

Positron emission tomography/computed tomography findings of lung invasive adenocarcinoma subgroups and comparison of their short-term survivals

Akciğere invazyon gösteren adenokarsinom alt gruplarının pozitron emisyon tomografi/bilgisayarlı tomografi bulguları ve kısa dönem sağkalımlarının karşılaştırılması

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ABSTRACT

Background: The aim of this study was to compare the maximum standardized uptake values on positron emission tomography/computed tomography and survival of lung invasive adenocarcinoma subgroups.

Methods: Between January 2010 and January 2016, a total of 152 patients (112 males, 40 females; mean age: 64.2±8.6 years; range, 41 to 88 years) who underwent lung resection for an invasive adenocarcinoma were retrospectively analyzed. The patients were divided into subgroups as follows: acinar, lepidic, micropapillary, papillary, and solid. The maximum standardized uptake values in the imaging study and their relationship with survival were examined.

Results: There were 84 acinar (55%), 31 solid (20%), 23 lepidic (15%), nine papillary (5%), and five micropapillary (3%) cases. The positron emission tomography/computed tomography enhancement showed a statistically significant difference among the subgroups (p=0.004). The solid subgroup was the most involved (9.76), followed by micropapillary (8.98), acinar (8.06), papillary (5.82), and lepidic (4.23) subgroups, respectively. According to Tumor, Node, Metastasis staging, Stage I was present in 48.68% (n=74) of the cases, Stage II in 25.0% (n=38), Stage III in 25.0% (n=38), and Stage IV in 1.31% (n=2). The one-year, three-year, and five-year survival rates were significantly different among the disease stages (p=0.01). The longest survival duration was in the lepidic subgroup, although it did not reach statistical significance among the subgroups (p=0.587).

Conclusion: The evaluation of invasive adenocarcinomas based on maximum standardized uptake values provides valuable information and may guide neoadjuvant and adjuvant therapies in the future.

Keywords: Classification, computed tomography, lung adenocarcinoma, positron emission tomography, survival.

ÖZ

Amaç: Bu çalışmada, akciğere invazyon gösteren adenokarsinom alt gruplarının pozitron emisyon tomografi/bilgisayarlı tomografideki maksimum standardize tutulum değerleri ve sağkalımları karşılaştırıldı.

Çalışma planı: Ocak 2010 - Ocak 2016 tarihleri arasında, invazyon gösteren adenokarsinom nedeniyle akciğer rezeksiyonu yapılan toplam 152 hasta (112 erkek, 40 kadın; ort. yaş: 64.2±8.6 yıl; dağılım, 41-88 yıl) retrospektif olarak incelendi. Hastalar şu şekilde alt gruplara ayrıldı: asiner, lepidik, mikropapiller, papiller ve solid. Görüntüleme çalışmasında maksimum standardize tutulum değerleri ve sağkalım ile ilişkisi araştırıldı.

Bulgular: Seksen dört asiner (%55), 31 solid (%20), 23 lepidik (%15), dokuz papiller (%5), ve beş mikropapiller (%3) olgu mevcuttu. Pozitron emisyon tomografi/bilgisayarlı tomografi tutulumu, alt gruplar arasında istatistiksel olarak anlamlı bir fark olduğunu gösterdi (p=0.004). En fazla tutulum, solid alt grubunda olup (9.76), bunu sırasıyla mikropapiller (8.98), asiner (8.06), papiller (5.82) ve lepidik (4.23) alt grupları izledi. Tümör, Nod, Metastaz evrelemesine göre, hastaların %48.68'inde (n=74) Evre I, %25.0'inde (n=38) Evre II, %25.0'inde (n=38) Evre III ve %1.31'inde (n=2) Evre IV hastalık mevcuttu. Bir yıllık, üç yıllık ve beş yıllık sağkalım oranları, farklı hastalık evreleri arasında anlamlı düzeyde farklı idi (p=0.01). En uzun sağkalım süresi lepidik alt grupta olmakla birlikte, bu fark istatistiksel olarak anlamlı değildi (p=0.587).

Sonuç: İnvaziv adenokarsinomların maksimum standardize tutulum değerlerine göre değerlendirilmesi değerli bilgiler sağlar ve ileride neoadjuvan ve adjuvan tedavilere yön verebilir.

Anahtar sözcükler: Sınıflama, bilgisayarlı tomografi, akciğer adenokarsinomu, pozitron emisyon tomografi, sağkalım.

