Original Article

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The relationship between quantitative positron emission tomography parameters, the invasive lung adenocarcinoma grading system of International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society, and survival

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Abstract:

BACKGROUND: The impact of newly defined subtypes and grades of adenocarcinoma on the survival and their reflection on imaging methods and nuclear medicine practices are popular research topics.

AIMS: The aim of the study is to investigate quantitative positron emission tomography (PET) parameters and the adenocarcinoma grading system of the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society in terms of survival and potential prognosis prediction value in operated lung adenocarcinoma patients.

STUDY DESIGN: One hundred and seventy-nine patients who were surgically treated for adenocarcinoma of the lung were included in the study. 2-deoxy-2-(18F) fluoro-D-glucose (FDG) PET/computerized tomography (CT) was applied for initial staging.

MATERIALS AND METHODS: For quantitative evaluation, maximum standardized uptake values (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) of the primary tumors were calculated.

RESULTS: There was a statistically significant relation between grade and radiological appearance, but tumor grade and SUVmax, TLG, and MTV parameters showed no significant correlation. Pathological tumor size and PET/CT had strong correlation ($P < 0.001$, $r = 0.816$). There was no relationship between mortality and tumor grade ($P = 0.980$). SUVmax, MTV, and TLG were more predictive

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for survival than disease grade (P = 0.022, 0.044, and 0.012, respectively). Survival differences were observed according to the cutoff values for TLG (49.66) and MTV (9.68) (P < 0.05). Vascular invasion and central settlement were related to lymph node involvement (P < 0.001). When the tumor/lymphadenopathy SUVmax ratio was <2.5, risk of metastatic lymph node was higher (P < 0.001).

CONCLUSION: Metabolic parameters are still superior to new adenocarcinoma grading system in terms of survival. Measurement of tumor size on PET/CT is an important predictive value about pathological T-stage.

Keywords:

2-deoxy-2-(18f) fluoro-D-glucose, adenocarcinoma of the lung, molecular imaging, positron emission tomography/computerized tomography

Introduction

In early-stage lung cancer, surgical resection is the standard of care. It is widely accepted that the most common predictor of survival is the pathologic stage of the tumor after resection. However, investigators continuously search for other possible reliable factors to foresee the course of this deadly disease. Recently, histopathologic classification criteria of lung adenocarcinoma were published by the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS).[1] According to the new classification, invasive adenocarcinomas were divided into three subgroups in addition to histological subtypes: Grade 1: lepidic adenocarcinoma, Grade 2: acinar and papillary adenocarcinoma, and Grade 3: micropapillary and solid-type adenocarcinoma.[1] It has been shown that there are differences between subtypes early-stage adenocarcinomas in terms of survival.

In lung cancer patients, 2-deoxy-2-(18f) fluoro-D-glucose (FDG) positron emission tomography/computerized tomography (PET/CT) is an important imaging modality for diagnosis, staging, evaluation of treatment response, and prognosis based on quantitative indices. Currently, the impact of newly defined subtypes and grades of adenocarcinoma on the survival and their reflection on imaging methods and nuclear medicine practices are popular research topics. Hence, we aimed to investigate the relations between several quantitative PET parameters and grades of lung carcinoma. With defining cutoff values for these parameters, we also analyzed the differences by the meaning of survival. Finally, the correlation of several radiological and pathological features was investigated.

Materials and Methods

The study included patients with adenocarcinoma of the lung who underwent surgical resection between 2010 and 2013 at our institution. Several demographic features, radiological findings, and clinical and laboratory data of the patients were collected retrospectively. Smoking history and performance status based on the Eastern Cooperative Oncology Group performance scale were documented.[2] Patients were staged according to the seventh edition of the Tumor, Node, and Metastasis (TNM) lung cancer staging system.[3] The data of magnetic resonance imaging, computerized tomography (CT), and PET/CT study were noted. Tumors were classified as nodules, ground-glass opacities (GGOs), subsolid nodules, consolidations, atelectasis, or masses according to their radiological appearance.

