research article

Prognostic role of positron emission tomography and computed tomography parameters in stage I lung adenocarcinoma

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Background. According to the current pathological classification, lung adenocarcinoma includes histological subtypes with significantly different prognoses, which may require specific surgical approaches. The aim of the study was to assess the role of CT and PET parameters in stratifying patients with stage I adenocarcinoma according to prognosis.

Patients and methods. Fifty-eight patients with pathological stage I lung adenocarcinoma who underwent surgical treatment were retrospectively reviewed. Adenocarcinoma *in situ* and minimally-invasive adenocarcinoma were grouped as non-invasive adenocarcinoma. Other histotypes were referred as invasive adenocarcinoma. CT scan assessed parameters were: ground glass opacity (GGO) ratio, tumour disappearance rate (TDR) and consolidation diameter. The prognostic role of the following PET parameters was also assessed: standardized uptake value (SUV) max, SUVindex (SUVmax to liver SUVratio), metabolic tumour volume (MTV), total lesion glycolysis (TLG).

Results. Seven patients had a non-invasive adenocarcinoma and 51 an invasive adenocarcinoma. Five-year disease-free survival (DFS) and cancer-specific survival (CSS) for non-invasive and invasive adenocarcinoma were 100% and 100%, 70% and 91%, respectively. Univariate analysis showed a significant difference in SUVmax, SUVindex, GGO ratio and TDR ratio values between non-invasive and invasive adenocarcinoma groups. Optimal SUVmax, SUVindex, GGO ratio and TDR cut-off ratios to predict invasive tumours were 2.6, 0.9, 40% and 56%, respectively. TLG, SUVmax, SUVindex significantly correlated with cancer specific survival.

Conclusions. CT and PET scan parameters may differentiate between non-invasive and invasive stage I adenocarcinomas. If these data are confirmed in larger series, surgical strategy may be selected on the basis of preoperative imaging.

Key words: adenocarcinoma; lung; surgery; computed tomography; PET

Introduction

The current IASLC/ATS/ERS pathological classification of lung adenocarcinoma includes histological subtypes with different tumour invasiveness and prognosis. In this classification the former term bronchoalveolar carcinoma (BAC) is no longer included and a distinction between adenocarci-

noma *in situ*, minimally invasive adenocarcinoma and invasive adenocarcinoma with its variants has been established.[1] Patients with adenocarcinoma *in situ* and minimally invasive adenocarcinoma have extremely high survival rates after surgery. Invasive stage I adenocarcinoma is on the other side associated with a relatively high risk of recurrence. Different surgical approaches have therefore been proposed according to the histological features of the tumour, with sublobar resection as a possible treatment option for adenocarcinoma *in situ* and minimally-invasive adenocarcinoma.[2,3] Conversely, major resection is still considered the treatment of choice of early-stage invasive adenocarcinomas.[4] Hence, the identification of pre-operative parameters that allow differentiating neoplastic lesions according to tumour invasiveness is crucial for the planning of surgical treatment. This point is even more important considering the relatively low accuracy in the definition of tumour invasion of the histological analysis obtained after needle biopsy or with intraoperative frozen section.[5,6]

At Computed Tomography (CT), tumours with lepidic growth pattern appear as ground-glass opacities (GGO), which may represent a variable part of the neoplastic lesion, while on the other hand the solid part of the tumour is mainly an expression of invasive adenocarcinoma.[7,8] CT scan derived parameters as GGO ratio, tumour disappearance rate (TDR) and consolidation diameter are an expression of the proportion of ground-glass and solid features of the tumour, and may correlate with histology and clinical behaviour. Previous reports have analysed the correlation of radiologic parameters with tumour invasiveness, but the prognostic role of these factors still has to be completely clarified.[9] Positron emission tomography (PET) derived parameters have also been progressively used in the differential diagnosis and as prognostic factors in patients with adenocarcinoma, the most used of which being the maximum standardized uptake value (SUVmax) of the tumour.[10,11] Moreover, a prognostic role of other PET derived parameters as SUVindex, metabolic tumour value (MTV) and total lesion glycolysis (TLG) was also demonstrated, and some studies showed a better predictive performance of these parameters in comparison with SUVmax.[12,13]

The aim of the current study was to assess the role of CT and PET parameters in the differentiation of non-invasive and invasive adenocarcinomas and in stratifying patients with stage I adenocarcinoma according to their prognosis.

