypofractionated or conventional regimen [14, 17, 22, 23]. The high LC is particularly notable. We believe there are two main reasons for this. First, all patients in this study received either Bp or Bq. Veronesi et al. [4, 24] reported that annual local recurrence was low for patients treated with Bq + radiotherapy (RT) whereas it was significantly higher for patients treated with Tm + RT. Another reason may be the definitions of "margin-free." In Japan, the definition of "stump-positive" is that cancer cells remain within 5 mm

Table 2 Characteristics of 327 breast cancer patients listed by the number of patients at risk, number of relapses, relapse-free survival, log rank test, Cox-regression, and specific hazard risk (HR)

Factor	No. of patients	No. of relapses	Relapse-free survival (5 years) (%)	*P*-value (log rank)	HR (CI 95%)†	*P* value (Cox-regression)	HR (CI 95%)††
Age							
<50	115	2	98.3		0.28 (0.06–1.24)		0.28 (0.06–1.25)
≥50	212	13	93.7	0.07	1.0 (reference)	0.09	1.0 (reference)
Bp or Bq	29	1	96.6		0.68 (0.08–5.67)		
+SNB	117	6	94.6		1.0 (reference)		
+Ax	181	8	95.5	0.92	0.85 (0.30–2.48)		
Chemotherapy							
Yes	109	7	93.5		1.0 (reference)		
No	218	8	96.2	0.26	0.56 (0.21–1.57)		
Hormone therapy							
Yes	261	7	97.3		1.0 (reference)		1.0 (reference)
No	66	8	87.4	0.0009	4.75 (1.72–13.10)	0.0027	4.71 (1.71–13.01)
PN stage							
0	261	11	95.7		0.69 (0.22–2.17)		
1	66	4	93.8	0.52	1.0 (reference)		
Margins							
Positive	66	5	92.3		1.0 (reference)		
Negative	261	10	96.0	0.18	0.49 (0.17–1.43)		
ER and/or PgR*							
Positive	253	11	95.5		1.0 (reference)		
Negative	38	4	89.5	0.09	2.59 (0.83–8.14)		
HER2*							
Positive	30	3	90.0		1.0 (reference)		
Negative	252	11	95.5	0.17	0.42 (0.11–1.51)		

For other abbreviations, see Table 1

* Some data are missing

† Univariate analysis

†† Multivariate analysis using Cox proportional hazard regression

Table 3 Comparison of our data with published data

Ref.	Patients	Operation type	RT dose/fraction	Overall survival	Local recurrence
Lyon [22]	1,024	Bp	50 Gy/25 fr	99% (4 years)	4.5% (4 years)
			50 Gy/25 fr + boost	99% (4 years)	3.5% (4 years)
EORTC [23]	5,318	Tm	50 Gy/25 fr	87% (5 years)	7.3% (5 years)
			50 Gy/25 fr + boost	91% (5 years)	4.3% (5 years)
OCOG trial [14]	622	Tm	42.56 Gy/16 fr	97.2% (5 years DFS)	3.4% (5 years)
START B trial [17]	1,110	BCS or Bt	40 Gy/15 fr ± boost	92% (5 years)	2.2% (5 years)
Our data	327	Bp or Bq	42.56 Gy/16 fr ± boost	96.0% (5 years)	0.3% (5 years)

Bt mastectomy; *fr* fraction; for other abbreviations, see Table 1

of the surgical margin; this is a more rigid criterion than that widely used in other countries. In our study, 66 patients had positive stumps and received additional boost irradiation. Several studies report that additional boost irradiation of the tumor bed after BCS reduced local recurrence irrespective of the stump status [4, 5, 7, 22, 23]. Therefore, the fact that many patients in our series received additional boost irradiation based on the rigid criterion may have resulted in good LC. Furthermore, our boosted dose of 13.3 Gy/5 fx seems relatively high, although the

appropriate dose of boost irradiation has not been established. These factors may be responsible for low local recurrence.

