Table 4 Multivariate analysis of prognostic factors in patients with small cell lung cancer

Prognostic factors	*P value*	*Hazard ratio*	*95% CI*
Gender (male vs. female)	0.94	1.855	0.620 – 5.556
Age (≥ 62 vs. < 62)	0.1104	1.741	0.881 – 3.438
Pathologic N factor (N1 – 3 vs. N0)	0.0102	2.409	1.232 – 4.711
Adjuvant chemotherapy (done vs. not done)	0.0039	0.404	0.218 – 0.748
Surgical procedure (pneumonectomy vs. lobectomy or bilobectomy)	0.0432	2.528	1.028 – 6.215

CI = confidence interval

vanced stages makes complete local elimination of cancer cells by surgery unlikely. In addition, survival after pneumonectomy was significantly worse than after lobectomy or bilobectomy, and survival of patients with clinical or pathologic lymph node involvement was significantly worse than without lymph node involvement.

The 5-year survival rate after surgery for p-stage I disease ranges from 22% to 67%, and that for p-stage II ranges from 17% to 50% [15 – 17]. Reported survival in p-stage IIIA or higher varies greatly, from 0% to 55.5% [15,18 – 20]. The randomized study by the Lung Cancer Study Group [5] showed that surgery does not prolong survival in c-stage IIIA SCLC even in patients who undergo induction therapy. Although 19% of resected tumors showed complete pathologic response, this good response to chemotherapy did not improve the survival. However, in our study, pathologic downstaging did predict improved survival. Thus, we believe pathologic downstaging may be a selection criterion for identifying surgical candidates. Evaluation of the residual tumor cells by positron emission tomography (PET) or by lymph node sampling by mediastinoscopy after induction chemotherapy are alternate strategies.

In conclusion, a 32% overall 5-year survival was obtained in selected patients with SCLC who underwent surgery. Survival after surgery clearly depended on disease stage. Nodal status and pathologic downstaging after induction therapy predict survival. A randomized study is needed to identify surgical candidates.

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Lung cancer patients showing pure ground-glass opacity on computed tomography are good candidates for wedge resection

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Summary Small lung cancers frequently have been detected in mass screening by computed tomography (CT) in recent years. Suitability of limited resection for these small lung cancers remains controversial. One hundred patients who underwent sublobular limited resection (wedge resection or segmentectomy) for lung cancer in our hospital from 1981 to 2002 were analyzed retrospectively. From CT findings, tumors were classified into two groups; pure ground-glass opacity (PGGO) and non-PGGO. Patients included 44 women and 56 men, and ages ranged from 40 to 92 years (mean, 71.0). Histologic types included 76 adenocarcinomas, 21 squamous cell carcinomas, and 3 large cell carcinomas. Clinical stages included 83 stage IA and 17 stage IB. By high-resolution CT, 27 tumors (27%) showed PGGO; at postoperative histopathologic examination, all of these were localized bronchioloalveolar carcinomas. Diameter of tumors showing PGGO was 9.3 ± 3.5 mm (mean $\pm$ S.D.); that of non-PGGO tumors was 21.2 ± 13.7 mm. Overall and lung cancer-specific 5-year survival rates in all patients were 58.0 and 64.8%, respectively. Overall 5-year survival rate with small adenocarcinomas ($\leq$20 mm) was 93.7%, significantly better than 24.8% with larger adenocarcinomas ($P < 0.0001$). No intrathoracic recurrence or distant metastasis has been observed in PGGO tumors. For peripheral localized bronchioloalveolar carcinoma showing PGGO, wedge resection appears to be the best operation. Definitive study of more patients with longer follow-up is needed.

1. Introduction

The present standard operation for primary lung cancer is considered to be lobectomy with systematic lymphadenectomy. However, suitability of limited resection has been examined by several investigators. Outcome of segmentectomy first was reported in a large number of patients by Jensik et al. [1] in the 1970s. They performed segmentectomy for 168 stage I peripheral lung cancers, obtaining a survival rate of 53% at 5 years after surgery; this survival rate was comparable to that with

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lobectomy. However, a later study [2] from the same institution demonstrated a higher recurrence rate with segmentectomy than with lobectomy in stage I lung cancer. In that study, the rate of locoregional recurrence was 22.7% (15/66) after segmentectomy versus 4.9% (5/103) after lobectomy. A randomized controlled trial comparing limited resection (segment or wedge) with lobectomy for T1N0 non-small cell lung cancer (NSCLC) was carried out by the Lung Cancer Study Group [3] beginning in the 1980s.That study clearly found outcome with limited resection to be inferior to that with lobectomy, in terms of both survival and locoregional recurrence. Since then, limited resection for stage IA lung cancer generally has been avoided, except for patients with impaired cardiopulmonary function.

On the other hand, small cancers with diameters less than 1 cm frequently have been found in the periphery of the lung since introduction of mass screening by computed tomography (CT) in recent years [4–6]. Most such small cancers are not detectable in chest radiopraphs; by CT, they show ground-glass opacity (GGO) [7]. Most of them are diagnosed pathologically as localized bronchioloalveolar carcinoma or as atypical adenomatous hyperplasia (AAH) [8,9], a precancerous lesion. Further, development of video-assisted thoracoscopic surgery (VATS) can permit relatively noninvasive wedge resection of small lung nodules in a short operating time, which is particularly important for poor-risk patients [10–12]. However, indications for sublobular resection and curability of these small lung cancers by such procedures still are controversial. Avoidance of excessive surgery for small lung cancers detected by increasingly wide spread mass CT screening will become an important issue. We therefore sought to identify the clinicopathologic characteristics of lung cancers suitable for wedge resection by retrospectively analyzing outcomes of patients with primary NSCLC removed by sublobular resection without systematic dissection of lymph nodes.

2. Patients and methods

2.1. Patients

We analyzed consecutive 100 patients with primary NSCLC initially treated at our hospital from January 1981 to December 2002 by wedge resection or segmentectomy without systematic dissection of lymph nodes. Patients who underwent lobectomy for primary lung cancer prior sublobular resection or who underwent sublobular resection as a palliative operation for advanced disease were excluded from the present analyses. As 2051 patients with NSCLC underwent surgery during this period, those undergoing sublobular resection represented 100/2051 of cases (4.8%). Patients included 44 women and 56 men, and their ages ranged from 40 to 92 years (mean, 71.0). The final histologic diagnosis was determined from the resection specimen. Histologic types included 76 adenocarcinomas, 21 squamous cell carcinomas, and 3 large cell carcinomas. All patients were staged according to UICC (Union Internationale Centre le Cancer) criteria [13]. Cases included 83 representing clinical stage IA and 17, stage IB. By high-resolution CT, 27 tumors (27%) showed pure GGO (PGGO). PGGO was defined as lesions with no solid component in the tumor detected by high-resolution CT [14,15]; this type of lesion has been referred to as "G type" in another report [16]. The mean follow-up period of all patients after surgery was 32.2 months.

2.2. Operation

Wedge resection or segmentectomy was performed as a sublobular limited resection. Systematic dissection of lymph nodes was not performed in any case. Wedge resection was performed for 97 patients and segmentectomy was performed for three patients, considering both size and anatomic location of the tumor. Informed consent regarding possible elevated risk of locoregional recurrence and inferior survival rate after limited resection was obtained from all patients whose cardiopulmonary function was adequate to permit lobectomy. VATS was performed in 62 patients, and open thoracotomy was performed in 38 patients. For patients with severe pleural adhesions or large tumors, open thoracotomy was performed. Mortality in the postoperative period was 2%.

2.3. Statistical tests

Significance of differences between groups was evaluated using the nonparametric Mann–Whitney U-test or the χ^2-test as appropriate. The survival rate was calculated by the Kaplan–Meier method. Survival differences were compared using the log rank test as a univariate analysis. A multivariate analysis also was carried out according to the Cox proportional hazards model in order to detect independent risk factors. $P < 0.05$ was considered significant.

Table 1 Clinicopathologic features of patients undergoing sublobular limited resection for non-small cell lung cancer

	All cases ($N = 100$)	PGGO ($N = 27$)	Non-PGGO ($N = 73$)	Difference between PGGO and non-PGGO P-value
Age (mean ± S.D.)	71.0 ± 9.7	66.4 ± 10.4	72.6 ± 9.0	0.0064
Gender				
Women	44	15	29	0.1568
Men	56	12	44	
Histology				
Ad	76	27	49	0.0029
WD	50	27	23	
MD	15	0	15	
PD	11	0	11	
Sq	21	0	21	
WD	2	0	2	
MD	15	0	15	
PD	4	0	4	
La	3	0	3	
Mean diameter (mm)	18.0 ± 13.0	9.3 ± 3.5	21.2 ± 13.7	<0.0001

PGGO: pure ground-glass opacity; S.D.: standard deviation; Ad: adenocarcinoma; Sq: squamous cell carcinoma; La: large cell carcinoma; WD: well-differentiated; MD: moderately differentiated; PD: poorly differentiated.

