schedule of HypoFXSRT for stage I NSCLC are unknown, the nationwide number of Japanese patients with stage I NSCLC who are treated with small-volume stereotactic RT (SRT) has increased rapidly.

Therefore, it is meaningful to investigate the results of SRT for stage I NSCLC from many institutions, even in a retrospective manner, despite the large differences in treatment protocols. Previously, we reported the result of a Japanese multi-institutional review of 300 patients with stage I NSCLC treated with SRT.[7] We concluded that SRT with a biological effective dose (BED) of less than 150 Gy is effective for the curative treatment of patients with stage I NSCLC and that the local control and survival rates are better with a BED of 100 Gy or more compared with less than 100 Gy.

The survival rates in selected medically operable patients with a BED of 100 Gy or more were promising and potentially comparable with those of surgery. These results for SRT were encouraging for stage I NSCLC patients; however, the 300 subjects in that report included 17 patients irradiated with comparatively small fractions (<4 Gy) and 26 patients irradiated in combination with conventional RT. This article presents the results for patients irradiated with HypoFXSRT alone in a multi-institutional study. In this study, we compared the reported results for surgery and conventional RT with those for HypoFXSRT.

PATIENTS AND METHODS

Eligibility Criteria

This was a retrospective study to review patients who were treated by HypoFXSRT for their stage I NSCLC in 14 different hospitals in Japan.

All the patients enrolled in this study satisfied the following eligibility criteria: identification of T1N0M0 or T2N0M0 primary lung cancer on chest and abdominal CT, bronchoscopy, bone scintigraphy, or brain magnetic resonance imaging; histological confirmation of NSCLC; performance status of 2 or less according to the World Health Organization (WHO) guidelines; and an inoperable tumor due to a poor medical condition or refusal to undergo surgery.

No restrictions were imposed concerning the locations of eligible tumors, irrespective of whether they were located adjacent to a major bronchus, blood vessel, chest wall, or the esophagus. Patients were informed of the concept, methodology, and rationale of this treatment, which was performed in accordance with the 1983 revision of the Declaration of Helsinki.

Patient Characteristics

The patient pretreatment characteristics are summarized in Table 1. From April 1995 to March 2004, a total of 257 patients with primary NSCLC was treated using high-dose HypoFXSRT in the following 14 institutions: Hokkaido University, Kyoto University, Cancer Institute Hospital, Tokyo Metropolitan Komagome Hospital, Kitasato University, Tohoku University, Hiroshima University, Tokyo Metropolitan Hiroo Hospital, Sapporo Medical University, Institute of Biomedical Research and Innovation, International Medical Center of Japan, Tenri Hospital, Kitami Red Cross Hospital, and University of Yamanashi. Of the 257 patients, 158 were considered medically inoperable mainly because of chronic pulmonary disease, advanced age, or other chronic illness. The remaining 99 patients were considered medically operable, but had refused surgery or had been advised to select HypoFXSRT by medical oncologists.

TABLE 1. Patient Pretreatment Characteristics

Total cases: 257
Age: 39–92 yr (median, 74)
Performance status: PS 0, 109; PS 1, 103; PS 2, 39; PS 3, 6
Pulmonary chronic disease: 168 positive, 89 negative
Histology: 111 squamous cell, 120 adenocarcinoma, 26 other
Stage: 164 IA, 93 IB
Tumor diameter: 7–58 mm (median, 28)
Medical operability: 158 inoperable, 99 operable

Treatment Methods

All the patients were irradiated using stereotactic techniques. For the purposes of this study, all the hypofractionated stereotactic techniques met five requirements: reproducibility of the isocenter of 5 mm or less, as confirmed for every fraction; slice thickness on CT of 3 mm or less for three-dimensional (3-D) treatment planning; irradiation with multiple noncoplanar static ports or dynamic arcs; dose per fraction size more than 4 Gy; and a total treatment period of fewer than 25 days. Details of the techniques and instruments used to achieve SRT in the 14 institutions were summarized in a previous report.[7] The clinical target volume (CTV) marginally exceeded the gross target volume (GTV) by 0 to 5 mm. The planning target volume (PTV) comprised the CTV, a 2- to 5-mm internal margin and a 0–5-mm safety margin. A high dose was concentrated on the tumor-bearing area, while sparing the surrounding normal lung tissues using SRT. The irradiation schedules also differed among the institutions. The number of fractions ranged between 1 and 14, with single doses of 4.4 to 35 Gy. A total dose of 30 to 84 Gy at the isocenter was administered with 6- or 4-MV x-rays within 20% heterogeneity in the PTV dose. No chemotherapy was administered before or during RT.

To compare the effects of various treatment protocols with different fraction sizes and total doses, the BED was used in a linear-quadratic model.[8] Here, the BED was defined as $nd(1 + d/\alpha/\beta)$, with gray units, where n is the fractionation number, d is the daily dose, and α/β is assumed to be 10 for tumors. The BED was not corrected with values for the tumor doubling time or treatment term. In this study, the BED was calculated at the isocenter. The median BED was 111.0 Gy (range, 57.6–180.0). The BED was 100 Gy or more in 215 patients and less than 100 Gy in 42 patients. The median BED for the less than 100 Gy and 100 Gy or more subgroups was 79.6 Gy (range, 57.6–98.6) and 117.0 Gy (range, 100.0–180.0), respectively.

Dose constraints were set for the spinal cord only. The BED limit for the spinal cord was 80 Gy (α/β was assumed to be 2 Gy for chronic spinal cord toxicity).

Evaluation

The objectives of this study were to retrospectively evaluate the toxicity, local control rate, and survival rate according to the BED. All patients underwent follow-up examinations by radiation oncologists. The first examination took place 4 weeks after treatment, and patients were subsequently seen every 1 to 3 months. Tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors by CT.[9] Chest CT (slice thickness, 2–5 mm) was usually obtained every 3 months for the first year and repeated every 4 to 6 months thereafter. A complete response (CR) indicated that the tumor had disappeared completely or was replaced by fibrotic tissue. A partial response (PR) was defined as a 30% or more reduction in the maximum cross-sectional diameter. It was difficult to distinguish between residual tumor tissue and radiation fibrosis. Any suspicious confusing residual density after RT was considered evidence of a PR, so the actual CR rate might have been higher than that given here. Local recurrence was considered to have taken place only when enlargement of the local tumor continued for more than 6 months on follow-up CT. Two radiation oncologists interpreted the CT findings. The absence of local recurrence was defined as locally controlled disease. Lung, esophagus, bone marrow, and skin were evaluated using version 2 of the National Cancer Institute–Common Toxicity Criteria (NCI-CTC).

Statistical Analysis

The local recurrence rates in the two groups were compared with the χ^2 test. The BED among patient groups at each pulmonary toxicity grade was compared using the Kruskal-Wallis test. The cumulative local control and survival curves were calculated and drawn applying the Kaplan-Meier algorithms with day of treatment as the starting point. Subgroups were compared using log-rank statistics. Values of $p < 0.05$ were considered statistically significant. Statistical calculations were conducted using version 5.0 StatView software (SAS Institute, Cary, NC).

RESULTS

All the patients completed the treatment with no particular complaints. The median duration of follow-up for all patients was 38 months (range, 2–128).

Local Tumor Response

Of the 257 patients evaluated using CT, CR was achieved in 66 (25.7%) and PR in 157 (61.1%). The overall response rate (CR + PR) was 86.8%. The overall response rates for tumors with a BED of 100 Gy or more ($n = 215$) or less than 100 Gy ($n = 42$) were 87.5% and 86.7% in 3 years (?), respectively. A typical case of a T1 tumor after HypoFXSRT is shown in Figure 1.

Toxicity

Symptomatic radiation-induced pulmonary complications (NCI-CTC criteria grade >1) were noted in 28 patients (10.9%). Pulmonary fibrosis or emphysema before treatment was observed in 25 (89%) of the 28 patients with pulmonary complications above grade 1. Pulmonary complications of NCI-CTC criteria above grade 2 were noted in only 14

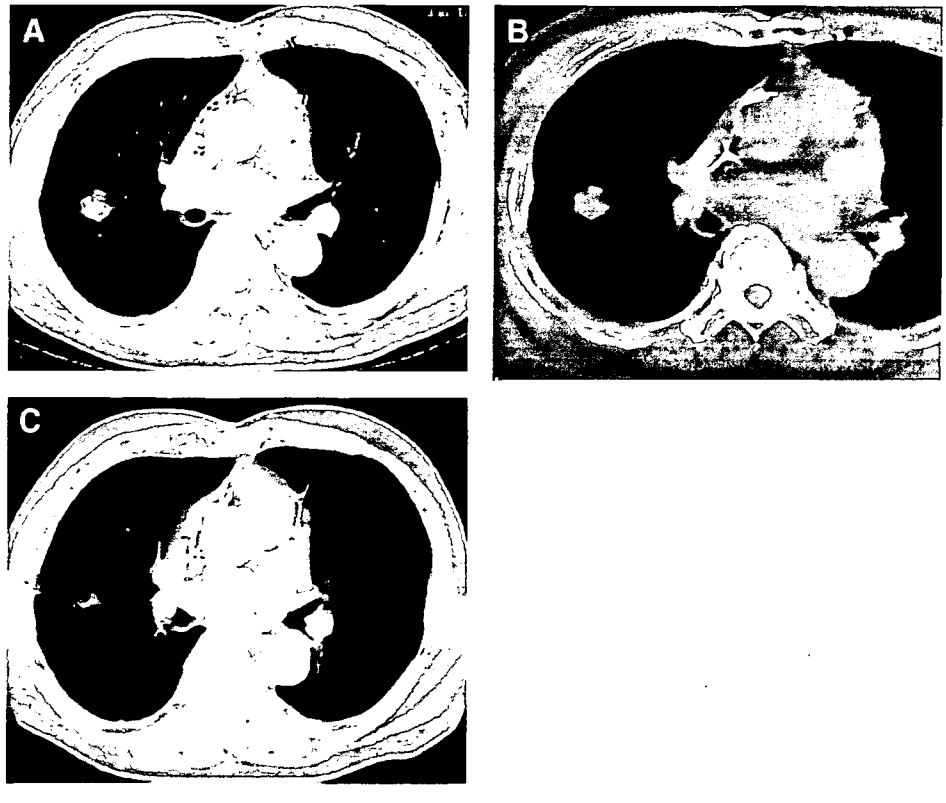

FIGURE 1. A typical example involving SRT for a 76-year-old man with T1N0 adenocarcinoma. He was treated with HypoFXSRT. (*A*) Before hypofractionated stereotactic radiotherapy (HypoFXSRT). (*B*) The calculated dose distribution. The isocenter dose was 75 Gy/10 fractions/5 days, and the tumor was fully enclosed with the 90% dose line. (*C*) Twelve months after HypoFXSRT, a scarred tumor is rated as a partial response.

