(D95), and the dose to 10% volume (D10) of the PTV was <110% of the prescribed dose to the PTV. When the prescribed dose to the PTV for the GTV was 70 Gy in 35 fractions, the maximum dose constraints used in the inverse planning for the spinal cord, brain, ipsilateral parotid gland and contralateral parotid gland were 40, 50, 25–30 and 20–25 Gy, respectively.

Treatment Delivery and Quality Assurance

Treatment was delivered using dynamic multileaf collimation with a Clinac-600C accelerator (Varian Associates) equipped with a 40 leaf dynamic multileaf collimator. Beam energy of 4 MV X-rays was used. The daily treatment time was 15–20 min.

During radiotherapy with IMRT, routine quality assurance (QA) was crucial. To verifiy the leaf motion of each beam, various QA performances were done. Details of QA procedures at our hospital have been described elsewhere (13).

Assessment of Xerostomia

Xerostomia was scored according to the subjective assessment of Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late salivary gland toxicity. Slight dryness not affecting QOL correlated with grade 1 toxicity, and moderate dryness requiring a water bottle correlated with grade 2 toxicity. Severe dryness causing a profound change in QOL was grade 3. Xerostomia was scored when acute mucositis subsided 3–4 months after the start of IMRT. Thereafter, xerostomia was scored every 2–3 months, up to 24 months of treatment. In the present analysis, the xerostomia score after 3–4 months of treatment was used as an end-point.

Dosimetric Parameters of the Parotid Glands

For all patients, dose–volume histograms were calculated for CT-1 and CT-2. The volumes of the parotid glands on CT-1 and CT-2 and the mean radiation doses to the contralateral and ipsilateral parotid glands were calculated for each patient. The mean doses to a parotid gland on CT-1 and CT-2 were added together to obtain the mean dose for the entire treatment.

RESULTS

The mean dose to the contralateral parotid gland could be reduced to 24.0 ± 6.2 Gy by IMRT. The mean dose to the ipsilateral parotid gland was 30.3 ± 6.6 Gy. In the 33 patients, xerostomia of grades 0, 1, 2 and 3 were noted in one, 18, 12 and two patients, respectively. Correlations between the grade of xerostomia and various dosimetric parameters were analyzed by the Spearman rank correlation with correction for ties. The mean dose to the contralateral parotid gland was not significantly correlated with the grade of xerostomia (Fig. 1, $P = 0.129$). Similarly, no significant correlation was noted for the mean dose to the bilateral parotid glands ($P = 0.287$). On the other hand, the initial volume of the parotid glands was significantly correlated with the grade of xerostomia (Fig. 2, $P = 0.040$).

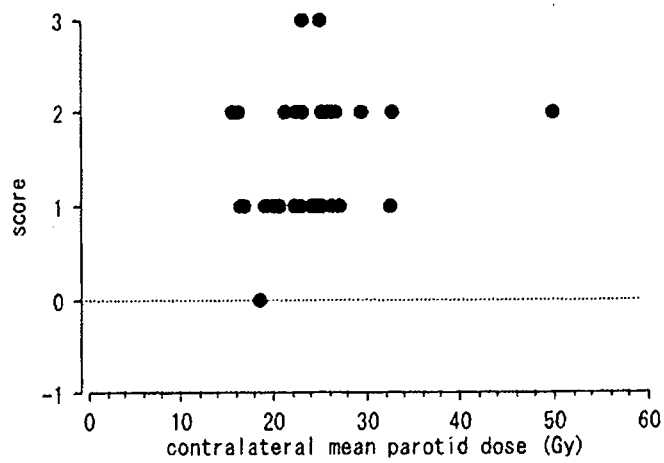

Figure 1. No significant correlation was noted between xerostomia score at 3–4 months and the mean dose to the contralateral parotid gland.

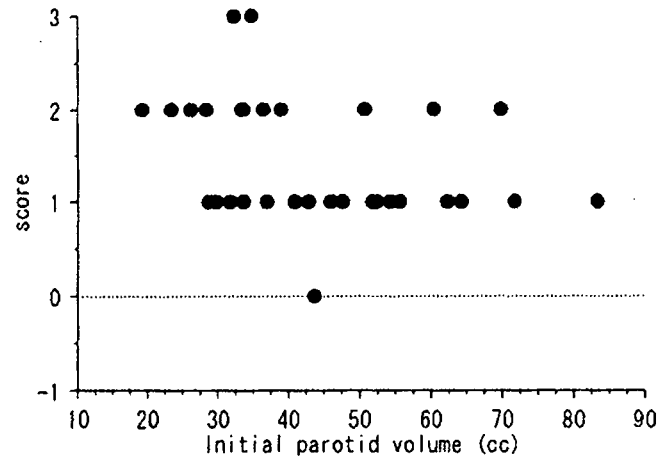

Figure 2. Correlation between xerostomia score at 3–4 months and the initial volume of the parotid glands.

Table 2 shows the xerostomia score according to the initial parotid gland volume. Of the 17 patients with smaller parotid glands with volumes equal to or less than the median volume (38.8 ml) on CT-1, nine had grade 2 xerostomia and two had grade 3 xerostomia (65%), whereas only three (19%) of 16 patients with larger parotid glands had grade 2 xerostomia ($P < 0.05$: χ^2 test with Yates' correction). The mean doses to the contralateral parotid gland did not differ between patients with smaller (25.3 ± 7.6 Gy) or larger parotid glands (22.6 ± 3.7 Gy).

Interestingly, parotid glands regressed significantly during the course of IMRT. Figure 3 shows the changes in the parotid volume between CT-1 and CT-2 for each patient. The mean ± SD and median of parotid gland volumes had decreased significantly from CT-1 (43.1 ± 15.2 and 38.8 ml) to CT-2 obtained after 3–4 weeks of IMRT [32.0 ± 11.4 ml (74%) and 30.4 ml; $P < 0.0001$, paired t-test]. The regression

Table 2. Xerostomia according to the initial volume of the parotid glands

Group	Smaller parotid	Larger parotid
No. of patients	17	16
Parotid volume	≤38.8 ml	>38.8 ml
Range	19.3–38.8 ml	40.7–83.2 ml
Median	32.1 ml	54.1 ml
Xerostomia at 3–4 months		
Grade 0	0	1
Grade 1	6	12
Grade 2	9	3
Grade 3	2	0
Dose to the contralateral parotid gland (mean ± SD) (NS)	25.3 ± 7.6 Gy	22.6 ± 3.7 Gy

NS, not significant.

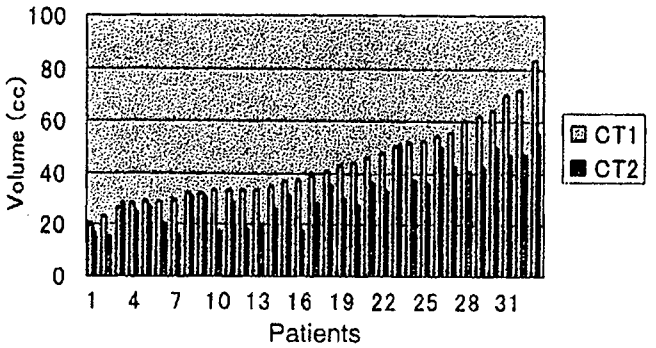

Figure 3. Changes in parotid volume between CT-1 and CT-2 for each patient. The mean volume of the bilateral parotid glands was significantly higher on CT-1 (43.1 ± 15.2 ml) than on CT-2 (32.0 ± 11.4 ml; $P < 0.0001$, paired t-test).

rate of parotid glands was not significantly correlated with the grade of xerostomia ($P = 0.186$).

DISCUSSION

In the present study, IMRT reduced the radiation dose to the parotid glands in patients with pharyngeal cancers, and resulted in a sparing of salivary function. Although the mean dose to the contralateral parotid gland was reduced to 24.0 ± 6.2 Gy, xerostomia of grade 2–3 was still noted in 14 (42%) of the 33 patients evaluated. To evaluate the predictors of xerostomia, dosimetric parameters of the parotid glands were compared with the grade of xerostomia. Many investigators have demonstrated a correlation between mean dose to the parotid gland and a reduction in stimulated saliva output or xerostomia-related QOL scores (1,4,6,14). Mean radiation doses reported to cause significant salivary reduction range from 26 to 39 Gy (1,2).

In the present study, however, the mean dose to the parotid glands was not correlated with the xerostomia score. Possible reasons for this finding are that all patients received bilateral neck irradiation with IMRT and that the mean doses to the contralateral parotid gland were, except in one patient, within a relatively narrow range (16–33 Gy, with a mean of 24.0 Gy) (Fig. 1). Concurrent chemotherapy given for 23 patients (70%) may also affect the degree of xerostomia, although the incidence of grade 2, 3 xerostomia was not affected by concurrent chemotherapy in the present study.

In addition to the relatively uniform dose to the contralateral parotid gland, the xerostomia score as an end-point was not more accurate than a more complicated xerostomia-specific questionnaire or measurement of saliva from the stimulated parotid gland to evaluate its function (1,4,6,14). In the present study, the xerostomia score in patients who needed to carry a water bottle or artificial saliva was classified as grade 2.

An important finding of this study was that the initial volume of the parotid glands is significantly correlated with the grade of xerostomia (Fig. 2 and Table 2). Several investigators have also noted the importance of parotid gland volume. Amosson et al. (6) analyzed the dosimetric predictors of xerostomia in patients with head and neck cancer treated with IMRT and demonstrated that patients reporting xerostomia had a significantly higher contralateral parotid volume receiving >25 Gy than did patients reporting adequate saliva. Eneroth et al. (15) have reported that large parotid glands have better pre-irradiation function, which is extinguished at much higher RT doses than is that of small parotid glands. It is very likely that the absolute volume of the parotid glands reflects the reserve of saliva output and becomes a predictor of xerostomia in parotid-sparing IMRT.

The volume of the parotid glands decreased significantly during the course of IMRT (Fig. 3). Recently, a similar finding has been reported by Barker et al. (16). They measured the volume and position of the parotid glands by serial CT examinations during RT for head and neck cancer, and found that parotid glands decreased in volume (0.6%/day of initial volume) and shifted medially. In the present study, parotid glands regressed to 74% of the initial volume at the third to fourth week of the treatment, which is very similar to the results reported by Barker et al. (16).