3. Results

Clinicopathologic features of the patients are shown in Table 1. Twenty-seven tumors (27%) showed PGGO by high-resolution CT (Fig. 1). These all were diagnosed histologically as localized bronchioloalveolar carcinoma in resection specimens, and none of these showed microscopic blood vessel or lymph vessel invasion (Fig. 2). Seventy-three tumors (73%) that included solid components of varying extent by CT were defined as non-PGGO tumors (Fig. 3). Patients with PGGO tumors were significantly younger than those with non-PGGO tumors. Although no statistical significance was obtained, PGGO tumors were somewhat more common in women than in men. Non-PGGO tumors showed various histologic types and different differentiation grades. In contrast, all PGGO tumors were bronchioloalveolar carcinomas. Diameter of tumors showing PGGO was 9.3 ± 3.5 mm (mean ± S.D.), while that of non-PGGO tumors was 21.2 ± 13.7 mm, a significant difference ($P < 0.0001$).

The distribution of the longest dimension of resected tumors is plotted in Fig. 4. Seventy-three tumors (73%) were 20 mm or less, while 36 (36%) were 10 mm or less.

Reasons to perform sublobular resection instead of standard lobectomy were small tumor size in 36 patients, poor pulmonary function in 35, advanced age in 18, heart disease in 8, and simultaneous multiple lung cancers in three. The surgical margin was positive for tumor upon postoperative histologic examination in nine cases. Overall and lung cancer-specific 5-year survival rates in all patients were 58.0 and 64.8%, respectively.

Survival rates in groups classified according to various possible prognostic factors are shown in Table 2. No survival differences were noted in relation to gender or age. Overall survival with squamous cell carcinoma was significantly worse than with adenocarcinoma ($P = 0.0382$). Significant overall survival differences were obtained for size of tumor (≤10 mm versus >10 mm, ≤20 mm versus >20 mm, and ≤30 mm versus >30 mm; $P = 0.0384$, $P = 0.0002$ and $P = 0.0047$, respectively) and degree of differentiation (well differentiated [WD] versus moderately differentiated [MD] and poorly differentiated [PD]; $P = 0.0007$). Survival rates in adenocarcinoma are shown in Table 3. Overall 5-year survival rate with small adenocarcinomas (≤20 mm) was 93.7%, which was significantly better than 24.8% with larger adenocarcinomas ($P < 0.0001$, Fig. 5). The overall 5-year survival rate with WD adenocarcinoma (81.2%) also was significantly better than in a group combining MD + PD adenocarcinomas (30.7%,

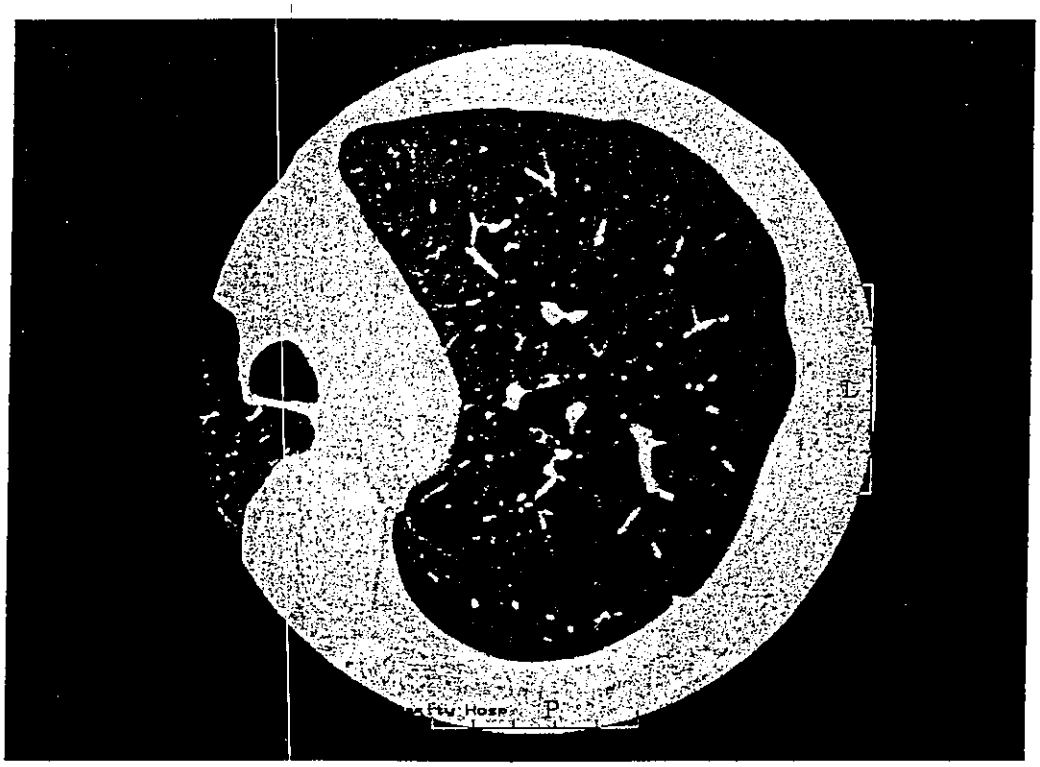

Fig. 1 Representative findings of high-resolution computed tomography (CT) showing a tumor with pure ground-glass opacity (PGGO). The pathologic diagnosis of this tumor was bronchioloalveolar carcinoma.

$P = 0.0003$; Fig. 6). When all patients were analyzed together by multivariate analysis including tumor size ($\leq$20 mm versus >20 mm) and degree of differentiation (WD versus MD + PD), both factors were independent significant predictors for survival ($P = 0.0338$ and 0.0364, respectively).

The observation period after surgery for patients with PGGO ranged from 1 to 64 months (mean, 25.4). Neither locoregional recurrences nor lung cancer-specific deaths have been observed in this group so far, though one patient died from other disease, specifically rupture of an aortic aneurysm (Fig. 7).

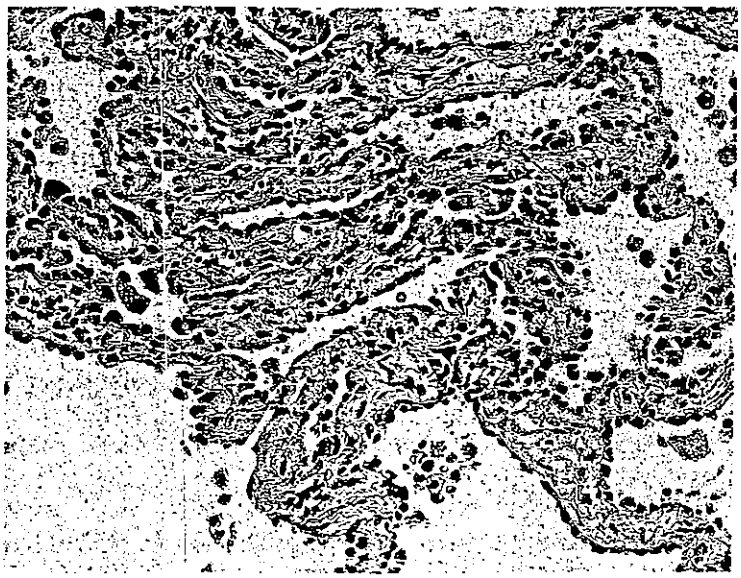

Fig. 2 As in the lesion shown here, the pathologic diagnosis in resection specimens of all pure ground-glass opacity (PGGO) tumors in this study was bronchioloalveolar carcinoma without microscopic blood vessel or lymph vessel invasion (hematoxylin and eosin; 200×).

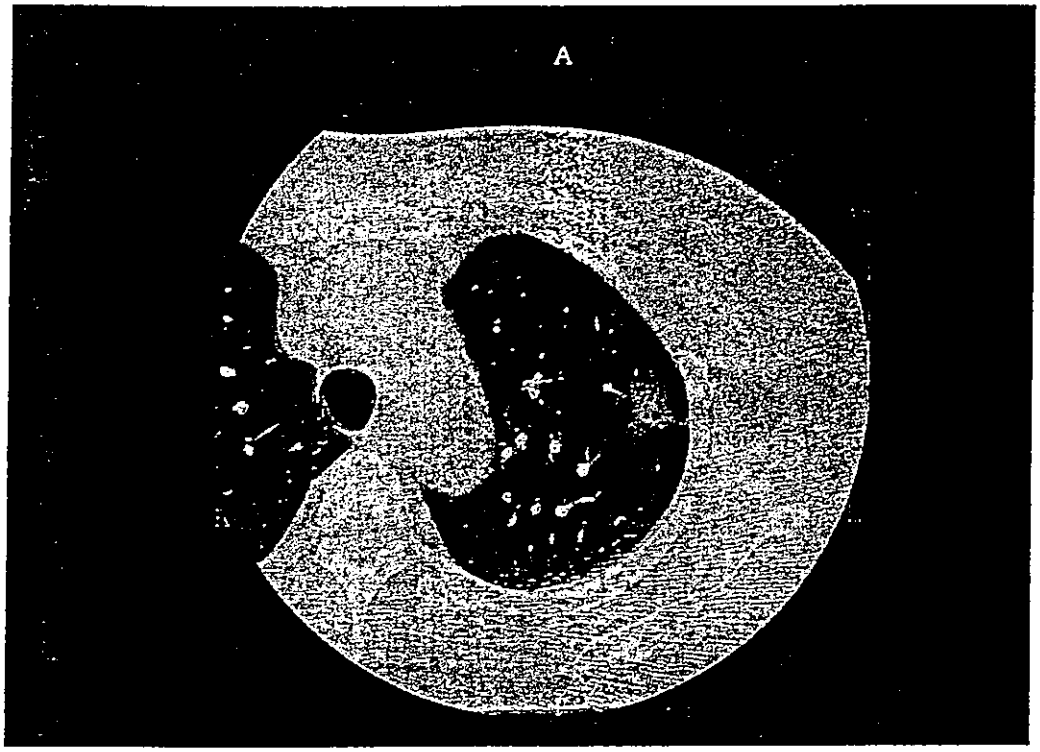

Fig. 3 Representative findings of high-resolution computed tomography (CT) showing a non-pure ground-glass opacity (non-PGGO) tumors. A solid component can be seen at the center of the tumor.