TABLE 2. Recurrence Rate According to the BED and Stage

	Total cases	BED <100 Gy	BED ≥100 Gy	p	Stage IA	Stage IB	p
Local tumor	36/257 (14.0%)	18/42 (42.9%)	18/215 (8.4%)	<0.01	20/164 (12.2%)	16/93 (17.2%)	0.21
Regional nodal metastasis	29/257 (11.3%)	9/42 (21.4%)	20/215 (9.3%)	<0.05	17/164 (10.4%)	12/93 (12.9%)	0.54
Distant metastasis	51/257 (19.8%)	11/42 (26.2%)	40/215 (18.6%)	0.3	32/164 (19.5%)	19/93 (20.4%)	0.87

BED, biological effective dose.

patients (5.4%). The pulmonary symptoms resolved in most patients without steroid therapy, but six patients who had very poor respiratory function or severe pulmonary fibrosis before irradiation needed continuous oxygen. Chronic segmental bronchitis and wall thickening causing atelectasis in the peripheral lung was observed in one patient (0.4%). Transient grade 3 esophagitis was observed in two patients (0.8%) with tumors adjacent to the esophagus. Grade 3 or 4 dermatitis was observed in three patients (1.2%) with tumors adjacent to the chest wall. Rib fracture adjacent to the tumor was found in four patients (1.6%). No vascular, cardiac, or bone marrow complications had been encountered as of the last follow-up.

Recurrence

The recurrence rates of local, regional nodal, and distant lesions according to the BED and stage are listed in Table 2. The local recurrence rate was significantly lower for a BED of 100 Gy or more compared with a BED of less than 100 Gy (8.4 versus 42.9%, $p < 0.01$). For greater BED subgroups, the local recurrence rate was 11.8% for a BED of 120 Gy or more ($n = 93$) and 8.1% for a BED of 140 Gy or more ($n = 37$). The local recurrence rates for adenocarcinoma and squamous cell carcinoma were 13.3% (16/120) and 17.1% (19/111), respectively in 3 years. The cumulative local control rate curves according to BED subgroup are shown in Figure 2. The 5 (3? according to Table 2)-year local control rates of the BED of 100 Gy or more and less than 100 Gy subgroups were 84.2% (95% confidence interval [CI]: 77.7%–90.8%) and 36.5% (95% CI: 10.4%–62.6%), respectively. According to subgroup analysis, stage IB patients had a significantly higher rate of local recurrence than stage IA patients. The nodal and distant recurrence rates were almost identical in the stage IA and IB subgroups.

In the patients with regional nodal recurrence, nodal failures overlapped local failure in 3.1%, distant metastases in 3.9%, or both in 0.8% of the patients. Isolated local, nodal, and distant recurrences were observed in 8.6%, 5.1%, and 13.6% of the patients, respectively.

Survival

The overall 3- and 5-year survival rates for all patients were 56.8% (95% CI: 50.2%–63.5%) and 47.2% (95% CI: 38.7%–53.5%), respectively. The cause-specific 3- and 5-year survival rates were 76.9% (95% CI: 70.6%–83.2%) and 73.2% (95% CI: 66.1%–80.2%), respectively. The overall survival rates differed significantly according to medical operability, with intercurrent death in 36.8% of inoperable patients and 10.3% of operable patients. The overall 5-year survival rates of medically operable and inoperable patients (Figure 3) were 64.8% (95% CI: 53.6%–75.9%) and 35.0% (95% CI: 25.9%–44.1%), respectively. The overall survival rates according to the BED in all patients differed significantly between the BED of less than 100 Gy and 100 Gy or more subgroups. The overall 5-year survival rates of the BED 100 Gy or more and less than 100 Gy subgroups were 53.9% (95% CI: 46.0%–61.8%) and 19.7% (95% CI: 5.9%–33.4%), respectively. For the subgroup of medically operable patients with a BED of 100 Gy or more, the 3- and 5-year overall survival rates were 80.4% (95% CI: 71.0%–89.7%) and 70.8% (95% CI: 59.3%–82.2%), respectively (Figure 2). The overall 5-year survival rate according to stage in the operable patients irradiated with a BED of 100 Gy or more was 72.3%

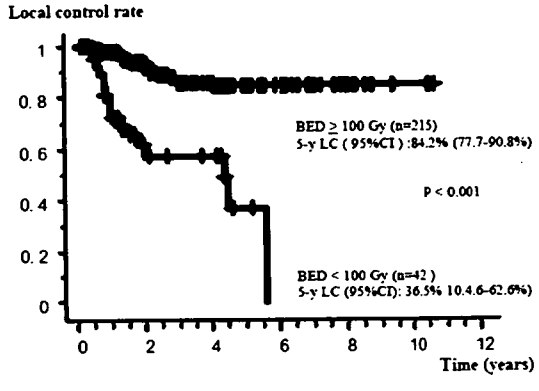

FIGURE 2. Cumulative local control rate according to the biological effective dose (BED). LC, local control rate; CI, confidence interval.

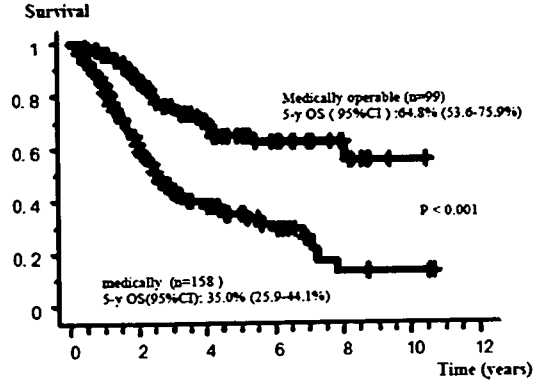

FIGURE 3. Overall survival rate according to medical operability. OS, overall survival rate; CI, confidence interval.

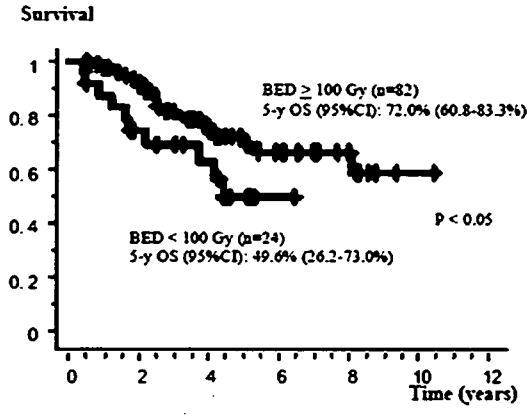

FIGURE 4. Overall survival rate in operable patients according to the biological effective dose (BED). OS, overall survival rate; CI, confidence interval.

(95% CI: 59.1%–85.6%) for stage IA and 65.9% (95% CI: 43.0%–88.9%) for stage IB patients (Figure 4).

Reproducibility of the Data Among Institutions

Table 3 compares the irradiation method and results for three major institutions enrolled in this study. These institutions used a BED of 100 Gy or more. The local control and 3-year survival rates were almost identical.

DISCUSSION

At present, surgery is the standard treatment for stage I NSCLC. RT is offered to patients who are unsuitable for surgery because of medical problems and to patients who refuse surgery. Most information on the results of RT for stage I NSCLC is based on retrospective studies of RT-treated inoperable NSCLC cases. Therefore, the role of RT for stage I NSCLC, as a curative modality, has not yet been established.

Qiao et al. summarized 18 papers on stage I NSCLC treated with conventional RT alone published between 1988 and 2000.[10] Local recurrence was the most common reason for treatment failure of stage I NSCLC with conventional RT, but the frequency of recurrence varied considerably according the report (between 6.4% and 70%). The 3-year recurrence rate was approximately 60%,[11–13] with a median time to relapse that ranged from 21 to 30 months.[12,14,15] Generally, smaller tumor size, low T stage, and increased dose had a favorable impact on local control, and increased local control was followed by increased survival.[14,16] However, the overall treatment results were disappointing. The median survival in these studies ranged from 18 to 33 months. The 3- and 5-year overall survival rates were 34 ± 9% and 21 ± 8% (mean ± 1 SE), respectively. The cause-specific survival rates at 3 and 5 years were 39 ± 10% and 25 ± 9% (mean ± 1 SE), respectively. Regarding treatment toxicity, severe (grade 3 or above) radiation esophagitis[14] and pneumonitis[11] occurred in 4.1% and 6.1% of the cases, respectively. Better local control may be achieved when the total dose is increased,[15,16] and a trend has been growing toward seeking better local control by increasing the BED[13–15] for a relatively limited span of doses (BED 59–76 Gy). Dose escalation has been the focus of developmental therapeutic strategies for inoperable stage I NSCLC to improve local control and survival.

Mehta et al.[17] provided a detailed theoretical analysis regarding the responses of NSCLC to RT and a rationale for dose escalation. They concluded that a greater BED irradiated during a short period must be given to gain local control of lung cancers. Giving a higher dose to the tumor without increasing the adverse effects was shown to be possible using the SRT technique; this is now feasible due to the technological progress that allows increasing the accuracy of localization to the tumor-bearing area using various imaging tools. SRT can also reduce the overall treatment time substantially, from several weeks for conventional RT to a few days, offering an important advantage to the patient.

After Uematsu et al.[18] reported a landmark study on SRT for stage I NSCLC using a CT-linac system, SRT has been actively investigated for stage I NSCLC in Japan and the United States. In the reports listed in Table 4,[3–6,19–21] the local control rates of primary lung cancer with SRT ranged from 87% to 97% when the BED exceeded 100 Gy. Uematsu et al.[3] showed excellent survival rates for medically operable patients, approximating those for full lobar surgical resection; however, they studied only a few patients, and it is not known whether the result is reproducible. Table 5 compares the results of Uematsu et al.[3] with the HypoFXSRT results presented here. These results suggest that the local control and survival rates of HypoFXSRT for stage I NSCLC are promising and reproducible when the BED exceeds 100 Gy.