All patients have undergone complete resection and mediastinal lymph node dissection. Survival time was determined as the time between the time of diagnosis and the time of death or last visit.

2-deoxy-2-(18F) fluoro-D-glucose positron emission tomography/computerized tomography imaging and quantitative positron emission tomography/computerized tomography parameters

PET/CT evaluation was performed with an integrated PET/CT scanner (Siemens, Biograph-6-HI-REZ; Siemens Medical Solutions, Knoxville, TN USA) using the same method defined in our previous study.[3]

PET/CT images were visually and quantitatively reevaluated, and the maximum standardized uptake values (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) of the primary tumors were calculated. SUVmax corrected for body weight was computed by standard methods from the activity at the most intense voxel in the three-dimensional tumor region from the transaxial whole-body attenuation-corrected PET/CT images. MTV (in cm^3) was measured using an automatic isocontour threshold method, which is based on a value >40% SUVmax of the primary tumor.[4] TLG values were calculated by multiplying the MTV and mean SUVmax values.

When tumor/lymphadenopathy (LAP) SUVmax ratio was <2.5, the risk of lymphatic metastasis was significantly higher.[5] Hence, we have used this cutoff to predict lymphatic metastasis.

Histopathologic classification

Patients were categorized according to the grade and histological subtypes. According to the 2015 WHO Lung Cancer Classification, invasive adenocarcinoma is >5 mm in the greatest dimension. Histological subtypes are lepidic, acinar, papillary, micropapillary, and solid according to the predominant histologic subtype. Definitions include acinar pattern with central luminal space surrounded by tumor cells, papillary pattern, a growth of glandular cells along the central fibrovascular cores, micropapillary tumor cells growing in papillary pattern tufts forming florets that lack fibrovascular cores, and solid pattern tumor cells forming sheets. We used comprehensive histologic subtyping for semiquantitative assessment of the percentages of the lepidic, acinar, papillary, micropapillary, and solid components using 5% increments. We excluded minimally invasive adenocarcinoma (MIA) and adenocarcinoma *in situ* (AIS) from this study. Adenocarcinoma cases were graded according to the architecture using the following reported prognostic associations: favorable (nonmucinous lepidic), intermediate (papillary and acinar), and poor (solid and micropapillary).[1] This is a retrospective study, so the pathologic slides reviewed for this paper.

Statistical analysis and ethics

The statistical analyses were conducted with PASW Statistics for Windows (SPSS Inc. Version 18.0, Released 2009, Chicago, USA) and MedCalc for Windows statistical software (Version 9, 2006, Mariakerke, Belgium). Descriptive data were defined as the mean ± standard deviation or the median (minimum–maximum) for continuous variables and as percentages for categorical variables. The Chi-square test, Fisher's exact test, and the odds ratios (ORs) were used to compare categorical variables. A linear-by-linear association test was used to assess the trends between categorical variables. Correlation analyses were done with Spearman or Pearson correlation tests. The Kaplan–Meier test was used for survival analyses, and receiver operating curve analysis was used to assess the defining discriminative threshold and the performance of several variables. $P < 0.05$ was assumed to be statistically significant.

Informed consent was deemed unnecessary since this is a retrospective study. The study was approved by the Institutional Ethical Committee with number 553/5.4.2017.

Results

The study included a total of 179 patients who underwent surgical resection for lung adenocarcinoma between 2010 and 2013 (153 men and 26 women). Several other demographic and histopathologic features of the cases were given in Table 1. There were 11 lepidic predominant (6.1%), 97 acinar predominant (54.2%), 9 papillary predominant (5%), 5 micropapillary predominant (2.8%), and 57 solid predominant (31.8%)