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Lung cancer is a major public health problem worldwide, not only due to its being a common cancer, but also due to its high mortality rate. About 80.7% of lung cancers are non-small-cell lung cancer (NSCLC), 16.4% are small-cell lung cancer (SCLC), and 2.9% are other subtypes.^[1] Adenocarcinoma (AC) is the most common subtype of lung cancer, accounting for 35 to 40% of all lung cancers.^[2] It constitutes 21.8% of all lung cancers in men and 4.9% in women.^[3]

In 2011, the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) working group proposed a new classification for lung ACs.^[4] According to this classification, ACs were divided into four main groups as preinvasive lesions, micro-invasive ACs, invasive ACs, and invasive AC variants. Invasive ACs are classified as lepidic dominant AC, acinar dominant AC, papillary dominant AC, micropapillary dominant AC, and solid dominant AC. This classification includes the subtyping of invasive ACs and emphasizes the prognostic significance of these histological subtypes, as well. The differences between these identified histopathological groups in lung cancer have significantly changed the treatment, prognosis, and management of the disease.^[2]

The stage of the tumor is the most important prognostic factor in patients with lung cancer. One of the imaging methods to determine the disease stage is positron emission tomography/computed tomography (PET/CT), which can provide information for the distinction of benign-malignant lesions, disease staging, demonstration of distant organ involvement, identifying recurrent tumors and evaluating the treatment response. The rate of fluorodeoxyglucose (FDG) uptake of the lesion on PET/CT is called standardized uptake value (SUV). A SUV value of over 2.5 to 3.0 is considered sensitive and specific for malignancy. Previous studies have shown that, despite the fact that the SUV value provides an idea on the distinction of malignant and benign lesions, it does not have a definite diagnostic value and it is recommended to be used for follow-up and evaluation of the treatment response.^[5-7]

The SUV, which is widely accepted as a semi-quantitative indicator of glucose metabolism, proposes malignancy at high values and benignity at low values.^[5] In some studies, however, no exact relationship has been shown between the SUV value and the prognosis.^[6-7] In the present study, we aimed to compare the SUV values on PET/CT and survival of the subgroups, i.e., lepidic dominant, acinar dominant, papillary dominant, micropapillary dominant, and solid dominant ACs in patients with lung invasive AC.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Dokuz Eylul University Hospital, Department of Thoracic Surgery between January 2010 and January 2016. A total of 152 patients (112 males, 40 females; mean age: 64.2±8.6 years; range, 41 to 88 years) who underwent lung resection and diagnosed with an invasive AC were included. The patients with mediastinal involvement on PET/CT were operated after invasive staging, while the patients without mediastinal involvement were operated without invasive staging. The SUV values, age, sex, predominant pathological subtype, survival time and the disease stage of the patients pathologically diagnosed with an AC were evaluated. All surgeries were performed via thoracotomy. A written informed consent was obtained from each patient. The study protocol was approved by the Dokuz Eylul University, Non-Invasive Research Ethics Committee (No: 2016/32-40). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The FDG-PET/CT images of the patients were obtained using the Philips Gemini TOF 16 Slice PET/CT scanner (Philips Medical Systems, Best, Netherlands) at the Nuclear Medicine Department of our institution. The preoperative PET/CT scans of 17 patients were missing and were excluded from the study.

Sixteen patients diagnosed with an AC without subtyping were re-evaluated by the pathology team of our hospital and the subtype of the tumors was identified.

Statistical analysis

Statistical analysis was performed using the SPSS version 15.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max), or number and frequency. The comparison between the groups was performed using the Kruskal-Wallis test. The Kaplan-Meier test was used for survival analysis. The survival curves were compared using the log-rank test. A *p* value of <0.05 was considered statistically significant.

RESULTS

Baseline demographic and histopathological characteristics of the patients are summarized in Table 1. There was no significant difference among the subgroups regarding the age (*p*=0.404). None of the patients underwent an invasive mediastinal staging before the operation, since no N2 was determined radiologically. Seven patients received

Table 1. Demographic and histopathological features of the participants (n=152)

Features	n	%	Mean±SD	Min-Max
Age (year)			64.2±8.6	41-88
Sex				
Female	40			
Male	112			
Operation type				
Lobectomy	133	87.5		
Pneumectomy	19	12.5		
Pathologic stages				
IA	40	26.3		
IB	34	22.4		
IIA	7	4.6		
IIB	31	20.4		
IIIA	28	18.4		
IIIB	10	6.6		
IV	2	1.3		
Predominant subtype				
Acinar	84	55.3		
Lepidic	23	15.1		
Papillary	9	5.9		
Micropapillary	5	3.3		
Solid	31	20.4		

