Turkish Journal of Thoracic and Cardiovascular Surgery 2018;26(4):614-620
http://dx.doi.org/doi: 10.5606/tgkdc.dergisi.2018.15846

Original Article / *Özgün Makale*

Prognostic factors for stage I lung adenocarcinoma and surgical management of subsolid nodules

Evre I akciğer adenokarsinomu için prognostik faktörler ve subsolid nodüllerin cerrahi yönetimi

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ABSTRACT

Background: This study aims to identify the prognostic factors for stage I lung adenocarcinoma and to evaluate the surgical management of subsolid nodules.

Methods: The study included 133 patients (90 males, 43 females; mean age 64.9 years; range, 29 to 82 years) who had undergone operation in our clinic for stage I lung adenocarcinoma between January 2007 and December 2015. Clinical, radiological and pathological data were retrospectively evaluated and their effects on recurrence and survival were examined by Kaplan-Meier and Cox regression analyses.

Results: Comparing the histopathological tumor types according to the pathological tumors size, we determined that the prevalence of invasive adenocarcinoma significantly increased with increasing tumor size (p<0.001). For all nodules, a tumor disappearance rate lower than 25% negatively influenced disease-free survival and a maximum standardized uptake value higher than 5.6 negatively influenced overall survival (p=0.027 for both). The grouping, which was performed considering the maximum standardized uptake value 5.6 as the cut-off value, was an independent prognostic factor for overall survival (hazard ratio: 5.973, 95% confidence interval: 1.186-30.073, p=0.03). Five-year overall survival rate was statistically significantly higher in patients who underwent wedge resection or segmentectomy for subsolid nodules compared to those who underwent lobectomy (100% vs. 79.3%, p=0.044).

Conclusion: Sublobar resections can be safely performed in subsolid nodules smaller than 2 cm in diameter with tumor disappearance rate ≥25% and maximum standardized uptake value ≤5.6.

Keywords: Adenocarcinoma; stage I; subsolid nodules.

ÖZ

Amaç: Bu çalışmada evre I akciğer adenokarsinomu için prognostik faktörler tespit edildi ve subsolid nodüllerin cerrahi yönetimi değerlendirildi.

Çalışma planı: Çalışmaya kliniğimizde Ocak 2007 - Aralık 2015 tarihleri arasında evre I akciğer adenokarsinomu nedeniyle ameliyat edilen 133 hasta (90 erkek, 43 kadın; ort. yaş 64.9 yıl; dağılım, 29-82 yıl) dahil edildi. Klinik, radyolojik ve patolojik veriler geriye dönük olarak değerlendirildi ve bunların nüks ve sağkalım üzerindeki etkileri Kaplan-Meier ve Cox regresyon analizleri ile incelendi.

Bulgular: Histopatolojik tümör tipleri patolojik tümör boyutlarına göre karşılaştırıldığında, invaziv adenokarsinom görülme sıklığının artan tümör boyutu ile anlamlı şekilde arttığı tespit edildi (p<0.001). Tüm nodüller için %25'den daha düşük tümör kaybolma oranı hastalıksız sağkalımı olumsuz etkiledi ve 5.6'dan yüksek maksimum standartlaştırılmış tutulum değeri genel sağkalımı olumsuz etkiledi (her ikisi için de p=0.027). Maksimum standartlaştırılmış tutulum değeri 5.6 eşik değer kabul edilerek yapılan gruplama genel sağkalım açısından bağımsız prognostik faktör (risk oranı: 5.973, %95 güven aralığı: 1.186-30.073, p=0.03) idi. Beş yıllık genel sağkalım oranı subsolid nodüller için kama rezeksiyon veya segmentektomi geçiren hastalarda lobektomi geçirenlere kıyasla istatistiksel olarak anlamlı şekilde daha yüksek idi (%100'e karşın %79.3, p=0.044).

Sonuç: Sublobar rezeksiyonlar çapı 2 cm'den küçük, tümör kaybolma oranı ≥%25 ve maksimum standartlaştırılmış tutulum değeri ≤5.6 olan subsolid nodüllerde güvenle uygulanabilir.

Anahtar sözcükler: Adenokarsinom; evre I; subsolid nodüller.

Received: January 17, 2018 *Accepted*: February 16, 2018

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Cite this article as:
Kocaman G, Yenigün MB, Elhan AH, Dizbay Sak S, Hamzayev E, Enön S, et al. Prognostic factors for stage I lung adenocarcinoma and surgical management of subsolid nodules. Turk Gogus Kalp Dama 2018;26(4):614-620.