The radiosensitivity of the parotid glands is apparently high. In the first week of conventional RT for head and neck cancer, after only 10 Gy has been delivered, salivary output declines by 60–90% (2,5). Experiments with rhesus salivary glands have shown acute degeneration and interphase cell death of serous cells 24 h after irradiation with 2.5–15 Gy (17). In addition, fractionation had no significant sparing effect on parotid gland function (17). The CT-2 for boost IMRT was performed at the third or fourth week of RT. At that time, accumulated mean doses to the parotid glands were 10–15 Gy. This small RT dose can cause significant loss of serous acini and reduce parotid volume.

To evaluate the dose–volume histograms of parotid glands, the change in parotid volume during IMRT should be considered. When only CT scans obtained before RT are used for treatment planning, the dosimetric parameters for the parotid gland may not be sufficiently accurate. As the gross tumor volumes also decreased significantly during the course of

fractionated RT (16), serial imaging and sequential IMRT boost planning may be necessary, although it is an expensive and time-consuming strategy.

In conclusion, the initial volume of the parotid glands is a predictor for xerostomia, and parotid volume regresses significantly during IMRT.

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References

1. Chao KS. Protection of salivary function by intensity-modulated radiation therapy in patients with head and neck cancer. *Semin Radiat Oncol* 2002;12(Suppl 1):20–5.
2. Eisbruch A, Ship JA, Kim HM, Ten Haken RK. Partial irradiation of the parotid gland. *Semin Radiat Oncol* 2001;11:234–9.
3. Franzen L, Funegard U, Ericson T, Henriksson R. Parotid gland function during and following radiotherapy of malignancies in the head and neck. A consecutive study of salivary flow and patient discomfort. *Eur J Cancer* 1992;28:457–62.
4. Lin A, Kim HM, Terrell JE, Dawson LA, Ship JA, Eisbruch A. Quality of life after parotid-sparing IMRT for head-and-neck cancer: a prospective longitudinal study. *Int J Radiat Oncol Biol Phys* 2003;57:61–70.
5. Mossman KL. Quantitative radiation dose–response relationships for normal tissues in man. II. Response of the salivary glands during radiotherapy. *Radiat Res* 1983;95:392–8.
6. Amosson CM, Teh BS, Van TJ, Uy N, Huang E, Mai WY, et al. Dosimetric predictors of xerostomia for head-and-neck cancer patients treated with the smart (simultaneous modulated accelerated radiation therapy) boost technique. *Int J Radiat Oncol Biol Phys* 2003;56:136–44.
7. Chao KS, Majhail N, Huang CJ, Simpson JR, Perez CA, Haughey B, et al. Intensity-modulated radiation therapy reduces late salivary toxicity without compromising tumor control in patients with oropharyngeal carcinoma: a comparison with conventional techniques. *Radiother Oncol* 2001;61:275–80.
8. Chao KS, Deasy JO, Markman J, Haynie J, Perez CA, Purdy JA, et al. A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three-dimensional radiation therapy: initial results. *Int J Radiat Oncol Biol Phys* 2001;49:907–16.
9. Lee N, Xia P, Quivey JM, Sultanem K, Poon I, Akazawa C, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. *Int J Radiat Oncol Biol Phys* 2002;53:12–22.
10. Suzuki M, Nishimura Y, Nakamatsu K, Kanamori S, Koike R, Kawamoto M, et al. Phase I study of weekly docetaxel infusion and concurrent radiation therapy for head and neck cancer. *Jpn J Clin Oncol* 2003;33:297–301.
11. International Commission on Radiation Units and Measurements (ICRU). Report number 50: prescribing, recording and reporting photon beam therapy. Bethesda, Maryland: ICRU;1993.
12. International Commission on Radiation Units and Measurements (ICRU). Report number 62: prescribing, recording and reporting photon beam therapy (supplement to ICRU Report 50). Bethesda, Maryland: ICRU;1999.
13. Suzuki M, Nakamatsu K, Kanamori S, Okumra M, Uchiyama T, Akai F, et al. Feasibility study of the simultaneous integrated boost (SIB) method for malignant gliomas using intensity modulated radiotherapy (IMRT). *Jpn J Clin Oncol* 2003;33:271–7.
14. Eisbruch A, Kim HM, Terrell JE, Marsh LH, Dawson LA, Ship JA. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2001;50:695–704.
15. Encroth CM, Henrikson CO, Jakobsson PA. Pre-irradiation qualities of a parotid gland predicting the grade of functional disturbance by radiotherapy. *Acta Otolaryngol* 1972;74:436–44.
16. Barker JL Jr, Garden AS, Ang KK, O'Daniel JC, Wang H, Court LE, et al. Quantification of volumetric and geometric changes occurring during fractionated radiotherapy for head-and-neck cancer using an integrated CT/linear accelerator system. *Int J Radiat Oncol Biol Phys* 2004;59:960–70.
17. Stephens LC, Ang KK, Schultheiss TE, King GK, Brock WA, Peters LJ. Target cell and mode of radiation injury in rhesus salivary glands. *Radiother Oncol* 1986;7:165–74.

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Irinotecan and etoposide for previously untreated extensive-disease small cell lung cancer: A phase II trial of West Japan Thoracic Oncology Group

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KEYWORDS
ED-SCLC;
Irinotecan;

Summary Irinotecan is a topoisomerase I inhibitor that is highly active against small cell lung cancer (SCLC). Etoposide is another drug that is effective for SCLC. Since combination of these two topoisomerase inhibitors revealed a synergistic

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Etoposide;
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Chemotherapy

effect in vitro and showed a safety in phase I study, we conducted a phase II study in patients with previously un-treated extensive disease (ED) SCLC to evaluate the efficacy and toxicity of this combination. Fifty patients with previously untreated ED-SCLC were enrolled. Irinotecan was administered intravenously at 60 mg/m^2 on days 1, 8, and 15, while etoposide was given at 80 mg/m^2 on days 2–4. Treatment was repeated every 4 weeks for four cycles. The overall response rate was 66.0%, with a complete response rate of 10.0%. The median survival time was 11.5 months and the 1- and 2-year survival rates were 43.2 and 14.4%, respectively. The major toxicity of this regimen was myelosuppression, including grade 3 or 4 neutropenia (62.9%) leukopenia (28.0%), and anemia (14%). The other grade 3 toxicity was diarrhea (2%). This irinotecan and etoposide regimen is active against ED-SCLC with relatively mild toxicity.

1. Introduction

Small cell lung cancer (SCLC) is highly responsive to chemotherapy and radiotherapy. Considerable improvement of survival has been achieved by using these treatments [1]. Despite high response rates and a longer survival time, recurrence eventually occurs in the majority of patients. Over the past two decades, several approaches have been explored in the treatment of extensive-disease (ED) SCLC, including non-cross resistant alternating chemotherapy [2], high-dose and dose-intensive chemotherapy with or without recombinant human granulocyte-colony stimulating factor (rhG-CSF) [3], and continuation of maintenance therapy beyond four to six cycles [4], to improve the standard regimen of cisplatin-etoposide or cyclophosphamide-adriamycin-vincristine alternating with cisplatin-etoposide. Unfortunately, these new concepts of chemotherapy regimens have not demonstrated any advantages over conventional treatment. For improvement of the results of treatment, introduction of new active agents and the development of more active combination regimens are needed.

During the 1990s, various new active anticancer agents were developed, including paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, and topotecan. Among them, irinotecan is a new camptothecin derivative that inhibits the nuclear enzyme topoisomerase I [5]. Clinical trials of this agent have demonstrated excellent activity against many solid tumors, including SCLC. Irinotecan monotherapy has been used to treat SCLC in Japan. When weekly regimen of this agent was administered to both chemotherapy-naive and previously treated patients with ED–SCLC, very promising results were obtained [6]. Etoposide is another active drug in the treatment of SCLC and inhibits the nuclear enzyme topoisomerase II. Etoposide and irinotecan have shown a synergistic effect against human SCLC cell lines [7], so combination chemotherapy with irinotecan and etoposide may be an attractive treatment strategy for SCLC. We previously conducted a phase I study of irinotecan plus etoposide with rhG-CSF support for the treatment of advanced lung cancer [8], and we found promising antitumor activity of this regimen, especially against SCLC, for which the response rate was 58.3%. The recommended dose for phase II studies in previously untreated patients was determined to be 80 mg/m^2 of irinotecan on days 1, 8, and 15 with 80 mg/m^2 of etoposide on days 1–3 plus 2 μg/kg of rhG-CSF. In the present study, we used this combination without prophylactic use of rhG-CSF because several trials of dose-intensive chemotherapy with prophylactic use of rhG-CSF have failed to reveal any survival advantage of using this cytokine [9]. The dose of irinotecan was reduced to 60 mg/m^2 because of non-prophylactic use of rhG-CSF support. In addition, administration of etoposide was performed on days 2–4, instead of days 1–3, because a synergistic effect may be obtained by sequential use of topoisomerase I and II inhibitors [10]. The present study investigated antitumor activity and toxicity profile of this combination regimen in patients with previously untreated ED-SCLC.

2. Patients and methods

2.1. Patient selection

Patients with histologically or cytologically confirmed SCLC were enrolled in this trial. Patients were eligible if they had no prior chemotherapy, or radiotherapy, had measurable or assessable disease, and had a life expectancy of at least 3 months. Extensive-disease was defined as distant

metastasis beyond the hemithorax, including contralateral hilar lymphadenopathy and excluding ipsilateral pleural effusion without distant metastasis. Additional enrollment criteria were as follows: (a) age ≤75 years; (b) a performance status of 0–2 on the Eastern Cooperative Oncology Group scale; (c) adequate function of the bone marrow (leukocyte count $\geq 4.0 \times 10^9\,L^{-1}$ and $\leq 12.0 \times 10^9\,L^{-1}$, hemoglobin concentration ≥10.0 g/dL, and platelet count $\geq 100 \times 10^9\,L^{-1}$), kidney (creatinine ≤1.2 mg/dL, and 24-h creatinine clearance ≥60 mL/min), liver (AST and ALT ≤100 IU/L, total bilirubin ≤1.5 mg/dL) and lung (PaO_2 ≥70 Torr). Patients with active concomitant or recent (<5 years) history of any malignancy, symptomatic brain metastases, severe superior vena cava syndrome, uncontrolled angina pectoris, myocardial infarction within 3 months before enrollment, heart failure, uncontrolled diabetes mellitus and/or hypertension, massive pleural effusion and/or ascites, active infection, ileus, pulmonary fibrosis, diarrhea, or a bleeding tendency were excluded. All patients gave written informed consent, and the Institutional Review Board for Human Experimentation approved the protocol at each participating center.

