ses.[3,7,11,15] Consistent with these reports, the detection rate in the SCLC patients in our study was 68.6%. Given that approximately half of our patients had nonmetastatic disease, we consider that CTCs are detected in a high percentage of cases of SCLC. Higher CTC counts have been reported as an indicator of the presence of distant metastases, such as bone metastasis in prostate cancer[20] and liver metastasis in colorectal cancer.[11] In patients with NSCLC, the CTC levels reportedly correlated with the number of organs showing metastatic involvement, and higher CTC levels are predictive of liver and bone metastasis.[15] Our results also showed an association between the CTC levels and the presence of metastasis, especially to the liver.

The CTC cutoff level (8 CTCs per 7.5 ml of blood) in our study to discriminate between groups with a favorable and unfavorable prognosis was higher than that reported for other tumors. In metastatic breast cancer, the cutoff level of 5 was chosen by comparing the median PFS and the Cox proportional HR for each threshold from 1 to 10,000 CTCs. The same cutoff was also shown to be correlated with the OS.[7] The cutoff of five cells was then applied to metastatic castration-resistant prostate cancer and was well validated to be predictive of the OS.[14] In metastatic colorectal cancer, the cutoff level of three cells was chosen by correlating the baseline CTC level with the response at the first follow-up imaging study. The cutoff level was well validated to be predictive of both the OS and PFS in a subsequent validation cohort.[11] Our cutoff level was based on a comparison of the Cox proportional HR for OS. The differences in the cutoff levels may be attributable to the statistical method used for choosing the optimal cutoff level or might reflect the highly metastatic potential of SCLC itself. In addition, we observed the prognostic significance of the baseline CTC only in the ED subset or patients treated by only chemotherapy in the subset analyses. As the previous studies in other malignancies have been conducted only in patients with metastatic disease, another study for ED-SCLC will be required to validate our results.

Conversion from an unfavorable baseline CTC level to a favorable follow-up CTC level reportedly has a strong impact on the survival. Patients with such conversion showed a favorable OS, statistically similar to that in patients with a persistent favorable CTC level in breast, prostate, and colorectal cancers.[7,11,14] In contrast, our study showed a relatively small impact of such conversion on the survival in SCLC patients. This difference might reflect the nature of SCLC itself, known to be aggressive and to rarely be in a dormant state.[2,3] A lower CTC level might be an appropriate treatment goal if minimal residual cancer cells after treatment had a larger impact on the survival in SCLC patients. Chemotherapeutic agents active against SCLC are as yet limited, and the classic platinum doublet with etoposide or irinotecan remains the standard first-line treatment regimen. Treatment options for relapsed SCLC are further limited to several cytotoxic agents,[21,22] and no molecular-targeted agents have yet been approved.[23] These limitations in treatment modalities might be related to the small impact of conversion after first-line treatment. NSE and ProGRP are commercially available serum biomarkers and are used as markers for monitoring of SCLC patients. They have been reported to be highly sensitive and specific for the diagnosis of SCLC, and elevated levels of these markers at baseline have been shown to be associated with poor prognosis.[24–26] LDH has also been reported to have prognostic significance in patients of SCLC.[27] We showed that the baseline CTC level showed a good discriminatory power for predicting the prognosis in SCLC patients, similar to serum NSE and LDH, and furthermore, that the baseline CTC level was probably a better predictor of survival than the serum ProGRP, by receiver operator characteristics curve analysis.

The treatment response was reported to be associated with the CTC level at the time of imaging in breast cancer.[28] In colorectal cancer, the CTC level measured 3 to 5 weeks after the initiation of therapy had a relatively low sensitivity (27%) for predicting PD.[11] In our study, we found no correlation between the results of the response assessment using the RECIST criteria and the baseline CTC level, posttreatment CTC level, or change in the CTC level associated with treatment. The changes in the tumor size might not always be related to the changes in the outflow of tumor cells from the tumors.

The major limitation of this study was that the study population was small. The threshold value was derived from a cohort at a single institution and not validated in an independent validation cohort. In addition, our study included not only patients receiving chemotherapy alone but also patients treated by chemoradiotherapy. Because the treatment goals are different for chemotherapy and chemoradiotherapy, that is, palliation versus cure, separate derivation studies will be required to choose the optimal CTC cutoff level.

There has been an increasing interest in several aspects of CTCs. First, measurement of the CTC levels has been expected to guide decision making, such as determining the timing of changing, continuing, or discontinuing the current treatment, or identifying appropriate candidates for adjuvant chemotherapy.[29–31] Second, CTC analysis is anticipated to provide samples for biomarker analysis. Monitoring of human EGFR-related 2-positive CTCs in breast cancer patients during human EGFR-related 2-targeted therapy[32–34] and analysis of androgen receptor gene alterations in the CTCs of prostate cancer patients[35,36] have been reported. In addition, the newly developed CTC analyzer shows a high detection power for CTCs and was used for the analysis of *EGFR*-gene alterations in the CTCs from patients with NSCLC.[37,38] These studies have established a new role for CTC analysis as a noninvasive method of tumor profiling or target monitoring during treatment with molecular-targeted agents. Although few molecular-targeted agents currently available are active against SCLC, the high detection rate of CTCs in cases of SCLC might provide an opportunity for the screening of active drugs and accelerate the development of new therapeutic strategies.

In conclusion, this study showed that CTCs are readily detectable by the CellSearch system in patients with SCLC and that the CTC levels before and after treatment had strong

prognostic significance. A large prospective multiinstitutional validation study is required to confirm our results.

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ORIGINAL ARTICLE

Patterns of recurrence and outcome in patients with surgically resected small cell lung cancer

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Abstract
Background Although prophylactic cranial irradiation (PCI) in limited-stage (LS) small cell lung cancer (SCLC) patients who are surgically resected and treated with adjuvant chemotherapy is considered to be a reasonable treatment option, the efficacy of PCI for those patients remains unclear.
Methods The records of 28 patients with SCLC undergoing curative surgery at the Aichi Cancer Center Hospital between 1995 and March 2008 were retrospectively reviewed to assess patterns of relapse and overall survival.
Results The patients were 27 men and 1 woman. Eight patients underwent induction chemotherapy. Fourteen patients (50%) had pathologic stage (p-stage) I disease, 7 patients (25%) had p-stage II, and 7 patients (25%) had p-stage III. Nineteen patients underwent adjuvant chemotherapy and one patient received adjuvant chemoradiotherapy. There were a total of 13 deaths and 8 were disease-related. Most patients developed hematogenous distant metastases before their death. The 5-year overall probability of survival was 47%. Ten (36%) of the 28 patients had a relapse. Two had a local relapse alone, one patient had combined local and distant relapses, and seven patients had distant metastases alone as their first site of failure. Four patients with p-stage II/III disease developed brain metastases with a cumulative incidence at 1 and 2 years of 25 and 36%, respectively.
Conclusions Our retrospective study suggested that PCI might have a role in surgically resected patients with p-stage II/III SCLC because of their relatively high frequency of brain metastasis.

Keywords Cranial irradiation · Metastasis · Small cell lung cancer · Thoracic surgery

Introduction

Lung cancer is a leading cause of cancer mortality in the United States and in Japan [1, 2]. Lung cancer consists of two main histologic types; small cell lung cancer (SCLC) accounting for about 15% of lung cancer and non-SCLC (NSCLC) [3]. Concurrent chemoradiation therapy and prophylactic cranial irradiation (PCI) for limited stage (LS)-SCLC results in 5-year survival for approximately 25% of patients [4], and chemotherapy with platinum and etoposide or with CPT-11 only results in 5-year survival for fewer than 1% of patients with extensive stage (ES)-SCLC [5]. Because of its aggressive nature, for example rapid growth and early dissemination in lymph nodes, bones, adrenal glands, liver, and brain, the efficacy of surgery for treatment of SCLC is regarded as very limited [6], although it has been established by publications in the 1970s and early 1980s which showed long-term survival in

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surgically treated early stage patients [7]. At present, surgery plus adjuvant chemotherapy is standard of care for patients with clinical stage (c-stage) I SCLC [8].

At the time of initial diagnosis, 10–14% of patients with SCLC have detectable brain metastases and at the time of death [9] approximately one-third of patients harbor clinically recognized brain metastases, and over 50% of patients have brain metastases at postmortem examination [10]. The risk of central nervous system metastasis developing 2 years after successful treatment of SCLC has been reported to be approximately 35–65% [11]. A meta-analysis of the efficacy of PCI in 987 SCLC patients revealed a 25.3% decrease in cumulative incidence of brain metastasis at 3 years after PCI and an absolute increase in overall survival of 5.4% at 3 years [12]. Although this study included 140 patients with ES-SCLC, PCI has traditionally been limited to patients with LS-SCLC after meaningful response from combined-modality treatment has been achieved. However, recent results from a randomized study provide evidence that PCI not only reduces the incidence of symptomatic brain metastases but also prolongs disease-free and overall survival in patients with ES-SCLC [13]. Consequently, PCI is recommended for patients with limited-stage disease and extensive-stage disease who achieve a complete or near complete response to treatment, and can be considered for patients with a partial response to initial therapy even in ES-SCLC.

However, there is limited information about the frequency of brain failure in patients with early LS-SCLC who underwent surgery with adjuvant chemotherapy. The issue whether all patients with LS-SCLC undergoing surgery should receive PCI remains unclear. So, in this study, we reviewed our surgical results for 28 patients with LS-SCLC in our institution to see the relapse patterns, the frequency of brain metastasis and overall survival.