In Japan, we consider a BED greater than 100 Gy to be a satisfactory dose for HypoFXSRT of stage I NSCLC, with a local control rate better than 85%, and a further dose escalation study is not necessary for tumors smaller than 4 cm in diameter. Conversely, in the United States, Timmerman et al.[22] concluded that 60 Gy in three fractions (BED = 180 Gy) is the proper dose, and they adopted this dose and fraction protocol for their prospective study. We need to observe the

TABLE 3. Comparison of the Irradiation Methods and Results for Three Major Institutions

Institution	No. of Patients	Total Isocenter Dose (Gy)	Single Isocenter Dose (Gy)	BED (Gy)	Median Follow-up (mo)	Local Failure, %	5-yr Overall Survival, %
Kyoto	42	48	12	106	40	3	64
Cancer Institute	30	50–62.5	10–12.5	100–141	25	4	77
Kitami	27	50–60	7.5–10	100–105	71	4	63

BED, biologically effective dose (α/β = 10) recalculated at the isocenter.

TABLE 4. Reports of Stereotactic Radiotherapy for Stage I Non-small Cell Lung Cancer

Author (ref.)	No. of Patients	Total Dose* (Gy)	Single Dose* (Gy)	BED† (Gy)	Median Follow-up (mo)	Local Progression, %	3-yr Overall Survival, %
Uematsu et al.[3]	50	72	7.2	124	60	6	66
Nagata et al.[4]	42	48	12	106	52	3	82
Fukumoto et al.[5]	17	48–60	6–7.5	99–137	24	6	NA
Onishi et al.[6]	28	72	7.2	124	24	8	75
Hof et al.[19]	10	19–26	19–26	55–94	15	20	NA
McGarry et al.[20]	47	75	25	263	15	13	NA
Wulf et al.[21]	12	26–57	19–26	94–165	11	5%	NA

BED, biologically effective dose; NA, not assessed.
*Stereotactic radiotherapy dose is calculated at the isocenter.
†BED (α/β = 10) recalculated at the isocenter.

results of ongoing phase II studies on SRT for stage I NSCLC conducted in Japan (12 Gy × 4 = 48 Gy prescribed to the isocenter) and the United States (20 Gy × 3 = 60 Gy prescribed to cover 95% of the PTV).

The 5-year overall survival rate for medically operable patients with HypoFXSRT is encouraging (Table 6). Representative 5-year overall survival rates for clinical stage IA and IB with surgery range from 61% to 72% and 40% to 50%, respectively.[23–25] According to our data, the survival rate for SRT was not worse than that for large surgical series. Furthermore, concerning toxicity, approximately 3% of patients died as a result of surgery, and chronic morbidity occurs in 10% to 15% of patients after surgery.[26] HypoFXSRT is much less invasive than surgery, and it is postulated that SRT will become a major treatment choice for stage I NSCLC, at least for medically inoperable patients.

TABLE 5. Comparison of the Results between the Multi-institutional Study and the Uematsu et al. Study

	Uematsu et al.[3]	Multi-institutional
Total no. of cases	50	215
T1N0M0	24	141
T2N0M0	26	75
Follow-up duration, mo (median)	22–66 (36)	2–128 (38)
Local control, %	94	90
Regional lymph nodes metastases, %	4	7
Distant metastases, %	14	19
Grade ≥3 toxicity, %	0	3
3-yr overall survival rate, %	66	64
3-yr cause-specific survival rate, %	88	83
5-yr overall survival rate, %	55	55
5-yr cause-specific survival rate, %	81	77
3-yr overall survival rate in operable patients, %	86	82
5-yr overall survival rate in operable patients, %	77	72

TABLE 6. Comparison of 5-Year Overall Survival Rate between Stereotactic Radiotherapy and Surgery

Stage	Author			
	Mountain[23]*	Naruke et al.[24]*	Shirakusa and Koybayashi[25]*	Onishi†
IA	61%	71%	72%	72%
IB	40%	44%	50%	66%

*Surgery.
†HypoFXSRT presented here.

Multi-institutional phase II studies of SRT for stage I NSCLC have been started in Japan (JCOG0403)[27] and the United States (RTOG0236).[28] However, it will take several years to obtain conclusive results, and an inevitable selection bias exists in comparing SRT with surgical series for patients in retrospective or phase II studies.

Although the differences in techniques and schedules of the institutions enrolled in this study may be large, it is meaningful that a safe, effective BED was suggested because the optimal dose-fraction schedule of SRT for stage I NSCLC is not known. Furthermore, this is the only report that gives the results of SRT for a large number of medically operable stage I NSCLC patients. Based on our excellent SRT results, it is arguable that a phase III study comparing surgery and SRT for medically operable patients is warranted. However, it is very difficult to perform a phase III study because most patients will opt for less invasive therapy such as SRT. We need much more experience and must study more patients with a longer follow-up duration to establish a safe, effective irradiation method that will instill both medical and social confidence in SRT for treatment of stage I NSCLC.

When we compare the results of conventional RT and surgery with those of HypoFXSRT, we conclude that HypoFXSRT has the following benefits for stage I NSCLC. First, HypoFXSRT is a safe and promising treatment modality. Second, the local control and survival rates are superior to those of conventional RT. Third, HypoFXSRT should be a standard of care for medically inoperable patients. Fourth, HypoFXSRT should be randomly compared with surgery for medically operable patients. Finally, we need additional experience with a longer follow-up duration to conclusively validate these points.

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CLINICAL INVESTIGATION **Head and Neck**

TREATMENT AND PROGNOSIS OF SQUAMOUS CELL CARCINOMA OF THE EXTERNAL AUDITORY CANAL AND MIDDLE EAR: A MULTI-INSTITUTIONAL RETROSPECTIVE REVIEW OF 87 PATIENTS

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Purpose: To examine the relative roles of surgery, radiotherapy, and chemotherapy in the management of patients with squamous cell carcinomas of the external auditory canal and middle ear.

Methods and Materials: The records of 87 patients with histologically confirmed squamous cell carcinoma who were treated between 1984 and 2005 were reviewed. Fifty-three patients (61%) were treated with surgery and radiotherapy (S + RT group) and the remaining 34 patients with radiotherapy alone (RT group). Chemotherapy was administered in 34 patients (39%).

Results: The 5-year actuarial overall and disease-free survival (DFS) rates for all patients were 55% and 54%, respectively. On univariate analysis, T stage (Stell's classification), treatment modality, and Karnofsky performance status had significant impact on DFS. On multivariate analysis, T stage and treatment modality were significant prognostic factors. Chemotherapy did not influence DFS. The 5-year DFS rate in T1, T2, and T3 patients was 83%, 45%, and 0 in the RT group ($p < 0.0001$) and 75%, 75%, and 46% in the S + RT group ($p = 0.13$), respectively. The 5-year DFS rate in patients with negative surgical margins, those with positive margins, and those with macroscopic residual disease was 83%, 55%, and 38%, respectively ($p = 0.007$).

Conclusions: Radical radiotherapy is the treatment of choice for early-stage (T1) diseases, whereas surgery (negative surgical margins if possible) with radiotherapy is recommended as the standard care for advanced (T2–3) disease. Further clarification on the role of chemotherapy is necessary. © 2007 Elsevier Inc.

Radiation therapy, Surgical resection, Chemotherapy, External auditory canal, Middle ear.

INTRODUCTION

The occurrence of squamous cell carcinoma of the external auditory canal and middle ear is rare, with a reported prevalence of 1 per 1 million persons (1, 2). Because of the rarity of the tumors, it has been difficult for a single institution to analyze data and formulate an optimal evaluation and treatment strategy. The reliability of the radiologic evaluation of disease extent, the surgical procedures, and the efficacy of radiotherapy are still matters of controversy. In addition, the lack of a universally accepted staging system poses a critical problem when attempting to compare treatment strategies and outcomes among multiple institutions (1, 3).

Several reports have indicated that the assessment of a tumor's extension is an important prognostic factor for squamous cell carcinoma of the external auditory canal and middle ear (1, 4–11). However, the studies were based on a small number of patients, and various treatment modalities were used (9, 12, 13). Therefore, the relative roles of surgery, radiotherapy, and chemotherapy in the management of patients with such lesions have remained controversial. Although several reports have indicated the efficacy of radio-

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Table 1. Stell's and Arriaga's staging systems for external auditory canal and middle ear

Stell's classification (10)	
T1	Tumor limited to site of origin *i.e.*, with no facial nerve paralysis and no bone destruction on radiography
T2	Tumor extending beyond the site of origin indicated by facial paralysis or radiologic evidence of bone destruction, but no extension beyond the organ of origin
T3	Clinical or radiologic evidence of extension to surrounding structures (dura, base of the skull, parotid gland, temporomandibular joint, etc)
TX	Patient with insufficient data for classification, including patients previously treated elsewhere
Arriaga's classification (1)	
T1	Tumor limited to the external auditory canal without bony erosion or evidence of soft tissue extension
T2	Tumor with limited external auditory canal bony erosion (not full thickness) or radiographic finding consistent with limited (<0.5 cm) soft-tissue involvement
T3	Tumor eroding the osseous external auditory canal (full thickness) with limited (<0.5 cm) soft-tissue involvement, or tumor involving middle ear and/or mastoid, or patients presenting with facial paralysis
T4	Tumor eroding the cochlea, petrous apex, medial wall of middle ear, carotid canal, jugular foramen or dura, or with extensive (>0.5 cm) soft-tissue involvement

therapy for these tumors (12, 14), there is little information available regarding the relationship between the extent of a tumor and the outcomes of radical radiotherapy. Therefore, it is imperative to formulate treatment guideline for these tumors.

In the present study, we performed a retrospective, multi-institutional review of 87 patients with squamous cell carcinoma of the external auditory canal and middle ear. We also investigated the optimal management of these patients, including the role of surgery, radiotherapy, and chemotherapy.

METHODS AND MATERIALS

Patient characteristics

A retrospective review of medical records from 1984 to 2005 identified 87 patients with documented, histologically confirmed, previously untreated squamous cell carcinoma of the external auditory canal and middle ear who were treated with radiotherapy at the following institutions: the Department of Radiology/Radiation Oncology at the University of the Ryukyus Hospital, Kyushu University Hospital, Chiba Cancer Center, Chiba University Hospital, Aichi Cancer Center, and International Medical Center of Japan. The patients ranged in age from 37 to 88 years (median, 67 years). Forty-three patients were male, and 44 patients were female. The Karnofsky performance status of the patients ranged from 40% to 100% (median, 90%). The primary tumor site was in the external auditory canal in 59 patients and in the middle ear in 28 patients. Computed tomography (CT) and/or magnetic resonance imaging (MRI) was performed on all patients before treatment, and of all 87 patients, MRI was performed in 40 (46%).