Pretreatment investigations included a complete medical history and physical examination, chest radiography, fiberoptic bronchoscopy, electrocardiography, computed tomography of the brain and chest, computed tomography or ultrasound examination of the abdomen, bone scintigraphy, and bone marrow aspiration and/or biopsy. Blood chemistry examinations included complete blood cell counts, liver function tests, serum electrolytes, serum creatinine, and blood urea nitrogen.

The efficacy parameters were to assess measurable lesions every cycle by physical examination and routine chest radiography, and computed tomography. The adverse events, toxicity symptoms, and laboratory tests to assess myelosuppression, renal and hepatic toxicity were performed every week.

2.2. Treatment

Chemotherapy was repeated every 4 weeks for four cycles. The treatment schedule and dose levels were based on the results of our phase I study [8]. Irinotecan was given on days 1, 8 and 15 at a dose of 60 mg/m^2 as a 90-min intravenous infusion, while 80 mg/m^2 of etoposide was intravenously administered over 60 min on days 2–4. Patients with progressive disease after one cycle of therapy or stable disease after two cycles of therapy were switched to salvage chemotherapy with cisplatin and etoposide. Restaging was carried out at the completion of chemotherapy to evaluate the response.

The dose levels and treatment schedule were modified to avoid severe adverse effects. Irinotecan was not given on days 8 or 15 if the leukocyte and/or platelet count was $<30 \times 10^9\,L^{-1}$ and/or $<100 \times 10^9\,L^{-1}$, respectively. It was also withheld if the patient developed diarrhea of grade 2 or worse according to the Japan Clinical Oncology Group common toxicity criteria [11]. The next course of treatment could only be initiated if the following conditions were met: a leukocyte count $\geq 4.0 \times 10^9\,L^{-1}$, a platelet count $\geq 100 \times 10^9\,L^{-1}$, AST/ALT level less than 100 IU/L, serum creatinine ≤1.2 mg/dL and improvement of nonhematologic toxicities to ≤grade 1. If a period of more than 6 weeks from the start of the last treatment was required before these criteria were satisfied, the patient was removed from the study. There was no dose modification for the leukocyte count, platelet count, and diarrhea during each course. However, the dose of irinotecan for the next course was reduced by 25% if grade 4 myelosuppression occurred and/or ≥grade 3 nonhematologic toxicity without nausea, vomiting, or alopecia.

2.3. Evaluation of response and survival

Tumor response was classified according to WHO criteria [12] and drug-induced toxicity was classified in accordance with the Japan Clinical Oncology Group common toxicity criteria. The duration of response was calculated from the start of treatment to the date of disease progression in patients who achieved a complete or partial response. Overall survival and progression free survival were calculated from the start of therapy until death and recurrence, respectively, or until last follow-up, using the Kaplan–Meier method.

2.4. Statistical analysis

The primary end-point of this study was the 1-year survival rate. The aim was to obtain a 1-year survival rate ≥45% with this irinotecan-etoposide regimen, and a 1-year survival rate of 30% was set as the lowest level of interest. A sample size of 50 eligible patients was calculated to be necessary with an α-value of 5% and a power of 80% using the minimax design of Simon [13] and was enrolled over 1.5 year with an additional 1 year of follow-up.

Table 1 Patient characteristics

Total number of patients	51
Number of eligible patients	50
Sex (male/female)	43/7
Age, median (range)	65 (28–73)
Performance status (ECOG[a]): 0/1/2	14/33/3
Number of metastatic sites	
1	32
2	14
3	4

[a] ECOG, Eastern Cooperative Oncology Group.

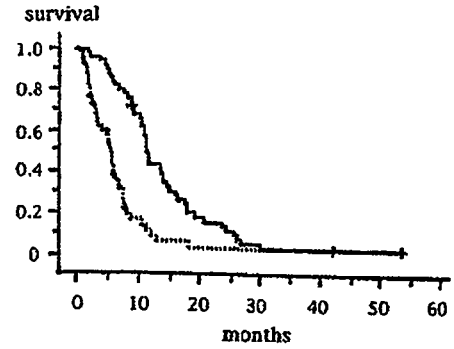

Fig. 1 Overall survival (—) and progression free survival (···) as determined by Kaplan–Meier method.

3. Results

3.1. Patient characteristics

From October 1995 to May 1998, 51 patients were enrolled in the study. The last follow-up was performed in September 2000. Fifty patients were eligible and were assessed for both response and toxicity. One patient was found to have adenocarcinoma at pathologic review after failing to respond to two cycles of treatment. The characteristics of the patients are summarized in Table 1. There were seven women and 43 men with a median age of 65 years, and 94% had a good performance status of 0 or 1. The sites of metastasis were as follows: liver in 19 patients, bone in 13, lung in nine, bone marrow in seven, brain in six, adrenal gland in four, and others in 14.

3.2. Response and survival

Among the 50 patients, five had a complete response and 28 had a partial response. The overall response rate was 66.0% (95% confidence interval; 52.9–79.1%), with a complete response rate of 10.0% (Table 2). The median duration of response for all responding patients was 6.9 months. Forty-seven of the 50 patients had died (94%) by the time of this analysis, while two patients were still alive and one was lost to follow up after 9 months of treatment. The median progression-free survival time was 5.6 months. The median survival time was 11.5 months (95% confidence interval; 7.6–15.4 months), and the 1- and 2-year survival rates were 43.2 and 14.4%, respectively (Fig. 1).

Table 2 Evaluation of response

Number of patients	50
Complete response	5
Partial response	28
No change	12
Progressive disease	5
Response rate	66 (52.9–79.1%)[a]
Complete response rate	10 (1.7–18.3%)[a]

[a] 95% confidence interval.

3.3. Toxicity

All 50 patients were assessable for toxicity and Table 3 lists the maximum toxicities that occurred during treatment. Myelosuppression was the most common toxicity; grade 3 or 4 leukopenia and neutropenia occurred in 28.0 and 62.9% of the patients, respectively. The median nadir leukocyte count and neutrophil count was $2.208 \times 10^9\,L^{-1}$ (range; $0.55 \times 10^9\,L^{-1}$ to $3.8 \times 10^9\,L^{-1}$) and $0.684 \times 10^9\,L^{-1}$ (range; $0.098 \times 10^9\,L^{-1}$ to $3.8 \times 10^9\,L^{-1}$), respectively, and the median time to nadir from the start of each course was 15 days (range; 7–22 days) and 16 days (range; 7–22 days), respectively. RhG-CSF support was required by 25 (50.0%) patients in 53 courses (34.2%) out of a total of 155 courses. The

Table 3 Toxicities

Toxicity	JCOG CTC[a] grade					
	1	2	3	4	≥Grade 3	%
Leukopenia	4	27	12	2	14	28.0
Neutropenia	5	7	20	14	68	62.9
Thrombocytopenia	1	1	2	0	2	4.0
Anemia	13	19	7	0	7	14.0
Diarrhea	17	17	1	0	2	2.0
Nausea/vomiting	12	8	0			
Alopecia	24	11	0			
Infection	0	1	0	0		
AST/ALT	4	0	0	0		
BUN	1	0	0	0		
Skin rash	1	1	0	0		
Pulmonary toxicity	1	0	0	0		

[a] JCOG CTC, Japan Cooperative Oncology group common Toxicity Criteria.

mean duration of rhG-CSF administration was 4.6 days (range; 2–8 days). Thrombocytopenia was infrequent throughout the study; two patients experienced grade 3 thrombocytopenia and only one patient (2.0%) required platelet transfusion. Anemia was also mild; seven patients developed grade 3 anemia and red blood cell transfusion was only required in two (4.0%) patients. The most prominent non-hematological toxicity of irinotecan was gastrointestinal toxicity, especially diarrhea; however this was not problematic with the present regimen. Grade 3 diarrhea only occurred in one patient, with grade 2 diarrhea in seven patients and grade 1 diarrhea in 17 patients. There were no other grade 3 or 4 non-hematological toxicities. No treatment-related deaths occurred with this regimen.

3.4. Treatment received

Twenty-four (48%) patients received the planned four cycles of chemotherapy, and the median total number of cycles was three. Fifteen (30%) patients did not receive further treatment after two cycles, because of stable disease in six, disease progression in five, pneumonia in one, deterioration of performance status in one, prolonged myelosuppression in one, and unknown reason in one. The total dose of etoposide and irinotecan were 720 mg/m^2 (range; 240–960 mg/m^2) and 420 mg/m^2 (range; 60–720 mg/m^2), respectively. In 84 out of 155 cycles (54.2%), the three doses per cycle administered to the patients, while two doses or one dose per cycle administered to the patients in 56 cycles (36.2%) or 15 cycles (9.7%), respectively. The mean doses of irinotecan on days 1, 8 and 15 were 58.1 mg/m^2 (96.8%), 50.4 mg/m^2 (84.0%) and 33.7 mg/m^2 (56.2%), respectively. Irinotecan was frequently skipped d on day 15 because of leukopenia and diarrhea.

Fifteen patients who did not respond after two cycles were encouraged to change to another combination chemotherapy regimen. Nine patients received cisplatin plus etoposide, and five of them responded to this regimen. One patient received carboplatin plus etoposide and achieved PR. Five patients did not receive any other chemotherapy because of deterioration of performance status and refusal to continue treatment.