Radiation dermatitis and pneumonitis after breast-conserving therapy in our institution has been surveyed previously. Yoden et al. [25] reported the incidence of this toxicity for patients treated with conventional regimen and Fujii et al. [21] reported it for patients treated with hypofractionated regimen. They reported similar results, and the results from this study are compatible with these two reports. Irradiation of the breast using a hypofractionated schedule may cause more severe skin telangiectasia, fibrosis, or indurations, which worsens the final cosmetic outcome. Two randomized trials proved, by long-term observation, there was no difference in cosmetic outcomes between conventional and hypofractionated regimens [14, 15, 17]; our study also obtained satisfactory results for late toxicity. The follow-up period of this study may not be long enough to clarify late toxicity, because it is known that occurrence and grade of late toxicity increase in proportion to the time from completion of radiotherapy. Longer follow up is needed.

The purpose of this study was to prove the efficacy and safety of hypofractionated radiotherapy after BCS in Japanese women. In conclusion, we observed acceptable local control and survival without severe late toxicity after 5 years in our retrospective study. Although cosmetic outcomes must be clarified with longer follow up, we believe that this hypofractionated regimen can be used as practical clinical treatment. We believe that widespread of hypofractionated radiotherapy after BCS will help to reduce financial and temporal burdens on patients, and also help to accommodate the exponentially increasing number of cancer patients needing radiotherapy.

Conflict of interest None.

References

1. Malmstrom P, Holmberg L, Anderson H, Mattsson J, Jonsson PE, Tenvall-Nittby L, et al. Breast conservation surgery, with and without radiotherapy, in women with lymph node negative breast cancer: a randomized clinical trial in a population with access to public mammography screening. Eur J Cancer. 2003;39:1690–7.
2. Liljegren G, Holmberg L, Bergh J, Lindgren A, Tabar L, Nordgren H, et al. 10-Year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. J Clin Oncol. 1999;17:2326–33.
3. Renton SC, Gazet JC, Ford HT, Corbishley C, Sutcliffe R. The importance of the resection margin in conservative surgery for breast cancer. Eur J Surg Oncol. 1996;22:17–22.
4. Veronesi U, Salvadori B, Luini A, Greco M, Saccozzi R, del Vecchio M, et al. Breast conservation is a safe method in patients with small cancer of the breast. Long-term results of three randomized trials on 1,973 patients. Eur J Cancer. 1995;31A: 1574–9.
5. Forrest AP, Stewart HJ, Everington D, Prescott RJ, McArdle CS, Harnett AN, et al. Randomised controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. Scottish Cancer Trials Breast Group. Lancet. 1996;348:708–13.
6. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002;347:1233–41.
7. Clark RM, Whelan T, Levine M, Roberts R, Willan A, McCulloch P, et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. Ontario Clinical Oncology Group. J Natl Cancer Inst. 1996;88:1659–64.
8. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Favorable and unfavorable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomized trials. Lancet. 2000;355:1757–70.
9. Vinh-Hung V, Verschraegen C. Breast-conserving surgery with or without radiotherapy: pooled-analysis for risks of ipsilateral breast tumor recurrence and mortality. J Natl Cancer Inst. 2004; 96:115–21.
10. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. Lancet 2005;366: 2087–106.
11. Ash DV, Benson EA, Sainsbury JR, Round C. Seven-year follow-up on 334 patients treated by breast conserving surgery and short course radical postoperative radiotherapy: a report of the Yorkshire Breast Cancer Group. Clin Oncol. 1995;7:93–6.
12. Olivotto IA, Weir LM, Kim-Sing C, Bajdik CD, Trevisan CH, Doll CM, et al. Late cosmetic results of short-fractionation for breast conservation. Radiother Oncol. 1996;41:7–13.
13. Shelly W, Brundage M, Hayter C, Paszat L, Zhou S, Mackillop W. A shorter fractionation schedule for postlumpectomy breast cancer patients. Int J Radiat Oncol Biol Phys. 2000;47(5): 1219–28.
14. Whelan T, MacKenzie R, Julian J, Levine M, Shelly W, Grimard L, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. J Natl Cancer Inst. 2002;94:1143–50.
15. Whelan T, Pignol J, Levine M, Julian J, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med. 2010;362:513–20.
16. The START Trialists' Group. The U.K. Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomized trial. Lancet Oncol. 2008;9:331–41.
17. The START Trialists' Group. The U.K. Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomized trial. Lancet. 2008;371:1098–107.
18. Cox J, Stetz J, Pajak T. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995;31(5):1341–6.
19. Peto R, Pike MC, Armitage P. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer. 1977;35:1–39.
20. Cox DR. Regression models and life-tables. J R Stat Soc B. 1972;334:187–202.
21. Fujii O, Hiratsuka J, Nagase N, Tokiya R, Yoden E, Sonoo H, et al. Whole-breast radiotherapy with shorter fractionation schedules following breast-conserving surgery: short-term morbidity and preliminary outcomes. Breast Cancer. 2008;15:86–92.

