Fluorodeoxyglucose Uptake Measured by Positron Emission Tomography and Standardized Uptake Value Predicts Long-Term Survival of CT Screening Detected Lung Cancer in Heavy Smokers

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Background: Fluorodeoxyglucose-positron emission tomography (FDG-PET) has proven its value in the diagnosis of undetermined pulmonary lesions, lung cancer staging, and assessment of prognosis. Purpose of this study is to clarify whether standardized uptake value (SUV) can predict clinical outcome of computed tomography (CT) screening detected lung cancer.

Methods: We tested the predictive value of FDG-PET using SUV on long-term survival of 34 lung cancer patients, detected from 1035 heavy smokers ≥50 years monitored by annual low-dose CT for 5 years, with a median follow-up of 75 months from diagnosis.

Findings: PET scan was performed in 34 (89%) of 38 lung cancer patients diagnosed during the 5 years of screening and was positive in 32 (94%). Complete resection was achieved in 30 cases (88%), 20 (59%) were pathologic stage I and 23 (68%) were adenocarcinoma. Median SUV was 5.0 overall, being significantly lower in stage I (2.5 vs. 10.1, $p = 0.001$) and in adenocarcinoma (2.5 vs. 13.0, $p = 0.001$). The 5-year survival of lung cancer patients was 100% for SUV levels ≤2.5, 60% for SUV more than 2.5 and less than 8, and only 20% for SUV ≥8 ($p = 0.001$).

Conclusions: FDG-PET using SUV can predict long-term survival of screening detected lung cancer, in a noninvasive manner. Metabolic assessment of biologic behavior might improve the clinical management of CT-detected lung cancer and reduce the risk of unnecessary treatments for indolent disease.

Key Words: FDG-PET, Lung cancer screening, Standardized uptake value.

(*J Thorac Oncol.* 2009;4: 1352–1356)

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Disclosure: The authors declare no conflicts of interest.

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ISSN: 1556-0864/09/0411-1352

Lung cancer causes over 1.3 millions annual deaths worldwide.[1] The overall survival of all detected lung cancers is 15% in the United States and 10% in Europe.[2,3]

In the last decade, nonrandomized trials on spiral computed tomography (CT) screening have provided conflicting results, where the higher proportion of CT detected stage I lung cancer and 90% estimated long-term survival,[4] was counterbalanced by a more than threefold excess of lung cancer diagnosis and no reduction of expected mortality at 5 years,[5] highlighting the risk of overdiagnosis and ineffective early treatment, already shown by the National Cancer Institute trials with chest radiography.[6]

Although the results of on-going randomized trial on CT screening mature, it is important to expand our knowledge on the biology of screening detected lung cancers through pilot CT trials.

Among the various biologic parameters tested in lung cancer patients, the concentration of fluorodeoxyglucose (FDG) metabolic activity, quantitatively expressed by standardized uptake value (SUV), seemed very promising for its ability to predict lung cancer prognosis and potentially modulate treatment, in a noninvasive manner.[7,8] This study was started in Milan in 2000 on 1035 heavy smokers and was the first screening experience to apply systematic use of positron emission tomography (PET) in the diagnostic algorithm of spiral CT, as a replacement of needle-aspiration biopsy for lesions ≥7 mm.[9]

In our lung cancer screening trial, we added PET imaging in an attempt to identify subjects who required further evaluation and eliminate unnecessary testing of benign pulmonary lesions. Furthermore, we aimed at better understanding of the biology of screening detected lung cancers and predicting long-term survival in a noninvasive manner.

This study evaluates the correlation between SUV and clinical features of screening detected lung cancers and the impact of SUV on patient's survival.

MATERIALS AND METHODS

Between June 2000 and June 2001, 1035 current or former smokers, ≥50 years of age, with ≥20 pack-years of smoking history, no prior malignant disease, and adequate

performance status to tolerate pulmonary resection were recruited in this study.[9] Informed consent included written agreement to accept annual spiral CT for 5 years, blood and sputum sampling, an epidemiologic questionnaire, and basic spirometry. Median age was 58 years (range 50– 84), 739 subjects (71%) were men, average tobacco consumption was 26 cigarettes per day for 37 years (median pack-years = 40), and 14% had stopped smoking before accrual.

During the 5 years of screening, a total of 4832 annual CTs have been performed; final compliance at 5th year was 86%, and cumulative recall rate 19%. Lung cancer was diagnosed in 38 cases, 11 at baseline and 27 from 2nd to 5th year, corresponding to 3.7% of enrolled and 20% of recalled subjects. This number includes one case of interval cancer at 4th year.

Baseline and annual single-slice spiral CT was performed without contrast material, with a low-dose protocol 140 kVp and 40 mA; pitch 2; 10 mm collimation; single breath; and reconstruction with lung algorithm at 5-mm interval (General Electric CT Hispeed, 1998). Effective radiation dose was equivalent to 0.7 mSv (0.014 mSv $mGy^{-1}cm^{-1} \times 50$ mGy cm). Calcified nodules or lesions $\leq$5 mm were scheduled for repeat low-dose CT at 1 year. Noncalcified lesions greater than 5 mm were further evaluated by high-resolution contrast CT, with thin-sections (140 kVp and 220 mA; pitch 1; 1 mm collimation) and assessment of contrast enhancement within 3 months of baseline CT.