4. Discussion

In the present study by the West Japan Thoracic Oncology Group, we demonstrated that the combination of irinotecan plus etoposide was active against previously untreated ED-SCLC and was well tolerated. Comparison with historical data indicates that these results seemed to be superior to those achieved by the standard regimens of cisplatin-etoposide, which obtain a median survival time of 8–10 months and a 1-year survival rate of about 33% [1–3]. Carboplatin-etoposide is another regimen that is commonly used; it achieves a response rate of about 55%, and a median survival time of 8 months [14–15]. Therefore, our irinotecan-etoposide regimen seems to be more effective than or equal to the platinum-etoposide regimen.

A phase II trial of irinotecan plus cisplatin was previously performed by our group [16]. In 35 patients ED-SCLC, the median survival time was 13.0 months. Furthermore, the Japan Clinical Oncology Group performed a randomized phase III trial that compared irinotecan plus cisplatin with the standard cisplatin-etoposide regimen [17]. In 77 patients with ED-SCLC, the irinotecan plus cisplatin regimen again achieved an excellent outcome with a median survival time of 12.8 months. Irinotecan plus cisplatin may be more effective than the present irinotecan-etoposide regimen, but it is also more toxic than the present treatment as described later. Masuda et al. conducted a phase II trial of irinotecan (70 mg/m^2, on days 1, 8, and 15), etoposide (80 mg/m^2, on days 1–3) with rhG-CSF support every 4 weeks in 25 patients with previously treated SCLC [18]. The objective response rate was 71% and the median survival time was 8.9 months. Although there were differences in the dosage of irinotecan and the prophylactic use of rhG-CSF support, effectiveness of the regimen may also be expected in patients with SCLC.

The major toxicity of the present regimen was myelosuppression, especially neutropenia (Table 3). The incidence of grade 3/4 neutropenia was 62.9%. We did not employ prophylactic administration of rhG-CSF and found that neutropenia was easily managed by temporary use of rhG-CSF. In case of other irinotecan-containing regimens, neutropenia is a common toxicity. When an irinotecan-etoposide regimen was used for patients with previously treated SCLC, neutropenia occurred in 56%, even though rhG-CSF was administered prophylactically [18], while irinotecan plus cisplatin induced neutropenia at nearly the same incidence [16–17]. With the standard cisplatin-etoposide, grade 3 or 4 neutropenia occurs in 70–90%, a higher rate than those with irinotecan-containing regimens. Compared with another commonly used etoposide-carboplatin regimen, neutropenia was similar rate [14] to that seen with the present regimen. Diarrhea is another major toxicity of irinotecan-containing

regimens. However, only one patient developed grade 3 diarrhea with the present regimen, and the similar result was noted in another study of pretreated patients with SCLC [18]. Diarrhea is less common with irinotecan-etoposide than with irinotecan-cisplatin regimen [16–17].

In the treatment of SCLC, the dose-intensity of chemotherapy agents may be a critical factor in achieving the optimum results. The dose-intensity of irinotecan and etoposide achieved with present regimen was not adequate, especially that of irinotecan. Less than half of the patients (48%) received the planned four cycles of treatment and three doses of irinotecan per cycle could be administered in about half (54.2%) of all 155 treatment cycles. What were the reasons for this relatively low dose intensity? First reason which we were considered is that we did not perform prophylactic administration of rhG-CSF. Second, our criteria for skipping irinotecan were quite severe (a leukocyte count $\geq 3.0 \times 10^9\,L^{-1}$, platelet count $\geq 100 \times 10^9\,L^{-1}$ and <grade 2 diarrhea). As a result, irinotecan administration was often skipped, especially on day 15, which was almost the same outcome as with irinotecan-cisplatin regimens. It might be preferable to employ a 3-week schedule for irinotecan plus etoposide or cisplatin, in which irinotecan is administered on days 1 and 8 at 3-week intervals. This type of irinotecan-containing regimen should be considered for the next study.

In conclusion, the present study demonstrated that this regimen was active and mild toxicity against ED-SCLC. Therefore, this regimen might be used as first-line chemotherapy for ED-SCLC in patients who are elderly or unfit for cisplatin-containing regimens.

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Appendix A

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References

[1] Laskin J, Sandler A, Johnson DH. An advance in small-cell lung cancer treatment—more or less. J Natl Cancer Inst 2003;95:1099–101.

[2] Roth BJ, Johnson DH, Einhorn LH, et al. Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. J Clin Oncol 1992;10:282–91.

[3] Furuse K, Fukuoka M, Nishiwaki Y, et al. Phase III study of intensive weekly chemotherapy with recombinant human granulocyte-colony stimulating factor versus standard chemotherapy in extensive-disease small cell lung cancer. J Clin Oncol 1998;16:2126–32.

[4] Spiro SG, Souhami RL, Geddes DM, et al. Duration of chemotherapy in small cell lung cancer: a Cancer Research Campaign trial. Br J Cancer 1989;59:578–83.

[5] Kunimoto T, Nitta K, Tanaka T, et al. Antitumor activity of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy-camptothecin, a novel water-soluble derivative of camptothecin, against murine tumors. Cancer Res 1987;47:5944–7.

[6] Negoro S, Fukuoka M, Niitani H, et al. Phase II study of CPT-11, new camptothecin derivative, in small cell lung cancer (SCLC). Proc Am Soc Clin Oncol 1991;10:241a.

[7] Takada M, Fukuoka M, Kudoh S, et al. Synergistic effects of CPT-11 and cisplatin or etoposide on human lung cancer cell lines and xenografts in nude mice. Proc Am Assoc Cancer Res 1992;33:226a.

[8] Masuda N, Fukuoka M, Kudoh S, et al. Phase I and pharmacokinetic study of irinotecan and etoposide with recombinant human granulocyte colony-stimulating factor support for advanced lung cancer. J Clin Oncol 1994;12:1833–41.

[9] Sculier JP, Paesmans M, Lecomte J, et al. A three-arm phase III randomized trial assessing, in patients with extensive-disease small-cell lung cancer, accelerated chemotherapy with support of haematological growth factor or oral antibiotics. Br J Cancer 2001;85:1444–51.

[10] Bertrand R, O'Connor PM, Kerrigan D, et al. Sequential administration of camptothecin and etoposide circumvents the antagonistic cytotoxicity of simultaneous drug

administration in slowly growing human HT-29 cells. Eur J Cancer 1992;28:743–8.
[11] Tobinai K, Kohno A, Shimada Y, et al. Toxicity grading criteria of the Japan Clinical Oncology Group. Jpn J Clin Oncol 1993;23:250–7.
[12] World Health Organization. WHO Handbook for Reporting Results of Cancer Treatment. WHO Offset Publication No. 48. Geneva, Switzerland: World Health Organization; 1979.
[13] Simon R. Optimal two-stage designs for phase II clinical trials. Controll Clin Trials 1989;10:1–10.
[14] Bishop JF, Raghavan D, Stuart-Harris R, et al. Carboplatin (CBDCA JM-8) and VP-16-213 in previously untreated patients with small-cell lung cancer. J Clin Oncol 1987;5:1574–8.
[15] Evans WK, Eisenhauer E, Hughes P, et al. VP-16 and carboplatin in previously untreated patients with extensive small cell lung cancer: a study of the National Cancer Institute of Canada Clinical Trials Group. Br J Cancer 1988;58:464–8.
[16] Kudoh S, Fujiwara Y, Takada Y, et al. Phase II study of irinotecan combined with cisplatin in patients with previously untreated small-cell lung cancer. J Clin Oncol 1998;16:1068–74.
[17] Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 2002;346:85–91.
[18] Masuda N, Matsui K, Negoro S, et al. Combination of irinotecan and etoposide for treatment of refractory or relapsed small-cell lung cancer. J Clin Oncol 1998;16:3329–34.

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Is radiotherapy optimally combined with chemotherapy in elderly patients with limited-stage small-cell lung cancer?

GLOSSARY

ECOG PERFORMANCE STATUS (ECOG PS)
A scoring system to assess the wellbeing of cancer patients and their ability to perform ordinary tasks (0 = fully active to 5 = dead)

Original article Schild SE *et al.* (2005) Results of combined-modality therapy for limited-stage small cell lung carcinoma in the elderly. *Cancer* 103: 2349–2354

SYNOPSIS

KEYWORDS cisplatin, combined-modality therapy, etoposide, radiotherapy, small-cell lung cancer

BACKGROUND

It is important to understand the effects of modern combined-modality therapy in elderly patients with lung carcinoma. Half of the patients who are diagnosed with lung carcinoma are ≥70 years of age.

OBJECTIVES

To determine the relationship between age and outcome in patients with limited-stage small-cell lung cancer (SCLC) treated with etoposide and cisplatin in addition to once-daily or twice-daily radiotherapy (QDRT or BIDRT respectively).

DESIGN AND INTERVENTION

From September 1990 to November 1996, this North Central Cancer Treatment Group phase III trial enrolled patients with limited-stage disease confirmed by pathology as SCLC, with ECOG PERFORMANCE STATUS (ECOG PS) ≤2 and sufficient organ function. Six 3-day cycles of etoposide and cisplatin were given, with a 28-day interval between cycles. Cisplatin (30 mg/m^2 given intravenously over 30–60 minutes), and etoposide (130 mg/m^2 given intravenously over 45 minutes) were administered on each chemotherapy day. After the first three cycles, the dose of etoposide was reduced to 100 mg/m^2 per cycle. Patients were randomized to receive thoracic radiotherapy (in parallel to chemotherapy cycles 4–5), either QDRT (50.4 Gy in 28 fractions) or BIDRT (48 Gy in 32 fractions).

OUTCOME MEASURES

Toxicity, disease control and survival.

