しては、本来治療に抵抗性のある腫瘍細胞の治療期間中にみられる再増殖を防ぐため、放射線治療期間中に休止期間をおかないことが望ましいとされているが、化学療法と放射線療法を同時併用する場合には、分離照射法でも良好な治療成績が報告されている[31]。しかし、RTOGの3つの臨床試験をまとめた分析では、放射線治療の中断は生存率を低下させる可能性を示しており[38]、今後の課題であると思われる。化学療法に用いる薬剤としては、放射線療法単独と化学放射線療法の臨床比較試験をまとめたメタアナリシス[25-27]で、シスプラチンを含む化学療法が良好であったことよりシスプラチンを含むレジメンとなる。Schaake-Koningらの報告[39]を除けば、放射線療法単独より化学放射線療法が有用であったランダム化比較試験は多剤併用療法である。多剤と単剤の比較を行った報告はない。

新規抗がん剤（ビノレルビン、パクリタキセル、ドセタキセル、イリノテカン、ゲムシタビン）と放射線併用療法に関しては、大規模臨床試験でのデータに乏しい。Cancer and Leukemia Group B (CALGB) では、ビノレルビン、パクリタキセル、ゲムシタビンの3剤をそれぞれシスプラチンと組み合わせた化学療法2コース後に、新規抗がん剤のみ約半量に減量し放射線療法と併用する第Ⅱ相比較試験を行っているが、従来の化学放射線療法より優れた結果は得られなかった[40]。イリノテカンについては、肺毒性のリスクを念頭におく薬剤であり、また、ゲムシタビンも胸部放射線療法との同時併用は、わが国では禁忌となっている。

低用量の化学療法をradiosensitizerとして放射線治療に組み合わせ、放射線治療の局所制御の向上を狙う試みも行われている[39,41]。Schaake-Koningらは胸部放射線療法単独群、シスプラチン30mg/m^{2}毎週投与と胸部放射線療法併用群、シスプラチン6mg/m^{2}連日投与と胸部放射線療法併用群の3群で比較を行い、シスプラチン連日投与と放射線療法併用群が優れていたと報告している[39]。低用量の化学療法をradiosensitizerとして放射線治療に組み合わせる治療法は、現時点では併存症などにより通常の化学放射線療法が困難な症例に対して放射線療法単独と比較検討する治療方法と考えられる。

また、化学放射線療法に治療防護剤としてamifostineを併用した報告もみられるが、一部の毒性軽減には有効であったが、治療効果には寄与しなかったと報告されている[42]。

新規抗がん剤はstageⅢB・Ⅳ期における化学療法で有用な薬剤であるが、前述のように放射線療法との併用に関しては制約がみられる。一方、化学放射線療法は早期に放射線療法を併用することが有用であるとされている。そこで近年consolidation chemotherapyと称される、標準的な化学放射線療法の後に新規抗がん剤による化学療法を加える試みが行われている。GandaraらはPE療法と胸部放射線療法併用後に従来であれば同じPE療法を追加投与する代わりに、ドセタキセルを3コース追加投与する第Ⅱ相試験を行い、生存期間中央値26ヵ月という良好な成績を報告した[43]。現在Hoosier Oncology Groupがこの第Ⅲ相試験を行っている。また、2005年の米国臨床腫瘍学会では、PE療法と胸部放射線療法併用後にドセタキセルを3コース追加投与し、さらにゲフィチニブ250mg/日を投与する群とプラセボを投与する群の2群間で比較試験を行い、その中間解析結果をSWOGが報告した（SWOG 0023）。ゲフィチニブ投与群は、プラセボ投与群と比較して全生存期間をより改善する可能性がみられないことが示唆された[44]。一方、Choyらはカルボプラチン/パクリタキセルによる通常の化学療法（3週毎）2コース後に胸部放射線療法を行う群、カルボプラチン/パクリタキセルによる通常の化学療法2コース後に、カルボプラチン/パクリタキセルを

1週毎の分割投与と胸部放射線療法の同時併用を行う群、カルボプラチン/パクリタキセルを1週毎の分割投与と胸部放射線療法の同時併用を先に行い、その後カルボプラチン/パクリタキセルによる通常の化学療法2コース行う群での3群間での比較試験を行った(LAMP trial)。中間解析の結果では早期に化学放射線療法を行った群が優れている傾向にあった[45]。

以上より、70歳以下のPSの良好な切除不能局所進行非小細胞肺癌に対しては、シスプラチンを含む多剤を用いた化学放射線療法を早期に行うことが有用であると考えられる。新規抗がん剤との併用については今後の課題と考えられる。

今後、肺癌における化学放射線療法は、分子標的薬を含めた新規抗がん剤と放射線療法の併用、三次元原体照射による放射線治療やpositron emission tomography (PET) を用いた治療計画法などについて検討が進むものと思われる。

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CLINICAL INVESTIGATION **Head and Neck**

RADIATION THERAPY FOR T2N0 LARYNGEAL CANCER: A RETROSPECTIVE ANALYSIS FOR THE IMPACT OF CONCURRENT CHEMOTHERAPY ON LOCAL CONTROL

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Purpose: The impact of concurrent chemotherapy on the local control in patients with T2N0 laryngeal cancer who receive radiation therapy (RT) was evaluated.

Methods and Materials: Sixty-three patients with T2N0 laryngeal cancer who were treated by definitive RT were analyzed. The primary site of the cancer was the glottis in 50 patients, the supraglottis in 9 patients, and the subglottis in 4 patients. Thirty-six patients were treated by RT alone and the remaining 27 patients received concurrent chemoradiotherapy (CRT).

Results: Complete response (CR) was obtained in 92% of the patients who received RT alone and 100% of the patients who received CRT. Voice preservation in the group who received CRT (89%) was significantly higher than that in the group treated by RT alone (61%). The 5-year disease-free survival rates in those who received concurrent CRT was significantly superior to that in the patients who received RT alone, although no significant difference was seen in the cause-specific survival rate between the 2 groups. The multivariate analysis revealed that the treatment method (RT alone vs. CRT) was the most significant risk factor that predicted recurrence after RT.

Conclusion: Concurrent CRT had a positive impact on the local control of T2N0 laryngeal cancer.

Laryngeal cancer, Radiation therapy, Chemotherapy, Voice preservation.

INTRODUCTION

The treatment of choice for early laryngeal cancer has been controversial. Options include radiation therapy (RT), transoral laser therapy, and partial laryngectomy (1–3). The goals of treatment are preservation of the larynx and voice and of the optimal voice quality, in addition to eradiation of the tumor. The control rate after RT alone has been reported to be in the range of 80% to 95% in patients with T1 cancer and 50% to 85% in patients with T2 cancer. These results suggest that although conventional RT alone or partial laryngectomy might yield a satisfactory local control rate in cases with T1 cancer, the local control in patients with T2 laryngeal cancer leaves much room for improvement. Several approaches have been employed in an attempt to improve the cure rate of T2 laryngeal cancer, including hyperfractionated RT, combined chemotherapy with RT, and induction chemotherapy followed by partial laryngectomy. Garden *et al.* (4) reported the results of hyperfractionated RT by use of 1.2 Gy/fraction or 1.1 Gy/fraction for stage T2 glottic cancer and demonstrated that patients treated with hyperfractionated RT with a median dose of 77 Gy showed an improved local control rate as compared with patients treated with 70 Gy in 35 fractions. Changes in daily fraction size are one of altered fractionation schemas. Yu *et al.* (5)

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reported that fractionation schedules that utilize a daily fraction size greater than 2 Gy yield better local control in T1 glottic cancer than do schedules that deliver 2 Gy/fraction, with no increase in the toxicity. In regard to the results of partial laryngectomy for T2 laryngeal cancer, local recurrence rates of 10% to 30% and 20% to 50% were reported in patients who had T2 laryngeal cancer with normal vocal-cord motion and impaired vocal-cord motion (6, 7). Laccourreye *et al.* (8) published the results of platinum-based induction chemotherapy followed by partial laryngectomy and reported that the 5-year actuarial local control rate was 95.7% (97.7% in patients with normal vocal-cord motion and 93.8% in patients with impaired vocal-cord motion).

Regarding the role of concurrent chemotherapy on the outcome of radiotherapy for T2 laryngeal cancer, few studies to date have compared the results with those of altered fractionation or partial laryngectomy. Kumamoto *et al.* (9) reported the results of "FAR" chemoradiotherapy for T2N0 glottic cancer; FAR therapy consists of 1 bolus i.v. administration of 5-FU, i.m. injection of vitamin A, and RT. They demonstrated that the 5-year voice preservation and complete laryngeal preservation rate were 91% and 87%, respectively. Thus, whereas the effect of chemoradiotherapy on improvement of the local control in cases of locally advanced head-and-neck cancer has been established, the role of concurrent chemotherapy with RT has not yet been investigated thoroughly, especially for T2 laryngeal cancer. In this context, we retrospectively analyzed the clinical records of patients with T2N0 laryngeal cancer who were treated by RT at our institution, where the use of concurrent chemoradiotherapy (CRT) for T2N0 laryngeal cancer was started in July 1999; until 1999, patients with T2N0 laryngeal cancer were treated by RT alone. In 1999, we changed our treatment policy to concurrent CRT for patients with T2N0 laryngeal cancer who had adequate renal and liver functions and a reasonably good performance status. The purpose of this study was to compare clinical outcomes, including the disease-free survival and voice-preservation rates, after RT alone and after concurrent CRT for T2N0 laryngeal cancer, to clarify the impact of concurrent chemotherapy on improvement of the local control in patients with T2N0 laryngeal cancer who received RT.