Patients and methods

Patients with pathological stage I lung adenocarcinoma who underwent surgical treatment at our Institution following CT and PET scan evaluation between August 2006 and July 2011 were reviewed. The study was approved by the local Ethics Committee and registered on Clinicaltrials.gov (NCT04202614).

Histological specimens were classified according to the current IASLC/ATS/ERS pathological classification of lung adenocarcinoma.[1] Adenocarcinoma *in situ* and minimally invasive adenocarcinoma were grouped as non-invasive adenocarcinoma. Other histotypes were referred as invasive adenocarcinoma. Tumours were re-staged according to the current 8th edition of the TNM staging system.[14]

Pre-operative imaging work-up included CT scan and whole body PET scan. Nodal involvement in patients with clinical N2/N3 disease was preoperatively excluded by invasive mediastinal assessment (EBUS-TBNA or mediastinoscopy). Major resections were considered the treatment of choice in patients with invasive adenocarcinoma. Wedge resections were performed in the treatment of adenocarcinoma *in situ* and minimally-invasive tumours, and in patients with invasive adenocarcinoma with a functional contraindication to major resection.

The features analysed for all patients were: age, sex, smoking habit, type of surgical resection, tumour histology, stage of disease, morbidity, mortality, overall survival, cancer specific survival and disease free survival, PET-derived and CT scan parameters.

CT scan parameters

CT images were obtained using a commercially available scanner (Toshiba X-press, Toshiba Medical Systems, Tokio, Japan). After infusion of intravenous contrast material spiral acquisition was obtained during breath-hold at the end of inspiration. The chest region was scanned with a detector configuration of 120 kVp, 200 mAs, 1 mm section thickness. The images were assessed using the mediastinal window setting (level, 40 Hounsfield units [HU]; width, 350 HU) and the lung window setting (level, 600 HU; width, 1500 HU).

CT scan assessed parameters were: ground glass opacity (GGO) ratio, tumour disappearance rate (TDR) and consolidation diameter. GGO ratio was defined as the percentage of the tumour with GGO

TABLE 1. Characteristics of 58 surgically-treated patients with stage I adenocarcinoma

	Non-invasive adenocarcinoma (7 patients)	Invasive adenocarcinoma (51 patients)	P
Gender			
Female	4	38	0.178
Male	3	13	
Age (median;range)	67 (46-75)	65 (48-85)	0.530
Type of surgery			
Wedge resection	3	10	
Lobectomy	4	40	0.188
Bilobectomy	0	1	
TNM			
Tis	1	0	
T1aN0	3	9	
T1bN0	1	17	0.056
T1cN0	2	16	
T2aN0	0	9	

appearance (1-[maximum dimension of consolidation on lung windows/maximum dimension of tumour on lung windows]) x 100, TDR% was defined as the ratio between the area of consolidation on mediastinal windows and the area of consolidation on lung window (1-[maximum area of consolidation on mediastinal windows/maximum area of tumour on lung windows]) x 100, consolidation diameter was defined as the maximum diameter of consolidation on lung window.

PET scan parameters

The prognostic role of the following PET-derived parameters was also assessed: standardized uptake value (SUV)max, SUVindex (SUVmax to liver SUVratio), MTV, TLG. PET-derived parameters (SUVmax, SUVindex, MTV and TLG) were calculated with a dedicated software (GE Advantage workstation - GEMS) developed for biomedical images. A volume of interest (VOI) was created for each lesion around the area of FDG uptake enclosing the tumour and SUVmax was obtained. SUVmean and MTV were measured using an automatic isocontour threshold method based on 50% of tumour SUVmax. SUVindex for each neoplastic lesion was calculated according to the method defined by Shiono et al.[12] A 6-cm circular region of interest (ROI) was drawn on three consecutive PET slices on the liver parenchyma. Liver SUVmean was defined as the mean of the SUVmax values of the three PET slices. SUVindex was calculated as the ratio of tumour SUVmax to liver SUVmean. TLG was calculated by multiplying MTV by tumour SUVmean.

