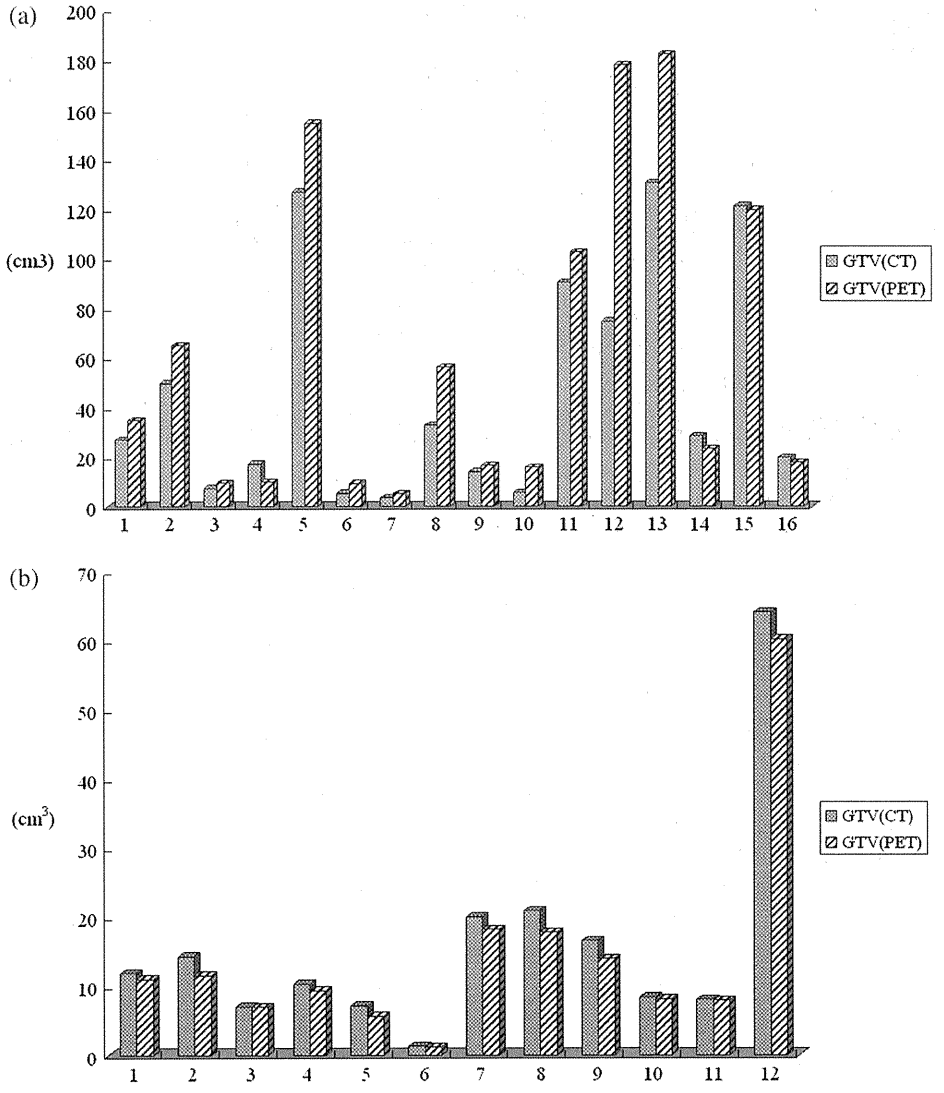

Fig. 1. Volumes of GTV for each patient with lung and pharyngeal cancer. (a) Volumes of GTV of lung cancer are shown. The volumes of GTVPET were significantly larger than those of GTVCT ($p < 0.0001$). (b) Volumes of GTV of pharyngeal cancer are shown. The volumes of GTVCT were slightly but significantly larger than those of GTVPET in all tumors ($p = 0.002$).

The size of the GTVPET in the axial plane was visually well fitted to those of GTVCT.

GTVs for each patient are shown in Fig. 1a. The mean ± SD volume of GTVCT was 47 ± 46 cm^3 (range, 4–131 cm^3) and that of GTVPET was 63 ± 64 cm^3 (range, 5–183 cm^3). The volumes of GTVPET were larger than those of GTVCT in 12 of 16 tumors. The volumes of GTVPET were significantly larger than those of GTVCT ($p < 0.0001$).

Among the 14 pharyngeal tumors, 2 small tumors could not be depicted on either CT or MRI. However, these two primary tumors could be clearly delineated on PET (Fig. 2). For the 2 tumors, a threshold of 2.5 SUV was adopted. Volumes of the remaining 12 primary tumors were evaluated. The mean maximum ± SD diameter of tumors in the axial plane on CT or MRI was 3.7 ± 1.3 cm (range, 1.2–5.3 cm). The numbers of tumors with maximum diameters of ≤2 cm, 2 to 5 cm, and >5 cm were 2, 8, and 2, respectively. Maximum ± SD diameter of GTVPET in the axial plane on the level of the largest GTVCT was 3.4 ± 1.1 cm (range, 1.7–5.1 cm). There were no significant differences in maximum diameter between GTVPET and GTVCT ($p = 0.063$). The sizes of GTVPET in the axial plan were visually well fitted to those of GTVCT.

GTVs for each patient are shown in Fig. 1b. The mean ± SD volume of GTVCT was 16 ± 16 cm^3 (range, 1.3–64 cm^3), and that of GTVPET was 14 ± 15 cm^3 (range, 1.2–60 cm3). The volumes of GTVCT were slightly but significantly larger than those of GTVPET in all tumors ($p = 0.002$).

Number of positive lymph nodes

For lung cancer, the numbers of LNCT, LNPET-RTP, and LNPET-2.5 SUV were 29, 28, and 34 in 18 patients, respectively. When LNPET-2.5 SUV was regarded as a gold standard for malignant lymph nodes, 34 lymph nodes were

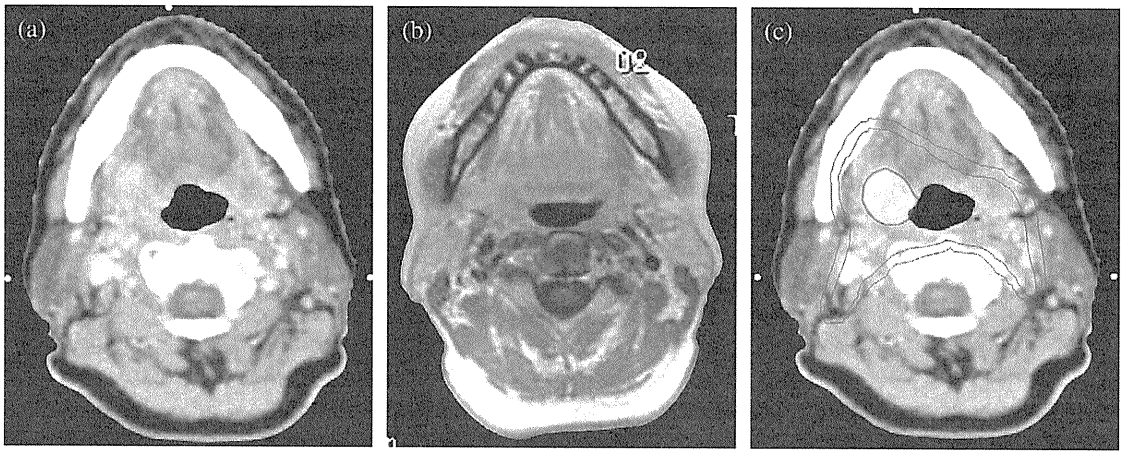

Fig. 2. CT (a), MRI (b), and PET (c) images of a pharyngeal tumor in the axial plane. The pharyngeal tumor was unclear on CT (a) and MRI (b) images. (c) A fused PET/CT image delineated the pharyngeal tumor clearly. The internal line shows the clinical target volume, and the external line shows the PTV.

malignant. In the actual RTP of this study, all LNPET-2.5 SUV were regarded as malignant lymph nodes and included in the target volume. All 29 LNCT were also positive for PET-2.5 SUV, and the remaining five LNPET-2.5 SUV with the shortest axial diameter of 6 to 7 mm were negative on CT. Thus, 28 (82%) of the 34 LNPET-2.5 SUV were positive for PET-RTP. In 1 patient with a primary tumor showing high FDG uptake, one LNCT was negative for PET-RTP.