Table 1: Demographic and histopathological features of patients

Features	*n* (%)
Number of patients	179
Age (years)	
Mean±SD	62±8
Minimum-maximum	43-87
Gender	
Female/male	26/153
Smoking history (active and ex-smokers)	53 (29.6)
Smoking (packyears)	41±20
Radiological pattern	
Solid mass	127 (70.9)
GGO	22 (13.3)
Consolidation	18 (10.1)
Cavitary lesion	12 (6.7)
Operation type	
Lobectomy	153 (85.5)
Pneumectomy	16 (8.9)
Wedge resection	4 (3.9)
Segmentectomy	3 (1.7)
Pathologic stages	
IA	28 (15.6)
IB	52 (29.1)
IIA	26 (14.5)
IIB	30 (16.8)
IIIA	40 (22.3)
IIIB	3 (1.7)
Clinical stages	
IA	46 (30.1)
IB	27 (17.6)
IIA	30 (19.6)
IIB	22 (14.4)
IIIA	22 (14.4)
IIIB	6 (3.9)
Predominant subtype	
Lepidic	11 (6.1)
Acinary	97 (54.2)
Papillary	9 (5.9)
Micropapillary	5 (2.8)
Solid	57 (31.8)
Tumor grade (ın all lesions)	
Grade 1	11 (6.1)
Grade 2	106 (59.2)
Grade 3	62 (34.6)
Tumor grade (ın solid masses) (*n*=127)	
Grade 1	4 (3.1)
Grade 2	79 (62.2)
Grade 3	44 (34.6)
Tumor grade (ınGGO lesions) (*n*=22)	
Grade 1	5 (22.7)
Grade 2	14 (63.3)
Grade 3	3 (13.6)

GGO: Ground-glass opacity, SD: Standard deviation

patterns. Most of the patients had Grade 2 tumor (59.2%), which is followed by Grade 3 tumors (34.6%) and only 6.1% of them had Grade 1. The most common radiological pattern was masses, which occurred in 127 cases (70.9%). GGO, consolidation, and cavitation were other presentations. There was a statistically significant relation between grade and radiological appearance; solid masses usually tend to occur as Grade 2 and 3, while GGO lesions were mostly Grade 1 and 2 (P = 0.003). While mostly pathological stage was IB (n = 52, 29.1%), it was Stage IA for clinical TNM (n = 46, 30.1%). In both groups, Stage IIIB was the less common. Platinum-based-doubled chemotherapy and palliative radiotherapy, when needed, was performed, and targeted mutations were analyzed in recurrent cases.

By the end of the study, 46 patients had died (25.6%). Median survival time was 37 months. The overall survival (OS) rates at 1, 2, 3, and 5 years were 88.9%, 77.8%, 76.4%, and 66.1%, respectively. No relation was found between mortality and tumor grade [P = 0.980, Table 2].

Table 2: Survival rates according to the tumor grade

Survival rates (%)	1 year	2 years	3 years	5 years	*P*
Grade 1	100	81.8	81.8	65.5	0.980
Grade 2	100	80	79.3	77	
Grade 3	86	79.1	76.6	71.6	
Overall	88.9	77.8	76.4	66.1	

SUVmax had a weakly negative correlation with survival (P = 0.004, r = –0.220). In patients with shorter survival rates, the metabolic parameters SUVmax, MTV, and TLG were significantly higher (P = 0.022, 0.044, and 0.012, respectively), and tumor size was greater in both pathological samples (P = 0.021) and PET/CT (P = 0.030).

In Cox regression analyses with surgical type, clinical, and pathological stage, only clinical TNM staging was negatively associated with OS (P = 0.027; Hazard ratio [HR] [95% confidence interval (CI)]: 1.16 [1.01–1.32]). OS time did not differ according to surgical procedure; 43 months for pneumonectomy, 40 months for lobectomy, 31 months for wedge resection, and 14 months for segmentectomy (P = 0.6).

Median progression-free survival (PFS) was 40.9 months (±17.1). Among 28 patients with recurrence, the lung was the most frequent side (n = 11), following with the brain (n = 6), bone (n = 3), surrenal (n = 2), and others. In Cox regression analyses with recurrence side and surgical procedure, there was not any significant relationship in terms of PFS (P > 0.05).