METHODS AND MATERIALS

Patients

Among the patients with laryngeal cancer who were treated by RT between January 1988 and October 2003, 63 patients with T2N0 laryngeal cancer who had not undergone any prior treatment were analyzed. All of the 63 cases had been histologically diagnosed to have squamous cell carcinoma. Of the 63 patients, 54 were male, and the average age of the patients was 69 years (range, 48–84 years). The distribution of the primary site was as follows: glottis, 50 cases; supraglottis, 9 cases; and subglottis, 4 cases. The initial examination before the start of the treatment included medical history; biopsy; clinical ear, nose, and throat examination; complete blood count; blood biochemical examination; electrocardiography; chest X-ray; computed tomography (CT) of the chest and abdomen; and CT or magnetic resonance imaging (MRI) of the head and neck. Dynamic helical CT or dynamic MRI, which detects adjacent signs (10), was not performed; hence, this study possibly included patients with paraglottic space invasion, which was classified as stage T3 tumors by the Union International Contre le Cancer criteria (UICC) sixth edition.

Table 1. Comparison of patients treated by RT alone with those treated by concurrent CRT

Characteristics	RT alone	Chemoradiation
Number of patients	36	27
Average age (range)	68 y (46–86 y)	71 y (58–84 y)
Sex		
Male	31	23
Female	5	4
Primary site		
Glottic	25	25
Supraglottic	7	2
Subglottic	4	0
Fractionation		
Once a day	34	27
Twice a day	2	0
Total dose (range)	87.5 Gy (60–72 Gy)	64.4 Gy (62–70 Gy)
Overall treatment time (range) (days)	49 days (38–75 days)	48 days (39–52 days)
Beam energy		
4-MV X-ray	0	4
6-MV X-ray	32	20
^{60}Co	4	3
Median follow-up (range)	66 mo (17–165 mo)	38 mo (20–72 mo)

Patients were staged according to the UICC criteria (11). Written informed consent was obtained from all of the patients before the commencement of the treatment. The median follow-up duration of the patients was 47 months (range, 14–172 months). Table 1 shows a comparison of the characteristics of patients who were treated by RT alone and those who were treated by concurrent CRT. The difference in the distribution of the primary site (glottic vs. supraglottic or subglottic) between the 2 groups was significant ($p < 0.05$); however, no significant differences were seen in any of the other variables, including the male/female ratio, total dose of RT, and the overall treatment time.

Radiation therapy and chemotherapy

All the patients received external-beam RT. The RT was administered with high-energy photons of 4 or 6 MV X-rays from a linear accelerator or ^{60}Co γ-rays. Basically, all patients were treated with parallel-opposed fields, and no elective irradiation for neck lymph nodes was performed. The average total dose of RT was 67 Gy (range, 61–71.4 Gy). Of the 63 patients, 61 were treated according to the conventional fractionation schema (2 Gy per fraction, 5 times a week), and 2 patients who received RT alone were treated according to an accelerated hyperfractionation (AHF) schema (1.6 Gy per fraction, twice a day, split after 38.4 Gy) at a total dose of 64 Gy. The distribution of the photon energy used in the patients was as follows: 4 MV, 4 patients; 6 MV, 50 patients; ^{60}Co γ-rays, 7 patients.

The chemotherapeutic regimen differed according to the period and consisted of daily administration of low-dose cisplatin (CDDP) alone, daily CDDP plus weekly docetaxel, or weekly docetaxel alone. Initially, low-dose CDDP (6 mg/m^2, 5 times a week) administered for 3 weeks was the standard regimen; however, subsequently, we adopted weekly docetaxel and low-dose CDDP as the standard regimen. In the weekly docetaxel and daily CDDP regimen, docetaxel (10 mg/m^2, once a week) was given to all patients up to 4 cycles, and CDDP (6 mg/m^2, 5 times a week) was administered for up to 3 weeks from the commencement of the RT if the renal function was found to be adequate, as determined by the creatinine clearance (CCr), for the administration of CDDP (12). If the CCr was less than 60 mL/min, docetaxel alone (10 mg/m^2, once a week) was administered for up to 4 weeks. The distribution of the chemotherapy regimens in the patients was as follows: daily CDDP alone, 8 patients; weekly docetaxel + daily CDDP, 16 patients; and weekly docetaxel alone, 3 patients. In the daily CDDP alone group, the mean treatment duration was 13.5 days. In the daily CDDP + weekly docetaxel or weekly docetaxel alone groups, the mean number of treatment cycles administered was 3.8 (completion rate, 79%), and the mean duration of administration of daily cisplatin was 10.5 days. Discontinuation of docetaxel or CDDP was usually necessitated by impairment of renal function (CCr; < 60 mL/min) or temporary myelosuppression; however, all the patients in our series had maintained renal function at the time of the analysis. RT was administered as soon as possible after the infusion of docetaxel or CDDP.

Evaluation of the local response and toxicity

Local response was estimated 1 month after the completion of RT, by CT or MRI of the head and neck. Local failure or recurrence was considered to have occurred when either laryngeal cancer showed clinical persistence at the end of the RT or local recurrence developed after initial complete response. The patients were then followed regularly as outpatients. Toxicity was monitored by daily medical examinations and weekly laboratory examinations. Sequelae were classified according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) guidelines, version 2.0 (13).

Univariate and multivariate analyses

The clinical factors predictive of recurrence, including local recurrence and distant metastasis, were analyzed by univariate and multivariate analyses. These analyses included the treatment method (RT alone vs. CRT), overall treatment duration, and the primary site of the cancer (glottic vs. supraglottic or subglottic).

Statistics

The Kaplan-Meier method was used to draw the time-to-event curves (14). The length of follow-up for estimation of the overall and cause-specific survival rates was calculated from the start of the treatment. Analysis of the differences between the 2 groups was performed by the unpaired two-tailed *t* test. The variables that were thought to influence clinical relapse were analyzed by multivariate analysis according to the Cox proportional-hazards model (15). A *p* value of less than 0.05 was considered as denoting statistical significance.

RESULTS

Response and recurrence

The 5-year overall, cause-specific and disease-free survival rates in all patients were 90%, 94%, and 76%, respectively (Fig. 1). At the time of analysis, after a median follow-up duration of 47 months (range, 14–172 months), 4 patients died of disease progression, and 6 patients died of causes unrelated to the laryngeal cancer. Three patients died of cerebral infarction (1 patient) and pneumonia (2 patients), with no clinical evidence of recurrence at the primary site, and 3 patients died of second primary cancers, including lung cancer, esophageal cancer, and oropharyngeal cancer. The median interval from the completion of RT to the occurrence of intercurrent disease was 62 months (range, 31–102 months).

In a comparison of the outcome of RT alone with that of concurrent CRT, complete response (CR) was achieved in 33 of the 36 patients (92%) treated by RT alone, whereas all of the patients treated by concurrent CRT showed CR. Among the patients who showed CR, recurrence was observed in 12 patients treated by RT alone and in 4 patients treated by concurrent CRT. Concerning the chemotherapeutic regimen administered in the latter 4 patients, 2 patients received daily CDDP alone, and 2 patients received daily CDDP + weekly docetaxel treatment. In the 16 patients who experienced recurrence, the sites of recurrence were as follows: local recurrence alone in 12 patients, regional lymph node metastasis alone in 2 patients, local and regional lymph node metastasis in 1 patient, and pulmonary metastasis in 1 patient. In regard to the treatment method, 12 of the 33 patients (33%) who initially showed CR in the RT-alone group experienced recurrence (local recurrence in 10 patients and regional lymph node metastasis in 2 patients). Among these patients, 9 patients could be salvaged by surgery, and 3 patients died of disease progression (local progression in 2 patients and pulmonary metastasis in 1 patient). Three patients who showed partial response were controlled by total laryngectomy. Ultimate local control that included initial radiation therapy and salvage surgery was achieved in 34 of 36 patents (94%); however, voice preservation was achieved in 22 patients (67%) in the RT-alone group. In the concurrent-CRT group, 4 of the 27 patients (15%) who initially showed CR experienced recurrence

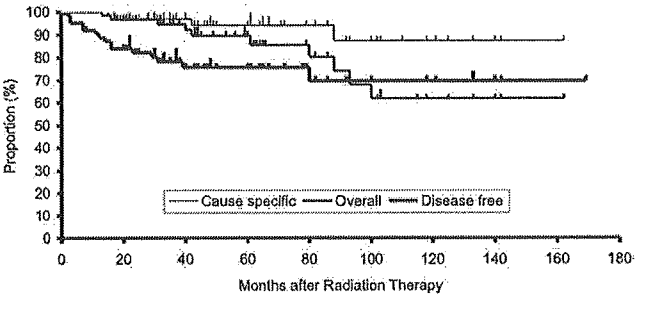

Fig. 1. The cause-specific and disease-free survival rates after radiation therapy in 63 patients.