For the 14 patients with pharyngeal cancer, the numbers of LNCT/MRI, LNPET-RTP, and LNPET-2.5 SUV were 14, 9, and 15, respectively. For pharyngeal cancer, LNPET-2.5 SUV and LNCT/MRI were regarded as malignant lymph nodes. CT/MRI-positive lymph nodes were also positive for PET-2.5 SUV in 12 (86%) of the 14 LNCT/MRI. CT/MRI-positive lymph nodes were negative for PET-2.5 SUV in two retropharyngeal lymph nodes with the shortest axial diameter of 6 mm. On the other hand, three cervical lymph nodes with the shortest axial diameter of 7 to 8 mm (CT/MRI-negative lymph nodes) were positive for PET-2.5 SUV. Thus, in total, 17 lymph nodes were regarded as malignant and were included in the target volume of the real RTP. Only 9 (53%) of the 17 malignant lymph nodes were positive for PET-RTP, and 5 retropharyngeal lymph nodes with the shortest axial diameter of 5 to 9 mm and 3 cervical lymph nodes with the shortest axial diameter of 7 to 8 mm were negative for PET-RTP.

DISCUSSION

The clinical applicability of the multiple-thresholds method for RTP was evaluated in the present study. Three threshold levels for FDG activity were adopted according to tumor size. For tumors of ≤2 cm, 2 to 5 cm, and >5 cm, threshold values were defined as 2.5 SUV, 35%, and 20% of the maximum FDG activity, respectively. The maximum FDG activity of small spheres of less than 22 mm was inaccurate due to the partial volume effect, and its values decreased rapidly depending on the size (19). For small spheres of less than 22 mm, an appropriate threshold value could not be expressed as the percentage of the maximum FDG activity. Thus, we adopted an absolute value of 2.5 SUV as the threshold for target delineation in PET images for tumors of ≤2 cm, according to published literature (24). One major finding of this study was that the sizes of primary tumors in the axial plane were not significantly different between GTVPET and GTVCT. In addition, GTVPET was visually well fitted to and overlapped with GTVCT. Therefore, our multiple thresholds for FDG activity were applicable for contouring primary tumors on PET/CT simulation.

The volumes of GTVPET for lung cancer were significantly larger than those of GTVCT. This result was attributable to the respiratory motion of the lung tumors, suggesting that PET images have the potential to delineate ITV. A few reports have described the benefit of PET images in delineating ITV (19, 22). However, both of the reports consisted of experiments using phantoms. To our knowledge, there have been no previous clinical reports of the potential of PET images in delineating ITV. For pharyngeal cancer, the volumes of GTVCT were slightly larger than those of GTVPET, although the difference was clinically negligible. This result may be related to the difficulty in delineation of pharyngeal tumors with CT/MRI. In fact, the site and size of two pharyngeal tumors could not be depicted by either CT or MRI (Fig. 2). For these tumors, PET/CT simulation was clinically useful to contour the target volumes.

PET/CT is a more accurate modality than CT for detecting malignant lymph nodes in lung cancer (34, 35). On the other hand, for head and neck cancer, MRI images are standard for detecting malignant lymph nodes (29, 36). Generally, potentially malignant lymph nodes should be defined as GTV in the RTP, and a definitive dose should be delivered to these lymph nodes. Therefore, in the present study, LNPET-2.5 SUV was regarded as the gold standard for malignant lymph nodes for lung cancer, and LNPET-2.5 SUV and LNCT/MRI were regarded as malignant for pharyngeal cancer and were

included in the target volume of the real RTP. Although biopsy samples of these lymph nodes were not obtained, the nodes regressed after RT. Thus, our definition of malignant lymph nodes seems clinically reasonable.

For lung cancer, 28 (82%) of the 34 LNPET-2.5 SUV were positive according to PET-RTP. For pharyngeal cancer, only 9 (53%) of the 17 malignant lymph nodes were positive by PET-RTP. Most of the negative lymph nodes in PET-RTP were retropharyngeal or cervical lymph nodes with the shortest axial diameter of 5 to 9 mm. Thus, delineation of malignant lymph nodes in PET-RTP should be performed with caution.

In the present study, PET scans were performed at 60 min postinjection of FDG. Several investigators have reported that delayed scanning until 2 to 3 hours after injection was better than early scanning for the depiction of tumors (37, 38). Nakamoto *et al.* suggest that delayed FDG-PET scanning until 2 hours postinjection may contribute to differentiation between malignant and benign lesions (37). However, in the RTP, differential diagnosis is not necessary, and early scanning is clinically convenient.

Recently, PET/CT simulation using other radioisotopes such as [^{18}F] fluoromisonidazole have been investigated (39–41). Lee *et al.* reported the feasibility of dose escalation for patients with head and neck cancer by using [^{18}F] fluoromisonidazole PET/CT without exceeding the normal tissue tolerance (39). PET/CT simulation is a useful tool that combines functional imaging and precise RT. However, it is a major challenge to determine an appropriate threshold for these new radioisotopes in RTP.

CONCLUSIONS

In conclusion, our multiple thresholds were applicable for the primary target delineation in PET/CT simulation. More accurate target delineation by PET/CT simulation than conventional CT simulation may contribute to safe dose escalation to primary tumors. However, these thresholds were inaccurate for depicting malignant lymph nodes, especially in cases of pharyngeal cancer. For contouring malignant lymph nodes on PET/CT simulation, LNPET-2.5 SUV and MRI images should be referred.

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Definitive Radiation Therapy for Moderately Advanced Laryngeal Cancer: Effects of Accelerated Hyperfractionation

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Objective: The purpose of this retrospective study was to analyze the results of accelerated hyperfractionation for patients with modeletaly advanced (T2 and T3) laryngeal cancer.

Methods: Between 1998 and 2007, 9 supraglottic carcinomas (6 T2N0M0, 2 T2N2M0, 1 T3N0M0), 30 glottic carcinomas (25 T2N0M0, 5 T3N0M0), and 1 T2N0M0 subglottic carcinoma were treated with definitive radiotherapy using accelerated hyperfractionation without concurrent chemotherapy. The dose-fractionation for 35 patients was 72.8 Gy/56 fractions/5.6 weeks, and that for four patients treated between 1998 and 2001 was 72 Gy/60 fractions/6 weeks. One patient who had been treated with steroid therapy for systemic lupus erythematosus was treated by 67.8 Gy/44 fractions/4.4 weeks.

Results: The local control and overall survival probabilities at 5 years for supraglottic carcinomas were 75% and 86%, respectively. Those for glottic carcinomas were 80% and 92%, respectively. The 5-year local control probabilities for T2 and T3 tumors were 85% and 56%, respectively. This excellent local control rate especially for T2 laryngeal carcinomas may be attributable to the effect of accelerated hyperfractionation. No late toxicities of grade 2 or more was noted among the 39 patients treated with 72.8 Gy/56 fractions or 72 Gy/60 fractions.

Conclusion: Accelerated hyperfractionation of 72.8 Gy/56 fractions/5.6 weeks using 1.3 Gy/fraction seems a safe and effective dose-fractionation for patients with moderately advanced laryngeal carcinomas.

Key words: accelerated hyperfractionated radiotherapy – laryngeal cancer – radiation therapy

INTRODUCTION

Radiotherapy (RT) is a well-established treatment method for patients with early laryngeal carcinomas, although laser therapy and partial laryngectomy can also treat early laryngeal carcinomas definitively (1–3). The goals of treatment are cure of the cancer, preservation of the vocal cord with acceptable voice quality and minimal treat-related mobility. Definitive RT can achieve all these goals for most of patients with early laryngeal carcinomas. In addition, salvage laryngectomy can be performed for patients with relapse after definitive RT, effectively. The ultimate local control late for the patients with salvage laryngectomy for recurrences after initial RT has been reported to be in the range 90–100% for early laryngeal carcinomas (4–9).

The local control rates for laryngeal cancers treated with conventional fractionation (CF) are from 80% to 90% for T1 glottic lesions and approximately 70% for T2 glottic lesions (8,10–12). Thus, although conventional RT alone yields an

adequate local control rate for T1 glottic lesions, the local control for T2 lesions has much scope for improvement. Several approaches have been employed to improve control rate for T2 glottic and supraglottic laryngeal cancer, including hyperfractionated RT, combined chemotherapy with RT and induction chemotherapy after partial laryngectomy. Garden et al. (13). reported that hyperfractionated RT improved the local control rate for patients with T2 glottic cancer as compared with CF.

Consistent radiobiological and clinical data suggest that increasing the overall treatment time (OTT) is detrimental to locoregional control as it enhances tumor repopulation during treatment (14–16). The importance of OTT on tumor control for T3–4 laryngeal cancers was first noted in 1983 by Maciejewski et al. (17). Nishimura et al. (11) demonstrated that 1 week prolongation of treatment time reduces the 5-year local control rate for patient with early laryngeal cancer from 89% to 74%. Accelerated hyperfractionation (AHF) is defined as a scheme with a significant reduction of OTT compared with CF. At our hospital, hyperfractionated RT of 72 Gy/60 fractions/6 weeks was given for moderately advanced laryngeal cancer since 1998, and this institutional protocol was changed to more accelerated scheme of RT using 1.3 Gy/fraction two fractions daily to a total dose of 72.8 Gy in 2001 because of the mild acute toxicities of the former fractionation. The present study is a retrospective analysis of the results of accelerated hyperfractionated RT for patients with modeletaly advanced laryngeal cancer at Kinki University Hospital.