SD: Standard deviation.

neoadjuvant chemotherapy, while two patients were applied neoadjuvant chemotherapy and radiotherapy. Lobectomy was performed in 113 (87.5%) patients and pneumonectomy in 19 (12.5%) patients. A total of 55% (n=84) of the cases were in the acinar subgroup, 20% (n=31) in the solid subgroup, 15% (n=23) in the lepidic subgroup, 5% (n=9) in the papillary subgroup, and 3% (n=5) in the micropapillary subgroup. According to the Tumor, Node, Metastasis classification, 40 patients were in Stage IA, 34 were in Stage IB, seven were

in Stage IIA, 31 were in Stage IIB, 28 were in Stage IIIA, 10 were in Stage IIIB, and two were in Stage IV (Table 1).

When the distributions according to sex were examined, the most common subtype observed in males was the acinar subtype (41%, n=63), the second was the solid subtype (16%, n=25), the third was the lepidic subtype (9%, n=14), the fourth was the papillary subtype (3%, n=6), and the fifth was the micropapillary subtype (2%, n=4). The most common

Table 2. Comparison of the mean SUV values among the subgroups (p=0.004)

Group	n	Mean±SD	Median	Min-Max
Acinar	73	8.1±6.4	6.30	0.00-30.80
Lepidic	23	4.2±3.3	3.40	0.00-14.00
Micropapillary	5	9.1±5.8	7.50	2.70-15.40
Papillary	8	5.8±3.3	6.20	0.00-9.80
Solid	26	9.8±6.2	9.45	0.00-26.80
Total	135	7.6±6.0	5.70	0.00-30.80

SUV: Standardized uptake value; SD: Standard deviation.

Table 3. Five-year survival rates of subgroups

Subgroups	n	Survivors		Deads	
		n	%	n	%
Acinar	84	50	59.5	34	40.5
Lepidic	23	16	69.6	7	30.4
Micropapillary	5	1	20	4	80
Papillary	9	6	66.7	3	33.3
Solid	31	20	64.5	11	35.5

subtype in women was the acinar subtype (13%, n=21), the second was the lepidic subtype (5%, n=9), the third was the solid subtype (3%, n=6), the fourth was the papillary subtype (1%, n=3), and the fifth was the micropapillary subtype (0.6%, n=1).

There was a statistically significant difference in the SUV values of the dominant subgroups of 135 AC patients (p=0.004). We found the highest mean SUV value in the solid subgroup, followed by

the micropapillary, acinar, papillary and the lepidic subgroups, respectively (Table 2).

The survival rate was the lowest in the micropapillary subgroup (20%), followed by the acinar (59.5%), solid (64.5%), papillary (66.7%) and lepidic (69.6%) subgroups, respectively. There was no significant difference in the survival rates among the subgroups (Table 3). The survival rates of the disease stages were evaluated using the Kaplan-Meier test and log-rank analysis (p=0.015). The mean survival duration of the patients with Stage I disease was 68.4 months, 59.5 months for Stage II, 43.4 months for Stage III, and 27.2 months for Stage IV. There was a significant difference between the disease stages in terms of the mean survival duration (p=0.009) (Figure 1).

There was a statistically significant difference among the detailed TNM stages in terms of the mean survival duration (p<0.004). The mean survival duration of the patients was 62.1 months in Stage IA, 69.0 months in Stage IB, 61.6 months in Stage IIA, 58.8 months in Stage IIB, 45.8 months in Stage IIIA, 36.3 months in Stage IIIB, 36.3 months in Stage IIIB, and 27.2 months in Stage IV.

There was no statistically significant difference between the subgroups in terms of survival duration

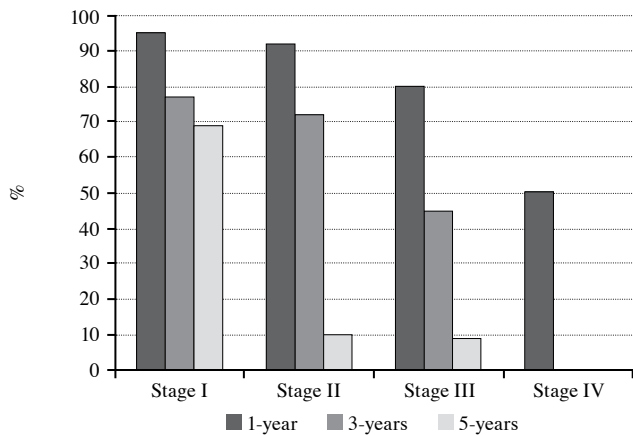


Figure 1. 1-year, 3-year and 5-year survival rates of the patients in each stage.

