Lung Cancer 69 (2010) 187–193

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

The variation of prognostic significance of Maximum Standardized Uptake Value of [18F]-fluoro-2-deoxy-glucose positron emission tomography in different histological subtypes and pathological stages of surgically resected Non-Small Cell Lung Carcinoma

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ARTICLE INFO

Article history:
Received 25 May 2009
Received in revised form 14 October 2009
Accepted 27 October 2009

Keywords:
Non-Small Cell Lung Cancer
Positron emission tomography
Standardized Uptake Value
Surgery
Prognosis

ABSTRACT

Even if the prognostic role of SUVmax of 18-FDG-PET has been largely investigated, many issues regarding its relationship with pathologic staging and histological subtypes still remain controversial. This retrospective study investigated the prognostic significance of SUVmax in 119 completely resected, pathologically proven NSCLC. The SUVmax values resulted significantly related to histological subtypes ($p < 0.001$), histological grading ($p < 0.001$), and pathologic stage ($p < 0.001$). The optimal cut-off value of SUVmax to predict prognosis in the whole series was 6.7 ($p = 0.029$). 2-Year disease-specific survival (DSS) was 91% for SUVmax $\leq$6.7 and 55% for SUVmax >6.7 ($p < 0.001$). SUVmax still remain a significant predictor of survival in Stage IB (2-year DSS of 100% for SUVmax $\leq$6.7; 51% for SUVmax >6.7, $p = 0.016$). The optimal cut-off values of SUVmax to predict prognosis were 5 for adenocarcinoma ($p = 0.027$) and 10.7 for other non-adenocarcinoma NSCLC subtypes ($p = 0.010$). These histologic-specific cut-offs resulted significantly related to survival when stratified for stage: 2-year DSS for Stage IB adenocarcinoma were 100% for SUV $\leq$ 5 and 40% for SUVmax >5 ($p = 0.051$); 2-year DSS for Stage IB non-adenocarcinoma were 83% for SUVmax $\leq$10.7 and 26% for SUVmax >10.7 ($p = 0.018$). Adenocarcinomas showed significantly lower survival results respect to other NSCLC for intermediate SUVmax level (range 5.5–11.3) ($p = 0.021$). High SUVmax resulted an independent negative prognostic factor at multivariate analysis (HR of 15.7, 95% CI of 2.50–98.44, $p = 0.003$). In conclusion, SUVmax represents a significant prognostic factor in surgically resected NSCLC but a great variability between different histological subtypes, even when adjusted for stage, is present and could be considered when planning future trials on prognostic role of FDG uptake.

1. Introduction

Lung cancer is still the leading cause of cancer-related death and, despite major advances in cancer treatment, its prognosis has not significantly improved in the past two decades [1]. Although surgical resection still remains the treatment of choice in early stages Non-Small Cell Lung Cancer (NSCLC), a recent pooled analysis has confirmed the effectiveness of Cisplatin-based adjuvant chemotherapy in completely resected Non-Small Cell Lung Cancer (NSCLC), with an estimated 5-year survival advantage from 4% to 15% [2]. Based on these results, adjuvant chemotherapy is now recommended in Stages II and IIIA NSCLC by the current American Society of Clinical Oncology (ASCO) guidelines [3]. Whether adjuvant chemotherapy could be useful in patients with Stage IB NSCLC is still unclear. However, a significant percentage of patients even at Stage IB disease will experience distant recurrences after a complete surgical resection [4]. Even if several prognostic factors have been studied in NSCLC, to date only stage is a well established prognostic determinant useful for selecting patients for different therapeutic protocols in daily clinical practice [5]. However, NSCLC is a heterogeneous disease including several histological subtypes with different biological behaviour and clinical aggressiveness. For this reason, more accurate and widely adoptable biologic markers

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doi:10.1016/j.lungcan.2009.10.015

are needed to identify patients with early stages NSCLC that could be benefited by adjuvant chemotherapy.

Positron emission tomography with 2-[18F]-fluoro-2-deoxy-D-glucose (18-FDG-PET) is currently a useful diagnostic tool to improve mediastinal and extrathoracic staging in patients with NSCLC being assessed for curative surgical resection [6,7]. The FDG uptake by cancer is related to the glycolysis hypermetabolism of the neoplastic cell and it has been reported that the level of FDG uptake is directly related to rates of tumour growth [8]. Since then, many authors have investigated the prognostic role of FDG uptake in NSCLC using semi-quantitative estimation of tumour metabolism either in surgical series and inoperable advanced disease [9–24]. A recent systematic review and meta-analysis performed by the European Lung Cancer Working party for the IALSC Lung Cancer Staging Project concluded that Standardized Uptake Value (SUV) measurement with 18-FDG-PET is a prognostic factor in patients with NSCLC [25]. However, many unresolved questions are related to the use of SUV as a prognostic marker, in particular regarding the optimal threshold values, the relationship with pathologic staging and different histological NSCLC subtypes.