Patients and methods

Patients

Approval for this study was obtained from, and the need for individual patient consent was waived by, the institutional review board. Between 1995 and March 2008, twenty-eight patients with SCLC underwent surgery with nodal resection at the Department of Thoracic Surgery of Aichi Cancer Center Hospital. We collected complete clinical data for all patients, none of whom was lost to follow up.

Histological diagnosis

For histological diagnosis patients were subjected to bronchoscopic biopsy or cytology and/or CT-guided biopsy. For 5 of 28 patients (18%), histological or cytological diagnosis was not obtained preoperatively. Preoperative diagnosis of SCLC was achieved for 10 patients only. For the remaining 13 patients, the preoperative diagnosis was large-cell neuroendocrine carcinoma (LCNEC) in three cases, adenocarcinoma in three cases, squamous cell carcinoma in three cases, carcinoma in two cases, NSCLC in one case, and large-cell carcinoma in one case. The histology of all the surgical resection specimens was reviewed. In all cases, diagnosis by light microscopy was confirmed by immunohistochemical methods. Histologic classification was performed according to the World Health Organization classification [14]. The postoperative diagnosis was SCLC in 15 cases and combined SCLC in 13 cases.

Diagnostic workup

Standard diagnostic workup for all patients consisted in X-ray of the chest and thoracic and abdominal computed tomography (CT), bronchoscopy, brain magnetic resonance imaging (MRI) or CT, and bone scintigraphy or positron emission tomography (PET). Mediastinoscopy was not done. We used the TNM classification system of the International Union Against Cancer in this study [15], because precise staging and discrimination between choices of different options of treatment were required for surgical approach for these selected LS-SCLC patients. Pretreatment c-stages were IA, 15 patients; IB, 6 patients; IIA, 2 patients; IIB, 3 patients; IIIA, 2 patients.

Treatment

Eight patients underwent induction chemotherapy. Among these, three patients with c-stage II/III disease who were preoperatively diagnosed as NSCLC on biopsy, received induction chemotherapy consisting of platinum (CDDP or carboplatin) and taxane (paclitaxel or docetaxel). Four patients with c-stage I SCLC and one patient with c-stage II SCLC consented to our in-house clinical procedure and received induction chemotherapy consisting of platinum and etoposide. Twenty-one patients received adjuvant treatment, and seven patients were not treated with adjuvant chemotherapy because of poor general condition ($n = 1$), refusal to consent ($n = 3$), and old age ($n = 3$). Nineteen patients underwent adjuvant chemotherapy consisting of platinum and etoposide or CPT-11. One double-cancer patient with pT1N1 SCLC and advanced hypopharynx cancer simultaneously received chemoradiotherapy consisting of CDDP plus 5-FU and intensity-modulated radiation therapy (IMRT: 66 Gy). One patient underwent adjuvant chemoradiotherapy consisting of CDDP plus etoposide and concurrent thoracic RT (42 Gy).

Survival was determined by use of the institutional database, which is updated with an annual institutional census or with each patient visit.

Statistical analysis

Statistical analysis was carried out using SPSS software (SPSS, Chicago, IL, USA). Overall survival of patients from the time of operation was estimated by means of the Kaplan–Meier method. The cumulative incidence of brain metastasis was also calculated. Patients suffering progression at non-central nervous system sites and/or death from any cause were considered censored.

Results

Patient characteristics

From January 1995 to March 2008, a total of 28 patients underwent complete resection for SCLC. Baseline characteristics of patients according to the postoperative diagnosis are listed in Table 1. Twenty-seven were men and 1 was a woman. The median age of patients was 64.5 years (range 41–77). All patients had a history of cigarette smoking. No patient had a central tumor. Preoperative diagnosis of SCLC was made in 36% ($n = 10$) of 28 patients; postoperative diagnosis of combined SCLC was made in 15% ($n = 2$) of 13 patients (Table 1). Among 7 patients with c-stage II/III disease, 6 cases were preoperatively diagnosed as NSCLC on biopsy. Eight patients underwent induction chemotherapy. Three patients with c-stage II/III disease whose preoperative diagnosis was NSCLC received chemotherapy with platinum and taxane. One patient with c-stage II SCLC and four patients with c-stage I SCLC received induction chemotherapy consisting of platinum and etoposide. All patients underwent lobectomy with mediastinal lymph node dissection.

There was no perioperative death. Regarding pathologic stage, 13 patients had IA disease, 1 patient had IB, 4 patients had IIA, 3 patients had IIB, 5 patients had IIIA, and 2 patients had IIIB. Postoperatively, 21 patients received adjuvant treatment and 7 patients were not treated with adjuvant chemotherapy because of poor general condition ($n = 1$), patient refusal ($n = 3$), or old age ($n = 3$). Nineteen patients underwent adjuvant chemotherapy and one patient received chemoradiotherapy (Table 1). One patient with pT1N1SCLC and advanced hypopharynx cancer simultaneously received chemoradiation therapy consisting of CDDP plus 5-FU and intensity-modulated radiation therapy (66 Gy). Relationship between pretreatment clinical stages and postoperative pathologic stages is shown in Table 2. Because of inaccuracy of clinical staging, clinical understaging rate was approximately 36% (10/28), although 8 patients received induction therapy.

Table 1 Demographics, clinical characteristics, and perioperative treatment of patients

	Postoperative diagnosis		
	Total ($n = 28$)	SCLC ($n = 15$)	Combined SCLC ($n = 13$)
Age (years)			
Median	64.5	64	65
Range	41–77	54–77	41–77
Sex			
Male	27	14	13
Female	1	1	0
Clinical stage			
I	21	12	9
II	5[a,b]	3	2
III	2[a]	0	2
Pathologic stage			
I	14	8	6
II	7	4	3
III	7	3	4
Preoperative diagnosis			
SCLC	10	8	2
LCNEC	3	1	2
Sq	3	2	1
Ad	3	1	2
La	1	0	1
NSCLC	1	0	1
Carcinoma	2	1	1
Tumor not diagnosed	5	2	3
Induction therapy			
Platinum + etoposide	5	5	0
Platinum + taxane	3	0	3
Adjuvant therapy			
Platinum + etoposide	12	10	2
CDDP + etoposide + RT	1	1	0
Platinum + CPT-11	7	1	6
CDDP + 5-FU + RT	1[c]	1	0

[a] Six cases of seven patients with clinical stage II/III disease were preoperatively diagnosed as NSCLC on biopsy

[b] One patient who was preoperatively diagnosed as SCLC received induction CDDP plus etoposide chemotherapy followed by surgery and two course of adjuvant chemotherapy

[c] One patient with advanced hypopharynx cancer and pT1N1 SCLC underwent chemoradiotherapy with CDDP + 5-FU + RT

Patient outcome

The median follow-up was 41.6 months (interquartile range 25.6–57.3) for all patients and 57.3 months (interquartile range 28.9–79.3) for those still alive. No patients

dropped out of the follow-up during the study period. The median survival for all patients was 59.2 months and the 5-year overall probability of survival was 47% (Fig. 1). Five-year survival for patients with c-stage I ($n = 21$), c-stage II ($n = 5$), and c-stage III disease ($n = 2$) were 53, 0, and 100%, respectively (Fig. 2). Five-year survival for patients with p-stage I ($n = 14$), p-stage II ($n = 7$), and p-stage III disease ($n = 7$) were 64, 25, and 43%, respectively (Fig. 3). There was no significant difference in survival among c-stages ($p = 0.08$, log-rank test) and between patients with p-stage I disease and those with p-stage II disease ($p = 0.35$, log-rank test). Despite small sample size, there were significant differences in survival between patients with p-stage I disease and those with p-stage III disease ($p = 0.04$, log-rank test). Overall survival did not differ significantly between patients with combined SCLC and those with SCLC ($p = 0.91$, log-rank test) (Fig. 4).

Ten (36%) of the 28 patients had a relapse (Table 3). Among these patients, two had a local relapse alone, one patient had combined local and distant relapses, and the other seven patients had distant metastases alone as their first site of failure. Nine patients relapsed within 2 years after surgery. Median relapse-free survival for all patients was 52.5 months (95%CI 16.6, N/A). There was no obvious difference in relapse pattern between patients with combined SCLC and those with SCLC. Four patients with p-stage II/III disease developed brain metastases with a cumulative incidence at 1 and 2 years of 25 and 36%, respectively (Fig. 5). One patient with p-stage III disease developed brain metastasis concurrently with liver and bone metastases. The other patient with p-stage III disease and two patients with p-stage II disease had brain metastases as the only site of first recurrence. There were a total of 13 deaths and 8 were disease-related. Most patients

Table 2 Relationship between clinical and pathologic stages

Clinical stage	Pathologic stage		
	I	II	III
I	12 (3)	4 (1)	5
II	1 (1)	3 (1)	1 (1)
III	1 (1)	0	1

Numbers in parentheses are the numbers of patients who received induction therapy