(local recurrence in 2 patients, regional lymph node metastasis in 1 patient, and pulmonary metastasis in 1 patient). Three patients could be salvaged by surgery, but the patient with pulmonary metastasis died of disease progression. Ultimate local control that included salvage surgery was achieved in 26 of the 27 patients (96%), and voice preservation was achieved in 24 of the 27 patients (89%). The difference in the voice-preservation rate between the RT-alone and concurrent-CRT groups was statistically significant, which indicated that the voice preservation rate was better with concurrent CRT than with RT alone.

The 5-year overall survival rates in the RT-alone group and concurrent-CRT group were 87% and 96%, respectively, and the difference was significant ($p < 0.05$). The 5-year cause-specific survival rates in the RT-alone group and concurrent-CRT group were 93% and 96%, respectively (Fig. 2a); the difference was not significant. In contrast, the 5-year disease-free survival rates in the RT-alone group and concurrent-CRT group were 68% and 89%, respectively (Fig. 2b), and the difference was statistically significant ($p < 0.05$). The 5-year cause-specific and disease-free survival rates only in the patients with glottic cancer were also evaluated. The cause-specific survival rates at 5 years in the 50 patients with glottic cancer who received RT alone and those who received concurrent CRT were 94.7% and 100%, respectively (Fig. 3a); the difference was not significant. The disease-free survival rates at 5 years in the same group of patients who received RT alone and those who received concurrent CRT were 70.9% and 91.8%, respectively (Fig. 3b). Similar to the result for the cause-specific survival rate, the difference in the disease-free survival rate between the 2 groups was also not statistically significant ($p < 0.05$).

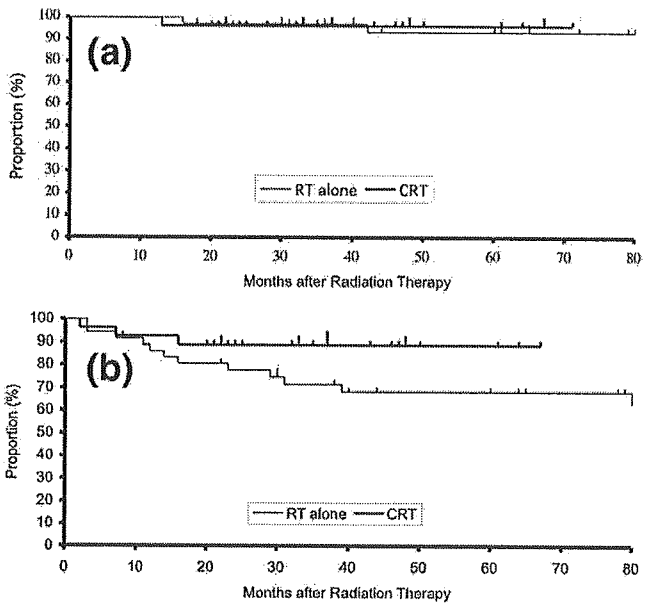

Fig. 2. Comparison of the cause-specific and disease-free survival rates between patients treated by radiation therapy (RT) alone and those treated by concurrent chemoradiotherapy (CRT). (a) Cause-specific survival after RT alone and after concurrent CRT. (b) Disease-free survival after RT alone and after concurrent CRT.

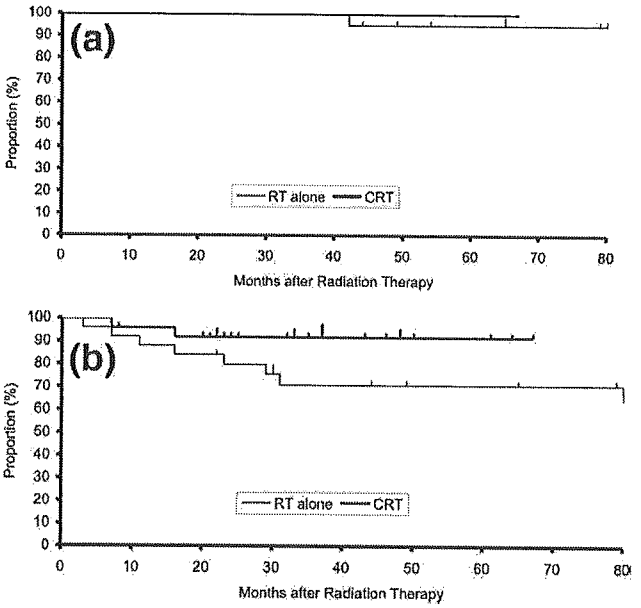

Fig. 3. Comparison of the cause-specific and disease-free survival between T2N0 glottic patients treated by radiation therapy (RT) alone and those treated by concurrent chemoradiotherapy (CRT). (a) Cause-specific survival after RT alone and after concurrent CRT. (b) Disease-free survival after RT alone and after concurrent CRT.

Acute toxicity

Acute mucositis that caused transient interruption of RT was observed in 4 patients. All of these patients received RT alone, and no split was caused by the acute toxicity in the CRT group. Grade 2 or more severe acute toxicity, as assessed by NCI-CTC, in the RT-alone group were as follows: Grade 2 in 5 patients and Grade 3 in 2 patients. All of these toxicities were nonhematologic toxicities, including Grade 3 acute mucositis in 2 patients, which necessitated transient i.v. hyperalimentation, and skin reaction (moist desquamation) in the radiation field. The distribution of the grades (Grade 2 or more severe) and types of acute toxicities in the concurrent-CRT group was as follows: acute mucositis, Grade 2 in 7 patients and Grade 3 in 2 patients; renal toxicity, Grade 2 in 1 patient; hematologic toxicity, Grade 2 in 2 patients and Grade 3 in 3 patients. No cases occurred with Grade 4 or more severe toxicity in either group. The only hematologic toxicity seen in the concurrent-CRT group was transient leucopenia.

Univariate and multivariate analysis

As shown above, the 5-year disease-free survival rate in the concurrent-CRT group was significantly superior to that in RT-alone group. To confirm the impact of concurrent chemotherapy on improvement of the local control in T2N0 laryngeal cancer patients who received RT alone, several clinical factors that affected the local control or recurrence

Table 2. Results of the multivariate analysis

Variables	Relative risk	95% CI	*p* Value
Treatment method			
RT alone vs. CRT	6.7	2.7–15.5	$p < 0.01$
Primary site			
Glottic vs. supraglottic or subglottic	1.0	0.6–1.8	0.9
Overall treatment time (days)			
≥50 vs. ≤49	0.8	0.4–1.6	0.5

Abbreviation: CI = confidence interval.

rate were analyzed by univariate and multivariate analyses, including the overall treatment duration and the primary site of the cancer. A previous study showed that the overall treatment duration was a significant factor predictive of local control in head-and-neck cancers, including glottic cancer, and several reports regarding the importance of the overall treatment duration on the local control in T1 glottic cancer have been already published (16, 17). The primary site of laryngeal cancer also influences the clinical outcomes; that is, radiotherapeutic outcome in supraglottic and subglottic cancer tends to be inferior, as compared with that in glottic cancer, for the same cancer stage (18).

The average overall treatment duration in all patients was 48.8 ± 6.4 (days). When the patients were stratified according to whether or not they experienced recurrence, the average treatment duration in the patients who experienced recurrence and those who did not experience recurrence was 50.3 ± 6.3 and 48.3 ± 6.5 (days), respectively. A trend was seen for the treatment duration to be longer in the patients who experienced recurrence than in those who did not experience recurrence; however, the difference was not significant. In regard to the primary site, the possibility that the primary site of the cancer may have an influence on the outcome is difficult to rule out; that is, the outcome may be superior in cases with glottic as compared with those with supraglottic or subglottic cancer, because this study included 13 patients in whom the primary site was the supraglottis or subglottis. The recurrence rates after RT alone stratified according to the primary site of cancer was as follows: 5 of 12 patients (33%) with supraglottic or subglottic cancer experienced recurrence, and 11 of 48 patients (23%) with glottic cancer experienced recurrence. Also a trend was seen for the recurrence rate to be higher in patients with supraglottic or subglottic cancer than in those with glottic cancer, but the difference was not significant. Of the 3 patients who showed partial response, 2 patients had glottic cancer, and 1 patient had subglottic cancer.