RESULTS

Of 263 evaluable patients (median age 63 years, range 37–81 years), followed for a median of 8.1 years (range 4.6–11.9 years), 209 were younger than 70 years old and 54 were 70 years old or older. Baseline ECOG PS and weight loss were worse in the older group. Tumor progression rates, survival, local control, and overall, hematologic and nonhematologic toxicities did not differ according to patient age. The 2-year and 5-year survival rates were 48% and 22% respectively, in patients aged <70 years, versus 33% and 17% in older patients (P=0.14). Hematologic toxicities ≥grade 3 or ≥grade 4 did not occur more frequently in elderly patients. Grade 3 toxicity or worse occurred in 91% of patients aged <70 years compared with 94% of elderly patients (P=0.58). Toxicities of grade 4 or more occurred in 46% of patients aged <70 years compared with 50% of older patients (P=0.65). Grade ≥3 nonhematologic toxicity occurred in 46% of those aged <70 years compared with 52% of older patients (P=0.45). Grade ≥4 nonhematologic toxicity occurred in 12% of patients aged <70 years compared with 11% of elderly patients (P=1.0). Of the nonhematologic toxicities, only grade ≥4 pneumonitis occurred more frequently in elderly patients. Grade ≥3 esophagitis occurred in similar numbers of patients in the two age groups. Treatment-related toxicity caused death in 4 of 263 patients (2%)—3 in the elderly group (pneumonitis) and 1 in the younger group (infection).

CONCLUSION

Elderly patients should be encouraged to receive combined-modality therapy, especially within clinical trials.

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COMMENTARY

Nagahiro Saijo

Cisplatin plus etoposide with concurrent thoracic radiotherapy is the standard treatment for limited-disease small-cell lung carcinoma (LD-SCLC) in the elderly.[1,2] In Intergroup study 0096, Turrisi *et al.* found that, when combined with etoposide plus cisplatin chemotherapy, a total radiation dose of 45 Gy administered as a twice-daily therapy (1.5 Gy twice daily) produced superior survival to the same total dose administered as a once-daily therapy (1.8 Gy once daily).[1] The Japan Clinical Oncology Group also obtained excellent survival data (median survival time 27 months) using concurrent chemotherapy and twice-daily irradiation (Japan Clinical Oncology Group 9104).[2] In 2004, Schild *et al.* reported that equivalent survival benefit was achieved with twice-daily and once-daily irradiation with etoposide plus cisplatin chemotherapy.[3] Once-daily radiotherapy was administered continuously, and twice-daily radiotherapy was administered with a 2.5-week intermission after 24 Gy. The treatment schedule of the Intergroup study differed from that of the present study in that concurrent radiotherapy was given from the start of chemotherapy, and radiotherapy was given without a break. The dose intensity of the combination of chemotherapy and radiotherapy in the Intergroup study was higher in the twice-daily group. Efficacy improved with increased intensity of combined-modality therapy, as did adverse events. Elderly patients usually experience more toxicity than younger patients, and cannot tolerate intensive treatment. Few studies have specifically targeted elderly populations.

The elderly patients in the present analysis (aged ≥70 years) experienced significantly greater weight loss and poorer performance status than the younger patients (aged <70 years). The 2-year and 5-year survival rates were 48% and 22% for younger patients, compared with 33% and 17% for elderly patients. The incidence of grade 4 pneumonitis was higher in the elderly patients. Grade 5 toxicity occurred in 1 of 209 younger patients versus 3 of 54 older patients. Schild *et al.* concluded that LD-SCLC patients over 70 years of age are candidates for clinical trials of aggressive treatment if they do not have severe comorbidity. Yuen *et al.* reviewed the elderly subset results from the Intergroup 0096 study.[4] Quon *et al.* also studied the influence of age on the delivery, tolerance, and efficacy of thoracic irradiation in the combined-modality treatment of limited stage small-cell lung cancer.[5] In both analyses it was suggested that an elderly subset seems to be at risk of toxicity, but that those patients completing therapy do as well as their younger counterparts. It is extremely difficult, however, to distinguish those patients who are at risk of toxicity before toxicity occurs.

LD-SCLC is curable by chemotherapy and radiotherapy without surgery. Since the average age of LD-SCLC patients will increase year by year, fit elderly patients with LD-SCLC should be encouraged to undergo combined-modality therapy. An initial cycle of chemotherapy before concurrent treatment might unveil the vulnerable subset. The role of sequential chemotherapy should be evaluated in elderly patients considered marginal, to help us to distinguish those patients that are able to tolerate aggressive therapy from those that are too easily tipped over into a less-fit category. In conclusion, it is extremely important to establish a safe and effective standard treatment for the elderly patient population.

References

1 Turrisi AT *et al.* (1999) Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* **340**: 265–271
2 Takada M *et al.* (2002) Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group study 9104. *J Clin Oncol* **20**: 3054–3060
3 Schild SE *et al.* (2004) Long-term results of a phase III trial comparing once-daily radiotherapy with twice-daily radiotherapy in limited-stage small-cell lung cancer. *Int J Radiat Oncol Biol Phys* **59**: 943–951
4 Yuen AR *et al.* (2000) Similar outcome of elderly patients in Intergroup trial 0096: Cisplatin, etoposide, and thoracic radiotherapy administered once or twice daily in limited stage small cell lung carcinoma. *Cancer* **89**: 1953–1960
5 Quon H *et al.* (1999) The influence of age on the delivery, tolerance, and efficacy of thoracic irradiation in the combined modality treatment of limited stage small cell lung cancer. *Int J Radiat Oncol Biol Phys* **43**: 39–45

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Competing interests
The author declared he has no competing interests.

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PRACTICE POINT
Further study of combined-modality therapy within clinical trials is needed to establish a safe and effective standard treatment for elderly patients with lung carcinoma

Locally Recurrent Central-Type Early Stage Lung Cancer < 1.0 cm in Diameter After Complete Remission by Photodynamic Therapy*

Kinya Furukawa, MD; PhD; Harubumi Kato, MD, PhD; Chimori Konaka, MD, PhD; Tetsuya Okunaka, MD, PhD; Jituo Usuda, MD, PhD; and Yoshiro Ebihara, MD, PhD

Background: **It is well known that central-type early stage lung cancer < 1.0 cm in diameter shows almost 100% complete response (CR) to photodynamic therapy (PDT). However, we have encountered cases of local recurrence after CR of tumors with a surface diameter < 1.0 cm.**
Patients and methods: **Ninety-three patients with 114 lesions were followed up, and cases of recurrence after CR has been obtained with initial tumors that had a diameter < 1.0 cm were examined. We compared the cytologic findings of local recurrence after CR to the cytologic findings before PDT. The relationship between the cell features and the depth of bronchial tumor invasion before PDT and on recurrence was evaluated.**
Results: **The CR and 5-year survival rates of patients with lesions < 1.0 cm were 92.8% (77 of 83 patients) and 57.9%, respectively; meanwhile, in the group of patients with lesions ≥ 1.0 cm, CR and 5-year survival rates were 58.1% (18 of 31 patients) and 59.3%. There was a significant difference in efficacy between the two groups ($p < 0.001$). Recurrences after CR were recognized in 9 of 77 lesions (11.7%) < 1.0 cm. When the recurrent tumor cells showed type I-II (low-to-moderate atypia) at the same site initially treated, CR could be obtained by a second PDT. Type III cells (high-grade atypia) showed the characteristics of tumor cells from deeper layers of the bronchial wall. Local recurrence at the same site may be caused by residual tumor cells from deep layers because of inadequate laser irradiation and penetration.**
Conclusions: **To reduce the recurrence rate, it is essential to accurately grasp the tumor extent and the depth of the bronchogenic carcinoma before performing PDT. Analysis of cell features of recurrent lesions after CR appears to be a useful source of information as to the depth of cancer invasion in the bronchial wall.** ***(CHEST 2005; 128:3269–3275)***

Key words: early stage lung cancer; occult lung cancer; photodynamic therapy; porfimer sodium

Abbreviations: AFB = autofluorescence bronchoscopy; CIS = carcinoma *in situ*; CR = complete remission; EBUS = endobronchial ultrasonography; ESLC = early stage lung cancer; PDT = photodynamic therapy; PR = partial remission

Lung cancer has a tendency to develop in older people, with a very poor prognosis. A total of 55,000 Japanese died from lung cancer in 2003, which made it the number-one cause of cancer death. Although diagnostic techniques such as high-resolution CT scan, video bronchoscopy, fluorescence bronchoscopy, and endobronchial ultrasonography (EBUS) have been developed recently, many patients with newly detected lung cancer still have inoperable advanced cancer. Therefore, the detection of early stage lung cancer (ESLC) is considered essential to reduce the mortality rate. Meanwhile, even when ESLC is detected, some cases are inoperable because of cardiopulmonary dysfunction due to age. Endoscopic procedures that are minimally invasive and do not compromise pulmonary function

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are considered useful modalities for centrally located lung cancer. In particular, photodynamic therapy (PDT) is considered a useful and attractive modality for central-type ESLC.[1-7] Its action mechanism is considered to involve singlet oxygen, which is generated through photochemical reactions and causes degenerative necrosis of cells that have taken up the photosensitizer, *ie*, tumor cells.[8]

PDT using red laser light and a tumor-specific photosensitizer was established as a new therapeutic modality for central-type ESLC in 1982.[1] The length of longitudinal tumor extent was the only independent predictive factor for complete remission (CR), and 100% CR in lesions < 1.0 cm in diameter treated by PDT was reported.[5] However, we have encountered local recurrences after CR of tumor even in cases with a surface diameter < 1.0 cm. Therefore, we investigated the characteristics and cytomorphologic features of primary lesions and recurrences after CR in patients with lesions < 1.0 cm in diameter.

Materials and Methods

Patient Selection

A total number of 145 patients with 191 lesions of endoscopic ESLC underwent PDT from February 1980 to April 2001 in the Department of Tokyo Medical University. Of the 145 patients with 191 lesions, 93 patients with 114 lesions were followed up, and cases of recurrence after CR was obtained with initial tumors with a diameter < 1.0 cm were examined.

