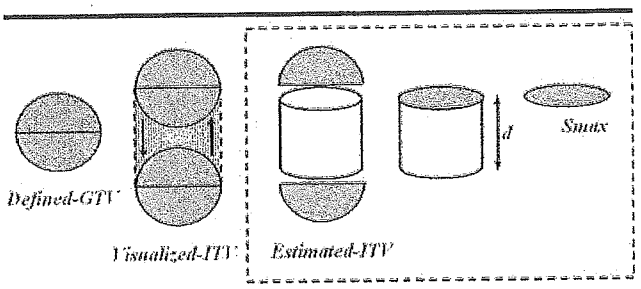

Figure 3. Diagram of defined gross tumor volume *(GTV)*, visualized internal target volume *(ITV)*, and estimated internal target volume. The maximum area of the tumor delineated on cross-sectional thin-section CT images *(Smax)* and the fluoroscopically measured breathing-induced tumor displacement in the craniocaudal direction *(d)* were used to calculate the tumor trajectory (ie, estimated internal target volume).

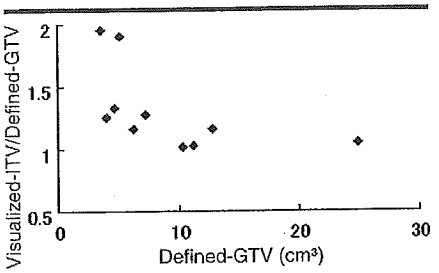

Figure 4. Graph of relation between the visualized internal target volume *(ITV)*/defined gross tumor volume *(GTV)* ratio and the defined gross tumor volume shows that smaller tumors have a larger ratio. This result implies that the treatment planning target volume must be determined more carefully prior to treatment of small tumors with stereotactic radiation therapy.

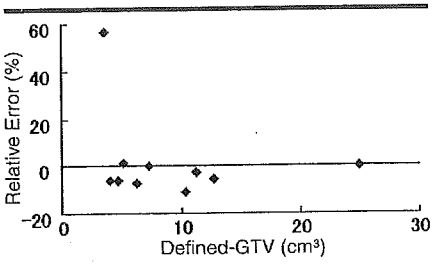

Figure 5. Scatterplot shows relation between defined gross tumor volume *(GTV)* and relative error in the study sample. For one tumor, there was a relative error of approximately 60%. For all the others, the relative error approached 0% (horizontal line) or was negative.

Target Volume Definition and Analysis

Images obtained with the two procedures just described were displayed on a planning workstation monitor with the window width set at 1500 HU and the window level at −600 HU. On thin-section CT images, a radiation oncologist (A.T.) with 10 years of experience in radiation oncology delineated the tumor contours (Sc) in each section and defined the maximum tumor area as S_{max}. On long-scan-time CT images, the tumor trajectory (Sl) was outlined on each section that included the tumor, which appeared as a solid mass with partial-volume-averaging effect due to motion. If the image showed an area with attenuation slightly higher than that of adjacent lung tissue, we included that area in the target volume. We did not consider the thin-section CT images while outlining the tumor trajectory on the long-scan-time CT images. The defined gross tumor volume and visualized internal target volume were calculated on the basis of thin-section CT images and long-scan-time CT images, respectively, by using the following equations:

$$GTV_{def} = \sum Sc \cdot h, \quad (A)$$

and

$$ITV_{vis} = \sum Sl \cdot h, \quad (B)$$

where GTV_{def} is the defined gross tumor volume, ITV_{vis} is the visualized internal target volume, and h denotes the section thickness (2 mm) for thin-section CT and long-scan-time CT. Then the estimated internal target volume (ITV_{est}) was calculated on the basis of S_{max}, GTV_{def}, and d (the fluoroscopically measured craniocaudal distance of breathing-related tumor movement), with $ITV_{est} = GTV_{def} + (S_{max} \cdot d)$ (Fig 3).

To examine the relation between the visualized internal target volume and the estimated internal target volume, we compared the two by calculating the relative error (RE) as a percentage, with $RE = (ITV_{vis} - ITV_{est})/ITV_{est} \cdot 100$ (4).

We analyzed the relation between the defined gross tumor volume and the ratio of the visualized internal target volume to the defined gross tumor volume, as well as the relation between the defined gross tumor volume and the relative error.

In all patients, the imaging features of the lesions on long-scan-time CT images and thin-section CT images were analyzed by the same radiation oncologist (A.T.).

Statistical Analysis

The Mann-Whitney test was used to analyze the relation between the defined gross tumor volume and the ratio of the visualized internal target volume to the defined gross tumor volume. Spreadsheet software (Excel 2002; Microsoft, Bellingham, Wash) and a commercial software program for statistical analysis (Statcel, version 1.1, 2002; OMS Publishing, Tokyo, Japan) were used.

RESULTS

The measured and estimated values of the internal target volume in patients are shown in the Table. The mean ± standard deviation for the distance of respiratory-related tumor movement was 4.4 mm ± 3.9 (range, 1–15 mm); for maximum tumor area, 5.2 cm^2± 2.7 (range, 2.9–11.7 cm^2); for defined gross tumor volume, 9.0 cm^3± 6.4 (range, 3.6–24.9 cm^3); for estimated internal target volume, 10.9 cm^3± 6.4 (range, 4.5–26.1 cm^3); and for visualized internal target volume, 10.8 cm^3± 6.1 (range, 5.1–26.1 cm^3). The coefficient for correlation between the estimated internal target volume and visualized internal target volume was $r = 0.98$ ($P < .001$).

The relation between the defined gross tumor volume and the ratio of the visualized internal target volume to the defined gross tumor volume is shown in Figure 4. For patients with small tumors with a defined gross tumor volume of 10 cm^3 or less, the ratio of the visualized internal target volume to the defined gross tumor volume was significantly greater (1.2–2.0) than that for patients with larger tumors (1.0–1.2) ($P < .05$).

The relation between defined gross tumor volume and relative error is shown in Figure 5. The relative error ranged from −11.0% to 56.4%, and the mean was 1.9% ± 19. Typical examples of tumor delineation on thin-section and long-scan-time CT images are shown in Figure 6, *A* and *B*, respectively.

Comparison between Estimated and Visualized Internal Target Volumes

Patient No.	Tumor Motion* (mm)	Maximum Tumor Area† (cm^2)	Defined Gross Tumor Volume (cm^3)	Estimated Internal Target Volume	Visualized Internal Target Volume	Relative Error (%)	ITV_{vis}/GTV_{def} Ratio‡
1	4	4.07	6.25	7.88	7.31	−7.23	1.25
2	15	3.02	5.15	9.68	9.82	1.44	1.33
3	4	5.06	7.26	9.29	9.30	0.10	1.94
4	4	7.49	12.73	15.73	14.79	−5.73	1.16
5	3	2.94	3.59	4.48	7.14	56.47	1.28
6	4	3.38	4.03	5.38	5.07	−5.76	1.90
7	3	4.88	10.34	11.80	10.53	−11.01	1.01
8	5	3.97	4.69	6.68	6.26	−6.28	1.02
9	1	5.82	11.24	11.82	11.51	−2.54	1.16
10	1	11.71	24.89	26.06	26.05	0.00	1.04
Mean for all patients	4.4	5.23	9.02	10.88	10.76	1.95	1.31

* Breathing-induced tumor displacement in the craniocaudal direction was measured with fluoroscopy.
† Tumor area was measured on thin-section CT images.
‡ Ratio of the visualized internal target volume to the defined gross tumor volume.

The relative error for patient 5 was 56.4%. On thin-section CT images in this patient, the shape of the tumor was irregular and complex (Fig 7, *A–D*). Figure 7, *E*, shows the tumor delineation on a long-scan-time CT image. In this case, the appearance of the tumor in corresponding and adjacent tumor sections on thin-section CT images (Fig 7, *F–H*) differed markedly from that on long-scan-time CT images. If patient 5 is excluded, the mean relative error is −4.1% ± 4.1.

For patient 7, a large negative relative error of −11.0% was found. The thin-section CT images showed fine spiculation, consolidation, and emphysematous changes surrounding the nodule. On the long-scan-time CT images, however, the tumor margin was depicted with attenuation lower than that on thin-section CT images, was blurred, and was indistinguishable from the surrounding emphysematous changes; consequently, this marginal area was erroneously excluded from the target volume (Fig 8).

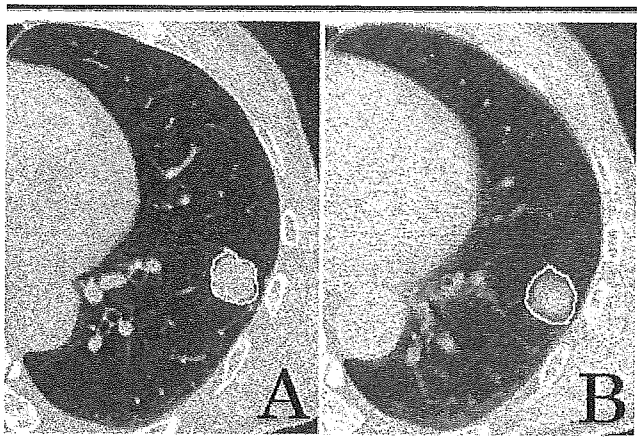

Figure 6. *A*, Transverse breath-hold thin-section CT image shows tumor contour (outline), tumor margin, and bronchovascular bundle. *B*, Transverse long-scan-time CT image shows delineation of tumor movement trajectory (outline) that includes ill-defined tumor margin.

DISCUSSION

With the aim of more precise administration of irradiation, the authors of a report published by the International Commission on Radiation Units and Measurements (9) proposed a new definition of the margin around the target volume to include an internal margin and a so-called setup margin. This explicit definition of tumor margins is particularly important for stereotactic radiation therapy, three-dimensional conformal radiation therapy, and intensity-modulated radiation therapy.

There is no proved rational basis, however, for adding this internal margin to the gross tumor volume, when treatment planning is based on measurements of gross tumor volume with breath-hold thin-section CT. While using this conventional planning method, we observed tumor motion only in the craniocaudal direction with fluoroscopy, and we added the area of this tumor movement to the gross tumor volume, as the internal margin; tumor movement in the anteroposterior and left-to-right directions, however, was not taken into account. The planning target volume that was defined on the basis of the resultant fixed expansion of the gross tumor volume usually was larger than the actual trajectory of tumor motion. When this fluoroscopy-based definition of the planning target volume is used, the defined volume might be too large if tumor movement in the craniocaudal direction is substantial.