PATIENTS AND METHODS

Patients

Between 1998 and 2007, 44 consecutive patients with moderately advanced (T2 and T3) squamous cell carcinomas of the larynx were treated with definitive RT at Kinki University Hospital. This retrospective analysis included 40 of the 44 patients treated with hyperfractionated RT without concurrent chemotherapy. Characteristics of the 40 patients are shown in Table 1. Patient's stage was defined according to the 2002 TNM classification (6th edition, International Union Against Cancer). The average age of the patients was 63 years (range; 49–83 years). Performance status (PS) for most patients was PS0 or PS1. The distribution of the primary site was follows; glottis in 30 patients; supraglottis in 9; subglottis in 1. All patients with glottic or subglottic carcinomas had no clinical neck metastasis. Two patients with supraglottic carcinomas had lymph node metastasis, and those patients were treated with neck dissection before definitive RT for primary tumors. Nine patients (23%) had double cancers; one head and neck cancer, three gastric cancers, one esophageal cancer, two liver tumors, one prostate cancer and one colon cancer. The median follow-up duration of the patients was 54 months (range; 7–95 months). Only one patient was lost with follow-up at 7 months.

Table 1. Patient characteristics

Characteristic	Supraglottic carcinoma	Glottic carcinoma[a]
Gender (*n*)		
Male	7	29
Female	2	2
Median ages (years)	64 (54–80)	62 (49–83)
Performance status (*n*)		
0	7	27
1	1	4
2	1	0
T stage (*n*)		
T2	8	26[a]
T3	1	5
N stage (*n*)		
N0	7	31
N1	0	0
N2	2	0
Clinical stage (*n*)		
II	6	26[a]
III	1	5
IVA	2	0

[a]One patient with subglottic carcinoma was included.

Radiation Treatment

The standard RT technique was parallel opposing lateral fields using ^{60}Co γ-ray in 5 patients (12%) between 1998 and 2000, or high energy photons of 4–6 mV X-ray in 35 patients (88%). A telecobalt unit was replaced to a 4 MV linear accelerator in 2000. During the period of its installation, two patients were treated with 6 mV X-ray. Patients were immobilized using a bite block and/or shell in the supine position. All patients received continuous-course irradiation using twice-a-day fractionation.

The details of RT methods and dose-fractionation are shown in Table 2. Irradiation for T2 glottic tumors was delivered by local portals (mostly 5–6 × 5–6 cm) covering only the primary lesion. The cervical lymph node chain was not electively treated. For T3 glottic tumors, larger portals (mostly 6–8 × 6–8 cm) which included the primary lesion and upper and middle jugular lymph nodes were used. The dose-fractionation for 28 of 31 patients (90%) with glottic carcinomas was AHF of 72.8 Gy/56 fractions/5.6 weeks, and that for the remaining 3 patients (10%) with glottic carcinomas treated between 1998 to 2001 was 72 Gy/60 fractions/6 weeks.

For patients with supraglottic carcinomas, RT field included upper and middle jugular lymph nodes. Supraclavicular lymph nodes were irradiated in separate low-neck portals for two patients with lymph node

Table 2. Radiotherapy and dose-fractionation

	Glottic carcinomas[a]	Supraglottic carcinomas
Total dose (median; range)	72.8 Gy (72–72.8 Gy)	72.8 Gy (67.8–72.8 Gy)
Fractionation (median; range)	56 Fr (55–60 Fr)	56 Fr (44–60 Fr)
Overall treatment time	42 days (38–44 days)	42 days (39–46 days)
Beam energy (*n*)		
^{60}Co γ-ray	4	1
4 mV X-ray	25	8
6 mV X-ray	2[a]	0

Fr, fractions.
[a]One patient with subglottic carcinoma was included.

metastasis. Initial portals were reduced after 45–46 Gy to exclude the spinal cord, and boost RT was given to the primary lesion. The dose and fractionation for seven patients of nine (78%) with supraglottic carcinomas was AHF of 72.8 Gy/56 fractions/5.6 weeks, and that for one patient treated at 1998 was 72 Gy/60 fractions/6 weeks. The remaining one patient who had been treated with steroid therapy for systemic lupus erythematosus (SLE) was irradiated by AHF using concomitant boost (1.2 Gy and 1.8 Gy/fraction) with total dose of 67.8 Gy/44 fractions/44 days.

Evaluation of the Local Response and Toxicity

Local response was estimated by laryngoscope 1 month after the completion of RT. Local failure or recurrence was considered to have occurred when local recurrence developed after initial complete response (CR). In evaluating acute or late effect, toxicity criteria of the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0) were used.

Statistical Evaluation

The endpoints were local control and overall survival, which were calculated from the first date of RT. All patients whose primary lesions failed but were successfully salvaged by surgery were counted as local failure of RT. For overall survival, all the causes of death were considered as events. Survival was plotted using the Kaplan–Meier method, with statistical significance assessed by using log-rank test.

RESULTS

Local Control and Overall Survival

Local control and overall survival curves for supraglottic and glottic carcinomas are shown in Figs 1 and 2. Local control probabilities at 5 years for supraglottic and glottic carcinoma were 75% and 80%, respectively (Fig. 1). The difference of local control probability between supraglottic and glottic carcinomas was not statistically significant ($P = 0.850$). Overall survival probabilities at 5 years for supraglottic and glottic carcinomas were 86% and 92%, respectively, without significant difference ($P = 0.541$; Fig. 2).

Figure 3 shows the local control probabilities for T2 and T3 supraglottic and glottic tumors. The 5-year local control probabilities for T2 and T3 tumors were 85% and 56%,

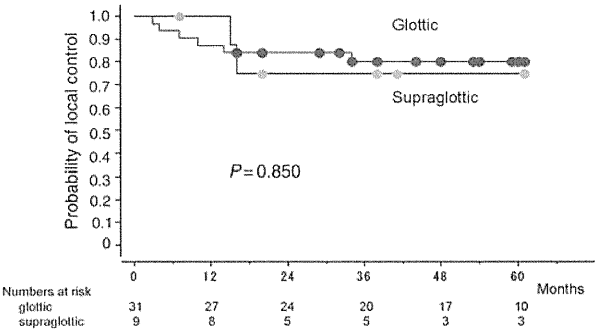

Figure 1. Local control probabilities at 5 years for supraglottic and glottic carcinoma.

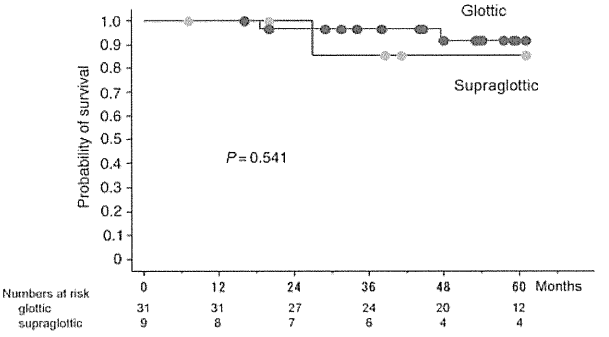

Figure 2. Overall survival probabilities at 5 years for supraglottic and glottic carcinomas.

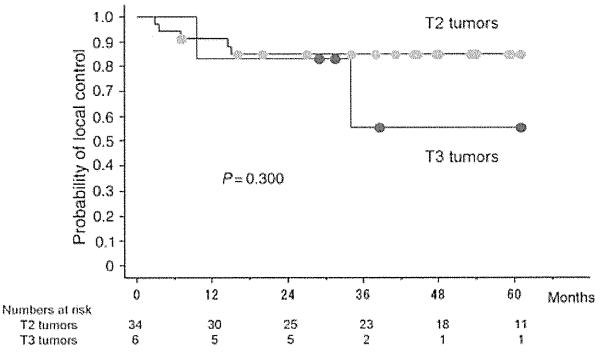

Figure 3. Local control probabilities for T2 and T3 supraglottic and glottic tumors.

respectively. No significant difference in local control probabilities was observed between T2 and T3 tumors ($P = 0.300$).

Salvage Treatment

Four local recurrences were noted and total or hemi-laryngectomy was performed for them, and surgical salvage was successful for three of the patients (Table 3). The voice was preserved in one patient successfully salvaged by hemi-laryngectomy.

Complications

Table 4 shows the acute and late complications of RT. Eight (20%) of the 40 patients had grade 2 acute dermatitis. Although six patients (15%) showed grade 3 acute mucositis, no patient showed grade 4 or more acute toxicities (Table 4).

Severe late complications were noted in one of the 40 patients (Table 4). The patient with T2N2bM0 supraglottic carcinoma was treated with AHF of 67.8 Gy/44 fractions/44 days without concurrent chemotherapy. The patient had used steroid therapy for SLE. This patient needed laryngectomy 9 months after RT due to laryngeal necnosis (grade 4), and skin ulcer (grade 4) developed 14 months after RT.