To confirm the significant factors that might predict recurrence after RT, multivariate analysis was performed. The multivariate Cox-regression analysis included the following variables: treatment method (RT alone vs. CRT), overall treatment duration (≥ 50 days vs. ≤49), and the primary site (glottic vs. supraglottic or subglottic). Table 2 shows the results of the multivariate analysis. Among the variables analyzed, the treatment method was found to be the most significant factor that influenced the risk of recurrence after RT, which indicates that concurrent CRT had a positive impact on disease-free survival.

DISCUSSION

The results of this study demonstrated that concurrent CRT yielded a significantly improved disease-free survival rate as compared with RT alone in cases of T2N0 laryngeal cancer. Although no significant difference occurred in the cause-specific survival rate between patients who received RT alone and concurrent CRT, the disease-free survival rate after concurrent CRT was significantly superior to that after RT alone. The results of the multivariate analysis also demonstrated that the treatment method was the most significant factor that influenced the risk of recurrence and indicated that concurrent CRT had a positive impact on the disease-free survival. The results suggested that concurrent CRT reduces the rate of recurrence after RT and played an important role in improving the radiotherapeutic outcome in patients with T2N0 laryngeal cancer. In this study, all of the patients, excluding 1 who showed pulmonary metastasis, experienced locoregional recurrence, and 12 of the 16 patients (75%) who experienced locoregional recurrence could be salvaged by surgery. These results suggest that T2N0 laryngeal cancer may not be a systemic disease and that improvement of local control is the most important issue in the radiotherapeutic management of T2N0 laryngeal cancer, because preservation of the larynx (voice preservation) is important for maintaining the quality of life (QOL).

Jones *et al.* (19) compared the clinical outcomes and speech and voice quality between patients who received RT and those who underwent surgery for T1 to T2 laryngeal cancer and reported that although no significant difference was seen in the recurrence rate at the primary site between the 2 treatment groups, the speech and voice quality was significantly superior in the patients treated by RT as compared with those treated by surgery. However, the local control rate in cases of T2 laryngeal cancer treated by RT alone ranged from 65% to 85%, and these figures were lower than those in cases of T1 laryngeal cancer (20, 21). These results suggest that RT may be the treatment modality of choice for T2 laryngeal cancer, although much room for improvement of the radiotherapeutic outcome apparently remains.

As described in the Introduction, hyperfractionated RT is a promising approach for improvement of the local control of head-and-neck cancer. Fu *et al.* (22) reported the results of the Radiation Therapy Oncology Group (RTOG) phase III randomized study that compared hyperfractionation and 2 variants of accelerated fractionation to standard fractionation radiotherapy for locally advanced head-and-neck cancer and demonstrated that patients treated by use of the hyperfractionation and accelerated fractionation schema with concomitant boost had significantly better locoregional outcomes than did those

treated by use of the standard fractionation schema. In regard to T2N0 laryngeal cancer, Garden *et al.* (4) reported that the 5-year local-control rates in patients with T2N0 glottic cancer treated by hyperfractionated RT or conventional fractionated RT were 79% and 67%, respectively.

An alternative approach for improving the local control in cases of head-and-neck cancer is concurrent chemotherapy with RT. Pignon *et al.* (23) performed a meta-analysis of 63 trials and reported that the clinical outcomes were significantly superior with the use of concurrent CRT but not with that of induction chemotherapy or adjuvant chemotherapy. RTOG also conducted a phase II study of concurrent RT and high-dose CDDP (100 mg/m^2 given every 3 weeks during the radiation therapy) for advanced head-and-neck cancer (24) and reported a complete response rate and 4-year survival rate of 71% and 34%, respectively. Regarding concurrent CRT for laryngeal cancer, the Intergroup Trial R91-11, which compared concomitant chemoradiotherapy in a randomized fashion with induction chemotherapy followed by RT for chemoresponders and RT alone for selected cases of Stage III or limited Stage IV laryngeal cancer (25, 26), demonstrated that the locoregional control rate was significantly superior in patients who received RT and concurrent CDDP therapy (78% vs. 61% with induction CDDP plus 5-FU followed by RT, and 78% vs. 56% with RT alone). Both of the chemotherapy-based regimens suppressed distant metastases and yielded better disease-free survival rates than did RT alone: however, the overall survival rates were similar in all the 3 groups (26). The chemotherapeutic regimen in both the RTOG study and the Intergroup Trial R91-11 was high-dose CDDP at the dose of 100 mg/m^2 for 3 cycles, and the addition of intensive chemotherapy to RT was associated with significant acute toxicities as compared with that after RT alone; however, these studies were justified by the fact that they included only patients with locally advanced (Stage III and IV) head-and-neck cancer.

Regarding concurrent CRT for T2N0 laryngeal cancer, few reports have been published, partly because the addition of chemotherapy to RT might represent overtreatment for T2N0 laryngeal cancer. Needless to say, combined high-dose CDDP at the dose of 100 mg/m^2 for 3 cycles with RT may be too intensive for T2N0 laryngeal cancer. The dosing schedule for docetaxel and CDDP in this study was determined on the basis of the results of the following studies. Hainsworth *et al.* (27) reported the results of a phase I study for weekly docetaxel therapy and indicated that the maximum-tolerated dose (MTD) was 43 mg/m^2/week; however, they also suggested that weekly scheduling allowed a maximization of the docetaxel dose, with increase in the maximum-tolerated dose to 20 mg/m^2/week when the drug was used concurrently with radiation therapy (28). In this study, we adopted 10 mg/m^2 as the dose of docetaxel because weekly docetaxel was administered concomitantly with daily CDDP. Concerning the validity of applying this approach to patients with T2N0 laryngeal cancer, the doses of docetaxel and CDDP were considered to be mild as compared with those in other studies. Mudad *et al.* (29) reported the result of a dose-finding study for concomitant weekly docetaxel and CDDP therapy for 6 weeks and radiation therapy for locally advanced non–small cell lung cancer, and reported that the MTD of weekly docetaxel was 25 mg/m^2 when the drug was combined with CDDP at the dose of 25 mg/m^2 and RT for locally advanced NSCLC. The total doses of docetaxel and CDDP in the study conducted by Mudad *et al.* (29) were 150 mg/m^2 and 150 mg/m^2 and in the current study were 40 mg/m^2 and 90 mg/m^2, respectively. On the basis of these differences, the dose schedule used in this study was considered to be mild and optimal for the treatment of T2N0 laryngeal cancer. In fact, no case required transient interruption of RT because of the development of acute toxicity in the concurrent CRT group. The hematologic toxicity was also mild namely, transient Grade 2 or 3 leucopenia.

In conclusion, because this study was conducted as a nonrandomized retrospective study, no definitive conclusions can be derived. However, the results of the study did demonstrate that concurrent CRT had a positive impact on the local control of T2N0 laryngeal cancer, and that it significantly improved voice preservation. This result suggests that a prospective trial of concurrent CRT in which an optimal dosing schedule for T2N0 laryngeal cancer is used is worth consideration.

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Prostate radiotherapy

Difference in rectal dosimetry between pre-plan and post-implant analysis in transperineal interstitial brachytherapy for prostate cancer

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Abstract

***Background and Purpose*:** To investigate differences in rectal dosimetry between pre-plan ultrasonography (US) and post-implant computed tomography (CT).

***Patients and Methods*:** Subjects comprised 49 patients who underwent prostate brachytherapy using ^{125}I seed implants. Prescribed dose was 145 Gy to the periphery of the prostate. Differences in rectal dosimetry between pre-plan US and post-implant CT analysis were evaluated. In addition, patients were divided into two groups according to timing of pre-planning (pre-plan group, $n=28$; intraoperative pre-plan group, $n=21$), and differences in rectal dosimetry between groups were assessed.

***Results*:** The average of volume differences between pre-plan and post-implant analysis (pre-plan minus post-implant analysis) for all patients were follows: -0.08 cm^3 in $V60$ (volume of rectal wall receiving 60% of prescribed dose); -0.05 cm^3 in $V70$; -0.16 cm^3 in $V80$; -0.38 cm^3 in $V90$; -0.40 cm^3 in $V100$; -0.32 cm^3 in $V110$; -0.22 cm^3 in $V120$; -0.15 cm^3 in $V130$; -0.10 cm^3 in $V140$; -0.07 cm^3 in $V150$; and -0.05 cm^3 in $V160$. Apparent differences between pre-plan US and post-implant CT in rectal dosimetry were small. However, considering the steep curve of the relationship between tolerable volume and dose, a large actual difference should be assumed. No advantage was identified for the intraoperative pre-plan group. Safe volume to avoid proctitis tended to be smaller on ultrasonography than on CT at 1 month.

***Conclusions*:** The present work shows that direct comparison of CT analysis and pre-plan US is unfavorable due to large differences in these modalities and overestimation of tolerable volume. However, by comprehending the degree of difference, comparison of data from CT analysis with a US pre-plan may be feasible and useful for providing feedback between these modalities.

