a risk estimate for recurrence using the survival tree method.

Materials and Methods

This retrospective study based on a review of medical records was conducted with the approval of our hospital's internal review board (SCC2012-225). From 1998 to 2009, 1,338 patients with NSCLC underwent complete resection (R0) with a segmentectomy or more extended pulmonary resection, followed by systemic mediastinal lymph node dissection; all the patients were followed up at our institution after resection. The seventh edition of the TNM staging system was applied in this study, and all 1,338 patients were restaged according to the seventh edition.[8] Information about the 1,338 patients, including the tumor histology, pathologic (p) stage, history of adjuvant chemotherapy, and the survival and recurrence data were carefully reviewed. Regarding the histology, we collected information not only on the histologic subtypes but also on the extent of lymphatic vessel invasion (ly), the extent of blood vessel invasion (v), and the G.

The specimens were stained with hematoxylin-eosin and elastica van Gieson and were examined under a × 200 magnification. The ly factor was semiquantitatively scored into four grades in accordance with the following criteria: ly0, no lymphatic vessel involvement; ly1, involvement of one lymphatic site per low-power field; ly2, involvement of two or three lymphatic sites per low-power field; and ly3, involvement of four or more lymphatic sites per low-power field. The v factor was similarly scored. The G factor was classified into four grades of severity according to the guidelines of the American Joint Commission on Cancer, as follows: G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; G4, undifferentiated.[9]

Survival data and recurrence data were obtained for all 1,338 patients in June 2011. Kaplan-Meier curves for recurrence-free survival (RFS) and the estimated hazard ratios were constructed according to the TNM stage. A definition of RFS in this study was a count of recurrence only as an event. Deaths were regarded as censored cases when recurrence was not known to have occurred.

To identify a population with a high risk of recurrence after resection, the survival tree method was used in this study. The algorithm for the survival tree method is as follows.[10] The survival tree model involves two components: (1) the examination of all allowable splits on each predictor variable and (2) the selection and execution (to create left and right daughter nodes) of the optimal splits. At each step of the analysis, all the possible splits into disjoint subsets are examined by a computer algorithm based on the log-rank test. The best split is then selected so that the split produces two subgroups of patients with the largest difference in Kaplan-Meier survival curves. The same procedure is applied recursively to increase the number of splits until each group contains only a few subjects. In this study, T factor, N factor, ly factor, v factor, G factor, histologic subtype, and history of adjuvant chemotherapy were evaluated as variables using the survival tree method according to the frequency of recurrence after resection, and the patients were classified into subgroups. Kaplan-Meier curves for RFS were constructed according to the subgroups identified by the survival tree method. The estimated hazard ratios for recurrence classified according to these subgroups were also calculated.

The survival tree analysis was performed using the rpart package in the R statistical software, and the hazard ratios for recurrence were estimated using the muhaz package in the R statistical software (http://www.r-project.org/). Other statistical analyses, including the Kaplan-Meier method, were performed using Stata, Ver. 11.2 (StataCorp LP). P values $< .05$ were considered to denote statistical significance.

Preoperative Workup and Postoperative Follow-up Protocol

All the patients who were considered to be candidates for surgical resection underwent a CT scan examination of the thorax and upper abdomen, abdominal ultrasonography, bone scintigraphy, and enhanced MRI of the brain. PET/CT scan was initiated in April 2006 at our institute. All the patients underwent PET/CT scan and an enhanced MRI examination of the brain as part of the preoperative workup thereafter.

During the first 2 years after surgery, a follow-up examination, including history taking and a physical examination, was performed every 3 to 4 months. During the next 3 years, the same follow-up procedures were repeated every 5 to 6 months. A CT scan examination of the thorax and upper abdomen was performed 12 months after the operation and was repeated annually. Chest radiography was performed 3 months and 6 months after the operation and was then repeated once a year between the CT scan examinations. The follow-up procedures, including the imaging examinations, were reduced to a minimum after the passage of 5 years after the operation but were nonetheless continued for up to 7 to 10 years.

It was important to distinguish metachronous lung cancer from recurrence when a new pulmonary malignancy was detected after resection. Lou et al[11] reported their protocol for distinguishing recurrence and metachronous lung cancer after resection. Our process was similar to the method of Lou et al.[11] When a new pulmonary malignancy was detected during the follow-up surveillance, restaging was performed just as was done during the preoperative workup, which included CT scan, PET/CT scan, MRI, ultrasonography, and bone scintigraphy. A diagnosis of recurrence was based on the image findings in most cases. In some cases in which it was difficult to discriminate between recurrence and metachronous lung cancer, histologic confirmation was performed, and a diagnosis of metachronous lung cancer was decided according to the criteria of Martini and Melamed[12] as follows: (1) the histologic results differed from those of the index tumor; (2) the same histologic results as the index tumor were obtained, but diagnosis was made 2 years after the primary tumor; or (3) the same histologic results as the index tumor were obtained, the diagnosis was made within 2 years of the primary tumor, but the tumors were located in different lobes or segments, with no positive intervening lymph nodes and no evidence of metastasis. When a new pulmonary malignancy fulfilled any one of these criteria, it was considered to be metachronous lung cancer. In addition, a new pulmonary malignancy was diagnosed as metachronous lung cancer when it was accompanied by a ground-glass opacity on high-resolution CT scan, regardless of its location and the timing of its appearance. A new pulmonary malignancy that met these criteria was considered to be metachronous lung cancer and was excluded from this study.

Results

The characteristics of the 1,338 patients are listed in Table 1. The median age was 66 years (range, 27-88 years), and 742 patients were men. Histologic examination revealed adenocarcinoma in 1,046 patients, squamous cell carcinoma in 226 patients, and others in 66 patients; the p stage was p-stage IA in 663 patients, IB in 305, IIA in 119, IIB in 73, IIIA in 140, and IIIB in four patients. No ly (ly0) was observed in 851 patients (65.7%), whereas 287 patients (22.2%) were classified as ly1, 134 patients (10.3%) were classified as ly2, and 22 patients (1.7%) were classified as ly3. Similarly, no v (v0) was observed in 731 patients (56.6%),

Table 1—*Patient Characteristics*

Characteristic	Value
Age, median (range), y	66 (27-88)
Sex	
Male	742 (55.5)
Female	596 (44.5)
Histologic subtype	
Adenocarcinoma	1,046 (78.2)
Squamous cell carcinoma	226 (16.9)
Other	66 (4.9)
p Stage	
IA	663 (50.8)
IB	305 (23.4)
IIA	119 (9.1)
IIB	73 (5.6)
IIIA	140 (10.7)
IIIB	4 (0.3)
pT	
1a	497 (38.1)
1b	243 (18.7)
2a	411 (31.5)
2b	42 (3.2)
3	105 (8.1)
4	5 (0.4)
Unknown	35 (2.6)
pN	
0	1,087 (81.2)
1	126 (9.5)
2	119 (8.9)
3	1 (0.1)
Unknown	5 (3.7)
ly	
0	851 (65.7)
1	287 (22.2)
2	134 (10.3)
3	22 (1.7)
Unknown	44 (3.3)
v	
0	731 (56.6)
1	334 (25.9)
2	188 (14.6)
3	37 (2.9)
Unknown	48 (3.6)
G	
Well differentiated (G1)	440 (35.0)
Moderately differentiated (G2)	521 (41.4)
Poorly differentiated (G3)	280 (22.2)
Undifferentiated (G4)	18 (1.4)
Unknown	79 (5.9)
Adjuvant chemotherapy	
No	1,011 (75.6)
Yes	327 (24.4)
Recurrence	
No	984 (73.5)
Yes	277 (26.5)
Dead or alive	
Alive	1,042 (77.9)
Dead	296 (22.1)

Data are presented as No. (%) unless otherwise noted. G = tumor differentiation grade; ly = lymphatic vessel invasion; p = pathologic; v = blood vessel invasion.

whereas 334 patients (25.9%) were classified as v1, 188 patients (14.6%) were classified as v2, and 37 patients (2.9%) were classified as v3. Regarding the G factor, 440 patients (35.0%) were classified as G1, 521 patients (41.4%) were classified as G2, 280 patients (22.2%) were classified as G3, and 18 patients (1.4%) were classified as G4. Preoperative chemoradiotherapy was performed in 29 patients, and postoperative adjuvant chemotherapy was performed in 327 patients.

The median follow-up period was 54.2 months (range, 1-159 months). Recurrence was observed in 277 patients (26.5%) during the study period, and 296 patients (22.1%) had died as of June 2011.

The 1-, 3-, and 5-year RFS for the all patients were 77.1%, 22.6%, and 7.9%, respectively, and most recurrences occurred within 5 years of resection. The RFS curves classified according to the TNM stage are shown in Figure 1. The 5-year RFS rates for stage IA, IB, IIA, IIB, and IIIA were 90.8%, 68.9%, 54.3%, 43.5%, and 22.0%, respectively, and the RFS was significantly different among the TNM stage ($P < .001$). The estimated hazard ratios for recurrence classified according to the TNM stage are shown in Figure 2. The estimated hazard ratios for recurrence increased and reached a peak at between 6 months and 2 years after resection, gradually decreasing thereafter. The hazard ratios for recurrence in stage IIB-IIIB disease seemed to reach their peak earlier than those in stage IA-IIA disease.