Statistical analysis

Analysis was performed by SPSS Statistics software, version 18.0 (SPSS Inc., Chicago, IL, USA). Differences between classes of patients were tested for significance with the X^2 or Fisher's exact test for discrete variables and with the Student's t test for continuous variables. Receiver-operating characteristic (ROC) curves for PET and CT derived parameters were generated to define the cut-off values to differentiate non-invasive and invasive tumours and dichotomize patients on the basis of cancer-specific survival. Survival curves were reconstructed according to the Kaplan and Meier method. Differences in survival rates of patients grouped according to selected variables were estimated by means of the log-rank test. The Cox regression analysis was performed to assess the independent value of the significant variables at univariate analysis. Results were considered significant when p-values less than 0.05 were observed. Confidence intervals were calculated at the 95% level.

Results

Fifty-eight patients (41 males, 17 females, mean age 66, range 46 to 85 years) with pathological stage I lung adenocarcinoma entered the study. The characteristics of the patients are depicted in Table 1. Forty-four patients underwent a lobectomy, one patient a bilobectomy and 13 a wedge resection. Seven patients had a non-invasive and 51 an invasive adenocarcinoma. The pathological staging was as follows: Tis in one patient, T1aN0 in 12 cases, T1bN0 in 18 cases, T1cN0 in 18 cases and T2aN0 in 9 cases. The follow-up was complete for all 58 patients. The median follow-up was 60 months (range 3–126). At the end of follow-up thirty-nine patients are alive without evidence of cancer recurrence, 10 patients are alive with evidence of relapse, 4 patients died of cancer recurrence and 5 patients died due to other causes.

Five-year disease-free survival (DFS) and cancer-specific survival (CSS) was 100% and 100% for non-invasive and 70% and 91% for invasive adenocarcinoma, respectively (Figures 1 and 2) (p = 0.115, p = 0.46). Significant differences in GGO ratio, TDR ratio, SUVmax and SUVindex values were observed between non-invasive and invasive adenocarcinoma groups. Mean GGO ratio was 42% in non-invasive and 19% in invasive adenocarcinoma (p = 0.011); mean TDR ratio was 53% in non-

invasive and 24% in invasive adenocarcinoma (p = 0.001); mean SUVmax was 2.75 in non-invasive and 7.16 in invasive adenocarcinoma (p = 0.033); mean SUVindex was 0.98 in non-invasive and 3.12 in invasive adenocarcinoma (p = 0.037) (Table 2).

According to the ROC curve analysis optimal GGO ratio and TDR cut-off ratios to distinguish non-invasive from invasive adenocarcinoma were 40% (area under the curve [AUC] 82%, sensitivity 67%, specificity 81%) and 56% (AUC 85%, sensitivity 67%, specificity 96%), respectively; SUVmax and SUVindex cut-off ratios were 2.6 (AUC 81.5%, sensitivity 84%, specificity 71%) and 0.9 (AUC 84%, sensitivity 90%, specificity 71%), respectively. Patients with higher SUVmax and SUVindex values had a significantly higher incidence of less differentiated and larger tumours (Table 3). CSS significantly correlated with SUVmax, SUVindex and TLG. The statistical analysis with ROC curves identified the following best cut-off values to differentiate the patients according to prognosis: SUVmax 8.6, SUVindex 4.08, TLG 9.38. Five-year CSS was 97% in patients with a SUVmax < 8.6 and 81% in patients with a SUVmax > 8.6 (p = 0.036) (Figure 3). Five-year CSS was 97% in patients with a SUVindex < 4.08 and 76% in patients with a SUVindex > 4.08 (p = 0.01) (Figure 4). Five-year CSS was 100% in patients with a TLG < 9.38 and 82% in patients with a TLG > 9.38 (p = 0.02) (Figure 5). The type of surgical resection did not have a prognostic role (Five-year CSS 89% in patients submitted to wedge resection and 93% in patients submitted to major resection, p = 0.822). In particular, in patients submitted to wedge resection a correlation of DFS and CSS with CT and PET parameters was not observed, although patients with a TLG value