Balter and colleagues (10) reported that tumor motion associated with breathing is not negligible and that free-breathing CT studies may erroneously indicate the position and volume of the critical structure and, thus, may lead to faulty planning on the basis of volume-dependent criteria. Since free-breathing CT scans are typically acquired at the rate of one or two sections per second, the individual images might reflect only a limited part of the tumor motion in the respiratory cycle. In comparison, long-scan-time CT was performed at the rate of 8 seconds per section acquired. The duration of scanning was programmed to be sufficiently long (ie, longer than that of the respiratory cycle), and the trajectory of

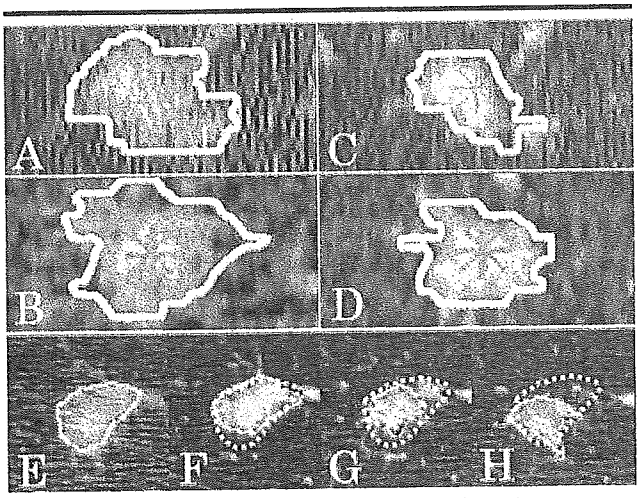

Figure 7. Patient 5. Pulmonary metastasis of adenoid cystic carcinoma. Coronal *(A, C)* and sagittal *(B, D)* images from long-scan-time CT *(A, B)* and thin-section CT *(C, D)* show tumor with extremely irregular contours. (*C* and *D* are approximately in the same plane and at the same level as *A* and *B*, respectively.) Transverse image obtained with long-scan-time CT *(E)* shows contour (outline) of visualized internal target volume. Transverse images obtained with thin-section CT (*F*, at a level 2 mm above that in *E*; *G*, at the same level as *E*; and *H*, at a level 2 mm below *E*) show the target volume with contour lines from *E* (dotted outlines) superimposed for comparison.

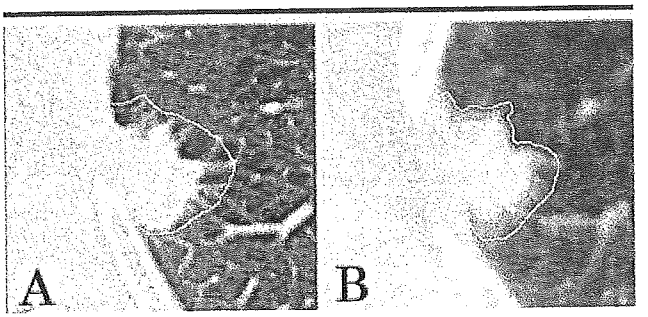

Figure 8. *A*, Transverse thin-section CT image shows tumor with surrounding spiculation that indicates traction-related emphysematous change. *B*, Transverse long-scan-time CT image shows ill-defined margin of tumor with lower attenuation than that on thin-section CT images, a factor that could lead to accidental omission of part of the tumor margin from the target volume. In delineation of tumor margin on long-scan-time CT images, careful reference to tumor features on thin-section CT images is required.

tumor movement during CT was reflected as greater or lesser attenuation because of the partial-volume-averaging effect, depending on the period for which the tumor was in the scanning range during each long-scan-time CT scan. Therefore, we hypothesized that our long-scan-time CT scans reflected the entire trajectory of tumor motion over the course of the respiratory cycle.

To validate this hypothesis, an equation (1) was used to obtain the estimated internal target volume, which was then compared with the visualized internal target volume. Although tumor motion due to breathing is generally greatest in the craniocaudal direction, motion in the left-to-right and anteroposterior directions is also observed (11). To simplify the model, however, we did not factor tumor motion in either the left-to-right or the anteroposterior direction into the equation for estimated internal target volume.

The results of our analysis showed a significantly larger ratio of the visualized internal target volume to the defined gross tumor volume for small tumors than for large tumors. These results indicate that special care must be used in taking internal motion into account when planning treatment of small tumors.

The values for the relative error were within a limited range, except in one case. For tumors that are ovoid and that have an axis of movement that coincides with the craniocaudal direction, our simple model could be applied. Conversely, when the tumor shape was very irregular or when the tumor moved in a different (not craniocaudal) direction, this simple model could not be applied. The shape of the tumor in patient 5, for which a large relative error was found, was so irregular that the simple model of estimated internal target volume could not be applied. The tumor area delineated on long-scan-time CT images was greater than that on corresponding and adjacent thin-section CT images. We surmised that the cause of the unusually large relative error was not the large value of the visualized internal target volume but rather the small value of the estimated internal target volume. We concluded, therefore, that the visualized internal target volume represented a reasonably accurate internal target volume. When we excluded patient 5 from our calculations of relative error, the mean relative error was $-4.1\% \pm 4.1$. The negative value of this result means that the visualized internal target volume was slightly smaller than the estimated internal target volume.

In the case of patient 7, for whom the relative error was an even higher negative value, we failed to delineate an adequate internal target volume on the basis of long-scan-time CT, in that we were not always able to include the fine margin of spiculation that appeared around the nodule on thin-section CT images. We consider this failure to have been caused by the visual merging and resultant obscuration of fine spiculation, consolidation, and emphysematous changes on long-scan-time CT images, whereas these areas were clearly visible on thin-section CT images. The shortcomings of long-scan-time CT therefore must be taken into account, and an area that is wider than the lesion on long-scan-time CT images must be delineated, with reference to thin-section CT images if necessary.

Lagerwaard et al (12) and van Sörnsen de Koste et al (13), on the basis of two helical CT scans and three "slow" CT scans, reported that planning target volumes derived by using slow CT consistently produced superior target coverage than did those from thin-section CT. On the other hand, attempts have been made at some institutions to avoid the influence of respiratory motion during radiation therapy by using active breathing control (14), breath holding (15), and real-time tumor tracking during radiation therapy (16). In some cases, these methods probably are effective for reducing the volume to be irradiated. Although our long-scan-time CT–based planning method might result in a larger target volume than that defined with use of breath control or synchronized irradiation methods, it is simple and can be implemented with a widely available CT scanner and workstation for the planning of radiation therapy.

In this study, one radiation oncologist analyzed the fluoroscopic images and delineated the contours of visualized internal target volumes and of defined gross

tumor volumes. The results of similar analyses performed by multiple clinicians might be inconsistent with our study results because of observer variation.

In addition, many factors, such as the tumor size, shape, and location (upper lobe vs lower lobe) and the pulmonary function, might influence the results of long-scan-time CT. The number of patients (10 patients) used for our analysis was not sufficient to investigate these parameters, and further investigation in a larger patient population is needed to resolve these questions.

In conclusion, the visualized internal target volume and estimated internal target volume were similar in most cases. Long-scan-time CT was capable of depicting virtually the entire trajectory of tumor movement during normal respiration. There were, however, some exceptional cases in which long-scan-time CT images did not accurately depict the internal target volume; therefore, when the tumor margin is delineated on long-scan-time CT images for planning of radiation therapy, thin-section CT images also should be carefully observed for reference.

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DIFFERENCES IN PULMONARY FUNCTION BEFORE VS. 1 YEAR AFTER HYPOFRACTIONATED STEREOTACTIC RADIOTHERAPY FOR SMALL PERIPHERAL LUNG TUMORS

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Purpose: To evaluate long-term pulmonary toxicity of stereotactic radiotherapy (SRT) by pulmonary function tests (PFTs) performed before and after SRT for small peripheral lung tumors.

Methods and Materials: A total of 17 lesions in 15 patients with small peripheral lung tumors, who underwent SRT between February 2000 and April 2003, were included in this study. Twelve patients had primary lung cancer, and 3 patients had metastatic lung cancer. Primary lung cancer was T1–2N0M0 in all cases. Smoking history was assessed by the Brinkman index (number of cigarettes smoked per day multiplied by number of years of smoking). Prescribed radiation doses at the 80% isodose line were 40–60 Gy in 5–8 fractions. PFTs were performed immediately before SRT and 1 year after SRT. Test parameters included total lung capacity (TLC), vital capacity (VC), forced expiratory volume in 1 s (FEV1.0), and diffusing capacity of lung for carbon monoxide (DLCO). PFT changes were evaluated in relation to patient- and treatment-related factors, including age, the Brinkman index, internal target volume, the percentages of lung volume irradiated with >15, 20, 25, and 30 Gy (*V15*, *V20*, *V25*, and *V30*, respectively), and mean lung dose.

Results: There were no significant changes in TLC, VC, or FEV1.0 before vs. after SRT. The mean percent change from baseline in DLCO was significantly increased by 128.2%. Univariate and multivariate analyses revealed a correlation between DLCO and the Brinkman index.

Conclusions: One year after SRT as compared with before SRT, there were no declines in TLC, VC, and FEV1.0. DLCO improved in patients who had been heavy smokers before SRT, suggesting a correlation between DLCO and smoking cessation. SRT seems to be tolerable in view of long-term lung function. © 2005 Elsevier Inc.

Stereotactic radiotherapy, Lung tumors, Pulmonary function.

INTRODUCTION

Stereotactic radiotherapy (SRT) has been shown to be highly effective for treating small and well-circumscribed brain metastases, regardless of the primary site or histology (1, 2). This suggests that small, well-circumscribed extracranial malignancies may be controlled with similar focal, high-dose radiation therapy (3). Uematsu *et al.* have performed CT-guided, small-volume hypofractionated radiotherapy, giving 50–60 Gy in 5–10 fractions, with excellent results (3, 4). They reported a 3-year overall survival rate of 66% for all 50 patients with Stage I non–small-cell lung carcinoma, and of 86% for 29 medically operable patients, suggesting the effectiveness of image-guided, small-volume radiotherapy for lung tumors (4).

We previously reported the serial radiologic changes of the pulmonary opacities after hypofractionated SRT on CT scans (5). Out of 22 lesions, ground-glass opacities were observed in 4 (18%) cases, and dense consolidation developed in 16 (73%).

However, there have been few published reports assessing impaired pulmonary function qualitatively by comparing values obtained before and after hypofractionated SRT (6). In this study, we determined changes in pulmonary function associated with hypofractionated SRT for small peripheral lung tumors to assess the safety of hypofractionated SRT in terms of long-term pulmonary function.

