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Research paper

Clinical significance of tumor cavitation in surgically resected early-stage primary lung cancer

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ABSTRACT

Objectives: The prognostic impact of tumor cavitation is unclear in patients with early-stage primary lung cancer. The aim of the present study was to examine the clinicopathological features and prognoses of patients with pathological stage I–IIA (p-stage I–IIA) primary lung cancers harboring tumor cavitation. This study was conducted according to the eighth edition of the TNM classification for lung cancer.

Materials and methods: We examined 602 patients with p-stage I–IIA primary lung cancer out of 890 patients who underwent pulmonary resection from January 2007 through March 2014 and searched for the presence of tumor cavitation, which is defined as the presence of air space within the primary tumor.

Results: A total of 59 out of the 602 patients had tumor cavitation (10%). Compared with patients without tumor cavitation, those with tumor cavitation had a significantly higher frequency of the following characteristics: high serum carcinoembryonic antigen (CEA) level ($\geq$5 ng/ml, $p = 0.027$), interstitial pneumonia ($p = 0.0001$), high SUVmax value on FDG-PET scan ($\geq$4.2, $p = 0.023$), tumors located in the lower lobe ($p = 0.024$), large tumor size (> 3 cm, $p = 0.002$), vascular invasion (66% vs 17%, $p < 0.0001$) and non-adenocarcinoma histology ($p = 0.025$). The overall survival period of patients with tumor cavitation was significantly shorter than that of patients without tumor cavitation (log-rank test: $p < 0.0001$, 5-year OS rate: 56% vs 81%). Tumor cavitation was found to be an independent and significant factor associated with poor prognosis in the multivariate analysis (hazard ratio: 1.76, 95% confidence interval: 1.02–3.10, $p = 0.042$).

Conclusions: Tumor cavitation is an independent factor for poor prognosis in patients with resected p-stage I–IIA primary lung cancer. Based on our analyses, patients with tumor cavitation should be regarded as a separate cohort that requires more intensive follow-up.

1. Introduction

Lung cancer is the leading cause of cancer-related death in many countries. Recently, diagnostic imaging advances have resulted in an increased number of patients diagnosed with early-stage lung cancer [1,2]. The Japanese Joint Committee of Lung Cancer Registry investigated patients with surgically resected lung cancer in Japan using the sixth edition of the TNM classification for lung cancer [3]. Based on this study, the percentage of patients with pathological-stage (p-stage) I disease increased from 52% in 1994–69% in 2004 [3], and the 5-year overall survival (OS) rates in patients with p-stage IA and IB disease improved from 79% and 60% in 1994–86% and 69% in 2004, respectively [3]. However, these survival rates are still disappointing, and survival time is also heterogeneous even in p-stage I patients. Therefore, additional studies to identify prognostic biomarkers are required.

Cavitation in lung lesions has been reported in 6–16% of cases and typically results from malignancy, infection, inflammation or ischemia [4]. Tumor cavitation in non-small cell lung cancer (NSCLC) has been associated with worse prognosis not only in patients with squamous cell carcinoma (SQ) [5–7] but also in those with adenocarcinoma (AD) [8]; however, the prognostic impact of tumor cavitation is unclear in patients with early-stage primary lung cancer. Identifying factors associated with a poor prognosis may help clinicians improve survival benefits and optimize therapeutic strategies for each patient. The aim of the present study was to examine the clinicopathological features and the prognosis of patients with early-stage primary lung cancers

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Table 1
Clinicopathological characteristics of patients with stage I primary lung cancer.

Patients' characteristics	All patients n = 602	Cavity (+) n = 59	Cavity (–) n = 543	p
Age (median, range)	69 (37–88)	69 (47–85)	69 (37–88)	0.104
Gender (male/female)	344/258	38/21	306/237	0.235
Smoking (never/ever)	345/257	37/22	308/235	0.377
CEA (ng/ml) (≥5/ < 5)	144/458	21/38	123/420	0.027
IP on chest CT (−/+)	572/30	50/9	522/21	0.0001
Right/left lobe	399/203	39/20	360/183	0.976
Lower/upper and middle lobe	225/377	30/29	195/348	0.024
Tumor size (cm) (> 3/ ≤3)	120/482	21/38	99/444	0.002
Standard/limited resection	504/98	54/5	450/93	0.087
pT2/pT1	165/437	25/34	140/403	0.007
Pleural invasion (−/+)	509/93	47/12	462/81	0.274
Vascular invasion (−/+/not available)	241/84/277	20/39/0	221/45/277	< 0.0001
PLC (−/+/not performed)	530/18/54	51/2/6	479/16/48	0.690
AD/non-AD	459/143	39/21	421/122	0.025
SQ/non-SQ	110/492	17/42	93/450	0.051
SUVmax (≥4.2/ < 4.2)	192/264	29/22	163/242	0.023

CEA: carcinoembryonic antigen, IP: interstitial pneumonia, CT: computed tomography, standard resection: pneumonectomy and lobectomy, limited resection: segmentectomy and partial resection, AD: adenocarcinoma, SQ: squamous cell carcinoma, SUVmax: maximum standardized uptake value.

harboring tumor cavitation.