TABLE 2. Differences in CT and PET scan parameters according to histology

CT and PET scan parameter	Non-invasive adenocarcinoma	Invasive adenocarcinoma	p
GGO%	42±7.05	19±2.91	0.011
TDR%	53±9.31	24±2.89	< 0.001
Consolidation diameter	13±2.19	21±1.44	0.07
SUVmax	2.75±0.91	7.16±0.73	0.033
SUVindex	0.98±0.25	3.12±0.36	0.037
MTV	3.6±1.74	5.3±0.49	0.293
TLG	12±7.31	19.5±4.34	0.541

GGO = gound-glass opacity; MTV = metabolic tumour volume; SUV = standardized uptake value; TDR = tumour disappearance rate; TLG = total lesion glycolysis

TABLE 3. Characteristics of patient population grouped by standardized uptake value (SUV)max and SUVindex

	SUVmax			SUVindex		
	< 2.6	≥ 2.6	p	< 0.9	≥ 0.9	p
Total No. patients	12	46		10	48	
Histology						
NIA (7)	4	3		5	2	
IA (51)	8	43	0.028	5	46	0.001
Gender						
male	9	32		6	35	
female	3	14	1.00	4	13	0.458
Smoke						
Yes	10	37		7	40	
No	2	9	1.00	3	8	0.381
T						
Tis–T1a	6	7		6	7	
T1b	5	13		3	15	
T1c	1	17	0.014	1	17	0.011
T2a	0	9		0	9	
Grading						
G1	3	1		3	1	
G2	9	38	0.011	7	40	0.004
G3	0	7		0	7	

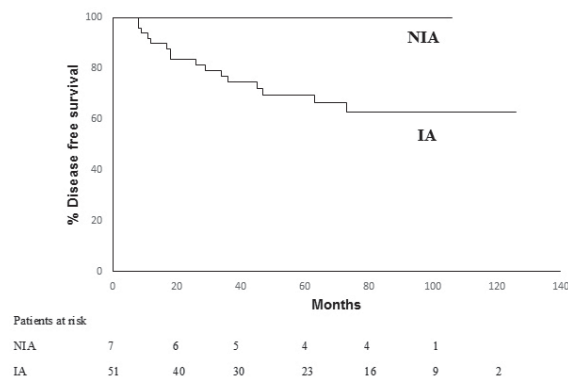IA = invasive adenocarcinoma; NIA – Non-invasive adenocarcinoma

FIGURE 1. Kaplan-Meier disease free survival (DFS) plot for non-invasive and invasive adenocarcinoma (Invasive adenocarcinoma). Five-year DFS (disease free survival) was 100% for non-invasive and 70% for invasive adenocarcinoma (p = 0.115).
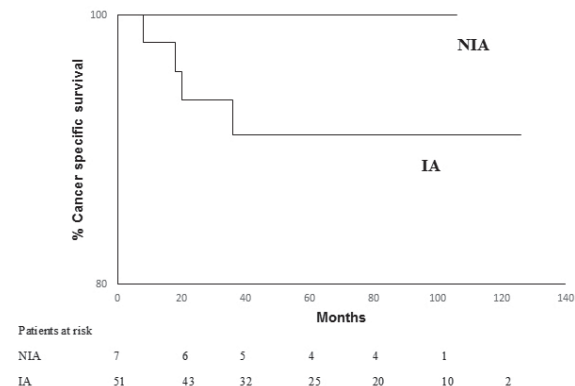