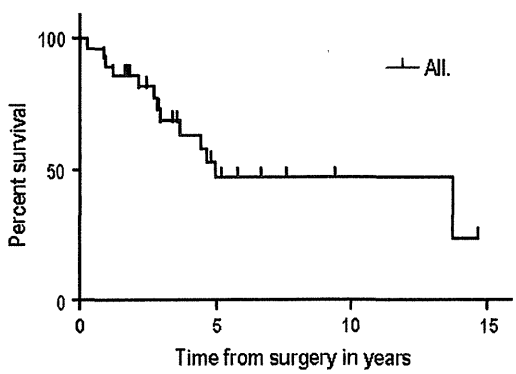

Fig. 1 Survival curve for patients with resected SCLC

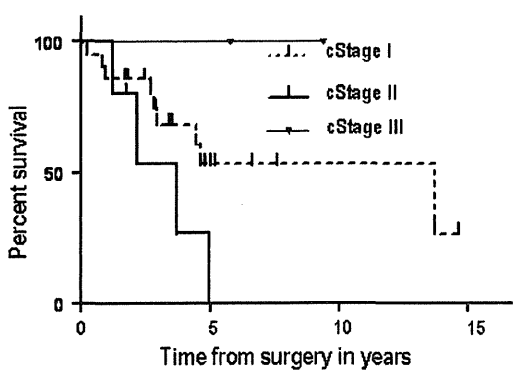

Fig. 2 Survival curves for patients with resected SCLC by clinical stages

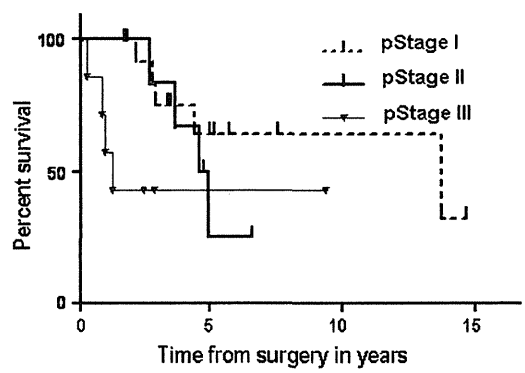

Fig. 3 Survival curves for patients with resected SCLC by pathologic stages

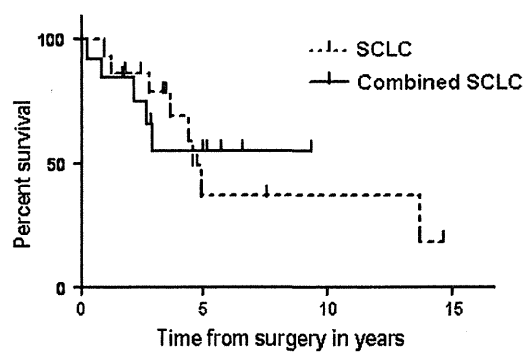

Fig. 4 Survival curves for patients with resected SCLC according to histologic subtypes

Table 3 Site of the first relapse by pathologic and clinical stages

Variables	Overall	p-Stage I	p-Stage II	p-Stage III	c-Stage I	c-Stage II	c-Stage III
No. of patients	28 (15)	14 (8)	7 (4)	7 (3)	21 (12)	5 (3)	2 (0)
No. of recurrences	10 (6)	3 (1)[a]	4 (3)	3 (2)[b]	5 (3)[a,b]	5 (3)	0
Recurrence							
Local							
Mediastinum	3 (1)	2 (1)[a]	0	1	2 (1)[a]	1	0
Distant							
Brain	4 (3)	0	3 (2)	1 (1)[b]	2 (2)[b]	2 (1)	0
Bone	3 (3)	1 (1)[a]	0	2 (2)[b]	2 (2)[a,b]	1 (1)	0
Liver	2 (2)	1 (1)[a]	0	1 (1)[b]	2 (2)[a,b]	0	0
Lung	1	1	0	0	1	0	0
Adrenal gland	1 (1)	0	1 (1)	0	0	1 (1)	0

Numbers in parentheses are the number of patients with postoperative diagnosis of SCLC

[a] One patient with clinical and pathological stage I disease developed local relapse concurrently with liver and bone metastases

[b] One patient with clinical stage I and pathological stage III disease developed brain metastasis simultaneously with liver and bone metastases

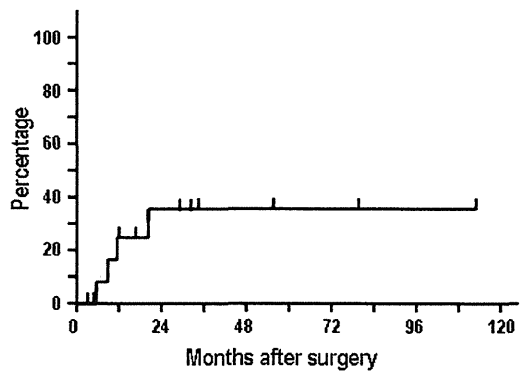

Fig. 5 Cumulative incidence of brain metastasis in patients with p-stages II/III disease

developed hematogenous distant metastases before their deaths.

Discussion

The prognosis of resected SCLC is considered to be poorer than that of surgically treated NSCLC. Vallieres et al. [16] has reported that 5-year survival of surgically treated LS-SCLC patients was approximately 50% for p-stage I disease, approximately 40% for p-stage II, and approximately 15% for p-stage III. A Japanese large-scale registry study reported that 5-year survival of resected SCLC patients was approximately 60% for p-stage I disease, approximately 40% for p-stage II, and approximately 30% for p-stage III [17]. In our study, the 5-year probability of survival was 64% for p-stage I disease, 25% for p-stage II, 43% for p-stage III. Our results are almost similar to those of the Japanese study.

Because of its aggressive nature, for example rapid growth and early dissemination in lymph nodes, bones, adrenal glands, liver, and brain, the role of surgery in treatment of SCLC is considered to be very limited [6]. SCLC usually occurs centrally, and typical initial radiographic images show a larger hilar mass with bulky mediastinal lymphadenopathy. Thus, SCLC for indication of surgical resection which often arises peripherally is relatively rare [7]. In fact, a large-scale registry study from Japan reported that there were a few SCLC patients (3%) among 13010 lung cancer patients who underwent surgery at the certified teaching hospitals in 1999 [17]. Although patients with very limited SCLC (cT1-2N0) basically proceed to surgical resection, there are several other situations in which surgery can be useful [18]. One situation is surgery for confirmation of diagnosis. Another situation is surgery for patients with preoperative diagnosis of resectable NSCLC. A third situation is improvement of local control in the combination treatment with chemotherapy and radiotherapy, because for patients with combined histology tumors, for example combined SCLC, the NSCLC component is less sensitive to chemotherapy and radiotherapy. Surgery for these situations may contribute to prolonged survival for undiagnosed lung cancer and T1-3N1-2 SCLC. In our study, histological or cytological diagnosis was not achieved preoperatively for 5 of 28 patients, and preoperative diagnosis of SCLC was achieved for 10 patients only. Furthermore, approximately half (13) of 28 patients had combined SCLC histology.

Recurrence in the brain is associated with substantial morbidity and mortality in SCLC [13]. Because of high risk of brain metastasis after diagnosis of SCLC, PCI has been studied in an attempt to treat and control metastatic brain tumors before clinical manifestation. The benefit of PCI is

greatest for patients with LS-SCLC and ES-SCLC who have complete or near complete response to treatment [12]. However, use of PCI after combined-modality treatment with surgery for resectable LS-SCLC has not yet been investigated sufficiently. As far as we are aware, only 2 Japanese studies have reported the frequency of brain relapse after surgery for LS-SCLC [19, 20]. One Japanese multi-institutional phase II study (JCOG9101) has reported that recurrence after surgery occurred in 43% (26/61) of patients overall, in 29% (10/35) of patients with p-stage I disease, in 50% (4/8) of patients with p-stage II, and in 67% (12/18) of patients with p-stage III, and that the incidence of brain metastasis was 15% (9/61) in patients overall, 11% (4/35) in patients with p-stage I disease, 38% (3/8) in patients with p-stage II, and 11% (2/18) in patients with p-stage III [20]. Another Japanese study showed that relapse after surgery occurred in 34 of 69 (49%) patients who underwent complete resection of SCLC and in 27% (8/30) of patients with p-stage I disease, 58% (7/12) of patients with p-stage II, 69% (18/26) of patients with p-stage III, and 100% (1/1) of patients with p-stage IV [19]. In this report, the frequency of brain relapse as a first relapse site was reported to be 7% (2/30) for patients with p-stage I disease, 25% (3/12) for patients with p-stage II, 27% (7/26) for patients with p-stage III, and 100% (1/1) for patients with p-stage IV. Combined results from our study and from two other Japanese studies revealed that brain metastases as first site of failure developed in 26 (16%) of the total of 158 patients who underwent surgery for LS-SCLC, in 6 (8%) of 79 patients with p-stage I disease, 8 (30%) of 27 patients with p-stage II, and 11 (22%) of 51 patients with p-stage III. For LS-SCLC patients treated with chemoradiation therapy, the frequency of brain metastasis as the first recurrence site has been reported to be 37% [21]. In addition, as for the role of PCI for treatment of NSCLC, the risk of brain metastasis has been reported to be 17% (71/422) for patients with stage III NSCLC treated with chemoradiation therapy [22]. Thus, although it is unclear whether PCI after combined modality treatment with surgery for resectable LS-SCLC could improve survival, PCI may be beneficial at least for patients with p-stage II/III disease to reduce the incidence of brain metastasis, although a randomized study is necessary.

The principal role of PCI is to prevent brain failure and to reduce its frequency, and to improve survival [13]. Surgically treated patients with p-stage I SCLC are the most favorable subset in SCLC. Combined results from our study and two other Japanese studies revealed that brain metastases as first site of failure developed in only 8% (6/79) of patients with p-stage I SCLC. It has been reported that in adjuvant trasuzumab studies of breast cancer PCI would not be justified by a frequency of less than 5% in incidence of brain metastasis [23]. In this regard, very early LS-SCLC, for example p-stage I disease, would be excluded from candidates for PCI, because of low frequency of brain relapse.

Our retrospective study suggested that PCI might be suitable for surgically resected patients with p-stage II/III SCLC to reduce the incidence of brain metastasis, although a randomized study is necessary. It is likely that very early LS-SCLC, for example p-stage I disease would be excluded from candidates for PCI.