2. Materials and methods

2.1. Patients

We examined 890 consecutive patients with primary lung cancer who underwent pulmonary resection at the Division of Thoracic Surgery in the Department of Surgery at Kindai University Faculty of Medicine from January 2007 through March 2014. Among them, 602 patients with p-stage I–IIA disease according to the eighth edition of the TNM classification for lung cancer [9] were analyzed in this study. Computed tomography (CT) images of the patients were re-evaluated by one investigator (K.T.). Tumor cavitation was defined as the presence of air space within a primary tumor, excluding tumors with traction bronchiectasis and pulmonary cysts. The maximum standardized uptake value (SUVmax) as determined by 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) was examined to evaluate glucose metabolism in lung cancers. The SUVmax values were available in 456 of 602 patients and the average SUVmax value was 4.2 (0.5–25.9). The cohort comprised 344 males and 258 females with a median age of 69 years old (range 37–88), and 257 individuals had a history of smoking. Regarding surgical procedures, 4 patients underwent pneumonectomy, 500 underwent lobectomy, and 98 underwent limited resections (either segmentectomy or partial resection). When neither pleural effusion nor dissemination was present after thoracotomy, pleural lavage cytology (PLC) was performed. There were 460 ADs, 110 SQs, 10 adenosquamous cell carcinomas (ASs), 6 small cell carcinomas (SMs), 5 large cell neuroendocrine carcinomas (LCNECs) and 4 large cell carcinomas (LAs) and 7 other histologies. The presence of vascular invasion was evaluated for 325 available samples based on Elastica van Gieson staining. The residual samples were not available because of archive samples.

Patients were routinely followed up at 3–6-month intervals for 5 years; these evaluations included physical examination, either chest radiography or CT, and an analysis of tumor markers. When recurrence was suspected, brain magnetic resonance imaging, bone scintigraphy, or FDG-PET was performed as needed. The medical records of all included patients were reviewed to extract data regarding their clinicopathological characteristics and prognosis. This study was reviewed and approved by the Ethics Committee of the Faculty of Medicine at Kindai University (28–178). Because many patients had already died or were lost to follow-up, we posted information regarding this research plan on our website (http://www.kindai-geka.jp/biomarker/2016/11/post-18.html) for those from whom informed consent could not be obtained. We also provided an opportunity for individuals to request exclusion of their data from the analyses through the website according to recommendations made by our institutional review board.

2.2. Histopathological analysis of cases with tumor cavitation

The histopathology specimens of 59 patients with tumor cavitation were independently examined by two observers (K.T. and S.S.). The following pathological features were examined; vascular occlusion, necrosis, and predominant subtype of ADs. The histologic classification was performed according to the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society Classification of Lung AD [10]. Recently, tumor spread through air spaces (STAS), which is defined as spread of lung cancer tumor cells into air spaces in the lung parenchyma adjacent to the main tumor [11], has been described as significant prognostic factor [11,12]. In this cohort, STAS was examined in patients with tumor cavitation.

Table 2
Logistic regression analysis of cavitary lung cancer.

Variables		Univariate analysis			Multivariate analysis		
		OR	95% CI	p	OR	95% CI	p
Age	≥70/ < 70	0.95	0.55–1.62	0.844			
Gender	Male/female	1.40	0.80–2.45	0.236			
CEA (ng/ml)	≥5/ < 5	1.89	1.07–3.34	0.030	1.10	0.57–2.13	0.769
IP on chest CT	+/−	4.47	1.94–10.29	0.001	3.35	1.33–8.46	0.011
Smoking status	Ever/never	1.28	0.74–2.23	0.378			
Location (lobe)	Right/left	0.99	0.56–1.75	0.976			
	Lower/other	1.85	1.08–3.17	0.026	1.77	0.97–3.22	0.064
cN	cN1-2/cN0	1.56	0.45–5.47	0.485			
pT	pT2/pT1	2.12	1.22–3.67	0.008	1.43	0.75–2.73	0.276
Histological type	AD/non-AD	1.91	1.08–3.37	0.026	0.91	0.44–1.87	0.796
Pleural invasion	+/−	1.46	0.74–2.87	0.276			
PLC	+/−	1.17	0.26–5.25	0.884			
SUVmax	≥4.2/ < 4.2	1.96	1.09–3.53	0.025	1.49	0.74–2.99	0.268

OR: odds ratio, CI: confidence interval, CEA: carcinoembryonic antigen, IP: interstitial pneumonia, CT: computed tomography, AD: adenocarcinoma, PLC: pleural lavage cytology, SUVmax: maximum standardized uptake value.