4. Discussion

Screening for lung cancer using chest CT is becoming more prevalent, and small peripheral lung cancers are being detected more frequently. Most of these lung cancers detected by chest CT but not by radiography are approximately 10 mm or less in diameter; histologically, they are well differentiated, bronchioloalveolar-type adenocarcinomas. The typical appearance of these lesions by high-resolution CT is so-called GGO, which resembles focal fibrosis or inflammatory change. In contrast, small lung cancers detected in chest radiographs include squamous cell carcinomas and poorly differentiated adenocarcinomas, which form solid nodules.

Because of a high incidence of intrathoracic recurrences after wedge resection [2,17], this surgical method has been used mainly for patients who could not tolerate lobectomy. However, we need to re-evaluate the role of wedge resection in the present era when many tiny peripheral lung cancers are detected and relatively noninvasive VATS techniques are commonly available [10,12]. In doing

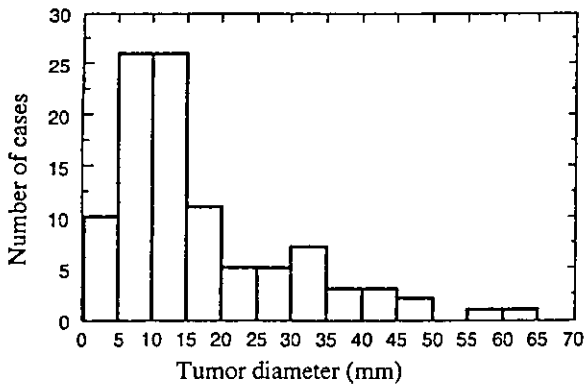

Fig. 4 Distribution of the longest dimension of the resected tumor.

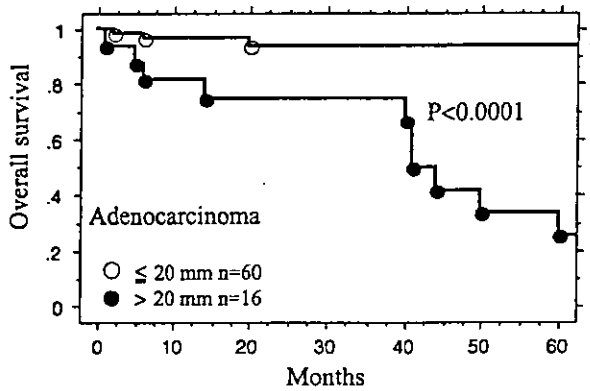

Fig. 5 An overall survival difference ($P < 0.0001$) was found between smaller adenocarcinomas (≤20 mm; $n = 60$; open circles) and larger adenocarcinomas (>20 mm; $n = 16$; filled circles).

Table 2 Univariate analysis for 100 patients with non-small cell lung cancer undergoing sublobular limited resection

Prognostic factor	Overall		Lung cancer-specific	
	Five-year survival rate (%)	*P*-value	Five-year survival rate (%)	*P*-value
Gender				
Women ($n = 44$)	57.7	0.6463	61.9	0.8782
Men ($n = 56$)	56.8		65.3	
Age				
≥73 ($n = 48$)	55.8	0.7185	64.2	0.8728
<73 ($n = 52$)	62.8		67.8	
Histologic type				
Ad ($n = 76$)	63.2	0.0382	66.4	0.7567
Sq ($n = 21$)	42.1		58.7	
Tumor size (1 cm)				
≤1 cm ($n = 36$)	65.6	0.0384	75.0	0.0403
>1 cm ($n = 64$)	52.4		58.2	
Tumor size (2 cm)				
≤2 cm ($n = 73$)	78.2	0.0002	87.6	<0.0001
>2 cm ($n = 27$)	33.2		37.6	
Tumor size (3 cm)				
≤3 cm ($n = 83$)	64.6	0.0047	72.5	0.0057
>3 cm ($n = 17$)	37.2		42.1	
Differentiation				
WD ($n = 52$)	79.7	0.0007	83.9	0.0041
MD + PD ($n = 45$)	38.0		45.7	

Ad: adenocarcinoma; Sq: squamous cell carcinoma; WD: well differentiated; MD: moderately differentiated; PD: poorly differentiated.

so, the group of patients for whom wedge resection is sufficient for cure must be identified. Miller et al. [18] compared outcomes of 25 sublobular resections (13 wedge resections and 12 segmentectomies) with those of 71 lobectomies for lung cancer less than 1 cm, and found that patients who underwent lobectomy had significantly better survival and fewer recurrences than patients who had wedge resection or segmentectomy. Landreneau

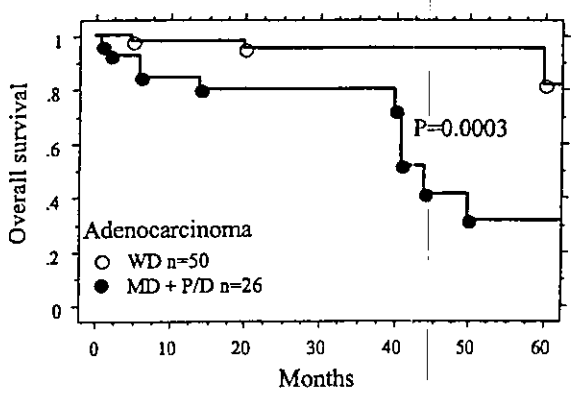

Fig. 6 An overall survival difference ($P = 0.0003$) was found between well-differentiated (WD) adenocarcinomas ($n = 50$; open circles) and a group including moderately–plus poorly–differentiated (MD + PD) adenocarcinomas ($n = 26$; filled circles).

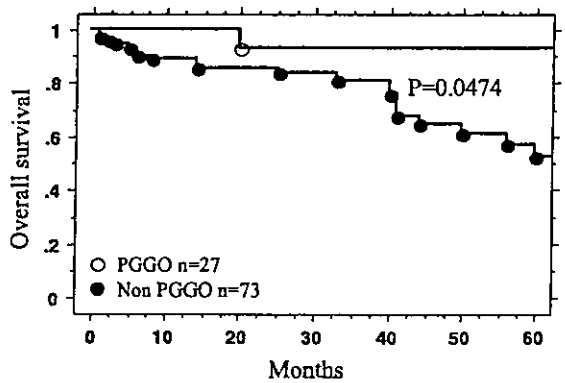

Fig. 7 An overall survival difference ($P = 0.0474$) was found between pure ground-glass opacity (PGGO) tumors ($n = 27$; open circles) and non-PGGO tumors ($n = 73$; filled circles).

Table 3 Univariate analysis for 76 patients with adenocarcinoma undergoing sublobular limited resection

Prognostic factor	Overall		Lung cancer-specific	
	Five-year survival rate (%)	*P*-value	Five-year survival rate (%)	*P*-value
Gender				
Women ($n = 35$)	78.3	0.5821	83.0	0.2765
Men ($n = 41$)	57.1		59.3	
Age				
≥71 ($n = 39$)	65.5	0.5235	67.2	0.7318
<71 ($n = 37$)	60.9		65.9	
Tumor size (1 cm)				
≤1 cm ($n = 29$)	94.4	0.0321	100.0	NC
>1 cm ($n = 47$)	51.6		53.9	
Tumor size (2 cm)				
≤2 cm ($n = 60$)	93.7	<0.0001	98.2	<0.0001
>2 cm ($n = 16$)	24.8		26.5	
Tumor size (3 cm)				
≤3 cm ($n = 66$)	71.5	0.0101	74.6	0.0180
>3 cm ($n = 10$)	35.0		38.9	
Differentiation				
WD ($n = 50$)	81.2	0.0003	83.9	0.0006
MD + PD ($n = 26$)	30.7		33.3	

Ad: adenocarcinoma; Sq: squamous cell carcinoma; WD: well differentiated; MD: moderately differentiated; PD: poorly differentiated; NC: not calculated.

et al. [19] analyzed pathologic stage IA NSCLC for which the patient underwent open wedge resection ($n = 42$), video-assisted wedge resection ($n = 60$), or lobectomy ($n = 117$). At 5 years survival was 58% for patients with open wedge resection, 65% for those with video-assisted wedge resection, and 70% for those with lobectomy. They concluded that this difference resulted from a significantly greater rate of deaths unrelated to cancer in the 5 years following wedge resection. These two studies failed to find clinicopathologic characteristics that might define tumors suitable for limited resection. In our present study, 93.7% 5-year survival was obtained following wedge resection in patients with WD adenocarcinomas less than 20 mm. Histopathologic differentiation also is a significant prognostic factor. Kodama et al. [20] performed limited resection for selected T1N0 patients despite sufficient pulmonary function to tolerate more extensive surgery, and reported a 5-year survival rate of 93%.