A cutoff value of 49.66 was determined for TLG to define the risk of death (sensitivity = 69.6%, specificity = 52.6%, area under the curve (AUC): 0.616 [0.95 CI = 0.540–0.687] P = 0.019) [Figure 1b]. When TLG was higher than the cutoff value, the survival rates at 1, 2, 3, and 5 years

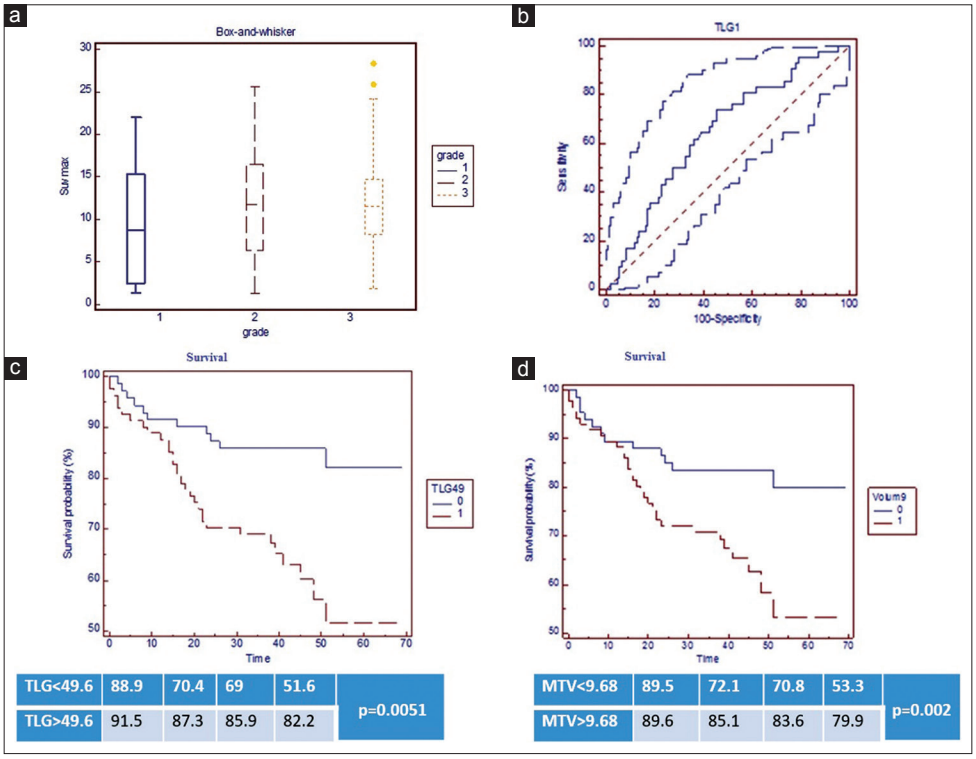

Figure 1: (a) Variance analysis between maximum standardized uptake values and grade, (b) receiver operating curve for total lesion glycolysis, (c) survival rates according to the cutoff value (49.6) for total lesion glycolysis, and (d) Survival rates according to the cutoff value (9.68) for metabolic tumor volume

Table 3: Survival rates according to defined cutoff values for total lesion glycolysis and metabolic tumor volume

Survival rates	1 year	2 years	3 years	5 years	*P*
TLG <49.6	90.5	71.5	70.4	54.1	*P*=0.005
TLG >49.6	90.4	86.5	83.7	80.3	HR=0.421
					0.242-0.778
MTV <9.68	91.1	73.8	72.6	57.0	*P*=0.002
MTV >9.68	89.6	85.3	82.2	78.9	HR=0.507
					0.291-0.937

TLG: Total lesion glycolysis, MTV: Metabolic tumor volume, HR: Hazard ratio

were determined as 90.4%, 86.5%, 83.7%, and 80.3%, respectively. When TLG is lower than 49.66, the survival rates decreased to 90.5%, 71.5%, 70.4%, and 54.1%, respectively. The difference was statistically significant (P = 0.0051, HR = 0.421 [0.242–0.778]) [Table 3 and Figure 1c].