Table 3. Salvage treatments and its results for four patients with local recurrence

Salvage treatments	
Hemi-laryngectomy	1
Total laryngectomy	3
Clinical results	
NED	3
DOD	1

NED, no evidence of disease; DOD, died of the disease.

Table 4. Acute and late toxicities

Grade	0 or 1	2	3	4
Acute toxicities				
Esophagitis	38	2	0	0
Dermatitis	32	8	0	0
Mucositis	28	6	6	0
Late toxicities				
Laryngeal edema	39	0	0	1[a]
Skin	39	0	0	1[a]
Spinal cord	40	0	0	0

[a]Occurred in the same patient.

DISCUSSION

In the present study, local control probabilities at 5 years for T2–3 supraglottic and glottic carcinomas were 75% and 80%, respectively. These results are better than other reports on the result of RT using CF (approximately 70%) (12,13,21), and consistent with other reports on the result of RT using hyperfractionated RT for laryngeal cancers (11,13,18,19,21). Literatures for supraglottic carcinomas treated by definitive RT are relatively limited compared with glottic carcinomas (19–18). Mendenhall et al. (19) reported an overall local control rate of 83% for supraglottic carcinomas treated with RT using CF (60 to 75 Gy, 1.8 to 2.0 Gy/fraction) or HF (74.4 to 79.2 Gy, 1.2 Gy/fraction). The other investigator reported that the local control rate for the primary site of patients with supraglottic carcinomas irradiated using CF was 57% (18). Thus, the 5-year local control rate of 75% at our hospital is quite consistent with the literatures using CF or HF (18–20).

The 5-year local control probability for T2 supraglottic and glottic tumors was 85% in the present study (Fig. 3). This excellent result may be attributable to AHF. When a fraction size of 1.1–1.2 Gy is adopted as a pure hyperfractionation schema, a total RT dose can be increased approximately 10% without shortening of OTT (13,21). Garden et al. (13). reported that a 79% local control rate for patients treated with hyperfractionation RT (1.2 Gy/fraction, a total of 74–80 Gy) compared with 68% for patients treated with CF (70 Gy/35 fractions; $P = 0.06$) in a series of 230 patients with T2 glottic carcinomas. In a randomized trial for patients with T2 glottic carcinomas, Trotti et al. (21). showed a higher local control rate of 79% by hyperfractionated RT of 79.2 Gy/66 fractions (1.2 Gy/fraction) compared with that of 70% by CF (70 Gy/35 fractions). Although there was no significant difference in local control rate between the two arms, there was a trend for improvement in disease-free survival with hyperfractionated RT ($P = 0.07$).

Although there are many papers on pure hyperfractionated RT using a fraction size of 1.1–1.2 Gy for laryngeal cancer, no literature using a fraction size of 1.3 Gy to a total of 72.8 Gy has been reported for laryngeal cancer. At the start of this series, hyperfractionated RT of 72 Gy/60 fractions (1.2 Gy/fraction)/6 weeks was adopted for four patients. As the acute toxicities for the patients were so mild, we increased a fraction size to 1.3 Gy with a total RT dose of 72.8 Gy. Using a fraction size of 1.3 Gy, OTT could be shortened several days compared with a pure hyperfractionation schema. Another reason for the increasing fractional size was convenience of patients and to reduce the labor of RT unit. By increasing a fraction size, total number of fractions could be reduced four times. Although a total RT dose of 72.8 Gy in the present series is lower than those of pure hyperfractionation (74–79.2 Gy), the local control rate in the present study is as high as those of pure hyperfractionation. As our fractionation is slightly an accelerated fractionation,

this result indicates the importance of OTT for local control of laryngeal cancer.

AHF could be completed within a planned OTT without treatment interruptions (Table 2), although the incidence and degree of acute toxicities of AHF were slightly high (Table 4). Incidence of severe late toxicities (grade 3–4) was rare, and one patient (3%) showed grade-4 toxicity (Table 4). As one of the patients was treated with steroid therapy for SLE, altered fractionation or concurrent chemo-radiotherapy may be contraindicated for patients with the collagen disease. No late toxicities of grade 2 or more was noted for the 39 patients treated with 72.8 Gy/56 fractions or 72 Gy/60 fractions.

In conclusion, we have demonstrated that definitive RT gives patients with moderately advanced laryngeal carcinomas high cure rates with maintaining the quality of life. AHF of 72.8 Gy/56 fractions/5.6 weeks using 1.3 Gy/fraction seems a safe and effective dose-fractionation for patients with T2–3 laryngeal carcinomas.

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Conflict of interest statement

None declared.

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Review Article: Study Group

JCOG Radiation Therapy Study Group: History and Achievements

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The Radiation Therapy Study Group (RTSG) of the Japan Clinical Oncology Group (JCOG) was established in 2003. The missions of this group are to develop new standards of care with innovative, advanced technology radiation therapy, both for single- and multi-modality cancer treatment, and to improve radiation therapy quality and outcomes of JCOG trials conducted by other organ-oriented groups. In 2004, the first RTSG trial, a Phase II study of stereotactic body radiation therapy for Stage IA non-small cell lung cancer (JCOG 0403), was initiated. Four other trials are currently open for accrual. JCOG 0702 is a Phase I study of stereotactic body radiation therapy in patients with T2N0M0 non-small cell lung cancer. JCOG 0701 is a Phase III study comparing accelerated fractionation with conventional fractionation radiation therapy for T1–2N0M0 glottic cancer. JCOG 0906 is a multicenter safety trial of hypofractionated radiation therapy after breast-conserving surgery in patients with margin-negative invasive breast cancer. JCOG 1015 is a Phase II study of intensity-modulated radiation therapy with chemotherapy for loco-regionally advanced nasopharyngeal cancer. Other RTSG activities include a medical physics working group responsible for dosimetry audits; a genetic analysis working group involved in accompanying research to analyze single-nucleotide polymorphisms to identify predictors of radiation toxicities; a working group that has developed atlases of clinical target volumes for uterine cervical cancer; and participation in the Harmonisation Group to promote global harmonization of radiotherapy and radiotherapy quality assurance among trial groups. Further efforts to improve radiation therapy quality and outcomes of cancer treatment are necessary.

Key words: radiation therapy – clinical trials – stereotactic body radiotherapy – intensity-modulated radiotherapy – quality assurance

BACKGROUND AND HISTORY

Radiation therapy (RT) is one of the three major options in cancer treatment. As the population is aging, the number of patients who receive RT has been increasing. The utility of RT in Japan has been relatively lower than that in western countries, but promotion of RT is now a high-priority issue in the Basic Plan to Promote Cancer Control Programs, which was approved in 2007. The missions of our group, the Radiation Therapy Study Group (RTSG) of the Japan Clinical Oncology Group (JCOG), are to develop new standards of care with innovative, advanced technology RT, both for single- and multi-modality cancer treatment, and to improve RT quality and outcomes in JCOG trials conducted by other organ-oriented groups.

Our group was established in 2003, with support from a grant for Clinical Research for Evidence-Based Medicine from the Ministry of Health, Labour and Welfare, Japan. It was chaired by Professor M.H., with a group secretary, S.I.,

MD. In 2004, the RTSG opened its first trial, JCOG 0403, a Phase II study of stereotactic body radiation therapy (SBRT) for Stage IA non-small cell lung cancer (NSCLC). This study included a strict quality control and quality assurance program (1), supported in part by the Advanced Technology Consortium (ATC). The digital data of each case from RT planning systems were submitted to the Image-Guided Therapy QA Center (ITC) at Washington University in St Louis, MO, USA, and the final review was performed with the Remote Review Tool provided by the ITC (2). Today, 33 institutions are participating in our five ongoing trials, and the number of accrued patients is now over 600.

ACHIEVEMENTS AND ONGOING TRIALS

JCOG 0403 is a single-arm, Phase II study (3). This study was planned to determine whether SBRT is superior to conventional radiotherapy for patients with medically inoperable cancer and to explore whether SBRT can achieve survival comparable to that with surgery for patients with operable, clinical Stage IA NSCLC. The primary endpoint is 3-year overall survival, and the planned accrual goals are 100 patients with inoperable and 65 patients with operable cancer. Local progression-free survival, patterns of failure and toxicity are included as secondary endpoints. The results for patients with operable cancer were reported at the 52nd annual meeting of the American Society for Radiation Oncology (ASTRO), with encouraging 3-year overall survival of 76% (95% confidence interval, 63–85%), and results for patients with inoperable cancer will be available in 2012 (4).

JCOG 0702 is a Phase I study of the efficacy and safety of SBRT in patients with T2N0M0 NSCLC. The primary endpoint is the incidence of Grade 2 or greater radiation pneumonitis within 180 days after SBRT. This study is employing a continual reassessment method to determine the maximal tolerated dose that will lead to shortening of the accrual period. The results of this study will have a great impact on the determination of the optimal SBRT dose for Stage I NSCLC.