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PATIENTS AND METHODS

Patient and tumor characteristics

Between February 2000 and April 2003, we performed SRT for a total of 17 lesions in 15 patients (14 men and 1 woman) with small-volume lung tumors, whose ages ranged from 57 to 89 years with a median age of 77 years, at the Tokyo Metropolitan Hiro-o General Hospital (Table 1). Twelve patients had primary lung cancer, and other patients had metastatic lung cancers. All 12 patients with primary lung cancer had histologically diagnosed non–small-cell lung carcinoma (adenocarcinoma, $n = 9$; squamous cell carcinoma, $n = 2$; undifferentiated carcinoma, $n = 1$) and were clinically staged as T1–2N0M0. Among the 5 lesions in the 3 patients with metastatic lung cancer, 2 were adenocarcinomas (originating from colonic cancer in 2 patients), and 3 were squamous cell carcinomas (originating from oropharyngeal cancer in 1 patient). For most patients, surgery was not indicated, because of patient age, multiple lesions, or poor pulmonary function. Two patients refused surgery despite having operable tumors. Five patients had chronic obstructive pulmonary disease. One patient had undergone pulmonary lobectomy.

Smoking history was expressed using the Brinkman index, as calculated by multiplying the number of cigarettes per day by the years of smoking, and ranged from 0 to 2640 (median, 875). None of the smokers resumed smoking after SRT. SRT was generally considered if the tumor was 4 cm or smaller in diameter, if craniocaudal breathing-associated motion of the lesion was 1 cm or less, if 3 or fewer lesions were present at the start of treatment, and if all lesions except pulmonary lesions were controlled. SRT and lung function examinations were approved by the institutional review board at each institution. Written informed consent was obtained from each patient before SRT.

Treatment

The planned target volume was determined using CT (Xvision, Toshiba) performed on patients who were breathing at rest. Serial 2-mm-thick scans were obtained in 2-mm increments at 8 s per slice (120 kVp, 200 mAs). Longer scanning periods were used to define the tumor trajectory associated with respiratory and other movements; i.e., the internal target volume (ITV) can be visualized (6). Planning target volume (PTV) was determined from the ITV, with setup margins of 8 mm in all directions.

Table 1. Patients, tumors, and treatment characteristics

Characteristics		Median
Age (year)	57–89	77
Gender		
Male	14	
Female	1	
Tumor		
Primary	12	
Metastatic	5	
Pathology		
Adenocarcinoma	11	
Squamous cell carcinoma	5	
Undifferentiated carcinoma	1	
Internal target volume (cm^3)	3–31	11
Planning target volume (cm^3)	20–86	38.2
Prescribed dose (Gy)	40–60	50
V15 (%)	4.0–18.0	8
V20 (%)	2.0–12.0	7
V25 (%)	2.0–10.0	5
V30 (%)	1.0–8.0	5
Mean lung dose (Gy)	2.25–8.95	4.12

Abbreviation: Vx = the percentage of lung volume irradiated with $>x$ Gy.

Target volumes were calculated according to the following formulas:

$$ITV = 4/3\pi \times R1 \times R2 \times R3 \quad (1)$$

$$PTV = 4/3\pi \times (R1 + 8\text{ mm}) \times (R2 + 8\text{mm}) \times (R3 + 8\text{ mm}) \quad (2)$$

where *R1* (half the maximum diameter), *R2* (half the diameter perpendicular to *R1*), and *R3* (half the maximum diameter in the craniocaudal direction) were obtained with calipers on CT. The diameter in the craniocaudal direction was defined as the product of the thickness and the number of slices from the top to the bottom of the lesion (6).

A radiation treatment planning system (FOCUS version 2.7.0., Computerized Medical Systems, Inc.; St. Louis, MO) was used. We set the treated volume so as to include the PTV within an 80% isodose of the maximum dose, and the 80% isodose was defined as the therapeutic dose. The multileaf collimator moved dynamically according to the tumor shape to irradiate the tumor from 8 different arcs.

In general, radiation doses of 50 Gy were delivered in 5 fractions over 5 to 7 days. Two patients also received conventional radiation therapy (30–40 Gy given in 15–20 fractions over 2–4 weeks) before SRT. No patients received chemotherapy or surgery within 1 year after SRT. The dose–volume histograms (DVHs) were analyzed: *V15*, *V20*, *V25*, and *V30* (the percentages of lung volume irradiated with >15, 20, 25, and 30 Gy, respectively), and mean lung dose (MLD) was obtained for each patient.

Pulmonary function tests

Typical pulmonary function tests (PFTs) were performed before SRT and approximately 1 year after SRT. Test parameters included total lung capacity (TLC), vital capacity (VC), forced expiratory volume in 1 s (FEV1.0), and diffusing capacity of lung for carbon monoxide (DLCO). The results obtained 1 year after SRT were compared with those before SRT.

Pulmonary symptoms

Patients were interviewed monthly for pulmonary symptoms, including dyspnea on exertion and shortness of breath, and the need for steroids and oxygen treatment. Simultaneously, transdermal oxygen saturation was measured. Toxicity was recorded based on the National Cancer Institute Common Toxicity Criteria, version 2.0 (7).

Statistical analysis

We analyzed factors correlating with PFT changes before vs. after SRT.

The Wilcoxon test was used to compare pulmonary function values obtained before and after SRT. Univariate analyses were performed to assess patient- and treatment- related factors, including age, smoking history (Brinkman index), ITV volume, *V15*, *V20*, *V25*, *V30*, and MLD. Multivariate analyses of the same factors were performed using the logistic regression test. Analyses were carried out using SPSS 12 (SPSS Inc., Chicago, IL). Statistical analysis was regarded as statistically significant at p value less than 0.05.

RESULTS

Lung dose and tumor response

The ITV volume, the PTV volume, *V15*, *V20*, *V25*, *V30*, and MLD are listed in Table 1.

Local control was achieved in 16 lesions (94.1%), whereas 1 lesion recurred. The patient with the recurrent lesion had no decline in pulmonary function. Lesions metastasized to other lung sites in 2 of the 15 patients (13.3%), but pulmonary function did not decrease in either patient. All are still alive, to date.

Pulmonary function tests

The results of PFTs before and after SRT are listed in Table 2. The median TLC after SRT was 96.0% of the baseline ($p = 0.08$) (Fig. 1). The median VC after SRT was 97.3% of the baseline ($p = 0.29$) (Fig. 2). The median FEV1.0 after SRT was 99.7% of the baseline ($p = 0.39$) (Fig. 3). The median percent change in DLCO from baseline was 128.2% after SRT; i.e., median DLCO increased significantly from 13.65 mL/min/mmHg before SRT to 17.85 mL/min/mmHg after SRT ($p = 0.039$) (Fig. 4).

Clinical symptoms

Thirteen patients had no respiratory symptoms of more than Grade 2. No narcotic antitussives or steroids were used. One patient experienced a temporary worsening of clinical symptoms, i.e., dyspnea and cough requiring antitussives on exertion. In 1 of the 2 patients treated with external irradiation followed by SRT, pneumonitis in the irradiation field corresponded to clinical manifestations, and steroids were prescribed. Oxygen saturation was 96%–99% before and after SRT in all patients, thus ruling out a decrease in oxygen saturation associated with SRT.

Statistical analysis

We performed univariate analyses for treatment-related factors to assess the mean percentage changes from baseline in PFT parameters. No factors were significantly related to mean changes in TLC, VC, and FEV1.0. On the contrary, there was a statistically significant positive correlation between mean percent changes in DLCO and the Brinkman index ($p = 0.013$, $r = 0.644$; Fig. 5). No other factors were significantly related to DLCO. According to multivariate analysis of the same factors using logistic regression analysis, only Brinkman index was significant ($p = 0.045$).

Changes in DLCO before vs. after SRT were analyzed in 2 clusters: 1 in which the Brinkman index was equal to or less than 400 and the other in which the index exceeded 400 (Fig. 6). Although changes in DLCO were not significant in the group with a Brinkman index ≤400, an elevation of DLCO was noted in the group with a Brinkman index >400.

DISCUSSION

Comparison with surgery

There are a large number of reports comparing pulmonary functions before and after surgery for peripheral lung cancer. Takizawa *et al.* reported postoperative pulmonary function in 40 patients undergoing segmentectomy and another 40 receiving lobectomy for peripheral lung cancer 2 cm or less in diameter. The mean percent changes in forced vital capacity and FEV1.0 from baseline 1 year after surgery were 94.9% and 93.3%, respectively, in the segmentectomy group and 91.0% ($p = 0.14$) and 87.3% ($p = 0.03$), respectively, in the lobectomy group (8).

Bolliger *et al.* compared pre- and postoperative pulmonary functions in 50 patients who underwent lobectomy and 18 who underwent pneumonectomy (9). They found that forced vital capacity, FEV1.0, and TLC decreased by 7%, 9%, and 10% in the lobectomy and by 36%, 34%, and 33% in the pneumonectomy group, respectively.

Kaseda *et al.* compared pre- and postoperative lung function and 5-year survival in 44 patients undergoing video-assisted thoracic surgery lobectomy (VATS) and 77 undergoing open thoracotomy. Percent changes from baseline (before operation) in postoperative VC and FEV1.0 were 84.9% and 84.8% in the VATS group and 66.8% and 71.2% in the open thoracotomy group ($p < 0.0001$ for both),

Table 2. Results of pulmonary function tests before and after stereotactic radiotherapy

	Before SRT		After SRT		
	Range	Median	Range	Median	p value
TLC (mL)	3,990–7,180	5,520	3,630–7,420	5,295	0.08
VC (mL)	2,360–4,990	2,870	2,220–5,080	2,740	0.29
FEV1.0 (mL)	850–3,800	1,990	860–3,600	1,800	0.39
DLCO (mL/min/mmHg)	7.4–29.4	13.65	9.69–28.9	17.85	0.039

Abbreviations: DLCO = diffusion capacity of the lung for carbon monoxide; FEV1.0 = forced expiratory volume in one second; SRT = stereotactic radiotherapy; TLC = total lung capacity; VC = vital capacity.

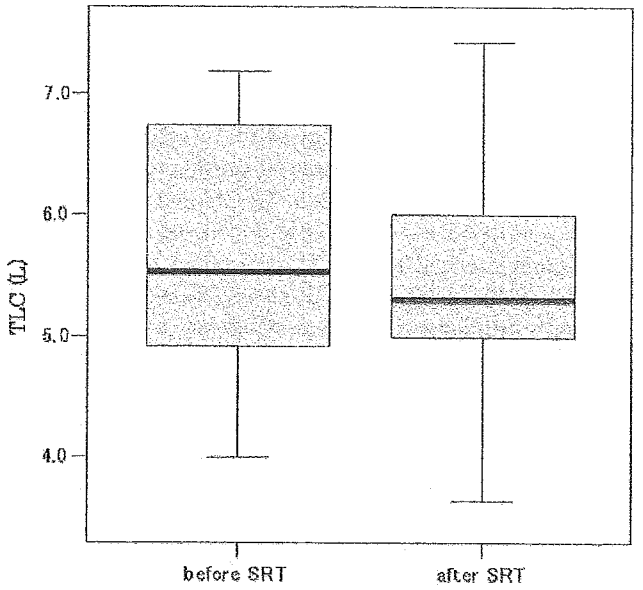

Fig. 1. Change in total lung capacity (TLC). There was no statistically significant difference in TLC before stereotactic radiotherapy (SRT) vs. 1 year after SRT ($p = 0.08$). The lowest and highest 10% of the data are shown as points beyond the error bars. The box includes the central 50% of the data (25–75%). The solid line within each box is the median of the data.

respectively. The 5-year survival rate was significantly higher in the VATS group (97.0%) than in the open thoracotomy group (78.5%) ($p = 0.0173$) (10).