We used the tumor staging system devised by Stell and McCormick (10) (Table 1), and the node and metastases staging devised by the Union Internationale Contre le Cancer (UICC) (15). In total, there were 13 T1, 37 T2, and 37 T3 tumors. Seventy-nine patients (91%) were N0, and 8 patients (9%) exhibited N1 disease. With regard to T stage, we also applied the staging system devised by Arriaga *et al.* (1) to determine whether it could be properly applied to our patient population. According to Arriaga's staging system, there were 14 T1, 29 T2, 20 T3, and 24 T4 tumors in our group.

Treatments

Fifty-three patients (61%) received surgery and radiotherapy (S + RT group), and the remaining 34 patients were treated with radiotherapy alone (RT group). In the present study there were no definitive treatment policies for squamous cell carcinoma of the external auditory canal and middle ear during the past 20 years; thus treatment was determined by the respective physicians at each institution. In the S + RT group, 23 patients underwent macroscopic total resection with negative surgical margins, 22 patients underwent macroscopic total resection with positive margins, and the remaining 8 patients underwent subtotal or partial resection. Of the 53 patients in the S + RT group, 18 were treated with preoperative radiotherapy, 29 were treated with postoperative radiotherapy, and the remaining 6 patients received both preoperative and postoperative radiotherapy.

Radiotherapy was administered with a ^{60}Co teletherapy unit (n = 2 patients) or a 4, 6, 10-MV linear accelerator. Daily fractions of 1.8–2.0 Gy 5 days per week were used most often. The treatment volume was based on the pretreatment CT or MRI scans, and the planning target volume included the primary tumor (n = 30, RT group), primary tumor bed (n = 29, S + RT group), or primary tumor/primary tumor bed and the lymph node area of the parotid, retroauricular, upper jugular, and upper accessory regions (n = 4, RT group; n = 24, S + RT group). Computed tomography–guided treatment planning was performed in 53 patients (61%). Three patients were treated with hyperfractionated radiotherapy using 2 fractions per day of 1.3–1.6 Gy to a total dose of 42.9–72 Gy. The total dose to the primary site in all 87 patients ranged from 20 to 72 Gy (median, 60 Gy). Two laterally angled, pair wedged fields were used in 54 patients (62%). Nineteen patients received a single lateral field with megavoltage irradiation from the linear accelerator or ^{60}Co teletherapy unit, or 15-MeV electron beam irradiation from a lateral port. The remaining 14 patients were treated with three or more fields with megavoltage irradiation. An immobilization device was used with most of the patients (70 patients, 80%) during radiotherapy. In the RT group with clinically negative lymph node involvement (n = 32), elective neck irradiation was supplemented in 2 patients.

Three patients were treated with high-dose-rate intracavitary brachytherapy in addition to external beam radiotherapy. After 30–50-Gy external beam radiotherapy, 15–42-Gy ^{192}Iridium high-dose-rate brachytherapy with a 370-GBq source (MicroSelectron; Nucletron, Veenendaal, The Netherlands) was supplemented for boost treatment with a single dose of 3 Gy at 5–7-mm applicator distance with 5 fractions (1 patient with a T2 tumor) or 10 fractions (2 patients with T1 tumors) per week.

Thirty-four patients (39%) received various regimens and doses of intravenous or oral chemotherapy before, during, and/or after

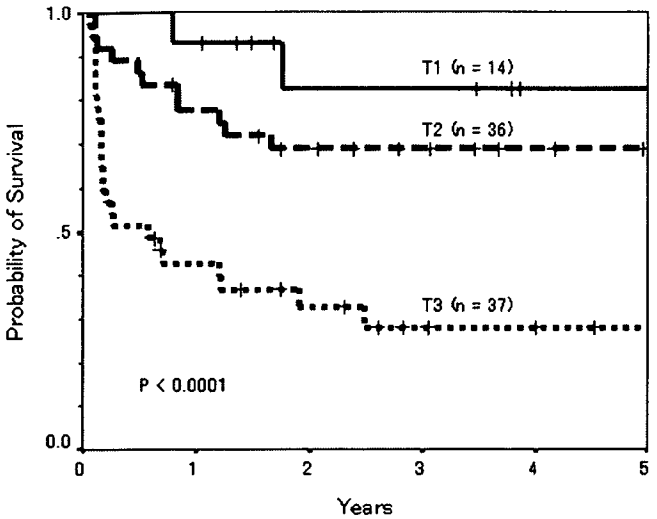

Fig. 1. Actuarial disease-free survival rates according to the T stage classification proposed by Stell *et al.* (10).

radiotherapy. The most commonly used regimen was concurrent intravenous 5-fluorouracil (250 mg/m^2 daily dose during radiotherapy) or oral fluoropyrimidine (TS-1) administration at a daily dose of 65 mg/m^2 for 4 weeks starting from the onset of radiotherapy (20 patients). The next most common was a combination of cisplatin (40–80 mg/m^2, 2–3 times) and 5-fluorouracil (250–750 mg/m^2, 2–17 times) in 6 patients. The remaining 8 patients received other chemotherapeutic regimens with the following agents either alone or in combination: carboplatin (20–200 mg/m^2, 1–20 times), bleomycin (15 mg, 12–20 times), and/or peplomycin (5 mg, 3–15 times).

Statistical analysis

The biologic effective dose (BED) and linear–quadratic effective dose (LQED) for early-responding tissues were calculated, and the BED converted to a LQED for a 2-Gy fraction (16). The BED and LQED were calculated using the LQ equation. For the LQ calculation, a value of α/β = 10 was assumed for tumors (Gy_{10}), and α/β = 3 was used for late complications (Gy_3) (17). Acute toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 3.0. Late complications were graded in accordance with the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) criteria (18).

The median follow-up period for 52 surviving patients was 42 months (range, 2–174 months), and no patients were lost to follow-up. Overall survival and disease-free survival (DFS) rates were calculated actuarially according to the Kaplan-Meier method (19) and were measured starting from the day of initial treatment. Differences between groups were estimated using the chi-square test and the log–rank test (20). Multivariate analysis was performed using the Cox regression model (21). A probability level of 0.05 was chosen for statistical significance. Statistical analysis was performed with the SPSS software package (version 11.0; SPSS, Chicago, IL).

RESULTS

We applied two staging systems, Stell's staging system (Fig. 1) and Arriaga's staging system (Fig. 2), to examine DFS. According to Stell's classification, the 5-year actuarial DFS rate was 83%, 69%, and 28% for T1, T2, and T3 tumors, respectively ($p < 0.0001$). According to Arriaga's staging system, the 5-year actuarial DFS rate was 83%, 65%, 55%, and 27% for T1, T2, T3, and T4 tumors, respectively ($p = 0.001$). Therefore, both staging systems could be applied properly to our patient population.

Of 87 patients, 34 (39%) died during the analysis period. Thirty-one patients died of their disease, whereas the remaining 3 died of other causes without any sign of clinical recurrence (1 T2-stage patient died of pneumonia, 1 T1-stage patient died of rectal cancer, and 1 T1-stage patient died of unknown causes). Of the 87 patients, 38 experienced recurrence: 34 patients with local recurrence, 3 with neck lymph node recurrence, and 1 with distant metastasis (lung) as a first failure. The 5-year actuarial overall survival and DFS rates for all 87 patients were 55% and 54%, respectively.

On univariate analysis, T stage (Stell's classification) ($p < 0.0001$), treatment modality (S + RT vs. RT) ($p = 0.002$), and Karnofsky performance status ($p = 0.03$) all had significant impact on DFS. On multivariate analysis, T stage ($p < 0.0001$) and treatment modality ($p < 0.0001$) were also found to be significant prognostic factors (Table 2). Other factors, such as tumor site and chemotherapy, did not influence DFS. The 5-year DFS rate for T1, T2, and T3 patients was 83%, 45%, and 0 in the RT group ($p < 0.0001$) (Fig. 3) and 75%, 75%, and 46% in the S + RT group ($p = 0.13$) (Fig. 4), respectively.

Because radiotherapy alone may be reserved for less fit patients or those with poor chance of respectability, we further compared DFS between the S + RT group and RT group according to T stage (Stell's) and Karnofsky performance status (Table 3). In T3 patients or those with KPS ≥70%, the S + RT group had significantly better DFS compared with those in the RT group, but in T1 and T2

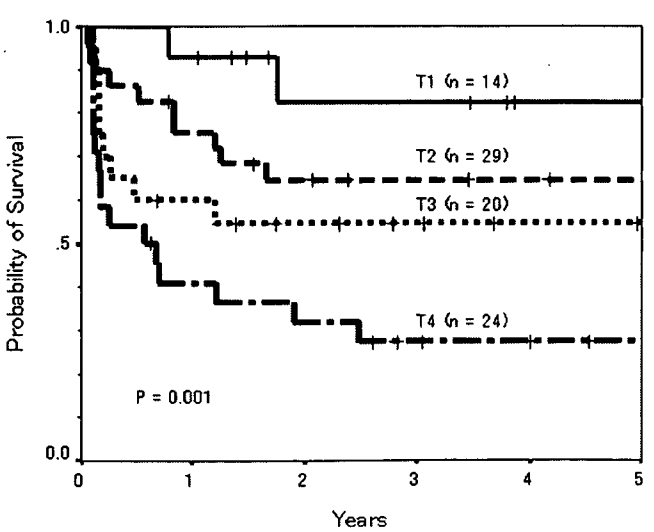

Fig. 2. Actuarial disease-free survival rates according to the T stage classification proposed by Arriaga *et al.* (1).

