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(注2)本様式はexcel形式にて作成し、甲が求める場合は別途電子データを納入すること。

# 学 会 等 発 表 実 績

委託業務題目「化学療法に対する抵抗性を克服することを目的とした希少がん（悪性胸膜中皮腫）治療薬開発のための医師主導治験の実施」

機関名　兵庫医科大学　呼吸器内科

１．学会等における口頭・ポスター発表

| 発表した成果（発表題目、口頭・ポスター発表の別） | 発表者氏名 | 発表した場所（学会等名） | 発表した時期 | 国内・外の別 |
|---|---|---|---|---|
| 繊維形成型悪性胸膜中皮腫のFDG-PET所見の検討（ポスター） | 寺田　貴普，田端　千春，堀尾　大介，柴田　英輔，金村　晋吾，政近　江利子，本田　実紀，神谷　瞳，三上　浩司，野木　佳孝，大搗　泰一郎，栗林　康造，家城　隆次，中野　孝司，　近藤　展行，長谷川　誠紀，鳥井　郁子，辻村　亨，塚本　吉胤，廣田　誠一 | 第５５回日本肺癌学術集会（京都） | 2014年11月 | 国内 |
| 悪性胸膜中皮腫における、胸膜切除・肺剥皮術を施行した症例に対する術後化学療法の検討（口頭） | 大搗泰一郎，家城隆次，堀尾大介，金村晋吾，柴田英輔，政近江利子，神谷瞳，本田実紀，三上浩司，野木佳孝，寺田貴普，栗林康造，田端千春，黒田鮎美，橋本昌樹，多久和輝尚，松本成司，近藤展行，長谷川誠紀，中野孝司 | 第５５回日本肺癌学会学術集会（京都） | 2014年11月 | 国内 |

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| じん肺症 | 中野孝司 | 今日の治療指針2015年度版 331-332 | 2015 | 国内 |

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機関名　国立病院機構　近畿中央胸部疾患センター

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| Gefitinib/chemotherapy vs chemotherapy in EGFR mutation-positive NSCLC after progression on first-line gefitinib : the Phase Ⅲ, randomised IMPRESS study（口頭） | Shinji Atagi, Jean-Charles Soria, Tony SK Mok, Yi-Long Wu, Sang-We Kim, Jin-Ji Yang, Myung-Ju Ahn, Jie Wang, Chih-Hsin Yang, You Lu, Santiago Ponce, Xiaojin Shi, Alan Webster, Haiyi Jiang, Kazuhiko NakagawaShinji Atagi, Jean-Charles Soria, Tony SK Mok, Yi-Long Wu, Sang-We Kim, Jin-Ji Yang, Myung-Ju Ahn, Jie Wang, Chih-Hsin Yang, You Lu, Santiago Ponce, Xiaojin | 第55回日本肺癌学会学術集会 | 2014. 11 | 国内 |
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ORIGINAL ARTICLE

# Clinical predictor of pre- or minimally invasive pulmonary adenocarcinoma: possibility of sub-classification of clinical T1a

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## Abstract

**OBJECTIVES**: A new pathological classification for pre- and minimally invasive adenocarcinoma has been established, with distinction prior to surgery crucial because of the extremely good prognosis.

**METHODS**: Of 412 patients who underwent surgery for lung cancer from 2008 to 2011, 110 classified as c-stage I had each of the following four parameters assessed for predictive power for pre- or minimally invasive adenocarcinoma and relapse-free survival (RFS): (i) whole tumour size (WS) shown by computed tomography (CT) , (ii) size of the solid (SS) component in CT findings, (iii) maximum standard uptake value in fluorodeoxyglucose positron emission tomography (FDG-PET)/CT scan images ($SUV_{max}$) and (iv) serum level of carcinoembryonic antigen.

**RESULTS**: For prediction of pre- or minimally invasive adenocarcinoma, the area under the receiver-operating curve was >0.7 for all the four parameters, while only SS was found to be an independent factor in multivariate logistic regression analysis. In Cox proportional hazard model analysis, SS and $SUV_{max}$ were statistically significant, and SS was exclusively independent in multivariate analysis. Differences in RFS between T1a and T1b were more pronounced when using SS compared with WS. In the sub-classification of T1a, we used a break-point of 1.0 cm in SS (T1a-α and T1a-β), which resulted in a 2-year RFS rate of 1.00 for T1a-α ($n = 21$), 0.89 for T1a-β ($n = 27$) and 0.68 for T1b ($n = 26$) ($P = 0.002$ between T1a-β and T1b).

**CONCLUSIONS**: The SS parameter was useful to distinguish pre- and minimally invasive adenocarcinoma from other types of lung cancer, and set a T1a sub-classification.

**Keywords:** Non-small-cell lung cancer • Computed tomography • Invasive adenocarcinoma • $SUV_{max}$ • Carcinoembryonic antigen • Surgery

## INTRODUCTION

Among patients with lung cancer who undergo surgery, the proportion of those with an adenocarcinoma or small lesions has been increasing, while the prognosis of clinical stage I non-small-cell lung cancer (NSCLC) has improved [1]. The histological classification of pulmonary adenocarcinoma has been revised according to the extent of invasiveness, such as pre-, minimally invasive and invasive [2], and is similar to the method used to calculate tumour size in breast cancer [3]. This is because the prognosis of pulmonary adenocarcinoma is well distinguished by the amount of invasion [2], which dominantly appears as a solid region in computed tomography (CT) findings, contrary to the ground glass opacity (GGO) appearance of a lepidic adenocarcinoma [2, 4]. In addition to CT findings, other clinical parameters including maximum standard uptake value ($SUV_{max}$) in fluorodeoxyglucose positron emission tomography (FDG-PET) images [5] and serum carcinoembryonic antigen (CEA) level [6, 7] are used as predictors of aggressiveness and/or prognosis in cases of NSCLC. Therefore, it is crucial to evaluate those clinical parameters prior to surgery in order to distinguish patients with a pre- or minimally invasive adenocarcinoma, because of the extremely good survival [2].