JCOG 0701 is a Phase III study comparing accelerated fractionation with conventional fractionation RT for T1–2N0M0 glottic cancer (5). Conventional fractionation RT consists of 66 Gy in 33 fractions for T1 tumors and 70 Gy in 35 fractions for T2 tumors. Accelerated fractionation RT consists of 60 Gy in 25 fractions for T1 tumors and 64.8 Gy in 27 fractions for T2 tumors. The primary endpoint is 3-year progression-free survival to examine the non-inferiority of accelerated fractionation. The accrual goal is 360 patients, and it will be reached at the end of 2012. In this trial, an accompanying analysis is ongoing to assess single-nucleotide polymorphisms (SNPs) from blood samples to find predictors of radiation toxicities.

JCOG 0906 is a multicenter safety trial of hypofractionated RT after breast-conserving surgery in patients with margin-negative invasive breast cancer. Hypofractionated RT consists of 42.56 Gy in 16 fractions over 22 days for the whole breast. For patients with close margins, boost irradiation of 10.64 Gy in four fractions for 4 days is added. The primary endpoint is the proportion of Grade 2 or greater late adverse reactions at 3 years. When its toxicity proves to be within an acceptable range, hypofractionated RT will be the new standard of care. The accrual goal is 310 patients, and it will be reached in mid-2012.

JCOG 1015 is the most recent trial, a Phase II study of intensity-modulated radiation therapy (IMRT) with chemotherapy for loco-regionally advanced nasopharyngeal cancer. The treatment regimen includes concurrent chemoradiotherapy with two-step IMRT (70 Gy in 35 fractions over 47 days) and three cycles of cisplatin (80 mg/m^2, day 1, q3w) followed by three cycles of adjuvant chemotherapy with 5-FU (700 mg/m^2, days 1–5) plus cisplatin (70 mg/m^2, day 1) repeated every 4 weeks (6). The primary endpoint is 3-year overall survival, and efficacy and toxicity will be analyzed. This trial also has a strict quality control and quality assurance program, including a dosimetry audit, dry-run, and individual case review with the ITC Remote Review Tool.

OTHER ACTIVITIES

JCOG RTSG has working groups (WGs) to tackle issues associated with clinical trials. The Medical Physics WG is responsible for dosimetry audits for SBRT and IMRT trials (7), and its members will serve as consultants when needed. The genetic analysis WG contributed to the development of a JCOG policy for genetic analysis and is now involved in the SNP analysis accompanying JCOG 0701. The Uterine Cervical Cancer WG developed atlases of clinical target volumes for uterine cervical cancer in collaboration with the JCOG Gynecologic Cancer Study Group (8,9). Another WG has started active discussions about future lung SBRT trials in close collaboration with the JCOG Lung Cancer Study Group and the JCOG Lung Cancer Surgical Study Group.

The JCOG RTSG has also supported the JCOG Radiotherapy Committee in the improvement of RT quality and outcomes of trials conducted by other organ-oriented groups. The introduction of RT quality assurance programs in these trials has led to substantial improvements in RT quality (10–12). JCOG is now joining the Harmonisation Group, which aims to promote global harmonization of RT and RT quality assurance among trial groups, including the European Organisation for Research and Treatment of Cancer (EORTC), the Radiation Therapy Oncology Group (RTOG), the Trans Tasman Radiation Oncology Group (TROG), JCOG, the International Atomic Energy Agency (IAEA), the Radiological Physics Center (RPC), the National Cancer Institute (NCI) and the ATC. Continuous efforts to improve quality, especially in advanced technology RT, are mandatory.

CONCLUSIONS

The JCOG RTSG was developed in 2003 and has made substantial achievements through five clinical trials. However, we shall keep trying to improve RT quality and outcomes of cancer treatment. Future research will include multidisciplinary cancer care collaboration with other organ-oriented groups; treatment of intractable cancers; clarification of the effectiveness and reasonable role of highly advanced technology RT, including particle therapy; and more enthusiastically, integration with molecular-targeted therapies.

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The principal investigators of the JCOG RTSG trials are M.H., MD, Kyoto University (JCOG 0403); Yoshikazu Kagami, MD, Showa University (JCOG 0701, 0906); Hiroki Shirato, MD, Hokkaido University (JCOG 0702); and Yasumasa Nishimura, MD, Kinki University (JCOG1015). Study coordinators are Yasushi Nagata, MD, Hiroshima University (JCOG 0403); Takeshi Kodaira, MD, Aichi Cancer Center and Naoto Shikama, MD, Saitama Medical University (JCOG 0701); Rikiya Onimaru, MD, Hokkaido University (JCOG 0702); Miwako Nozaki, MD, Dokkyo Medical University and Michihide Mitsumori, MD, Kyoto University (JCOG 0906); and S.I., MD, Nagoya City University (JCOG1015). The members of the JCOG Radiotherapy Committee are Kazushige Hayakawa, MD, Kitasato University; S.I., MD, Nagoya City University; Keiji Nihei, MD, Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital; Takafumi Toita, MD, Ryukyu University; and Y.I., MD, National Cancer Center Hospital. The JCOG RTSG also wishes to thank all of the investigators at its participating institutions for their great collaborative efforts.

Conflict of interest statement

None declared.

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Single-agent gefitinib with concurrent radiotherapy for locally advanced non-small cell lung cancer harboring mutations of the epidermal growth factor receptor

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ABSTRACT

Introduction: A feasibility study was performed to examine the safety and toxicity profile of daily gefitinib (250 mg) administration with concurrent definitive thoracic radiation therapy (TRT) in patients with unresectable non-small cell lung cancer (NSCLC) of stage III.
Methods: Patients received a 14-day induction therapy with gefitinib at 250 mg daily. TRT was initiated on day 15 in 2-Gy fractions administered five times weekly to a total dose of 60 Gy. The primary end point of the study was the rate of treatment completion. Mutation status of the epidermal growth factor receptor gene (*EGFR*) was evaluated for patients with available tumor specimens.
Results: Nine eligible patients enrolled in the study received induction gefitinib monotherapy. Two patients were unable to begin TRT because of the development of progressive disease during the first 2 weeks of the protocol. Three of the remaining seven patients treated with gefitinib and concurrent TRT were unable to complete the planned treatment (two because of pulmonary toxicity and one because of progressive disease), and the study was therefore closed according to the protocol definition. Tumor samples were available for eight patients. *EGFR* mutations (deletion in exon 19) were detected in two patients, both of whom achieved a partial response and exhibited an overall survival of >5 years.
Conclusions: Our results do not support further trials of gefitinib and TRT for unselected NSCLC patients. This therapeutic strategy may hold promise, however, for locally advanced NSCLC in patients with sensitizing *EGFR* mutations.

1. Introduction

Lung cancer remains the most common cause of cancer-related mortality worldwide [1]. Non-small cell lung cancer (NSCLC) is a heterogeneous disease that accounts for ~80% of lung cancer cases, and about one-third of individuals with newly diagnosed NSCLC present with locally advanced disease not amenable to curative resection [2]. The current standard of care for patients with unresectable locally advanced NSCLC is concurrent chemotherapy and definitive thoracic radiation therapy (TRT); however, most treated individuals experience disease recurrence, with the 5-year survival rate being only ~20% [3–5]. Further improvement in treatment outcome for patients with locally advanced NSCLC will require the development of more effective combined-modality therapies.

The expression and activity of the epidermal growth factor receptor (EGFR) are important determinants of radiation sensitivity in several cancers including NSCLC [6–9]. Irradiation of tumor cells has been shown to activate EGFR via ligand-dependent and ligand-independent mechanisms, possibly accounting for the radiation-induced acceleration of tumor cell repopulation and the development of radioresistance [9,10]. Such radiation-induced activation of EGFR-dependent processes provides a rationale for combined treatment with radiation and EGFR inhibitors. Indeed, preclinical models have shown that EGFR inhibition enhances the antitumor activity of radiation [11–14]. Gefitinib is a small-molecule tyrosine kinase inhibitor (TKI) of EGFR that competes with ATP for binding to the tyrosine kinase pocket of the receptor, thereby inhibiting receptor tyrosine kinase activity and EGFR

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signaling pathways [15]. Although several clinical studies have examined the use of gefitinib in patients with advanced or metastatic NSCLC [15–17], no data have been available regarding the efficacy of single-agent gefitinib combined with TRT in individuals with locally advanced NSCLC. We have now performed a feasibility study of gefitinib with concurrent TRT in patients with locally advanced NSCLC in order to establish the safety and toxicity profile of this therapeutic strategy. Midway through this study, the discovery of somatic mutations in *EGFR* and of the association of such mutations with a high response rate to EGFR-TKIs had a profound impact on the treatment of metastatic NSCLC [18–20]. We therefore examined the potential relation between the presence of *EGFR* mutations as detected in diagnostic biopsy specimens and treatment outcome.