FIGURE 2. Kaplan-Meier cancer specific survival (CSS) plot for non-invasive and invasive adenocarcinoma. Five-year CSS was 100% for non-invasive and 91% for invasive adenocarcinoma (p = 0.46).
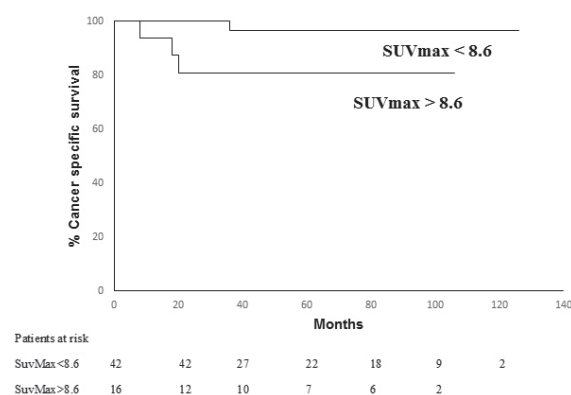
FIGURE 3. Kaplan-Meier cancer specific survival curves according to SUVmax value. Five-year cancer specific survival (CSS) was 97% in patients with a SUVmax < 8.6 and 81% in patients with a SUVmax > 8.6 (p = 0.036).
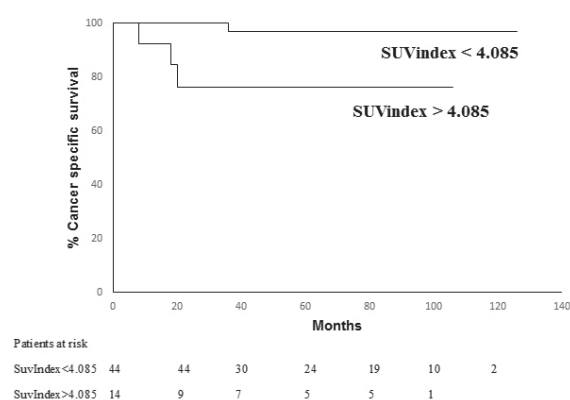

FIGURE 4. Kaplan-Meier cancer specific survival curves (CSS) according to SUVindex value. Five-year CSS was 97% in patients with a SUVindex < 4.08 and 76% in patients with a SUVindex > 4.08 (p = 0.01).
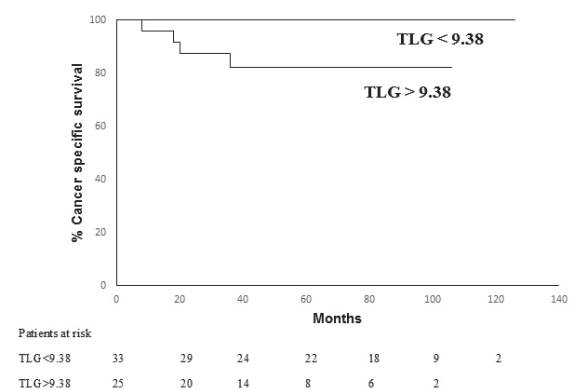

FIGURE 5. Kaplan-Meier cancer specific survival curves (CSS) according to total lesion glycolysis (TLG) value. Five-year CSS was 100% in patients with a TLG < 9.38 and 82% in patients with a TLG > 9.38 (p = 0.02).

under the 9.38 cut-off value tended to have a better survival (p = 0.061). No significant correlation with outcome was identified at multivariate analysis.

Discussion

The current classification of lung adenocarcinoma identifies different histologic subtypes with a clear differentiation between non-invasive and invasive tumours, due to their significantly different prognosis.[1] Preoperative assessment of the invasiveness of stage I adenocarcinoma has become increasingly important for the definition of the ideal surgical treatment. In fact, the standard of care of stage I adenocarcinoma is at present lobectomy with mediastinal lymphadenectomy.[4,15] Conversely, non-invasive lesions may benefit of lung-sparing limited resections. Sublobar resections have in fact been reported as being oncologically equivalent to major anatomical resections in non-invasive and minimally invasive tumours.[2,3] However, tumour invasiveness is hard to be determined at preoperative or intraoperative assessment, since significant limitations exist in the definition of tumour invasiveness in histological specimens obtained by needle biopsy and with intraoperative frozen section.[5,6] Thus, the identification of CT and PET features of non-invasive and invasive tumours may be essential to differentiate invasive and non-invasive lesions, in order to select the optimal surgical treatment.

Previous studies have investigated the role of imaging techniques in distinguishing different adenocarcinoma subtypes. In particular, the proportion of GGO, which reflects the presence of a lepidic pattern, may predict adenocarcinoma invasiveness and prognosis.[7,8,9] In the present retrospective analysis a significant difference in GGO ratio, TDR, SUVmax and SUVindex was observed between non-invasive and invasive adenocarcinoma. These data confirm that CT and PET parameters reflect tumour invasiveness and may be useful for the preoperative differentiation between invasive and non-invasive lesions. Moreover, the combination of PET and CT scan parameters may increase the accuracy of such evaluation.