## MATERIALS AND METHODS

Of 412 patients with lung cancer who underwent surgery from 2008 to 2011 at Osaka University Medical Hospital, 110 classified as clinical stage I underwent a segmentectomy or lobectomy (video-assisted thoracic surgery in 72 cases) with removal of lymph nodes, which was greater than the minimal requirement noted in Union for International Cancer Control (UICC) Tumor Node Metastasis (TNM) classification ver. 7, which states the following: 'Histological examination of hilar and mediastinal lymphadenectomy specimens(s) will ordinarily include 6 or more lymph

nodes/stations. Three of these nodes/stations should be mediastinal including the subcarinal nodes and 3 from N1 nodes/stations' [3]. The number of lymph nodes removed ranged from 6 to 31, with a median of 20. The tumour histology of the p-N2 cases varied (invasive adenocarcinoma $n = 3$, squamous cell carcinoma $n = 1$ and pleomorphic carcinoma $n = 1$). Cyto-pathological staging of the affected lymph nodes was not performed prior to surgery, and thus clinical staging was accomplished mainly using CT and FDG-PET findings. In these cases, each of the following four parameters was assessed for their predictive power for pre- or minimally invasive adenocarcinoma and relapse-free survival (RFS): (i) WS shown by thin section CT, (ii) size of the solid (SS) component in CT findings, (iii) $SUV_{max}$ in FDG-PET/CT scan findings ($SUV_{max}$) and (iv) CEA (Tables 1 and 2). For the WS parameter, the size (mean ± standard deviation (SD)) according to tumour histology was 2.9 ± 1.0 cm for adenocarcinoma and 3.1 ± 1.3 cm for non-adenocarcinoma. There were no missing data for any of the four parameters. Representative appearances in thin-sliced CT are shown in Fig. 1. The pathological diagnosis of each tumour was defined according to clinical records, except for adenocarcinoma lesions that required rediagnosis according to the new classification [2], which was performed by a pathologist (E.M.). Adjuvant therapy was carried out in 17 cases (oral administration of tegafur-uracil for pathological stage IB in 9, platinum doublet for pathological stage II or III in 8).

The follow-up periods ranged from 12 to 44 months, with a median of 23 months. In the follow-up examinations, all the patients were evaluated at 3-month intervals, which included a physical examination, chest X-ray and blood tests including tumour markers, while additional thoraco-abdominal CT scans were generally performed at 6-month intervals. During the follow-up period, cancer relapse occurred in 19 cases (pathological stage IA in 9 cases, IB in 6, IIA in 2, IIIA in 1, and V in 1), which included local recurrence in 8, distant recurrence in 6, local plus distant recurrence in 5 and death in 8 (original lung cancer in 6, heart attack in 1 and suicide in 1).

### Assessment of prediction of pre- or minimally invasive adenocarcinoma

The area under the curve (AUC) of the receiver-operating curve (ROC) was calculated using JMP 9 (SAS Institute Japan, Tokyo, Japan) for WS, SS, $SUV_{max}$ and CEA. In addition, the relative risk (RR) of the four parameters was calculated by logistic regression analysis, while multivariate analysis was performed using variables that showed statistical significance in the individual analysis using StatView 5.0 (HULINKS, Tokyo, Japan).

### Assessment of survival

RFS was defined as the period from the day of initial surgery to the day of relapse shown in clinical findings (primarily radiography). Survival curves were figured with the Kaplan–Maier method and a log-lank test was used to assess statistical significance. The hazard ratio (HR) was calculated using Cox proportional hazard model analysis and multivariate analysis was performed using variables that showed statistical significance in the individual analysis. These analyses were done using StatView 5.0 (HULINKS, Tokyo, Japan).

**Table 1.** Patient characteristics

| | |
|---|---|
| Total number | 110 |
| Gender | |
| Male | 63 |
| Female | 47 |
| Age in years | |
| Median | 69 |
| Minimum | 40 |
| Maximum | 88 |
| Mean ± SD | 67.8 ± 9.8 |
| Tumour histology | |
| Adenocarcinoma | 81 |
| preinvasive | 8[a] |
| Minimally invasive | 12 |
| Invasive | 61 |
| Squamous cell carcinoma | 23 |
| Other | 6 |
| GGO status by CT | |
| Pure GGO | 4 |
| Mixed GGO | 33 |
| Pure Solid | 73 |
| c-T factor | |
| T1a | 26 |
| T1b | 38 |
| T2a | 41 |
| T2b | 5 |
| c-stage | |
| IA | 72 |
| IB | 38 |
| p-T factor | |
| T1a | 38 |
| T1b | 31 |
| T2a | 39 |
| T2b | 0 |
| T3 | 2 |
| p-N factor | |
| N0 | 102 |
| N1 | 3 |
| N2 | 5 |
| p-M factor | |
| M0 | 109 |
| M1a | 1 |
| p-stage | |
| IA | 64 |
| IB | 35 |
| IIA | 2 |
| IIB | 3 |
| IIIA | 5 |
| IV | 1 |
| Operation | |
| Lobectomy | 103 |
| Segmentectomy | 7 |

[a]There were no cases of atypical adenomatous hyperplasia.
GGO: ground glass opacity; CT: computed tomography.

This retrospective investigation was approved by the institutional review board of Osaka University Medical Hospital.

## RESULTS

### RFS curves for pre- or minimally invasive adenocarcinoma

The present pre- and minimally invasive cases had 100% RFS, confirming extremely good prognosis (Fig. 2).

## Prediction of pre- or minimally invasive adenocarcinoma

For prediction of pre- or minimally invasive adenocarcinoma, the AUC of the ROC was >0.7 for all the four parameters (0.80 for WS, 0.95 for SS, 0.91 for $SUV_{max}$ and 0.70 for CEA) (Fig. 3). In logistic regression analysis, each parameter was statistically significant (Table 3), while SS was exclusively independent in multivariate analysis (Table 4).

**Table 2:** Variables examined as clinical prognostic indicators

| | |
|---|---|
| WS ($n$ = 110) | |
| Median | 2.6 |
| Minimum | 0.9 |
| Maximum | 6.6 |
| Mean ± SD | 2.8 ± 1.1 |
| SS ($n$ = 110) | |
| Median | 2.2 |
| Minimum | 0 |
| Maximum | 6.6 |
| Mean ± SD | 2.4 ± 1.4 |
| $SUV_{max}$ ($n$ = 110) | |
| Median | 2.9 |
| Minimum | 0 |
| Maximum | 20.6 |
| Mean ± SD | 4.2 ± 4.0 |
| CEA ($n$ = 110) | |
| Median | 3 |
| Minimum | 0 |
| Maximum | 137 |
| Mean ± SD | 5.5 ± 13.5 |

WS: whole size of tumour in CT; SS: size of the solid component in CT; $SUV_{max}$: maximum standard uptake value in FDG-PET/CT images; CEA: serum level of carcinoembryonic antigen.

## RFS based on clinical-T classification using WS or SS

When analysing survival, SS provided a better distinction between T1b and T2a compared with WS. In our assessment of RFS according to clinical T classification based on WS, the 2-year RFS rate was 89% for T1a ($n$ = 26), 79% for T1b ($n$ = 38), 78% for T2a ($n$ = 41) and 80% for T2b ($n$ = 5). There were no statistically significant differences between any neighbouring groups. As for assessment of RFS according to clinical T classification by SS, the 2-year RFS rate was 95% for T1a ($n$ = 48), 68% for T1b ($n$ = 26), 72% for T2a ($n$ = 32) and 75% for T2b ($n$ = 4). There was no statistically significant difference between any neighbouring groups, except between T1a and T1b ($P$ = 0.002).