2. Materials and methods

2.1. Eligibility criteria

Patients with pathologically confirmed unresectable NSCLC of stage III were eligible for enrollment in the study, whereas those with T3N1 disease, contralateral mediastinal lymph node metastasis, malignant pleural effusion, pericardial effusion, or pleural dissemination were excluded. Additional eligibility criteria included no previous disease treatment, the presence of any measurable lesion, an Eastern Cooperative Oncology Group performance status score of 0–1, an age of ≤75 years, no history of malignancy within the previous 5 years, a leukocyte count of ≥4000/μL, a platelet count of ≥100,000/μL, a hemoglobin level of ≥9 g/dL, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of ≤50 IU/L, a serum creatinine concentration of ≤1.2 mg/dL, and an arterial oxygen pressure (PaO_2) of ≥70 mm Hg. Patients were excluded if they had interstitial pneumonitis, uncontrolled diabetes mellitus, or any serious underlying disease or complications. Staging workup included a chest radiograph, computed tomography (CT) scans of the chest and abdomen, either a CT scan or magnetic resonance imaging of the brain, and a radioisotopic bone scan. All subjects provided written informed consent to participation in the study, which was approved by the Institutional Review Board of each participating center (Kinki University School of Medicine and Yokohama Municipal Citizen's Hospital) and was performed in accordance with the Declaration of Helsinki.

2.2. Gefitinib therapy

Patients started taking 250 mg of gefitinib per day orally 14 days before initiation of TRT and continued doing so during TRT. At the completion of TRT, patients were maintained on gefitinib at 250 mg daily until evidence of disease progression or toxicity for up to 1 year. In the event of development of toxicities of grade 2 or higher, gefitinib was postponed until the toxicities had improved to grade 1 or lower. In the case that cessation of TRT was warranted, gefitinib was withheld until resumption of the remainder of the concurrent phase of the treatment. If patients experienced toxicities of grade 3 or higher or any grade of pneumonitis related to gefitinib, the treatment was terminated.

2.3. Radiation therapy

TRT was administered from day 15 of gefitinib using a linear accelerator photon beam of 6-MV or more. Three-dimensional (3D) treatment planning systems using computed tomography were used at both hospitals. Lung inhomogeneity correction was not performed in dose calculation. Radiation doses were specified at the center of the target volume.

The primary tumor and involved nodal disease received 60 Gy in 2-Gy fractions over 6 weeks. The initial 40 Gy was delivered to clinical target volume 1 (CTV1), and the final 20 Gy was delivered to a reduced volume defined as clinical target volume 2 (CTV2). CTV1 included the primary tumor, ipsilateral hilum, and mediastinal nodal areas from the paratracheal (#2) to subcarinal lymph nodes (#7). The contralateral hilum was not included in CTV1. The supraclavicular areas were not to be treated routinely, but could be treated when supraclavicular nodes were involved. For the primary tumors and the involved lymph nodes of 1 cm in the shortest diameter, a margin of 1.5–2 cm was added. CTV2 included only the primary tumor and the involved lymph nodes with a margin of 0.5–1 cm. The spinal cord was excluded from the fields for CTV2 by appropriate methods such as the oblique opposing method. Appropriate PTV margin and leaf margin were added for CTV1 and CTV2.

The objectives were to restrict the relative volume of the normal lung treated with a dose of >20 Gy (V20) to <35%, and the maximum spinal cord dose was restricted to <44 Gy. If patients experienced grade 3/4 esophagitis or dermatitis, pyrexia of 38 °C or more, or a decrease in *P*aO2 of >10 mm Hg compared to baseline, TRT was withheld until esophagitis or dermatitis improved to grade 2 or clinically acceptable toxicity level. If patients experienced grade 1 or more pneumonitis related to gefitinib, TRT was terminated.Assessment of toxicity and responseAll eligible patients who received any portion of the treatment regimen were considered assessable for toxicity and response. A CT scan of the chest was performed within 14 days of initiation of study treatment and was repeated on day 14 of gefitinib monotherapy in order to exclude individuals with disease progression or pneumonitis related to gefitinib. Chest X-rays, complete blood counts, and blood chemistry analysis were performed weekly until completion of TRT. Toxicities were assessed with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events v2.0. Treatment response was evaluated according to the Response Evaluation Criteria in Solid Tumors [21]. The initial tumor response was defined as the best response recorded within 3 months after the start of treatment. Progression-free survival (PFS) and overall survival (OS) were calculated from the date of registration in the study until the first documented instance of disease progression or death, respectively, with the use of the Kaplan–Meier method. Follow-up assessments included a posttreatment CT scan at 4–12 weeks after completion of TRT.

2.5. Study design and statistical considerations

The primary end point of the study was the rate of treatment completion. Complete treatment delivery was defined as completion of the planned 60 Gy of TRT within 63 days and administration of gefitinib for >3 weeks during TRT. We selected a 90% completion rate as a desirable target level and a 75% completion rate as uninteresting with an alpha error of 0.1 and a power of 0.8, resulting in a requirement for 28 patients. If 24 or more treatment completions were achieved among the 28 total assessable patients, the treatment was considered worthy of further consideration. Secondary end points included estimation of the objective response rate as well as of PFS and OS.

2.6. Analysis of EGFR mutation

Tumor specimens (embedded in paraffin) were collected during previous diagnostic procedures. *EGFR* mutations that confer sensitivity to EGFR-TKIs were identified by the PCR-Invader method (BML, Tokyo, Japan). Some patients had already died before the initiation of our genetic analysis, preventing us from obtaining informed consent. The Institutional Review Boards therefore approved our study protocol with the conditions that samples

Table 1
Treatment details and outcomes for the study cohort.

Patient	Age/sex	Smoking history	Histology	TNM stage	Gefitinib (total days of therapy)	TRT (total dose, Gy)	Treatment completion	Initial tumor response	Pattern of recurrence	PFS (months)	OS (months)	*EGFR* status
1	68/M	48/day × 20 years	Large cell	T1N2	13	0	No	PD	Locoregional	0.5	6.3	Wild type
2	71/M	60/day × 60 years	NSCLC	T2N3	58	34	No	SD	Locoregional + distant (bone)	5.7	5.9	Wild type
3	69/M	50/day × 60 years	Adeno	T1N2	134	60	Yes	PR	Distant (bone)	4.5	5.9	Wild type
4	56/M	41/day × 40 years	Adeno	T4N0	604	60	Yes	PR	None	73.6+	73.6+	NA
5	62/M	30/day × 30 years	Adeno	T1N2	107	60	Yes	PR	Distant (brain)	19.6	67.5	Exon 19 del
6	59/M	40/day × 40 years	Adeno	T1N2	13	0	No	PD	Locoregional	0.5	3.1	Wild type
7	62/F	None	Adeno	T4N1	302	60	Yes	PR	Distant (brain)	14.6	63.7+	Exon 19 del
8	63/M	20/day × 20 years	Adeno	T4N2	23	60	No	PD	Locoregional	2.4	11.5	Wild type
9	67/M	40/day × 15 years	Squamous	T4N2	50	46	No	PD	Locoregional	1.9	2.5	Wild type

NA, not applicable.

Table 2
Toxicity of induction gefitinib monotherapy ($n = 9$).

Toxicity	Grade			
	1	2	3	4
Hematologic				
Leukopenia	1	0	0	0
Neutropenia	0	0	0	0
Anemia	4	0	0	0
Thrombocytopenia	1	0	0	0
Febrile neutropenia	NA	NA	0	0
Nonhematologic				
Fever	1	0	0	0
Fatigue	0	1	0	0
Dry skin	1	0	0	0
Skin rash	5	0	0	0
Elevated AST	2	0	0	0

NA, not applicable.

would be processed anonymously and analyzed only for somatic mutations (not germline mutations) and that the study would be publicly disclosed, according to the Ethical Guidelines for Human Genome Research published by the Ministry of Education, Culture, Sports, Science, and Technology, the Ministry of Health, Labor, and Welfare, and the Ministry of Economy, Trade, and Industry of Japan.

3. Results

3.1. Patient characteristics

Between August 2003 and January 2005, nine eligible patients were enrolled in the study at the two participating centers (Table 1). The patients included one women and eight men, with a median age of 63 years (range, 56–71). Five patients had stage IIIA disease and four had stage IIIB disease. Histological subtypes included adenocarcinoma in six patients, squamous cell carcinoma in one patient, large cell carcinoma in one patient, and unspecified NSCLC in one patient. Eight of the nine patients were current smokers.