The RFS was analyzed according to the grade of the ly factor, and the results indicated that the grade of the ly factor was significantly related to the RFS ($P < .001$). The RFS of patients with ly0 was better than those with ly1, ly2, and ly3, and the RFS became worse as the grade of the ly advanced. Similarly, the RFS was analyzed according to the grade of the v factor and the G factor, and the results indicated that the RFS also became worse as the grade of the v factor and the G factor advanced. Regarding the histologic subtype, patients with adenocarcinoma had a better RFS than the patients with other histologic subtypes ($P < .001$).

To identify a population with a high risk of recurrence after resection, the T factor, N factor, ly factor,

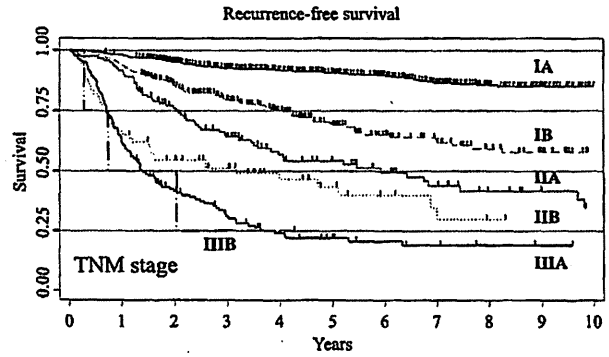

FIGURE 1. Recurrence-free survival curve classified according to the TNM stage.

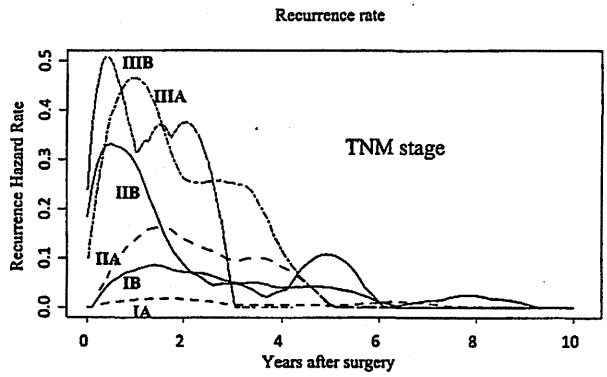

FIGURE 2. Estimated hazard rates for recurrence classified according to the TNM stage.

v factor, G factor, histologic subtype, and history of adjuvant chemotherapy were analyzed using the survival tree method. The T, N, v, and ly factors were selected as variables in the split steps, but the G factor, histologic subtype, and history of adjuvant chemotherapy were not selected in this study (Fig 3). The first split was produced by the v factor, and the patients were separated according to $v = 0$ vs $v \geq 1$. The second split of the $v = 0$ branch was produced by the T factor, and the patients were separated according to $T \leq 1b$ vs $T \geq 2a$. The $V = 0$, $T \leq b$ group was separated with $ly = 0$ vs $ly \geq 1$ at the third sprit. Similarly, in the $v \geq 1$ branch, the second split was produced by the N factor, and the patients were separated according to $N \leq 1$ vs $N \geq 2$. The third split of the $v \geq 1$, $N \leq 1$ group was produced by the T factor, and the patients were separated according to $T \leq 2b$ vs $T \geq 3$. Finally, the 1,338 patients were classified into six groups; group A: $v = 0$, $T \leq 1b$, $ly = 0$; group B: $v = 0$, $T \leq 1b$, $ly \geq 1$; group C: $v = 0$, $T \geq 2a$; group D: $v \geq 1$, $N \leq 1$, $T \leq 2b$; group E: $v \geq 1$, $N \leq 1$, $T \geq 3$; and group F: $v \geq 1$, $N \geq 2$.

The Kaplan-Meier curves for the RFS classified according to these six groups are shown in Figure 4.

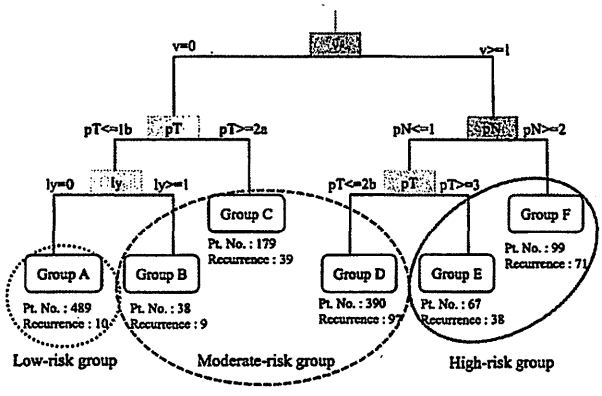

FIGURE 3. Survival tree. ly = lymphatic vessel invasion; p = pathologic; Pt. No. = patient number; v = blood vessel invasion.

The curves for groups B, C, and D were identical; similarly, those for groups E and F were also almost identical. The six groups were further classified into three risk groups, as follows: a low-risk group (group A), a moderate-risk group (groups B, C, and D), and a high-risk group (groups E and F) (Figs 3, 4). The 5-year RFS rates were approximately 98% for the low-risk group, 75% for the moderate-risk group, and 30% for the high-risk group. The estimated hazard ratios for recurrence classified according to these three groups are shown in Figure 5. The estimated hazard ratios for recurrence increased and reached their peak at between 1 and 2 years after resection, then gradually decreased thereafter. The hazard ratio for recurrence in the high-risk group seemed to reach its peak earlier than that in the low-risk group.

DISCUSSION

The TNM staging system is based on the characteristics of the primary tumor, the status of metastasis to the lymph nodes, and the presence/absence of distant metastasis. It is used worldwide, because it is simple and is correlated with patient prognosis. In patients with lung cancer, other factors, such as ly, v, and G factors, and more recently, the presence/absence of epidermal growth factor receptor mutation and the expressions of excision repair cross-complementation group 1 and ribonucleotide reductase M1 polypeptide, have been reported to be correlated with prognosis.[5-7,13-16] However, testing for epidermal growth factor receptor mutation and the expressions of excision repair cross-complementation group 1and ribonucleotide reductase M1 polypeptide are not routinely performed in clinical practice. In this study, we focused on the T, N, ly, v, and G factors, all of which are easily evaluable in typical clinical practice, in an attempt to identify the risk factors for recurrence after resection in patients with lung cancer. The results of this study suggest that the combining of T, N, ly, and v factors in the risk estimation allowed the precise identification of a population with a high risk of recurrence.

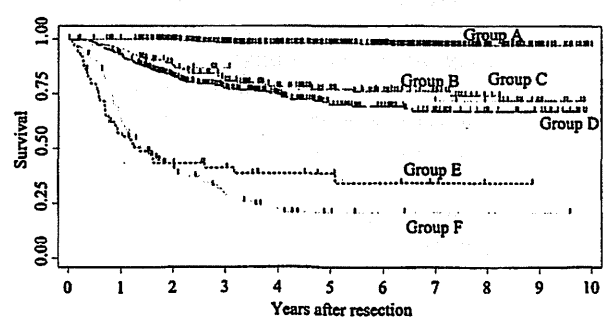

FIGURE 4. Recurrence-free survival curves classified according to the six groups identified using the survival tree method.

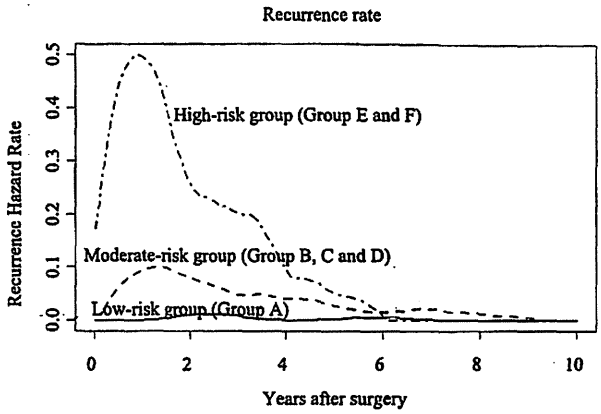

FIGURE 5. Estimated hazard rates for recurrence classified according to the low-, moderate-, and high-risk groups.

A precise identification of the high-risk population for recurrence after resection might contribute to optimizing the postoperative follow-up surveillance. For instance, postoperative follow-up examinations might be unnecessary in the low-risk group (group A: $v = 0$, $T \leq 1b$, $ly = 0$), since recurrence is expected to be rare in this group.

The Cox proportional hazards analysis is commonly used for multivariate analyses in many medical studies. The primary assumption in a Cox proportional hazards analysis is that the hazard functions of all data groups are proportional to one another. The survival tree model makes no assumption of proportional hazards; through a precise and complex program, it segregates groups by sequential partitioning based on statistical parameters related to the number of events (recurrences, deaths), allowing the progressive segregation of smaller groups with statistically significantly differences.[17] The survival tree model, therefore, can identify meaningful prognostic subsets in a study population, which usually do not emerge from a routine proportional hazards analysis.[10,18,19] At each step of the analysis in the survival tree model, all the possible splits into disjoint subsets are examined by a computer algorithm based on the log-rank test. The best split is then selected so that the split produces two subgroups of patients with the greatest differences in their Kaplan-Meier survival curves. Therefore, the variable that is used for the first split is considered to be the most significant factor. The first separation was created based on the presence/absence of v ($v = 0$ vs $v \geq 1$) in this study. This outcome suggested that the presence/absence of v might be the most critical predictive factor of recurrence after resection. Interestingly, the variable in the third step, which separated group A and group B, was the presence/absence of ly ($ly = 0$ vs $ly \geq 1$). Although the grades of the v factor and the ly factor were significantly related to the RFS, the presence/absence of vessel invasion might have more influence than the grade for the prediction of recurrence. Another factor considered to be associated with recurrence might be visceral pleural invasion. Several investigators have reported that visceral pleural invasion is related to survival,[20,21] but this factor was not evaluated in this study. Including the visceral pleural invasion factor among the ly and v factors study might have led to different results.