Table 2. Univariate and multivariate analysis of various potential prognostic factors for disease-free survival in patients with squamous cell carcinoma of the external auditory canal and middle ear

Variable	No. of patients	Univariate analysis 5-y DFS rate (%)	Univariate analysis p	Multivariate analysis RR (95% CI)	Multivariate analysis p
T stage			<0.0001	0.183 (0.089–0.375)	<0.0001
T1, T2	51	74			
T3	36	25			
Treatment modality			0.002	3.577 (1.816–7.048)	<0.0001
RT	34	38			
Surgery + RT	53	65			
KPS (%)			0.03	0.577 (0.260–1.279)	0.18
≥70	75	58			
<70	12	28			
N stage			0.07	0.417 (0.171–1.018)	0.06
N0	79	57			
N1–3	8	25			
Tumor site			0.15	—	
External auditory canal	59	61			
Middle ear	28	41			
Total radiation dose (Gy)			0.16	—	
≤60	53	50			
>60	34	61			
Use of CT-based treatment planning			0.53	—	
Yes	62	53			
No	25	60			
Gender			0.54	—	
Female	44	56			
Male	43	52			
Age (y)			0.86	—	
<75	50	53			
≥75	17	60			
Use of chemotherapy			0.98	—	
Yes	34	57			
No	53	54			
Use of immobilization device during RT			0.99	—	
Yes	70	55			
No	17	53			

Abbreviations: DFS = disease-free survival; RR = relative risk; CI = confidence interval; RT = radiotherapy; KPS = Karnofsky performance status.

patients or those with KPS <70%, no significant difference was found between the groups.

Concerning surgical margin status in the S + RT group, the 5-year DFS rate in patients with negative surgical margins, those with positive margins, and those with macroscopic residual disease was 83%, 55%, and 38%, respectively (Fig. 5; $p = 0.007$). Concerning the timing of radiotherapy in the S + RT group, the 5-year DFS rate in patients treated with preoperative, postoperative, and both pre- and postoperative radiotherapy was 64%, 71%, and 50%, respectively ($p = 0.75$). Although there was a trend toward greater negative surgical margins in the preoperative group, there were no significant differences with the timing of radiotherapy and surgical margin status (Table 4) ($p = 0.06$).

With regard to local control, the 5-year local control rate in T1, T2, and T3 patients was 83%, 45%, and 0, respectively, in the RT group ($p < 0.0001$). Of 10 patients with T1 stage tumors (total, 10 patients), 9 had no local recurrence, and 2 of these 9 patients were treated with external beam

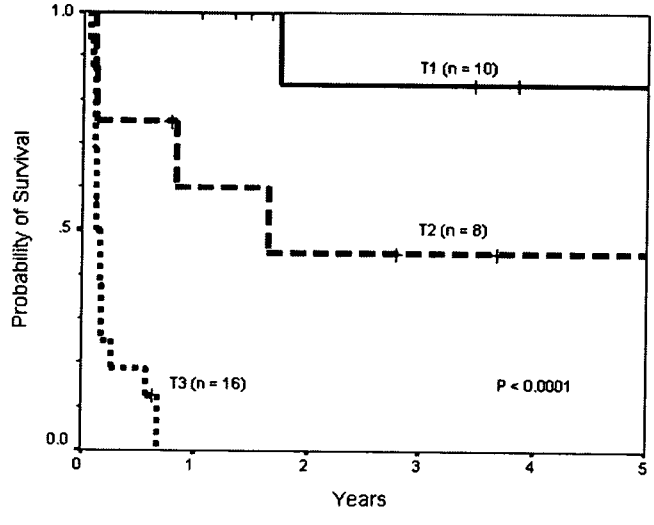

Fig. 3. Actuarial disease-free survival rates in patients treated with radiotherapy, according to T stages proposed by Stell *et al.* (10).

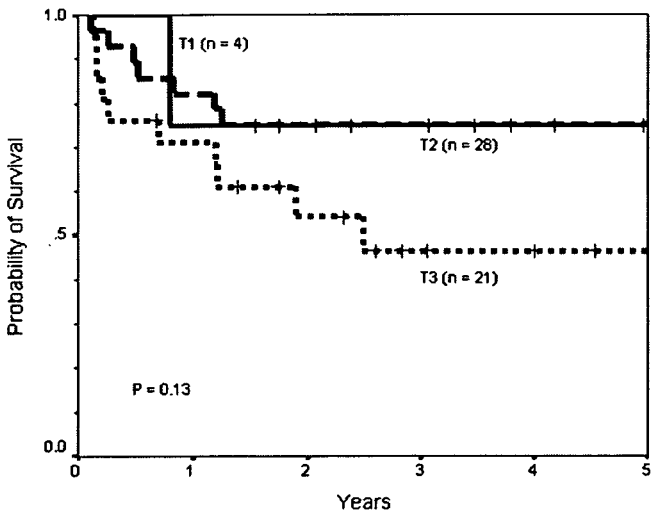

Fig. 4. Actuarial disease-free survival rates in patients treated with surgery and radiotherapy, according to T stages proposed by Stell *et al.* (10).

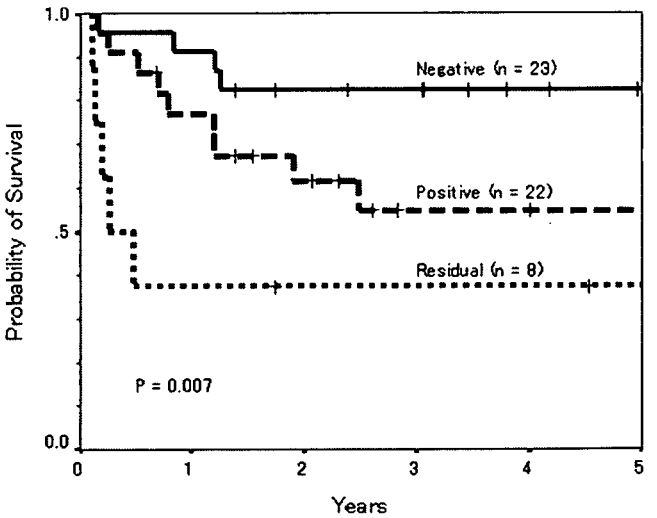

Fig. 5. Actuarial disease-free survival rates in patients treated with surgery and radiotherapy, according to surgical margin status.

radiotherapy and intracavitary brachytherapy. The remaining 1 patient with T1 disease had local recurrence with marginal field recurrence and was treated with a ^{60}Co teletherapy unit without the use of CT-based treatment planning. The BED for T1 patients ranged from 72 Gy_{10} to 90.6 Gy_{10} (median, 84 Gy_{10}), and LQED for the T1 patients ranged from 60 to 76 Gy (median, 70 Gy). In the RT + S group, the 5-year local control rate in T1, T2, and T3 patients was 75%, 79%, and 53%, respectively ($p = 0.32$). Concerning surgical margins, the 5-year local control rate in patients without negative surgical margins, those with positive margins, and those with macroscopic residual disease was 95%, 55%, and 38%, respectively ($p < 0.0002$). Concerning neck control in the RT group, only 1 of 32 patients (3%) with N0 disease developed neck recurrence at the time of analysis.

Concerning acute toxicity, 77 patients had Grade 2 or less dermatitis, and 10 patients had Grade 3 dermatitis. However, there were no treatment-related deaths for any of the patients. In addition, most patients had no late complications ($n = 80$) or RTOG/EORTC Grade 1–2 late complications ($n = 5$). However, 2 patients experienced radiation-induced Grade 4 late complications. One patient experienced osteoradionecrosis with a total dose of 72 Gy in conventional fractionation (BED = 115 Gy_3), and the other had ulceration with a total dose of 67.2 Gy in 2 fractions per day of 1.6 Gy (BED = 103 Gy_3). No other severe radiation-induced complications were observed at the time of the analysis. With regard to T1 tumors, no apparent hearing impairment was documented after treatment for either the S + RT group or the RT group.

Table 3. Comparison of DFS in patients treated with S + RT and those treated with RT according to T stage and KPS

	No. of patients		5-y DFS rate (%)		
	S + RT	RT	S + RT	RT	*p*
T stage (Stell's [10])					
T1	4	10	75	83	0.98
T2	28	8	75	45	0.12
T3	21	16	46	0	<0.0001
KPS (%)					
≥70	47	28	69	39	0.003
<70	6	6	25	33*	0.50

Abbreviations: DFS = disease-free survival; S = surgery; RT = radiotherapy; KPS = Karnofsky performance status.
* 3-y DFS rate.

DISCUSSION

A rational comparison of treatment strategies from the literature on squamous cell carcinoma of the external auditory canal and middle ear is difficult, owing to heterogeneity of staging classification and the types of treatment used (12). Although many classification methods have been proposed, none has been accepted by the UICC. Of the various staging systems, the one proposed by Stell and McCormick (10) is based on 47 tumors of the external auditory canal and middle ear, and several investigators have used this staging system for classification (14, 22–24). Arriaga *et al.* (1) also proposed a staging system based on pretherapeutic radiologic findings in CT scans and clinical examination. This staging system correlated well to the histopathologic tumor extension (25) and has been used for classification in several reports (3, 4, 12, 26, 27). In the present study we applied these two staging systems and found that they corresponded well and were applicable to our patients. Several other reports also indicated that these staging classifications were a reproducible and objective method of subdividing patients for evaluation of efficacy of treatment (3, 4, 10, 13, 14, 26–28). We believe that these two staging systems can be used to properly classify squamous cell carcinoma of the

Table 4. Mode of radiotherapy and surgical margin status in patients with squamous cell carcinoma of the external auditory canal and middle ear

Timing of RT	Total no. of patients	Surgical margin status		
		Negative	Positive	MRD
Preoperative	18	11	6	1
Median RT dose (Gy)		50 (20–60)	50 (40–70)	50
Pre- and postoperative	6	1	5	0
Median RT dose (Gy)		60	70 (63–72)	—
Postoperative	29	11	11	7
Median RT dose (Gy)		55.2 (45–60)	60 (50–70)	66 (50–70)
Total no. of patients	53	23	22	8

Abbreviations: RT = radiotherapy; MRD = macroscopic residual disease. Values in parentheses are ranges.

external auditory canal and milled ear. Recently, MRI has been frequently performed in patients with these tumors, and information from MRI may provide useful information regarding the precise staging of tumors. Further studies are required to elucidate whether a more appropriate staging system can be formulated using additional information, such as from MRI.

In the present study, the patient's T stage was found to be an independent prognostic factor for DFS. This result is consistent with those of previous reports, and it is widely accepted that local tumor extension is an important prognostic factor for squamous cell carcinoma of the external auditory canal and middle ear (1, 4–11, 25, 29, 30). For early-stage tumors, several investigators have also reported favorable results. Arriaga *et al.* (1) reported a survival rate of 100% in 5 cases of T1 disease drawn from 39 cases of external auditory canal squamous cell carcinoma that they studied. Austin *et al.* (4) have reported a survival rate of 100% in 3 cases of T1 disease in which surgical resection and adjuvant radiotherapy were performed. On the other hand, for advanced tumors, there is a significantly worse prognosis than for those with early-stage tumors (1, 5, 26, 31, 32). Prasad *et al.* (32) reviewed 96 reports and selected 26 reports containing information on 144 comparable patients. They noted that in cases of advanced disease, only 2 of 144 patients survived more than 5 years. Many investigators also reported that advanced tumors with the presence of bone erosion or invasion had decreased survival rates compared with those without bone erosion or invasion (1, 4, 5, 8, 33). These results imply that early diagnosis is an important factor for improving prognosis.