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Conflict of interest The authors declare no conflicts of interest.

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Treatment-Related Death in Patients with Small-Cell Lung Cancer in Phase III Trials over the Last Two Decades

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Abstract

Introduction: Treatment-related death (TRD) remains a serious problem in small-cell lung cancer (SCLC), despite recent improvements in supportive care. However, few studies have formally assessed time trends in the proportion of TRD over the past two decades. The aim of this study was to determine the frequency and pattern of TRD over time.

Methods: We examined phase 3 trials conducted between 1990 and 2010 to address the role of systemic treatment for SCLC. The time trend was assessed using linear regression analysis.

Results: In total, 97 trials including nearly 25,000 enrolled patients were analyzed. The overall TRD proportion was 2.95%. Regarding the time trend, while it was not statistically significant, it tended to decrease, with a 0.138% decrease per year and 2.76% decrease per two decades. The most common cause of death was febrile neutropenia without any significant time trend in its incidence over the years examined ($p = 0.139$). However, deaths due to febrile neutropenia as well as all causes in patients treated with non-platinum chemotherapy increased significantly ($p = 0.033$).

Conclusions: The overall TRD rate has been low, but not negligible, in phase III trials for SCLC over the past two decades.

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Introduction

Chemotherapy is the mainstay of treatment for small-cell lung cancer (SCLC); it is widely accepted that patients with limited-stage SCLC (LD-SCLC) have prolonged survival with systemic chemotherapy when combined with thoracic irradiation [1,2]. Even in patients with extended-stage SCLC (ED-SCLC), chemotherapy has yielded a survival advantage, with a median survival time of over 1 year [3–5].

However, chemotherapy-related toxicity sometimes leads to treatment-related death (TRD) and often to deterioration in the patient's quality-of-life. Thus, toxicity profile information as well as data on efficacy from phase III trials are essential for a full discussion by physicians and patients in clinical practice.

Although there have been many phase III trials involving SCLC patients investigating the efficacy of chemotherapy, few studies have focused specifically on the frequency or pattern of chemotherapy-related fatal toxicity. The aim of this study was to clarify this issue and its time trends over the last two decades, using data from phase III systemic treatment trials that included about 25,000 patients.

Materials and Methods

Trials

We conducted a search for trials reported from January 1990 to March 2010. To avoid publication bias, we identified both published and unpublished trials through a computer-based search of the PubMed database and abstracts from ten past conferences of the American Society of Clinical Oncology, European Society for Medical Oncology, and the International Association for the Study of Lung Cancer. We used the following search terms: *lung cancer, chemotherapy, and randomized controlled study*. The search was extended by a thorough examination of reference lists from original articles, review articles, relevant books, and the Physician Data Query registry of clinical trials.

Trial Selection

Phase III trials that investigated the systemic treatment of previously untreated LD- and ED-SCLC patients with cytotoxic agents were eligible. Trials designed with concurrent thoracic radiotherapy (TRT) or prophylactic cranial irradiation sequentially after the induction of chemotherapy were included. Some phase III trials incorporated patients with both LD- and ED-SCLC. Trials that provided data for TRD in each report were

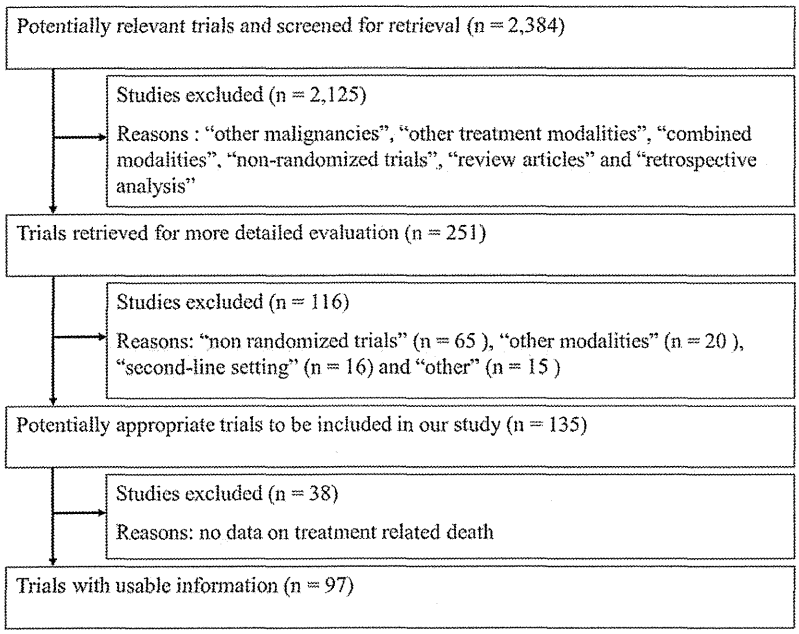

Figure 1. PRISMA flow diagram showing the progress of trials through the review.
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included. Clinical trials of salvage chemotherapy (second-line or later-setting) were ineligible.

Data collection and data items

To avoid bias in the data abstraction process, four medical oncologists (NO, IO, YF, and KH), three of whom (NO, IO, and KH) hold board certificates in medical oncology, abstracted data independently from the trials and subsequently compared the results, as described previously [5–13].

The following information was obtained from each report: year of trial initiation, year of publication, number of patients enrolled and randomized, proportion of patients with a good performance

Table 1. Characteristics of the 97 trials.

Variables	Values
Proportion of randomized patients with a good performance status* (%)	
<80	43.3
80–90	27.8
>90	19.6
Median proportion (range)	80.0 (23.0–100)
Proportion of male patients (%)	
<80	63.0
80–90	19.0
>90	12.0
Median proportion (range)	71.0 (41.0–99.0)
Type of disease stage included (LD only/others)	19/78
No. of treatment arms	
2	84
3	10
4	3
Published year (median; range)	1997 (1990–2009)
Trials designed to assign TRT (yes/no)	53/44

*A good performance status (PS) was defined as an Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1.
LD, limited disease; TRT, thoracic radiotherapy.
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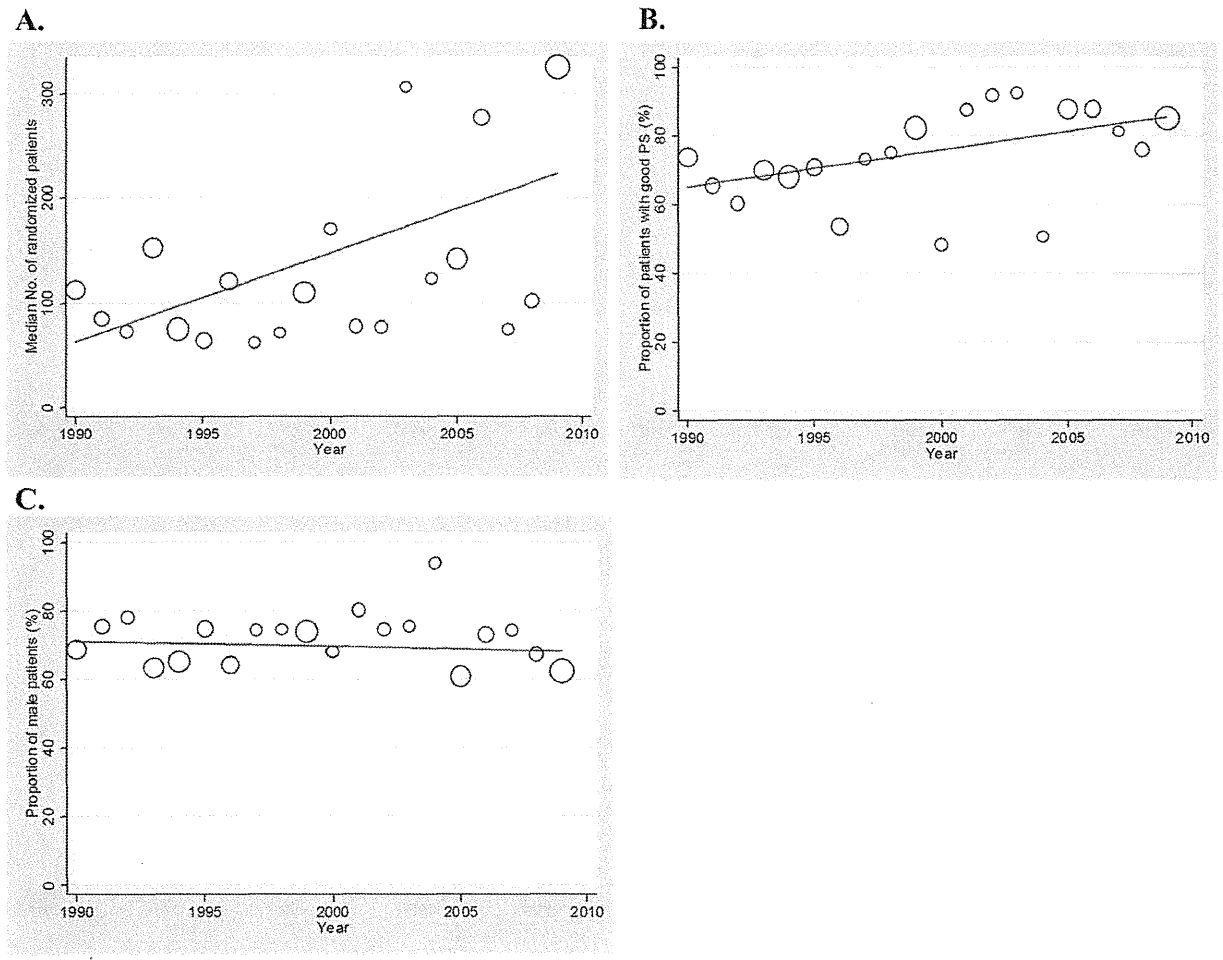

Figure 2. Time trends in the demographics of patients randomized in phase III trials. A good PS was defined as an Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1. All analyses were weighted by sample size. A. Median number of randomized patients. B. Proportion of patients with a good PS. C. Proportion of male patients.
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status (PS), proportion of male patients, median age of patients, number of chemotherapeutic regimens, description of the administration of concurrent or sequential thoracic irradiation, treatment regimens in each treatment arm, total number of patients with TRD, cause of TRD in each treatment arm, and the definition of LD or ED (the definitions of LD- and ED-SCLC varied somewhat from trial to trial, but we did not reallocate each patient strictly in this study because we were unable to access individual patient data).