22. Romestaing P, Lehingue Y, Carrie C, Coquard R, Montbarbon X, Ardiet JM, et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of randomized clinical trial in Lyon, France. J Clin Oncol. 1997;15(3):963–8.
23. Bartelink H, Horiot JC, Poortmans P, Struikmans H, Van den Bogaert W, Barillot I, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. N Engl J Med. 2001;345(19):1378–87.
24. Veronesi U, Volterrani F, Luini A, Saccozzi R, Del Vecchio M, Zucali R, et al. Quadrantectomy versus lumpectomy for small size breast cancer. Eur J Cancer. 1990;26(6):671–3.
25. Yoden E, Hiratsuka J, Imajyo Y. Radiation dermatitis and pneumonitis following breast conserving therapy. J Jpn Soc Ther Radiol Oncol. 2000;12:237–46 (in Japanese with English abstract).

Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring *EGFR* mutations (JO25567): an open-label, randomised, multicentre, phase 2 study

Takashi Seto, Terufumi Kato, Makoto Nishio, Koichi Goto, Shinji Atagi, Yukio Hosomi, Noboru Yamamoto, Toyoaki Hida, Makoto Maemondo, Kazuhiko Nakagawa, Seisuke Nagase, Isamu Okamoto, Takeharu Yamanaka, Kosei Tajima, Ryosuke Harada, Masahiro Fukuoka, Nobuyuki Yamamoto

Lancet Oncol 2014; 15: 1236–44
Published Online August 28, 2014
http://dx.doi.org/10.1016/S1470-2045(14)70381-X
This online publication has been corrected. The corrected version first appeared at thelancet.com/oncology on September 29, 2014

See Comment page 1184

National Kyushu Cancer Center, Fukuoka, Japan (T Seto MD); Kanagawa Cardiovascular and Respiratory Center, Kanagawa, Japan (T Kato MD); The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan (M Nishio MD); National Cancer Center Hospital East, Chiba, Japan (K Goto MD); Kinki-chuo Chest Medical Center, Osaka, Japan (S Atagi MD); Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan (Y Hosomi MD); National Cancer Center Hospital, Tokyo, Japan (Noboru Yamamoto MD); Aichi Cancer Center, Aichi, Japan (T Hida MD); Miyagi Cancer Center, Miyagi, Japan (M Maemondo MD); Kinki University Faculty of Medicine, Osaka, Japan (Prof K Nakagawa MD); Tokyo Medical University Hospital, Tokyo, Japan (S Nagase MD); Kyushu University Hospital, Fukuoka, Japan (I Okamoto MD); National Cancer Center, Chiba, Japan (T Yamanaka PhD); Chugai Pharmaceutical Co Ltd, Tokyo, Japan (K Tajima MSc, R Harada BS); Izumi Municipal Hospital, Osaka, Japan (M Fukuoka MD); and Wakayama Medical University, Wakayama, Japan (Prof Nobuyuki Yamamoto MD)

Summary

Background With use of EGFR tyrosine-kinase inhibitor monotherapy for patients with activating *EGFR* mutation-positive non-small-cell lung cancer (NSCLC), median progression-free survival has been extended to about 12 months. Nevertheless, new strategies are needed to further extend progression-free survival and overall survival with acceptable toxicity and tolerability for this population. We aimed to compare the efficacy and safety of the combination of erlotinib and bevacizumab compared with erlotinib alone in patients with non-squamous NSCLC with activating *EGFR* mutation-positive disease.

Methods In this open-label, randomised, multicentre, phase 2 study, patients from 30 centres across Japan with stage IIIB/IV or recurrent non-squamous NSCLC with activating *EGFR* mutations, Eastern Cooperative Oncology Group performance status 0 or 1, and no previous chemotherapy for advanced disease received erlotinib 150 mg/day plus bevacizumab 15 mg/kg every 3 weeks or erlotinib 150 mg/day monotherapy as a first-line therapy until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival, as determined by an independent review committee. Randomisation was done with a dynamic allocation method, and the analysis used a modified intention-to-treat approach, including all patients who received at least one dose of study treatment and had tumour assessment at least once after randomisation. This study is registered with the Japan Pharmaceutical Information Center, number JapicCTI-111390.