Because surgery for lung carcinoma is associated with removal of both air passages and parenchymal lung tissue, FEV1.0 can diminish, as evidenced by lung perfusion scans and predicted by the following formula: *postoperative FEV1.0 = preoperative FEV1.0 × percent perfusion of remaining lung* (11). When patients are predicted to have FEV1.0 of 800–1000 mL after surgery, they are not generally considered to be appropriate candidates for surgery (12). In this study, even a pre-SRT FEV1.0 of less than 1000 mL was not associated with a post-SRT decline in FEV1.0, indicating that SRT is feasible even for inoperable patients, because of their decreased pulmonary function.

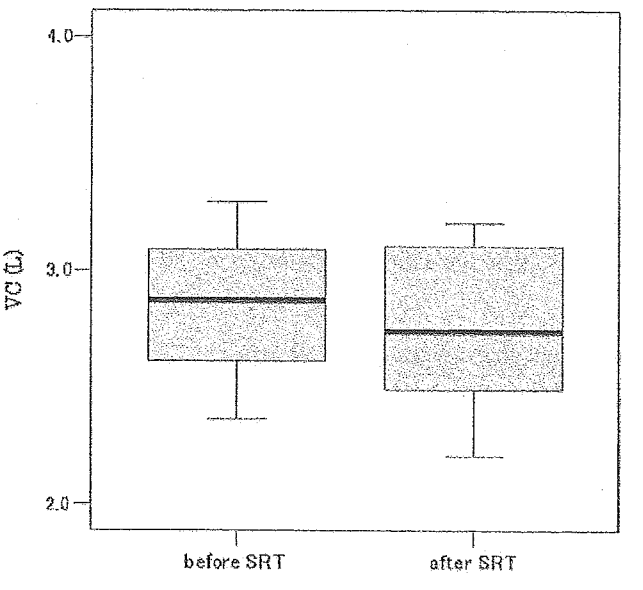

Fig. 2. Change in vital capacity (VC). There was no statistically significant difference in VC before stereotactic radiotherapy (SRT) vs. 1 year after SRT ($p = 0.29$).

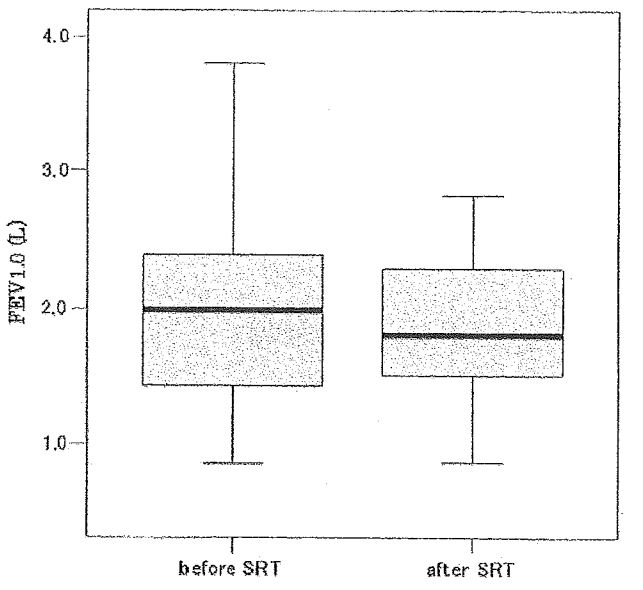

Fig. 3. Change in forced expiratory volume in 1 s (FEV1.0). There was no statistically significant difference in FEV1.0 before stereotactic radiotherapy (SRT) vs. 1 year after SRT ($p = 0.39$).

Comparison with conventional radiotherapy

Some authors have reported the results of pulmonary function tests after conventional radiotherapy for lung can-

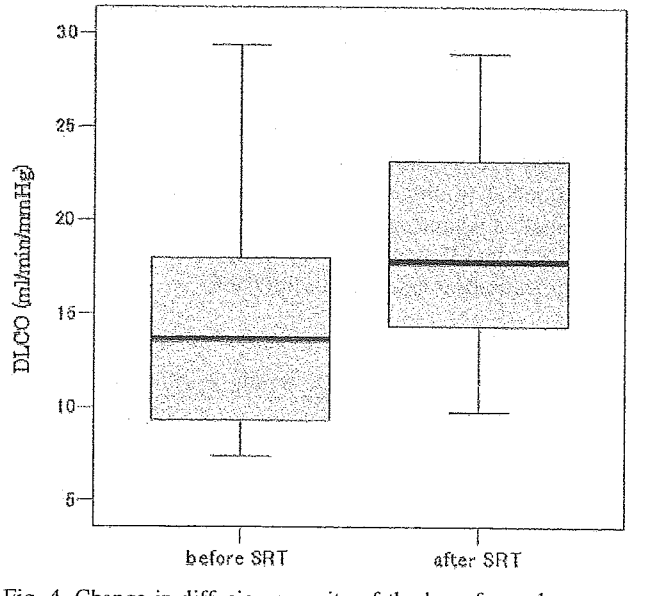

Fig. 4. Change in diffusion capacity of the lung for carbon monoxide (DLCO). There was a statistically significant difference in DLCO before stereotactic radiotherapy (SRT) vs. 1 year after SRT ($p = 0.039$).

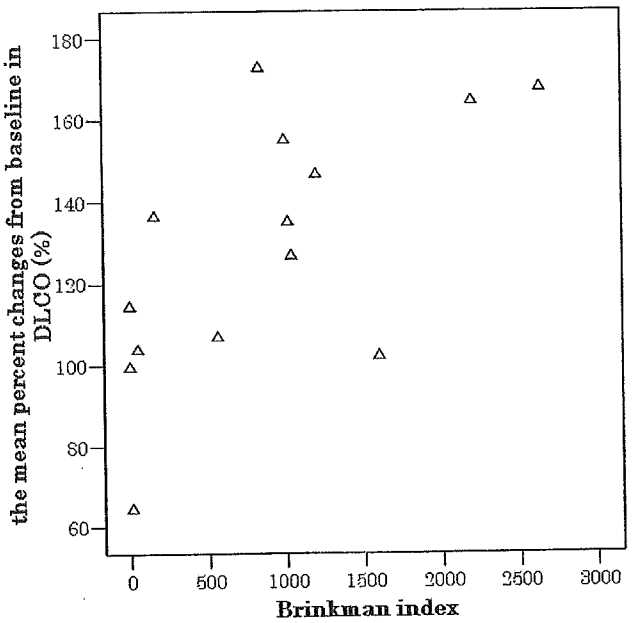

Fig. 5. Scatter plot of the Brinkman index (calculated by multiplying cigarettes per day and years of smoking) vs. the mean percent changes from baseline in diffusion capacity of the lung for carbon monoxide (DLCO).

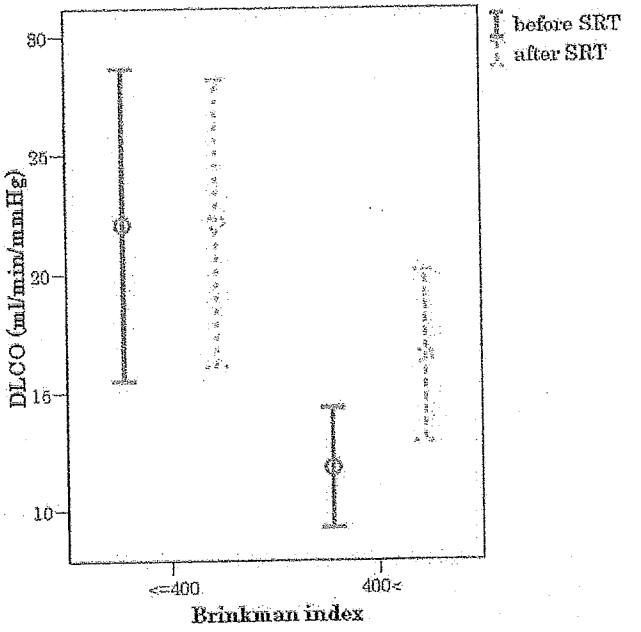

Fig. 6. Comparison of diffusion capacity of the lung for carbon monoxide (DLCO) before vs. after stereotactic radiotherapy (SRT) between the group with a Brinkman index ≤400 and the group with a Brinkman index >400.

cer (13, 14). Sunyach *et al.* reported that three-dimensional conformal radiotherapy for non–small-cell lung carcinoma (Stage I in 8 patients, Stage II in 13 patients, Stage IIIA in 17 patients, and Stage IIIB in 16 patients) significantly decreased TLC by 6.5% as compared with the predicted value, but there was no significant change in DLCO or FEV1.0 (14). In another study, Abratt and Wilcox reported that a conventional anteroposterior parallel-opposed field significantly decreased DLCO, by 14%, and that TLC had decreased by 7% at 6 months (15).

To our knowledge, there are no reports concerning changes in pulmonary function associated with conventional radiotherapy in patients with early lung cancer. Onimaru *et al.* reported changes in pulmonary function immediately after image-guided radiotherapy (IGRT) for non–small-cell lung carcinoma. They performed IGRT in 46 patients with lung cancers 0.6–6 cm in diameter and measured VC before and after IGRT in 9 patients and FEV1.0 and DLCO in 8 of the 9. These authors found no significant changes in VC, FEV1.0, or DLCO (5). Our study showed percent changes from baseline to be 96.8% for VC and 99.3% for FEV1.0; i.e., symptoms did not worsen after SRT. Our findings are more favorable than those obtained with surgical procedures, including lobectomy, segmentectomy, and VATS. Furthermore, our results are also better than those obtained with conventional radiotherapy.

Although the results for both VC and FEV1.0 in our study were equivalent to those in the study of Onimaru *et al.* (5), DLCO improved after SRT in our patients, with the percent change from pretreatment DLCO being 128%. There was a significant correlation between the improvement in DLCO and the Brinkman index; i.e., although no changes in DLCO were observed in the group with a Brinkman index ≤400, DLCO markedly improved in the pre-SRT heavy smokers (Brinkman index >400). Sansores *et al.* reported a significant increase in DLCO 1 week after smoking cessation, but no further increase was noted 1 or 3 months later (16). Because complete post-SRT smoking cessation was documented in our facilities, we speculate that smoking cessation may be more beneficial in terms of improving DLCO than SRT.