In the sub-classification T1a, we used 1.0 cm as the breakpoint to provide a suitable sensitivity of 0.91 and specificity of 0.85 for

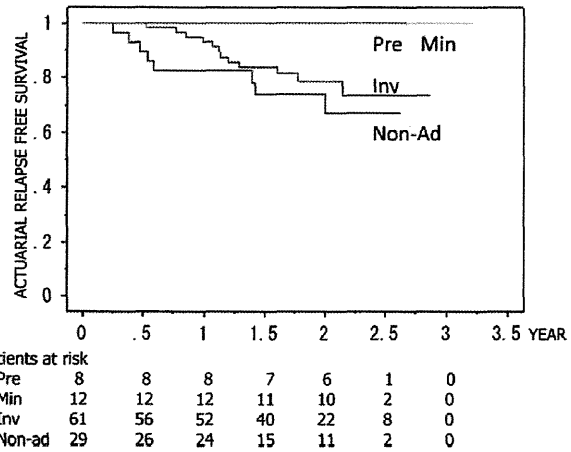


**Figure 2:** RFS curves according to histology type. Pre: preinvasive adenocarcinoma ($n$ = 8); Min: minimally invasive adenocarcinoma ($n$ = 12), Inv: invasive adenocarcinoma ($n$ = 61); Non-AD: non-adenocarcinoma ($n$ = 29). The 2-year RFS rate (95% CI) was 1.00 (1.00–1.00) for Pre, 1.00 (1.00–1.00) for Min, 0.79 (0.67–0.91) for Inv and 0.74 (0.54–0.94) for Non-AD.

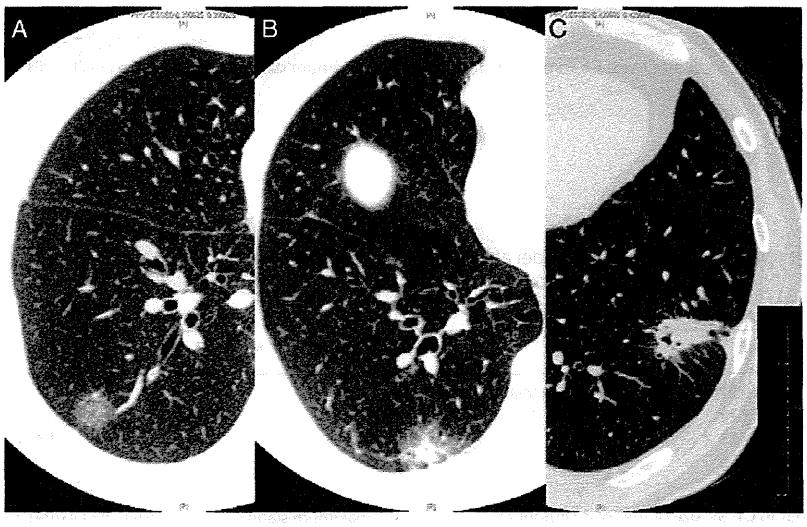


**Figure 1:** Representative appearances of pure GGO lesion (**A**), GGO with solid component lesion (**B**) and pure solid lesion (**C**) in thin-sliced CT. Whole size of the lesion is 1.8 cm in (A), 2.8 cm in (B) and 2.8 cm in (C), and size of the solid component is 0 cm in (A), 1.5 cm in (B) and 2.8 cm in (C).

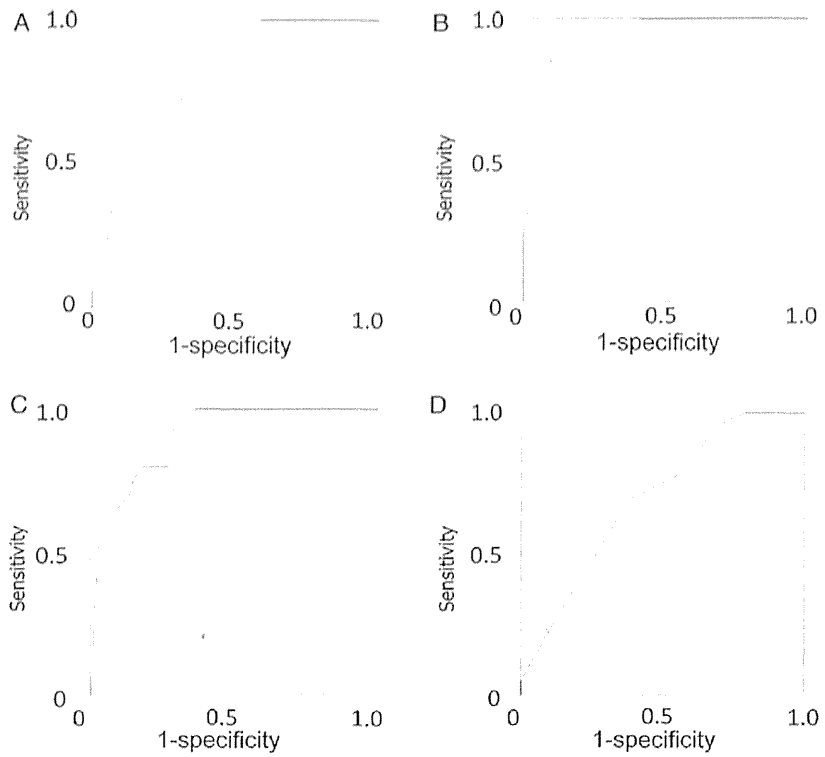


Figure 3: Receiver-operating curves. The AUC was 0.80 for the entire size of the tumour in CT findings (A), 0.95 for the SS (B), 0.91 for $SUV_{max}$ in FDG-PET)/CT images (C) and 0.70 for serum level of CEA (D).

**Table 3:** Results of logistic regression analysis for prediction of pre- or minimally invasive adenocarcinoma

| Variables | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | RR | 95% CI | *P*-value | RR | 95% CI | *P*-value |
| WS ($n$ = 110) | 0.217 | 0.095–0.497 | 0.0003 | 0.377 | 0.105–1.351 | 0.1 |
| SS ($n$ = 110) | 0.051 | 0.013–0.198 | <0.0001 | 0.067 | 0.011–0.421 | 0.004 |
| $SUV_{max}$ ($n$ = 110) | 0.239 | 0.108–0.529 | 0.0004 | 0.725 | .0322–1.631 | 0.4 |
| CEA ($n$ = 110) | 0.647 | 0.443–0.957 | 0.03 | 0.702 | 0.440–1.119 | 0.1 |

WS: whole size of the tumour in CT; SS: size of the solid component in CT; $SUV_{max}$: maximum standard uptake value in FDG-PET/CT images; CEA: serum level of carcinoembryonic antigen; CI: confidence interval.