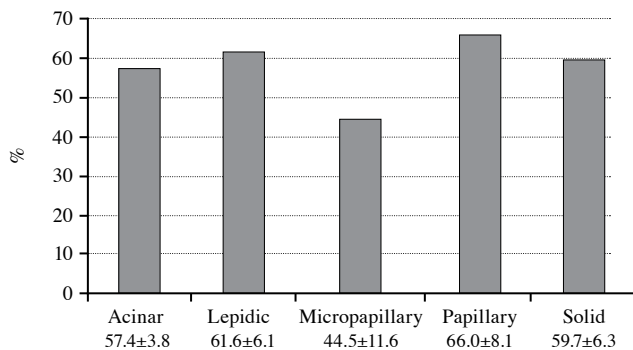


Figure 2. Mean survival durations of subgroups (months).

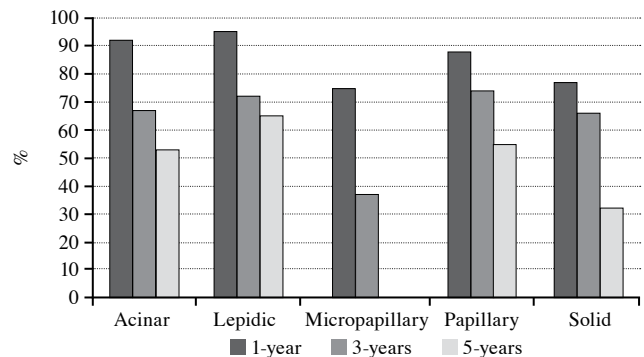


Figure 3. 1-year, 3-year and 5-year survival rates of the subgroups.

($p=0.578$) (Figure 2). The five-year survival rate was the lowest in the micropapillary subgroup with 20%, followed by the acinar with 59.5%, solid with 64.5%, and papillary subgroup with 66.7%. The lepidic subgroup had the highest five-year survival rate with 69.6% (Figure 3).

DISCUSSION

Lung AC is a very heterogeneous group in many aspects such as pathological, molecular, clinical, radiological, and surgical. Therefore, the classification of the disease made in 2004 was revised in 2011. The most important reason for the revision was the unmet need for demonstrating differences by multidisciplinary approaches after remarkable developments in medical oncology, molecular biology, and radiology.^[8,9]

When the former and current classifications were compared in terms of subgroups, we found that acinar ACs were 100% compatible and papillary and solid ACs were 75% compatible with each other. In previous studies, no significant relationship has been shown between lymph node metastases and subtypes according to the new classification. Besides, in cases with minimally invasive AC, the entire tumor should be sampled and reflected in the report.^[8-12]

For thoracic surgeons, AC surgery may offer different surgical alternatives, compared to other histopathological types. These are sublobar or wedge resections in early-stage lung cancer, lymph node dissection width, and new approaches associated with intra-operative pathological analysis. Following the new classification, Warth et al.^[13] retrospectively reviewed the cases who were previously diagnosed with the mixed-type AC and re-examined a total of 100 archived lung AC resection specimens. The most frequent subgroup in this cohort was the predominant solid pattern subgroup (37%), followed by acinar (35%), lepidic (20%), papillary (5%), and micropapillary (3%) subgroups. In our study, the subgroups identified were acinar (55%), solid (20%), lepidic (15%), papillary (5%), and the micropapillary^[3] subgroups. There was no significant difference among the subgroups in terms of age and sex in our study population ($p=0.404$). These results are consistent with the literature. However, considering the racial genetic characteristics of ACs, complete consistency should not be expected.

Although there are studies reporting that the SUV values of ACs are lower than other types of lung cancer, there are also studies showing that there is no difference in the maximum (SUV) (SUV_{max}) value between all types of lung cancers.^[14,15] We found that there was a statistically significant difference in PET

enhancement values between the subgroups ($p=0.004$); the highest mean SUV value was in the solid (9.8 ± 6.2) group, followed by micropapillary (9.0 ± 5.8), acinar (8.1 ± 6.4), papillary (5.8 ± 3.3) and the lepidic (4.2 ± 3.3) subgroups. Similar to our study, Nakamura et al.^[16] found that the preoperative SUV_{max} value was closely related to AC subtypes. The highest SUV_{max} value was shown in micropapillary dominant AC, followed by solid dominant AC.