Graham *et al.* analyzed 99 cases of non–small-cell lung cancer and found *V20* to correlate well with the incidence of symptomatic pneumonitis. Furthermore, values of *V20* less than 25%, 25%–37%, and more than 37% were associated with estimated radiation pneumonitis incidences of 0–4%, 2–12%, and 19–30%, respectively (17). Tsujino *et al.* suggested that the *V20* can serve as a predictor of radiation pneumonitis after concurrent chemoradiation for lung cancer (18). In the present study, none of our patients who had *V20* of less than 25% developed symptomatic radiation pneumonitis. However, further study is required to determine whether the results of Graham *et al.* are applicable, because there are differences in single radiation doses, the number of irradiations, and the duration of the entire treatment between conventional radiation therapy and SRT (17).

CONCLUSIONS

Lung function testing, performed before and after SRT for small peripheral lung tumors, showed decreases in VC

and FEV1.0 to be less than those after surgical procedures, including lobectomy, segmentectomy, and VATS. However, the DLCO improvement in this study requires further investigation. In terms of long-term pulmonary function, SRT seems to be feasible and applicable to patients with poor lung functions.

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Standard Thoracic Radiotherapy With or Without Concurrent Daily Low-dose Carboplatin in Elderly Patients with Locally Advanced Non-small Cell Lung Cancer: a Phase III Trial of the Japan Clinical Oncology Group (JCOG9812)

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Background: The purpose of this study was to evaluate whether radiotherapy with carboplatin would result in longer survival than radiotherapy alone in elderly patients with unresectable stage III non-small cell lung cancer (NSCLC).
Methods: Eligible patients were 71 years of age or older with unresectable stage III NSCLC. Patients were randomly assigned to the radiotherapy alone (RT) arm, irradiation with 60 Gy; or the chemoradiotherapy (CRT) arm, the same radiotherapy and additional concurrent use of carboplatin 30 mg/m^2 per fraction up to the first 20 fractions.
Results: This study was terminated early when 46 patients were registered from November 1999 to February 2001. Four patients (one in the RT arm, three in the CRT arm) were considered to have died due to treatment-related causes. The JCOG Radiotherapy Committee assessed these treatment-related deaths (TRDs) and the compliance with radiotherapy in this trial. They found that 60% of the cases corresponded to protocol deviation and 7% were protocol violation in dose constraint to the normal lung, two of whom died due to radiation pneumonitis. As to the effectiveness for the 46 patients enrolled, the median survival time was 428 days [95% confidence interval (CI) = 212–680 days] in the RT arm versus 554 days (95% CI = 331 to not estimable) in the CRT arm.
Conclusions: Due to the early termination of this study, the effectiveness of concurrent use of carboplatin remains unclear. We re-planned and started a study with an active quality control program which was developed by the JCOG Radiotherapy Committee.

Key words: non-small cell lung cancer – elderly patients – carboplatin – chemoradiotherapy

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in the USA, Europe and Japan. In Japan, the number of elderly is increasing dramatically. In 2001, the proportion of Japanese population older than 65 years was 18%; in other words, the number of people older than 65 years exceeded 22 million (1). Lung cancer death rates for men and women aged 75 or more have increased to ~531 and 138 per 100 000 population, respectively (1). To establish the effective treatment for the elderly with lung cancer has thus become of greater importance.

Until recently, the standard treatment for locally advanced non-small cell lung cancer (NSCLC) was radiotherapy alone. However, the 5-year survival rate of patients with stage III remained under 10% (2–4). To improve the survival rates, many clinical trials comparing radiotherapy with chemoradiotherapy have been conducted (5–11). A recent meta-analysis suggested that the combination of chemotherapy containing cisplatin (CDDP) and radiation could improve the survival rate compared with radiotherapy alone (12,13). However, it is still unclear whether the combined chemoradiotherapy is also suitable for elderly patients. This is partly because the elderly had been considered inappropriate as study patients.

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Almost all evidence available has thus been derived from subset analysis of trials for locally advanced NSCLC. A secondary analysis of RTOG 94-10 revealed a greater survival benefit for concurrent chemotherapy (14). Schild et al. reported no significant difference in tumor regression between younger and older patients in an NCCTG trial (15). Meanwhile, some reports on inoperable NSCLC patients indicate that chemoradiotherapy has survival benefit compared with radiotherapy, but this may not be applicable for those >70 years of age, for whom radiation alone could be most beneficial (16,17).

Therefore, we cannot treat the elderly in the same way as we can younger patients: first, as elderly patients have poorer prognosis than younger patients, they may think that their quality of life is more important than risking radical treatment. Secondly, the elderly tend to be vulnerable to intensive care and toxicities of treatment drugs (18–21). Less toxic therapy may be more effective for the elderly with NSCLC.

Some clinical trials, in which the elderly were not included, showed some efficacy of carboplatin (CBDCA), an analog of CDDP, having no nephrotoxicity, neurotoxicity or ototoxicity and being much less emesis-provoking than CDDP (22–24). Additionally, some investigators found the same radiosensitizing properties of CBDCA (25–28) as also found for CDDP. Therefore, we hypothesized CBDCA to be more acceptable in the treatment of elderly patients. A phase II study has reported the use of radiotherapy and concurrent low-dose daily CBDCA in elderly patients with locally advanced NSCLC (29). For stage III patients, the median survival time (MST) was 15.1 months. Given an MST of ~10 months by radiation alone (5,6,8,9,11,17), this combined chemoradiotherapy seemed promising. Here we performed a randomized study to determine whether this combined chemoradiotherapy has an impact on survival in elderly patients with unresectable locally advanced NSCLC compared with radiotherapy alone.

PATIENTS AND METHODS

PATIENTS

Eligibility criteria for this study were as follows: age ≥71 years; a histologically confirmed non-small cell carcinoma; unresectable disease; stage IIIA except T3N1M0 and IIIB which does not have disease extended to any contralateral hilar nodes or any supraclavicular nodes, atelectasis of the entire lung or malignant pleural effusions; measurable disease; a required radiation field of less than one half of one lung; no previous chemotherapy or radiotherapy; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; PaO_2 ≥70 torr, white blood cell count ≥4000/μl, hemoglobin level ≥9.5 g/dl, platelet count ≥100 000/μl, serum bilirubin level ≤1.5 mg/dl, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ twice the upper limit of normal, and serum creatinine level ≤ the upper limit of normal; a life expectancy of at least 3 months; and written informed consent. Exclusion criteria included patients with active infection, interstitial pneumonia or active lung fibrosis, chronic obstructive pulmonary disease (COPD) or uncontrolled heart disease, an active synchronous cancer, or a metachronous cancer within three disease-free years.

Staging was performed by chest radiograph in two directions, computed tomography (CT) scan or magnetic resonance imaging (MRI) of the head, CT scan of the chest, CT scan or ultrasound of the abdomen, and bone scintigraphy.

TREATMENT

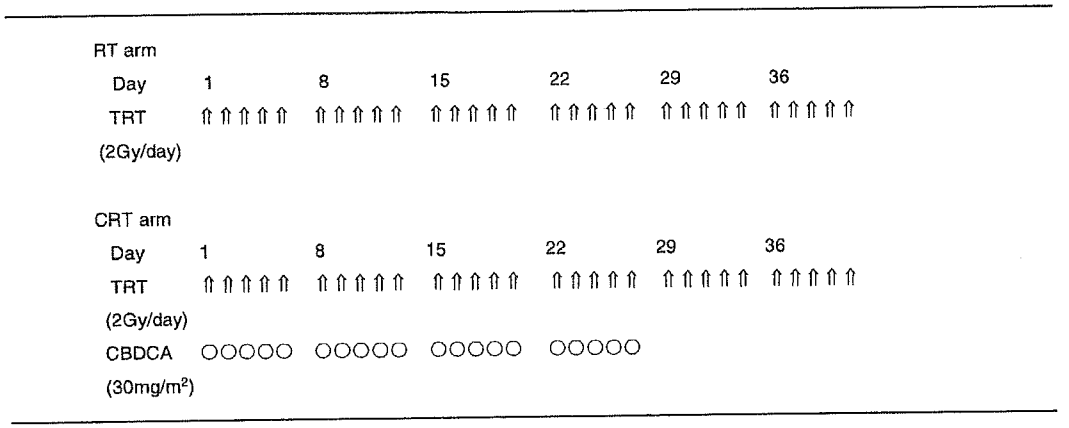
Patients were randomly assigned to the radiotherapy (RT) arm or the chemoradiotherapy (CRT) arm, by the minimization method of balancing PS (0 or 1 versus 2), stage (IIIA versus IIIB) and institution. The RT consisted of 60 Gy in 30 fractions over 6 weeks. In the CRT arm, patients received the same radiotherapy as in the RT arm and concurrent intravenous administration of CBDCA 30 mg/m^2 (30 min infusion) 1 h before every radiation treatment up to the first 20 fractions (Fig. 1).

Radiotherapy was delivered with megavoltage (6–10 MeV photons) equipment using anterior/posterior opposed fields up to 40 Gy including the primary tumor, the metastatic lymph nodes and the regional node. A booster dose of 20 Gy was given to the primary tumor and the metastatic lymph nodes for a total dose of 60 Gy using bilateral oblique fields. The clinical target volume (CTV) for the primary tumor was defined as the gross tumor volume (GTV) plus 1 cm taking account of subclinical extension. CTV and GTV for the metastatic nodes (>1 cm in shortest dimension) were the same. Regional nodes excluding contra-lateral hilar and supraclavicular nodes were included in the CTV; however, lower mediastinal nodes were included only if the primary tumor was located in the lower lobe of the lung. The planning target volumes for the primary tumor, the metastatic lymph nodes and regional nodes were determined as CTVs plus 0.5–1.0 cm margins laterally and 1.0–2.0 cm margins cranio-caudally taking account of set up variations and internal organ motion. Lung heterogeneity corrections were not used.

The criteria for stopping the treatment are pulmonary toxicities, which include the National Cancer Institute-Common Toxicity Criteria (NCI-CTC; version 2.0) grade 2 respiratory distress and <60 torr PaO_2, other than hematopoietic toxicities (leukopenia, neutropenia and thrombocytopenia) or gastrointestinal toxicities (dysphagia).

EVALUATION

To assess the rate of tumor response and toxicity, all patients received a complete blood cell count; blood chemistry, including AST, ALT, lactate dehydrogenase, bilirubin, serum creatinine, blood urea nitrogen, total protein, serum albumin, serum electrolytes and calcium; and weekly chest X-rays during the treatment period. Best overall response was evaluated as tumor response by mono- or bi-dimensional measurement in accordance with the World Health Organization (WHO) criteria (30), and toxicity was evaluated in accordance with the NCI-CTC (version 2.0).