**Table 4:** Results of Cox proportional hazards model analysis for disease-free survival

| Variables | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *P*-value | HR | 95% CI | *P*-value |
| WS ($n$ = 110) | 1.397 | 0.089–1.908 | 0.2 | | | |
| SS ($n$ = 110) | 1.574 | 1.171–2.115 | 0.003 | 1.434 | 1.006–2.044 | 0.04 |
| $SUV_{max}$ ($n$ = 110) | 1.123 | 1.035–1.219 | 0.005 | 1.063 | 0.959–1.178 | 0.2 |
| CEA ($n$ = 110) | 1.006 | 0.948–1.066 | 0.9 | | | |

WS: whole size of the tumour in CT; SS: size of the solid component in CT; $SUV_{max}$: maximum standard uptake value in FDG-PET/CT images; CEA: serum level of carcinoembryonic antigen; HR: hazard ratio; CI: confidence interval.

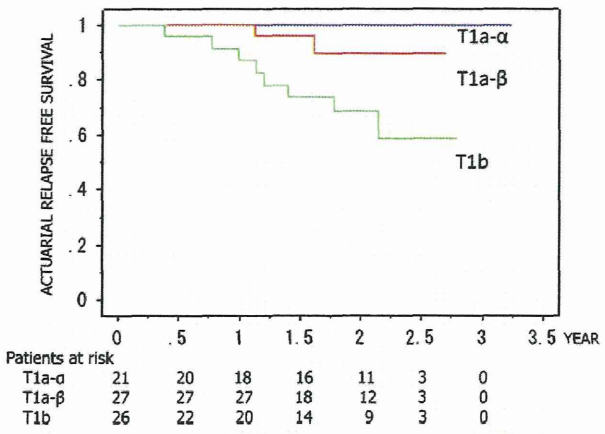


**Figure 4:** RFS curves according to clinical T1 sub-classification. T1a-α, SS < 1.0 cm ($n$ = 21); T1a-β, SS < 2.0 cm ($n$ = 27); T1b, SS < 3.0 cm ($n$ = 26) in CT findings. The 2-year RFS rate (95% CI) was 1.00 (1.00–1.00) for T1a-α, 0.89 (0.74–1.04) for T1a-β and 0.68 (0.48–0.88) for T1b. There was a statistically significant difference between T1a-β and T1b ($P$ = 0.002).

the SS parameter (T1a-α and T1a-β) (Fig. 4). As a result, the 2-year RFS rate was 1.00 in the T1a-α group ($n$ = 21), 0.89 in the T1a-β group ($n$ = 27) and 0.68 in the T1b ($n$ = 26) group ($P$ = 0.002 between T1a-β and T1b).

## DISCUSSION

Pre- and minimally invasive are known to be associated with scant cancer spreading and a very low chance of recurrence following surgery [2], and thus, prediction of such histology type is crucial for important decisions related to surgical treatment. In this investigation of clinical parameters reported to be predictive indicators of cancer spread and recurrence, we found that SS, which indicates the SS, was an independent predictor and indicated a sub-classification of T1a.

At present, the entire tumour size without exclusion of the GGO region in CT findings is employed for detecting the clinical T factor [3]. However, the GGO region corresponds to the lepidic component of an adenocarcinoma and possesses a very low level of invasiveness, and thus has a very low chance of causing cancer relapse [8]. Okada *et al.* [9] reported results of a multicentre prospective study and showed that $SUV_{max}$ and bronchioloalveolar carcinoma ratio, tumour disappearance rate and GGO ratio mirrored the pathological aggressiveness of tumour malignancy, nodal metastasis, recurrence and prognosis. In addition, Tsutani *et al.* [10] found that cases with a pure solid adenocarcinoma had inferior prognosis compared with those with a mixed GGO adenocarcinoma, though when $SUV_{max}$ and solid component size were matched, the differences in pathological prognostic parameters and disease-free survivals between patients with solid and mixed tumours disappeared. Those results led us to consider SS as an effective parameter for tumour invasiveness and prognostic factor, in addition to $SUV_{max}$.

Some have reported that $SUV_{max}$ is a predictive indicator of the aggressiveness of pulmonary carcinoma as well as prognosis [5, 11, 12], even though $SUV_{max}$ is difficult to calculate with GGO lesions [5] and underestimated in small tumours [13]. The strong clinical implication of $SUV_{max}$ noted above [9, 10] may be due to use of an absorption revision technique for small lesions. In the present study, $SUV_{max}$ was shown to be a predictive indicator of pre- and minimally invasive adenocarcinomas as well as poor prognosis, though it was not found to be an independent factor. This may have been because our specimens included a large number of lesions with SS <1 cm and we did not employ an absorption revision technique. Tsutani *et al.* [10] reported the clinical usefulness of both SS and $SUV_{max}$ using an absorption revision technique for patients with a large number of exclusive pulmonary adenocarcinoma tumours. However, that technique is not universally applied.

Tumour markers are also predictive indicators of the aggressiveness of pulmonary carcinoma and patient prognosis [14], with CEA the most frequently employed. Sawabata *et al.* [15] reported a concept that used a sub-normal level of less than half of the maximum point of normal and showed that a low serum CEA level can be useful clinically to predict prognosis. Their observations may indicate a relationship between serum CEA and adenocarcinoma invasiveness. In the current study, serum CEA level was shown to be a predictive indicator of a pre- or minimally invasive adenocarcinoma, even though serum CEA levels were normal in a large number of our patients.

We performed an intentional segmentectomy procedure in cases with small peripheral GGO dominant lesions and that on an emergency basis in high-risk patients. In all cases, sufficient tumour margin distance and negative margin cytology are mandated based on a concept of previous reports [16–18].

For the present study, we used the clinical parameters: entire size of the tumour in thin section CT findings, SS in CT findings, $SUV_{max}$ in FDG-PET/CT findings and serum level of CEA, as they have been reported to be predictive factors of tumour aggressiveness and prognosis. Among those, only SS was shown to be an independent predictive factor of pre- or minimally invasive (RR, 0.067; 95% CI, 0.011–0.421 and $P$-value, 0.004 in multivariate analysis), and chance of recurrence (H.R., 1.434; 95% C.I., 1.006–2.044 and $P$-value, 0.04 in multivariate analysis).

Since this is a retrospective clinical investigation with a limited number of patients and the observation period was rather short, there are some limitations that must be seriously considered. Above all, care should be taken with assessing prognosis using only RFS. In addition, analysis of RFS using a specific T factor or 1.0 cm as the breakpoint for solid portion size may not show a significant distinction between RFS curves. Therefore, additional analysis of a greater number of patients is mandatory prior to establishment of a classification. Although this is a very crucial limitation of this study, we consider that our findings may be helpful for a future prospective investigation.