Subsolid nodules consisting of pure ground glass nodules and partly solid ground glass (PSGG) nodules have been detected more frequently owing to the advanced and widely used radiological imaging methods. Surgery provides nearly 100% disease-free survival (DFS) for these lesions.[1] However, at what circumstances these lesions require surgery and which surgical method are to be performed remain debatable. For this reason, radiological identification of the invasive component of subsolid nodules is quite important for determining the type of both resection and lymph node dissection. Therefore, in this study, we aimed to identify the prognostic factors for stage I lung adenocarcinoma (AC) and to evaluate the surgical management of subsolid nodules.

PATIENTS AND METHODS

In this study, 165 patients who had undergone surgical operation in Ankara University School of Medicine Thoracic Surgery Department between January 2007 and December 2015 for stage I lung cancer were retrospectively evaluated. Patients having tumor with different histopathology than AC, tumor size >3 cm, with lymph node metastasis, synchronous and/or metachronous tumors, and those who had received preoperative chemotherapy and/or radiotherapy were excluded.

Clinical, radiological and pathological data of 133 patients (90 males, 43 females; mean age 64.9 years; range, 29 to 82 years) were retrospectively reviewed. All patients were preoperatively evaluated by means of medical history, physical examination, routine complete blood count, biochemical analysis, pulmonary function tests, cranial-thoracic computed tomography (CT) and positron-emission tomography (PET)/CT. Transthoracic fine-needle aspiration biopsy was performed in the patients considered to require preoperative diagnosis, whereas transbronchial fine-needle aspiration biopsy was performed in the patients with suspicious lymph node metastasis. Decision for surgical operation was made during weekly tumor council of the thoracic surgery department (depending on the structure of nodule, increment in nodule size or the nodule's exhibiting signs of malignant degeneration and based on the biopsy results for suspicious nodules by the majority of votes). The eighth tumor, node, metastasis system was used for the tumor staging. Patients were called for control visits every three months for the first two years, every six months between the third and fifth years, and every year after the fifth year of surgery and routine examination and screening tests were performed for recurrence.

While sublobar resections (wedge/segmentectomy) were preferred for peripheral subsolid nodules with long diameter smaller than 2 cm and in the patients with pulmonary function tests showing restriction, lobectomy was preferred for solid and central nodules greater than 2 cm and in the patients with suitable pulmonary reserve. Lobe-specific lymph node dissection was performed in all patients.

Patients' smoking status, structure of the nodule, pleural invasion, histopathological type, pathological size, tumor disappearance rate, maximum standardized uptake value (SUV_{max}) on PET/CT, lymphovascular and/or perineural invasion, positive surgical margin, number of dissected lymph node stations and resection method were recorded and analyzed. For the patients with missing follow-up information, recurrence and survival status were evaluated using hospital automation system or via phone call, as well as searching by citizen identity number in the Ministry of Health Death Report System.

Tumor disappearance rate (TDR) was obtained proportioning the longest diameter (Dlong) multiplied by the perpendicular diameter (Dper) of the nodule on mediastinum and parenchyma windows of CT: [1-(Dlong × Dper mediastinum window/ Dlong × Dper parenchyma window)] × 100.

Pathological typing was performed according to the 2015 World Health Organization Classification of Lung Cancer. After classifying the ACs according to the dominant pattern (lepidic, acinar, papillary, micropapillary, solid), invasive ACs were divided into three groups (group 1: lepidic type, group 2: acinar or papillary type, group 3: micropapillary, solid or variant type).

The study protocol was approved by the Ankara University School of Medicine Clinical Researchs Ethics Committee. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

Descriptive statistics were presented as mean±standard deviation for the variables distributed normally and as median (minimum-maximum) for the variables distributed not normally, whereas they were presented as number and percentage (%) for nominal variables.

The significance of the difference between the groups in terms of the mean values was analyzed by Student's t-test, and the significance of the difference between the groups in terms of the median values

Table 1. Characteristics of solid and subsolid nodules

	Solid nodules				Subsolid nodules				
Patient characteristics	n	%	Median	Min-Max	n	%	Median	Min-Max	*p*
Age (year)			62.5				65		0.401
Histopathological group									
AIS + MIA									
AC									
Gender									0.005
Male	68	75.6			22	51.2			
Female	22	24.4			21	48.8			
Smoking history									
Smokers	81	90			29	67.4			0.001
Tumor disappearance rate			19	3.5-82.8			73.6	4.1-100	<0.001
SUV_{max}			8.55	0-28.1			2.1	0-10	<0.001
Lymph + perineural invasion									
Positive	4	4.4			4	9.3			0.272
Surgical margin									
Positive	0	0			1	2.3			0.323
Pleural invasion									
Positive	22	24.4			11	25.6			0.887
Number of dissected lymph node stations			4	0-10			3	0-8	0.006
Resection									<0.001
Lobectomy	74	82.2			21	48.8			
Segmentectomy	8	8.9			6	14			
Wedge	8	8.9			16	37.2			
Pathological tumor size									0.021
0-10 mm	7	7.8			10	23.3			
11-20 mm	37	41.1			19	44.2			
21-30 mm	46	51.1			14	32.6			