All data were checked for internal consistency, and disagreements were resolved by discussion among the investigators.

Definition of TRD

We defined TRD should satisfy all the followings:

1) death occurring within 4 weeks of the completion of treatment,
2) death 'possibly,' 'probably,' or 'definitely' related to treatment reported by investigators, as defined previously [6,7].
3) death without clear evidence of any other cause of death (i.e., disease progression)

We also defined febrile neutropenia (FN)-associated death, the most common cause of fatal toxicity during chemotherapy [7], as death related to fever of unknown origin without clinically or microbiologically documented infection with absolute neutrophil count $<1.0\times10^9$/L and fever >38.3°C. In general, more recent trials included in this study defined TRD and/or FN-related death clearly in their reports. However, previous studies tended to be left their definitions vague and not to state them specifically. In response to that situation, we tried best to contact the principal authors of the reports for each trial to clarify this and to get precise number of TRD and FN-related death. In case we could not obtain any additional information despite these intensive efforts, we accepted the number of TRDs and FN-related deaths as was described in those reports.

The data we collected from each trial also included the number stratified by representative cause of toxic death other than FN-related one. On the basis of our previous study, the causes of TRD were collected as follows [7]: FN, hemorrhage, renal failure, central nervous system (CNS) disorder, cardiovascular disorder and pulmonary disorder. Hemoptysis, upper and lower gastrointestinal hemorrhages, and disseminated intravascular coagulation-

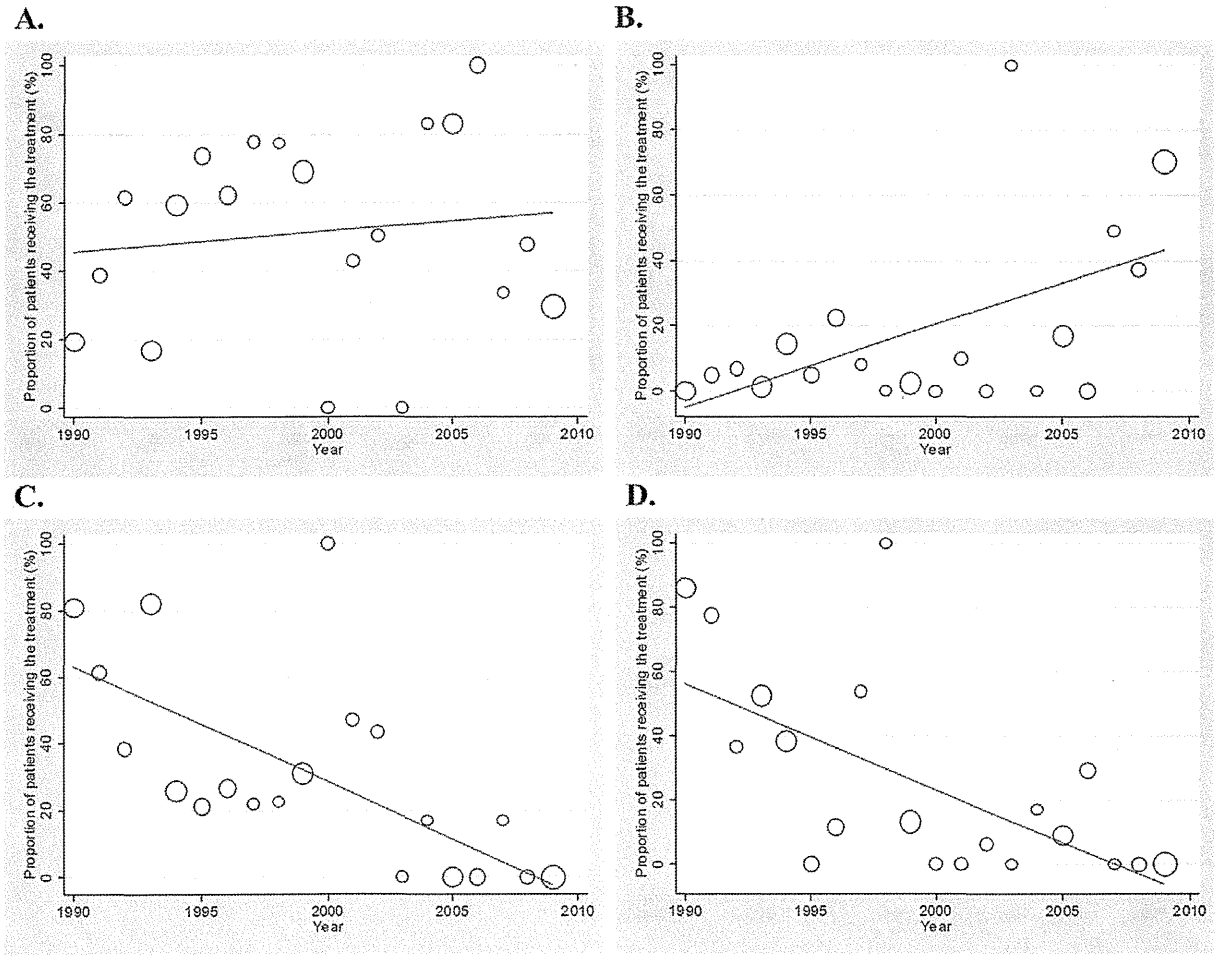

Figure 3. Time trends in chemotherapeutic regimen. All analyses were weighted by sample size. A. Cisplatin-containing regimen. B. Carboplatin-containing regimen. C. Non-platinum regimen. D. CAV (cyclophosphamide, doxorubicin and vincristine)-based regimen.
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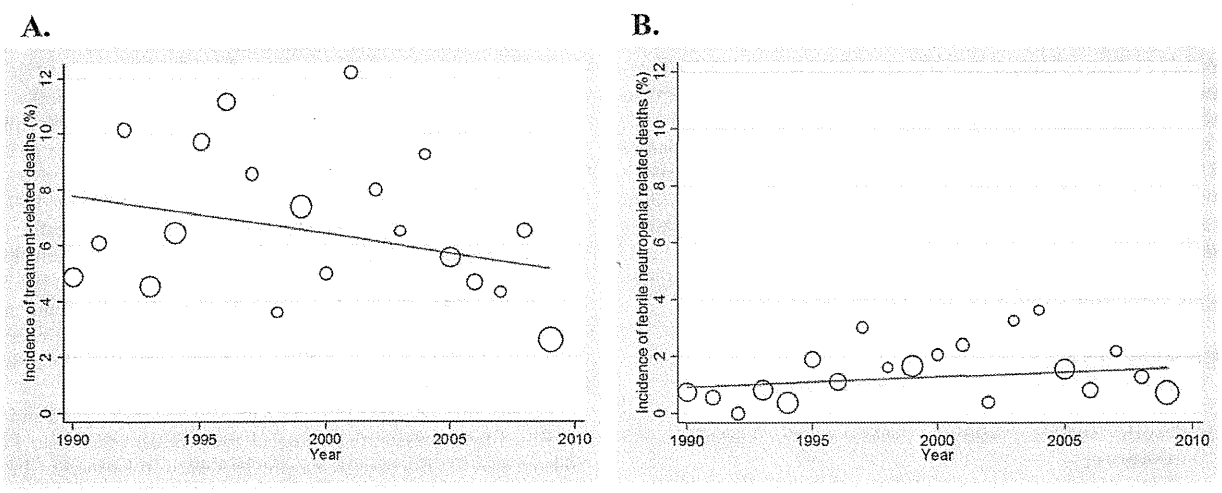

Figure 4. Time trend in the incidence of TRDs (treatment-related deaths). The analysis was weighted by sample size. A. Overall incidence of TRDs. B. Incidence of FN (febrile neutropenia)-related TRDs.
doi:10.1371/journal.pone.0042798.g004

Table 2. Time trends in the incidence of treatment-related deaths in various clinical settings (simple regression analysis).

Subgroups	Regression coefficient	p-value
Trials designed to assign TRT		
Yes	−0.021	0.820
No	−0.290	0.073
Type of disease stage included		
LD only	−0.012	0.873
Other	0.049	0.394
Proportion of randomized patients with a good performance status (%)**		
≥80	0.018	0.681
<80	−0.774	0.233
Proportion of male patients (%)**		
≥70	−0.050	0.438
<70	0.024	0.568
Chemotherapeutic regimens		
Cisplatin-containing regimen	−0.064	0.270
Carboplatin-containing regimen	−0.087	0.390
Non-platinum regimen*	0.146	0.033
CAV-based regimen	−0.038	0.570

All analyses were weighted by sample size.
TRT, thoracic radiotherapy; CAV, cyclophosphamide, doxorubicin and vincristine.
*Regression coefficient means a slope of the fitted line in each subgroup.
**The median score was used as a cutoff level for each subclassification.
doi:10.1371/journal.pone.0042798.t002

related hemorrhage were all categorized as "hemorrhage", while both CNS ischemia and hemorrhage were classified as "CNS disorder". "Cardiovascular disease" included ischemia, infarction, or embolism in any organ other than the CNS (i.e., myocardial infarction and pulmonary embolism). "Pulmonary disorders" included all pulmonary diseases other than pulmonary embolisms, including infection without neutropenia (i.e., pneumonia) [7].