Preoperative chemoradiotherapy was performed in 29 patients, and postoperative chemotherapy was performed in 327 patients; these patients were analyzed together in this study. Especially in the cases with preoperative chemoradiotherapy, the ly factor and v factor might have been influenced by the treatment. However, only 29 patients underwent preoperative chemoradiotherapy, and this number was so small that the effect of preoperative chemoradiotherapy was unlikely to have had a significant influence on the results. The presence/absence of adjuvant chemotherapy was included and analyzed using the survival tree method to evaluate the influence on recurrence but was not selected as a variable. Ideally, the patients with preoperative chemoradiotherapy and adjuvant chemotherapy should have been analyzed separately, or a subgroup analysis might have been needed.

Metachronous lung cancer was diagnosed according to the criteria described in the Materials and Methods section, and patients with metachronous lung cancer were excluded from the present study. Of the 1,338 patients who were evaluated in this study, 53 patients (4.0%) developed metachronous lung cancer during the study period. The time intervals from the resection of the first lung cancer until the development of the second lung cancer ranged from 8 to 99 months. The hazard rate for the development the metachronous lung cancer over time is shown in Figure 6. The hazard rate increased gradually and reached a plateau at approximately 2 years, then decreased approximately 8 years after the first lung cancer. The possible reasons for the reduction in hazard rate might be related to patient age and

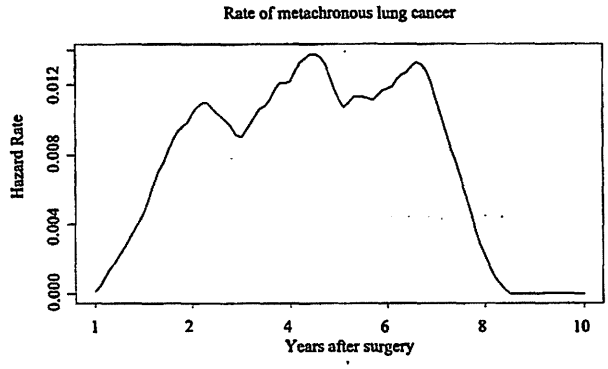

FIGURE 6. Estimated hazard rates for the development of metachronous lung cancer.

the follow-up period of the study. The median age of the 53 patients with metachronous lung cancer was 69 years, and the patients would have been 77 years old after the passage of 8 years. Such an age might be too old for the development of second lung cancer. The longest follow-up period in this study was approximately 12 years. The number of patients who developed metachronous lung cancer would have likely increased if the follow-up period had been longer.

The hazard rate for recurrence increased after resection and reached a peak between 1 and 2 years, gradually decreasing thereafter, as shown in Figures 1 and 5. In theory, the shape of the recurrence risk curve should be a single-peaked smooth curve; however, our results revealed curves with multiple peaks. One reason for this result might have been the study size. There were only 277 patients with recurrence in this study, which might not be a sufficiently large sample size to allow a smooth single-peaked curve to be obtained. However, Demicheli et al[22] analyzed the recurrence dynamics after resection in a larger study and reported a similar multipeak recurrence risk curve. They explained this result using the tumor dormancy theory, which proposes that disseminated tumor cells interact with the microenvironment and show growth arrest if the environment is not permissive; then, once the environment becomes favorable again, the cells start to show uncontrolled proliferation and form metastases.[23-26] This theory has been previously discussed in detail in relation to breast cancer, but it is still not clearly understood.[27,28] Another possibility explaining the multipeak pattern might be related to our postoperative follow-up surveillance. As described in the Materials and Methods section, chest CT scan examinations were routinely repeated every year after resection in all patients. This procedure possibly detected asymptomatic recurrences, explaining the small peaks in the recurrence risk curves observed at around 2 and 3 years after resection. There is insufficient evidence, however, to arrive at a definitive conclusion, and as far as this study was concerned, we considered the multipeak pattern of the recurrence risk curve to be attributable to our postoperative follow-up surveillance protocol.

Conclusions

Risk factors for recurrence after resection were analyzed using the survival tree model in patients who had undergone a complete resection for NSCLC. The patients were classified into three groups (low, moderate, and high risk) according to the risk of recurrence by the combining the T, N, ly, and v factors. The results suggested that combining the T, N, ly, and v factors might enable an accurate estimation of the risk of recurrence after resection.

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Author contributions: Dr Sawada takes responsibility for the integrity of the data and the accuracy of the data analysis.
Dr Sawada: contributed to the design, overseeing, and conduct of the study and to the writing and editing of the manuscript.
Dr N. Yamashita: had full access to the data and contributed to the statistical analysis and drafting of the manuscript.
Dr Suehisa: contributed to the study conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and revision of the manuscript.
Dr M. Yamashita: contributed to the study conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and revision of the manuscript.
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Case report

A case report of tuberculous abscess of the chest wall accompanied with pulmonary carcinoma☆

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ABSTRACT

With the decreasing incidence of tuberculosis (TB), tuberculous abscess of the chest wall (TACW) is becoming rare. Pulmonary carcinoma coexisting with pulmonary TB has been reported in the past, but reports of pulmonary TB accompanied with TACW are scarce. We present the first case of a 66-year-old male with TACW accompanied with pulmonary carcinoma.

1. Introduction

Although Japan currently has an intermediate burden in terms of incidence of tuberculosis (TB), the number of patients with TB is decreasing because of advances in chemotherapy. The incidence of tuberculous abscess of the chest wall (TACW) is low and accounts for 1%–10% of skeletal TB cases [1,2]. Because of the rarity of TACW, treatment strategies involving surgery are controversial because extremely few cases have been reported.

Pulmonary carcinoma coexisting with pulmonary TB has been reported in the past [3–5], but the coexistence of chest TB and pulmonary carcinoma is rare. To the best of our knowledge, no reports on the coexistence of these diseases have been published in the English literature. We report a rare case of TACW accompanied with pulmonary carcinoma.

2. Case report

A 66-year-old man with no past history of pulmonary TB or immunocompromised status presented at the National Hospital Organization Shikoku Cancer Center with a chief complaint of a painless mass in his left chest wall. Computed tomography (CT) revealed an 8-cm tumor and peripherally enhancing fluid collection in the chest wall adjacent to the seventh and eighth ribs, without osteolytic change (Fig. 1A). A pulmonary nodule demonstrating a mixed ground glass opacity (GGO) measuring 19 × 15 mm in segment 4 of the left lung (Fig. 1B) was detected incidentary. Blood tests revealed that white blood cell count was within the normal range. Levels of C-reactive protein, carcinoembryonic antigen, and cytokeratin 19 fragments in the serum were 0.82 mg/dl, 2.2 ng/ml, and 1.4 ng/ml, respectively. Results of acid-fast staining from the sputum culture and the aspiration specimen were negative. The aspirated specimen from the chest wall tumor was positive for *Mycobacterium tuberculosis* (polymerase chain reaction). The tumor was therefore diagnosed as TACW. Pulmonary nodule was clinically diagnosed as lung cancer T1aN0M0 stage IA. Surgery was performed at the regional TB ward of the National Hospital Organization Ehime Medical Center.

Lingulectomy and lymph node dissection (levels 10 and 11) were performed. Video-assisted procedure was performed through a 6-cm access thoracotomy over the mid-axillary line in the fourth intercostal space, 1-cm access ports in the mid-axillary line in the

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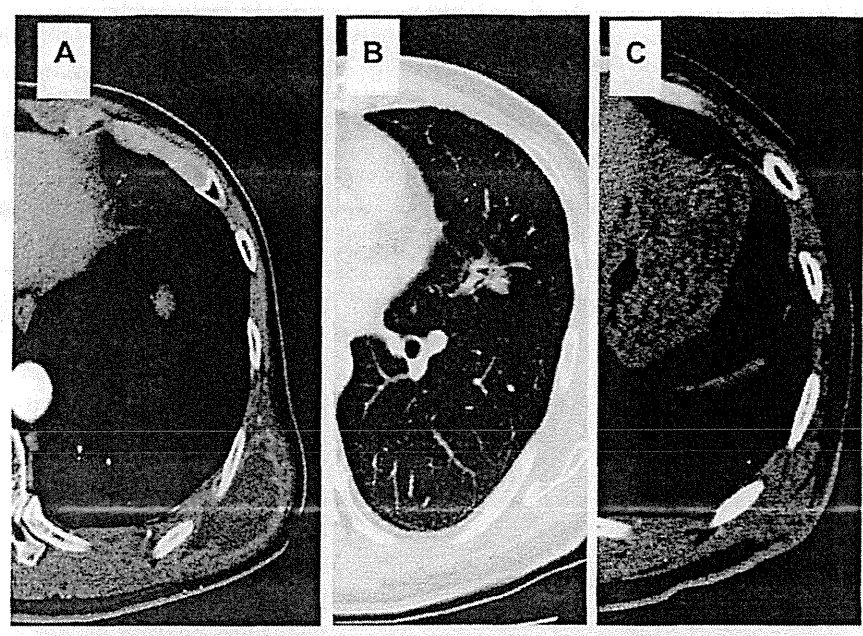

Fig. 1. A. Enhanced chest computed tomography (CT) showing a peripherally enhancing fluid collection in the chest wall adjacent to the seventh and eighth ribs. B. A mixed ground glass opacity was detected in segment 4 of the left lung. C. Chest CT 3 months after the surgery showing minimal inflammatory change.

sixth intercostal space and posterior axillary line in the fifth intercostal space. No penetration of the parietal pleura by the abscess was evident. Slight adhesion was found in the pleural cavity but not between the lower lobe and the parietal pleura adjacent to the abscess. For the abscess, debridement without rib resection was performed. Debridement of the necrotic tissue and the abscess wall was performed through another 5-cm incision right over the abscess. Chest wall cavity and the pleural cavity were drained with silicon drains. These were removed on postoperative day 5 and postoperative day 7 respectively. The postoperative course was uneventful. Antituberculous chemotherapy consisting of isoniazid (300 mg), rifampicin (600 mg), ethambutol (750 mg), and pyrazynamide (1.5 g) per day was initiated on postoperative day 14. The patient was discharged on postoperative day 17.