Procedures of PDT and Follow-up

The depth of tumor invasion was judged by biopsy specimen and CT scan, and was also evaluated by bronchoscopic findings based on the diagnostic criteria of ESLC defined by the Japan Lung Cancer Society.[9] To determine tumor size, bronchoscopic biopsies of the proximal and distal sites of the lesion and bronchoscopic measurements using forceps were performed. PDT procedures were performed with the combination of porfimer sodium (Photofrin; Wyeth Japan K.K.; Tokyo, Japan) that is taken up selectively in tumor, and an argon gas laser system (model 770; Spectra-Physics; Mountain View, CA) or excimer dye laser (EDL-1; Hamamatsu Photonics; Hamamatsu, Japan). Laser irradiation was performed via a quartz fiber inserted through the biopsy channel of the endoscope at 48 h after the IV administration of 2.0 mg/kg of porfimer sodium. The total energy of the laser irradiation was 100 J/cm^2, and energy levels in this range do not cause any heat degeneration or other adverse effects. The duration of irradiation required usually 10 to 20 min. Clean-up bronchoscopies to remove necrotic tissue produced by the PDT reaction were performed at 1, 3, and 7 days after PDT. Both cytologic and histologic examinations via fiberoptic bronchoscopy were performed at 1, 2, and 3 months, and thereafter at 3-month intervals in the first year and 6-month intervals after the second year until 5 years after PDT.

Efficacy Evaluation

The antitumor effect of initial treatment was rated based on endoscopic measurement of tumor size using forceps, morphologic observations, and histopathologic examination by biopsy, according to the general rules of the Japan Lung Cancer Society[9] and the Japan Society of Clinical Oncology.[10] The antitumor effect was rated at 1 month and 2 months after PDT. Antitumor effect was rated as CR (no demonstrable tumor microscopically by brushing and/or biopsy for a period of 4 weeks), partial remission (PR) [≥ 50% reduction in tumor size], no change (< 50% reduction or < 25% increase in tumor size), progressive disease (> 25% increase in tumor size), or not evaluable.

Evaluation of Cytomorphologic Features of Local Recurrences

In the central-type ESLC < 1.0 cm in greatest dimension, we have compared the cytologic findings of local recurrence after CR to the cytologic findings before PDT using bronchial brushing specimen. Cytologic findings were classified into three cytologic morphotypes using the classification of cell features proposed by Konaka and coworkers,[11] which appears to yield information as to the depth of cancer invasion in the bronchial wall. The classification was described as follows: type I cell, low-grade atypia (resembling atypical squamous cell metaplasia); type II cell, moderate-grade atypia (resembling early stage squamous cell carcinoma); and type III cell, high-grade atypia (resembling invasive squamous cell carcinoma). The biopsy specimens before PDT and on recurrence, or resected materials, in cases of resection after recurrence, were examined histopathologically, and the depth of bronchial wall invasion was classified into three groups: grade 1, carcinoma *in situ* (CIS) or microinvasion; grade 2, extramuscular bronchial wall invasion; and grade 3, intracartilaginous to extracartilaginous invasion. The relationship between the cell features and the depth of bronchial tumor invasion before and after PDT was evaluated.

Statistical Analysis

Statistical analysis were done using statistical software (Stat Flex for Windows, version 5.0; Artec; Osaka, Japan). The χ^2 test was used to compare the efficacy of PDT between lesions < 1.0 cm and > 1.0 cm in diameter. Differences between the survival rates of two groups in the Kaplan-Meier survival curves were analyzed using the log-rank test; $p < 0.05$ was considered to indicate a statistically significant difference.

Results

Results of PDT for Central-Type ESLC

A total of 93 patients with 114 lesions of central-type ESLC who underwent PDT were examined. Thirteen synchronous lesions in six cases, 15 metachronous lesions in six cases, and 5 synchronous/metachronous lesions in one case were observed. The evaluation of the efficacy of PDT is shown in Table 1. CRs and PRs were obtained in 75 patients with 95 lesions (83.3%) and in 18 patients with 19 lesions (16.7%) out of 93 patients with 114 lesions. Each lesion with PR was subsequently treated with other modalities, including surgery in 13 cases, chemotherapy in 5 cases, or radiotherapy in 1 case, and finally achieved 100% CR. Recurrences after CR were recognized in 12 of 95 lesions (12.6%). The 114 lesions were classified in two groups according to the

Table 1—*Results of PDT for Central-Type ESLC

Tumor Size, cm	Lesions, No.	CR	PR	Recurrence After CRT
< 1.0	83	77 (92.8)	6 (7.2)	9 (11.7)
≥ 1.0	31	18 (58.1)	13 (41.9)	3 (16.7)
Total	114	95 (83.3)	19 (16.7)	12 (12.6)

*Data are presented as No. (%) unless otherwise indicated.
†$p < 0.001$.

maximum longitudinal tumor extent. Of these, 83 lesions (72.8%) were < 1.0 cm and 31 lesions (27.2%) were ≥ 1.0 cm in diameter. The CR and PR rates in the group of patients with lesions < 1.0 cm in maximum diameter were 92.8% (77 of 83 patients) and 7.2% (6 of 83 patients), respectively. Meanwhile, in the group of patients with lesions ≥ 1.0 cm in diameter, the CR and PR rates were 58.1% (18 of 31 patients) and 41.9% (13 of 31 patients), respectively. Neither no change nor partial disease were observed in these groups. There was a significant difference in efficacy between the two groups using the χ^2 test ($p < 0.001$). Recurrences after CR were recognized in 9 of 77 lesions (11.7%) in the group < 1.0 cm and 3 of 18 lesions (16.7%) in the group ≥ 1.0 cm in diameter. The overall 5-year survival rates of the two groups were 57.9% and 59.3%, respectively (Fig. 1). There was no significant difference between the two groups on the basis of the log-rank test ($p = 0.207$).

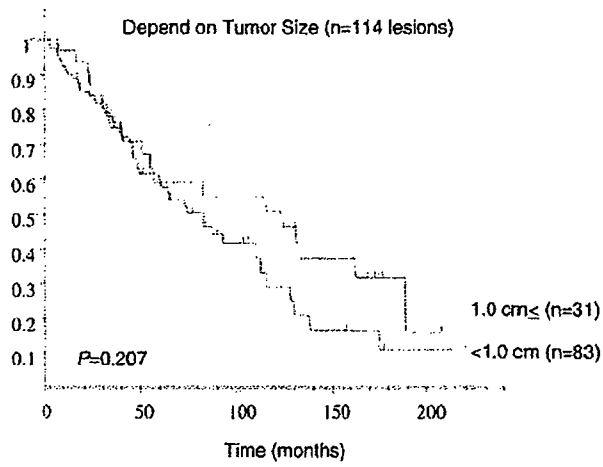

FIGURE 1. The overall 5-year survival rates were 57.9% in the group of patients with tumors < 1.0 cm and 59.3% in the group with tumors ≥ 1.0 cm in diameter, respectively. There was no significant difference between the survival rates of two groups in the Kaplan-Meier curves on the basis of the log-rank test ($p = 0.207$).

Characteristics of Local Recurrence < 1.0 cm in Diameter After CR

The information on nine patients with nine lesions in the group of patients with lesions < 1.0 cm in diameter who had recurrence after CR had been achieved by initial PDT are presented in Table 2. All patients with recurrence were male, and the age distribution ranged from 64 to 71 years (average age, 67.6 years at the time of initial diagnosis). Evidences of local recurrence were found in nine patients with nine lesions at the site of the primary lesion. The recurrent lesions were located on the trachea in one patient, lobar bronchus in one patient, segmental bronchi in five patients, and subsegmental bronchi in two patients. The average diameter of the nine recurrent lesions was 0.46 cm. All lesions were squamous cell carcinoma, and endoscopic findings showed nodular type in two lesions and superficial type in seven lesions. The disease-free interval of these nine patients ranged from 3 to 18 months (average, 10 months).

Local recurrence at site corresponding to the

Table 2—*Recurrent Cases After PDT for Central-Type ESLC < 1.0 cm in Diameter*

Case No.	Patient Age, yr	Lesion	Size, cm	BF Findings	CR, mo	Recurrence	Additional Treatment	Prognosis
1	66	Segmental bronchus rB^3	0.3	Superficial	18	PM	PDT, OP (RUL)	Alive (24 mo)
2	64	Subsegmental bronchus IB^3 a-b	0.3	Superficial	13	PM	PDT, OP (LPn)	Dead (56 mo), other disease
3	69	Subsegmental rB^{10} a-b	0.4	Superficial	10	PM	PDT Brachy	Alive (41 mo)
4	64	Segmental bronchus IB^{1+2}	0.6	Nodular	5	SS (CIS)	PDT	Alive (24 mo)
5	66	Segmental bronchus rB^1	0.5	Superficial	3	SS (CIS)		Dead (5 mo), other disease
6	69	Segmental bronchus IB^{1+2}	0.4	Superficial	14	SS (CIS)	PDT	Alive (27 mo)
7	71	Trachea	0.3	Nodular	10	SS (CIS)	PDT	Alive (27 mo)
8	70	Lobar bronchus rMid.-low	0.9	Superficial	6	SS (intracartilage)	OP (RML)	Dead (56 mo), other disease
9	69	Segmental IB^{1+2} B^3	0.4	Superficial	11	SS (extracartilage)	Nd-YAG, radiation, OP	Alive (65 mo)

*PM = peripheral margin initially treated; SS = same site initially treated; OP = operation; RML = right middle lobe; RUL = right upper lobe; LPn = left pneumonectomy; BF = bronchofiberscopic.