The best cutoff value for MTV to define the risk of death was 9.68 cm^3 (sensitivity = 69.6%, specificity = 47.4%, AUC = 0.605 [0.523–0.683], P = 0.044). When the cutoff value was over 9.68, the survival rates at 1, 2, 3, and 5 years were 89.6%, 85.3%, 82.2%, and 78.9%. When the MTV value was lower than the cutoff, survival rates were 91.1%, 73.8%, 72.6%, and 57.0%, respectively. The difference was statistically significant (P = 0.002, HR = 0.507 [0.291–0.937]) [Table 3 and Figure 1d].

The mean tumor diameter was 3.7 ± 1.7 cm. A strong correlation was detected between pathologic tumor size and the metabolic size on PET/CT (P < 0.001, r = 0.816). The mean quantitative values for SUVmax, MTV, and TLG were 11.7 ± 6.5, 41.2 ± 61.5, and 307.1 ± 511.1, respectively. There was no relation between tumor grade and the tumor size (P = 0.191), SUVmax value [P = 0.282 and Figure 1a], MTV (P = 0.440), and TLG (P = 0.763).

The SUVmax value of tumors (P = 0.533, LbLA = 0.388) and MTV (P = 0.688, LbLA = 0.161) were not related to the presence of lymph node metastasis. However, when the cutoff value for the tumor/LAP SUVmax ratio was considered as <2.5, there was a significantly higher rate of detecting metastatic lymph nodes (P < 0.001, OR = 4.3, 95% CI = 2.0–9.0). The presence of lymphatic metastasis was not related to grade (P = 0.603), gender (P = 0.696), smoking status (P = 0.791), or visceral pleura invasion (P = 0.402). There was no relation between MTV and presence of lymphatic metastasis (P = 0.688, LbLA = 0.161). However, vascular invasion (P < 0.001; OR = 20.9, 95% CI = 2.5–170.3) and central settlement (P = 0.001; OR = 3.4, 95% CI = 1.6–7.2) were related to the presence of lymph node involvement. Furthermore, lymph node involvement was significantly lower in lesions with GGO (P = 0.008, OR = 0.1, 95% CI = 0.0–0.8).

Discussion

Adenocarcinoma is a subtype of non-small cell lung cancer (NSCLC) and is known to have a bad prognosis. The new IASLC/ATS/ERS histopathological classification clearly determined subtypes of adenocarcinoma and their grades. In currents study, clinical TNM staging was significantly related to OS as expected.[1] Low-grade adenocarcinomas are expected to have better prognosis. Prognostic features of histopathological subgroups were assessed in many studies.[6-8] In cases of advanced stages, only diagnosis of adenocarcinoma without subtype can be obtained by small biopsy specimens. Radiological and metabolic features (SUVmax, MTV, and TLG) of adenocarcinoma subgroups have been investigated.[9-11]

In the current study, 11 patients were Grade 1, 106 patients were Grade 2, and 62 patients were Grade 3. There were no significant differences in terms of survival among different grades, in contrast to other studies.[12,13] This might be due to the nonhomogenous distribution of the number of patients and the significantly higher number of patients in Grade 2. Nakamura *et al*. demonstrated a significant correlation between preoperative SUVmax, adenocarcinoma subtype, and tumor grade in a retrospective study.[10] Our study group included only invasive adenocarcinoma subgroups, while AIS and MIA were excluded from the study. The metabolic activity according to PET/CT and the prognosis were similar in all invasive histopathological subgroups with all grades. SUVmax, MTV, and TLG were more predictive determinants for prognosis and survival than disease grade.

GGO is an important prognostic factor, and a large area of GGO indicates good prognosis in cases of adenocarcinoma. It is usually associated with lepidic, acinar, or papillary predominant adenocarcinomas. Thus, the GGO component could be related to low-grade and low tumor cellularity or a less aggressive tumor.[9] Of the lesions with the mass pattern, 62.2% were Grade 2 and 34.6% were Grade 3. Only 3.1% of them were Grade 1. In contrast, cancers presenting as GGO lesions mostly formed Grades 1 and 2. There was a statistically significant relation between grade and radiological pattern (P = 0.003).