Small tumor size alone probably is inadequate as an indication for limited surgery. Ohta et al. [21] found nodal micrometastasis in 21.7% (23/106) of patients with adenocarcinomas with diameters of 2 cm or less. However, when Noguchi et al. [22] analyzed cases by histopathologic type, localized bronchioloalveolar carcinoma showed no lymph node metastasis. In our 27 bronchioloalveolar carcinomas showing PGGO, we have not yet encountered a locoregional recurrence or a distant metastasis after wedge resection. These PGGO tumors included 18 type A, 6 type B and 3 type C in Noguchi's classification [22]. Watanabe et al. [15] also reported absence of cancer death or relapse during median follow-up time of 32 months after wedge resection of 17 bronchioloalveolar carcinomas showing PGGO. In addition, Nakata et al. [8] found that none of 34 adenocarcinomas showing focal GGO and measuring 2 cm or less in diameter had lymph node involvement. Thus, we believe that this group of adenocarcinomas is slow-growing and relatively noninvasive. For instance, Hasegawa et al. [16] reported a mean volume doubling time in PGGO tumors of 813 days, which was significantly longer than in partly GGO tumors with a solid central component (457 days) or in entirely solid nodules (149 days). The higher growth rate presumably reflects an increase in malignant biologic characteristics during development of adenocarcinoma. Accordingly, we believe that wholly PGGO tumors are good candidates for VATS wedge resection

without lymphadenectomy. To obtain definitive evidence, a multi-institutional trial now is underway with the sponsorship of the Japan Clinical Oncology Group (JCOG 0201). In that study, nodal status in clinical stage IA adenocarcinoma including PGGO is being examined by standard lobectomy and systematic lymphadenectomy. If absence of lymph node metastasis is proven in PGGO tumors in this trial, wedge resection for these lesions should become accepted as standard surgery.

In conclusion, relatively good outcome was obtained by wedge resection for small (≤20 mm), peripheral WD adenocarcinomas. VATS wedge resection for these tumors is an important option for patients with impaired cardiopulmonary function. However, since locoregional recurrence developed in 4/60 (6.7%) of these patients in our study, we still consider lobectomy to be the "gold standard". For peripheral localized bronchioloalveolar carcinoma showing PGGO, however, wedge resection appears to be the best option. Study over a longer follow-up period is needed, and larger numbers of cases should be examined with respect to histologic nodal status.

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Randomized Trial of Oral Versus Intravenous Antibiotics in Low-risk Febrile Neutropenic Patients with Lung Cancer

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Background: Neutropenic fever is one of the most serious adverse effects of cancer chemotherapy. Neutropenia may cause a life-threatening bacterial infection. Therefore, febrile neutropenic inpatients are empirically treated with intravenous broad-spectrum antibiotics. Recently, several studies have suggested the presence of low-risk groups among febrile neutropenic patients.

Methods: A prospective randomized trial was conducted to compare treatment with oral ciprofloxacin (200 mg) and amoxicillin-clavulanate (375 mg) administered every 8 h against that with intravenous ceftazidime (1 g) administered every 12 h in low-risk febrile neutropenic patients with lung cancer. All patients received chemotherapy and antibiotic therapy while being hospitalized.

Results: A total of 177 patients with lung cancer agreed to participate in this study prior to undergoing chemotherapy. Among them, a total of 36 neutropenic patients with 42 febrile episodes were enrolled in the study. Treatment was successful without the need for modification in 91% of the episodes in patients receiving the oral regimen and 79% of the episodes in patients receiving the intravenous regimen. No treatment-related deaths occurred. One patient developed nausea while receiving the oral regimen, so the oral regimen was changed to the intravenous regimen in this patient.

Conclusions: This prospective study suggested that treatment with oral antibiotics ciplofloxacin plus amoxicillin-clavulanate was effective for low-risk febrile neutropenic patients after chemotherapy.

Key words: oral antibiotics – low-risk – febrile neutropenia

INTRODUCTION

Neutropenic fever is one of the most serious adverse effects in cancer chemotherapy. Neutropenia may cause a life-threatening bacterial infection. The risk of infection increases in patients with a neutrophil count of <1000/mm^3 (1). As a result, most cancer patients remain in hospital after undergoing chemotherapy in Japan, and empirical broad-spectrum intravenous antibiotics are administered to febrile neutropenic patients. This approach is effective in reducing morbidity and mortality but is associated with toxicity related to intravenous antibiotics, as well as physical and psychological discomfort for the patient. In addition, parenteral antibiotic administration requires insertion of an intravenous catheter, which carries a risk of infection. Prolonged hospitalization may cause infection to drug-resistant organisms, is expensive, and has a detrimental effect on quality of life.

Recently, several studies have suggested the presence of low-risk groups among febrile neutropenic patients (2–4). Medical complications were less frequent overall for patients whose neutropenia (<500/mm^3) resolved in 7 days or less, compared to other patients (4). A study demonstrated that neutropenia lasted for 1 week or less in 85% of the patients selected using the following exclusion criteria: hepatic insufficiency (alanine aminotransferase activity > four times normal), a history of recurrent pyrexia of undetermined origin (PUO), shock (systolic blood pressure <80 mmHg or peripheral circulatory failure), any other comorbid conditions requiring hospitalization (except for anemia or thrombocytopenia) and the expectation of prolonged neutropenia (>7 days) based on the presence of aplastic anemia, myelodysplasia, leukemia or other causes (5). Patients who did not meet any of these exclusion criteria were considered to belong to a low-risk group. A randomized trial comparing oral ciplofloxacin and amoxicillin-clavulanate with

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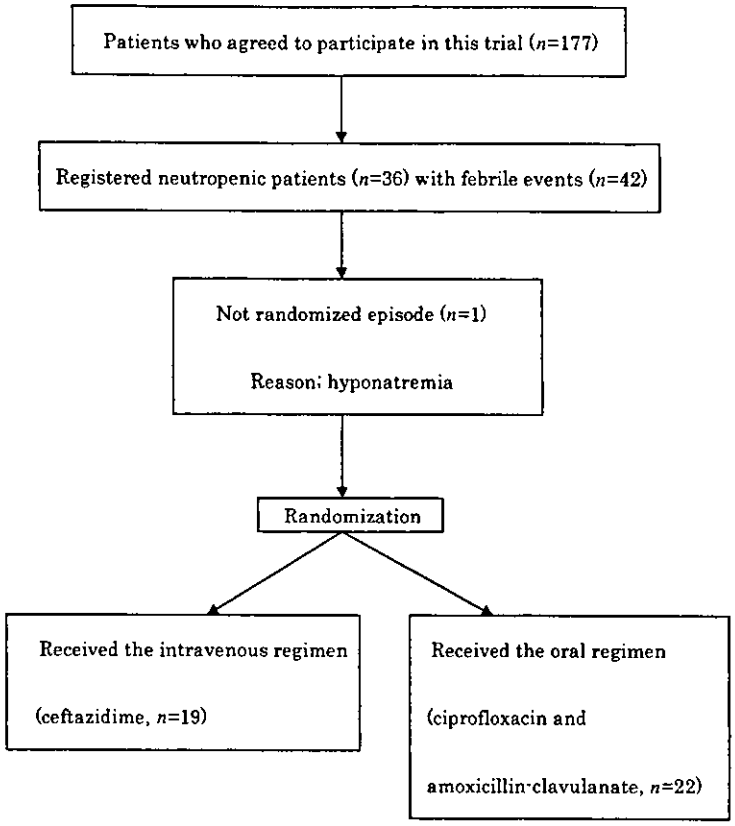

Figure 1. Study flow diagram.

intravenous aztreonam and clindamycin was conducted in these low-risk febrile neutropenic patients (6). This trial demonstrated that oral antibiotics were as effective as intravenous ones.

We conducted a randomized trial to compare oral ciplofloxacin and amoxicillin-clavulanate with intravenous ceftazidime, which was empirically used, in low-risk febrile neutropenic patients with lung cancer. The combination of ciplofloxacin and amoxicillin-clavulanate provides sufficient coverage against gram-negative enteric bacilli and gram-positive cocci. The aim of our trial was to determine whether an oral regimen was an acceptable alternative to an intravenous regimen in low-risk patients.