Quantitative Data Synthesis

The incidence of TRD was defined as the number of TRDs divided by the number of randomized patients. To derive the annual change in TRD incidence during the observation period, we calculated this number for each year of publication. The association between the year of publication and incidence of TRD was analyzed using linear regression analysis, weighted by sample size. All *p*-values corresponded to two-sided tests, and significance was set at $p<0.05$. Statistical analyses were conducted using STATA software (ver. 10; StataCorp, College Station, TX, USA).

Results

Trial flow and characteristics of the eligible trials

Figure 1 shows a flow chart for this study. In total, we identified 97 trials as a result of computer-based and manual searches (File S1). In total, 24,152 patients were randomized and allocated to 208 treatment arms. Table 1 shows the characteristics of all eligible trials. The median proportion of randomized patients with a good PS (0 or 1) and that of male patients in all trials was 80.0 and 71.0%, respectively. Most trials had two chemotherapy arms (86.6%). The number of trials designed to assign TRT in addition to chemotherapy was 53 (54.6%).

The median number of randomized patients and proportion of patients with a good PS in each trial increased significantly, with 8.489 patients and 1.075% per year, respectively (regression coefficients = 8.489 and 1.075, corresponding to an 8.489 and 1.075% increase per year; $p = 0.003$ and 0.009, respectively; Fig. 2A and B). The proportion of male patients, however, showed no particular change over time (Fig. 2C).

Time trends in treatment regimens

Figure 3 shows the changes in treatment regimens over the past two decades. Regarding platinum-based regimens, the proportion of cisplatin use was largely constant during the period (regression coefficient = 0.599, corresponding to a 0.599% increase per year; $p = 0.549$; Fig. 3A), while carboplatin (CBDCA)-containing regimens increased yearly (regression coefficient = 2.527 [2.527% increase per year]; $p = 0.004$; Fig. 3B). In contrast, the use of non-platinum combination regimens and that of cyclophosphamide, doxorubicin, and vincristine (CAV)-based regimens decreased significantly during the two decades, at 3.438% ($p<0.001$) and 3.300% ($p = 0.001$) per year, respectively (Fig. 3C and D).

Time trends in overall TRD incidence

Data for the calculation of the overall incidence of TRD were available for all 97 trials with their 208 chemotherapy arms (24,152 patients), whereas information about the causes of death were provided for 154 arms (74.0%; 17,570 patients). The crude TRD proportion in the overall cohort was 2.95%. Of these, the most common cause of death was febrile neutropenia (FN) (1.25%), followed by pulmonary disorder (0.45%). The crude TRD proportions of other causes collected in this study were very low compared with FN and pulmonary disorder (hemorrhage 0.03%, renal failure 0.05%, CNS disorder 0.02%, cardiovascular disorder 0.12%, and others 0.18%).

Next, we assessed the time trends in TRD incidence. It was stable over the last two decades, with no statistically significant

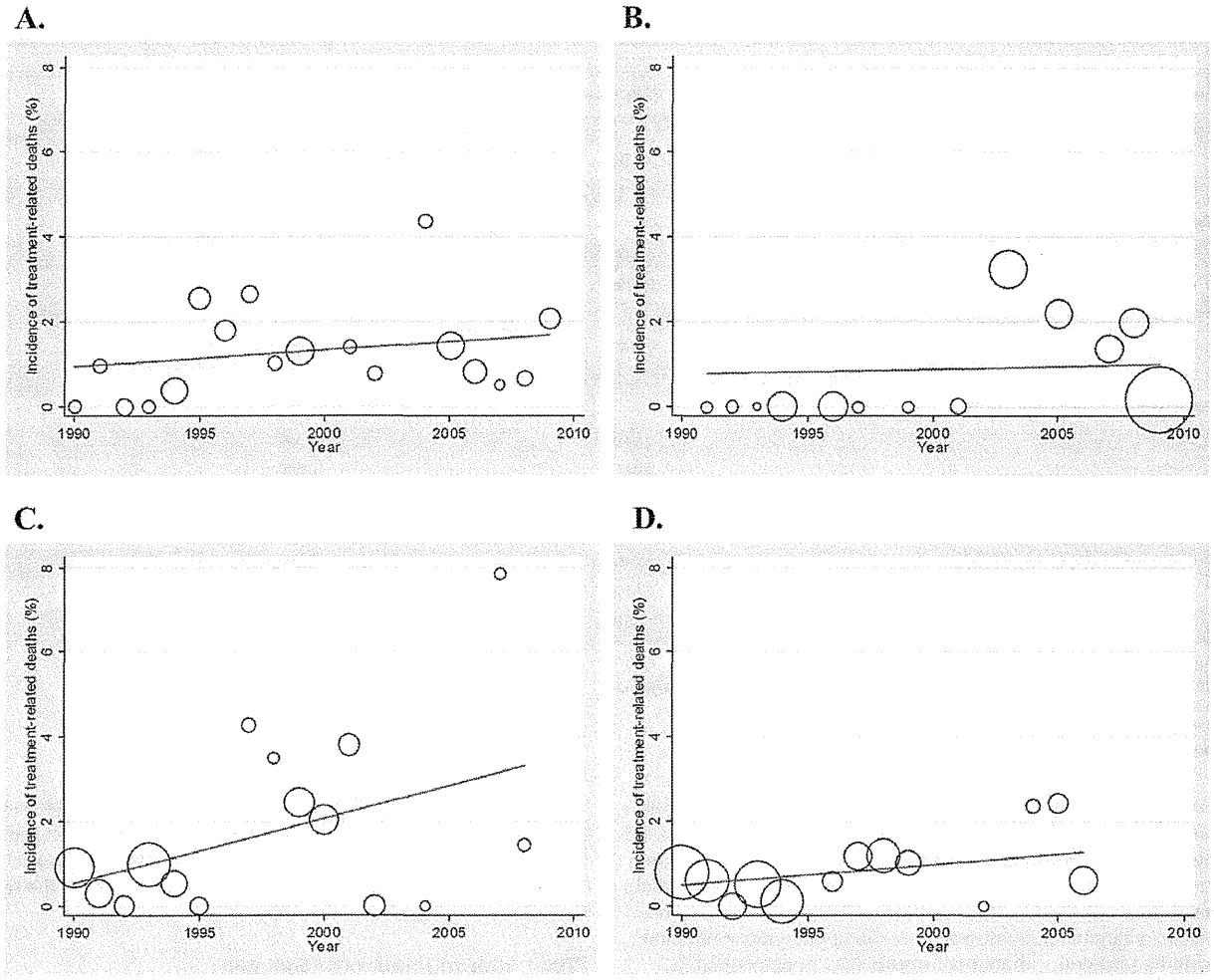

Figure 5. Time trend in the incidence of TRDs in relation to FN (febrile neutropenia). All analyses were weighted by sample size. A. Cisplatin-containing regimen. B. Carboplatin-containing regimen. C. Non-platinum-regimen. D. CAV (cyclophosphamide, doxorubicin and vincristine)-based regimen.
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difference (regression coefficient = −0.138; p = 0.15). This corresponds to a 0.138% decrease per year; however, it does mean that, theoretically, the TRD incidence decreased by 2.76% per two decades (Fig. 4A). Further, we assessed which clinical factor affected this time trend (Table 2). In most clinical settings, there was no particular difference in the time trend, whereas, interestingly, when limited to patient cohorts treated with a non-platinum regimen, there was a significant increase in TRD incidence (0.146% increase per year; p = 0.033). We observed no significant increase or decrease in TRD incidence with other treatment regimens, including cisplatin-, carboplatin-, and CAV-based regimens (p = 0.270, 0.390, and 0.570, respectively).

Because FN was the most common cause of fatal toxicity during chemotherapy, we focused specifically on the incidence and pattern of FN-related deaths. Overall, there was no significant time trend in TRD, with a regression coefficient of 0.035 and p-value of 0.259 (Fig. 4B). Through the entire period, the proportion of FN-related deaths was similar across the four regimens (cisplatin-based 0.649%, carboplatin-based 0.652%, non-platinum 0.645%, and CAV-based regimens 0.704%). However, the pattern of the time trend was different among the regimens (Fig. 5A D). Non-platinum regimens were associated with a significant increase in death over the years, with a 0.155% increase per year (regression coefficient = 0.155; p = 0.037; Fig. 5C), while no yearly change in the proportion was observed for the other treatment regimens (cisplatin-, carboplatin- and CAV-based regimens; p = 0.337 [Fig. 5A], 0.857 [Fig. 5B], and 0.123 [Fig. 5D], respectively).

Discussion

We found that the incidence of overall TRDs tended to decrease over the past two decades, although it was not statistically significant (p = 0.15; Fig. 4A). In contrast, the incidence of FN-related death was fairly stable (Fig. 4B). Additionally, stratified by treatment regimen, non-platinum chemotherapy produced an increased incidence of both TRD (Table 2) and FN-related deaths (Fig. 5C) year by year.