In summary, in our assessment of surgical patients with clinical stage I NSCLC, the SS showed high potential to distinguish pre- and minimally invasive adenocarcinoma from other types of lung cancer, and may provide important information for a sub-classification of T1a.

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ORIGINAL ARTICLE

# Multimodality treatment for advanced thymic carcinoma: outcomes of induction therapy followed by surgical resection in 16 cases at a single institution

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**Abstract**
*Objective* We reviewed our institutional experience with cases of multimodality treatment for advanced thymic carcinoma to determine patient outcomes and prognostic indicators.
*Methods* Between 1998 and 2014, 16 patients with a Masaoka stage III or IV thymic carcinoma underwent surgical resection after induction therapy at Osaka University Hospital. These were considered to have great vessel invasion or metastasis to the mediastinal or intrathoracic lymph nodes based on the preoperative workup findings, and received induction therapy.
*Results* Complete tumor resection was achieved in 11 (69 %) after the induction therapy. Pathological findings revealed that 10 patients had Masaoka stage III disease, 1 had IVa, and 5 had IVb. The histological diagnosis was squamous cell carcinoma in 13, neuroendocrine carcinoma in 2, and undifferentiated carcinoma in 1. The 5-year survival rate for all patients was 71 %. Survival was significantly better in patients who underwent a complete resection (R0 disease) as compared to those with incompletely resected tumors (R1 or R2 disease).
*Conclusions* Multimodality treatment offers encouraging results and complete resection provides high survival rate for patients with advanced thymic carcinoma.

**Keywords** Thymic cancer · Prognosis · Induction therapy · Complete resection · Great vessel invasion

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## Introduction

Complete surgical resection is not always possible in cases of advanced stage thymic carcinoma because of local regional invasion [1]. It is considered that a multimodality treatment strategy may increase resectability, and reduce the incidence of local and systemic relapse for patients with advanced thymic tumors considered to be initially inoperable in preoperative workup findings [2]. We reviewed our institutional experience with cases of surgical resection after induction therapy for thymic carcinoma to determine patient outcomes and prognostic indicators.

## Patients and methods

Between 1998 and 2014, 24 patients with a Masaoka stage III or IV thymic carcinoma underwent surgical resection at Osaka University Hospital. Sixteen were considered to have great vessel invasion or metastasis to the mediastinal or intrathoracic lymph nodes based on the preoperative workup findings, and received induction therapy. Their clinical and pathological data were retrospectively reviewed after obtaining approval from our Investigational Review Board.

Cases with World Healthy Organization (WHO) classification type B3 thymoma (well-differentiated thymic carcinoma) and carcinoid tumors were excluded from the study. Apparent pleural or pericardial dissemination, extrathoracic lymphogenous metastasis, or distant metastasis were not surgical indications, and thus such patients were also excluded from the study. Patients with a tumor involving the great vessels or metastasis to the anterior mediastinal or intrathoracic lymph nodes, as judged by joint consensus of a multimodal thoracic oncology team

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(thoracic surgery, medical oncology, radiation oncology), underwent induction therapy. Surgical resection after induction therapy was performed for patients with partial remission or stable disease, based on the computed tomography (CT) scan, magnetic resonance imaging (MRI), and $^{18}$F-fluorodeoxy glucose-positron emission tomography (FDG-PET) scan findings, with a goal of complete resection to include the tumor and all attached structures, thymus, and involved lymph nodes. Complete surgical resection was defined as a macroscopically radical resection and disease-free resection margins shown in a histological evaluation. Postoperative chemotherapy or radiation was planned for cases with incomplete resection, as well as those judged to be at high risk for recurrence, such as patients with a close margin.

Overall survival (OS) rates were compared using a log-rank test. All statistical analyses were performed using JMP10 for Windows (SAS institute, Cary, NC, USA). A $p$ value of $<0.05$ was considered to be statistically significant.

## Results

Patient characteristics are presented in Table 1. Eleven were diagnosed preoperatively with Masaoka stage III disease, while 5 had IVb due to metastasis to the anterior mediastinal or intrathoracic lymph nodes. Of those, all patients were diagnosed with a thymic carcinoma based on the preoperative biopsy findings, of whom 13 showed invasion to the great vessels, such as the superior vena cava (SVC), ascending aorta, and main pulmonary artery, 3 had metastasis to the anterior mediastinal lymph nodes, and 2 had metastasis to the intrathoracic mediastinal lymph nodes, based on the findings of a preoperative workup performed by our oncology group. Two patients had both invasion to the great vessels and metastasis to the lymph nodes, thus a total of 16 received induction therapy. The sites of infiltration of the surrounding structures were evaluated preoperatively using CT or MRI, with those results shown in Table 1. The patients received cisplatin- or carboplatin-based chemotherapy, and the regimens are shown in Table 2. Twelve patients received concurrent radiation therapy at an irradiation volume of 40–60 Gy (mean 43 Gy). Induction therapy was well tolerated in all, with no episodes of major toxicity noted. When a partial remission (PR) was defined as a more than 50 % decrease in the size of any lesion and stable disease (SD) was defined as a less than 50 % regression of measurable lesions without new lesions, 7 patients had stable disease and 9, a partial response, while none showed progression during induction treatment.

**Table 1** Patient characteristics

| | |
|---|---|
| Sex (M/F) | 11/5 |
| Age (median) | 52 ± 12 |
| Clinical Masaoka stage | |
| III | 11 |
| IVa | 0 |
| IVb | 5 |
| Involved structures at POW | |
| Ao | 9 |
| SVC | 6 |
| Main PA | 2 |
| Lymph nodes | 5 |
| Resection | |
| Complete | 11 |
| Incomplete | 5 |
| Resected organs | |
| SVC replacement | 6 |
| BA replacement | 2 |
| Lobectomy | 2 |
| Aorta replacement | 1 |
| Phrenic nerve | 10 |
| Pathological Masaoka stage | |
| III | 10 |
| IVa | 1 |
| IVb | 5 |
| Histology | |
| Squamous cell carcinoma | 13 |
| Neuroendocrine carcinoma | 2 |
| Undifferentiated carcinoma | 1 |

*POW* preoperative workup, *Ao* aorta, *SVC* superior vena cava, *PA* pulmonary artery, *BA* brachiocephalic artery, *N/A* not applicable

**Table 2** Chemotherapy regimen for patients with thymic cancer

| Modality | |
|---|---|
| CDDP + TXT | 9 |
| CBDCA + PTX | 4 |
| CODE | 1 |
| CDDP + VP-16 | 1 |
| ADOC | 1 |

*CDDP* cisplatin, *TXT* docetaxel, *PTX* paclitaxel, *VP-16* Etoposide, *CODE* cisplatin + vincristine + doxorubicin + etoposide, *ADOC* cisplatin + doxorubicin + vincristine + cyclophosphamide