Histologically, GGO consisted of an adenocarcinoma mixed subtype (bronchioloalveolar carcinoma + papillary adenocarcinoma) without lymph node metastasis. Pathologically, the tumor was diagnosed as T1aN0M0 stage IA. Caseation necrosis surrounded by Langhans-type giant cells was seen in the specimen from the chest wall abscess, was compatible with tuberculoid granuloma. *M. tuberculosis* was identified in an 8-week culture of the pus from the abscess.

3. Discussion

Although Japan is a country with an intermediate TB burden, the incidence of TB is low. According to a World Health Organization report, the incidence of TB was 20 cases per 100,000 people per year in 2011. The development of effective anti-TB drugs has decreased the incidence of TB.

TACW is considered to be rare. Skeletal TB accounts for 2.6% of all TB cases [6]. TACW is found in 1%–10% of bony TB cases [1,2]. The incidence of TACW is low, and retrospective reports tend to include a small number of patients. The appropriate surgical treatment is controversial. In recent decades, some cases of TACW from East Asia have been reported, including a relatively large number of surgical cases (60–120 patients) with TACW, although these were retrospective studies [7–10]. Surgical methods in these reports include abscess debridement, complete excision with or without rib resection, and coverage using muscle flap. Relapses were reported in 2.5%–15% of patients in these series. However, the appropriate surgery according to the extent of the TACW lesion remains unclear. Rib resection may be too invasive in cases without destruction of bony structure. "Stain plombage procedure" presented by Sakakura and co-workers using saline solution of indigo carmine to fill the abscess cavity [11] may be helpful to identify the cyst wall when it is difficult to determine the range of surgical resection. In the present case, the abscess was simply localized and the adjacent rib was intact, and there was rapid shrinkage of the structures surrounding the TACW lesion (Fig. 1C). Therefore, debridement and drainage followed by antituberculous chemotherapy seemed to be the appropriate treatment. Recurrence is reported more than 5 years after treatment [8]. Thus, long-term follow-up is necessary in our case.

Coexistence of lung cancer and TACW is rare. However, coexistence of pulmonary carcinoma and pulmonary TB has been reported [3–5] in the past. The reported incidence of pulmonary carcinoma accompanied with TB is 1%–2% and that of pulmonary TB accompanied with pulmonary carcinoma is 1%–5% [5]. Metastasis or intrinsic factors may activate or cause recurrence of the TB lesion [3]. Coexistence of TACW and lung cancer has rarely been reported. To the best of our knowledge, this is the first reported case of the coexistence of these two diseases.

4. Conclusion

TACW is becoming a rare disease because of the decreasing incidence of TB. We report a case of chest wall TB accompanied with lung cancer. Coexistence of these diseases has not been previously reported.

Conflict of interest

The authors have no conflict of interest to disclose.

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総　説

がん補完代替療法における薬剤管理指導による医療コミュニケーションに関する検討

A study of health communication in pharmaceutical care for inpatients receiving complementary and alternative medicine for cancer

宮部貴識*・所　昭宏**・山下素弘***
Takashi MIYABE　*Akihiro TOKORO*　*Motohiro YAMASHITA*

要　旨：【目的】通常臨床として実施されている入院時持参薬管理指導時を利用したCAM医療コミュニケーションの実施可能性を検討する。
【方法】対象は当センターの入院肺がん患者である。入院時持参薬管理指導時にCAM準備性アンケートを実施しCAMコミュニケーション内容を探索的にアンケート調査した。
【結果】16名よりアンケートを回収した（回収率100%）。CAMコミュニケーション件数は6件（37.5%）、CAM利用の準備性については先行調査研究と同様の結果が得られた。
【考察】コミュニケーションツールを用いた積極的な問いかけは薬剤師への相談が見込まれ、未申告のCAM利用が判明することは相談向上や適切で双方向な受療行動につながることが今後期待される。

キーワード：がん、補完代替療法、CAM、コミュニケーション、薬剤管理指導

ABSTRACT: [Objectives] The aim of the study was to examine the feasibility of health communication with patients receiving complementary and alternative medicine (CAM). Communication was performed in pharmaceutical care provided as part of general clinical practice to control the drugs brought by the patients upon admission to hospital.
[Methods] The subjects were inpatients with pulmonary cancer at our center. We performed an exploratory questionnaire survey of readiness for CAM and examined the details of communication in CAM, with the goal of control of the drugs that the patients had upon admission.
[Results] Answers were collected from 16 patients (response rate: 100%). Six cases used communication (37.5%) and the results regarding readiness for CAM were the same as those in a previous study.
[Discussion] Active use of a communication tool is likely to increase the rate of consultation with pharmacists. Clarification of non-use of CAM through bi-directional medical communication may further increase consultations with pharmacists in the future.

Key Words: Cancer, Complementary and Alternative Medicine, CAM, Communication, Pharmaceutical Care

Ⅰ．はじめに

米国NCI（national cancer institute)の調査[1]によると、補完代替療法（Complementary and Alternative Medicine：以下、CAM）利用に際して患者が医療者と相談するのは3割以下と言われている。わが国では、兵頭らによるがん患者のCAM利用実態調査[2]によると患者の約6割は、医師にCAMのことを相談せず、逆に医師の約8割は、患者にCAMについての問診をしていない。また厚生労働省「がんの代替療法の科学的検証と臨床応用に関する研究班」（住吉班）が行なった調査[3]にても「医師や看護師に相談することは役立つと思う」31%、「薬剤師に相談することは役立つと思う」34%、「医師や看護師に相談したことがある」22%、「薬剤師に相談したことがある」8%で相談率は低く、特に他医療職に比べ薬剤師へのCAM相談は希薄である（図1）。さらに平井らの調査[4]によれば、家族からの期待がCAMの最大の利用促進要因である。上記の種々の調査研究により我が国においてがん患者のCAMを

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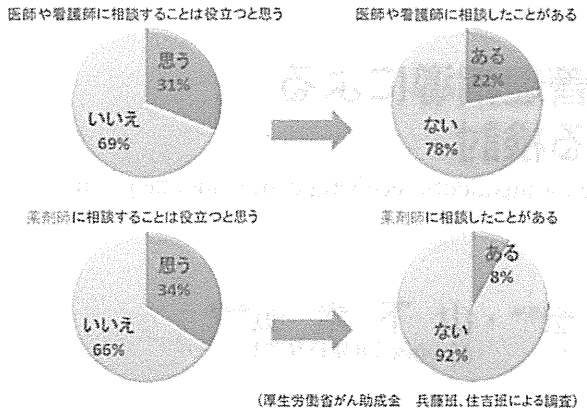
＊＊＊　国立病院機構四国がんセンター呼吸器外科



（厚生労働省がん助成金　兵藤班、佳吉班による調査）

図1　医療者へのCAM相談について（がん患者における補完代替療法の受療行動に関するアンケート調査）

めぐる患者－医療者間のコミュニケーションの希薄さがうかがえる。

医療における安全、安心の関心が高まり、その推進としてチーム医療が普及している[5]。薬剤師の通常業務として入院時の持参薬チェック（入院時持参薬管理指導）が多くの施設で取り入れられ実施されている。薬剤師による入院時持参薬管理指導に関しては、後発医薬品の使用の促進等により医師、看護師が識別できない非採用薬を持参する場合が多くなるため、薬品名違い、規格違い用法用量違い等を未然に防止できることから、その重要性が増してきている。また持参薬チェックすることにより持参薬による有害事象の重篤化・遷延化を回避、紹介状と持参薬の相違、手術前の投与禁忌薬の回避等、多くの成果が示され、その有用性はプレアボイド報告でも実証されている[6]。またがん領域においても薬剤師のチーム医療への参画が推進されており医療職種間での連携、コミュニケーションの必要性が進められている[7]。

本研究では、わが国のがん患者のCAMをめぐる患者と医療者のコミュニケーションに着目し、適切で双方向な受療行動としての医療コミュニケーションを実地臨床に応用できる指針を明らかにすることを目的に調査を行ったので報告する。