Min: Minimum; Max: Maximum; MAIS: Adenocarcinoma in situ; MIA: Minimal invasive adenocarcinoma; AC: Adenocarcinoma; SUV_{max}: Maximum standard uptake value.

was analyzed by Mann-Whitney U test. Categorical variables were evaluated using Pearson's chi-square test or Fisher's exact test.

In the present study, receiver operating characteristic analysis was performed to identify a threshold value for SUV_{max}, and a threshold value of 5.6 was chosen for both overall survival (OS) and DFS analyses.

Overall survival indicates the time between the surgical procedure and death, whereas DFS indicates the time between the surgical procedure and recurrence. The subsolid nodules suspicious

Table 2. Distribution of histopathological groups according to pathological tumor size

	Pathological tumor size (mm)						
Pathological	0-10		11-20		21-30		
Groups	n	%	n	%	n	%	*p*
AIS + MIA	10	58.8	6	10.7	3	5	<0.001
AC	7	41.2	50	89.3	57	95	
Total	17		56		60		

AIS: Adenocarcinoma in situ; MIA: Minimal invasive adenocarcinoma; AC: Adenocarcinoma.

for malignancy and squamous-cell tumors were classified as second primary tumors. After calculating the OS and DFS by Kaplan-Meier method, the difference between the distributions of risk factors among survival was analyzed by using log-rank test. Multivariate survival analysis was performed by Cox regression model. A p value <0.05 was considered statistically significant.

RESULTS

A total of 43 (32.3%) nodules were subsolid and 90 (67.7%) were solid. According to the new classification for AC, 12 nodules were adenocarcinoma in situ (AIS), seven nodules were minimal invasive adenocarcinoma (MIA) and 114 nodules were invasive AC. Totally, 95 (71.5%), 14 (10.5%) and 24 (18%) patients underwent

Table 3. Results of univariate analysis for disease-free survival and overall survival

	Five-year DFS		Log-rank	Five-year OS	Log-rank
Variables	n	%	*p*	%	*p*
Overall patients	133	72		81.5	
Recurrence					<0.001
Negative	117			88	
Positive	16			43.3	
Age (year)			0.847		0.457
≤65	72	73.8		80.9	
>65	61	68.7		82.2	
Gender			0.558		0.268
Male	90	69.5		77.9	
Female	43	77		89.1	
Smoking status			0.858		0.489
Smokers	110	72.7		79.9	
Non-smokers	23	72.5		88.8	
Nodule structure			0.256		0.248
Subsolid	43	79.2		89.1	
Solid	90	68.8		78.9	
Resection			0.485		0.582
Lobectomy	95	74.4		81.1	
Wedge/segmentectomy	38	59.4		79.6	
Pathological subtypes			0.748		0.529
AIS	12	100		100	
MIA	7	75		80	
Group 1	36	77		77.8	
Group 2	57	69		77.6	
Group 3	21	67.9		80.5	
TDR			**0.027**		0.267
<25%	57	63		54.1	
≥25%	76	75		71.2	
SUV_{max}			0.175		**0.027**
≤5.6	62	88.2		90.3	
>5.6	71	59.1		66.3	
Pathological T stage			0.520		0.395
Tis	12	100		100	
T_{1a}	14	68.6		80	
T_{1b}	37	77.7		74.6	
T_{1c}	37	66.7		84.3	
T_{2a}	33	67		79.9	

DFS: Disease-free survival; OS: Overall survival; AIS: Adenocarcinoma in situ; MIA: Minimal invasive adenocarcinoma; TDR: Tumor disappearance rate; SUV_{max}: Maximum standard uptake value.