Complete tumor resection was achieved in 11 patients (69 %). The reason for incomplete resection was a positive resected margin in 2, dissemination in 2, and impossible replacement of the aorta due to physical condition in 1. Two had a minimal residual tumor (R1 disease) and 3 had a grossly debulked tumor (R2 disease). The resection was

**Table 3** Clinicopathological factorsand prognosis

| Variables | Number of cases | 5-year survival rate (%) | Significance (log-rank test) |
|---|---|---|---|
| Gender | | | |
| Male | 11 | 72.4 | 0.08 |
| Female | 5 | 66.0 | |
| Clinical Masaoka stage | | | |
| III | 10 | 100 | 0.33 |
| IV | 6 | 50.0 | |
| Effect of ITx | | | |
| PR | 9 | 71.4 | 0.47 |
| SD | 7 | 75.0 | |
| Resectability | | | |
| Complete | 11 | 100 | 0.007 |
| Incomplete | 5 | 40.0 | |
| Pathological Masaoka stage | | | |
| III | 9 | 100 | 0.40 |
| IV | 7 | 53.6 | |
| SVC replacement | | | |
| Yes | 6 | 53.3 | 0.26 |
| No | 10 | 74.3 | |
| Pathological vessel invasion | | | |
| Yes | 6 | 60.0 | 0.04 |
| No | 10 | 75.0 | |

*ITx* induction therapy, *PR* partial response, *SD* stable disease, *SVC* superior vena cava

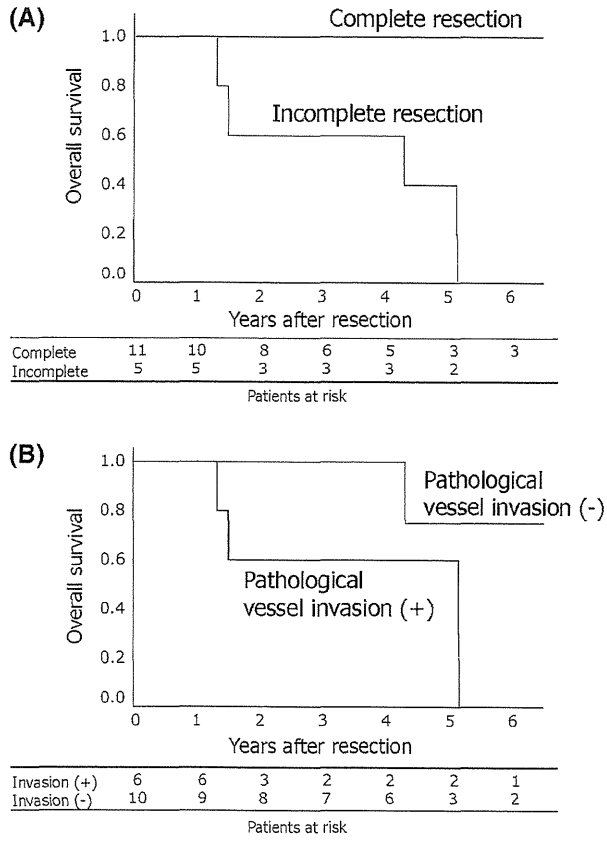


**Fig. 1** **a** Overall survival according to resectability. **b** Overall survival according to pathological great vessel invasion

extended to the surrounding organs, with the details shown in Table 1. Pathological findings revealed that 10 patients had Masaoka stage III disease due to vessel invasion in 6, pericardium in 2, invasion to other organs in 2, 1 had IVa due to pleural or pericardial dissemination, and 5 had IVb due to metastasis to the anterior mediastinal lymph nodes in 2, cervical lymph nodes in 2, or the lung in 1. The histological diagnosis was squamous cell carcinoma in 13, neuroendocrine carcinoma in 2, and undifferentiated carcinoma in 1. Pathological down-staging (clinical Masaoka stage IVb to pathological Masaoka stage III) was found in 2 in whom preoperatively histologically examined lymph node metastasis was disappeared after induction therapy. However, upstaging was found in 3 because of dissemination or lymph node metastasis was found after operation.

No postoperative mortalities occurred in either group. Six patients had complications, such as bleeding, cardiac depolarization, cardiac tamponade, chylothorax, and bilateral recurrent nerve palsy, after surgery. The median follow-up period was 72 months and the 5-year survival rate for all patients was 71 %. Postoperative adjuvant therapy was performed in 6 (46 %) patients. Univariate analysis using gender, Masaoka staging, the effect of induction therapy, and replacement of superior vena cava (SVC) revealed no significant difference (Table 3). As shown in Fig. 1a, survival was significantly better in patients who underwent a complete resection (R0 disease) as compared to those with incompletely resected tumors (R1 or R2 disease). When we compared patient outcomes between R1 and R2 diseases, there was no significant difference ($p = 0.20$). Great vessel invasion evaluated by pathological examination was detected in 6 (invasion to SVC in 4 and invasion to Aorta in 2) whose survival was significantly worse as compared to that of patients without pathological vessel invasion (Fig. 1b).

## Comments

The optimum treatment for advanced thymic tumors remains controversial. Invasion of mediastinal and other intrathoracic structures, including the major blood vessels, pericardium, heart, and lung in stage III disease, as well as dissemination of pleural and pericardial implants in stage IVa and lymph node metastasis in IVb, makes complete resection difficult to achieve [3]. When complete resection cannot be anticipated for the patients without apparent

pleural or pericardial dissemination, extrathoracic lymphogenous metastasis, or distant metastasis after a review of preoperative workup findings, induction therapy is administered. Induction therapy facilitates and increases the amount if surgically resectable material is available by reducing the size of the mass and down-staging the tumor. Furthermore, induction therapy is thought to prevent local and systemic relapse, and provide better assessment of the activity and efficacy of administered drugs. Thus, induction therapy has become the standard approach at several oncological centers for stage III and IV thymic tumors, with good clinical response rates reported [4]. On the other hand, a thymic carcinoma is an uncommon malignancy, thus therapeutic modalities have not been established and induction therapy similar to that for an invasive thymoma is generally applied to increase resectability [5]. The rationale for the addition of radiotherapy to induction chemotherapy is an attempt to enhance the rate of complete resection and the pathologic response compared with induction chemotherapy alone [4]. Whereas definitive radiation therapy is generally used for patients who are not candidates for surgery and radiation doses of 60–66 Gy are recommended to control gross disease [6], the most commonly used dose of radiation for induction therapy may be 40–45 Gy [7]; thus we generally selected 40 Gy as the concurrent radiation dose to avoid high morbidity and mortality rates after concurrent chemoradiation. We previously reported that induction chemoradiotherapy appeared to be useful for enabling complete resection of advanced thymic carcinomas using 40 Gy as the concurrent radiation dose [8, 9]. In the present study, the complete resection rate was 69 % after induction therapy. This good result is important, because complete initial resection was judged to be not feasible in these cases based on the preoperative workup findings. The disadvantages of induction therapy include increased toxicity of combined therapy. No postoperative mortalities occurred after induction therapy followed by surgery in the present cohort. Furthermore, neoadjuvant chemotherapy or chemoradiotherapy results in dense fibrosis involving the structures at the site of infiltration and makes dissection difficult. For this reason, en bloc resection may sometimes be required even in cases where true neoplastic invasion is not histologically proven [10].

