Tumor necrosis as a prognostic factor for stage IA non-small cell lung cancer

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Tumor necrosis as a prognostic factor for stage IA non-small cell lung cancer

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Seong Yong Park

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<ABSTRACT>

Tumor necrosis as a prognostic factor for Stage IA non-small cell lung cancer

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In stage IA non-small cell lung cancer (NSCLC), lobectomy and mediastinal lymph node dissection is considered the standard treatment. However, 20%-30% of patients who underwent surgical resection have cancer recurrences. The purpose of this study was to determine the patterns and risk factors for recurrence in patients with stage IA NSCLC.

We retrospectively reviewed the medical records of 201 patients who had confirmed stage IA NSCLC by lobectomy and complete lymph node dissection. There were 131 male patients with a mean age of 60.68 ± 9.26 years. The median follow-up period was 41.4 months. Recurrences were reported in 16 patients. One hundred fourteen and 87 patients were T1a (≤ 2 cm) and T1b (>2

cm to ≤ 3 cm), respectively. The pathologic results were as follows: adenocarcinomas and bronchoalveolar carcinomas (n=134); squamous cell carcinomas (n=57); and other pathologies (n=10). Tumor necrosis and lymphatic invasion were significant adverse risk factors for recurrence based on univariate analysis. Multivariate analysis showed that tumor necrosis was the only significant risk factor to predict cancer recurrence (hazard ratio=4.336, p=0.032). The 5-year overall survival was 94.8% for necrosis-negative patients and 86.2% for necrosis-positive patients (p=0.04). The 5-year disease-free survival was 92.1% for necrosis-negative patients and 78.9% for necrosis-positive patients (p=0.016).

Tumor necrosis was shown to be an adverse risk factor for survival and recurrence in patients with stage IA non-small cell lung cancer. Thus, close observation and individualized adjuvant therapy might be helpful for patients with stage IA NSCLC with tumor necrosis.

Key words : Lung cancer surgery, survival analysis, lung pathology

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I. INTRODUCTION

Lung cancer is the leading cause of cancer deaths among men and women worldwide[1]. Fewer than 20% of patients diagnosed with lung cancer are candidates for surgical resection. Of those patients who are candidates for surgical resection, stage IA non-small cell lung cancer (NSCLC) has increased due to the use of low-dose computed tomography for screening. In pathologic stage IA NSCLC, the 5-year overall survival is approximately 83.9%[2]. However, even though it is an early stage, up to 10% of patients with stage IA NSCLC relapse after surgery.

According to recent studies, tumor size is a prognostic factor in stage IA NSCLC and the 5-year survival of patients with tumors > 2.0 cm in size is less than that of patients with tumors < 2.0 cm in size[3, 4]. In addition, according to the Surveillance, Epidemiology, and End Result (SEER) Program database, age, gender, and extent of resection are also important prognostic factors[4]. However, other pathologic and molecular markers have been proposed because prognostic factors, such as size, age, gender, and extent of resection, do not accurately predict and explain the recurrence in patients with stage IA NSCLC. The following pathologic characteristics have also been proposed as risk factors in patients with stage I NSCLC: vascular invasion[5], lymphatic invasion[6], perineural invasion[7], poor differentiation[8], tumor necrosis[9], and high mitosis count. The following molecular markers have also been studied for evaluation of recurrence in patients with stage IA NSCLC: E-cadherin, p53, and Ki-67[9, 10]. Moreover, E-cadherin, p53, and Ki-67 reflect tumor behavior, and are considered to represent histologic features of tumor 'aggressiveness.' Vascular, lymphatic, and perineural invasion implicates tumor characteristics of invasiveness and tumor necrosis implies the aggressive rate of tumor growth. Thus, these post-operative pathologic characteristics might help in identifying patients at high-risk for recurrence, and in predicting prognosis and recommending individualized adjuvant therapy.

Therefore, this study was conducted to determine the survival of patients with stage IA NSCLC who underwent lobectomy and mediastinal lymph node dissection. Furthermore, the patterns of recurrence and the risk factors for recurrence in patients with stage IA lung cancer were determined. These prognostic factors were analyzed in a multivariable Cox proportional hazards model to determine which factors remain independent predictors of survival.