All patients with nodules of 7 mm or greater underwent a PET-FDG study. In particular, each patient received an intravenous injection of about 100 μCi/kg body weight (3.7 MBq/kg body weight) of FDG in fasting condition for at least 6 hours. At the time of tracer injection, glucose blood level was measured and only patients with glycemia less than 180 mg/dl were injected. One hour after injection, each patient was positioned supine on the tomographic bed with arms over the head, and a whole-body emission scan (5 minutes per bed position) was started covering a field of view from neck to pelvis. Imaging data were acquired with a GE Advance PET scanner (General Electric Medical Systems, Milwaukee, WI; axial field of view of 15 cm and spatial resolution of approximately 5 mm). Transmission scan (3 minutes per bed position) was then performed on thorax region to measure attenuation. Raw data were corrected for measured attenuation using segmented transmission data and then reconstructed in transaxial images using an iterative algorithm with 16 subset and order 4. No correction for partial-volume effect was performed. Parametric SUV transaxial images were obtained normalizing each pixel for injected dose and body weight as follows: SUV = (pixel-by-pixel activity in Bq/ml)/(injected dose in MBq/body weight in kg). Circular regions of interest were manually drawn on transaxial images around the FDG-uptake area, and the maximum SUV was calculated to minimize the partial volume effect. The regions of interest with the maximum value of SUV of different slices of each nodule was considered for statistical analysis, and throughout the study SUV is equivalent to SUV_{max}. Lesions with positive FDG uptake (SUV >2.0) were candidates for biopsy.

Cutoff values for SUV analysis were selected to obtain the best discriminatory power in terms of clinical features (stage and histology) and outcome, with the specific aim of identifying slow-growing tumors and highly metastatic cancers on the basis of metabolic profile.

Survival curves were computed with the Kaplan-Meier method and compared with the log rank test. Statistical analyses were carried out using SAS. Two-sided p values below 0.05 were considered statistically significant. Median follow-up of lung cancer patients was 75 months.

The study protocol followed internal review board principles and was approved by the Ethics Committee.

RESULTS

PET scan was performed in 68 subjects (1.4% of all CTs, 35% of recalled individuals), and in 34 (89%) of the 38 lung cancer patients, being positive in 32 (94%) of them. Adenocarcinoma was the most frequent histology, with 23 cases (68%); other types included six squamous, three small cell, and two large cell carcinomas. Pathologic stage was the following: 18 Ia, 2 Ib (stage I 59%), 3 IIb, 7 IIIa, 2 IIIb, and 2 IV. Complete resection was achieved in 30 of 34 cases (88%).

Four CT-detected cancers could not be assessed by PET because of inadequate blood sugar control or claustrophobia. True-negative studies were 28. Two false-negative cases occurred in well-differentiated adenocarcinomas (8 and 11 mm of size) with significant bronchioloalveolar carcinoma (BAC) component. Three false-positive cases occurred at baseline (bronchiectasis, pulmonary sclerosis with lymphocytic infiltrates, and inflammatory pseudotumor), and three cases in the following 4 years (two nonnecrotising granulomatosis and one organized bronchiolitis obliterans). Overall diagnostic sensitivity of PET was 94%, specificity 82%, accuracy 88%, positive predictive value 84%, and negative predictive value 93%.

Table 1 shows the intensity of SUV by clinical features of lung cancer patients. Based on SUV distribution, the population was divided in three different SUV groups: lower level $\leq$2.5, medium level more than 2.5 and less than 8, higher level $\geq$8.

Median SUV was 5.0 overall, being significantly lower in stage I than in stage II–IV (2.5 vs. 10.1, $p = 0.001$). A further decrease of was observed in the subset of stage I $\leq$15 mm of diameter, where median SUV was 2.0. A similar difference was observed for histology, where adenocarcinomas showed a significantly lower SUV than the other cell types (2.9 vs. 10.1, $p = 0.001$).

TABLE 1. Results of PET

	SUV			
	≤2.5	>2.5, <8	≥8	Median
All cancers	10	11	13	5.0
Stage I	10 (100%)	8 (73%)	2 (15%)	2.5
Stage II–IV	0 (0%)	3 (27%)	11 (85%)	10.1
Adenocarcinoma	9 (90%)	7 (64%)	6 (46%)	2.9
Other types	1 (10%)	4 (36%)	7 (54%)	10.1