The present study also indicated that the treatment modality (S + RT vs. RT) was an independent prognostic factor for DFS. Previous reports have also indicated that a combination of surgery and radiotherapy is better than radiotherapy alone for these tumors (4, 26, 30). Testa *et al.* (26) reported that the 5-year survival rate for patients who underwent radiotherapy was 29%, but for patients who underwent a combination of surgery and radiotherapy it was 63%. Austin *et al.* (4) indicated that combination therapy involving surgery and radiotherapy provided a higher 5-year survival rate than either surgery or radiotherapy alone. In the present study, the 5-year DFS rate in patients treated with surgery and radiotherapy (65%) was significantly higher than in those treated with radiotherapy (38%). These results indicate that the combination of surgery and radiotherapy is a preferable treatment to radiotherapy alone for these tumors.

Although the combination of therapy and radiotherapy is generally more effective than radiotherapy alone, the role of radical radiotherapy for early-stage tumors remains controversial. Previous reports have indicated that radiotherapy alone is inadequate as a primary therapy regardless of extent of disease and that most patients so treated present with rapid local recurrence (2, 4, 34, 35). On the other hand, recent reports have suggested the usefulness of radical radiotherapy for early-stage disease. Hashi *et al.* (22) indicated that disease control was 100% in 8 patients with T1 disease when treated with radiotherapy alone. Pemberton *et al.* (14) analyzed 123 patients treated with radiotherapy alone, and the 5-year cancer-specific survival rate was 85% for 27 patients with early-stage disease (T1 by Stell's classification). In the present study, the 5-year disease rate in 10 T1 patients treated with radiotherapy was 83%, and 9 of 10 patients had no local recurrence at the time of analysis. The remaining 1 patient had local recurrence at the marginal radiation field and was treated with ^{60}Co teletherapy without CT-based treatment planning. Moreover, radical radiotherapy did not seem to impair hearing function in patients with T1-stage tumors. These results indicate that radical radiotherapy is a viable treatment modality for T1-stage tumors, as well as surgery plus radiotherapy. Using external beam radiation based on three-dimensional CT treatment planning, tumoricidal doses can be administered without a serious threat of brainstem damage and brain injury. Although the optimal dose of radiotherapy remains uncertain, several investigators indicated that total doses of 65–75 Gy were sufficient to control disease (22). In the present study, total doses (LQED) of radiotherapy for T1-stage patients ranged from 60 to 76 Gy (median, 70 Gy). A dose of 70 Gy for radical radiotherapy seems to be appropriate for achieving local control for early-stage tumors.

However, a total dose of 70 Gy or more may cause late complications, such as osteoradionecrosis of the temporal

bone and ulcerations (36, 37). In the present study, 2 patients suffered radiation-induced complications. These patients were treated with more than 70 Gy (BED = 115 Gy_3) in conventional fractionation or approximately 70 Gy (BED = 103 Gy_3) in accelerated hyperfractionated radiotherapy. Several investigators also indicated that when a total dose of 70 Gy in conventional fractionation is used, the risk of complications, such as osteoradionecrosis, increases (36, 37). Therefore, it is necessary to reduce the occurrence of late complications when treating with radical radiotherapy. Recently, brachytherapy has emerged as an attractive boost treatment that can be applied for curative intent when the disease is locally confirmed or with a recurrent tumor (12, 38). With the use of multiple fractions, one may deliver a dose sufficient for local control while decreasing the risk of unacceptable side effects and late complications (38). In the present study, 3 patients treated with external beam radiotherapy and brachytherapy had no local recurrence without serious late complications (T1: 2 patients; T2: 1 patient). Suzuki *et al.* (39) also treated a patient with early-stage carcinoma of the external auditory canal by high-dose-rate intracavitary brachytherapy irradiation (20 Gy/8 fractions) followed by 40-Gy external beam irradiation. They found no severe side effects, and the tumor disappeared after treatment. These results suggest that the additional use of brachytherapy followed by external beam radiotherapy may be useful in achieving curative therapy without serious late complications for early-stage diseases. Recently, advanced techniques such as intensity-modulated radiotherapy have also been emerging as an attractive method for achieving local control while effectively sparing normal tissues. These advanced techniques may also help to improve the patient's quality of life by avoiding late complications or preserving hearing function.

On the other hand, our study showed that patients with advanced disease (T2 and T3) did poorly when treated by radical radiotherapy alone (4, 10, 29). Several investigators also indicated that combination therapy with surgery and radiotherapy provided a higher 5-year survival rate than surgery or radiotherapy alone (4, 10, 24, 29, 35). Wagenfield *et al.* (35) indicated that the 4-year survival rate for patients treated with surgery and radiotherapy was 67% but was 0 for those treated with radiotherapy alone. Pemberton *et al.* (14) indicated that the 5-year survival rate was only 44% for 96 patients with advanced-stage tumors when treated with radiotherapy alone. In the present study, the 5-year DFS rate was 45% and 0, respectively, in patients with T2 and T3 tumors treated with radiotherapy, whereas a significantly higher rate of 75% and 46% was seen in patients with T2 and T3 tumors treated with both surgery and radiotherapy. These results indicate that surgery and radiotherapy should be recommended as a standard treatment for advanced (T2–3) disease.

Concerning the method of surgery, most investigators agree that wide en bloc resection of the tumor with free surgical margins is the optimal treatment (3, 4, 12, 27, 40–42). Pfreundner *et al.* (12) indicated that patients with completely resected tumors had a 5-year survival rate of 100%, and the rate was 66% for patients with tumors extending beyond surgical margins. Yin *et al.* (27) indicated that positive surgical margins provided a 5-year survival rate of 20.8%, which was significantly lower than the 5-year survival rate of 76.5% for free margins. In the present study, the 5-year disease-free survival rate was significantly higher in patients who had negative surgical margins than for those with positive surgical margins or macroscopic residual disease. These results indicate that surgery with negative surgical margins may be the preferable treatment for these diseases.

On the other hand, optimal timing of radiotherapy (preoperative or postoperative) has not been established for squamous cell carcinoma of the external auditory canal and middle ear (3, 8, 24, 26). Several investigators emphasized the effectiveness of postoperative radiotherapy to control residual tumors at the margins (3, 4, 7, 8, 12, 13, 29, 43). Concerning postoperative radiotherapy, the recommended doses were 54–60 Gy for patients with radical tumor resection and 66 Gy or more for patients with tumors beyond the surgical margins, owing to hypoxia and reduced sensitivity to radiation of the tumor cells at the margin of resection (12, 26, 30). However, several investigators indicated that incomplete resection was the major cause of recurrence and that postoperative radiotherapy was not beneficial (25, 44). In the present study, patients who were treated with preoperative radiotherapy tended to have more negative margins at operation than those who were treated with postoperative radiotherapy, but there were no significant differences with regard to DFS among patients with preoperative, postoperative, or both pre- and postoperative radiotherapy. Further studies are required to clarify the optimal management of radiotherapy when combined with surgery.

The role of chemotherapy in the management of squamous cell carcinoma of the external auditory canal and middle ear also remains uncertain. Because distant metastases are not commonly reported from these tumors, systemic chemotherapy is not routinely used (8, 25, 43). In the present study, the use of chemotherapy did not affect DFS. However, our results concerning chemotherapy should be interpreted with caution owing to the variability in chemotherapy regimens, doses, and timing that were used. Recently, to obtain a negative surgical margin at operation, several investigators have tried using both radiotherapy and chemotherapy (3, 27). When combined, chemotherapy may enhance the radiotherapeutic effects. Several randomized clinical trials for various tumors comparing concurrent chemoradiotherapy with radiotherapy alone have shown that concurrent chemoradiotherapy improved local control and often resulted in the absence of a tumor at the surgical margin and sometimes in no residual tumor at all (45–47). Further clarification on the role of chemotherapy is necessary for these tumors.

In conclusion, our results indicate that radical radiotherapy is the treatment of choice for patients with early-stage squamous cell carcinoma of the external auditory

canal and middle ear. In addition, surgery, with negative surgical margins if possible, and radiotherapy are recommended as the standard care for cases of advanced-stage disease. We did not find the effectiveness of chemotherapy in the present study. However, this was a retrospective study comprising a relatively small number of patients, and further studies with a larger number of patients are necessary to confirm our results concerning squamous cell carcinoma of the external auditory canal and middle ear.

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ORIGINAL ARTICLE

Experimental verification of the utility of positron emitter nuclei generated by photonuclear reactions for X-ray beam monitoring in a phantom

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Abstract
Purpose. The utility of positron emitter nuclei generated by photonuclear reactions was verified for X-ray beam monitoring in a phantom.
Materials and methods. Positron emission tomography-computed tomography (PET-CT) images of a gelatinous water phantom (H_2O target) and a polyethylene phantom (CH_2 target) were acquired 5 min after delivering a dose of 17 Gy with an X-ray beam energy of 21 MV. Reconstructed PET images and the calculated half-life showed that the positron emitters of ^{15}O (half-life 122.2 s) in the H_2O target and ^{11}C (half-life 20.4 min) in the CH_2 target were generated by photonuclear reactions.
Results. A comparison was made between measured activity and dose distributions for each target. The measured times of annihilation gamma rays from the positron emitter nucleus were 10 and 30 min for the ^{15}O nucleus in the H_2O target and the ^{11}C nucleus in the CH_2 target, respectively. The activity distributions of the ^{15}O and ^{11}C positron emitter nuclei were similar to the measured dose distributions for both depth and lateral directions except for dose buildup and collimator edge regions. It was confirmed that no activity was detected at an X-ray energy of 14 MV, which was far below the energy threshold for both photonuclear reactions.
Conclusion. It was estimated that the PET-CT image acquired from the activity of the ^{15}O and ^{11}C positron emitter nuclei might provide the area of X-ray beam irradiation in a phantom.