II. MATERIALS AND METHODS

1. Patients

This retrospective study was approved by the institutional review board of the hospital (IRB No. NCCNCS-10-401). Two hundred one patients who were confirmed to have pathologic stage IA NSCLC after lobectomy and complete lymph node dissection between May 2001 and November 2007 were enrolled. We retrospectively reviewed the medical records and pathologic data. Chest computed tomography (CT), positron emission tomography (PET), bronchoscopy, and pulmonary function testing were performed pre-operatively. Post-operatively, chest CT scans were obtained at 3-month intervals and PET-CT scans were obtained annually to detect recurrences.

Local recurrences were defined as those occurring on resection margins, such

as bronchial stumps or stapler lines. Regional recurrences were defined as those occurring in the hilar or mediastinal lymph nodes, pleural cavity, and ipsilateral lung. Distant recurrences were defined as those occurring in the contralateral lung, brain, liver, adrenal glands, bone, and other locations. Double primary lung cancer was defined according to Martini's criteria[11].

2. Histopathologic reviews

Two different pathologists independently reviewed all of the histologic slides, and one pathologist confirmed the findings following the World Health Organization 2004 classification. The pathologic features recorded included the following: tumor cell type, degree of differentiation, tumor size, tumor necrosis, vascular invasion, lymphatic invasion, perineural invasion, and lymphoplasmacytic reaction. Tumor necrosis was defined when there were necrotic tissues in the tumor mass at low magnification (x40) in hematoxylin and eosin-stained (H-E) slides (Figure. 1). When cancer cells were observed in the intratumoral vessel lumen, the specimen was considered positive for vascular invasion. The differential diagnosis between lymphatics and blood vessels were made by presence of red blood cells in the lumen. The presence of perineural invasion was defined as tumoral involvement of the epineurium.

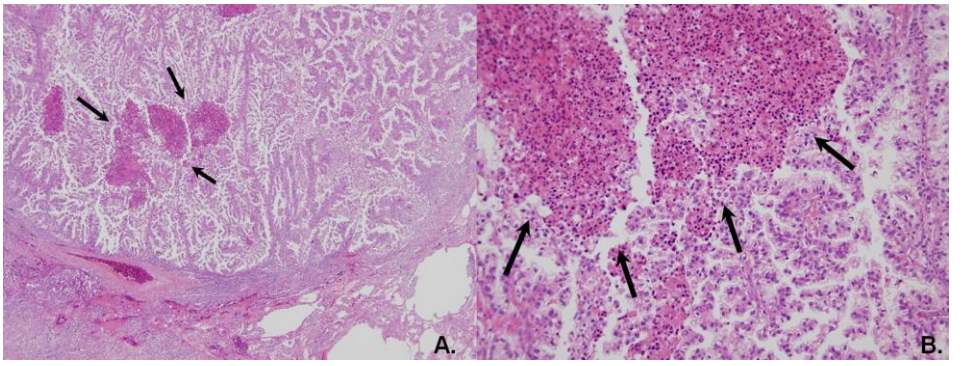

*Figure 1. Hematoxylin and eosin-stained section of non-small cell lung cancer with tumor necrosis. A. low-powered slide x10. B. high-powered slide x400 * arrows ; portion of necrosis*

3. Statistical analysis

Statistical analysis was performed using the SPSS software system (SPSS for Windows, version 13.0; SPSS, Inc., Chicago, IL, USA). The Kaplan-Meier method and log-rank test were used to perform univariate survival analysis and the Cox proportional hazard model was used to identify independent prognostic factors. The parameters were included in the Cox proportional hazard model if the *p*-value was < 0.2 on the log-rank test or if it is previously proven risk factor such as tumor size or differentiation. The criterion for significance was a $p < 0.05$. Statistical analysis was reviewed and verified by statistician.