PATIENTS AND METHODS

Criteria for Eligibility

Eligible patients included those with lung cancer and neutropenia after having undergone platinum-based chemotherapy. Patients were required to have a single axillary temperature of 37.5°C or higher after platinum-based chemotherapy, an absolute leukocyte count $\leq 1000/mm^3$ or a neutrophil count $\leq 500/mm^3$. Other criteria included an age of 20 years or more and an ECOG performance status (PS) of between 0 and 2 (inclusive). The exclusion criteria included the following conditions: previous anaphylactic reactions or hypersensitivity to any of the antibiotics used or related products; antibiotic treatment within the preceding 96 h; prior administration of non-steroidal anti-inflammatory drugs (NSAIDs); recurrent PUO; renal insufficiency (serum creatinine ≥2.5 mg/dl or need for dialysis); hepatic insufficiency (aspartate aminotransferase/alanine aminotransferase levels > four times the normal value); systolic blood pressure ≤90 mmHg or peripheral circulatory failure; uncontrolled hypercalcemia; altered sensorium; respiratory rate ≥30 breaths/min; serum sodium ≤128 mg/dl; and the inability to take oral medications because of painful mouth ulcers, intestinal malabsorption or severe nausea and vomiting. All patients were required to provide their written informed consent prior to undergoing chemotherapy, and the institutional review board at the National Cancer Center approved the study's protocol.

Treatment Plan

All patients received chemotherapy and antibiotic therapy on an inpatient basis. The baseline evaluation included a physical examination (blood pressure, pulse and respiratory rate, temperature). Cultures were obtained of blood, sputum, throat, urine and feces (anal swabs). Patients were randomly assigned to one of two regimens using consecutive sealed envelopes. The oral regimen consisted of ciprofloxacin (200 mg) plus amoxicillin-clavulanate (375 mg) administered every 8 h, while the intravenous regimen consisted of ceftazidime (1 g) administered every 12 h. Granulocyte colony-stimulating

Table 1. Patient characteristics

Characteristic	Oral ciprofloxacin and amoxicillin-clavulanate	Intravenous ceftazidime
Eligible episodes	22	19
Age (year)		
Median (range)	68 (54–76)	67 (51–75)
Gender		
Male/female	15/7	15/4
ECOG PS		
0/1	6/16	2/17
Smoking status		
Never	5	4
Past	4	5
Current	13	10
Smoking index		
Median (range)	910 (0–3480)	880 (0–2400)
Histologic type		
Adenocarcinoma	5	7
Squamous cell carcinoma	4	4
Large cell carcinoma	1	2
Small cell carcinoma	12	6
Absolute neutrophil count (at randomization)		
≤100/mm^3	3	0
101–500/mm^3	14	12
501–1000/mm^3	5	7
Duration of neutropenia after randomization (days)		
Median (range)	4 (2–7)	4 (2–12)
Treatment with G-CSF [no. (%)]	19 (86)	14 (74)

factor (G-CSF) support was allowed. The administration of NSAIDs was not allowed. The administration of aluminum- and magnesium-containing antacids and oral iron preparations was allowed if they were administered more than 3 h after the administration of ciplofloxacin. The use of other antibiotics was prohibited during the trial.

Diagnostic Criteria and Evaluation

Each febrile episode was classified as either a clinically or microbiologically documented infection or PUO. Microbiologically documented infection necessitated the isolation of a bacterial pathogen from blood, urine, pus or exudates, along with clinical, laboratory or radiographic evidence of infection at the same site. Clinical infection was diagnosed when clear evidence of an infection was present but an organism could not be isolated. PUO was defined as the requisite temperature elevation with no clinical or microbiologic evidence of infection within 72 h of enrolment in the study.

Clinical outcomes were evaluated at 48 h and 7 days after the start of antibiotic treatment. Each patient was physically examined every day. Patients who remained febrile (without a downward trend) after 48 h or who had a body temperature ≥37°C on day 7 were removed from the study and treated with appropriate therapy; antibiotic treatment in these patients was considered to have failed. Treatment outcome was classified into three categories (7). 'Success without modification' referred to episodes in which the patient successfully recovered from fever and neutropenia without the need of additional antimicrobial agents or the modification of the initial randomly assigned regimen. 'Success with modification' referred to episodes in which the patient successfully recovered from the fever and neutropenia but required a modification of the assigned regimen. 'Failure' referred to all other cases. The response rate was defined as the percentage of 'success without modification' cases among all eligible patients.

Statistical Analysis

Assuming a response rate to the intravenous regimen of 80%, the study was designed to enroll 63 patients per treatment arm to ensure that the oral regimen would not be 20% worse (i.e. 60%) at a level of significance alpha = 0.05 and 80% power using a two-sided chi-square test. An interim analysis was

Table 2. Response rate

	Oral regimen ($n = 22$)		Intravenous regimen ($n = 19$)	
	PUO	Documented infection	PUO	Documented infection
Success without modification	16	4	10	5
Success with modification	0	2	0	4
Response rate	91%		79% $P = 0.39$	

Response rate was defined as the percentage of success without modification cases among all eligible patients.

planned at an accrual level of 40 patients. If a significant difference in response rates ($P < 0.01$) was observed, or if septic shock appeared in more than 10% of the patients undergoing the oral regimen, the study was to be terminated. Comparisons between proportions were done using a Pearson chi-square test or a Fisher exact test, when appropriate.

RESULTS

Patient Population and Treatment

A total of 177 patients with lung cancer agreed to participate in this study prior to undergoing chemotherapy between May 1995 and February 2001. Among them, a total of 36 neutropenic patients with 42 febrile episodes were enrolled in the study. One episode was ineligible because of hyponatremia. Of the 41 episodes (in 35 patients) included in the analysis, four patients were enrolled more than once: three patients had two episodes each, and one patient had four episodes. The patient characteristics are listed in Table 1. Twenty-two episodes were assigned to the oral regimen and 19 episodes were assigned to the intravenous regimen (Fig. 1). No statistically significant difference was seen between the two groups with regard to age, gender, PS, smoking status, histologic subtype and absolute neutrophil count. During 33 episodes, G-CSF was administered in addition to the assigned treatment. The median duration of neutropenia was 4 days in both groups.

Evaluation before Antibiotic Therapy

PUO was observed in approximately two-thirds of all febrile episodes. Infection was documented in 15 episodes. Most documented infections consisted of bronchus or lung infections (10 episodes) or urinary tract infections (three episodes). Other infections included colitis and alveolar pyorrhea. Microbiological pathogens were detected in five episodes. *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae* were isolated from sputum and *Pseudominas aeruginosa* and *Enterococcus faecalis* were isolated from urine.

Efficacy

The response rates were similar in the two groups (91% versus 79%, $P = 0.39$) (Table 2). PUO was successfully treated in all 26 episodes. On the other hand, documented infection was successfully treated in 60% of the patients (four out of six episodes in patients receiving the oral regimen and five out of nine episodes in patients receiving the intravenous regimen). A total of six patients received changes to their treatment regimen. Two patients in the oral regimen group were switched to piperacillin sodium or ceftazidime. Four patients in the intravenous regimen group were switched to carbapenem with or without the addition of clindamycin or amikacin.

In approximately half of the episodes in both groups, the fever disappeared by day 4 of the treatment. By day 8, the fever had resolved in 90% of all episodes.

Adverse Effects

Few adverse effects were encountered. One patient developed nausea while receiving the oral regimen. The oral regimen was therefore changed to an intravenous regimen (piperacillin sodium) in this patient.

DISCUSSION

Febrile neutropenia can be a life-threatening complication of cancer chemotherapy. Therefore, febrile neutropenic patients are usually hospitalized for the administration of empiric, broad-spectrum, intravenous antibiotic therapy. Several analyses have demonstrated that febrile neutropenic patients comprise heterogeneous subgroups among which are low-risk patients with a high response rate to antibiotic therapy and a low risk of serious complications (2–4). We conducted a randomized trial to compare the oral administration of ciplofloxacin and amoxicillin-clavulanate with the intravenous administration of ceftazidime in low-risk febrile neutropenic patients with lung cancer. However, this study was terminated in February 2001 because of slow enrolment and the publication of two large randomized trials comparing oral with intravenous antibiotic therapy for low-risk febrile patients who developed neutropenia during cancer chemotherapy (8,9). In one trial, oral ciplofloxacin plus amoxicillin-clavulanate was compared with intravenous ceftazidime (8). These regimens were almost identical to those in our trial. In the other trial, oral ciplofloxacin plus amoxicillin-clavulanate was compared with intravenous ceftriaxone plus amikacin (9). Both trials demonstrated that oral therapy with ciplofloxacin plus amoxicillin-clavulanate was as safe and effective as intravenous therapy. Our trial confirmed these results, in spite of the smaller sample size.

The selection of low-risk patients with febrile neutropenia is very important. A multinational trial demonstrated that predictive factors for low risk complications included a burden of illness indicating the absence of symptoms or the presence of mild symptoms [weight, 5; odds ratio (OR), 8.21] or moderate symptoms (weight 3; OR, 3.70); the absence of hypotension (weight, 5; OR, 7.62); the absence of chromic obstructive pulmonary disease (COPD) (weight, 4; OR, 5.35); the presence of a solid tumor or the absence of previous fungal infection in patients with hematologic malignancies (weight, 4; OR, 5.07); an outpatient status (weight, 3; OR, 3.51); the absence of dehydration (weight, 3; OR, 3.81); and an age <60 years (weight, 2; OR, 2.45). A risk-index score ≥21 was considered to indicate a low-risk (10). In our trial, all of the enrolled patients had solid tumors (lung cancer) without hypotension or dehydration and no or mild symptoms. All but one patient had no COPD, producing a risk score of 21 or greater.