Key words High-energy photon therapy · Beam monitoring · Photonuclear reaction · PET-CT imaging

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Introduction

The quality of radiotherapy largely depends on tumor dose conformity and patient positioning. Assessment of the conformal dose has been realized by rotational three-dimensional conformal radiation therapy (3D CRT)[1] and intensity-modulated radiation therapy (IMRT).[2] Intensity-modulated arc therapy (IMAT)[3] is regarded as a combination of 3D CRT and IMRT.

Accurate patient positioning prior to dose delivery has been achieved using millivolt CT,[4] in-room CT,[5] or kilovolt CT mounted on a linac gantry[6]; and radio-

therapy employing these accurate patient positioning methods is now called image-guided radiation therapy (IGRT). However, these IGRT techniques cannot fully ensure dose conformity to a moving tumor during treatment. Gated irradiation was proposed using an airbag sensor, CCD camera, laser sensor, and so on to monitor the patient's breathing cycle.[7–9] Recently, real-time embedded-marker detection using fluoroscopy[10] and real-time image correlation of 3D ultrasonographic images[11] were also proposed, with the objective of more accurate real-time tumor localization.

In the meantime, dose verification immediately after treatment was proposed using PET imaging of positron emitter nuclei generated in the target by a therapeutic irradiation beam. Simulation studies and experimental results were reported for charged ion treatment.[12–16] For high-energy photon treatment, the use of PET-CT at 50 MV was proposed; and experimental results[17–20] and Monte Carlo calculation results were also reported for in-beam PET imaging.[21]

The purpose of this article is to show that ^{15}O and ^{11}C positron emitter nuclei can be detected using a commercial PET-CT in the photonuclear reaction with X-ray energy as low as 21 MV. Furthermore, the PET-CT image obtained from such activity can provide the area of X-ray beam irradiation in a phantom.

Materials and methods

Photonuclear reactions by absorption of high-energy photons

When a high-energy photon reaches a nucleus, the photon is absorbed in the nucleus. If the excited states of the nucleus for the absorption of the energy have an energy higher than the binding energy of the nucleons, the nucleon goes outside the nucleus, thereby causing nuclear transmutation. The human body comprises carbon, nitrogen, oxygen, and hydrogen, and the main composition is carbon and oxygen.[22] For ^{16}O and ^{12}C nuclei, positron emitter nuclei of ^{15}O and ^{11}C are generated by X ray beams of energies exceeding 15.7 and 18.7 MeV, respectively. These are summarized in the following equations.

$$\begin{cases} {}^{16}\mathrm{O}(\gamma,\mathrm{n})\,{}^{15}\mathrm{O}\left({}^{+}\beta;T_{1/2}=122.2\,\mathrm{sec}\right) \\ {}^{12}\mathrm{C}(\gamma,\mathrm{n})\,{}^{11}\mathrm{C}\left({}^{+}\beta;T_{1/2}=20.4\,\mathrm{min}\right) \end{cases} \quad (1)$$

where $T_{1/2}$ is the half life of each positron emitter nucleus. The photonuclear reaction cross section at the energy of the incident photon[23] is shown in Fig. 1.

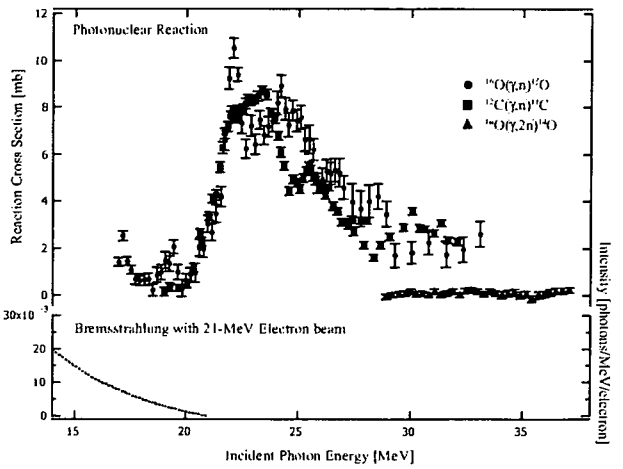


Fig. 1. Intensity of bremsstrahlung with a 21-MeV electron beam and photonuclear reaction cross section of $^{12}C(\gamma,n)^{11}C$, $^{16}O(\gamma,n)^{15}O$, and $^{16}O(\gamma,2n)^{14}O$ at the energy of incident photons in the National Nuclear Data Center[23]

The intensity of a photon emitted from a tungsten target irradiated with a 21-MeV electron beam by bremsstrahlung, I, is calculated using Wu's approximation[24] of a radiation yield and is expressed as follows.

$$I[\text{photons/MeV/electron}] = 2.5\times10^{-2}\cdot\left\{4\cdot\left(1-\frac{E_x}{21}\right)+\frac{E_x}{7}\cdot\ln\left(\frac{E_x}{21}\right)\right\}. \quad (2)$$

where E_x is the energy of an X-ray by the bremsstrahlung. The calculation result is shown in Fig. 1.

High-energy photon beam to H_2O and CH_2 targets

The X-ray energy of 21 MV for the photonuclear reaction was generated by a microtron accelerator (Hitachi, HTM2200). H_2O and CH_2 targets were used previously for research of the photonuclear reaction in Eq. (1). The H_2O target was gelatinous water (99% pure water),[25] and the CH_2 target was high-density polyethylene. Each had dimensions of $10 \times 10 \times 40\,cm^3$. It should be noted that liquid water is not an appropriate phantom due to diffusion of the positron emitter nuclei. A dose of 17 Gy was delivered to each of the H_2O and CH_2 targets at the peak depth of 31 mm with a field size of $5 \times 5\,cm^2$ at the target surface. The X-ray beam was directed perpendicular to the $10 \times 10\,cm^2$ square surface with the beam axis centered on the square surface. The source-to-surface distance was 100 cm, and approximately 10 min were required to deliver 17 Gy. In addition, the percentage depth dose (PDD) and off-center ratio (OCR) were separately measured using a water phantom (CMS, Dynascan water phantom) and an ion chamber (0.125 cc, PTW 31005).

The positron emitter nuclei were not generated in the photonuclear reaction with an X-ray energy of 14 MV.

Activity measurement using PET-CT apparatus

PET-CT (GE, Discovery LS8) was used to measure 3D positron activity distributions, where 12096 BGO crystals were mounted having a dimension of $4 \times 8 \times 30\,mm^3$. A 3D reconstruction algorithm of ordered subsets expectation maximization (OSEM) was employed with a transverse resolution of 4.8–5.2 mm and an axial resolution of 6.5–7.5 mm depending on the imaging position. The axial field of view (FOV) was 15.2 cm.

After dose delivery, the H_2O and CH_2 targets were moved to a PET-CT room. Measurement of the ^{16}O and ^{12}C activities was started 5 min after the irradiation. Each of the H_2O and CH_2 targets was positioned so the X-ray beam direction was parallel to the transverse imaging plane, thereby allowing full detection of all the annihilation gamma rays generated from the positrons (Fig. 2). At first, the PET-CT images of the ^{16}O and ^{12}C activities were reconstructed after 10-min annihilation gamma counting. Subsequently, the counting time for CH_2 was extended to 30 min for more precise activity measurements in the depth and lateral directions. To derive a half-life for the H_2O target with 21-MV X-ray irradiation, the annihilation gammas were counted for every minute with a total measurement time of 10 min. For the CH_2 target with 21-MV irradiation, resulting annihilation gammas were counted for every 3 min with a total measurement time of 30 min. For 14-MV irradiation, annihilation gammas were always counted for every minute. The summary is shown in Table 1.

Results and discussion

Activity distributions in H_2O and CH_2 targets

Figure 3a shows a 3D PET-CT fusion image of a gelatinous water phantom (H_2O target), and Figure 3b depicts that of a polyethylene phantom (CH_2 target) after delivering a dose of 17 Gy with an X-ray beam energy of 21 MV. Each reconstructed 3D PET image along with

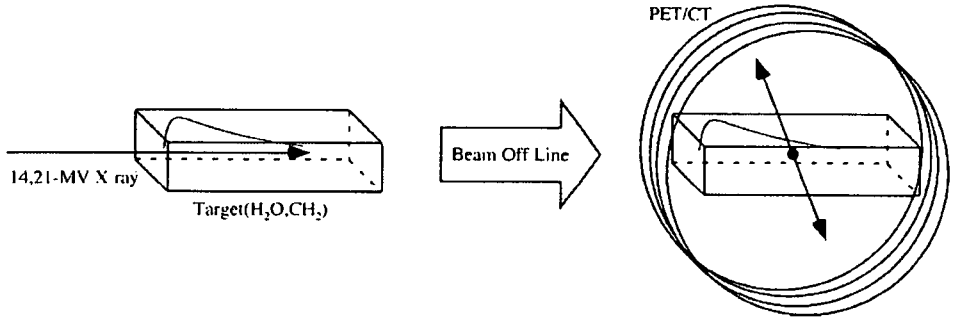


Fig. 2. Flow figure of X-ray irradiation to the target and measurement of annihilation gamma rays using a positron emission tomography-computed tomography (PET-CT) apparatus. The irradiated target was delivered from the irradiation room to the PET-CT room after X-ray irradiation (*Beam Off Line*). The target was positioned so the X-ray beam direction was parallel to the transverse imaging plane

Table 1. Condition of X-ray irradiation and activity measurement

Target	Activity measurement (min)
Activity distribution (X-ray energy 21 MV; irradiation dose 17 Gy)	
H_2O	10
CH_2	10, 30
Decay curve	
X-ray energy 21 MV; irradiation dose 17 Gy	
H_2O	10 (1 × 10 times)
CH_2	30 (3 × 10 times)
X-ray energy 14 MV; irradiation dose 17 Gy	
H_2O	10 (1 × 10 times)
CH_2	10 (1 × 10 times)