3.2. Toxicity

Safety analysis included all nine patients who received at least one dose of gefitinib. All adverse events were monitored continuously during treatment and for 2 years after the end of treatment. Five patients did not complete the planned trial therapy and subsequent enrollment was stopped according to the protocol definition (Table 1). Two subjects (patients 1 and 6) showed progression of their primary lung tumors on planned CT evaluation on day 14 of gefitinib monotherapy and were thus unable to start TRT according to the protocol. Patient 2 manifested acutely deteriorating dyspnea and hypoxemia with a PaO_2 of 46.0 mm Hg after 24 days of gefitinib therapy and 34 Gy of radiotherapy. A CT scan of the chest revealed diffuse ground-glass opacities that were consistent with the known pulmonary toxicity of gefitinib. Discontinuation of gefitinib and radiotherapy and initiation of steroid treatment resulted in improvement of the patient's condition. Patient 8 presented with pneumonitis of grade 1 at 23 days after initiation of gefitinib. This condition was interpreted as a gefitinib-related toxicity, and the patient had gefitinib withdrawn but continued with radiotherapy up to 60 Gy without further toxicity. V20 parameters in the two patients (patients 2 and 8) who suffered from pulmonary toxicities were 25 and 20%, respectively. Patient 9 discontinued the trial treatment after 46 Gy of radiotherapy because of enlargement of the primary lung lesion at 50 days after initiation of gefitinib administration.

Table 3
Acute toxicity during concurrent gefitinib and TRT ($n = 7$).

Toxicity	Grade			
	1	2	3	4
Hematologic				
Leukopenia	3	1	0	0
Neutropenia	1	0	0	0
Anemia	1	1	0	0
Thrombocytopenia	2	0	0	0
Febrile neutropenia	NA	NA	0	0
Nonhematologic				
Esophagitis	5	1	0	0
Skin rash	4	1	0	0
Elevated ALT	0	2	3	0
Elevated AST	1	1	3	0
Fatigue	3	1	0	0
Anorexia	1	1	0	0
Fever	1	1	0	0
Dry skin	2	0	0	0
Pneumonitis	1	0	1	0

NA, not applicable.

The incidence of adverse events of all grades during the entire treatment period is shown in Tables 2 and 3. Although esophagitis and skin rash were most commonly encountered, these conditions were only of grade 1 or 2. Toxicities of grade 3 occurred in four patients: an increase in the serum levels of hepatic transaminases in three patients and pneumonitis in one patient. No hematologic toxicities of grade 3 or 4 were observed. There were no treatment-related deaths.

3.3. Treatment outcomes

At the time of analysis, two patients were still alive and seven patients had died. Eight patients had progressed, four experiencing local progression, three distant progression, and one local and distant progression (Table 1). All four patients who completed the planned treatment schedule experienced a partial response at the end of combined treatment, with a PFS of 4.5, 14.6, 19.6, and ≥73.6 months. Three of these four patients were alive >60 months without local recurrence from entry into the study.

3.4. EGFR mutation analysis

Tumor specimens were available for eight of the nine patients enrolled in the study and were successfully tested for *EGFR* mutations. Sensitizing *EGFR* mutations were detected in two individuals (patients 5 and 7), both of whom completed the planned trial treatment and exhibited an OS of >5 years.

4. Discussion

In this study, we sought to investigate the tolerability and safety of gefitinib when combined with definitive TRT in patients with locally advanced NSCLC. Given that five of the first nine patients enrolled in the study were unable to complete the planned treatment (two developing pulmonary toxicity and three progressive disease), the combination of gefitinib with TRT was not considered feasible in unselected patients according to the protocol definition and the study was closed.

Life-threatening interstitial lung disease (ILD) related to gefitinib has previously been identified as the most problematic toxicity of this drug, with an incidence thought to be ~4% and with about one-third of the cases being fatal in Japan [22,23]. The predictive risk factors for ILD development include male sex, smoking, and the existence of idiopathic pulmonary fibrosis [22]. In the present study, two male smokers experienced pneumonitis (one of the grade 3 and one of the grade 1) during concurrent gefitinib administration and TRT, both cases necessitating discontinuation of gefitinib treatment. It remains unclear whether TRT increases the risk for development of gefitinib-related ILD. We have recently completed a multicenter single-arm trial [Japan Clinical Oncology Group (JCOG) 0402] consisting of induction cisplatin and vinorelbine followed by gefitinib and concurrent TRT in patients with locally advanced NSCLC [5]. Eligibility for enrollment in the JCOG trial, the criteria for which were changed midway through the study to reduce the risk of gefitinib-induced ILD, was limited to individuals with adenocarcinoma who were either never-smokers or former light-smokers. Safety data for concurrent gefitinib and TRT in such selected patients are eagerly awaited. With the exception of pulmonary adverse events possibly resulting from gefitinib treatment, the combination of gefitinib and TRT did not show any unexpected toxicity, with no marked increase in radiation-induced toxicities, in the present study. Other recent studies that incorporated EGFR-TKIs into chemoradiation for locally advanced NSCLC also showed that such combination therapy was safe and feasible [24–26].

In the present study, gefitinib monotherapy was instigated 2 weeks before the onset of concurrent TRT because of concern about the relatively high risk for development of gefitinib-induced ILD during the initial exposure to the drug [22,23]. The study protocol also required assessment of antitumor effect after the induction gefitinib monotherapy, and, indeed, two patients were withdrawn before the start of concurrent TRT because of the development of progressive disease. This approach was adopted to avoid ineffective therapy given that platinum-based chemotherapy with concurrent TRT has been established as the standard treatment for locally advanced NSCLC [3]. At the time the trial was initiated, clinical data showing the association between sensitizing *EGFR* mutations and response to EGFR-TKIs were unavailable. Several prospective clinical trials of EGFR-TKI treatment for NSCLC patients with *EGFR* mutations have subsequently revealed radiographic response rates of 55–91% [27–36]. Furthermore, *EGFR* mutations are more frequent in females, individuals with no history of smoking, and patients with adenocarcinoma, all of which characteristics are associated with a low risk of gefitinib-induced ILD [22,37,38]. These findings suggest that patient selection on the basis of *EGFR* mutation status can minimize the risk of gefitinib-related ILD and maximize the efficacy of gefitinib combined with TRT.

Unique to our present study is the post hoc analysis of *EGFR* mutation. We detected *EGFR* mutations in two of the eight patients with available tumor specimens, and both of these individuals survived for >5 years. These two *EGFR* mutation-positive patients (patients 5 and 7) presented with brain metastasis as the first site of treatment failure, consistent with previous reports that the brain is a frequent site of recurrence after curative multimodality approaches for locally advanced NSCLC [39]. Patient 5 were treated with gamma knife radiosurgery for his solitary brain metastasis at 19.6 months after the start of protocol treatment; however he died of meningeal carcinomatosis with an overall survival of 67.5 months. Patient 7 received gamma knife radiosurgery for brain metastases and thereafter remained well without recurrence. It is noted that both of these *EGFR* mutation-positive patients have never experienced local progression. These clinical courses differ from those of metastatic *EGFR* mutation-positive NSCLC, for which most tumors are initially responsive to EGFR-TKIs but almost invariably develop resistance to the drug, leading to recurrence and death. Preclinical studies have shown that NSCLC cells harboring *EGFR* mutations have a predominantly radiosensitive phenotype associated with a delay in the repair of radiation-induced DNA damage, defective radiation-induced arrest of DNA synthesis or mitosis, and a pronounced increase

in the frequency of radiation-induced apoptosis [40]. Given these radiosensitivity characteristics, *EGFR* mutation-positive NSCLC patients treated with radiotherapy may avoid the emergence of resistance to gefitinib. The implications of these findings for optimal design of future trials of molecularly based combined-modality treatments including EGFR-TKIs and radiotherapy are under consideration.

In conclusion, the combination of gefitinib with TRT for locally advanced NSCLC is not recommended for unselected patients because of concerns with efficacy and toxicity. We did, however, observe that *EGFR* mutation-positive patients had a favorable clinical outcome with this combination therapy. We have recently completed phase III trials in *EGFR* mutation-positive patients with advanced NSCLC and found that first-line gefitinib monotherapy was associated with a significantly better response rate and PFS compared with platinum-based chemotherapy [41]. Although the number of patients in the current study was too small to be able to draw firm conclusions, our preliminary findings suggest that TRT combined with gefitinib in place of platinum-based chemotherapy is a potential option for the treatment of patients with locally advanced NSCLC who have sensitizing *EGFR* mutations. Further development of EGFR-TKI treatment in combination with TRT in molecularly selected patients is warranted.

Conflict of interest

The authors declare no actual or potential conflicts of interest.

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S-1 Plus Cisplatin with Concurrent Radiotherapy for Locally Advanced Non-small Cell Lung Cancer

A Multi-Institutional Phase II Trial (West Japan Thoracic Oncology Group 3706)

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Purpose: To evaluate the combination chemotherapy using oral antimetabolite S-1 plus cisplatin (SP) with concurrent thoracic radiotherapy (RT) followed by the consolidation SP for locally advanced non-small cell lung cancer.