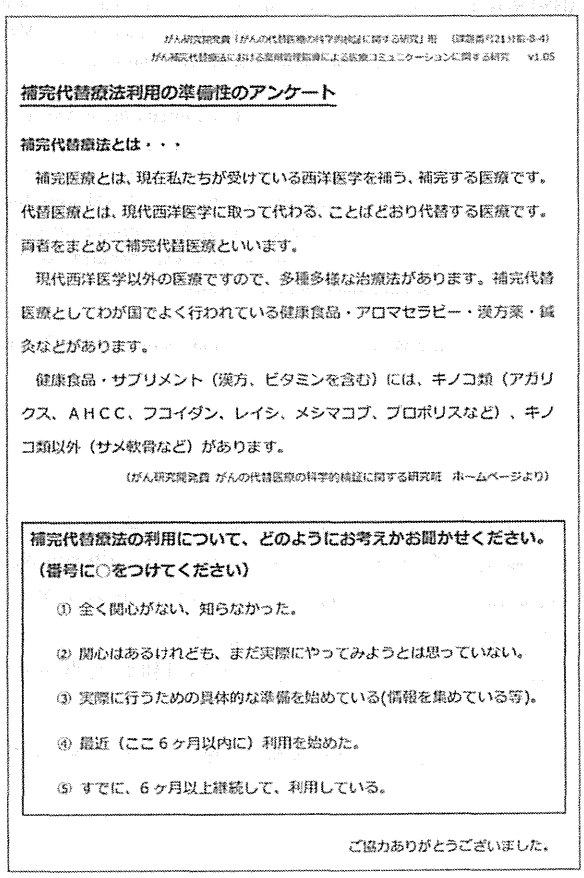
Ⅱ．目的

通常臨床で薬剤師により実施されている入院時持参薬管理指導を利用し、適切で双方向な受療行動としてのCAM医療コミュニケーションの実施可能性を検討する。

Ⅲ．対象と方法

平成23年4月より当センターで適格基準を満たす入院肺がん患者を対象に、入院時の薬剤管理指導の際にCAM準備性アンケートを実施し、退院までに患者とのCAMコミュニケーション内容を探索的に調査した。アンケートには、補完代替療法についての定義の説明とCAM準備性を問う補完代替療法の利用状況の5段階、①前熟考期（全く関心がない、知らなかった）、②熟考期（関心はあるけれども、まだ実際にやってみようとは思っていない）、③準備期（実際に行うための具体的な準備を始めている、情報を集めている等）、④実行期（最近（ここ6ヶ月以内に）利用を始めた）、⑤維持期（すでに、6ヶ月以上継続して、利用している）について記載した（図2）。

薬剤管理指導は入院7日目までに実施する入院時持参薬管理指導を対象とし、CAM準備性は入院時のCAM利用状況を評価した。なお同一患者への複数介入は行わないこととした。主要評価項目は薬剤師への相談件数および相談率、副次評価項目は、①入院時のCAM準備性（利用状況）、②CAMの相談



がん研究開発費「がんの代替医療の科学的検証に関する研究」班　（課題番号21分担-3-4）
がん補完代替療法における薬剤管理指導による医療コミュニケーションに関する研究　v1.05

補完代替療法利用の準備性のアンケート

補完代替療法とは・・・

補完医療とは、現在私たちが受けている西洋医学を補う、補完する医療です。代替医療とは、現代西洋医学に取って代わる、ことばどおり代替する医療です。両者をまとめて補完代替医療といいます。

現代西洋医学以外の医療ですので、多種多様な治療法があります。補完代替医療としてわが国でよく行われている健康食品・アロマセラピー・漢方薬・鍼灸などがあります。

健康食品・サプリメント（漢方、ビタミンを含む）には、キノコ類（アガリクス、AHCC、フコイダン、レイシ、メシマコブ、プロポリスなど）、キノコ類以外（サメ軟骨など）があります。

（がん研究開発費 がんの代替医療の科学的検証に関する研究班　ホームページより）

補完代替療法の利用について、どのようにお考えかお聞かせください。
（番号に○をつけてください）

① 全く関心がない、知らなかった。

② 関心はあるけれども、まだ実際にやってみようとは思っていない。

③ 実際に行うための具体的な準備を始めている(情報を集めている等)。

④ 最近（ここ6ヶ月以内に）利用を始めた。

⑤ すでに、6ヶ月以上継続して、利用している。

ご協力ありがとうございました。

図2　CAM準備性アンケート

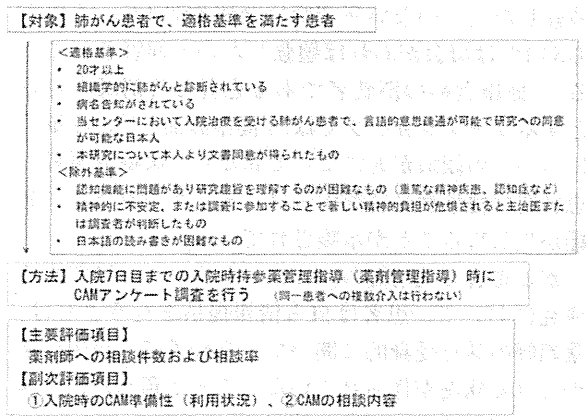


図3　調査方法

内容とした。（図3）。

CAM参考ツールには「がんの代替療法の科学的検証と臨床応用に関する研究」班（住吉班）、「がんの代替医療の科学的検証に関する研究」班（山下班）により作成された「がんの補完代替医療ガイドブック」（四国がんセンター　ホームページ内　がんの補完代替医療：http://www.shikoku-cc.go.jp/kranke/cam/index.html）を利用した。本研究において補完代替療法とは当ガイドブックに記載された米国NCCAM（National Center for Complementary and Alternative Medicine）による補完代替医療の分類に準じ、健康食品・サプリメント（漢方、ビタミンを含む）・アロマセラピー・漢方薬・鍼灸など健康保険の適用になっていないものすべてを補完代替医療と定義とした。

Ⅳ．倫理的配慮

本研究はヘルシンキ宣言を遵守し、研究対象者の心身の負担と苦痛を配慮し、自身の意思で回答できることや、調査に協力しなくても不利益を被らないことを保障するため、倫理的配慮について明記された文書を交付し研究者が説明を行った。個人情報は調査実施施設内で連結可能匿名化を行い調査担当者が取扱った。回収したアンケート用紙は、個人が特定できないようにデータ化し、シュレッダーで処分をした。調査実施施設内で匿名化した後に回収したデータを、鍵がかかるロッカーに保管し、そのロッカーが設置してある部屋も常に施錠し管理した。結果は学会や医学雑誌などに発表される可能性があることを説明同意文書にて明示した。研究終了後は回収したデータを再生不能な状態で破棄することとした。本研究に先立ち、近畿中央胸部疾患センターの臨床研究審査委員会の承認を受けて実施した。

Ⅴ．結果

16名中16名（100%）よりアンケートを回収した。回答者は男性／女性8／8人（50／50%）、平均年齢66.5才、中央値69才であった（表1）。主要評価項目である患者自身から薬剤師への相談件数は6件、相談率は37.5%であった（図4）。具体的なCAMの相談内容としては、①CAMについて薬剤師と話しやすくなった、3件（18.6%）、②自己申告していないCAM利用が判明した1件（6.3%）、③CAMの利用中止理由について打ちあけられた2件（12.5%）、であった。CAM利用中止理由については、医師の推薦があるCAMは高価なことが多く、継続が困難だった、主治医よりCAMの併用は現在の治療に影響がないと言われ、このことよりCAMは効果の少ないものだと感じた、であった（表2）。

副次評価項目であるCAM準備性（利用状況）については、①前熟考期（全く関心がない、知らなかった）4人（25.0%）、②熟考期（関心はあるけれども、まだ実際にやってみようとは思っていない）

表1　アンケート回答者の背景

		n=16	(%)
性別			
	男性	8	(50.0)
	女性	8	(50.0)
年齢			
	40代	1	(6.3)
	50代	5	(31.3)
	60代	2	(12.5)
	70代	7	(43.8)
	80代	1	(6.3)
	中央値（才）	69	
	平均（才）	66.5	

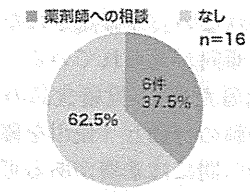
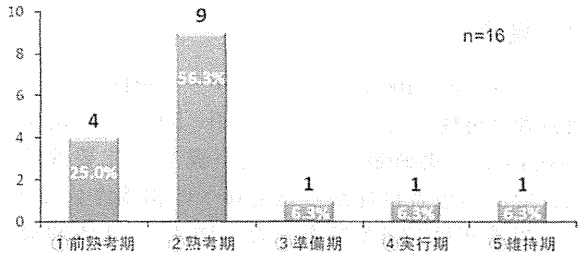


図4　患者自身から薬剤師への相談件数と相談率

表2　相談内容と相談件数

① 患者と薬剤師間で話しやすくなる印象があった。【3件（18.6%）】
② CAMを医療者へ申告なしで利用中であることが判明。【1件（6.3%）】
③ CAM利用中止理由について話された。【2件（12.5%）】
・医師の推薦があるCAMは高価なことが多く、継続が困難だった。
・主治医よりCAMの併用は現在の治療に影響がないと言われ、このことはCAMの効果が少ないのだと感じた。



①前熟考期：全く関心がない、知らなかった。
②熟考期：関心はあるけれども、まだ実際にやってみようとは思っていない。
③準備期：実際に行うための具体的な準備を始めている(情報を集めている等)。
④実行期：最近(ここ6ヶ月以内に)利用を始めた。
⑤維持期：すでに、6ヶ月以上継続して、利用している。

図5　CAM準備性（利用状況）

9人（56.3%）、③準備期（実際に行うための具体的な準備を始めている、情報を集めている等）1人（6.3%）、④実行期（最近（ここ6ヶ月以内に）利用を始めた）1人（6.3%）、⑤維持期（すでに、6ヶ月以上継続して、利用している）1人（6.3%）であった（図5）。