PUO was observed in 63% of the low-risk febrile neutropenic patients. The PUO percentage was identical to that reported in previous trials. All patients with PUO were successfully treated with oral or intravenous antibiotic therapy in our trial. Oral ciplofloxacin plus amoxicillin-clavulanate was effective for the treatment of PUO. Documented infections were successfully treated with an oral regimen in four out of six episodes and with an intravenous regimen in five out of nine episodes. Six patients needed to modify their regimen to an intravenous regimen containing cephalosporin or carbapenem. Oral ciplofloxacin plus amoxicillin-clavulanate was also effective in selected low-risk patients with documented infections.

Oral antibiotics produced a successful outcome in 91% of the patients, although 86% of the patients also received G-CSF support. Whether G-CSF support is needed in low-risk patients remains uncertain. The clinical practice guidelines of the American Society of Clinical Oncology recommend that G-CSF should not be routinely used as adjunct therapy for the treatment of uncomplicated fever and neutropenia (11). Uncomplicated fever and neutropenia are defined as follows: fever of ≤10 days in duration; no evidence of pneumonia, cellulites, abscess, sinusitis or hypotension; and no uncontrolled malignancies. Oral antibiotics with ciplofloxacin plus amoxicillin-clavulanate are probably effective even if G-CSF support is not performed and can be easily administered to febrile neutropenic outpatients. In a randomized trial, oral antibiotics (ciplofloxacin plus amoxicillin-clavulanate) with early hospital discharge was compared with inpatient intravenous antibiotics (gentamicin plus tazocin) for the treatment of low-risk febrile neutropenic patients with cancer (12). This study suggested that oral antibiotics with early discharge was feasible and an alternative to conventional intravenous antibiotic regimens.

In conclusion, our trial suggested that oral antibiotic therapy with ciplofloxacin plus amoxicillin-clavulanate is effective for the treatment of low-risk febrile neutropenic patients, although the trial was prematurely terminated because of slow enrolment.

Acknowledgments

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REVIEW ARTICLE

Yasumasa Nishimura

Rationale for chemoradiotherapy

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Abstract The rationale for combining chemotherapy (CT) and radiotherapy (RT) is based mainly on two ideas, one being spatial cooperation and the other the enhancement of radiation effects. Spatial cooperation is effective if CT is sufficiently active to eradicate subclinical metastases and if the primary local tumor is effectively treated by RT. In this regard, no interaction between RT and CT is required, but differing toxicities are needed so that both modalities can be used at effective dosages. To enhance RT by CT, five major mechanisms of CT-RT interactions are required. CT can enhance RT effects by: (1) direct enhancement of the initial radiation damage by incorporating drugs into DNA, (2) inhibiting cellular repair, (3) accumulating cells in a radiosensitive phase or eliminating radioresistant phase cells, (4) eliminating hypoxic cells, or (5) inhibiting the accelerated repopulation of tumor cells. However, virtually all chemotherapeutic agents enhance radiation damage to normal tissues as well. Consequently, therapeutic benefits are only achieved if the enhanced tumor response is greater than that for normal tissues. Due to the complex interaction between CT and RT, the sequence of CT and RT is important. Clinical results of induction CT followed by RT are disappointing, and improvements in local control rates of RT by induction CT have not been observed. On the other hand, clinical trials, including metaanalyses, have clearly shown that CT given concurrently with RT results in improved local control and survival. Although acute toxicities are inevitably increased in concurrent chemoradiotherapy (CRT), no significant increases in late toxicities were reported in most clinical trials. Thus, a therapeutic benefit was observed with the use of concurrent CRT.

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Key words Radiation therapy · Chemotherapy · Chemoradiotherapy · Therapeutic gain · Rationale

Introduction

Chemoradiotherapy (CRT) represents definite progress in clinical oncology. Recently, the concurrent use of chemotherapy (CT) and radiation therapy (RT) has become a standard treatment for many types of cancer. In this short review, the rationale for combining CT and RT to improve the therapeutic ratio is discussed. During the development of CRT, in vitro and in vivo laboratory models have been helpful both in identifying drugs that are true enhancers of RT and in elucidating the mechanism of interaction.[1-3] Although laboratory data are useful for predicting the nature of the interaction, clinical trials are required to determine efficacious combinations that yield higher local control with an improvement in the therapeutic ratio. To obtain a therapeutic benefit, greater cytotoxicity in tumor cells than in normal cells is more important than synergic interactions between CT and RT. The rationale for CRT and the essential steps of basic and clinical investigations of CRT are summarized.

Therapeutic ratio

In general, tumor response and normal tissue damage are positively correlated with the dose of radiation, and this relationship is commonly described by a sigmoid curve (Fig. 1). The therapeutic ratio is defined as the ratio of the dose that produces a given probability (50% is most commonly used in experimental studies) of normal tissue damage and the dose that produces the same probability of tumor control. When CT is combined with RT, the tumor control curve shifts to the left, along with the response curve for normal tissue damage. The goal of combining CT and RT is to obtain a positive therapeutic ratio, and thus to

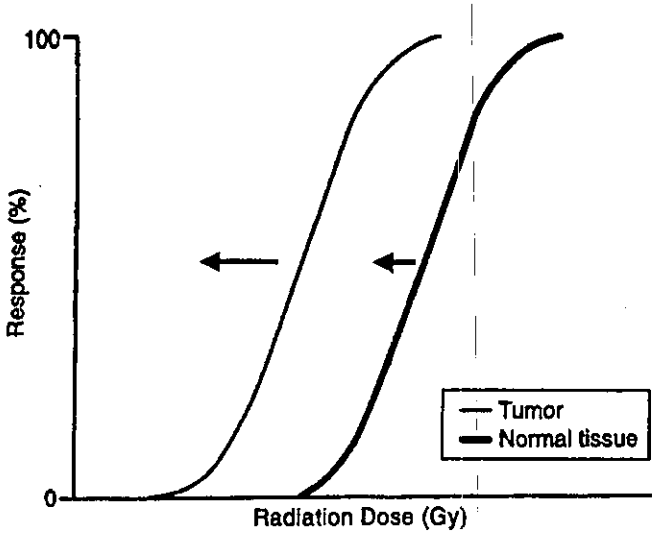

Fig. 1. Dose-response curves for tumor control and normal tissue damage. When chemotherapy (CT) is combined with radiotherapy (RT), the tumor control curve shifts to the left (*long arrow*), and the response curve for normal tissue damage also shifts in the same direction, as indicated by the *short arrow*

enhance the antitumor effect while minimizing toxicity to critical normal tissues.

Rationale for combining CT and RT

The rationale for combining CT and RT is mainly based on two ideas,[1-3] one being spatial cooperation, and the other the enhancement of radiation effects. Spatial cooperation is effective if CT is sufficiently active to eradicate subclinical metastases and if the primary local tumor is effectively treated by RT. In this regard, no interaction between RT and CT is required, but differing toxicities are needed so that both modalities can be used at effective dosages. A major limitation is the relatively poor efficacy of anticancer drugs against common solid tumors in adults. It is often difficult to eradicate even small subclinical metastases by CT. Also, local failure rates of a primary tumor following RT are high for many tumor sites.

To decrease the local failure rate, the enhancement of RT effects is necessary. In the presence of chemotherapeutic drugs, an increased response such as enhancement occurs within the irradiated volume. However, virtually all chemotherapeutic agents enhance radiation damage to normal tissues as well. Consequently, a therapeutic benefit is only achieved if enhancement of the tumor response is greater than that for normal tissues.

Among the many chemotherapeutic agents used, cisplatin is one of the best agents for yielding a therapeutic benefit. An enhancing effect by the additional use of daily cisplatin before each RT fraction was observed in an in vivo animal study.[4] This study found iso-effective enhancement factors of up to 2.2 for tumors and from 1.0 to 1.5 for normal tissues, such as mucosa, kidneys, and esophagus, suggesting a therapeutic gain.[4] These results were confirmed by a randomized clinical trial comparing RT alone and RT with additional daily cisplatin for inoperable non-small-cell lung cancer (NSCLC).[5] Concurrent daily cisplatin with RT improved local control and survival in NSCLC without increasing the toxicity of RT.