In this study, the overall TRD incidence seems to have decreased over the last two decades, with a regression coefficient

of −0.138, meaning a decrease of 0.138% per year and 2.76% per two decades (Fig. 4A). This phenomenon might be partly correlated with the observation that the number of trials designed to assess TRT, which included potentially induced fatal pulmonary fibrosis, decreased over the years, with a regression coefficient of −0.162 (0.162% decrease per year; $p = 0.042$). Another hypothesis is the improvement in supportive care. In NSCLC, even in patients allocated to the best supportive care alone arm, the median survival time was prolonged [14]. Similarly, in SCLC, supportive care improved over time, resulting in a decrease in the incidence of overall TRD. Further exploration is warranted to clarify the essential factors that contributed to this trend.

On the other hand, FN-related death was similar over the study period (Fig. 4B). One possible reason for this is that chemotherapeutic agents with relatively high myelotoxicity, such as etoposide or anthracyclines, have been repeatedly studied in clinical trials over the past two decades in SCLC [3,15,16]. Second, one would wonder consider the potential impact of the use of granulocyte-colony stimulating factor (G-CSF) on reduction in the risk of FN-related death [17], but G-CSF has been used in phase III trials since the early 1990s, corresponding approximately to the beginning of the target period investigated here [18–20]. Thus, G-CSF usage would likely have equally influenced the incidence of FN-related deaths throughout the study period. Further, controversy persists as to the impact of the prophylactic or routine use of G-CSF on clinical outcome, including treatment-related and overall mortality [21,22]; there is as yet no definitive evidence regarding the impact of its use on outcome. Finally, we have no definitive data to validate the above hypotheses. Novel agents that possess less myelotoxic profiles should be developed to decrease FN-related deaths.

Meanwhile, both the overall incidence of TRD and incidence of FN-related death have increased in non-platinum regimens over the years (Table 2 and Fig. 5C). Most of the non-platinum regimens investigated here consisted of multiple agents (i.e., alternating regimens, switching regimens, and combination regimens with three or more drugs) [23–28], which seemed to be more toxic [7]. Assuming that the proportion of FN-related deaths accounted for a large fraction of overall TRDs, the overall TRD incidence in non-platinum regimens may have simply increased in accordance with the increase in FN-related deaths. The absolute number of trials investigating non-platinum regimens has decreased; thus, these findings seem to have less importance for clinical practice.

Our study has several limitations. First, this analysis tried to cast a wide net to capture several heterogeneous studies for the database, and the results of this study have several potential confounders and a degree of uncertainty. Second, our analyses were not based on individual patient data. Differences in patient clinical characteristics, unlike differences in the characteristics of the trial arms (chemotherapy regimen), would directly have affected the toxicity profiles. Third, a publication bias may exist. Severely toxic agents or regimens may not have been reported, resulting in an underestimation of the TRD incidence. To reduce this bias, we included both published and unpublished (abstract only) trials. Fourth, actual TRD numbers in this study seemed to be low compared with that was seen in clinical practice [29]. One explanation for this discrepancy may be that the patients eligible in such clinical studies generally tend to have better general conditions than those patients treated in clinical practice. Another explanation is that, in clinical trials, investigators might tend to produce "positive" results; that is, they would deal with true treatment-'related' deaths as treatment-'unrelated' deaths unconsciously. Thus, observed TRD numbers in the clinical trials might be smaller than the true value.

Finally, the definition of TRD and/or FN-related death might have been somewhat vague. We initially defined both TRD and FN-related death in this study as described in Methods section. However, all the trials we included here did not have identical TRD and FN definitions, which was the major limitation in our abstracted data-based analysis. Given that mentioned above, all our results should be interpreted cautiously.

In conclusion, the overall TRD proportion was low and has decreased quite gradually, but is still not negligible in phase III trials for SCLC. Physicians should be aware of these trends and do their best to reduce the risk of fatal toxicity.

Supporting Information

File S1 The list of 97 trials included in this study and its characteristics.
(DOCX)

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Author Contributions

Conceived and designed the experiments: NO KH YF. Performed the experiments: NO KH YF IO. Analyzed the data: NO KH. Contributed reagents/materials/analysis tools: NO KH YF IO. Wrote the paper: NO KH NT IO YF EI AH M. Tabata M. Tanimoto KK.

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Influence of the timing of tumor regression after the initiation of chemoradiotherapy on prognosis in patients with limited-disease small-cell lung cancer achieving objective response

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ABSTRACT

Purpose: Chemoradiotherapy (CHRT) yields a favorable antitumor activity in patients with limited-stage small-cell lung cancer (LD-SCLC) with a response rate of around 80%. Even in such responders, the majority recur, indicating the importance of identifying a subset of patients with a poor outcome earlier through the treatment. We investigated whether the timing of obtaining tumor regression with the CHRT could affect the prognosis in LD-SCLC patients who finally achieved the objective response through the treatment.
Patients and methods: We retrospectively reviewed medical charts of 70 LD-SCLC patients who obtained complete response (CR) or partial response (PR) with the 3 or 4 cycles of first-line CHRT between 1988 and 2006.
Results: In the whole 70 patients with CR/PR, the median survival time and median progression free survival (PFS) were 39.6 and 12.3 months, respectively. Fifty-two (74.3%) of the 70 patients entered CR/PR after the first cycle of CHRT, and their 2-year survival rates were significantly longer than that in the remaining 18 patients without entering CR/PR yet at the end of first cycle (72.3% and 7.1%, respectively, $p < 0.001$). Cox regression analysis showed that the early response to the treatment was a significant prognostic factors (hazard ratio = 0.098; 95% confidence interval = 0.036–0.269). Regarding PFS, similar findings were observed.
Conclusions: Patients without entering CR/PR yet after the first course had a poorer outcome even though the objective response was finally confirmed through the treatment. Development of more effective treatments for these high-risk patients is warranted to improve their poor prognosis.

1. Introduction

Lung cancer remains the leading cause of cancer-related mortality in many industrialized countries. Small cell lung cancer (SCLC), which accounts for about 15% of all lung cancer histology, is clinically categorized as the two stages, limited disease (LD) and extensive disease [1–4]. Improving the clinical outcome of LD-SCLC is one of the major challenges for medical oncologists. Based on the meta-analysis [5], the combined modality therapy with cisplatin-based chemotherapy and thoracic irradiation is now considered the standard treatment for LD-SCLC.

Historically, in many malignancies, measurement of objective response could be the effective tool for predicting overall survival [6–9]. In the treatment of LD-SCLC the high response rate is expected (80–90%), but this favorable radiological efficacy does not seem to correspond to the survival benefit, with a 5-year survival rate of only around 20% [10]. It means that even not all responders are expected to have a better survival. As one of the strategies for improving the unsatisfactory treatment outcome, it would seem reasonable to select LD-SCLC patients who would benefit least from the standard chemoradiotherapy in terms of survival prolongation among those responding to its therapy, and then develop novel treatment strategies for such high-risk subpopulation.

Interestingly, in advanced non-small-cell lung cancer (NSCLC) patients who obtained objective response to the initial chemoradiotherapy (CHRT), slow tumor regression after the initiation of CHRT, as compared with early tumor regression, was significantly associated with poor treatment outcome even though the radiological response could be once confirmed [11]. Taking a hint from its

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observation, we here investigated whether the timing of obtaining tumor regression with first-line CHRT could affect the prognosis in LD-SCLC patients who finally achieved the objective response through the treatment courses.

2. Patients and methods

2.1. Patients

Between July 1988 and December 2006, a total of 81 patients who were diagnosed with untreated, pathologically documented LD-SCLC obtained complete response (CR) or partial response (PR) with its confirmation by the platinum-based CHRT at the Okayama University Hospital. Of these, 11 (14%) patients were excluded in the further analysis mainly because of no available data regarding unconfirmed response rate just at the end of first cycle chemotherapy. LD was defined as disease confined to the ipsilateral hemithorax within a single radiation port [1–3]. Our routine staging work-up had been consistently done by using CT scan, MRI examination of the brain, and bone scintigraphy. PET-CT scan has not always been used for staging work-up. The details of initial treatments and response criteria were described as below. The main purpose of this study was to clarify whether overall survival could be influenced by the early tumor regression after the completion of the first cycle, the earliest time point at which we could get information on response, and thus, those who successfully received the first cycle of the chemotherapy and survived at least during the first cycle were included in the study. Written informed consent was obtained from each patient before treatment.

2.2. Chemotherapy and thoracic radiotherapy

Patients received a platinum-based chemotherapy, predominantly etoposide and cisplatin (EP) regimen [12]. The other regimens used included etoposide and carboplatin (EC), irinotecan and cisplatin (IP) and cyclophosphamide, doxorubicin, and vincristine (CAV) regimens [13–15]. All these regimens were administered for three or four cycles.

All patients included in this study were also treated with thoracic radiotherapy (TRT). In the concurrent group, TRT was given twice daily (1.5 Gy per fraction, with ≥6 h between fractions) and directed to the primary tumor for a total dose of 45 Gy in 3 weeks. RT was initiated early in the cycle 1 of chemotherapy. The initial field included the primary disease site, and the involved ipsilateral hilum, mediastinum, and supraclavicular lymph nodes. In the sequential group, the field was also based on the pretreatment tumor volume. The target volume before chemotherapy was set similarly as that in the cases with the concurrent arm.

2.3. Definitions of early tumor regression and best overall response

Since the original responses documented by the attending physicians were based on various response criteria including WHO criteria, tumor responses were validated for this study according to the Standard Response Evaluation Criteria in Solid Tumours [16] independently by the two medical oncologists (M.F., K.H.) holding a board certificate. Tumor markers were not used to assess response. The first assessment of tumor response was generally performed just before the initiation of the second cycle, that is, 3 weeks after the initiation of the treatment. At that time, if at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter, was observed, we defined it as early tumor regression. A minimum duration of further four weeks was required for confirming it. The response after cycle 1 was retrospectively assessed on CT images in all cases. Finally, best overall response was defined as the best response recorded from the start of treatment until disease progression or recurrence.