The new classification provides a new aspect for T-staging by the meaning of size. Invasive tumor size has been demonstrated as more predictive than total tumor size for the lepidic predominant pattern when assessing T-staging.[10,11] Thus, it has been suggested that AIS and MIA should be staged as T-*in-situ* and T-microinvasive, unlike T1 staging.[13] In our study, patients with the GGO pattern preoperatively (Grade 1) had less lymphatic metastasis. Studies show that the presence of solid and

microinvasive adenocarcinoma patterns is related to higher incidence of lymphatic metastasis.[14] Similarly, in a retrospective study including 573 operated adenocarcinoma patients, the incidence of lymphatic metastasis was 27.9%, and all of these cases had a predominance of micropapillary and solid tumors.[15]

We did not detect any relation between tumor grade and lymphatic metastasis, but when the tumor/LAP SUVmax ratio was <2.5, the risk of lymphatic metastasis was significantly higher ($P < 0.001$), which is similar to previous data.[5] This ratio could be a predictive factor for determining patients who need invasive nodal staging preoperatively. In addition, centrally located tumors and vascular invasion are other predictors for lymphatic invasion.

Surgery is the most satisfactory treatment in lung cancer, but it is important to decide whether operation is appropriate for the patient. Classical test theory is the most frequent technique for assessing clinical T-staging in the preoperative period. However, adenocarcinomas are not always presented in solid nodule or mass forms. Thus, in this study, 11.1% of patients presented with GGO or consolidation. It is hard to assess the size of these lesions by radiological methods, but it is suggested that measurements be done on an axial CT image during inspiration for clinical T-staging. On pathological specimen, fixation can cause 20% shrinkage,[16,17] so there is a question of which radiological technique is better for determining pathological T-staging. We found that there is a strong correlation between pathological specimen and PET/CT for determining tumor size ($P < 0.001$, $r = 0.816$). Therefore, measurement of the metabolic parameters by FDG PET/CT can increase the accuracy of T-staging. Only one-dimensional measurement is used in T-staging, but tumors with the same length but different volumes can be detected. Three-dimensional volumetric evaluations for more accurate T-staging could help in making operation decisions. FDG PET/CT plays an important role for staging, evaluation of the treatment response, disease recurrence, and prediction of prognosis based on quantitative parameters.[10]

Previous lung cancer studies showed relations between SUVmax values and tumor aggression. SUVmax of the primary tumor is an independent predictor for survival.[11] In studies according to the quantitative volume parameters, MTV and TLG also have potential to provide prognostic information. We did not detect a relationship between tumor grade and metabolic parameters (MTV and TLG), but survival was noticeably worse in patients with high SUVmax, MTV, and TLG values. The probability of survival significantly decreased in patients with MTV more than 9.68 cm^3. By revealing the tumor burden, SUVmax, MTV, and TLG were more predictive determinants for prognosis and survival than the grade of the disease.

Even if, it was not primary endpoint of this study, surgical technic was not significantly related to OS and PFS. According to a study with 784 Stage I NSCLC patients sublobar resections was superior to lobectomy in terms of PFS, but there was no significant difference in terms of OS.[18] However, distribution of pathological/clinically stages had heterogeneity in the current study, so these data could not be generalized.

Conclusion

Although there was no correlation between tumor grade and PET parameters, PET/CT is an important imaging modality for more accurate T-staging and the prediction of lymphatic metastasis. SUVmax, MTV, and TLG may contribute to the prediction of survival. While GGO is associated with low tumor grade and cellularity and could indicate a good prognosis in cases of adenocarcinomas, vascular invasion and central settlement are related to higher rates of lymph node involvement.

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Conflicts of interest
There are no conflicts of interest.

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