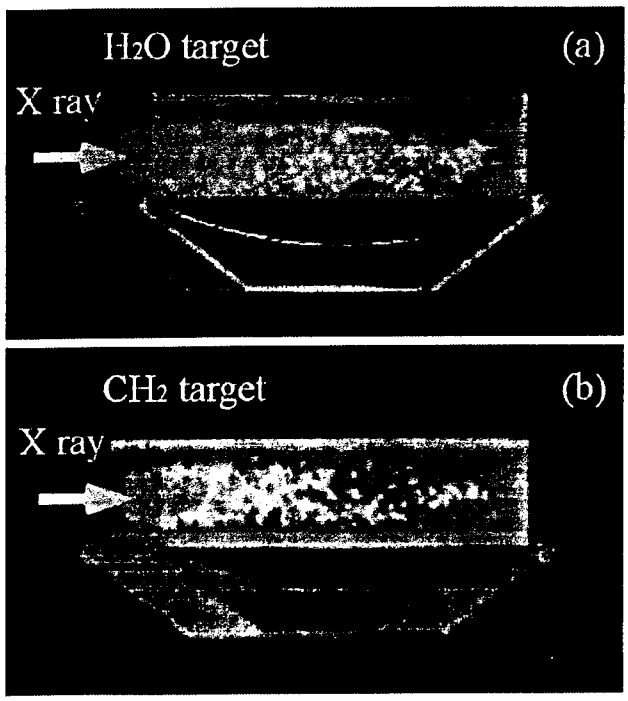
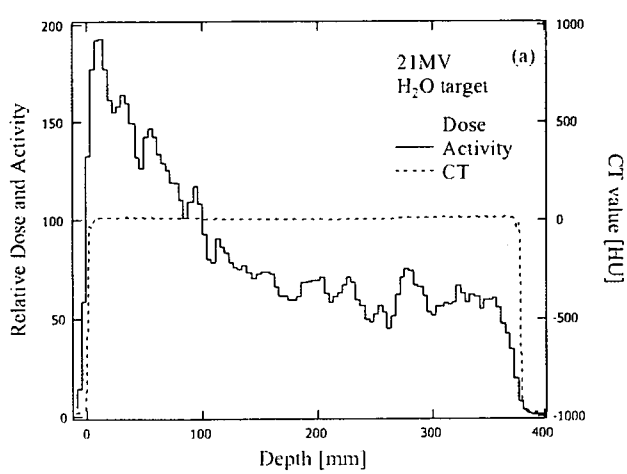


Fig. 3. Three-dimensional PET-CT images of (a) a gelatinous water phantom (*H_2O target*) and (b) a polyethylene phantom (*CH_2 target*) after delivering a dose of 17 Gy with an X-ray beam energy of 21 MV. The activities of the PET images were the positron emitter nuclei of ^{15}O and ^{11}C from H_2O and CH_2 targets, respectively. Both PET images were reconstructed after 10 min of annihilation gamma counting

the fused CT image indicates that positron emitters were generated in each target. The detected total counts of annihilation gamma rays for the H_2O target were 478 494, and those for the CH_2 target were 129 843. The statistical error of the activity in each voxel unit of 0.0064 cm^3 is about 20%.

Figure 4 shows comparisons between activity and dose distributions for the H_2O target with an annihilation gamma counting time of 10 min. Figure 4a represents depth distributions on the beam axis, where both activity and dose were normalized to 100 at a depth of 100 mm. The CT image profile is also shown. Figure 4b shows lateral distributions at a depth of 100 mm, where both activity and dose were normalized to 100 at the beam center. Figure 5 shows comparisons between activity and dose distributions for the CH_2 target with an annihilation gamma counting time of 30 min. Figure 5a represents depth distributions on the beam axis, where both activity and dose were normalized to 100 at a depth of 100 mm. The CT image profile is also shown. Figure 5b shows lateral distributions at a depth of 100 mm, where both activity and dose were normalized to 100 at the beam center. The statistical error of the activity in each 4-mm step of the lateral position is about 10%.

The reaction cross section of σ, which determines the rate of the generation, depends on the kind of the target nucleus (mass number of A_i, atomic number of Z_i) and the X-ray energy of E_X. The number of the positron emitter nuclei generated by the photonuclear reaction at each point $\vec{r}$, N_{act}, is given as follows.[16,25]



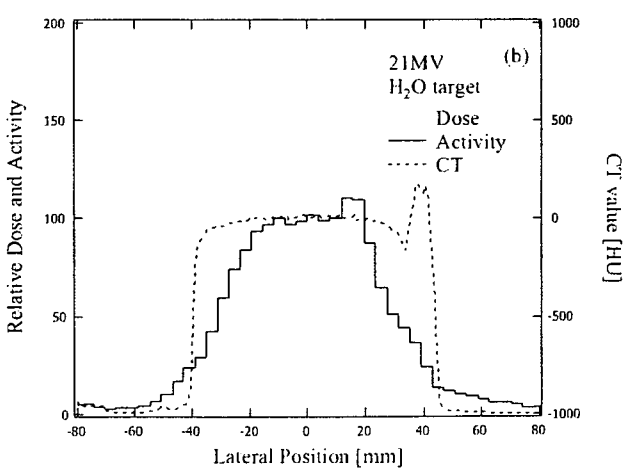
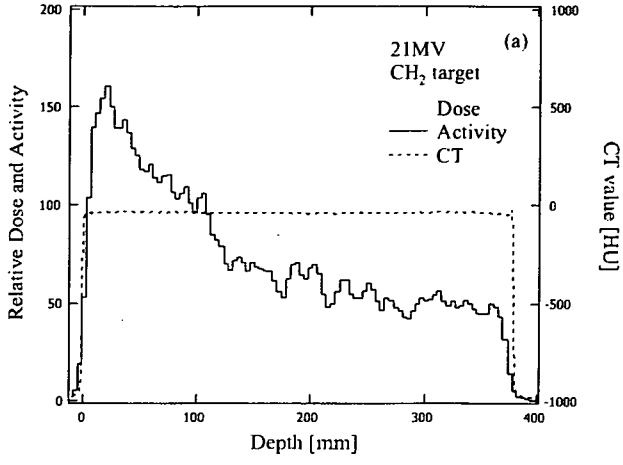


Fig. 4. Comparisons between activity and dose distributions for the H_2O target with an annihilation gamma counting time of 10 min. a Depth direction on the beam axis. Both activity and dose were normalized to 100 at a depth of 100 mm. A computed tomography (CT) image profile is also shown. b Lateral direction at a depth of 100 mm. Both activity and dose were normalized to 100 at the beam center



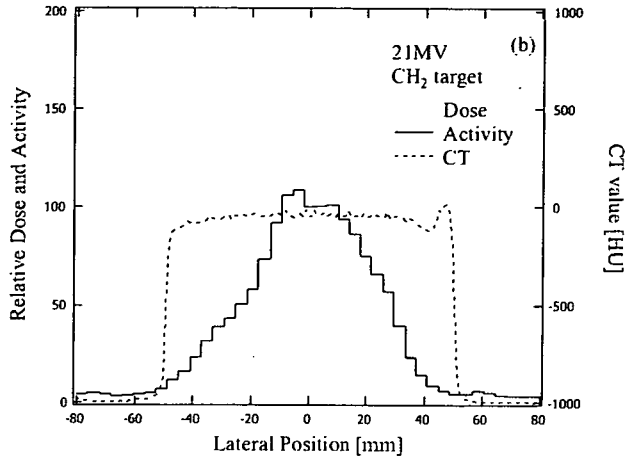


Fig. 5. Comparisons between activity and dose distributions for the CH_2 target with an annihilation gamma counting time of 30 min. **a** Depth direction on the beam axis. Both activity and dose were normalized to 100 at a depth of 100 mm. CT image profile is shown. **b** Lateral direction at a depth of 100 mm. Both activity and dose were normalized to 100 at the beam center

$$
\begin{aligned}
&N_{act}(\vec{r},T_i,T_0,T_m,E_e,A_t,Z_t,n)\\
&=\left[\int_{E_{th}}^{E_e}\left\{\frac{d}{dE_x}F(\vec{r},E_X)\right\}\right.\\
&\left.\times\sigma(E_X,A_t,Z_t)\cdot n(\vec{r},A_t,Z_t)\cdot\Delta(A_t,Z_t)dE_X\right]\\
&\times\left[\frac{T_{1/2}}{T_i\cdot\ln 2}\cdot\left(1-2^{-T_i/T_{1/2}}\right)\right]\times 2^{-T_0/T_{1/2}}\\
&\times\left(1-2^{-T_m/T_{1/2}}\right)\cdot\varepsilon^2\cdot\frac{\Omega_{PET}}{4\cdot\pi}.
\end{aligned}
\tag{3}
$$

Here, F is the flux of the photon at each point $\vec{r}$. T_i denotes the time of the X-ray irradiation; T_0, the time between the completion of the X-ray irradiation and the start of PET measurement; T_m, the time of PET measurement; $T_{1/2}$, the half-life time of the positron emitter nuclei generated by the X-ray irradiation; ε, the detection efficiency at 511-keV single gamma ray; and Ω_{PET}, the total solid angle of the PET apparatus. E_{th} is the threshold energy for the photonuclear reaction; E_e, the energy of the incident electron beam for the bremsstrahlung; n, the number of target nuclei per volume; and Δ, the thickness of the target.

The relation between the X-ray dose and the activity distributions is expressed by Eq. (3).

$$
\frac{N_{act}(\vec{r})}{D(\vec{r})}\propto\frac{\int_{E_{th}}^{E_e}\left\{\frac{d}{dE_X}F(\vec{r},E_X)\right\}\cdot\sigma(E_X)\cdot n(\vec{r})\cdot\Delta dE_X}{\int_{0}^{E_e}\left\{\frac{d}{dE_X}F(\vec{r},E_X)\right\}\cdot TK(\vec{r},E_X)dE_X}
\tag{4}
$$

Here, TK denotes the total X-ray energy deposited kernel. The X-ray energy deposition strongly depends on the secondary electrons by the primary photons. If the energy deposited kernel and the photonuclear reaction cross section are in proportion, the dose distribution form is similar to the activity distribution form.

Figures 4 and 5 suggest that the activity distribution is different from the dose distribution in the dose buildup and collimator edge regions. The dose distribution in the buildup regions is determined with the secondary electrons by the primary photons. However, the fluence of high-energy photons is significant for determining the activity distribution. For the depth activity and dose distributions, the fluence is maximum in the dose buildup region.[18] In addition, compared to the lateral dose distribution, the lateral activity distribution is anomalous in the collimator edge region; notably, it is significantly decreased at a larger off-axis distance for the CH_2 target. One possible interpretation of this is a reduction of mean X-ray energy due to collimator scattering in the collimator edge regions as well as the use of 21-MV beams with a higher energy threshold of 18.7 MeV for the photonuclear reaction of the ^{12}C nucleus.

Decay curve of activity for H_2O and CH_2 targets

Figure 6 shows decay curves of the total annihilation gamma counts detected by PET-CT as a function of time for H_2O and CH_2 targets at two X-ray energies: 21 MV and 14 MV. At 21 MV, curve-fitting functions for H_2O and CH_2 targets are given as follows.