Keywords: Prostate cancer; Brachytherapy; Dosimetry; ^{125}I; rectum

Ultrasonography (US)-guided transperineal interstitial permanent prostate brachytherapy (TIPPB) for adenocarcinoma of the prostate is quickly growing in popularity as a therapeutic option for patients with early-stage, localized prostate cancer [2-4,11]. With TIPPB, pre-planning is performed using US before the scheduled implantation, while post-implant analysis is performed using computed tomography (CT). Inherent dosimetric differences exist between pre-plan and post-implant analyses, due to the different modalities, timings and body positions used [1,8,10,13,18]. Although one of the purposes of post-implant dosimetric analysis is to provide feedback to the clinician for improving implantation technique, little data has been reported regarding differences between the two modalities in rectal dosimetry, making feedback difficult to interpret. We believe the lack of information regarding differences between pre-plan and post-implant analysis represents a crucial issue.

Snyder et al. [14] reported on the relationship between the volume of rectal wall receiving a given dose and 5% risk of developing Grade 2 radiation proctitis at 5-years based on CT analysis at 1 month after implantation. According to their data, a steeper response curve is shown for higher dose levels. When using the volume of rectal wall receiving a high dose (e.g. 200 Gy) as an indicator of proctitis risk in preplanning, very precise conformity is required between

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US and CT analyses. The question must therefore be asked: Is there an acceptable level of conformity level between US and CT? The present study investigated differences in rectal dosimetry between pre-plan US and post-implant CT analysis.

Materials and methods

Treatment

Subjects comprised 49 patients who underwent TIPPB. The prescribed dose to the periphery of the prostate was 145 Gy. Patients were divided in two groups. In pre-plan group (n=28), dosimetry was planned based on US images taken 4 weeks before implantation [7]. In the intraoperative pre-plan group (n=21), dosimetry was planned intraoperatively based on US images taken just before implantation in the anesthetized patient. Patients underwent CT with a 2-mm slice thickness at 1 day and at 1 month after implantation. Chest and abdominal radiography was performed for every patient, and migrated seeds were checked.

Dosimetry

Both pre-plan and post-implant analysis used a radiotherapy planning system (RTPS) dedicated for TIPPB (Interplant® version 3.2 CMS), and all doses were defined using TG43 criteria [12]. In pre-planning, only the anterior one-third of the rectal wall was contoured, because the US field is restricted to this area. In post-implant CT analysis, to evaluate the rectal wall under conditions as equal as possible to those using US, only the anterior one-third of the rectal wall was contoured. The rectal wall was outlined including sphincter muscle on the same slice to prostate contouring. As described by Snyder et al. [14], the inner wall of the rectum was defined by the edge of the lumen, taking care to exclude any feces. If the lumen was absent, the inner wall was approximated based on diameter of the outer rectal wall and thickness of the rectal wall in abutting slices. A protractor was used to precisely measure one-third of the rectal wall. Contouring was performed by the same person (I.H.). Migrated seeds or seeds excreted into urine were excluded from the number of implanted seeds. Seed location was automatically checked by RTPS after inputting the number of implanted seeds. Dose volume histograms were calculated for every pre-plan and every post-implant analysis.

Study parameters and analysis

Differences in rectal wall volume receiving a given dose were evaluated as follows: (a) difference between pre-plan US and next day CT analysis ($\Delta V_{pn,D}$); and (b) difference between pre-plan US and one month CT analysis ($\Delta V_{pm,D}$).

$$\Delta V_{pn,D} = V_{pre,D} - V_{next,D} \quad (1)$$

$$\Delta V_{pm,D} = V_{pre,D} - V_{month,D} \quad (2)$$

where $V_{pre,D}$ is the volume of rectal wall receiving a given dose in preplan, $V_{next,D}$ is next day CT analysis and $V_{month,D}$ is one month CT analysis.

Dose levels examined were 10% ($V10$) to 160% ($V160$) of the prescription dose, in 10% intervals. For statistical analyses, t-tests were used.

To convert Snyder's data into a form available for US preplanning, data were modified using the value of $\Delta V_{pm,D}$. The approximated curve (Fig. 1) derived from Snyder's data is described by the function:

$$Y = -2.28X^3 + 24.38X^2 - 110X + 275.52 \quad (3)$$

We modified this function as below to describe the modified curve:

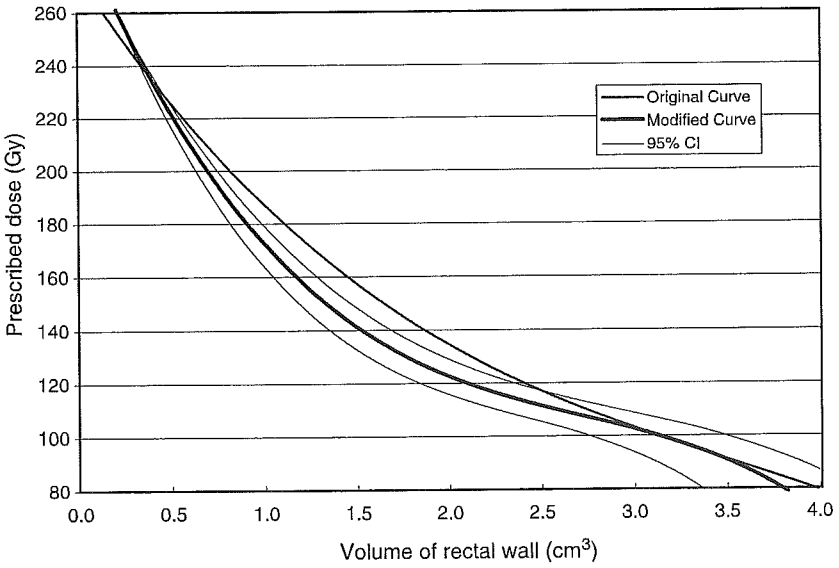

Fig. 1. Comparison of original and modified Snyder's curves. These curves show the rectal thresholds associated with ≤ 5% risk of Grade 2 proctitis at 5 years. [14].

$$Y = -2.28(X + \Delta V_{pm,D})^3 + 24.38(X + \Delta V_{pm,D})^2 - 110(X + \Delta V_{pm,D}) + 275.52 \quad (4)$$

Results

Values of $\Delta V_{pn,D}$ and $\Delta V_{pm,D}$ are shown in Table 1. Values of $\Delta V_{pm,D}$ were significantly smaller than those of $\Delta V_{pn,D}$ except at low doses. No significant difference was identified between pre-plan and intraoperative plan groups except at low dose levels.

The values of $\Delta V_{pm,D}$ from $V60$ to $V160$ were used for modifying Snyder's data, as no significant differences were detected between groups at these dose levels. Apparent differences between pre-plan US and post-implant CT analysis were small.

A comparison of the original Snyder's curve and that modified by function (4) is shown in Fig. 1. The safe volume to avoid Grade 2 proctitis tended to be smaller on US than on CT at 1 month after implantation.

Discussion

Although the apparent difference between pre-plan and post-implant analysis is small, especially in high dose levels, considering the steep curve of the relationship between tolerable volume and dose, a large actual difference should be assumed (Fig. 1). According to Snyder's original data, an interval of only 0.1 cm^3 is present between a tolerance volume of 0.5 cm^3 to 220 Gy and 0.4 cm^3 to 240 Gy, whereas a mean difference of 0.05 cc was seen for the same dose levels in our data (Table 1). A difference of 0.05 cm^3 thus warrants a difference of 10 Gy. The finding of differences between pre-plan and post-implant analysis indicates that direct comparison of data from CT analysis and preplan US is not useful.

The modified Snyder's curve suggests that the safe volume to avoid Grade 2 proctitis tends to be smaller on US than on CT analysis at 1 month after implantation. The difference varies widely and a risk of rectal overdosing is present even after taking these differences into account. Although no clear explanation of the difference is apparent, we consider that shape of the rectum is likely to be involved. On preplanning with US, shape of the rectum changes with insertion of the probe, taking on an unnaturally straight course. The, natural shape of the rectum is bending (Fig. 2). On post-implant CT analysis, shape of the rectum is naturally bending and the anterior rectal wall would be closer to the mid-portion of the prostate than seen on US. We consider that the dose of rectum wall tends to be smaller on US than on CT analysis.

The rectum is a difficult organ to spare in both prostate brachytherapy and external radiotherapy, due to close proximity to the prostate, and radiation proctitis represents a potential late complication of TIPPB [5,19]. However, the definition of rectal dose has not been standardized in prostate brachytherapy due to personal preferences and the capabilities of computer software. Definitions reported in previous studies include rectal surface dose [6,17], rectal wall dose [14], dose to the entire rectum including filling [6,9,15], and dose to the rectal mucosa (inner wall of the rectum) [8]. These various definitions reflect both personal preference and the capability of computer software used for prostate brachytherapy. If the risk of late rectal morbidity is defined on the basis of a particular definition of rectal dose, the results may not be useful or interpretable by clinicians using a different definition.