III. RESULTS

1. General characteristics and pathologic reports

Among 201 patients, there were 131 male (65.2%) and 70 female patients (34.8%) with a mean age of 60.68 ± 9.26 years. The median follow-up period was 41.4 months (range, 1.7 ~ 95.7 months). One hundred fourteen and 87 patients were reported to have T1a (≤ 2 cm) and T1b (> 2 cm to ≤ 3 cm), respectively. The mean number of dissected lymph nodes was 33.75 ± 11.38. The pathologic results were as follows: adenocarcinomas and bronchoalveolar carcinomas (n=134); squamous cell carcinomas (n=57); and other pathologies (n=10). The general characteristics of the patients are shown in Table 1.

The pathologic characteristics are described in Table 2. Vascular and lymphatic invasion was noted in 19 (9.4%) and 24 patients (11.9%), respectively. Tumor necrosis was detected in 54 patients (26.8%).

Table 1. General characteristics of patients

Variables	Numbers (%)
Age (years)	60.68 ± 9.26
Gender (Male / Female)	131 (65.2%) / 70 (34.8%)
FEV1 (Liters) / FVC (Liters)	2.43 ± 0.56 / 3.25 ± 0.72
VATS*	64 (31.8%)
Dissected lymph nodes	33.75 ± 11.38
T stage	
≤ 2cm	114 (56.7%)
2 - 3cm	87 (43.3%)
Postoperative morbidity	17 (8.4%)
Postoperative mortality	0
Pathology	
Pure BAC#	24 (11.9%)
Adenocarcinoma	110 (54.8%)
Squamous cell carcinoma	57 (28.4%)
Others	10 (4.9%)
Differentiation	
Well differentiated	79 (39.3%)
Moderate differentiated	95 (47.3%)
Poorly differentiated	13 (6.4%)
Not defined	14 (7.0%)

* Video-assisted thoracoscopic surgery

Bronchoalveloar carcinoma

Table 2. Pathologic characteristics

Pathologic characteristics	n	%
Vascular invasion		
With	19	9.4
Without	191	90.6
Lymphatic invasion		
With	24	11.9
Without	177	88.1
Perinueral invasion		
With	4	1.9
Without	197	98.1
Tumor necrosis		
With	54	26.8
Without	147	73.2
Lymphoplasmacytic invasion		
With	30	14.9
Without	171	85.1

2. Patterns of recurrence

Recurrence was reported in 16 patients, as follows: regional recurrences (n=6, 2.9%; 1 pleural mass, 1 mediastinal lymph node, and 4 lung); combined recurrences (n=3, 1.6%; regional recurrence with distant recurrence); and distant recurrences (n=7, 3.5%; 1 contralateral lung, 3 brain, 2 liver, 1 neck node, and 1 bone. One patient suffered from liver and brain metastasis concomitantly). Double primary lung cancer was diagnosed in 3 patients (Figure 2).

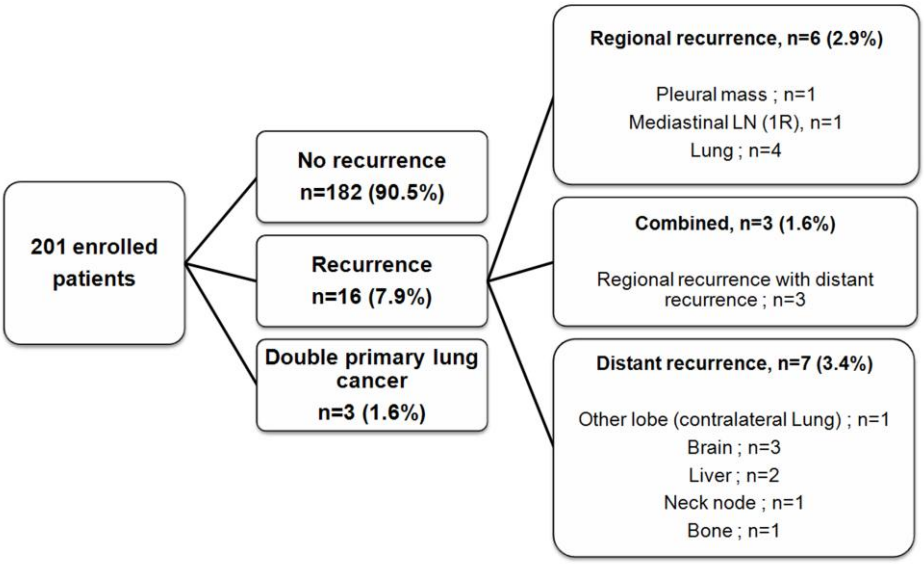

Figure 2. Patterns of recurrence in surgically-resected stage IA non-small cell lung cancer.