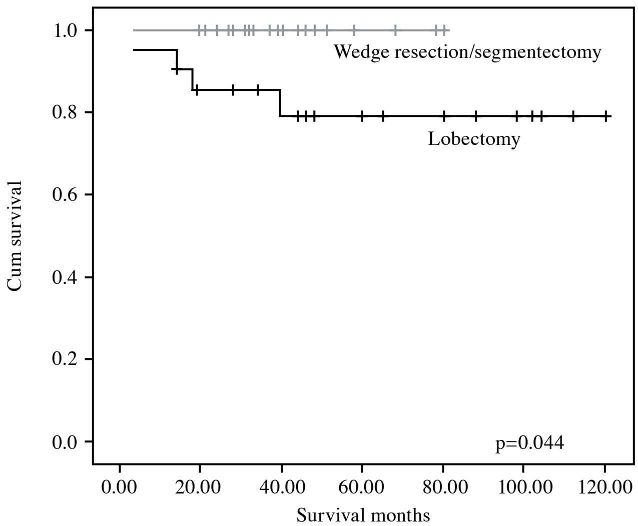

Figure 1. Overall survival analysis according to type of resection in subsolid nodules.

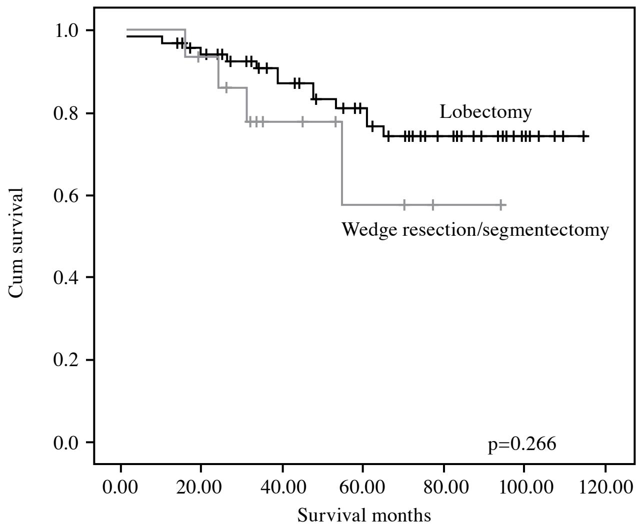

Figure 2. Overall survival analysis according to type of resection in solid nodules.

lobectomy, segmentectomy, and wedge resection, respectively.

We divided the patients into two groups as those with solid or subsolid nodules and determined no significant difference between the groups in terms of lymphovascular and perineural invasion, positive surgical margin or visceral pleural invasion. Non-invasive or minimal invasive AC was more likely seen in the subsolid nodules vs. solid nodules (32.6% vs. 5.6%, p<0.001). Dissected lymph node stations were higher in number in the patients operated for solid nodules vs. subsolid nodules (4 vs. 3, p=0.006). While the rate of lobectomy was significantly higher in solid nodules, subsolid nodules were associated with higher rate of sublobar resections (wedge resection or segmentectomy) (p<0.001). Comparison of pathological tumor size between the groups revealed that solid nodules consisted of tumors >2 cm more commonly than subsolid nodules (51.1% vs. 32.6%, p=0.021) (Table 1).

The prevalence of non-invasive or minimal invasive AC was significantly higher in the patients with TDR ≥25% as compared to the patients with TDR <25% (25% vs. 3.3%, p=0.019). Comparing the histopathological types according to the pathological tumor size, the prevalence of invasive AC significantly increased with increasing tumor size (0-10 mm vs. 11-20 mm vs. 21-30 mm and 41.2% vs. 89.3% vs. 95%, respectively; p<0.001) (Table 2).

The median patient follow-up period was 47.5 months. While 16 patients developed recurrence, 22 patients died. Five-year OS rate and DFS rate were 81.5% and 72%, respectively. Recurrence or death was not observed in AIS or MIA patients. Univariate survival analyses suggested that OS was unfavorably influenced by recurrence most (p<0.001). Besides, a TDR <25% unfavorably influenced the DFS, whereas a SUV_{max} >5.6 unfavorably influenced the OS (p=0.027 for both) (Table 3).

In the multivariate analyses performed for DFS and OS using the parameters of recurrence, age, gender, nodule structure, resection type, TDR and SUV_{max}, only a SUV_{max} of 5.6 was found to be an independent prognostic factor for OS (hazard ratio [HR]: 5.973, 95% confidence interval [CI]: 1.186-30.073, p=0.03).

For subsolid nodules, five-year OS rate was significantly better in patients who underwent wedge resection/segmentectomy vs. lobectomy (100% vs. 79.3%, p=0.044) (Figure 1). For solid nodules, five-year OS rate was better in patients who underwent lobectomy, although it was not statistically significant (81.7% vs. 59%, p=0.266) (Figure 2).