Table 1
Comparison between $\Delta V_{pn,D}$ and $\Delta V_{pm,D}$

	$\Delta V_{pn,D}$ $n=49$		$\Delta V_{pm,D}$ $n=49$		
	Mean (cm^3)	(95% CI)	Mean (cm^3)	(95% CI)	p
$V10$	−1.88	(−2.58, −1.19)	−1.53	(−2.28, −0.79)	0.195
$V20$	−1.56	(−2.24, −0.87)	−1.29	(−2.02, −0.55)	0.280
$V30$	−0.98	(−1.66, −0.30)	−0.92	(−1.63, −0.21)	0.791
$V40$	−0.22	(−0.84, 0.41)	−0.53	(−1.18, 0.12)	0.088
$V50$	0.36	(−0.15, 0.86)	−0.28	(−0.81, 0.25)	<0.001*
$V60$	0.69	(0.29, 1.09)	**−0.08**	**(−0.50, 0.34)**	<0.001*
$V70$	0.72	(0.41, 1.04)	**−0.05**	**(−0.39, 0.29)**	<0.001*
$V80$	0.53	(0.28, 0.78)	**−0.16**	**(−0.45, 0.13)**	<0.001*
$V90$	0.19	(0.00, 0.37)	**−0.38**	**(−0.60, −0.16)**	<0.001*
$V100$	0.03	(−0.10, 0.02)	**−0.40**	**(−0.57, −0.23)**	<0.001*
$V110$	−0.02	(−0.11, 0.07)	**−0.32**	**(−0.44, −0.19)**	<0.001*
$V120$	−0.03	(−0.10, 0.04)	**−0.22**	**(−0.32, −0.13)**	<0.001*
$V130$	−0.03	(−0.08, 0.02)	**−0.15**	**(−0.22, −0.08)**	0.001*
$V140$	−0.02	(−0.06, 0.02)	**−0.10**	**(−0.16, −0.05)**	0.003*
$V150$	−0.02	(−0.05, 0.01)	**−0.07**	**(−0.11, −0.03)**	0.016*
$V160$	−0.01	(−0.03, 0.01)	**−0.05**	**(−0.08, −0.01)**	0.042*

Value in bold were used for modifyng Snyder's data.

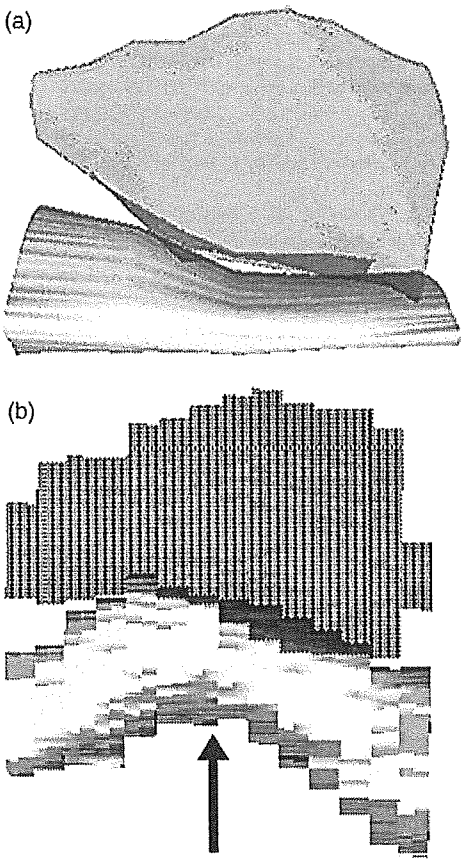

Fig. 2. Differences in rectal shape between US and CT. Although the rectum has an unnaturally straight shape due to the probe for US (a), the rectum in CT displays natural bends (b).

Absolute volume was used as opposed to percentage volume for the same reasons described as Snyder et al. [14]. First, proctitis was hypothesized to depend only on the absolute amount of rectal tissue receiving a given dose, rather than the percentage of entire rectal tissue receiving that same dose. Second, possible errors in underestimating or overestimating total rectal volume are reduced when deciding where the rectum begins and ends or in outlining the inner wall of the rectum. This approach is less dependent on contoured rectal volume.

The volume at low-dose levels such as *V*10 should be strongly influenced by contouring, as 10% of prescribed dose (only 14.5 Gy) is distributed widely. However, we think the volume at high-dose levels is unlikely to be strongly influenced by contouring. This is because only a very small portion of rectum close to the radiation source is exposed to high-dose radiation. We thus consider the influence of contouring errors on the results would be within acceptable limits.

The definition of rectal surface dose was not used, because data generated for a dose-surface relationship cannot be converted into the more widely used dose-volume relationship to predict complications. The definition of rectal mucosal dose was not used because a rectal obturator needs to be inserted before CT to identify the anterior rectal mucosa on each CT slice. Use of an obturator is not practical for large groups of patients, and may also distort the rectum.

The value of $\Delta V_{pm,D}$ was significantly smaller than $\Delta V_{pn,D}$ except at low-dose levels (Table 1). This finding confirms the fact that volume receiving a given dose on CT analysis at 1 month post-implant was larger than that on CT analysis at 1 day post-implant, according to the function:

$$\Delta V_{pn,D} - \Delta V_{pm,D} = V_{month} - V_{next} \quad (5)$$

The fact that the received dose would be increasing in 1 month later has been reported previously [16]. Prostate swelling is considered to influence dose at the rectal wall.

In conclusion, the present study shows that direct comparison of post-implant CT analysis and pre-plan US is unfavorable due to large differences between these modalities. However, a relationship exists between pre- and post-plan rectal volume receiving a certain dose. By identifying the degree of difference, conversion of data from CT analysis into US pre-plan may be feasible and useful for feedback between modalities.

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CLINICAL INVESTIGATION **Lung**

CLINICAL OUTCOMES OF A PHASE I/II STUDY OF 48 Gy OF STEREOTACTIC BODY RADIOTHERAPY IN 4 FRACTIONS FOR PRIMARY LUNG CANCER USING A STEREOTACTIC BODY FRAME

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Purpose: To evaluate the clinical outcomes of 48 Gy of three-dimensional stereotactic radiotherapy in four fractions for treating Stage I lung cancer using a stereotactic body frame.

Methods and Materials: Forty-five patients who were treated between September 1998 and February 2004 were included in this study. Thirty-two patients had Stage IA lung cancer, and the other 13 had Stage IB lung cancer where tumor size was less than 4 cm in diameter. Three-dimensional treatment planning using 6–10 noncoplanar beams was performed to maintain the target dose homogeneity and to decrease the irradiated lung volume >20 Gy. All patients were irradiated using a stereotactic body frame and received four single 12 Gy high doses of radiation at the isocenter over 5–13 (median = 12) days.

Results: Seven tumors (16%) completely disappeared after treatment (CR) and 38 tumors (84%) decreased in size by 30% or more (PR). Therefore, all tumors showed local response. During the follow-up of 6–71 (median = 30) months, no pulmonary complications greater than an National Cancer Institute-Common Toxicity Criteria of Grade 3 were noted. No other vascular, cardiac, esophageal, or neurologic toxicities were encountered. Forty-four (98%) of 45 tumors were locally controlled during the follow-up period. However, regional recurrences and distant metastases occurred in 3 and 5 of T1 patients and zero and 4 of T2 patients, respectively. For Stage IA lung cancer, the disease-free survival and overall survival rates after 1 and 3 years were 80% and 72%, and 92% and 83%, respectively, whereas for Stage IB lung cancer, the disease-free survival and overall survival rates were 92% and 71%, and 82% and 72%, respectively.

Conclusion: Forty-eight Gy of 3D stereotactic radiotherapy in 4 fractions using a stereotactic body frame is useful for the treatment of Stage I lung tumors. © 2005 Elsevier Inc.

Stereotactic body radiotherapy, Conformal radiotherapy, Lung cancer, Stereotactic body frame, Stereotactic radiotherapy.

INTRODUCTION

Stereotactic radiotherapy (SRT) for extracranial tumors has been recently performed to treat primary and secondary lung cancer and has subsequently been named stereotactic body radiotherapy. The advantages of hypofractionated radiotherapy for treating lung tumors are a shortened treatment course that requires fewer trips to the clinic than a conventional program and the adoption of a smaller irradiated volume allowed by greater setup precision. The disadvantages are uncertain effects of altered fractionation and the theoretical risk of worsening the ratio of normal tissue to tumor tissue through the use of a high dose per fraction. We previously published our setup accuracy (1), initial clinical results (2), computed tomography (CT) change after SRT (3), positron emission tomography (PET) evaluation after SRT (4) and treatment planning for SRT (5). In this study, the clinical results of lung cancer on our initial 5 years' worth of experiences are evaluated.