The aim of the present study was to correlate the maximal Standardized Uptake Value (SUVmax) with different histological NSCLC subtypes and surgical stages and to evaluate its prognostic significance in a selected population of patients with completely resected, pathologically proven NSCLC.

2. Materials and methods

2.1. Patients

This retrospective study includes 119 consecutive patients treated at the Division of Thoracic Surgery of the University of Modena and Reggio Emilia who met the inclusion requirements, from June 2006 to December 2008. The inclusion criteria were the following: a [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET) examination in the preoperative staging, a surgical treatment with curative intent without preoperative induction chemotherapy or radiotherapy, a definitive diagnosis of Non-Small Cell Lung Carcinoma (NSCLC) after a surgical histopathological examination. For all patients we recorded the following features: age at diagnosis, gender, maximal Standardized Uptake Value (SUVmax) on FDG-PET examination, type of surgical procedure, postoperative mortality (within 30 days from the surgical procedure), pathological staging, histological diagnosis and grading, tumour diameter, percentage of bronchioloalveolar carcinoma (BAC) component in mixed adenocarcinoma, type of adjuvant chemotherapy. A surgical treatment with curative intent was considered a complete resection with no residual neoplastic tissue left (R0 resection); patients with incompletely resected tumours (R1 or R2 resection) were not considered in the study. Major anatomical resection was considered the standard procedure. Limited resections (wedge resection or segmentectomy) were reserved for patients with compromised pulmonary function. All the patients underwent ipsilateral mediastinal lymph node dissection. All patients were staged according to the 1997 IASLC/UICC TNM staging system for lung tumours [26].

2.2. FDG-PET/CT examinations

Whole-body FDG-PET/CT was performed with a combined PET/CT scanner (GE Discovery DSTE). Transverse PET resolution is approximately 3-mm full width at half maximum with use of the highest resolution filter. The field of view and pixel size of the reconstructed images are 50 cm and 3.3 mm respectively. This scanner also allows multi-detector row helical CT scanning with 16 array of detectors. The technical parameters used for the CT portion of PET/CT were as follows: a detector row configuration of four sections of 3.75-mm thickness, pitch of 1.375:1, KVp: 120, gantry rotation speed of 0.8 s, and 80–100 mA. The CT examination was used for attenuation correction of PET images.

After at least 6 h of fasting, patients (weight: 73.8 ± 13.8 kg) received an intravenous injection (via catheter to avoid dose infiltration) of 3.7 MBq/kg of FDG (injected dose: 314.5 ± 59.2 MBq). About 50 min later (time elapsed from injection to start of PET imaging: 52.6 ± 6.3 min) a whole-body emission PET scan were acquired from the meatus of the ear to the middle of the thigh. Emission PET scan was obtained with 2.5 min acquisition per bed position (typically, six or more bed positions are obtained) with the scanner operating in the three dimensional mode (3D mode), matrix size 128×128, Voxel size $0.546 \times 0.546 \times 3.75$, reconstruction algorithm: OSEM using 2 iterations.

2.3. PET quantitative analysis

For semi-quantitative analysis of the 18F-FDG uptake, region of interest (ROI) 1 cm diameter were placed manually over the most intense area of 18F-FDG accumulation on the attenuation corrected FDG-PET images. The maximum SUV is selected using the region of interest placed on the axial PET slice with the highest uptake.

SUV bw (body-weight) is according to the following equations, taken from Kim and colleagues [27]:

$$\text{SUV bw} = \frac{(\text{PET image Pixels}) \times (\text{weight in grams})}{(\text{injected dose})}$$

Maximum Standardized Uptake Values (SUVmax) were used in order to minimize the effect of partial volume effects on the uptake values.

2.4. Histopathological examination

All the pathological slides for each patients were reviewed by an expert pathologist (GR) and classified according to the criteria set by the current 2004 World Health Organization (WHO) classification of lung tumours [28]. All the specimens were formalin fixed, paraffin-embedded, and tumours were completely sampled with a mean of 8.5 blocks per tumour (range 3–16), even using whole-mounted sections available for histological review.

Within cases with a diagnosis of adenocarcinoma, the percentage of bronchioloalveolar component (BAC) (as a non-replacing type adenocarcinoma according to the 2004-WHO classification) was assessed. BAC percentage was measured by quoting the percentage of BAC component in each haematoxylin-eosin stained tumour slide at light microscope and then averaging the BAC component across all slides. The process was repeated twice for each case, and the final average was used as the percentage of BAC for a given tumour case.

2.5. Follow up

All patients were followed directly at the Division of Thoracic Surgery with periodic office visits, at the Oncologic Institutes treating them or by telephone interviews with the patient and/or his/her relatives. Data regarding long-term survival were recorded.

2.6. Statistical analysis

The descriptive analysis was expressed in terms of frequency, mean and standard error. Frequencies were compared with the chi-square test for categorical variables; Fischer's exact test was used for small samples. *T*-test and ANOVA were performed when comparing continuous variables. Correlation between SUVmax and