RT, radiotherapy; CRT, chemotherapy; TRT, thoracic radiotherapy; CBDCA, carboplatin.

Figure 1. Treatment schema.

Study Design and Statistical Analysis

This trial was a multi-center randomized phase III study. The study protocol was approved by the JCOG Clinical Trials Review Committee and the institutional review board of each participating institution before the initiation of the study.

The primary end-point was overall survival, which was defined as the interval from randomization to death from any cause. Secondary end-points were response rate, which was the proportion of the patients evaluated as having a complete reponse (CR) or partial response (PR) in best overall response out of all eligible patients; progression-free survival (PFS) defined as the interval from randomization to the diagnosis of progression or death from any cause; sites of progression; and toxicity. The estimate of survival time was performed by the Kaplan–Meier method (31). The trial was designed to have an 80% power to detect 5 months difference in MST (10 months in the RT arm and 15 months in the CRT arm) with a one-sided alpha of 0.05 by log rank test (32). The planned sample size was 190 patients by Shoenfeld and Richter's methods (33) with 1.5 years follow-up after 3 years accrual.

In-house interim monitoring is performed by the JCOG Data Center to ensure data submission, patient eligibility, protocol compliance, safety and on-schedule study progress. The monitoring reports are submitted and reviewed by the JCOG Data and Safety Monitoring Committee (DSMC) twice yearly.

An expedited report was required by the JCOG DSMC to allow rapid identification of any life-threatening adverse events or unexpected toxicities according to the JCOG toxicity reporting system based on the ICH-E2A guidelines.

RESULTS

From November 1999 to February 2001, 46 patients were enrolled in this study: 23 in the RT arm and 23 in the CRT arm. Four treatment-related deaths (TRDs) had been reported, however, before the forty-sixth patient were assigned. Therefore, we suspended the registration and checked the details of all randomized patients to assess the safety of treatment regimens. As a result, it was revealed that three of these deaths were due to pneumonitis. The JCOG DSMC advised consultation with the JCOG Radiotherapy Committee (RC) about the radiotherapy compliance in all patients. The JCOG RC collected each patient's irradiation planning data retrospectively and found poor protocol compliance which was related to TRD. Consequently, we decided to terminate this trial in August 2001 following the recommendation of the JCOG DSMC.

PATIENTS CHARACTERISITICS

Patient characteristics are listed in Table 1. No specific characteristics of patients were found in the elderly patients with locally advanced NSCLC compared with younger patiests and the two treatment arms were well balanced with respect to age and stage.

Toxicity of Treatment

Both hematological and non-hematological toxicities during the treatment and follow-up period were assessed. Table 2 summarizes the hematological toxicity. Patients receiving CBDCA suffered from leukocytopenia, neutropenia and thrombocytopenia more than patients receiving RT alone. There was no grade 4 hematological toxicity in the RT arm. Two (8.7%) and four (17.4%) patients in the CRT arm experienced grade 4 leukocytopenia and neutropenia, respectively.

Non-hematological toxicity observed in this study is listed in Table 3. None of the patients developed grade 3 esophagitis in either treatment arm. In the RT arm, other grade 3/4 toxicities were edema, fatigue, dyspnea and pneumonitis in one patient each. In the CRT arm, other grade 3/4 toxicities were neutropenic fever, dyspnea and pneumonitis. Grade 3/4 (RTOG/EORTC Radiation Toxicity Score) of late lung toxicity was observed in two patients in the RT arm and four patients in the CRT arm. Four TRDs were observed in this study. Three of

Table 1. Patient characteristics

Characteristics	RT arm	CRT arm
No. of eligible patients	23	23
Age (years)		
Median	77	77
Range	72–84	71–83
Male/female	19/4	16/7
Type of tumor		
Adenocarcinoma	6	11
Squamous cell	16	11
Large cell	1	1
PS (ECOG)		
0	3	9
1	19	13
2	1	1
Stage of disease		
IIIA	11	12
IIIB	12	11
Weight loss		
<10%	21	23
≥10%	2	0

RT, radiotherapy; CRT, chemoradiotherapy; PS, performance status.

Table 2. Hematological toxicity

	RT arm (n = 23)					CRT arm (n = 23)				
Grade	1	2	3	4	%grade 4	1	2	3	4	%grade 4
Leukocytes	10	2	2	0	0	3	7	11	2	8.7
Neutrophils	4	3	0	0	0	2	8	6	4	17.4
Hemoglobin	5	3	0	0	0	5	8	3	0	0
Platelets	2	0	2	0	0	4	5	8	0	0

RT, radiotherapy; CRT, chemoradiotherapy.

these patients were thought to have died as a result of pneumonitis. The details of these cases are follows. Case 1: a 78-year-old man had stage IIIA (T3N2) squamous cell carcinoma. He was treated with RT alone and died of pneumonitis at 28 days after therapy. Case 2: a 79-year-old man had stage IIIB (T4N2) adenocarcinoma. He was treated with CBDCA + RT and died of bacterial pneumonia at 37 days after therapy and had been taking steroid hormone due to radiation pneumonitis. Case 3: a 73-year-old man had stage IIIA (T3N2) squamous cell carcinoma. He was treated with CBDCA + RT and died of pneumonitis at 80 days after therapy. Case 4: a 80-year-old man had stage IIIB (T4N2) squamous cell carcinoma. He was treated with CBDCA + RT and died of pneumonitis at 54 days after therapy. Thus, three out of four TRDs were in the CRT arm and one was in the RT arm.

Table 3. Non-hematological toxicity

	RT arm (n = 23)					CRT arm (n = 23)				
Grade	1	2	3	4	% grade 4	1	2	3	4	% grade 4
Edema	0	0	0	1	4.5	0	0	0	0	0
Fatigue	1	0	0	1	4.5	7	1	0	0	0
Fever	3	0	0	0	0	1	1	0	0	0
Esophagitis	13	2	0	0	0	10	2	0	0	0
Nausea	0	0	0	–	–	2	2	0	–	–
Vomiting	0	0	0	0	0	1	0	0	0	0
Febrile neutropenia	–	–	0	0	0	–	–	1	0	0
Cough	3	1	0	–	–	6	0	0	–	–
Dyspnea	–	0	0	1	4.5	–	2	1	0	0
Pneumonitis	1	0	0	–	4.5	1	0	1	0	0
Creatinine	1	0	0	0	0	0	0	0	0	0
Hyponatremia	7	–	0	0	0	5	–	1	0	0
Heart	0	0	0	0	0	0	1	0	0	0
Lung	8	4	2	0	0	9	6	1	3	13.0

RT, radiotherapy; CRT, chemoradiotherapy.

Protocol Compliance

In the RT arm, 22 (95.6%) patients received full treatment doses. In the CRT arm, 20 (87.0%) patients completed the treatment. As to the administration of CBDCA, there were few protocol deviations.

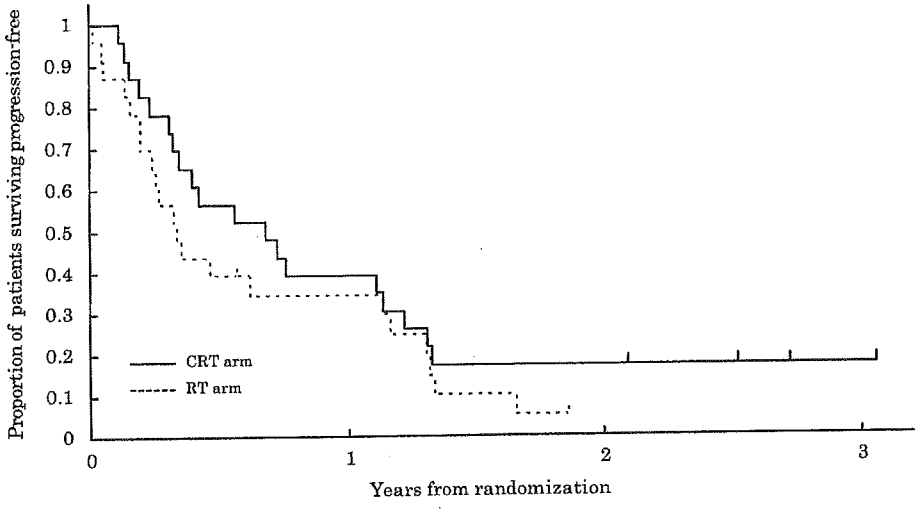
Three of the patients discontinued the protocol treatment: one was due to grade 2 eruption, one was due to cerebral infarction and one was due to insufficient recovery from leukopenia. One patient in the RT arm did not start the treatment due to local progression (Table 4).

Quality Assurance of Radiotherapy

We evaluated the quality of radiotherapy retrospectively based on the collected radiation therapy planning data. The data of 45 patients were reviewed and evaluated for the analysis. Details of this analysis have been reported by Ishikura et al. (34); three cases were revealed to be protocol violation due to normal lung volume constraint defined in the protocol. Unacceptable protocol deviations were identified as follows; 17, 15 and 31 cases on field border placement for the primary tumor, the metastatic lymph nodes and the elective nodal irradiation, respectively. Overall, 27 of 45 cases (60%) had at least one unacceptable deviation. Most cases judged to have protocol violation were primarily due to a smaller radiation field. Only 18 cases (40%) were judged to be protocol compliant.

Response and Survival

The tumor response in each arm is listed in Table 5. No patients achieved a CR in either arm. Of the 23 patients in the RT arm, 12 [52.2%, 95% confidence interval (CI) = 30.6–73.2%] achieved PR and six (26.1%) had stable disease. Of the



RT, radiotherapy; CRT, chemoradiotherapy.

Figure 2. Progression-free survival for patients treated with radiation alone or radiation with concurrent daily CBDCA.

Table 4. Protocol compliance

Pattern	RT arm (n = 23)	CRT arm (n = 23)
Complete protocol treatment	22	20
Progression/relapse*	1	0
Adverse events		
Cerebral infarction	0	1
Eruption	0	1
Leukopenia	0	1
Patient refusal	0	0
Death on protocol	0	0
Other	0	0

*Before starting the radiotherapy.
RT, radiotherapy; CRT, chemoradiotherapy.

Table 5. Response to treatment

Response	RT arm (n = 23)	CRT arm (n = 23)
Complete response	0 (0)	0 (0)
Partial response	12 (52.2)	11 (47.8)
Stable disease	6 (26.1)	7 (30.4)
Progression	4 (17.4)	4 (17.4)
Not evaluable	1 (4.4)	1 (4.4)
Objective response	52.2%	47.8%

RT, radiotherapy; CRT, chemoradiotherapy.

23 patients in the CRT arm, 11 (47.8%, 95% CI = 26.8–69.4%) achieved PR and seven (30.4%) had stable disease.