Among the present patients, great vessel invasion, as determined by pathological examination findings, was detected in 6. The aorta was the most frequently involved organ, with pathological tumor invasion of the aorta detected in 2. In the others, the tumor was excised from the aortic tunica adventitia by sharp dissection, then an intraoperative pathologic examination showed fibrous change without viable cells, indicating that induction therapy might have down-staged the tumor. These findings also suggested that preoperative CT and MRI can overestimate the degree of aortic invasion. Accurate evaluation of great vessel invasion is an important key for treatment decisions, thus a more accurate preoperative workup method is necessary. The addition of PET–CT to the staging armamentarium may increase the accuracy of preoperative evaluation for patients with great vessel invasion.

Some authors have reported that incomplete surgical resection did not negatively impact long-term survival in cases that received postoperative cisplatin-based therapy [11], whereas other have noted that total resection of a thymic carcinoma significantly increased survival rate [12–14]. The present analysis also demonstrated that patients who received total resection had better prognosis. Based on the previously reported findings, the treatment of locally advanced thymic tumors has changed to an induction strategy with chemotherapy and radiation therapy, followed by complete removal of the tumor. Tseng et al. [13] also reported poor prognosis in patients with tumor invasion of the great vessels. We also showed that survival was significantly worse in patients with pathological great vessel invasion as compared to that of patients without vessel invasion. Of those 6 patients, 4 were not able to achieve complete resection due to positive resected margin in 2 and dissemination in 2, thus incomplete surgical resection might negatively impact survival.

Treatment of patients with pleural dissemination (Masaoka IVa) or metastasis to the lymph nodes is controversial. In the present study, there was no significant difference in prognosis between cases of Masaoka stage III disease and those with stage IV (Table 3), and 2 cases with stage IVb disease were alive at more than 5 years after receiving total resection. Thus, we consider that Masaoka stage IVb disease without a disseminated disease or metastasis to extrathoracic lymph nodes can be included in the operative indication criteria if complete resection is considered possible after induction therapy in preoperative evaluation. Since our goal of treatment for thymic cancer is complete resection, we do not perform surgical debulking as part of the treatment plan. In patients with tumors that appear to be invasive to the great vessels or metastasis to the lymph nodes, a biopsy should be performed prior to the treatment to decide the strategy. We consider that surgical debulking is acceptable for an invasive thymoma, because of the potential for favorable outcome [15]. Thus, all of the patients in the present study had an initial biopsy, which confirmed thymic carcinoma.

Our study has several limitations. Selection for induction treatment was somewhat dependent on the decision of the attending surgeon, oncologist, and radiation oncologist. Treatment was not performed based on a standard protocol, but rather using a domestic institutional formula. To establish a more effective regimen for such induction therapy, multicenter trials are necessary.

## Conclusion

Our results showed that complete resection is a prognostic indicator for patients with thymic cancer after multimodality treatment.

**Conflict of interest** None declared.

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ORIGINAL ARTICLE

# Impact of cardiopulmonary complications of lung cancer surgery on long-term outcomes

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**Abstract**
*Purpose* The impact of postoperative cardiopulmonary complications on long-term outcomes has not been established. We investigated the effects of acute postoperative cardiopulmonary complications not only on cancer recurrence, but also on cardiovascular or respiratory events in the chronic phase after lung cancer surgery.
*Methods* From a prospective single-institution database of 496 consecutive patients, who underwent lung cancer surgery between August, 2008 and December, 2011, medical records, including information about cardiovascular or respiratory events and cancer recurrence in the chronic phase (>6 months) after surgery, were analyzed retrospectively. Results were compared between patients with vs. those without postoperative cardiopulmonary complications in the acute phase.
*Results* Postoperative cardiopulmonary complications were identified in 90 (20 %) patients. There were significantly more cardiovascular or respiratory events in the chronic phase after lung cancer surgery in the patients who had suffered postoperative cardiopulmonary complications in the acute phase than in those who had not (23 vs. 5 %; $p < 0.0001$).
*Conclusions* Postoperative cardiopulmonary complications in the acute phase were associated with a higher incidence of cardiovascular or respiratory events in the chronic phase after lung cancer surgery.
*Clinical trial registration number* JPRN-UMIN2370

**Keywords** Lung cancer surgery · Postoperative complications · Long-term outcome

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## Introduction

Surgery is considered the best option for cure in patients with resectable non-small cell lung cancer (NSCLC), but it is still associated with a high complication rate [1, 2]. Postoperative cardiopulmonary complications are a major source of morbidity and mortality in the acute phase after lung cancer surgery. It has been reported that elderly patients and patients with chronic obstructive pulmonary disease (COPD) have an increased risk of postoperative cardiopulmonary complications after lung cancer surgery [3, 4]. Even without surgery, these patients are at risk of suffering cardiovascular events, such as arrhythmias, and respiratory events, such as pneumonia or acute respiratory distress syndrome [5, 6]. Thus, we hypothesized that patients with cardiopulmonary complications in the acute phase after surgery are at increased risk of the development of cardiovascular or respiratory (CVR) events in the chronic phase after surgery.

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B-type natriuretic peptide (BNP) is a useful biomarker for acute heart failure or cardiovascular events and elevated BNP levels have been reported in elderly or COPD patients [5, 7]. We previously reported that elevated preoperative BNP levels were associated with postoperative atrial fibrillation or cardiopulmonary complications after lung cancer surgery in elderly patients [8, 9]. It is possible that patients with elevated BNP levels before surgery have a higher risk not only of cardiopulmonary complications in the acute phase, but also of CVR events in the chronic phase after surgery. However, once the acute phase of surgery has passed, greater attention is generally paid to cancer recurrence because of its associated mortality in the chronic phase. Yet, CVR events in the chronic phase are also important for mortality and quality of life in patients with or without cancer recurrence. The objective of this study was to investigate the effect of postoperative cardiopulmonary complications in the acute phase, not only on cancer recurrence, but also on CVR events in the chronic phase after lung cancer surgery.