Ⅵ. 考察

がん患者における補完代替療法の受療行動に関するアンケート調査においてCAMの相談対象者として薬剤師は医師や看護師と同等の期待を持たれているが、相談率については他医療職に比べ低い傾向が見られた[3]（図1）。医療用医薬品の服用者を対象とした朝比奈らのアンケート調査では医療従事者に健康食品の使用の有無を確認されなかった場合、患者が自主的に使用を伝えない理由として最も多かったのは、医師、薬剤師ともに「聞かれないから」だったと報告している[8]。また、健康食品使用に関する薬剤師の行動実態調査においては、入院時に健康食品の使用を「患者から申し出がない限り確認しない」とした病院薬剤師は10%前後に過ぎなかった。一方、患者を対象とした意識調査（三村ら）では「使用について聞かれない」、「確認されない」とする割合が著しく多い傾向が見られている[9]。これら異なる調査の比較は困難だが、「健康食品の使用を確認する」という薬剤師の行動と「使用を確認される」という患者の認識の間には乖離がある可能性が示されている。また薬剤師の健康食品に関する知識の取得が必ずしも健康食品に関する積極的なコミュニケーションにつながらない可能性が示唆されており、さらに、「患者の健康食品の使用を確認する」という薬剤師ほど健康食品情報の不足を感じていた[10]。がん診療における漢方薬に対する薬剤師の実態調査では、がん患者に対して処方された漢方薬の処方意図が分かると回答した薬剤師は25.6%、漢方医学を勉強したことのない薬剤師は全体の69.4%、そのうち53.1%は機会があれば勉強したいと回答されている[11]。健康食品の消費者である患者と薬剤師を対象とするワークショップでは、「健康食品」という単語についての認識が人によって異なり、医療従事者－患者間で健康食品に関するコミュニケーションに齟齬が生じ得ることが示唆されている[12]。

がん患者と薬剤師のコミュニケーションに関する研究において、患者は自ら情報提供を行うよりは、薬剤師の話を受身的に聞いている様子で、自由に話ができる状況が作られていないことが窺えた、と報告されている[13]。

日本のがん患者のCAMの使用目的は、がんの進行抑制、治療などの直接的な治療効果をあげる人が多く、欧米の報告では、がんの進行に伴う痛みなどの症状緩和や心理的不安の軽減、通常のがん治療に伴う副作用の症状緩和などが挙げられている[2, 14]。外来通院中のCAMに関する思いと主観的影響の研究対象者は、経済的負担を感じ医師や看護師に気を配りながらも、病気や症状の改善と精神的な安定を期待してCAMを使用していた。現在病気の改善が実感されていない人は、CAMは精神的な安定に役立っていると考え、使用の継続を検討している傾向があった[15]、と報告されている。

今回アンケートを用いた薬剤師からCAMの問いかけを行ったことで、薬剤師と患者間でのコミュニケーション向上が図られた。本調査ではCAMの定義について明記した文書を交付することで情報共有でき医療者と患者間での齟齬の回避につながったと考えられる。利用状況について患者自身に記載してもらうことで解放型の質問形式となり、使用状況の確認については薬剤師と患者間での認識の乖離軽減につながったと考えられる。また積極的に使用確認を行う薬剤師ほどその情報不足を感じていることが多く、今回使用したがんの補完代替医療ガイドブックをはじめCAM参考ツールはCAM利用者だけでなく医療従事者の情報源となり、コミュニケーション向上につながるものと考えられた。

CAM利用の準備性については先行研究と同様の結果が得られ、潜在的なCAM利用者の割合が高いことが示唆された。

米国NCCAMにおいて“TIME TO TALK.”とCAM使用について患者が賢明な医療上の意思決定を行うため患者とその医療提供を奨励する教育キャンペーンが実施されている[16]。

薬剤師よりコミュニケーションツールを用いて積

極的に問いかけすることは、未申告のCAM利用の判明や副作用および相互作用等のプレアボイドにつながると考えられる。これらのことよりCAMの相談向上や適切で双方向な受療行動につながることが今後期待される。

Ⅶ. 結語

今回アンケートを用いた薬剤師からCAMの問いかけを行ったことで、薬剤師と患者間でのコミュニケーション向上が図られた。通常臨床において実践されている薬剤管理指導を利用したCAM医療コミュニケーションの実施可能性が示唆された。また潜在的なCAM利用者の割合が高いことより、今後も双方向のコミュニケーションの必要性が高まると考えられる。今後さらに実地臨床に応用できる医療コミュニケーションの指針を明らかにしていきたいと考える。

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Preoperative Concurrent Chemoradiotherapy of S-1/Cisplatin for Stage III Non-Small Cell Lung Cancer

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Background. Concurrent chemoradiotherapy using S-1 containing tegafur, an oral 5-FU prodrug, plus cisplatin has been reported to show promising efficacy against locally advanced non-small cell lung cancer with acceptable toxicity. The purpose of this study is to assess the impact of this induction treatment followed by surgery on survival for those patients.

Methods. Potentially resectable locally advanced non-small cell lung cancer patients were eligible. The concurrent phase consisted of S-1 (orally at 40 mg/m^2 twice a day on days 1 to 14 and 22 to 36) and cisplatin (60 mg/m^2 on days 1 and 22) with radiation of 40 Gy/20 fractions beginning on day 1 followed by surgical resection.

Results. Forty-two consecutive patients, between June 2005 and February 2011, were retrospectively analyzed. The median age was 59 (42 to 77) years, there were 34 males and 8 females, 26 cStage IIIA and 16 IIIB, each 21 adenocarcinomas and others. There were 26 partial responses and 16 stable disease cases after current induction treatment without uncontrollable toxicity. Of the 42 patients, 39 underwent surgical resection; 27 underwent a lobectomy and 12 pneumonectomies. One patient died due to thoracic empyema 65 days after surgery. The median follow-up time was 32.0 months. Three- and 5-year disease-free survival rates in all 39 resected patients were 52.0% and 44.0%, respectively, and 3- and 5-year overall survival rates were 77.4% and 61.7%, respectively.

Conclusions. Concurrent chemoradiotherapy using S-1 plus cisplatin followed by surgery may provide a better prognosis for locally advanced non-small cell lung cancer patients. Further prospective clinical investigation should be required.

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Stage III locally advanced non-small cell lung cancer (LA-NSCLC) comprises more than 30% of cases at the time of diagnosis [1]. Recent randomized phase III trials of concurrent chemoradiotherapy have shown better locoregional control, which leads to higher survival rates and is considered to be the current standard treatment for LA-NSCLC [2].

We previously reported concurrent chemoradiotherapy using uracil-tegafur (a 5-FU prodrug, UFT; Taiho Pharmaceutical Co, Ltd, Tokyo, Japan) plus cisplatin with concurrent thoracic radiotherapy of 60 Gy (UP-RT). The response rate and median survival time for unresectable LA-NSCLC patients treated with UP-RT were 80% and 16.5 months, respectively, with a lower incidence of adverse events than those of other trials [3]. The S-1 (TS-1; Taiho Pharmaceutical Co) is a second generation oral anticancer agent based on uracil-tegafur, which has a dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidine. The S-1 is composed of tegafur, 5-chloro-2,4-dihydroxypyridine (an inhibitor of DPD) and potassium oxonate (an inhibitor of phosphoribosyl transferase), in a molar ratio of 1:0.4:1, and combination treatment with S-1 and cisplatin (SP) for advanced NSCLC has shown a better response rate of 33% to 47% and a median survival time of 11 to 16 months [4, 5] compared with the usual response rate of 29.1% and median survival time of 40 weeks for combination chemotherapeutic regimens using UFT plus cisplatin [6]. Of interest, the incidence of grade 3/4 hematologic and non-hematologic adverse events was lower in our study than that of other platinum-based combination regimens [7, 8]. According to the recent results of 2 randomized phase III trials of S-1 and carboplatin or cisplatin for advanced NSCLC, this regimen is now a standard regimen for chemotherapy in Japan [9, 10]. In addition, the West Japan Thoracic Oncology Group has reported a better prognosis; a median progression-free survival of

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20 months, excellent local control with an objective response rate of 84%, and has demonstrated the safety of the SP with concurrent radiotherapy (SP-RT) [11] for patients with stage III NSCLC.

In contrast, the role of surgery for LA-NSCLC has been controversial, especially due to the heterogeneity of stage III NSCLC patients who have various numbers, stations, or conditions of mediastinal lymph node metastases, modes of tumor invasion to adjacent thoracic structures, or organs such as the great vessels, mediastinum, vertebral body, carina, esophagus, and so on, which might affect the prognosis of such patients. Such diversity of LA-NSCLC patients has precluded the establishment of an optimal treatment strategy.

We have previously reported the feasibility of SP-RT as an induction therapy that can be followed by curative intent resection for 18 patients with potentially resectable LA-NSCLC [12]. In the present study, we retrospectively analyzed the prognostic benefit for a larger number of patients treated with this strategy.