3. Risk factors for recurrence

Tumor necrosis and lymphatic invasion were the significant adverse risk factors for recurrence based on Kaplan-Meier survival analysis and the log-rank test (p=0.009 and p=0.021, respectively). Tumor size did not predict tumor recurrence (p=0.292) in this analysis. The Cox proportional hazard model showed that tumor necrosis was the only significant risk factor to predict tumor recurrence (hazard ratio=4.336, p=0.032; Table 3).

Table 3. Risk factors for tumor recurrence in stage IA NSCLC

	Univariate analysis (Log-rank test)		Multivariate analysis (Cox hazard model)	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age	1.037 (0.979~1.098)	0.215	1.021 (0.954~1.092)	0.551
Sex (male vs female)	0.587 (0.189~1.819)	0.356	0.565 (0.153~2.091)	0.392
Tumor size (T1b vs T1a)	1.690 (0.629~4.541)	0.292	1.150 (0.363~3.645)	0.813
Adenocarcinoma (vs non-adenocarcioma)	0.618 (0.230~1.660)	0.335	0.840 (0.250~2.821)	0.778
Poorly differentiation (vs moderate & well)	0.940 (0.124~7.119)	0.952	2.291 (0.262~20.040)	0.454
Vascular invasion	2.302 (0.656~8.080)	0.193	1.189 (0.282~5.017)	0.814
Lymphatic invasion	3.487 (1.211~10.039)	0.021	1.364 (0.341~5.459)	0.661
Tumor necrosis	3.759 (1.399~10.097)	0.009	4.336 (1.134~16.578)	0.032
Perineural invasion	2.946 (0.389~22.331)	0.296	…	…
Lymphoplasmacytic reaction	0.318 (0.047~2.697)	0.332	…	…

4. Overall survival and disease-free survival according to tumor necrosis

According to the Kaplan survival model and log-rank test, the 5-year overall survival was 90% in all patients. The 5-year overall survival was 94.8% for necrosis-negative patients and 86.2% for necrosis-positive patients (p=0.04). The 5-year disease-free survival was 92.1% for necrosis-negative patients and 78.9% for necrosis-positive patients (p=0.016; Figure 3).

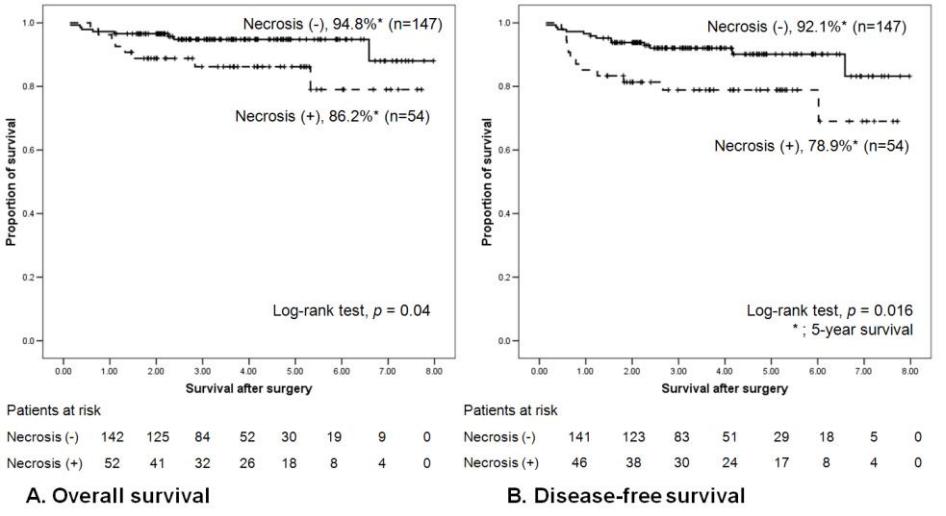

Figure 3. Overall survival and disease-free survival curves according to the presence of tumor necrosis.