Findings Between Feb 21, 2011, and March 5, 2012, 154 patients were enrolled. 77 were randomly assigned to receive erlotinib and bevacizumab and 77 to erlotinib alone, of whom 75 patients in the erlotinib plus bevacizumab group and 77 in the erlotinib alone group were included in the efficacy analyses. Median progression-free survival was 16·0 months (95% CI 13·9–18·1) with erlotinib plus bevacizumab and 9·7 months (5·7–11·1) with erlotinib alone (hazard ratio 0·54, 95% CI 0·36–0·79; log-rank test p=0·0015). The most common grade 3 or worse adverse events were rash (19 [25%] patients in the erlotinib plus bevacizumab group *vs* 15 [19%] patients in the erlotinib alone group), hypertension (45 [60%] *vs* eight [10%]), and proteinuria (six [8%] *vs* none). Serious adverse events occurred at a similar frequency in both groups (18 [24%] patients in the erlotinib plus bevacizumab group and 19 [25%] patients in the erlotinib alone group).

Interpretation Erlotinib plus bevacizumab combination could be a new first-line regimen in *EGFR* mutation-positive NSCLC. Further investigation of the regimen is warranted.

Funding Chugai Pharmaceutical Co Ltd.

Introduction

Lung cancer is a leading cause of death worldwide; it is the primary cause of cancer deaths in men and the secondary cause in women.[1] Most patients with lung cancer have non-small-cell lung cancer (NSCLC) and a clinically significant proportion of patients have activating mutations of *EGFR*.[2] In this subgroup of patients, EGFR tyrosine-kinase inhibitors have consistently led to better outcomes than has standard chemotherapy.[3–6] Erlotinib and gefitinib have been shown to prolong progression-free survival compared with chemotherapy in several phase 3 trials.[7–10] Unfortunately, most patients with NSCLC with activating *EGFR* mutations who are given EGFR tyrosine-kinase inhibitors eventually develop resistance and relapse within about 1 year of initiation of treatment.[5,7–11] To improve outcomes, the foundation treatment of EGFR tyrosine-kinase inhibitors should be built on through investigation of biologically synergistic combinations.

The anti-angiogenic monoclonal antibody bevacizumab targets the VEGF signalling pathway and has been shown to provide additional efficacy when used in combination with first-line platinum-based chemotherapy in several trials in non-squamous NSCLC.[12–14] The combination of erlotinib and bevacizumab has the potential to prolong progression-free survival in unselected populations of patients with NSCLC.[15,16] In a subgroup analysis of *EGFR*

mutation-positive participants in the phase 3 BeTa study of second-line treatment of NSCLC (12 patients treated with erlotinib and bevacizumab and 18 with erlotinib alone), median progression-free survival with erlotinib plus bevacizumab in patients with *EGFR* mutation-positive disease was substantially higher than with erlotinib alone (17·1 months *vs* 9·7 months).[16,17] However, this analysis was post-hoc and *EGFR* mutation status was not a prespecified stratification factor in this trial. Because of this limitation, we undertook this phase 2 trial to examine the combination of erlotinib and bevacizumab in patients with *EGFR* mutation-positive NSCLC.

Methods

Study design and patients

JO25567 was a randomised, open-label, multicentre, phase 2 study in patients with stage IIIB/IV (according to the 7th edition of the General Rule for Clinical and Pathological Record of Lung Cancer[18]) or recurrent NSCLC with activating *EGFR* mutations. Patients were enrolled from 30 centres across Japan.

Eligible patients had histologically or cytologically (excluding sputum cytology) confirmed stage IIIB/IV or postoperative recurrent non-squamous NSCLC with activating *EGFR* mutation (either exon 19 deletion or Leu858Arg mutation). Tumour samples were screened for *EGFR* mutation by PCR-based hypersensitive *EGFR* mutation testing in local laboratories, according to standard testing practices. Other criteria included age 20 years or older when giving informed consent; Eastern Cooperative Oncology Group performance status 0 or 1; adequate haematological, hepatic, and renal function; and life expectancy 3 months or more at the time of registration. No previous chemotherapy for advanced disease was allowed, but postoperative adjuvant or neoadjuvant therapy of 6 months or more previously was allowed. Previous radiotherapy was also allowed, but only for non-lung lesions. Patients had to have one or more measurable lesion based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

Major exclusion criteria included confirmation of Thr790Met mutation, presence of brain metastases, history or presence of haemoptysis or bloody sputum, any coagulation disorder, tumour invading or abutting major blood vessels, coexistence or history of interstitial lung disease, and previous receipt of EGFR inhibitors or VEGF receptor inhibitors.