Patients and Methods

We retrospectively reviewed 42 consecutive patients with potentially resectable stage III LA-NSCLC who underwent preoperative induction concurrent chemoradiotherapy using SP-RT followed by curative-intent surgical resection between June 2005 and February 2011 in the Department of Thoracic Oncology, National Kyushu Cancer Center, Japan. The clinical or pathologic stage of the disease was diagnosed based on the general rules for the TNM Classification of Malignant Tumors (6th edition) [13]. Eligible patients had to have cytologically or histologically confirmed clinical stage III NSCLC that was considered to be potentially resectable. The other eligibility criteria were an age between 20 and 80 years, Eastern Cooperative Oncology Group performance status of 0 to 1, absence of previous chemotherapy or radiotherapy, and adequate hematologic, hepatic, and renal function. Patients with standard laboratory tests results, included the following: a leukocyte count of 3.500/μL or greater; a platelet count of 100,000/μL or greater; serum bilirubin level less than 1.5 mg/dL; serum glutamic oxaloacetic transaminase-glutamic pyruvic transaminase levels 100 IU/mL or less, a creatinine level 1.2 mg/dL or less, or a creatinine clearance level of 60 mL/minute or greater, and a blood gas oxygen tension of 60 Torr or greater, or oxygen saturation as measured by pulse oximetry equal to or greater than 95% in room air were considered to be eligible for this treatment. In addition, pulmonary function tests, chest radiography, computed tomography of the chest and the upper abdomen, computed tomography or magnetic resonance imaging of the brain, bronchoscopy using a flexible optical bronchoscope, and a bone scan or fluorodeoxyglucose-positron emission tomography were routinely performed for all patients. Patients who had malignant pleural effusion, malignant pericardial effusion, or a concomitant malignancy or serious comorbidities such as clinically significant cardiac dysfunction, active infection, or neurologic or psychiatric disorders were excluded.

Treatment Schedule

Chemotherapy With SPS-1 (40 mg/m^2 twice a day [b.i.d.]) in the form of 20 mg and 25 mg capsules containing 20 and 25 mg of tegafur, respectively, were taken orally in 2 separate doses from days 1 to 14 and days 22 to 35 as follows: in a patient with a body surface area (BSA) less than 1.25 m^2, 40 mg b.i.d.; for those with a BSA of at least 1.25 m^2 but less than 1.5 m^2, 50 mg b.i.d.; and for those with a BSA greater than 1.5 m^2, 60 mg b.i.d. was administered. Cisplatin, at a dose of 60 mg/m^2, was administered as a 120-minute infusion on days 1 and 22 while the patients were hydrated with 2,500 mL of saline by infusion. In general, this dose and schedule is equivalent of that of patients without radiotherapy. An antiemetic agent was administered at the discretion of each patient's physician.

Radiotherapy (RT)

All patients were treated with a linear accelerator photon beam of 6 MV or more from day 1. The primary tumor and involved nodes received 40 Gy in 2 Gy fractions over a period of 4 weeks. A three-dimensional treatment planning system was used. Radiation doses were specified at the center of the target volume. The delivered 40 Gy/20 fractions included the primary tumor, ipsilateral hilum, and mediastinal nodal areas from the paratracheal to subcarinal lymph nodes. For the primary tumors and the involved lymph nodes that were 1 cm or larger in the shortest diameter, a margin of at least 0.5 cm was added. The contralateral hilum was not included. The treatment of supraclavicular areas was not mandatory, but they were treated when the supraclavicular nodes were involved.

During the concurrent chemoradiotherapy period, chest X-rays, complete blood cell counts, and blood chemistry studies were repeated once a week, and the treatment was interrupted when a grade 4 hematologic or non-hematologic toxicity, including grade 3 to 4 esophagitis or dermatitis, pyrexia of 38°C or greater, or a decrease in the partial pressure of arterial oxygen of 10 Torr or more, compared with that before radiation therapy, occurred.

Surgical Resection

Immediately after completing the induction SP-RT, the patients were assessed for their response to the induction therapy and were restaged. If disease control, such as a complete response, partial response, or stable disease, was achieved a curative intent resection was planned for 3 to 6 weeks after completion of the concurrent chemoradiotherapy. The principles of resection were en bloc removal of the affected lobe or more lung parenchyma with adjacent structure(s) if necessary, with complete hilar and mediastinal lymph nodal dissection.

Evaluation of the Response and Toxicity

The response was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors version 1.0 guidelines [14]. The histologic analysis of the tumor was based on the World Health Organization classification for cell types [15]. The toxicity for all patients who received any treatment was assessed and graded by using

the National Cancer Institute Common Terminology Criteria for Adverse Event version 3 [16].

Statistical Analysis

To determine the response rate, the exact binomial confidence interval was calculated. Disease-free survival was defined as the time from the starting date of induction concurrent chemoradiotherapy until disease progression or death, and was calculated for the 39 resected patients. Overall survival was defined as the time from the starting date of induction concurrent chemoradiotherapy until death from any cause. The Kaplan-Meier method was used to describe overall survival and disease-free survival curves. All statistical analyses were done with the IBM SPSS Statistics 18 software package (SPSS Japan, an IBM company, Tokyo Japan).

This retrospective analysis was approved by the Institutional Review Board of the National Kyushu Cancer Center. Written informed consent was obtained from all patients before treatment.

Results

Patient Characteristics

As shown in Table 1, there were 34 males (81.0%) and 8 females (19.0%) with the median age of 59 years (range 42 to 77) who were included in this study. Thirty-three (78.6%) patients showed an ECOG performance status of 0. Twenty-one of the 42 patients (50.0%) had adenocarcinoma, while 12 patients had squamous cell carcinoma (28.6%), 8 had non-small cell carcinoma (unclassified), and 1 had large cell carcinoma. The 26 cStage IIIA patients included 24 cases of T1-3N2 and 2 of T3N1, and the 16 cStage IIIB patients included 13 cases of T4N0-2 and 3 of T2-4N3. All N3 patients had ipsilateral supraclavicular lymph node metastasis. The location of the primary tumor was the upper lobe in 38 patients (90.5%) and other lobes in 4 patients (9.5%).

Table 1. Patient Characteristics That Were Eligible for Induction Treatment

Subject	No.	(%)
No. of patients	42	
Age, years		
Median (range)	59 (47–77)	
Gender		
Male to female	34:8	(81.0:19.0)
ECOG PS		
0:1	33:9	(78.6:21.4)
Histology		
Adenocarcinoma	21	(50.0)
Squamous cell carcinoma	12	(28.6)
Large cell carcinoma	1	(2.4)
Unclassified NSCLC	8	(19.0)
cTN[a]		
T3N1	2	
T1-2N2	20	
T3N2	4	
T4N0	2	
T4N1	5	
T4N2	6	
T2-4N3	3	
cStage[a]		
IIIA	26	(61.9)
IIIB	16	(38.1)
Primary site		
Upper lobe	38	(90.5)
Middle/lower lobe	4	(9.5)

[a] TNM Classification of Malignant Tumors (6th edition).

ECOG PS = Eastern Cooperative Oncology Group performance status; NSCLC = non-small cell carcinoma.

Induction Treatment

All patients received the planned dose of radiotherapy, and 41 (97.6%) had 2 cycles of chemotherapy as induction treatment. As shown in Table 2, no grade 4 toxicity was observed during this induction therapy. The most frequently observed adverse event was grade 3 leukopenia, but its incidence was less than 10%; the incidence of the other grade 3 adverse events was 2.4% for neutropenia and febrile neutropenia and 4.8% for thrombocytopenia. One patient received 1 cycle of chemotherapy and another patient required a dose reduction of cisplatin [CDDP] during the second cycle of chemotherapy due to grade 2 serum creatinine level elevation. After receiving the induction treatment, 26 (61.9%) of the 42 patients achieved a partial response (PR), and stable disease (SD) was observed in 16 patients (38.1%). No progressive disease was observed.

Surgical Resection

Among the 42 patients, 39 patients (92.9%) were able to undergo surgical resection. One patient proved to be unresectable after thoracotomy because of the left atrial invasion around the inferior pulmonary vein that could not be detected preoperatively, and 2 patients refused surgical treatment at the end of their induction treatment. Among the 39 patients who received the curative intent resection, 27 patients (69.2%) underwent a lobectomy, including 6 sleeve lobectomies and 12 pneumonectomies (5 in right side and 7 in left side) (30.8%) including 10 intrapericardial pneumonectomies. Sixteen of the 39 patients (41.0%) required combined resection of an adjacent structure or organ: the chest wall with rib(s) in 12 cases; combined partial resection of the vertebra in 3 cases; the internal jugular or brachiocephalic vein that required vascular replacement with a vascular prosthesis each in 1 case; the superior vena cava in 1 case; and the left atrium in 1 case (Table 3). Complete resection was performed in all patients. Of the 3 patients with ipsilateral supraclavicular lymph node metastasis, two underwent a systemic mediastinal and supraclavicular lymph nodal dissection via a median sternotomy, and the other one was confirmed to have no metastasis in his supraclavicular lymph nodes by a pathological examination during surgery, and subsequently underwent systemic

Table 2. Toxicities (n = 42); National Cancer Institute Common Terminology Criteria for Adverse Event Version 3

	Grade		Frequency of 3 or 4 (%)
	3	4	
Hematologic			
Leukopenia	3	0	7.1
Neutropenia	1	0	2.4
Thrombocytopenia	2	0	4.8
Anemia	0	0	/
Non-hematologic			
Febrile neutropenia	1	0	2.4
Nausea	0	0	/
Vomiting	0	0	/
Creatinine	0	0	/
AST to ALT	0	0	/
Diarrhea	0	0	/
Stomatitis	0	0	/
Pneumonitis	0	0	/
Esophagitis	0	0	/

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

mediastinal lymph nodal dissection via posterolateral thoracotomy.