Table 1
Demographics of the patients, first-line chemotherapy regimens, and timing of thoracic irradiation.

	Early tumor regression		Total (n=70)
	Yes (n=52)	No (n=18)	
Age, year, median (range)	66 (39–78)	67 (48–79)	67 (39–79)
Gender			
Male/female	43/9	18/0	61/9
Performance status			
0/1/2	23/28/1	7/11/0	30/39/1
Smoking status			
Brinkman index ≤600/>600	10/42	2/16	12/58
Chemotherapy regimens			
EP	39	13	52
EC	9	2	11
IP	3	1	4
CAV/IP	1	0	1
Other platinum based combination	0	2	2
Radiation			
Concurrent	45	14	59
Sequential	7	4	11

If at least a 30% decrease in the sum of the longest diameter of target lesions was observed just before the initiation of the second cycle, we defined it as early tumor regression. *Abbreviations*: EP: etoposide, cisplatin; EC: etoposide, carboplatin; IP: irinotecan, cisplatin; CAV: cyclophosphamide, doxorubicin, vincristine.

2.4. Statistical analysis

Patients were divided into two groups depending on tumor shrinkage after the completion of the first course of initial CHRT (early tumor regression group versus late tumor regression group). Differences in the demographics between groups were assessed by Mann–Whitney U test. The overall survival (OS) was measured from the date of the initiation of the treatment until any death. PFS was measured from the date of first treatment until progression or any death, or censored at last follow-up.

The influence of early tumor regression on PFS and OS was assessed using the Kaplan–Meyer method and log-rank statistic. In addition, Cox's proportional hazard analysis was used for PFS and OS adjusting other confounding factors including age, sex, performance status (PS), smoking status, irradiation type, and best overall response. The hazard risk of death, together with its 95% confidence interval (CI), was calculated. All analyses were done using SPSS statistical package (Ver. 8.0, SPSS Inc., Chicago, IL, USA). All p-values were two-sided, and those of less than 0.05 were defined as statistical significance.

3. Results

3.1. Patients and treatments

The demographics of the 70 patients are summarized in Table 1. The median age of the patients was 67 years (range; 39–79), the majority of the patients had an Eastern Cooperative Oncology Group performance status of 0–1. Of these, 59 patients received platinum-based concurrent CHRT, while 11 received sequential CHRT as first-line treatment. In the concurrent group, forty-nine patients received EP, and 10 EC. In the sequential group, four patients received IP, 3 EP, 1 CE, 1 CAV/PE and 2 others (platinum-based). Each regimen was administered for three or four cycles. Sixty-three patients received 4 cycles, and 7 received 3.

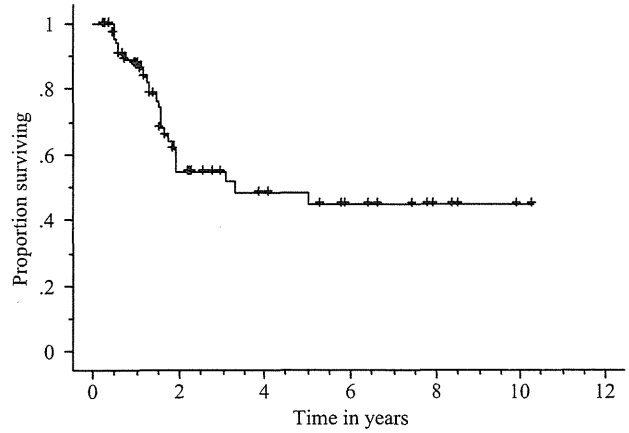

Fig. 1. Overall survival curve of all 70 patients with limited-disease small-cell lung cancer. Median survival time and 5-year survival rate of 39.6 months and 44.5%, respectively.

3.2. Response and survival

The best overall response to the CHRT was CR in 31 patients (44.3%) and PR in 39 patients (55.7%). The median follow-up time was 22.7 months for the surviving patients, and in the whole cohort the median OS and median PFS time were 39.6 and 12.3 months, respectively (Fig. 1).

After the first course of treatment, 52 patients (74.3%) attained early tumor regression, 25 and 27 of whom had the best overall responses of CR and PR, respectively. The remaining 18 (25.7%) did not reach it yet at the end of the first cycle. Of note, the OS in the former 52 patients with the early tumor regression was significantly better than that in the latter 18 patients without it (logrank test; $p < 0.001$) with 2-year survival rates of 72.3% versus 7.1% and 5-year survival rates of 67.7% versus 0%, respectively (Fig. 2A). Similarly, the PFS in patients with the early tumor regression was significantly better than those without (logrank test; $p < 0.001$) (median PFS; 14.8 and 7.3 months, respectively) (Fig. 2B).

As shown in Table 2, the multivariate analysis revealed that obtaining the early tumor regression to the treatment yielded a better OS (HR = 0.098; $p < 0.001$) in addition that attaining the best overall responses did it (HR = 0.332; $p = 0.037$). Among the independent valuables used in the multivariate model, the factor "best overall response" was considered strongly associated with "early tumor regression to the treatment". Thus, we constructed another multivariate model excluding this variable (the best overall response), which revealed the early tumor regression still remained a statistically significant prognostic factor (HR = 0.077, 95% CI = 0.028–0.211). Regarding PFS, we could obtain similar pattern of the multivariate analysis results (Table 3).

4. Discussion

We found that among 70 patients with LD-SCLC achieving confirmed objective tumor response to the initial CHRT, the median survival time and PFS time were 39.6 and 12.3 months, respectively. Notably, the timing of obtaining tumor regression could affect the prognosis in these patients; the 2-year survival rate and 5-year survival rate in those without entering PR after the first course of CHRT were 7.1% and 0%, respectively, while those with the early tumor regression had a better prognosis with the 2-year survival rates and 5-year survival rates of 72.3% and 67.7%, respectively.

As a similar study, Sirohi et al. [11] investigated the importance of the early tumor regression predicts patient outcome in 320 patients with stage III/IV NSCLC who received and responded to the standard first-line cisplatin-based CHRT. They showed that early response was 35.9% of those achieved PR, and the 2-year survival rates for patients entering PR after two courses was significantly higher than those without (23% versus 11%, $p = 0.002$). These results would support our findings, suggesting that in lung cancer patients, those without early tumor progression might have a poorer outcome even though the objective response is finally confirmed through the treatment course of the chemoradiotherapy. Considering this obvious survival difference between the early and late tumor regression groups, the issue as to how fast tumor could regress after the initial exposure to cytotoxic agents would be clinically important. Although there are no definitive biological explanations for their and our data, one would consider the need for new approaches to improve outcome in those without the early tumor regression.

Clinically, our findings may be translated into the potential importance of early switching the chemotherapy regimen. The Japanese phase II trial, investigating the efficacy of IP therapy following the concurrent CHRT with one cycle of EP regimen and 45 Gy of twice-daily TRT, showed a favorable treatment outcome with the

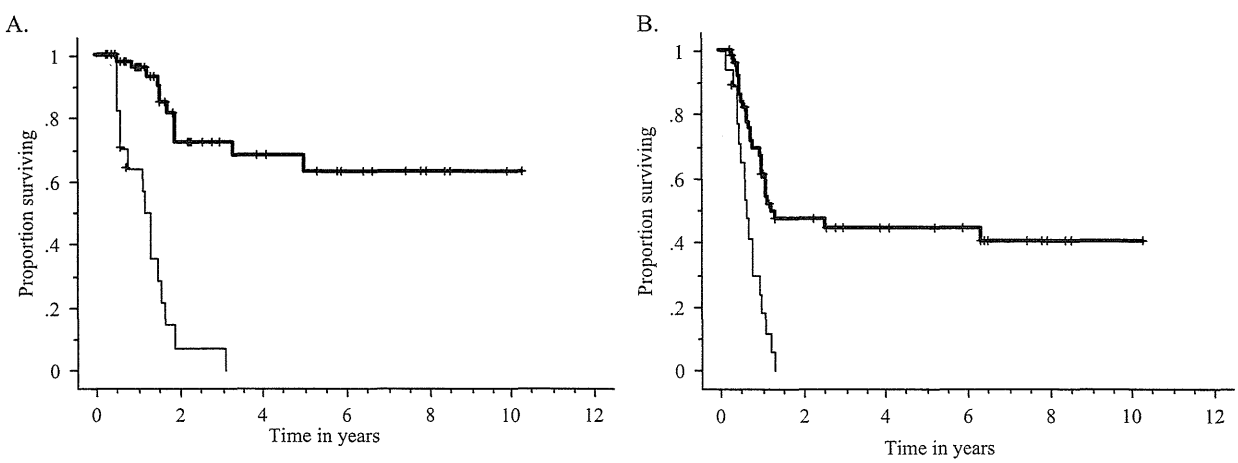

Fig. 2. Survival curves stratified by the timing of tumor regression. Bold and thin lines represent patients with and without early tumor regression results, respectively. (A) Overall survival curves (the 2-year survival rates and 5-year survival rates in those without early tumor regression (=late tumor regression group) were 7.1% and 0%, respectively, while in those with the early tumor regression were 72.3% and 67.7%, respectively, log-rank test; $p < 0.001$). (B) Progression-free survival curves (median progression-free survival times were 14.8 and 7.3 months in those with early tumor regression and with late tumor regression, respectively, log-rank test; $p < 0.001$).