DISCUSSION

In the present study, the subsolid nodule group comprised higher numbers of nonsmoker and female patients compared to the solid nodule group (p=0.001 and p=0.005, respectively). In a study conducted by Xu et al.,[2] numbers of male and smoker patients were reported to be higher in more invasive AC subgroups (solid and papillary) (p=0.046 and p=0.001, respectively). This may be explained by the higher prevalence of smoking among males vs. females and the role of smoking in the etiopathogenesis of lung cancer.

A comparison of the radiological types and histopathological groups of the nodules revealed that non-invasive or minimally invasive ACs are significantly more likely to be present in the subsolid nodules vs. solid nodules (p<0.001). This also applies to the nodules with TDR ≥25% (p=0.019). Complementing these data, the prevalence of invasive AC increased with increasing pathological tumor size (p<0.001). Takahashi et al.[3] determined the TDR of 75% and consolidation diameter of 10 mm as threshold values to determine the presence of invasive tumors in stage IA lung AC. In the present study as well, the greatest increase in the prevalence of invasive AC was between the tumor size groups of 0-10 mm and 11-20 mm (41.2% vs. 89.3%). These data suggest that presence of invasive AC can be predicted radiologically by using the tumor size and tumor disappearance rate together.

Since we did not include patients with lymph node metastasis in this study, we are unable to establish any statements about the ideal lymph node dissection type, while in a study published in 2017, Zhaoming et al.[4] declared that systematic lymphadenectomy is indicated in all patients with pure solid nodules and those with mixed nodules with solid component ≥5 mm in diameter. They included 364 clinical $T_{1a}N_0M_0$ AC patients and found 15 (4.1%) N_1 and nine (2.5%) N_2 metastases. This study may give us an opinion about the necessity of lymph node dissection for stage I lung AC.

We found no significant relationship between AC subtypes and survival (DFS p=0.748, OS p=0.529, respectively). Urer et al.[5] also studied the relationship between survival and invasive AC subtypes among 226 patients and did not find any relationship. These results may be due to the limited number of patients included in both studies.

Five-year DFS and OS rates for all patients were 72% and 81.5%, respectively. Recurrence or death was not observed in AIS or MIA patients. These results are consistent with the results of OS reported for stage I lung cancer and 100% DFS estimated for non-invasive or minimally invasive lesions.[6,7]

Univariate analyses demonstrated that recurrence is the most critical prognostic factor for OS (p<0.001) and this is a well-known situation in the literature.[8] Univariate analyses indicated TDR (threshold value: 25%) as the prognostic factor for DFS and SUV_{max} (threshold value: 5.6) as the prognostic factor for OS (p=0.027 for both). In the multivariate analysis performed for OS, grouping according to a SUV_{max} of 5.6 was found to be an independent prognostic factor (HR: 5.973, 95% CI: 1.186-30.073, p=0.03). Lee et al.[9] published a study in 2015, in which they performed receiver operating characteristic analysis for OS and DFS in ACs, and determined 15% and 9.5 as the best threshold values for TDR and SUV_{max}, respectively. Statistically significant survival rates were obtained also in the survival analyses performed using these two values (p<0.001). The above-mentioned study comprised also the ACs with lymph node metastasis.

Higher five-year OS rates were obtained in the subsolid nodules that were performed wedge resection or segmentectomy and in the solid nodules that were performed lobectomy. Wang et al.[10] published a study in 2017 and found five-year DFS and OS as 86.1% and 83.6%, respectively, for ≤3 cm peripheral pulmonary AC treated with wedge resection. Okada et al.[11] compared segmentectomy vs. lobectomy for clinical stage IA lung AC and found that three year DFS and OS for segmentectomy and lobectomy were comparable (90.2%/91.5%, 94.8%/93.3%, respectively). Another study conducted by Tsutani et al.[12] including ground-glass opacity (GGO)-dominant clinical stage IA lung AC favored wedge resection for T_{1a} tumors and segmentectomy for T1b tumors. Almost 100% DFS rates were reported with sublobar resections containing high rates of wedge resection in numerous prospective and retrospective studies focusing on PSGG nodules with tumor size <3 cm and GGO rate >50%.[13-21]

Our study has some limitations. This is a retrospective study with limited number of patients. Also, the radiographic evaluation of patients was performed with a non-randomized method which may have caused some variations in radiographic interpretation. Moreover, median follow-up time for the study was 47.5 months which could be too short to evaluate early stage lung AC recurrence.

In conclusion, sublobar resections can be safely performed in subsolid nodules <2 cm in diameter with tumor disappearance rate ≥25% and maximum standardized uptake value ≤5.6. However, further prospective randomized studies with higher number of patients including more subsolid nodules are needed to verify these results.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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