## Patients and methods

### Study design and population

From a prospective single-institution database of 496 consecutive patients who underwent elective pulmonary resection of lung cancer at our institute between August 2008 and December 2011, the medical charts of patients who underwent curative surgery with complete follow-up were analyzed retrospectively. Patients with limited surgery ($n = 32$) and patients who died in the immediate postoperative period ($n = 4$) were excluded from the analysis. Data of the remaining 460 patients were analyzed for the incidence of CVR events or cancer recurrence in the chronic phase (>6 months after surgery) after surgery. Complete preoperative and follow-up data were obtained for all of these patients. This study was performed at the National Hospital Organization Toneyama Hospital. The study protocol was approved by the Institutional Review Board, and all patients provided written, informed consent before participation (trial registration number: JPRN-UMIN2370). Results were compared between patients with vs. those without postoperative cardiopulmonary complications in the acute phase.

### Surgical procedure

All patients underwent anterolateral thoracotomy or video-assisted thoracic surgery (VATS). In VATS, three access ports were inserted through 1–2 cm skin incisions in the side of the chest. One of these skin incisions was extended by 4–5 cm, through which the resected lung lobe was removed in a plastic bag without using a rib retractor. When VATS was replaced intraoperatively with open thoracotomy, this was classified as open thoracotomy.

### Measurement of serum BNP levels

Serum BNP concentrations were measured using a chemiluminescence enzyme immunoassay (MI02 Shionogi BNP, Shionogi Pharmaceutical, Osaka, Japan) before and 1 month after surgery. The minimum quantity of BNP detectable with this system was 4 pg/mL.

### Postoperative cardiopulmonary complications

All patients were followed up prospectively after surgery and complications occurring during the same hospitalization as the index procedure were recorded. We defined cardiopulmonary complications as respiratory complications, including pneumonia, diagnosed by a fever >38 °C, purulent sputum, and abnormal findings on chest X-ray; acute respiratory distress syndrome, diagnosed by a partial pressure of oxygen in arterial blood ($PaO_2$)/fraction of inspired oxygen ($FiO_2$) of less than 200 mmHg; respiratory insufficiency requiring tracheostomy; respiratory failure requiring mechanical ventilation; atelectasis with bronchoscopic therapy; and cardiovascular complications, including arrhythmias such as atrial fibrillation, paroxysmal supraventricular tachycardia, and ventricular tachycardia; angina pectoris; myocardial infarction; congestive heart failure; and thromboembolic events. Operative mortality was defined as death within 30 days of surgery.

### Postoperative follow-up examinations

All patients were followed up routinely in our institute, at 3-month intervals postoperatively. Each evaluation comprised a physical examination, chest X-ray, and blood tests, including tumor markers. Thoraco-abdominal CT scans were generally performed at 6-month intervals and additional bone scintigraphy and magnetic resonance imaging (MRI) of the brain for the detection of cancer recurrence were performed every year. Positron-emission tomography (PET) using the glucose analog tracer fluorine-18 fluorodeoxyglucose (FDG) could be used as a substitute for bone scintigraphy for assessing distant metastases. In addition to the scheduled examinations, any CVR events occurring during follow-up were recorded for all patients.

### Statistical analysis

Data are presented as mean ± standard deviation (SD) or as medians with an interquartile range. Categorical variables

are shown as the percentage of the sample. Comparisons between the groups were assessed by Student's *t* test or the Mann–Whitney *U* test for continuous variables and by the $\chi^2$ test or Fisher's exact test for categorical variables. All data were analyzed with SAS for Windows 9.3 (SAS Institute, Cary, NC, USA). *P* value less than 0.05 were considered to be significant.

**Table 1** Postoperative cardiopulmonary complications

| Variable | Number of patients (%) ($N = 460$) |
|---|---|
| All cardiopulmonary complications | 90 (20 %) |
| Cardiovascular complications | 76 (17 %) |
| Atrial fibrillation | 63 |
| Paroxysmal supraventricular tachycardia | 11 |
| Acute heart failure | 1 |
| Acute cerebral infarction | 1 |
| Respiratory complications | 15 (3 %) |
| Pneumonia | 12 |
| Acute respiratory distress syndrome | 3 |

## Results

### Subjects

Postoperative cardiopulmonary complications were identified in 90 (20 %) of the 460 patients and are listed in Table 1. One patient had both cardiovascular and respiratory complications. Overall, the most common complications were arrhythmias, especially atrial fibrillation, while pneumonia was the most common respiratory complication.

Table 2 summarizes the characteristics of the patients with vs. those without postoperative cardiopulmonary complications. The mean age of the patients was 68 years (range 19–84 years). There was a significantly higher incidence of advanced age, hypertension, COPD, ischemic heart disease, induction chemotherapy, and thoracotomy (non-VATS procedure) in the group of patients with postoperative cardiopulmonary complications. There were also significantly higher BNP levels before and after surgery among the patients with postoperative cardiopulmonary complications. The median follow-up period was 36 months from surgery (range 24–60 months).

**Table 2** Characteristics of patients with vs. those without postoperative cardiopulmonary complications in the acute phase (<1 month) after lung cancer surgery

| Variable | With cardiopulmonary complications ($N = 90$) | Without cardiopulmonary complications ($N = 370$) | *p* value |
|---|---|---|---|
| Age, years | 71 (64–75) | 67 (60–73) | 0.004 |
| Male | 61 (68 %) | 217 (59 %) | 0.112 |
| Comorbidity | | | |
| Hypertension | 50 (56 %) | 146 (40 %) | 0.005 |
| Dyslipidemia | 28 (31 %) | 102 (28 %) | 0.473 |
| Diabetes mellitus | 17 (19 %) | 45 (12 %) | 0.087 |
| COPD | 33 (37 %) | 79 (21 %) | 0.001 |
| Ischemic heart disease | 10 (11 %) | 11 (3 %) | 0.003 |
| Preoperative BNP levels (pg/mL) | 30 (13–47) | 15 (8–24) | <0.0001 |
| Lung cancer stage | | | 0.072 |
| IA | 36 (40 %) | 191 (52 %) | |
| IB | 23 (26 %) | 86 (23 %) | |
| IIA, IIB | 20 (22 %) | 46 (12 %) | |
| IIIA, IIIB | 11 (12 %) | 47 (13 %) | |
| Induction chemotherapy | 7 (8 %) | 10 (3 %) | 0.027 |
| VATS procedure | 47 (52 %) | 270 (73 %) | <0.0001 |
| Mediastinal lymph node dissection | 73 (81 %) | 311 (84 %) | 0.500 |
| Adjuvant chemotherapy | 27 (30 %) | 101 (27 %) | 0.576 |
| Postoperative BNP levels (pg/mL) | 21 (13–48) | 16 (10–28) | 0.035 |

*BNP* B-type natriuretic peptide, *COPD* chronic obstructive pulmonary disease, *VATS* video-assisted thoracic surgery