In our study ROC analysis identified a cut-off value of 40% for GGO ratio to differentiate between invasive and non-invasive adenocarcinoma. These findings are similar to those of a previous study performed by Takahashi et al., who identified a GGO ratio of > 50% to differentiate between non-invasive and invasive adenocarcinoma, data

confirmed by Honda et al.[9,15] More recently, Huang et al. have on the other hand observed that a GGO ratio ≥ 75% is a favourable prognostic factor in resected lung adenocarcinoma.[16] Another CT feature analysed in our study which allowed to differentiate between non-invasive and invasive adenocarcinoma was TDR. In our series a TDR value > 56% was more frequently associated with non-invasive adenocarcinoma. In previous studies Takahashi et al. reported a TDR cut-off between non-invasive and invasive adenocarcinoma of 75%, while Nakayama et al. observed that a TDR > 50% was a favourable prognostic factor in resected pulmonary adenocarcinoma.[9,17] The results of our analysis confirm the role of these CT scan derived parameters in the definition of tumour invasiveness.

We also analysed the role of PET derived parameters in predicting invasive tumour features in resected stage I adenocarcinomas. SUV is the most widely used parameter in the diagnosis and prognostic analysis of lung cancer.[10,11,18] However, despite its usefulness in diagnosis, staging and prognostic assessment, the role of SUV in predicting tumour invasiveness in adenocarcinoma has not been completely investigated. Furthermore, the use of SUV is impaired by two major factors: it depends on biologic and technological variables that limit its reproducibility, and is not representative of the neoplastic volume.[19] Shiono et al. therefore proposed to correct the value of lung cancer SUV using the liver as internal control (SUVindex).[12] The present study demonstrated that SUVindex was also a predictive factor for recurrence in stage I adenocarcinoma. The cut-off values of SUVmax and SUVindex which allowed to differentiate between invasive and non-invasive adenocarcinomas were 2.6 and 0.9, respectively. In a previous study Hattori et al. identified a SUVmax < 1 as a cut-off value to predict adenocarcinoma in situ.[20]

Considering cancer specific survival, the univariate statistical analysis in our series demonstrated that SUVmax, SUVindex and TLG could be identified as prognostic factors. The best cut-off values to differentiate the patients according to prognosis were: SUVmax 8.6, SUVindex 4.08, TLG 9.38. Similar results concerning the SUVmax value were observed in a previous study by Lee et al., where patients with a SUVmax ≤ 9.5 had a significantly higher overall and disease-free survival.[18] Dichotomizing the patients according to the cut-off values of SUVmax, SUVindex and TLG it was therefore possible to stratify the groups of patients according to their prognosis. Patients with parameters over the cut-off value of SUVmax,

SUVindex and TLG had in fact a worse CSS. These data confirm the prognostic role of these PET derived parameters. Besides considering the advantages of SUVindex in terms of reproducibility, it is also important to highlight the role of TLG, which seems to be a promising prognostic factor as it is representative of both tracer uptake and metabolic tumour burden.

Considering the results of our study and previous data of the literature, it is reasonable to try to discriminate preoperatively between non-invasive and invasive adenocarcinoma by integrating CT and PET parameters. The association of CT and PET parameters could in fact allow improving the preoperative differential diagnosis of invasive and non-invasive tumours in order to differentiate the surgical approach. Moreover, PET derived parameters as SUVmax, SUVindex and TLG may play an additional role to that of histology in the definition of the prognosis of patients with stage I adenocarcinoma.

The present study, aiming at focusing the attention on both CT and PET parameters in providing prognostic information in stage I adenocarcinoma, has some limitations, being a retrospective and single-institution study based on a relatively limited series of patients. In particular, the two groups of patients (non-invasive and invasive tumours) were relatively unbalanced, a point which could have limited the results. Even so, the advantage of a single-institution study is that the methodology to assess CT and PET parameters could be homogeneous and clinical data were uniform. Further studies with a larger cohort of patients are nevertheless required to confirm the results of our analysis.

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