Mechanisms responsible for CT-RT interactions

Recent clinical trials, including metaanalyses, have shown that CT given concurrently with RT results in improved local control and survival,[6-10] implying interactions between CT and RT. Five major mechanisms responsible for CT-RT interactions are discussed in the following paragraphs.[1-3]

Initial radiation damage

The first mechanism responsible for CT-RT interaction is the direct enhancement of the initial radiation damage, resulting from the incorporation of the chemotherapeutic drugs into DNA. The primary target for radiation injury is DNA, where halogenated pyrimidines such as 5-fluorouracil (5-FU) are incorporated, making the DNA more susceptible to RT. Cisplatin interacts with nucleophilic sites on DNA or RNA to form intra- and interstrand cross-links.[3] When cisplatin cross-links to DNA are formed during RT, radioenhancement by cisplatin may occur.[3] This has been observed in both hypoxic and oxygenated cells.[3]

Inhibition of radiation damage repair

Secondly, the inhibition of cellular repair increases radiation damage. Cells have the ability to repair sublethal and potentially lethal radiation damage,[2] and halogenated pyrimidines, nucleoside analogs, and cisplatin interfere with cellular repair mechanisms. This inhibition of cellular repair can be effective when drugs are administered following fractionated RT. In general, nucleoside analogs such as fludarabine and gemcitabine are potent radiosensitizers. In animal experiments, the effect of fludarabine on radiocurability was greater when fludarabine was combined with fractionated RT than when it was combined with single-dose RT.[11] This implies that the inhibition of sublethal or potentially lethal damage repair is a significant mechanism responsible for the enhancement of the tumor radioresponse to fludarabine.

Cell-cycle effects

The third mechanism focuses on a cell-cycle effect. The cytotoxicity of most chemotherapeutic agents and that of radiation is highly dependent on the phase of the cell cycle.

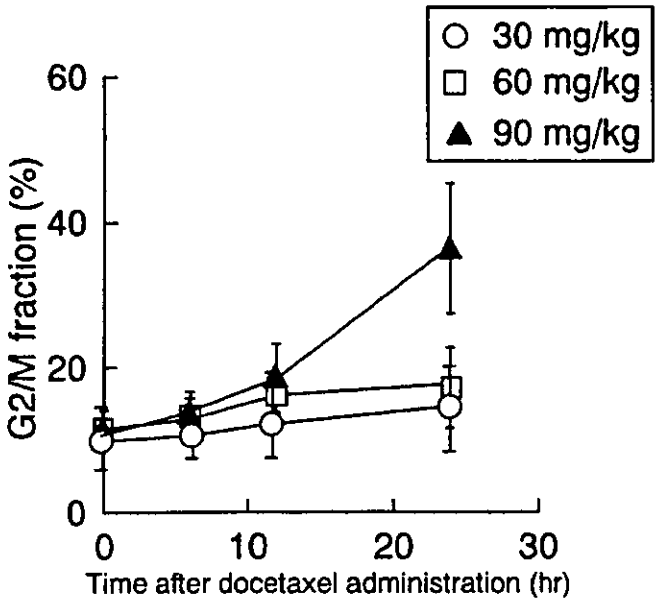

Fig. 2. Changes in the percentages of cells in the G2/M phase after different doses of docetaxel. The *data points* and *vertical lines* represent the means and SD of 12 to 16 mice (reproduced from M. Suzuki et al.,[14] with permission)

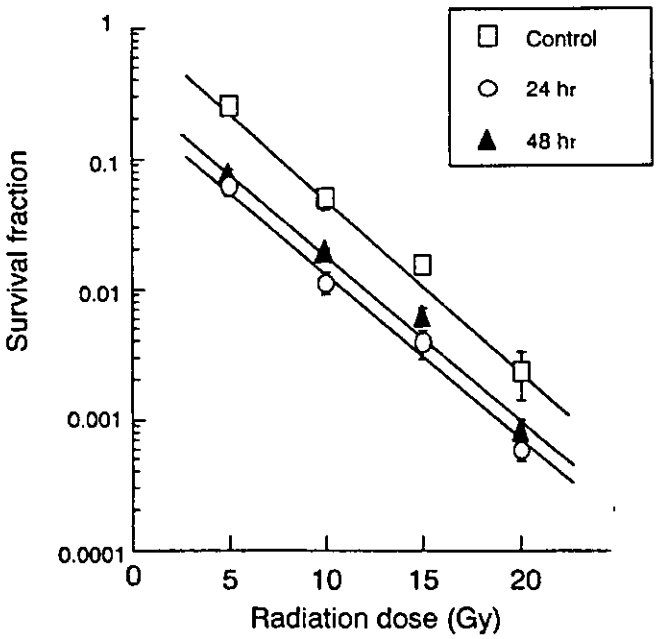

Fig. 3. Cell survival curves for SCCVII tumors. The *data points* and *vertical lines* represent the means and SD of 12 to 16 mice. The slopes of the cell survival curve are parallel, indicating an additive effect of 90 mg/kg docetaxel administered 24 h and 48 h before RT (reproduced from M. Suzuki et al.,[14] with permission)

Both chemotherapeutic agents and radiation are more effective against proliferating cells than against non-proliferating cells. Among proliferating cells, cells in the G2 and M phases are the most radiosensitive, and the cells in the S phase are the most radioresistant.[2] Based on this variation in radiosensitivity over the cell cycle, there exist two strategies for CRT, the use of chemotherapeutic agents that accumulate cells in a radiosensitive phase or those that eliminate radioresistant S-phase cells. The latter strategy is related to the mode of action of nucleoside analogs. Fludarabine and gemcitabine are incorporated into radioresistant S-phase cells, many of which die by apoptosis. This preferential removal of S-phase cells therefore contributes to the radioenhancement effects.

Taxanes such as paclitaxel and docetaxel inhibit tubulin depolymerarization and promote microtubule assembly and stability, which leads to cell-cycle arrest in the radiosensitive G2 and M phases.[12-14] The ability of taxanes to block cells in the G2/M phases is the biological rationale for combining these agents with radiation. Although the radiosensitizing effects of taxanes have been reported in various in vitro and in vivo studies,[12,13] our experiment using SCCVII tumors showed only additive effects of radiation and docetaxel.[14] The accumulation of cells in the G2/M phase was significantly increased 24 h after the administration of 90 mg/kg docetaxel (Fig. 2). When RT was given 24 and 48 h after this drug administration, only additive effects were noted (Fig. 3). Flow cytometry data suggested that docetaxel-arrested G2/M phase cells did not enter the next cell cycle and were killed by docetaxel alone. Thus, the synergic mechanism resulting from the combination of taxanes and RT may not work on all tumors.

Hypoxic cells

Hypoxic cells are 2.5–3.0 times less sensitive to radiation than well-oxygenated cells.[1,2] Tumors often include hypoxic areas, which is a cause of radioresistance. Chemotherapeutic agents can improve the RT effect by: (1) eliminating well-oxygenated tumor cells, which leads to tumor reoxygenation, (2) selectively eliminating hypoxic cells, or (3) sensitizing the hypoxic cells to radiation. Tumor reoxygenation is a major mechanism that results in the taxol-induced enhancement of the tumor radioresponse.[13] Milas et al.[13] have reported that radiosensitization by paclitaxel in vivo only occurs when RT is given under air-breathing conditions and not under hypoxic conditions. Improved tumor oxygenation by administration of paclitaxel was also observed by direct measurement of the intratumoral partial pressure of oxygen (PO_2).[13]

Several chemotherapeutic drugs, such as tirapazamine and mitomycin, selectively kill hypoxic cells.[1,2] These bioreductive drugs are reduced to a toxic intermediate under hypoxic conditions. Another approach to conquer hypoxic cells is the use of hypoxic cell radiosensitizeres. These drugs mimic the effect of oxygen by increasing radiation damage. Nitroimidazoles, such as misonidazole and nimorazole, are highly effective at enhancing the radioresponsiveness of tumors in rodents.[1,2] A metaanalysis of 50 randomized clinical trials showed that modification of tumor hypoxia significantly improved locoregional tumor control and overall survival after radiotherapy.[15] According to the tumor site, treatment benefits were observed for head

and neck tumors as well as bladder tumors.[15] However, no significant improvement occurred for uterine cervix, lung, esophagus, or central nervous system cancers.

Repopulation of tumor cells

The importance of the overall treatment time (OTT) for local tumor control by RT has been documented in a number of studies of head and neck cancers, uterine cervical cancer, and esophageal cancer.[16–18] Withers and colleagues[16] found that the TCD_{50} (the radiation dose which yields local control in 50% of tumors) progressively increased over time if the OTT was prolonged beyond 30 days.[16] Our analysis of esophageal and laryngeal squamous cell carcinomas treated by RT alone showed that the prolongation of OTT significantly reduced the local control rate.[17,18] One mechanism responsible for this may be the accelerated repopulation of tumor cells during fractionated RT.

Thus, any approach that reduces or eliminates the accelerated repopulation of tumor cells improves the efficacy of RT. This is likely to be one of the major mechanisms by which CT improves local tumor control when given concurrently with RT. Even a small decrease in repopulation between radiation fractions can significantly improve the tumor response to fractionated RT. However, most chemotherapeutic drugs inhibit repopulation not only in the tumor, but also in the compensatory cell regeneration of normal tissues that occurs during fractionated RT. Thus, a therapeutic benefit is expected if drugs are tumor-selective or if repopulation is faster in the tumor.