METHODS AND MATERIALS

Stereotactic radiotherapy was started for patients with lung tumor in July 1998 at Kyoto University. An integrated radiother-

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apy system, including a CT simulator (CT-target, Shimadzu Corp., Kyoto, Japan), a three-dimensional (3D) radiotherapy treatment planning (RTP) machine (CADPLAN Ver 3.1, ECLIPSE Ver 7.1, Varian Associates, Palo Alto, CA), and a linear accelerator (CLINAC 2300C/D, Varian Associates) were in clinical use, and, in 1998, a stereotactic body frame (Stereotactic Body Frame, Elekta Corp., Stockholm, Sweden) was introduced for stereotactic body radiotherapy (SBRT).

Patients were fixed in the stereotactic frame (6, 7) using a vacuum pillow, and thereafter, six points were marked on the anterior chest wall with a laser marker and Indian ink. Then, respiratory movement of the tumor was observed with an X-ray simulator, where it was regulated when it was larger than 8 mm in the craniocaudal direction. A device called a diaphragm control, which is a board that pushes against the epigastric abdominal wall, was used for respiratory control. Serial CT scanning with 1 to 3 mm intervals around the tumor was performed over 4 s per slice without using the breath-hold technique. After the patient left the room, the target outlines of internal target volume (ITV) were drawn using the RTP machine. Our CT images included the respiratory movement of the target. Therefore, ITV including internal margins with clinical target volume (CTV) was delineated. ITVs and CTVs were not edited for anatomy. The setup margins between ITV and planning target volume (PTV) were 5 mm for the anteroposterior, 5 mm for the lateral, and 8–10 mm for the craniocaudal directions. Selection of the optimal direction of noncoplanar beams or dynamic arcs was performed by three experienced oncologists and technologists with the goal of the RTP being 6 to 10 portals for noncoplanar static beams. The beam energy used was 6 MV and the isocenter was single for all beams. All patients received four single treatments with 12 Gy of radiation prescribed at the isocenter. The mean ITV volume was 13 mL. The target dose homogeneity of ITV was within 20%, and the irradiated lung volume for >20 Gy (V20) was made as small as possible. As a result, the minimal and maximal ITV dose per fraction was 92% and 102.6%, respectively. The V20 ranged from 0.3% to 11.6% with a mean value of 4.3%. The irradiated dose–volume histograms of the other organs at risk, including the spinal cord, pulmonary artery, bronchus, and heart were also calculated. As a result, the mean and maximal single dose per fraction was 0.5 and 1.9 Gy for esophagus, 0.8 and 1.8 Gy for bronchus, 0.8 and 2.6 Gy for pulmonary artery, 0.3 and 2.7 Gy for heart, and 0.1 and 0.5 Gy for spinal cord, respectively (5). The target reference point dose was defined at the isocenter of the beam.

Before each treatment, anteroposterior and lateral portal films were taken for verification. The position of each patient was verified by three experienced oncologists and technologists at each treatment time. When the setup error was larger than 2 mm between the X-ray simulation film and portal film in any direction, the patient was repositioned and portal films were taken and verified again. Fractionated radiotherapy was performed with 4 days of 12 Gy over 5 to 13 (median = 12) days.

Using a linear-quadratic model (8), the biologic effective dose (BED) was here defined to be $nd\ (1+d/\alpha-\beta)$ Gy, where n is the fractionation number, d is the daily dose, and the α-β ratio was assumed to be 10 for tumors. The value was 105.6 Gy-BED for 48 Gy in four fractions (our study).

Forty-five patients with histologically confirmed Stage I primary lung cancer were treated between September 1998 and February 2004. Of them, 32 patients were Stage IA (T1N0M0); the other 13 were Stage IB (T2N0M0). Thirty-three patients were males and 12 were females, respectively. Their ages ranged between 51 and 87 years, and 77 years was the median for Stage IA, whereas they ranged between 68 and 80 years with 73 years as the median for Stage IB. Sixteen Stage IA patients were inoperable and the other 16 were operable but refused surgery, whereas 11 of the Stage IB patients were inoperable and the other 2 refused surgery. The histologies of the Stage IA patients were 16 squamous cell carcinoma, 15 adenocarcinoma, and 1 non–small-cell cancer and the Stage IB histologies were 8 squamous cell carcinoma and 5 adenocarcinoma.

The follow-up period was 6 to 71 (median = 30) months for the Stage IA patients and 6 to 61 (median = 22) months for Stage IB patients.

The eligibility criteria for the patients for Stage I primary lung cancer were *(1)* surgery was contraindicated or refused, *(2)* the patient could remain stable in the body frame for longer than 30 min (World Health Organization performance status ≤2), *(3)* oxygen was not required under normal conditions, *(4)* no active interstitial pneumonitis, and *(5)* written informed consent was obtained.

All patients were staged by bronchoscopy, CT, and after 1999 18-fluoro-deoxy-glucose (FDG)-PET scanning. The initial CT-based stage was changed in 2 patients with FDG-PET. For follow-up after the SRT, chest films were taken every month, and CT films were taken every 2 to 4 months for the first year and every 6 months between 1 year and 5 years after treatment. Toxicity was evaluated using the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Version 2.0.

Local tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors criteria (9). Differentiation between radiation pneumonitis and residual tumor is difficult. However, new irregular densities which appeared within radiation field 2 to 6 months after radiotherapy and were thereafter reduced in size were considered to be radiation pneumonitis. All cases whose tumors decreased in size by 30% or more after radiotherapy were classified as PR. The cumulative survival rates were calculated using the Kaplan-Meier method.

RESULTS

Local tumor response

Of the 45 tumors, 7 (6 T1, 1 T2) (16%) completely disappeared after treatment (CR) and 38 (84%) decreased in size by 30% or more (PR). Also, all tumors showed a local response, but the distinction between tumor control from therapeutic effect was difficult. We considered any residual density surrounding a tumor after radiotherapy to be PR, and therefore the pathologic CR rate may have been much higher than 16%. During the follow-up, only one local failure that may be considered either marginal failure or regional nodal failure was encountered at 24 months, as shown in Fig. 1.

Toxicities

No severe symptomatic pulmonary complications (NCI-CTC Grade 3 or larger) were encountered. However, 2 patients (4%)—1 with T1 and the other with T2—received steroids after symptomatic pneumonitis and were categorized as NCI-CTC Grade 2. CT exams every 2 to 4 months after SRT showed mild pulmonary CT changes (NCI-CTC Grade 1) in the other 43 (96%) cases. Symptoms such as a

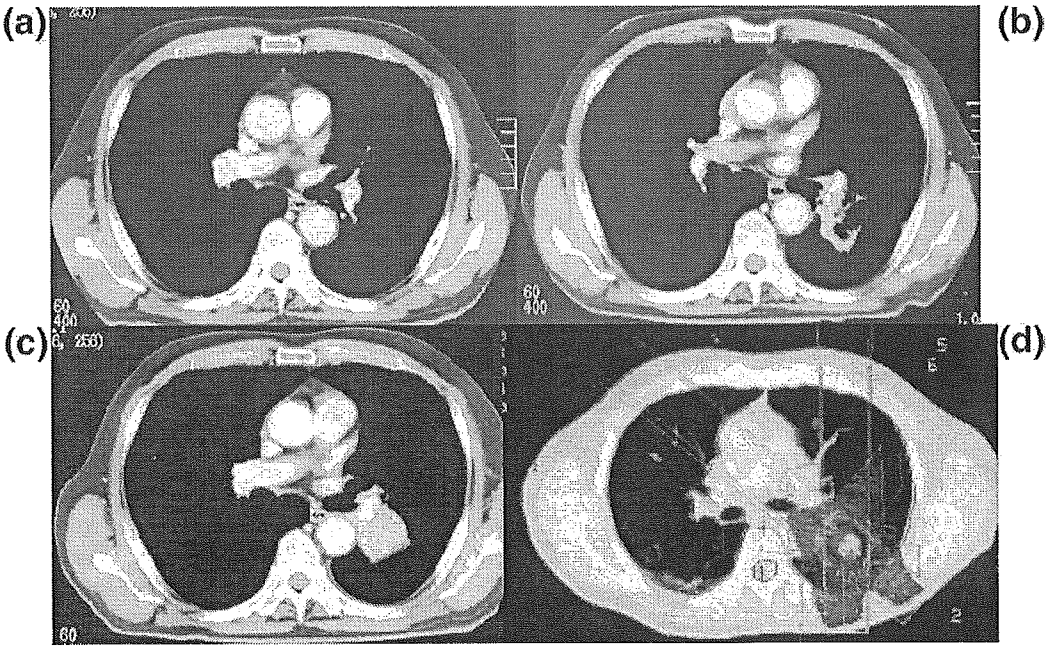

Fig. 1. A case of T1N0M0 lung cancer showing recurrence after stereotactic radiotherapy (SRT). The computed tomography images at 7 months (b, upper right) after SRT demonstrated a new soft-tissue density as well as radiation-induced lung damage (RILD) in the marginal area of the SRT that could not be observed at 2 months (a, upper left) after SRT. Initially, the density was considered to be RILD. However, the density increased in size at 16 months (c, lower left). The tumor was finally diagnosed as a local failure from either marginal failure or regional lymph nodal failure. The dose distributions are also shown (d, lower right).

mild cough, general malaise, and slight fever were present in 10 patients (22%) and were relieved without steroids at the outpatient clinic. A CT change in the liver was temporarily observed with the transient elevation of liver enzymes in a patient with a tumor in the right lower lung. As a result, no vascular complications, cardiac complications, esophageal complications, or neurologic complications were encountered.