Seventeen (73.9%) patients in the RT arm and 15 (65.2%) patients in the CRT arm had died at the time of analysis. The median progression-free survival time was 122 days (95% CI = 88–413 days) on the RT arm versus 248 days (95% CI = 127–416 days) on the CRT arm (Fig. 2.). The MST was 428 days (95% CI = 212–680 days) on the RT arm versus 554 days (95% CI = 331 to not estimable) on the CRT arm (Fig. 3.). The 1-year survival rate was 60.9% (95% CI = 40.9–80.8%) on the RT arm versus 65.2% (95% CI = 45.8–84.7%) on the CRT arm.

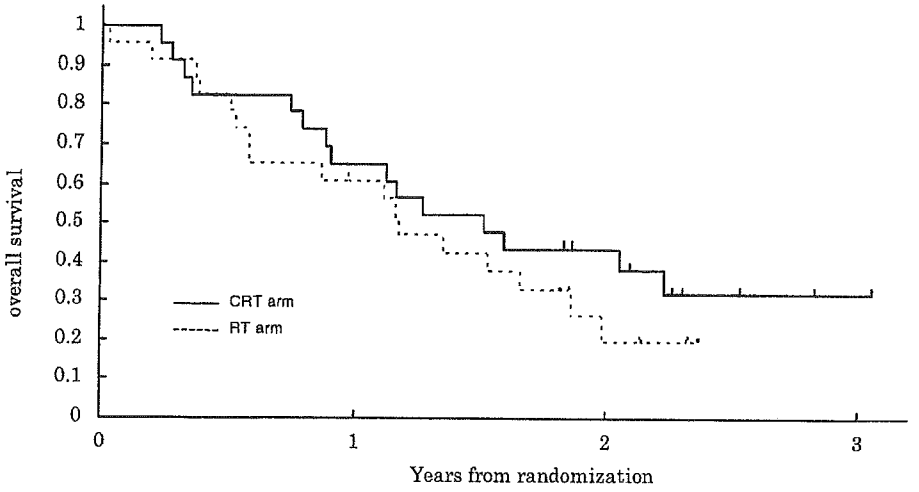
Pattern of Progression/Relapse

The first site of disease progression or relapse is listed in Table 6. Sixteen patients in the RT arm and 13 patients in the CRT arm had relapsed or had disease progression at the time of analysis. Eight patients (out of 16, 50.0%) in the RT arm and seven patients (out of 13, 53.8%) in the CRT arm had relapse or disease progression within the radiation field whether relapse outside the radiation field occurred or not.

DISCUSSION

We conducted this randomized controlled trial to determine whether chemoradiotherapy was superior to radiotherapy alone with respect to overall survival of elderly patients with locally advanced NSCLC. The study was terminated early when 24% of the planned sample size was accrued because of a high proportion of TRDs due to radiation pneumonitis and protocol violation.

Pulmonary toxicities including radiation pneumonitis and fibrosis caused by radiation therapy are, in general, common but not severe. In this study, however, the risk of TRD was 8.7% (four out of 46) and was much higher than in other trials. For instance, Ohe et al. (35) retrospectively analyzed the incidence of TRDs in the treatment of thoracic radiotherapy and/or chemotherapy for patients with locally advanced NSCLC, and reported that seven of 448 patients (1.6%)



RT, radiotherapy; CRT, chemoradiotherapy.

Figure 3. Overall survival for patients treated with radiation alone or radiation with concurrent daily CBDCA.

Table 6. First site of disease progression

	RT arm ($n = 23$)	CRT arm ($n = 23$)
Local	8	5
Distant	8	6
Local + distant	0	2

RT, radiotherapy; CRT, chemoradiotherapy.

died of radiation-induced pneumonitis. The high proportion of pulmonary toxicities in our trial may be due partly to the high age of the patients. Schild et al. (15) reported that they found 6% of elderly (older than 75 years) with NSCLC had grade 4 pneumonitis whereas this was the case in only 1% of younger patients ($P = 0.02$). It was controversial that the four TRDs out of 46 was sufficient reason to terminate the on-going trial; however, we thought it was serious that half of the TRDs (two out of four) were judged to be associated with protocol violation concerning the radiation field, which was to be less than half of one lung. Because the JCOG had not yet established the quality control/assurance system for radiotherapy before this trial, we concluded that we would not be able to control the risk of radiation pnuemonitis due to protocol deviation if we continued this study. What was an issue in this study was not only the high TRD rate, but also the poor protocol compliance of RT. The reasons for the poor protocol compliance are limited participation of radiation oncologists during protocol development, limited educational resources for attending radiation oncologists and no quality control program. Although the retrospective systematic review of radiation planning and protocol compliance of radiotherapy was the first experience in the JCOG, both the Lung Cancer Study Group and the entire JCOG had become aware of the importance of a quality control system for radiotherapy. The JCOG Executive Committee decided to establish the Radiation Therapy Quality Assurance Center (RTQAC) within the JCOG Data Center under the supervision of the JCOG Radiotherapy Committee. The RTQAC started the prospective quality control and quality assurance (QC/QA) program in September 2002 with a new activated phase III study for limited disease of small cell lung cancer, JCOG0202. Up to 2004, the QC/QA program has been expanded to the other group studies, such as esophageal cancer study, breast cancer study, prostate cancer study and brain tumor study. In addition, the JCOG Executive Committee mandates the QC/QA program by the RTQAC for all JCOG trials when protocol treatment includes radiation therapy.

The clinical question raised in this trial has not been answered. The data from the 46 patients enrolled were not considered to be conclusive because of the small sample size. No remarkable difference was found between the arms in terms of safety and efficacy such as tumor response, PFS and overall survival. We considered that it still remained an important clinical question to be investigated whether the daily low-dose CBDCA plus radiotherapy was effective or not. Therefore, we re-planned and started a new phase III trial (JCOG0301), in which the prospective QC/QA program by the RTQAC is added to the identical design to this JCOG9812. The protocol involves initial review of radiation planning and final review of the actual radiation record for all randomized patients. The JCOG0301 was activated in September 2003, and we have achieved very good protocol compliance upto now.

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Original Paper

Thermo-Chemo-Radiotherapy for Advanced Gallbladder Carcinoma

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ABSTRACT

Background/Aims: Many gallbladder carcinomas are detected at an advanced stage, and the outcome of the patients with these tumors is dismal despite aggressive tumor removal. We have treated advanced gallbladder carcinoma with chemoradiotherapy combined with hyperthermia. In this study, clinical effectiveness of thermo-chemo-radiotherapy (TCRT) for advanced gallbladder carcinoma was evaluated in comparison with other treatment modalities.

Methodology: Two hundred and seventy patients with advanced gallbladder carcinoma (Stage VI) were treated. According to treatments received, they were divided into five groups as follows: group 1; 30 patients treated with TCRT, group 2; 19 patients underwent R0-resection, group 3; 39 patients underwent R1,2-resection, group 4; 57 patients treated with chemo- and/or radiotherapy, group 5; 125 patients with only supportive therapy.

Results: In group 1, there were 19 objective responses (5 complete response and 14 partial response) in respect to tumor regression, and 15 (6 complete response and 9 partial response) of 20 patients with obstructed bile duct showed resolution of the bile duct. The survival rate was best in group 2. A significant improvement of long-term survival was exhibited in group 1 and 3 compared to group 4 and 5, and there was no significant difference between group 1 and 3 ($p<0.01$).

Conclusions: TCRT can produce significant response and improvement of survival time in patients with advanced gallbladder carcinoma, and may be a favorable alternative to aggressive surgical approaches.

KEY WORDS: Hyperthermia; Gallbladder carcinoma; Thermo-chemo-radiotherapy

ABBREVIATIONS: Thermo-chemo-radiotherapy (TCRT); American Joint Committee on Cancer (AJCC); Cis-platinum (CDDP); 5-Fluorouracil (5-Fu); Methotolexate (MTX); Intraoperative Radiation Therapy (IORT); External Beam Radiation Therapy (EBRT); Complete Regression (CR); Partial Regression (PR); No Change (NC); National Cancer Institute Common Toxicity Criteria (NCI-CTC); Percutaneous Transhepatic Cholangiodrainage (PTCD); Radiotherapy (RT)

INTRODUCTION

Despite recent tremendous advances in diagnostic technologies, many gallbladder carcinomas are detected at an advanced stage when the tumor has already invaded adjacent organs or major vessels. Then, various kinds of combined resection are required to obtain higher resectability and curability. Recently, aggressive surgical approaches, including resection of the liver, pancreas, and major vessels have been challenged, but their results have been discouraging and long-term survivors are the exceptions (1,2).

Hyperthermia has been used in combination with radiation therapy and/or chemotherapy and is considered to be effective for certain type of tumors (3). Since 1985, we have performed triodality treatment with hyperthermia, chemotherapy and radiotherapy (thermo-chemo-radiotherapy: TCRT) for advanced gallbladder carcinoma (4). The aim of this report is to assess the value of TCRT for advanced gallbladder carcinoma in comparison with other treatment modalities.

METHODOLOGY

Patients

We experienced 357 patients with gallbladder carcinoma in Tokyo Metropolitan Komagome Hospital between 1976 and 2001. According to the pTNM system proposed by the American Joint Committee on Cancer (AJCC) (5), 270 cases were advanced gallbladder carcinomas histologically or roentographically confirmed as Stage IV tumors. Stage IV gallbladder carcinoma is defined as tumor extending more than 2cm into liver and/or into two or more adjacent organs (T4), or with metastasis in peripancreatic, periduodenal, periportal, celiac and/or superior mesenteric lymph nodes (N2), or with distant metastasis (M1). Roentographic diagnosis was based on the results of more than three imaging diagnostic techniques: computed tomography, ultrasonography, magnetic resonance cholangiopancreatography, angiography, percutaneous transhepatic cholangiography or endoscopic retrograde cholangiopancreatography. Thus, 270 patients were analyzed in this study.

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TABLE 1 Patient Characteristics and pTNM Staging in Each Group

Group	Treatment regimens	No. of patients	Male/ Female	Age (mean SD)	T4N0,1M01	T4N2M0	T4AnyNM1
1	Thermo-chemo-radiotherapy	30	9/21	63.4 8.8	16	6	8
2	R0-resection	19	6/13	65.3 8.6	19	0	0
3	R1,2-resection	39*	12/27	67.7 9.1	13	15	11
4	Chemo- and/or radiotherapy	57	21/36	66.2 9.9	18	12	27
5	Supportive therapy	125	45/80	72.2 10.1	28	30	67
	Total	270	93/177	68.5 9.5	94	63	113

39*: including 13 patients who also underwent intraoperative therapy.