Surgical Morbidity and Mortality

The postoperative morbidity in this series of patients were the following: 3 cases each of postoperative bleeding and arterial fibrillation; 2 cases of chylothorax; and 1 each of prolonged air leakage, pulmonary edema, empyema, heart failure, and spinal cord injury. Among these cases, 3 patients underwent re-thoracotomy; 2 for postoperative bleeding and 1 for chylothorax. One patient who had undergone a left upper lobectomy experienced postoperative thoracic empyema without a bronchopleural fistula and died on the 65th postoperative day due to massive intrathoracic bleeding.

Table 3. Type of Resection (n = 39)

Subject	No. (%)
Pneumonectomy	12 (30.8)
Intrapericardial pneumonectomy	10
Lobectomy[a]	27 (69.2)
Sleeve lobectomy	6
Combined resection	16 (41.0)
Site of combined resection (redundant)	
Chest wall (ribs)	12
Vertebra	3
Internal jugular or brachiocephalic vein	2
SVC (replacement with graft)	1
Left atrium	1

[a] One patient with a bilobectomy was included.

SVC = superior vena cava.

Pathologic Findings

Concerning the clinical and pathologic response to induction concurrent chemoradiotherapy using SP-RT in the 39 patients who underwent surgical resection, 9 of the 39 (23.1%) patients showed a complete pathologic response in both the primary tumor and involved lymph nodes, while 6 of these 9 presented clinical PR and 3 clinical SD. Among the other 30 patients (76.9%) with partial pathologic response, 18 showed clinical PR and 12 clinical SD.

Adjuvant Chemotherapy

Twenty-five (64.1%) patients received adjuvant chemotherapy, mainly with cisplatin-based regimens. The regimens were determined by the attending surgeon. Ten of these 25 patients received more than 3 cycles of adjuvant chemotherapy.

Survival and Recurrence

The median follow-up time was 32.0 months. One-, 3-, and 5-year disease-free survival rates in all 39 surgically resected patients were 73.8% (95% CI: 59.95% to 87.7%), 52.0% (95% CI: 34.9% to 69.1%), and 44.0% (95% CI: 26.4% to 61.6%), respectively (Fig 1A). One-, 3- and 5-year overall survival rates were 84.3% (95% CI: 72.7% to 95.9%), 77.4% (95% CI: 63.3% to 91.5%), and 61.7% (95% CI: 42.1% to 81.3%), respectively (Fig 1B). When patients were stratified into those with cStage IIIA versus cStage IIIB, pN0 versus pN1-3, clinical response (ie, PR versus SD and lobectomy versus pneumonectomy), there were no statistically significant differences in either disease-free survival or overall survival (data not shown). However, when patients were stratified by their pathologic response, 3-year disease-free survival rates in the 9 patients with pathologic complete response were 76.2% (95% CI: 47.2% to 100%), while those of the other 30 patients with any pathologic response were 44.5% (95% CI: 24.7% to 64.3%) (Fig 2A). Three-year overall survival rates were 88.9% (95% CI: 68.3% to 100%) in the 9 patients with pathologic complete response, whereas those of the other 30 patients were 74.0% (95% CI: 56.9% to 91.1%) (Fig 2B).

Of the 39 resected patients, recurrence developed in 18 patients. The first site of recurrence in 16 patients was a distant region. The most common first recurrence site was the brain (7 cases) and the lungs (6 cases). Two patients had recurrence in the contralateral mediastinal lymph nodes that was out of the irradiated field during induction treatment. One of the 9 patients who achieved a pathologic complete response experienced recurrence in the contralateral lung.

Comment

The data presented here imply that treatment with concurrent chemoradiotherapy using SP-RT followed by surgery might provide better local disease control and better survival in patients with potentially resectable LA-NSCLC. Because LA-NSCLC is associated with a high risk of local and systemic recurrence of approximately 80% and 60%, respectively [17], combined local and systemic treatments are warranted. In this regard, the

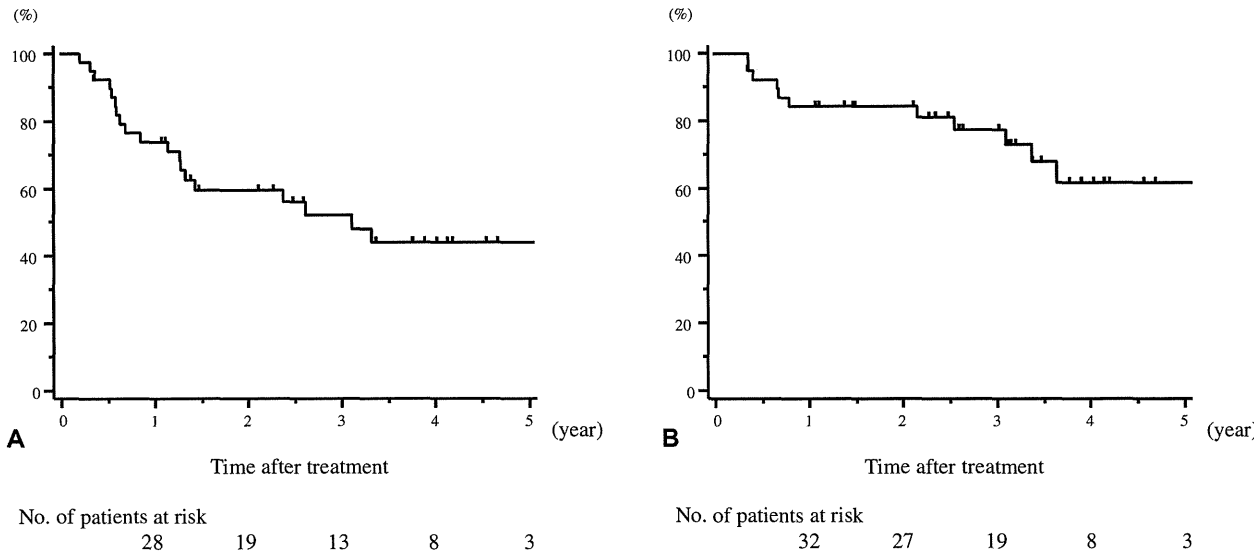

Fig 1. The survival curve of all 39 resected patients. (A) Disease-free survival and (B) overall survival.

optimal treatment strategy for LA- NSCLC is generally considered to be concurrent chemoradiotherapy [18]; however, the most frequent relapse site after concurrent chemoradiotherapy is at a distant region. A possible reason for this type of relapse is that the full-dose chemotherapeutic regimens developed for metastatic-NSCLC in the 1990s cannot be used at the full doses concurrently with radiotherapy due to the associated acute toxicities. Recently, Ichinose and colleagues [11] showed that the combination of full dose SP and concurrent radiotherapy of 60 Gy could be administered with acceptable toxicity, and the treatment with this regimen demonstrated a favorable survival, with a median progression-free survival of 20 months and an ORR of 84%.

Some phase III trials of concurrent chemoradiotherapy with radiation doses ranging from 56 to 66 Gy have shown good response rates of approximately 55% to 80% [19, 20]. In the present study, we observed that 59.5% of patients had a partial response and 40.5% had stable

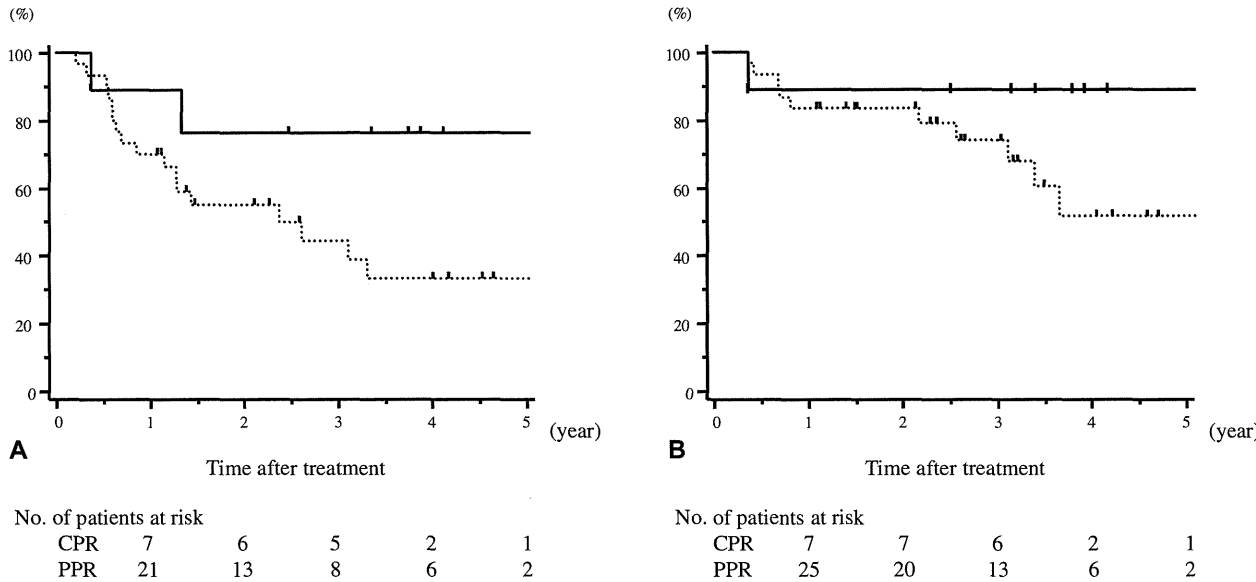

Fig 2. The prognosis of patients stratified by the pathologic response of the resected specimen. Solid line represents patients with complete pathologic response (CPR), while dashed line represents the patients with partial pathologic response (PPR). (A) Disease-free survival; (B) overall survival.