Table 3—*Cell Feature and Depth of Bronchial Invasion*

Case No.	Before PDT		Recurrence	
	Cytology (Brush) Type	Pathologic Grade	Cytology (Brush) Type	Pathologic Grade
4	I	1	I	1
5	I	1	I	1
6	I–II	1	I–II	1
7	I	1	II	1
8	I–II	1	II–III	3 (intracartilaginous invasion)
9	I	1	III	3 (extracartilaginous invasion)

peripheral margin of the lesion initially treated by PDT was observed in three patients (cases 1 to 3), while local recurrence at the same site as the initial tumor initially treated was observed in six patients (cases 4 to 9). The local recurrences at the site corresponding to the peripheral lesion were initially located in the subsegmental bronchus in two of three primary lesions. The patients with three local recurrences at the site corresponding to the peripheral margin underwent a second PDT session; however, CR was not obtained in any of these patients. Therefore, additional conventional surgery was performed in two patients and brachytherapy in one patient. The pathologic examinations of two operated patients showed residual tumor at the peripheral site. Right upper lobectomy was performed for case 1, and the resected material revealed superficial tumor invasion peripheral to the right B^3b. Left pneumonectomy was selected for case 2 (ipsilateral double cancer) because an ESLC was located at the bifurcation of left B^3a-b and a malignant lymphoma was in left B^6. This patient died due to malignant lymphoma at 56 months after the initial PDT session. Four patients (cases 4 to 7) with six local recurrences at the same site as the initial tumor local showed superficial tumor invasion (CIS), and a second PDT session was performed in three of four patients. CRs were again obtained in all three patients, who are presently disease free. One double cancer patient who had advanced stomach cancer underwent systemic chemotherapy without a second PDT but died 5 months after the initial PDT session. The pathologic examinations of the two other surgically treated patients (cases 8 and 9) revealed intracartilagious invasion of the bronchial wall. One multiple lung cancer patient (case 8) who received right middle and lower lobectomy after local recurrence died of hemoptysis due to another advanced lung cancer at 56 months after the initial PDT session. At the last follow-up of the nine patients who had local recurrence after CR had been obtained by initial PDT in whom the original primary lesion had been < 1.0 cm

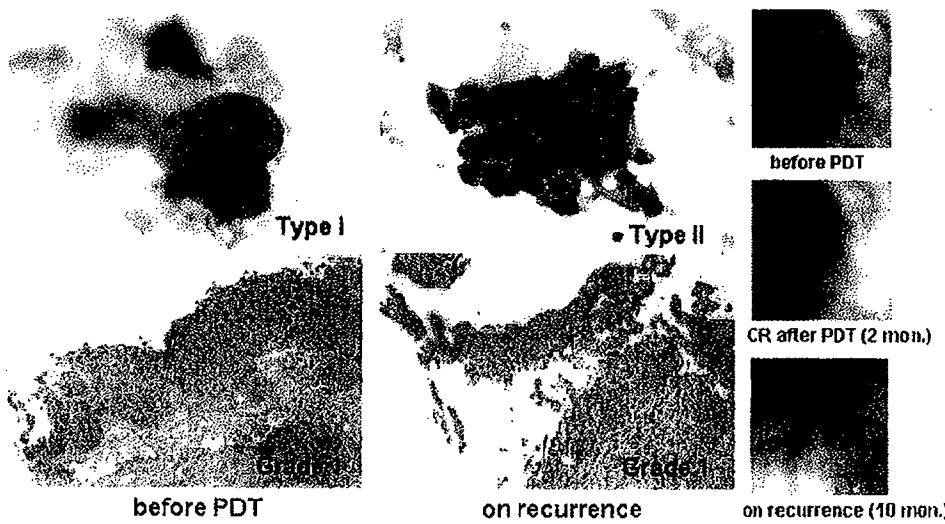

FIGURE 2. The cytopathologic and bronchoscopic findings in case 7. Bronchoscopic findings showed a small nodular tumor at the right side of the tracheal wall before PDT. Redness of the tracheal mucosa was observed on recurrence at 10 months after PDT. Cytologic findings before PDT were classified as type I because cell features showed a round shape and slight increase of nuclear chromatin but low-grade nuclear atypia. The biopsy specimen showed CIS (grade 1). Cytologic findings on recurrence were classified as type II because a sheet formation of polymorphic-shaped cells, increase of nuclear chromatin, and nuclear body were observed. Biopsy specimen on recurrence showed superficial tumor invasion (CIS) beneath the thin epithelial layer (grade 1). A second PDT was performed, and CR was again obtained in this patient.

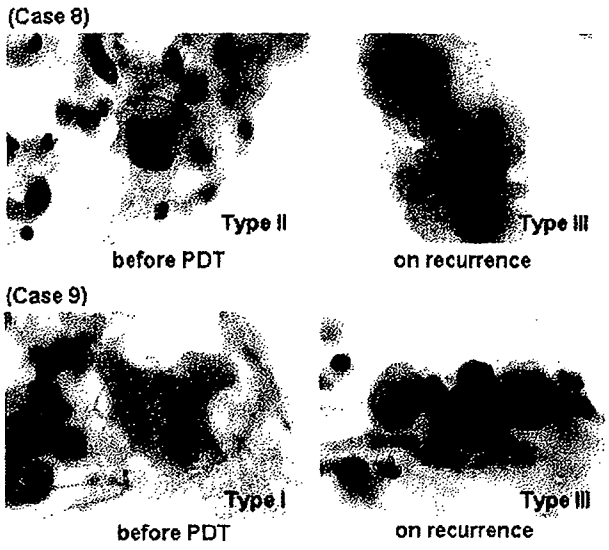

FIGURE 3. The findings of brushing cytology mainly observed in cases 8 and 9 before PDT and on recurrence after CR. Cytologic findings before PDT in case 8 were classified as type II because of a slight increase of nuclear chromatin. Cytologic findings before PDT in case 9 were classified as type I because of low-grade nuclear atypia. The findings of recurrent tumor cells in cases 8 and 9 were classified as type III because of severe increases of nuclear chromatin, high nuclear/cytoplasmic ratio, and high grade of nuclear atypia.

in diameter, three patients had died of other diseases and six patients were alive, and there were no deaths from the primary lesion.

Evaluation of Cytomorphologic Features of Local Recurrences

As mentioned above, local recurrence of the carcinoma at the same site as lesions < 1.0 cm in diameter initially treated successfully by PDT was observed in six out of nine locally recurrent patients (cases 4 to 9). A summary of the cell features and depth of bronchial wall invasion before PDT and after recurrence are shown in Table 3. The brushing cytology specimens before PDT mainly showed type I or II, and biopsy revealed grade 1 in all six cases. The majority of cell features in cases 4 to 7 showed type I or II, and the biopsy specimens showed grade 1 on recurrences. The cytopathologic and bronchoscopic findings of case 7 are shown Figure 2. Populations of type I and II cells were predominant in the recurrent lesions in these cases, which implied that the recurrent tumor was located in a superficial layer of bronchial wall. When the recurrent tumor cells showed type I-II (low-to-moderate atypia) local recurrence at the same site as the initial tumor initially treated, CR could be obtained by a second PDT. In cases 8 and 9, mainly type III cell features were observed in brushing cytology on recurrence (Fig 3). These two cases underwent resection, and the resected specimens revealed intracartilaginous tumor invasion of bronchial wall (grade 3), which implied the residual tumor located in a deep layer of bronchial wall.

DISCUSSION

PDT for cancer using a combination of low-power laser irradiation and tumor specific photosensitizer was first applied clinically by Dougherty et al[12] in 1978 to the skin metastasis of breast cancer. Since then, we performed the first reported endoscopic clinical application of PDT in cooperation with Dougherty and coworkers.[12] In Japan, PDT using porfimer sodium, a tumor-specific photosensitizer and excimer dye laser, was recognized by the government; and from April 1996, hospitals could receive reimbursement for PDT of early stage carcinomas of the lung, esophagus, stomach, and cervix from the national health insurance system.

The best PDT candidates in lung cancer are cases with central-type ESLC because of their endoscopic accessibility; therefore, selection of patient is important to achieve CR. Nagamoto et al[13] demonstrated that no lymph node involvement was found in 59 cancers with a longitudinal extent of < 20 mm; in another study,[14] histology by serial block sectioning showed that there was no nodal involvement in any CIS cases. Nakamura et al[15] retrospectively analyzed resected cases of central-type ESLC to clarify the relation between the endoscopic findings and the histologic extent of tumor. They demonstrated a significant difference is the maximum dimension according to the depth of bronchial invasion between CIS and extramuscular invasion and CIS and invasion into or beyond the cartilaginous layer. Lesions with a maximum diameter < 1.0 cm have a high possibility of being CIS. Their preoperative bronchoscopic diagnosis of centrally located ESLC was correct in 74.0%. In another study, Akaogi et al[16] demonstrated that polypoid or nodular lesions < 1.0 cm and flatly spreading lesions < 1.5 cm in greatest dimension were limited to within the cartilaginous layer without regional lymph node involvement. Also, Furuse et al[5] demonstrated that the length of longitudinal tumor extent was the only independent predictive factor for CR by PDT, and that lesions < 1.0 cm in diameter showed 100% CR. According to these data, therapy for CR requires satisfaction of the following endoscopic conditions: (1) no evidence of lymph node metastasis; (2) the lesion is superficial with a maximum diameter of < 1.0 cm; (3) no invasion into or beyond the cartilaginous layer; (4) the histologic type is squamous cell carcinoma; and

(5) the lesion is located in a position that can be easily irradiated with the laser.

In this study, excellent efficacy with a significant difference of CR rate was seen in patients with lesions < 1.0 cm (92.8%) compared to ≥ 1.0 cm (58.1%) in diameter; however, the overall 5-year survival rate of the two groups showed no significant difference (57.9% vs 59.3%). This may be because it was possible to perform additional alternative modalities such as surgery, second PDT, and brachytherapy to achieve CR after failure of initial PDT or recurrence after PDT. Considering that the 5-year survival rate of pathologic stage Ia (T1N0M0) patients who underwent surgery is approximately 67.0%,[17] our data are favorable because the majority of the PDT group consisted of patients with advanced age and poor cardiopulmonary function. Therefore, we consider that PDT may be used as first-line therapy for central-type ESLC prior to surgery, especially in cases with poor cardiopulmonary function. Also, Edell et al[18] and Cortese et al[19] demonstrated that PDT is an alternative to surgical resection in the management of early superficial squamous cell carcinoma.

In this study, recurrence after CR was recognized in 9 of 77 lesions (11.7%) in the group of patients with lesions < 1.0 cm in diameter. Despite the average diameter of the nine initial lesions being relatively small (0.46 cm), recurrence was recognized in eight of nine lesions (88.9%) within 12 months. Therefore, intensive follow-up studies should be performed until 1 year after PDT even for small primary lesions. The reasons why recurrences after CR were observed in the lesions < 1.0 cm in diameter could be explained by inappropriate estimation of the peripheral margin in cases of local recurrence at the site corresponding to the peripheral margin and insufficient laser irradiation or miss estimation of tumor depth in the cases of local recurrence at the same site as the initial tumor.