Survival

T1N0M0 (Stage IA) primary lung cancer. For the 32 patients with histologically confirmed T1N0M0 Stage IA primary lung cancer, all but one of the tumors were locally controlled during the follow-up period. In 1 patient, a tumor locally recurred 24 months after SRT. In 3 patients, cancer recurred in regional hilar or mediastinal lymph nodes after 6, 12, and 24 months; in 4 patients, lung metastases after 2, 3, 20, and 55 months; and in the remaining patient, bone metastases were noted after 15 months without local recurrence. One patient died during the follow-up period from intercurrent causes.

Thus, the 1-year and 5-year local relapse-free survival rates were 100% and 95% as shown in Fig. 2. The disease-free survival rates after 1, 2, 3, and 5 years were 80%, 72%, 72%, and 72%, respectively, and the overall survival rates were 93%, 90%, 83%, and 83%, respectively.

T2N0M0 (Stage IB) primary lung cancer. Of the 13 patients with T2N0M0 Stage IB primary lung cancer, all tumors were locally controlled during the follow-up period. In 2 patients, cancer recurred distantly in the lung after 7 and 52 months, in 1 patient brain metastasis occurred after 10 months, and in the remaining patient liver metastases was noted after 12 months without local recurrence. Two patients died during the follow-up period from intercurrent causes.

Thus the 1- to 5-year local relapse free survival rates were also 100%. The disease-free survival after 1, 2, 3, and 5 years were 92%, 71%, 71%, and 71%, respectively, and the overall survival rates were 82%, 72%, 72%, and 72%, respectively, as shown in Fig. 3.

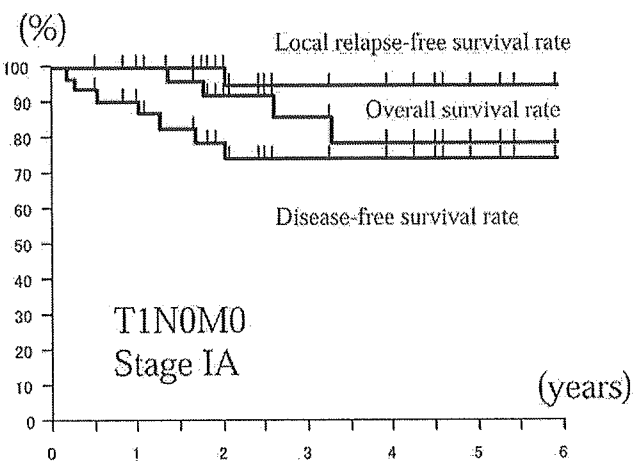

Fig. 2. The overall, local relapse-free, and overall disease-free survival rates of the patients with Stage IA (T1N0M0) lung cancer.

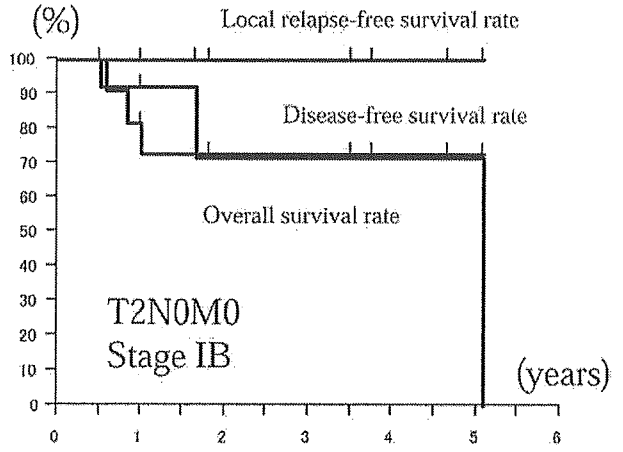

Fig. 3. The overall, local relapse-free, and overall disease-free survival rates of the patients with Stage IB (T2N0M0) lung cancer.

DISCUSSION

Local control rates of primary lung cancer with SRT has been previously reported by several authors: 94% (47/50) for 50 to 60 Gy in five fractions with a median follow-up of 36 months (10), 92% (22/24) for 60 Gy in eight fractions with a median follow-up of 24 months (11), 87% (30/37) for 60 Gy in three fractions with a median follow-up of 15 months (12), 85% for 48 to 60 Gy in eight fractions with a median follow-up of 17 months (13), 95% for 45 to 56.2 Gy in three fractions with a median follow-up of 10 months (14), and 97% (44/45) for 48 Gy in four fractions with a median follow-up of 22 to 30 months (as shown in Table 1 in this study). Using a linear-quadratic model with an α-β ratio = 10, our fractionation of 12 Gy × 4 was equal to 2 Gy × 44 = 88 Gy. A BED larger than 100 Gy may be effective for STI of solitary lung cancer with a local control rate of more than 85%. Timmerman (12) concluded that a 60 Gy marginal dose in three fractions is the limiting dose. Considering our clinical results, a further dose escalation study of more than 48 Gy in four fractions is not necessary for tumors smaller than 4 cm in diameter.

The current standard choice for Stage IA lung cancer treatment is lobectomy (15). However, for many patients this is not indicated because of accompanying diseases, such as chronic obstructive pulmonary disease, cardiac disease, and diabetes. For them, various minimal surgical techniques are indicated, including wedge resection and video-assisted thoracoscopic surgery as well as ablation. The local control rates of various other modalities for primary Stage I lung cancer previously reported was 93% for wedge resection and 83–95% for VATS and the 5-year survival rates were 82% and 50–70%, respectively (16).

Onishi (17) recently reported results for 13 institutions in Japan, where they summarized 245 patients, 155 with Stage IA lung cancer and 90 with Stage IB lung cancer. The operable and inoperable patients totalled 87 and 158, respectively, and their results showed that the intercurrent death rate was especially high in the inoperable patient group. Moreover, the 5-year survival rates of operable patients irradiated with more than BED = 100 Gy was 90% for Stage IA and 84% for Stage IB, and their clinical results were as good as those for surgery.

During our follow-up, no serious complications were encountered, and only mild radiation pneumonitis (NCI-CTC Grade 2 or less) was detected by CT. Graham (18) reported that the tolerance of the pulmonary dose >20 Gy (V20) is 25% of the whole lung with low risk. Our >20 Gy irradiated volume (V20) of the whole lung was 1.0% to 11.6% (average = 4.5%), which was markedly smaller than that in their report. However, the V20 of the standard fraction with 2 Gy and that of the SRT with 12 Gy must be different. Further close follow-up is required. Another concern of our study was the effects on the central bronchus, pulmonary artery, esophagus, heart, and spinal cord. The effects of the hypofractionated dose on the main bronchus, pulmonary artery, heart, and esophagus have not been followed for a long enough time. For our clinical experiences thus far, no severe complications have been encountered. However, lethal pulmonary bleeding and esophageal ulcer have been previously reported by other institutions (19). A case with a skin ulcer that finally caused thoracocutaneous fistula and another case with acute cholecystitis due to abdominal press were reported in Japan. Therefore, long-term follow up is still necessary.

Considering the tumor control dose, after dose escalation from 40 Gy to 48 Gy, only one local recurrence was encountered for primary lung cancer, and no severe complications were encountered for all tumors. Therefore, we will continue this schedule for the treatment of primary lung cancer. Systemic chemotherapy may be considered when the local tumor is well controlled and regional/distant metastases are frequent. On the other hand, the underlying pulmonary diseases could be a limiting factor for SRT of a solitary lung tumor. However, this should be discussed for each case. In our cases, 1 patient who had severe interstitial pneumonitis died of progression of pneumonitis 6 months after SRT. Because the occurrence of this pneumonitis was far distant from the irradiated tumor in the opposite lung, death was considered to be unrelated to the treatment. However, the effect of the scattered radiation dose cannot be completely neglected and the indications of SRT for the patients with interstitial pneumonitis should be limited. Our current indications are that a patient does not require oxygen under normal conditions and has no active interstitial pneumonitis shadow on a chest X-ray film. If these requirements are satisfied, this treatment can be performed without serious complications.

Recently, we started a multi-institutional Phase II study for T1N0M0 non–small-cell lung cancer under Japan Clinical Oncology Group (http://www.jcog.jp/) number 0403. Sixteen institutions have entered together and started the same dose SBRT with 48 Gy at the isocenter in four fractions for T1N0M0 lung cancer. The results of SRT for inoperable and operable Stage I lung cancer patients are awaited.