IV. DISCUSSION

This study demonstrates that tumor necrosis correlates with poor outcomes in patients with surgically-resected stage IA NSCLC. Several studies have reported that tumor necrosis is related to poor outcome in patients with NSCLC, and this result is correlated with previous studies[12-14]. However, this study is the largest study which has specifically performed a survival analysis involving patients with stage IA lung cancer and tumor necrosis. Swinson and colleagues[12] reported that tumor necrosis was a prognostic factor in 178 patients with stages I-IIIA NSCLC. Shahab and colleagues[13] reported that tumor necrosis was a prognostic factor in 28 patients with stage IA NSCLC; however the study compared 'long-term survivors' and 'short-term survivors' by the Wilcoxon rank-score test instead of survival analysis, such as a Cox model[13]. Eerola and colleagues[14] reported that tumor necrosis was related to poor survival in a small number of patients with large cell neuroendocrine tumor.

Recently, molecular pathways of tumor necrosis induced by hypoxia have been elucidated. Hypoxia could result from an imbalance between tumor cell proliferation and blood supply. Rapid tumor growth outstripping the vascular supply creates a hypoxic environment and subsequently results in hypoxia, and finally tumor necrosis. In a hypoxic environment, hypoxia-inducible factor (HIF)-1α and -2α are induced and modulate many cellular responses to hypoxia, including angiogenesis and up-regulation of glycolytic enzymes, and possibly

improves intracellular buffering[15]. HIF-1α and -2α manipulates the expression of many enzymes, including carbonic anhydrase IX (CA IX)[16]. CA IX also has been reported to be associated with a poor prognosis in patients with NSCLC[17]. CA IX, an endogenous marker for tumor hypoxia, is a transmembrane enzyme that catalyzes the reversible hydration of carbon dioxide into carbonic acid[18]. Although the role of CA IX in tumor progression is still unclear, CA IX might help maintain a normal pH in tumor cell proliferation away from blood vessels. Also, CA IX is associated with up-regulation of epidermal growth factor receptor (EGFR), c-erbB-2, and Mucin 1 (MUC1)[19]. All three proteins disrupt cell-cell adhesion by degrading the catenin-cadherin complex, or the intergrin-mediated cell adhesion system[20]. The c-erbB2 proteins are well-known to mediate cellular motility and migration, and MUC1 is involved in endothelial adhesion and cancer metastasis[21]. These molecules and mechanisms explain the strong association of CA IX with the poor prognosis in cancer.

The current analysis of tumor necrosis in stage IA NSCLC explains why the overall survival and recurrence-free survival rates are significantly different as a function of tumor necrosis. Thus, it might be helpful for patients with tumor necrosis with stage IA NSCLC to be treated with further therapy post-operatively. However, the necessities and efficacies of adjuvant treatment in patients with stage IA lung cancer have not been confirmed. Currently, approved adjuvant therapy in patients with early stage lung cancer who have

undergone surgery is uracil-tegafur (UFT). The survival benefit with UFT treatment has been documented in patients with stage IA and IB NSCLC if the tumor diameter is > 2 cm[22]. Specifically, in patients with stage IA NSCLC, tumor size is the only indicator for adjuvant therapy. However, some patients have cancer recurrence even though the tumor mass is < 2 cm in size. It is important to predict prognosis and select a subgroup of patients with stage IA disease who might benefit from adjuvant therapy, and for this reason we have attempted to identify the factors that predict poor prognosis through analysis of clinical and histopathologic factors. We have reasoned, based on these results, that tumor necrosis could be another prognostic factor and indicator for adjuvant therapy in patients with stage IA non-small cell lung cancer. It is thus possible to tailor individualized therapy to stage IA lung cancer, although a large-scale, prospective study is needed for confirmation of these results.