According to treatments received, the 270 patients were divided into five groups as follows: group 1 consisting of 30 patients with nonresectable tumors treated with TCRT, group 2 consisting of 19 patients underwent R0-resection without post-residual tumor microscopically, group 3 consisting of 39 patients underwent R-1,2 resection with post-residual tumor microscopically or macroscopically, group 4 consisting of 57 patients treated with chemo- and/or radiotherapy, group 5 consisting of 125 patients with only supportive therapy. Patient characteristics and T, N, and M categories of each group are summarized in **Table 1**.

Thermo-Chemo-Radiotherapy (TCRT)

The heating equipment was RF-capacitive heating device, Thermotron RF-8 [Yamamoto Vinita company, Osaka, Japan (6)]. The patient lay in the prone position. The target was sandwiched with upper and lower electrodes, and an 8-MHz RF wave was applied. We administered heat to the patient for 40 minutes after the intratumor temperature had risen to 42°C. Intratumor temperature was measured using a needle thermosensor every time. The thermosensor was inserted beside or into the tumor from the skin surface through an 18-G angiocatheter under the aid of ultrasonography. The chemotherapeutic agents employed were cisplatinum (CDDP, 50mg/m^2) in combination with 5-fluorouracil (5-Fu, 800mg/m^2) or methotolexate (MTX, 30mg/m^2) in combination with 5-Fu (800mg/m^2). Hyperthermia and chemotherapeutic agents were administered simultaneously once weekly immediately following radiotherapy at 2 Gy. Usually it started within 15 min after the irradiation (**Figure 1**). Number of heat treatments ranged from 2 to 11 times (mean 4.5). Three cases were retreated.

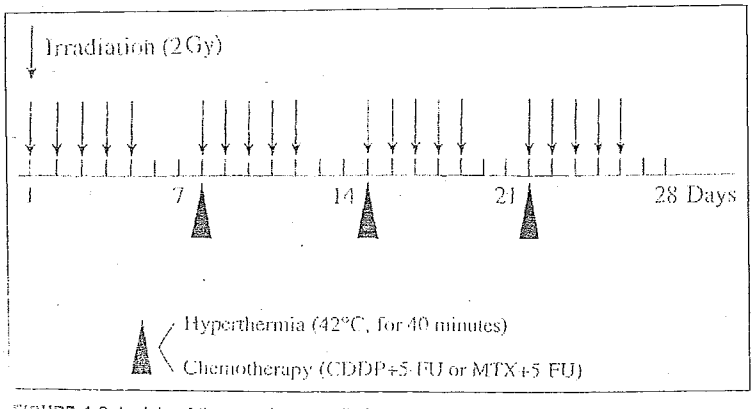

FIGURE 1 Schedule of thermo-chemo-radiotherapy.

Surgical Procedures, Intraoperative Radiation Therapy (IORT), External Beam Radiation Therapy (EBRT), and Chemotherapy

Combined resection of the involved organs such as liver, bile duct, pancreas, duodenum, or colon (31 cases), hepatic resection (39 cases), pancreatic duodenectomy (11 cases), partial resection of transverse colon (14 cases) was performed as far as anatomically possible.

Immediately after tumor removal, a high energy electron beam from a betatron was applied to the resected portions (intraoperative radiation therapy: IORT) was administered to 13 patients whose tumors had spread to the hepatoduodenal ligament or hepatic hilus in attempt to suppress the development of local recurrence (Group 3). The dose of IORT ranged from 18 to 20 Gy with energies of 8 to 12 million electron volts.

External beam radiation therapy (EBRT) was administered five times per week at a dose of 2 Gy per fraction. Total radiation dose ranged from 30 to 60 Gy. EBRT other than TCRT was performed for 13 patients with nonresected tumors.

Chemotherapy not combined with hyperthermia was performed by MTX, CDDP, 5-Fu, mitomycin C, or adriamycin for 49 patients with nonresected tumors.

Response and Toxicity Criteria

The effectiveness of TCRT on nonresectable tumors was evaluated about tumor regression by follow-up CT, and resolution of biliary obstruction by cholangiographies. Tumor regression was graded as complete regression (CR: more than 80% tumor volume reduction), partial regression (PR: more than 50% and less than 80% regression), and no change (NC). Response of stenotic or obstructed bile duct was graded as CR: complete resolution of the bile duct, PR: partial resolution of the bile duct, and NC.

We examined histologically the state of the gallbladder and bile duct, and hematogenous, lymphogenous metastases at autopsy in 11 patients with advanced gallbladder carcinoma treated with TCRT. Modes of hematogenous and lymphogenous metastases were evaluated by high and moderate degree according to the criteria reported before (7).

Side effects were evaluated and graded according

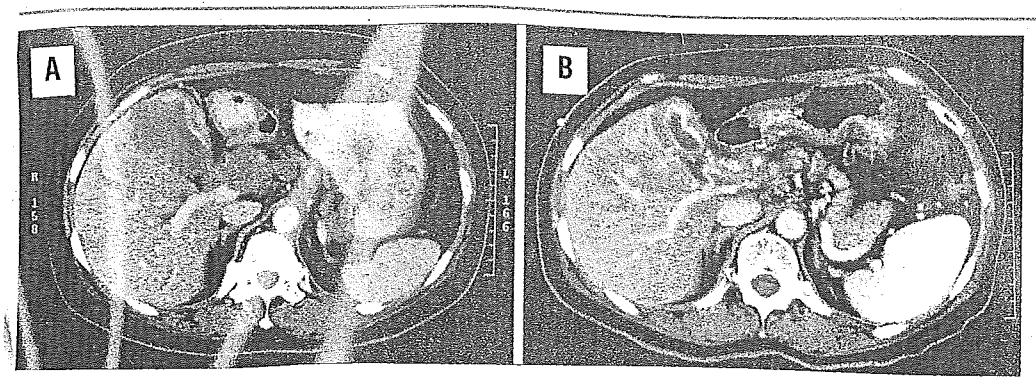

FIGURE 2
CT scan of Case 4. A large gallbladder carcinoma with thickening of the gallbladder wall (A) had almost completely disappeared after TCRT (B).

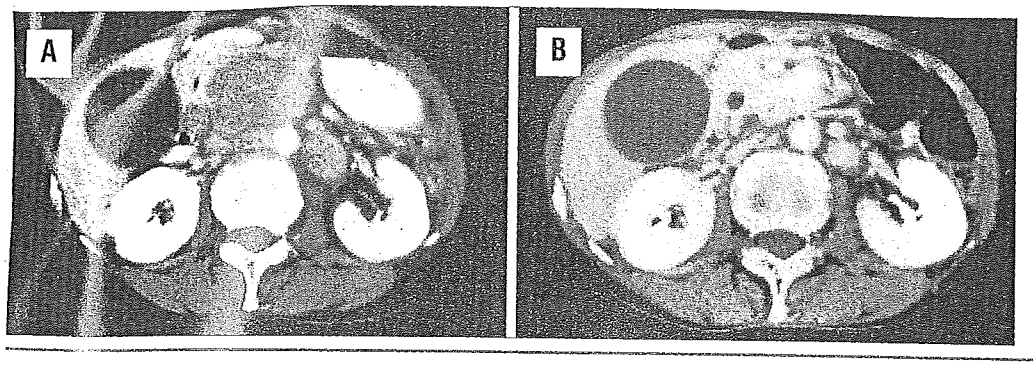

FIGURE 3
CT scan of Case 2. A large peripancreatic lymph node metastasis (A) had completely disappeared four months after TCRT (B).

to National Cancer Institute Common Toxicity Criteria (NCI-CTC) (8).

Statistical Analysis

Life table survival probabilities were calculated using the Kaplan-Meier method. The generalized Wilcoxon test was used to assess the difference in survival rates. A p-value of less than 0.01 was considered statistically significant.

RESULTS

Effectiveness of TCRT

In respect to tumor regression by TCRT, there were 5 CR, 14 PR, and 11 NC. CR rate and CR+PR rate was 17% and 63%. Marked reduction of the gallbladder tumor or lymph node metastasis was observed in some cases after TCRT (**Figures 2 and 3**).

As for resolution of the bile duct, there were 6 CR, 9 PR, and 5 NC in 20 patients with obstructed or markedly stenotic bile duct. CR rate and response rate was 30% and 75%. In four patients with resolution of the obstructed bile duct, percutaneous transhepatic cholangiodrain (PTCD) could be removed (**Figure 4**). However, as the four patients developed obstructive jaundice again due to disease progression, we placed self-expandable metallic stent after TCRT into the patency-restored bile duct for prevention of restenosis and the partially resolved bile duct for improvement of patients' quality of life (**Table 2**).

Long-term Survival Results

Three patients of group 2 survived for more than three years. No patient of group 3, 4 and 5 survived for more than two years, but one patient of group 1 survived for 33 months. Mean survival months (mean±SD) and the 1-year survival rates for patients of groups 1-5 were 9.5±6.3 - 33%, 24.7±26.8 - 79%, 8.4±4.9 - 21%, 5.7±4.2 - 11%, and 3.4±3.5 - 3%, respectively. The survival rate was best in group 2 ($p<0.01$). A significant improvement of long-term survival was exhibited in group 1 and 3 compared to group 4 and 5 ($p<0.01$). The difference of survival rate between group 1 and 3 was not significant (**Figure 5**).

Histological Findings at Autopsy in Patients Treated with TCRT

In almost all cases, marked hyalinization or fibrosis with necrosis replaced extensively gallbladder tumor and wall, in which suppressed cohesiveness of

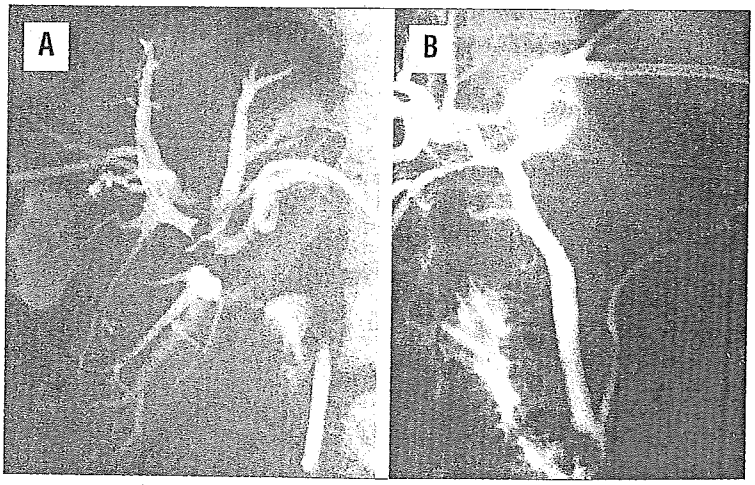

FIGURE 4 Percutaneous transhepatic cholangiography of Case 3. Complete obstruction of the upper bile duct (A) had completely resolved after TCRT (B).