This study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was reviewed and approved by the institutional review boards of the participating institutions (appendix p 10), and written informed consent was obtained from all patients.

Randomisation and masking

Patients were randomly assigned (1:1) to receive either erlotinib plus bevacizumab or erlotinib alone with a dynamic allocation method. Central randomisation was done by a clinical research organisation (EPS Corporation, Tokyo, Japan). Patients were stratified according to sex (men *vs* women), disease stage (stage IIIB *vs* stage IV *vs* postoperative relapse), smoking history (never smokers or former light smokers *vs* others), and type of *EGFR* mutation (exon 19 deletion *vs* Leu858Arg mutation). All patients and investigators were unmasked to treatment allocation.

Correspondence to:
Prof Nobuyuki Yamamoto, Wakayama Medical University, 811-1, Kimiidera, Wakayama-shi, Wakayama 641-8509, Japan
nbyamamo@wakayama-med.ac.jp

Procedures

Patients assigned to the erlotinib plus bevacizumab group received bevacizumab 15 mg/kg by intravenous infusion on day 1 of a 21-day cycle and erlotinib orally once daily at 150 mg/day, starting from day 1 of cycle 1. Patients in the erlotinib alone group received erlotinib orally once a day at 150 mg/day. Patients remained on treatment until disease progression or unacceptable toxicity. Changes to dose of erlotinib or bevacizumab because of adverse events were allowed, as per the protocol. The dose of bevacizumab was not to be reduced except when dose adjustment was needed because of change in bodyweight. Dose reduction of erlotinib was allowed for up to two doses (100 mg/day and 50 mg/day) in a stepwise decrease. After two steps of dose reduction, erlotinib was discontinued. Patients who required suspension of erlotinib for more than 3 weeks consecutively, or of bevacizumab for more than 6 weeks from the date of previous administration, were discontinued from study treatment. In the erlotinib plus bevacizumab group, if either drug was discontinued, the other could be

See Online for appendix

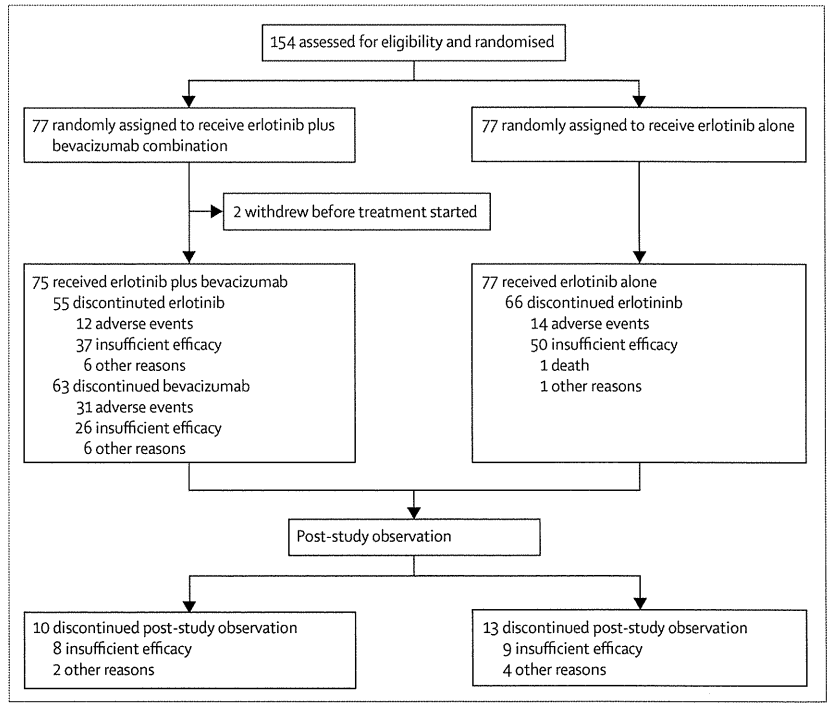

Figure 1: **Trial profile**