From our experiences, to achieve CR with PDT for central-type ESLC, it appears that not only the analysis of cell features but also the comprehension of tumor extent to the peripheral site and tumor invasion to the bronchial wall are of considerable significance. Kurimoto et al[20] demonstrated that endobronchial EBUS was useful to determine the depth of tumor invasion into the bronchial wall, and the accuracy of EBUS from the histopathologic findings was 95.8%. The EBUS image at 20 MHz shows five layers in the cartilaginous portion of bronchial wall. The third to fifth layers are images of cartilage. Therefore, it is feasible to evaluate the depth of invasion using EBUS whether or not the tumor invades into or beyond the cartilaginous layer.. In lesions with an intact third layer on EBUS, CR could be achieved with PDT. Miyazu et al[21] demonstrated that the depth of tumor invasion estimated by EBUS was accurate by histopathologic findings after surgical resection. They found 5 of 14 lesions (35.7%) < 1.0 cm in diameter that showed extracartilaginous invasion on the EBUS image that was later confirmed histopathologically; also, 3 of 5 lesions appeared bronchoscopically superficial but were shown to be extracartilaginous by EBUS. The indications of PDT for centrally located ESLC with a longitudinal extension of < 1.0 cm are unquestionable; meanwhile, we should realize that even < 1.0 cm in diameter can have extracartilaginous invasion. To comprehend the surface extent of superficial tumor invasion in the bronchial lumen, autofluorescence bronchoscopy (AFB) is considered useful.[22–25] The green autofluorescence of the lesion was decreased because of the lack of endogenous fluorophors, thickening of the membrane, and increased microvasculature.[26] We sometimes encountered unexpected surface invasion by AFB.

It is essential to know the extent of the tumor and the depth of bronchogenic carcinoma accurately for the selection of treatment modality. Corresponding to the previous study by Konaka et al,[11] the analysis of cell features is a useful source of information to evaluate the depth of cancer invasion in the bronchial wall. In addition, we believe that it could be beneficial information when choosing the treatment modality, such as recurrence after CR by PDT demonstrated in our study. Additionally, we now perform EBUS and AFB to determine the indications of PDT in all patients who have ESLC for the purpose of achieving 100% CR and reduction of recurrence rate. A comparative study of PDT for the treatment of ESLC before and after the adoption of EBUS and AFB will enable accurate evaluation of the benefits of these new diagnostic tools in the near future.

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REFERENCES

1 Hayata Y, Kato H, Konaka C, et al. Hematoporphyrin derivative and laser photoradiation in the treatment of lung cancer. Chest 1982; 81:269–277

2 Kato H, Konaka C, Kawate N, et al. Five-year disease-free survival of a lung cancer patient treated only by photodynamic therapy. Chest 1986; 90:768–770

3 Edell ES, Cortese DA. Bronchoscopic phototherapy with hematoporphyrin derivative for treatment of localized bronchogenic carcinoma: a 5-year experience. Mayo Clin Proc 1987; 62:8–14

4 Edell ES, Cortese DA. Bronchoscopic localization and treatment of occult lung cancer. Chest 1989; 96:919–921

5 Furuse K, Fukuoka M, Kato H, et al. A prospective phase II

study on photodynamic therapy with Photofrin II for centrally located early-stage lung cancer. J Clin Oncol 1993; 11:1852–1187
6 Kato H. Photodynamic therapy for lung cancer: a review of 19 years' experience. J Photochem Photobiol 1998; B42:96–99
7 Kato H, Furukawa K, Sato M, et al. Phase II clinical study of photodynamic therapy using mono-L-aspartyl chlorin e6 and diode laser for early superficial squamous cell carcinoma of the lung. Lung Cancer 2003; 42:103–111
8 Niedre M, Patterson MS, Wilson BC. Direct near-infrared luminescence detection of singlet oxygen generated by photodynamic therapy in cells *in vitro* and tissues *in vivo*. Photochem Photobiol 2002; 75:382–391
9 General rules for clinical and pathological records of lung cancer. 4th ed. In: Japan Lung Cancer Society, eds. Tokyo, Japan: Kanehara and Company, 1995; 123–133
10 Niiya H. Toxicity grading criteria of the Japan Clinical Oncology Group. Int J Clin Oncol 1997; 32:61–65
11 Konaka C, Miura H, Ikeda N, et al. The characteristics of early bronchogenic carcinoma evaluated by cytomorphological features. Lung Cancer 2002; 38:267–271
12 Dougherty TJ, Lawrence G, Kaufman JH, et al. Photoradiation in the treatment of recurrent breast carcinoma. J Natl Cancer Inst 1978; 62:231–237
13 Nagamoto N, Saito Y, Ohta S, et al. Relationship of lymph node metastasis to primary tumor size and microscopic appearance of roentgenographically occult lung cancer. Am J Surg Pathol 1989; 13:1009–1013
14 Nagamoto N, Saito Y, Sato M, et al. Clinicopathological analysis of 19 cases of isolated carcinoma in situ of the bronchus. Am J Surg Pathol 1993; 17:1234–1243
15 Nakamura H, Kawasaki N, Hagiwara M, et al. Endoscopic evaluation of centrally located early squamous cell carcinoma of the lung. Cancer 2001; 91:1142–1147
16 Akaogi E, Ogawa I, Mitsui K, et al. Endoscopic criteria of early squamous cell carcinoma of the bronchus. Cancer 1994; 74:3113–3117
17 Mountain CF. Revisions in the international system for staging lung cancer. Chest 1997; 111:1710–1717
18 Edell ES, Cortese DA. Photodynamic therapy in the management of early superficial squamous cell carcinoma as an alternative to surgical resection. Chest 1992; 102:1319–1322
19 Cortese DA, Edell ES, Kinsey JH. Photodynamic therapy for early stage squamous cell carcinoma of the lung. Mayo Clin Proc 1997; 72:595–602
20 Kurimoto N, Murayama M, Yoshioka S, et al. Assessment of usefulness of endobronchial ultrasonography in determination of depth of tracheobronchial tumor invasion. Chest 1999; 115:1500–1506
21 Miyazu Y, Miyazawa T, Kurimoto N, et al. Endobronchial ultrasonography in the assessment of centrally located early-stage lung cancer before photodynamic therapy. Am J Respir Crit Care Med 2002; 165:832–837
22 Lam S, Kennedy T, Unger M, et al. Localization of bronchial intraepithelial neoplastic lesions by fluorescence bronchoscopy. Chest 1998; 113:696–702
23 Ikeda N, Hiyoshi T, Kakihana M, et al. Histopathological evaluation of fluorescence bronchoscopy using resected lungs in cases of lung cancer. Lung Cancer 2003; 41:303–309
24 Sutedja TG, Codrington H, Risse EK, et al. Autofluorescence bronchoscopy improves staging of radiographically occult lung cancer and has an impact on therapeutic strategy. Chest 2001; 120:1327–1332
25 Sutedja TG, Venmans BJ, Smit EF, et al. Fluorescence bronchoscopy for early detection of lung cancer: a clinical perspective. Lung Cancer 2001; 34:157–168
26 Furukawa K, Ikeda N, Miura T, et al. Is autofluorescence bronchoscopy needed to diagnose early bronchogenic carcinoma? J Bronchol 2003; 10:64–69

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Microwave Coagulation Therapy in Canine Peripheral Lung Tissue[1]

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Background. **New modalities for local treatments that destroy tumor effectively but which are less invasive and less damaging to normal lung tissue must be developed for patients who are unable to undergo even video-assisted thoracic surgery (VATS) due to poor cardiopulmonary function, severe adhesion, or advanced age, etc. We evaluated the use of microwave coagulation therapy (MCT), which has been used successfully for coagulation of hepatic tumors, in normal canine lung tissue to evaluate its efficacy and safety.**

Materials and methods. **Measurements of thermal response and coagulation area and histological examinations after microwave coagulation were performed in normal canine lung tissue.**

Results. **The temperature in normal canine lung tissue increased to 90–100°C at 5 mm from the electrode after 60 s and 70–80°C at 10 mm after 90 s at 40 or 60 W. The coagulation area was approximately 20 mm in diameter at 40 W and 60 W. Histological analysis demonstrated thickening of collagen fiber shortly after coagulation, stromal edema and granulation tissue after 3 months, and, finally, scar tissue was seen after 6 months.**

Conclusions. **Microwave coagulation therapy (MCT) is a useful modality for minimally invasive therapy in peripheral lung tumors.**

Key Words: **microwave coagulation; MCT, PMCT, ablation; lung tumor; peripheral lung cancer.**

INTRODUCTION

Recently, the problem of population aging on a global scale is calling for minimally invasive therapies providing good quality of life (QOL) and activity of daily living (ADL). Many investigators are looking into the problems of poor cardiopulmonary function as a result of advanced age, previous surgery, and/or synchronous or metachronous carcinoma. Meanwhile, the detection rate of early-stage carcinoma or precancerous lesions has increased due to recent advances in medical technology. In the field of chest diseases, the detection rate of tiny tumors in the peripheral lung, such as early-stage lung cancer, small metastases, or atypical adenomatous hyperplasia (AAH) has increased with the increasing use of high-resolution CT scans. Video-assisted thoracic surgery (VATS) usually is used for many of these cases. However, we believe that less-invasive therapy is necessary for patients who are inoperable due to poor cardiopulmonary function, severe adhesion, or advanced age.

There is, therefore, a need for local treatment that effectively destroys tumor but is minimally invasive and less damaging to normal tissue than surgery. In the present study, we focused on microwave coagulation therapy (MCT), which has successfully been used to coagulate hepatic tumors [1–4]. The mechanism of coagulation is dielectric heating, *i.e.*, frictional heat of water molecules. Since the dielectric heat energy cannot be generated in the presence of air, selective tumor damage may be achieved and damage to the surrounding normal air-filled lung tissue may be limited. To assess the application of PMCT for lung tumors, we evaluated its efficacy and safety in experimental studies.

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