In another study, to detect the relationship between PET/CT parameters and the stages of invasive ACs, the authors calculated the SUV_{max} , metabolic tumor volume (MTV), and the total lesion glycolysis (TLG) values and found that the survival rates were significantly lower in the patients with high SUV_{max} , MTV, and TLG values.^[17] In our study, micropapillary and solid groups had the highest SUV values; however, there was no statistically significant difference between the subgroups in terms of the duration of survival in months ($p=0.587$).

In their study including subgroups of ACs, Yoshizawa et al.^[10] categorized the patients into three different prognostic groups. Adenocarcinoma *in situ* (AIS) and minimally invasive AC (MIA) were defined as the low-grade and the five-year disease-free survival was reported as 100% in this group. Lepidic, acinar, and papillary subgroups were defined as the moderate grade and the five-year disease-free survival rate was reported as 90%, 83% and 84% in these groups, respectively. The invasive mucinous AC, solid and micropapillary subgroups were defined as the high-grade and the five-year disease-free survival rates were reported as 70% and 67%, respectively ($p<0.001$).

In a series of 210 Australian patients with Stage I, Stage II, and Stage III lung AC, Russell et al.^[11] retrospectively investigated the relationship between the new classification subgroups and the survival rates. The survival rates were significantly lower in the micropapillary and solid ACs, whereas they confirmed that the five-year survival rates were close to 100% in AIS, MIA, and lepidic ACs. Papillary and acinar ACs were subgroups with a moderate prognosis.

In our study, the mean follow-up duration of the patients was 40.2 ± 22.0 months. The mean outcome of the patients was 59.7 ± 2.8 (range, 54.13 to 65.16) months, and this long follow-up period is one of the strengths of our study.

The mean survival duration was 66.0 ± 8.1 months in the papillary group, 61.6 ± 6.1 months in the lepidic group, 59.7 ± 6.3 months in the solid group, 57.4 ± 3.8 months in the acinar group, and 44.5 ± 11.6 months

in the micropapillary group; however, there was no statistically significant relationship between the survival duration of the patients having the same stage disease ($p=0.587$). At the end of the five-year follow-up duration, 80% of the patients in the micropapillary subgroup, 40.5% of those in the acinar subgroup, 35.5% of the solid subgroup, 33.3% of the papillary subgroup, and 30.4% of the lepidic subgroup died. In addition, the highest SUV value in the micropapillary and solid groups of our study population is consistent with these previous studies.^[10,11]

When we evaluated the one-year, three-year, and five-year survival rates according to the stages, we showed a statistically significant difference in the survival rates between the disease stages ($p=0.015$). The survival rates in the patients with Stage I disease were 95%, 77%, and 69%, respectively; they were 92%, 72%, and 10% in Stage II; 80%, 45%, and 9% in Stage III; and 50%, 0%, and 0% in Stage IV disease. The mean survival durations in the subgroups were as follows: 57.4 ± 3.8 months in the acinar group, 61.6 ± 6.1 months in the lepidic group, 44.5 ± 11.6 months in the micropapillary group, 66.0 ± 8.1 months in the papillary group, and 59.7 ± 6.3 months in the solid group, whereas there was no statistically significant difference among the subgroups for patients in the same stage ($p=0.587$). Stage III disease was more frequent, particularly in the acinar group, suggesting that PET-CT has high false-negative rates and invasive staging should be performed in all conditions.

Warth *et al.*^[12] retrospectively evaluated patients with Stage I-IV AC who underwent surgical resection. They reported that staging of lung ACs according to the new IASLC/ATS/ERS scheme based on structural patterns was a quick, simple, and effective distinguishing factor in terms of long-term prognosis, and showed that it could contribute to the selection of proper patients for targeted therapies.

The fact that there are differences in the number of patients in the subgroups is the main limitation of the present study, preventing us from commenting on the survival of the subgroups. Further larger-scale studies would provide more accurate results.

In conclusion, lung adenocarcinoma is an issue of interest that many scientists closely follow and work on. In our study, the standardized uptake values were significantly higher in the subgroups with poorly differentiated tumors, compared to the other subgroups. The diagnostic and clinical diversity among all subgroups of lung adenocarcinomas suggests that the diagnosis and treatment protocols of lung cancers can be updated in the following years. The

identification of subgroups of lung adenocarcinomas would be in parallel with revealing the molecular and genetic differences. Due to the development of health technologies, the current cancer treatments are progressing toward the targeted therapies based on these molecular and genetic differences.

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