Recently, various molecular targeting drugs have become clinically available. Several drugs, such as epidermal growth factor receptor (EGFR) inhibitors, block the membrane receptors of growth factors or interfere with the signaling pathways involved in cell proliferation. These agents offer another possible method for inhibiting the accelerated repopulation of tumor cells during fractionated RT.[19,20]

Sequencing of CT and RT

According to the sequencing of CT and RT, CT is designated as either induction (neoadjuvant) CT, concurrent CT, or adjuvant CT, when it is given before, during, or after the course of RT, respectively. As clinical trials of adjuvant CT following RT have not been systematically studied, the aims and clinical results of induction CT and concurrent CT are described in the following paragraphs.

Induction CT

Induction CT has two main objectives,[1,2] one being the eradication of micrometastases while they contain small numbers of tumor cells, and the other being to reduce the size of the primary tumor that is to be irradiated. Reducing the number of clonogenic cells in the tumor increases the probability of tumor control by RT. In addition, CT-induced tumor shrinkage may provide a smaller target volume for RT, thereby limiting normal tissue damage.

Clinically, induction CT followed by RT was first investigated for most tumor sites because of anxiety over enhanced toxicities due to the use of concurrent CRT. Many randomized clinical trials have compared induction CT followed by RT with RT alone. However, in general, their results have not been encouraging for induction CT.[1,2,6,21–25] No improvement in the local control rate was obtained for uterine cervical cancer, head and neck cancer, esophageal cancer, or NSCLC.[6,21–25] Induction CT improved the overall survival rate for NSCLC,[23–25] although no improvement in survival was observed for the other tumor sites studied.[1,2,6,21,22] Chevalier and colleagues[23] reported that induction CT for NSCLC reduced the distant metastasis rate, although there was no improvement in the local control rate (Fig. 4). Thus, only for locally advanced NSCLC does induction CT decrease distant metastasis and work as expected.

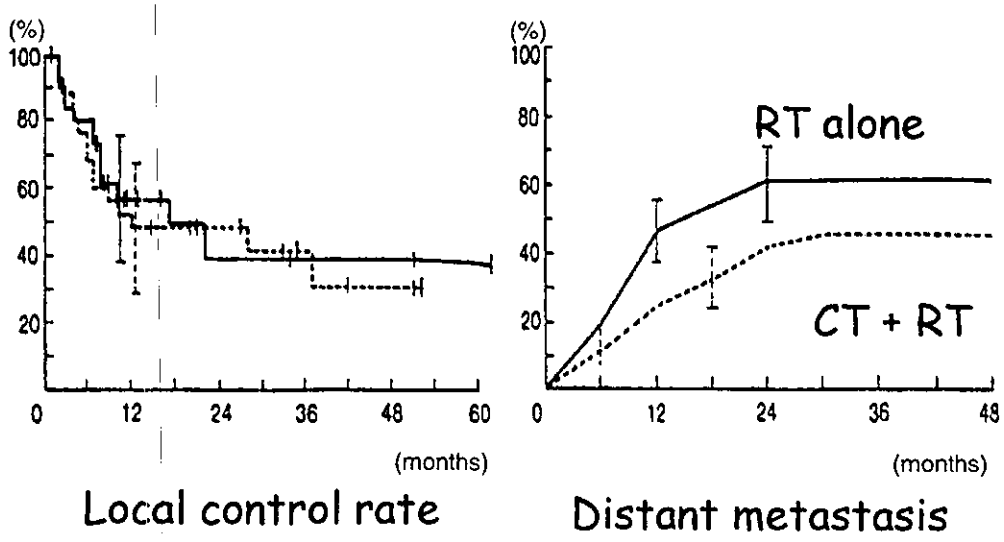

Fig. 4. Local control and distant metastasis rates for nonresectable non-small-cell lung cancer (NSCLC). Three hundred and fifty-three patients with nonresectable NSCLC were randomly allocated to RT alone (65 Gy/26 fractions) or to three courses of induction CT followed by RT. In this randomized trial, the distant metastasis rate was reduced by induction CT, while the local control rate was not improved. As a result, a marginal benefit in the overall survival rate was shown by the combining of induction CT with RT ($P = 0.08$; reproduced from T.L. Chevalier et al.,[23] with permission)

Clinical results of induction CT followed by RT have been disappointing, and improvement in the local control rates of RT by induction CT has not been observed for all tumor sites. Several possible explanations exist for the failure of induction CT to improve RT, the most likely being that induction CT induces the accelerated repopulation of tumor cells.[1,2] Induction CT leads to cell killing and tumor shrinkage. However, improved oxygenation, or other changes in the tumor microenvironment, may cause a higher rate of tumor cell proliferation when RT is initiated. Recently, the accelerated regrowth of NSCLC after induction CT was reported.[26] During the time between the end of induction CT with gemcitabine and cisplatin and the start of RT, rapid tumor progression occurs, due to the accelerated repopulation. The tumor volume doubling time ranges from 8.3 to 171 days, with a median of 29 days,[26] and this value is far less than the mean values for untreated NSCLC.

Another possibility is that induction CT does not affect tumor cells that are resistant to RT. This explanation is not generally valid, because most drugs used for induction CT do not produce cross-resistance effects with RT.[2] However, CT and RT are resistant to non-cycling quiescent cells. From this viewpoint, we investigated the effects of induction CT on the proliferation parameters of tumor cells, using biopsy and surgical specimens of esophageal cancer treated with or without induction CT involving cisplatin.[27] Our study revealed that the mean Ki-67 labeling indexes for surgical specimens treated with or without induction CT were 47% or 67%, with a significant difference ($P < 0.005$).[27] This indicates that CT decreases the percentage of cycling and proliferating tumor cells. This is not surprising, because cisplatin is more effective against proliferating cells than against non-cycling quiescent cells. As a result of induction CT, the percentage of quiescent cells, also known as radioresistant cells (closely related to hypoxic cells) was increased. These perturbing effects of CT may be also attributed to the failure of induction CT before RT.

Concurrent CT

For concurrent CRT, CT can act on both systemic and primary lesions. However, the main objective of concurrent CT is to use CT-RT interactions to maximize the antitumor effect, even though it inevitably increases the acute toxicity of the treatment.[1-3] Therefore, it should be remembered that the therapeutic benefit of concurrent CRT only occurs when enhancement of the tumor response is greater than the toxic effects on critical normal tissues.

For one mode of concurrent CRT, an alternating schedule of CT and RT can be used.[7,28] For this combination, RT and CT are given alternately, without a treatment gap, to minimize excessive toxic effects on normal tissues and to enhance the tumor response by perturbing cell cycling or reoxygenation. Several clinical trials involving alternating schedules have yielded promising results.[28]

Clinically, randomized clinical trials for various tumors, comparing concurrent CRT with RT alone, showed an improved local control rate by CRT.[5,6,9,10] So far, this improvement, and the survival benefit of concurrent CRT, have been noted for head and neck cancer, nasopharyngeal cancer, NSCLC, small-cell lung cancer, esophageal cancer, uterine cervical cancer, and anal canal cancer.[3,5-10] At present, concurrent CRT is regarded as a standard regimen for these tumor sites. For unresectable NSCLC, induction CT followed by RT was compared with concurrent CRT. Several randomized trials showed that concurrent CRT provided higher local control rates and survival in patients with stage III NCSLC.[8]

During concurrent CRT, acute toxicities are inevitably increased. Hematological and gastrointestinal toxicities are significantly greater during concurrent CRT than for control groups for most tumor sites.[6-10] Therefore, concurrent CRT is not indicated for patients with poor performance status, poor bone marrow function, or poor renal function. Although no significant increase in late toxicities has been reported in most clinical trials,[6-10] there is still insufficient data to conclude that late toxicity is not increased by concurrent CRT.

The optimal schedule for drug administration during concurrent CRT is still unclear. In the United States, for locally advanced esophageal cancer, full-dose CT involving cisplatin and 5-FU is combined with RT.[9] On the other hand, several Japanese investigators, including us, have shown promising clinical results for low-dose protracted infusion CT combined with RT for esophageal squamous cell carcinomas.[29,30] To obtain maximum radiosensitization by CT, daily or weekly administration of CT combined with RT may be better than full-dose CT and RT. To elucidate this question, we have started a multi-institutional randomized phase II clinical trial of 5-FU/cisplatin concurrent CT-RT for locally advanced esophageal cancer (KROSG-0101; JROSG-021; Kyoto Radiation Oncology Study Group; Japanese Radiation Oncology Study Group) (Fig. 5). In this trial, the total dose of CT and RT is the same for both groups, and the type of CT infusion is being compared in terms of the overall survival rate and toxicity. This trial will should explain which type of CT infusion is better for treating esophageal cancer.

Future directions of CRT

Recent advances in CRT have changed the clinical practice of RT for many tumor sites. Concurrent CRT is now a standard treatment for various malignant tumors. To improve the therapeutic ratio further, there are several strategies for the use of RT and CT.

First, recent advances in RT technology should be integrated with CRT to deliver higher doses to the tumor and lower doses to organs at risk. Intensity-modulated RT (IMRT), one of the most advanced RT techniques, allows the sparing of normal tissues without decreasing the dose to a target. At our hospital, concurrent CRT is given by IMRT for head and neck cancer, as well as esophageal cancer.[31,32] One excellent example of the use of IMRT in CRT has been reported for pediatric medulloblastoma.[33] IMRT delivered