The current study had some limitations. A previously known risk factor (tumor mass size) was not reported as a risk factor in this study. The IASLC study enrolled more than 1200 patients with stage IA NSCLC and concluded that tumor size was a prognostic factor[23]. Because the number of patients in this study was one-sixth of the IASLC study, the authors could not statistically prove that tumor mass was not a risk factor, even though our hazard ratio of tumor size was 1.69. Furthermore, pathologic diagnoses, such as vascular and lymphatic invasion, are ambiguous. Some researchers have used

immunochemical stains, such as elastica van Gieson staining to distinguish blood vessels and lymphatics[24]. However, in the current study, immunochemical studies were not performed, and vascular and lymphatic invasion were only diagnosed by H-E stain. In spite of these limitations, the advantage of this study was that the authors performed lobectomy and mediastinal lymph node dissection in all cases, and did not limit the extent of resection. Therefore, the 5-year overall survival was 90% and this survival rate was higher than previous reports which reported the 5-year overall survival to be 84%[2].

V. CONCLUSION

In conclusion, tumor necrosis was shown to be a risk factor for recurrence in patients with stage IA NSCLC. Patients with stage IA NSCLC with tumor necrosis need close observation and might benefit from adjuvant therapy. A prospective study to evaluate the survival benefit of adjuvant chemotherapy against tumor necrosis in patients with stage IA NSCLC is needed.

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ABSTRACT(IN KOREAN)

병기 IA 비소세포성폐암에서 예후인자로서의 종양괴사

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박 성 용

병기 IA 비소세포성폐암에서 폐엽절제술 및 종격동림프절 절제술은 표준 치료로 알려져 있다. 그러나 20-30%의 환자들은 수술 이후에도 재발을 경험하게 된다. 본 연구에서는 병기 IA 비소페포성폐암에서 재발 유형과 재발에 관련된 인자들에 대해서 알아보고자 하였다.

폐엽절제술 및 종격동림프절 절제술을 시행받고 병기 IA로 판명된 201명의 비소세포성폐암 환자에 대해서 의무기록에 근거한 후향적 연구를 실시하였다. 이 환자들의 조직병리결과를 분석하고 예후와 조직병리 결과의 연관성을 조사하였다.

환자군 중 남자환자는 131명이 있었으며, 평균 나이는 60.68 ± 9.26 세였다. 중앙 추적관찰기간은 41.4 개월이었다. 전체 환자 중 재발은 16명의 환자에서 발생하였다. 114명의 환자가 종양 크기가 2cm 이하인 T1a 병변이었으며, 87명의 환자는 종양 크기가 2cm

보다 크고 3cm 이하인 T1b 병변이었다. 선암 134명, 편평상피암 57명이었다. 단변량분석에 따르면, 병리 소견 중 종양괴사와 림파선 침범이 재발의 유의한 인자로 보고되었다. 다변량분석에서는 종양괴사만이 폐암의 재발을 예측이하는 유일한 인자로 보고되었다 (hazard ratio=4.336, p=0.032). 종양괴사가 없었던 환자들에서 5년 생존율은 94.8%이었으며, 종양괴사를 보인 환자들에서 5년 생존율은 86.2%이었다 (p=0.04). 종양괴사가 없었던 환자들에서 5년 무병생존율은 92.1%이었으며, 종양괴사를 보인 환자들에서 5년 무병생존율은 78.9%이었다 (p=0.016).

결과적으로 병기 IA 비소세포성폐암 환자들에 있어 종양괴사는 환자의 생존율과 재발에 밀접한 관련이 있는 예후인자로 보고되었다. 따라서 종양괴사를 보이는 병기 IA 비소세포성폐암 환자들에 대한 주의깊은 추적관찰과 개인화된 수술 후 치료는 환자의 생존율을 높이는데 도움이 될 것이다.

핵심되는 말 : 폐암 수술, 예후 분석, 조직 병리

PUBLICATION LIST

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