Patients and Methods: Patients with stage III non-small cell lung cancer, 20 to 74 years of age, and Eastern Cooperative Oncology Group performance status 0 to 1 were eligible. The concurrent phase consisted of full dose S-1 (orally at 40 mg/m^2/dose twice daily, on days 1–14) and cisplatin (60 mg/m^2 on day 1) repeated every 4 weeks for two cycles with RT delivered beginning on day 1 (60 Gy/30 fractions over 6 weeks). After SP-RT, patients received an additional two cycles of SP as the consolidation phase.

Results: Fifty-five patients were registered between November 2006 and December 2007. Of the 50 patients for efficacy analysis, the median age was 64 years; male/female 40/10; Eastern Cooperative Oncology Group performance status 0/1, 21/29; clinical stage IIIA/IIIB 18/32; and adenocarcinoma/others 20/30. There were 42 clinical responses including one complete response with an objective response rate of 84% (95% confidence interval [CI], 71–93%). The 1- and 2-year overall survival rates were 88% (95% CI, 75–94%) and 70% (95% CI, 55–81%), respectively. The median progression-free survival was 20 months. Of the 54 patients for safety analysis, common toxicities in the concurrent phase included grade 3/4 neutropenia (26%), thrombocytopenia (9%), and grade 3 esophagitis (9%) and febrile neutropenia (9%). In one patient, grade 3 pneumonitis was observed in the consolidation phase. There were two treatment-related deaths caused by infection in the concurrent phase.

Conclusions: SP-RT showed a promising efficacy against locally advanced NCSLC with acceptable toxicity.

Key Words: Concurrent chemoradiotherapy, Non-small cell lung cancer, Phase II trial, S-1, Cisplatin.

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The standard treatment modality in patients with unresectable stage III non-small cell lung cancer (NSCLC) is concurrent chemoradiotherapy.[1] Nevertheless, this combined treatment is associated with greater acute toxicity, including bone marrow[2] suppression, pneumonitis, and esophagitis,[2] compared with the sequential combination of chemotherapy and radiotherapy (RT). About a decade ago, we developed a concurrent chemoradiotherapy regimen using uracil-tegafur (UFT, Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) plus cisplatin (UP) with concurrent thoracic RT (2 Gy per fraction, total 60 Gy) (UP-RT).[3] The response rate and median survival time of locally advanced unresectable stage III (IIIA 20%, IIIB 80%) patients treated with the UP-RT were 80% and 16.5 months, respectively, and these figures are similar to those reported in other concurrent chemoradiotherapy trials.[4,5] Nevertheless, the incidence of leukopenia and esophagitis of grade 3 or 4 was 16% and 3% of the patients, respectively,[3] and these figures are far lower than those of other trials.

S-1 (TS-1, Taiho Pharmaceutical Co., Ltd) is a second-generation oral anticancer agent based on uracil-tegafur, which has a dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidine. S-1 comprises tegafur (a 5-FU Pro-

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drug), 5-chloro-2, 4-dihydroxypyridine (an inhibitor of DPD), and potassium oxonate (an inhibitor of phosphoribosyl transferase), in a molar ratio of 1:0.4:1 and has been shown to induce a comparable response to the other single agents for metastatic NSCLC.[6] Furthermore, combination chemotherapy using S-1 plus cisplatin (SP) for advanced NSCLC has been reported to show a response rate of 33 to 47% and a median survival time of 11 to 16 months.[7,8] Those data were better than the usual response rate of 29 to 38% and the median survival time of 8 to 13 months for the combination chemotherapeutic regimens using UP,[9,10] whereas the frequency of severe hematological and nonhematological adverse events induced by both UP and SP was lower than that of other platinum-based combination regimens such as carboplatin plus paclitaxel (CP), cisplatin plus docetaxel, and so on.[11–13] In addition, West Japan Oncology Group (WJOG) recently demonstrated that chemotherapy using S-1 plus carboplatin was noninferior in terms of overall survival (OS) compared with CP in advanced NSCLC.[14]

The above-mentioned observations indicated that it might be possible to use the same dose of SP as is used for metastatic advanced NSCLC for the treatment of locally advanced NSCLC with concurrent thoracic RT, similar to UP-RT. If this is possible, SP and concurrent thoracic RT (SP-RT) would be expected to provide several advantages over UP-RT. First, SP could have stronger antitumor activity for both locally advanced NSCLC and micrometastatic lesions than UP. Second, although both cisplatin and 5-FU have been reported to have a radiosensitizing effect,[15,16] the level of the latter in the blood by SP could not only be maintained at a higher level than by UP[17,18] but also 5-chloro-2, 4-dihydroxypyridine in S-1 has been recently reported to have a radiosensitizing effect as well as a strong DPD activity.[19,20] A single-institutional experience with SP-RT in 11 patients was reported showing that all the patients had a partial response, with acceptable hematological and nonhematological toxicities. On the basis of these findings, the WJOG (formally, West Japan Thoracic Oncology Group) conducted a multiinstitutional phase II trial to confirm the antitumor effects and safety of SP-RT.

PATIENTS AND METHODS

Eligibility Criteria

The eligibility requirements for enrollment in this phase II trial were cytologically or histologically confirmed, unresectable stage III NSCLC, for which radical dose RT could be prescribed. The staging was performed according to the 6th edition of tumor, node, metastasis (TNM). All patients were required to meet the following criteria: measurable disease; an Eastern Cooperative Oncology Group performance status of 0 or 1; a projected life expectancy of more than 3 months; a leukocyte count of $\geq$4000/μL; a platelet count of $\geq$100,000/μL; a blood gas oxygen level of $\geq$70 torr; a serum bilirubin level below 1.5 mg/dL; serum glutamic oxaloacetic transaminase/glutamic pyruvic transaminase levels of no more than 100 IU/ml; a creatinine level of $\leq$1.2 mg/dL; and a creatinine clearance level of $\geq$60 mL/min. Other eligibility criteria included no prior treatment and an age $<$75 years. All eligible patients underwent computed tomography (CT) scans of the thorax and upper abdomen and a radioisotope bone scan. Patients who had malignant pleural effusion, malignant pericardial effusion, a concomitant malignancy, or serious concomitant diseases were excluded from the study. Written informed consent was required from all patients, and the protocol was approved by the institutional ethics committee of each participating institute. All data were centrally monitored by the WJOG datacenter. This study is registered with the University Hospital Medical Information Network in Japan (number 000001370).

Treatment Schedule

Chemotherapy with SP

S-1 (40 mg/m^2/dose) in the form of 20 and 25 mg capsules containing 20 and 25 mg of tegafur, respectively, were taken orally twice a day after meals between days 1 and 14 as follows: in a patient with a body surface area (BSA) $<$1.25 m^2, 40 mg twice daily; for those with BSA 1.25 m^2, but $<$1.5 m^2, 50 mg twice daily; and BSA $>$1.5 m^2, 60 mg twice daily. Cisplatin (60 mg/m^2) was administered as a $\geq$120-minute infusion on day 1. The patients were also hydrated with 1000 to 2000 mL saline by infusion before cisplatin was administered. An antiemetic agent was administered at the discretion of each patient's physician.

The combination chemotherapy with SP was repeated twice, with a 4-week interval, concurrently with thoracic RT (SP-RT). At 2 to 4 weeks after the completion of the concurrent chemoradiotherapy, two further cycles of the same SP regimen were administered as a consolidation chemotherapy as shown in Figure 1.

A leukocyte count of 3000/μL or greater and the entry eligibility criteria regarding organ functions had to be satisfied for the patients to start the next cycle. If these criteria were satisfied 4 weeks after day 1 of each cycle of chemotherapy, the next cycle was administered. The doses of S-1 were adjusted according to the degree of hematological and nonhematological toxicity. The dose was reduced by one level (20 mg day) in patients whose BSA was 1.25 m^2 or more if there was evidence of grade 4 hematologic toxicity or grade 3 or more nonhematological toxicity during any cycle

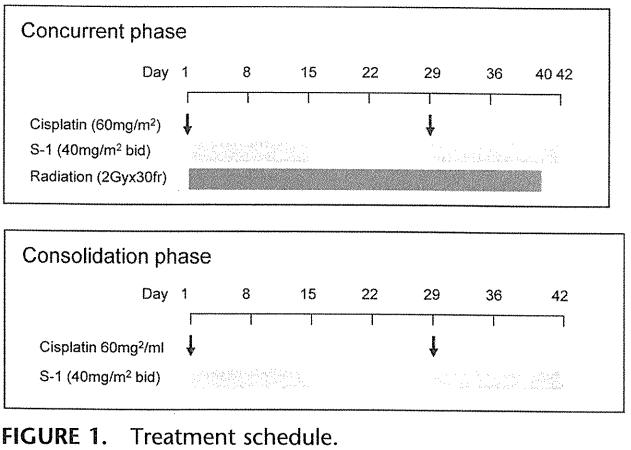

FIGURE 1. Treatment schedule.