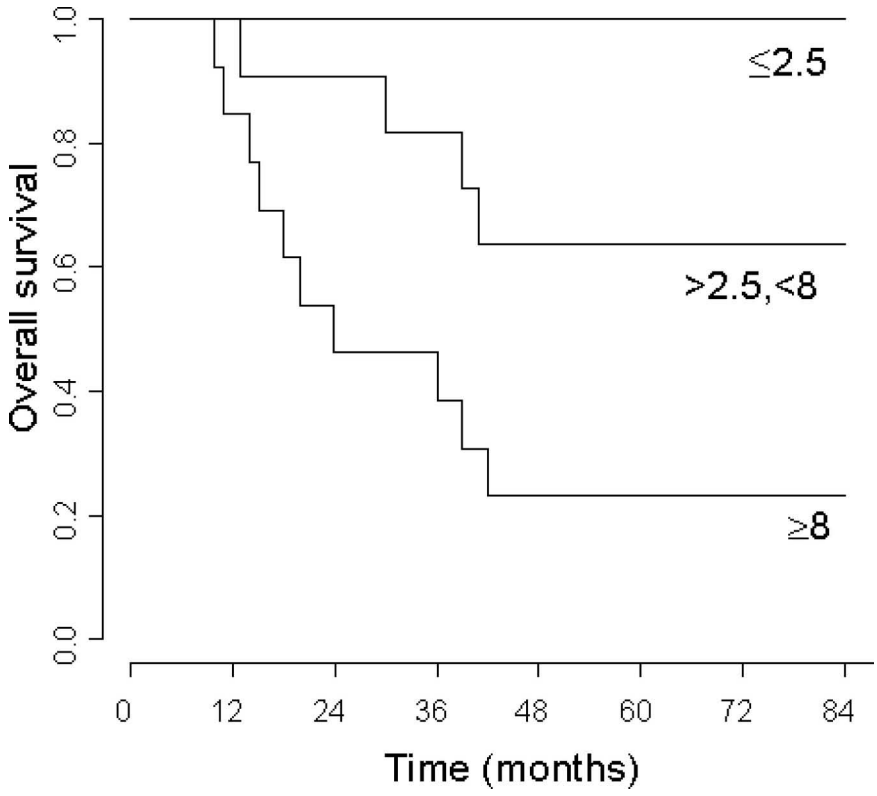

FIGURE 1. Overall survival of lung cancer patients by SUV_{max} values.

Interestingly, all cases with SUV ≤2.5 were stage I and 90% adenocarcinomas. Among them, none was a pure (100%) BAC but the majority showed a mixed pattern with significant (30–90%) BAC component. However, only half of stage I tumors had a SUV ≤2.5. On the contrary, 85% of patients in the higher group (SUV ≥8) were advanced stages and 54% other types than adenocarcinoma.

Figure 1 shows the long-term survival according to SUV levels. With a median follow-up of 75 months, 5-year survival was 100% for SUV levels ≤2.5, 60% for SUV more than 2.5 and less than 8, and only 20% for SUV_{max} ≥8 ($p = 0.001$).

DISCUSSION

The clinical value of FDG-PET in the differential diagnosis of undetermined pulmonary nodules detected by spiral CT has been confirmed by several meta-analyses, showing a sensitivity of 96 to 97% and a specificity of 78 to 82%,[10,11] with the accuracy reaching 92% with PET tomographs[12] and 93% with PET-CT integrated tomographs.[13] The benefit of PET staging has been advocated by several retrospective studies, showing high accuracy in the characterization of multiple pulmonary lesions[14,15] and detection of regional and distant metastases;[16–18] however, the randomized PLUS trial provided definitive evidence that preoperative PET prevented useless surgery in over 20% of deemed resectable patients.[19] Nonetheless, PET imaging is not a replacement for pathologic staging. Nonetheless, PET imaging is not a replacement for pathologic staging and tissue biopsy of positive sites is often required to modify patients management.

In our study, PET has proved effective in the management of nodules ≥7 mm, to avoid complex needle-aspiration biopsies and achieve final diagnosis in less than 3 months. The 5-year results of our CT screening program are consistent with those observed in the Mayo CT trial,[20] with a cumulative lung cancer detection rate of 3.7% (0.7% per year), a resectability rate of 87%, and a proportion of stage I disease of 63%, and confirm the validity of a diagnostic algorithm that considered nonsuspicious all lesions with maximum diameter of 5 mm.

At the end of 5th year, PET had been applied only to a small minority (1.4%) of all low-dose spiral CTs, with diagnostic accuracy of 86% at baseline and 90% thereafter, with high sensitivity (94%) and negative predictive value (93%). As expected, main limiting factors in early detection were false-positive findings because of inflammatory lesions and false-negative findings because of small size adenocarcinomas with predominant BAC component.[21–24] However, the apparent diagnostic failure of PET in small cancers, with predominant BAC features,[24] may turn positive when quantification through SUV is performed with prognostic purposes. Only four CT-detected cancers (11%) could not be assessed by PET because of inadequate blood sugar control or claustrophobia.

Although TNM classification, with its continuous refining,[25] remains the fundamental instrument to assess lung cancer prognosis, there is a growing demand for quantitative and qualitative prediction of biologic aggressiveness across anatomic TNM stages, to improve clinical management and implement targeted therapies. This is particularly true for

screening detected cases, where it will become essential in the future to discriminate indolent disease from potentially metastatic cancer.

A systematic review on predictive and prognostic significance of SUV at the time of lung cancer diagnosis, showed in all the 11 included studies a significantly longer survival for patients with low FDG uptake values,[26] and SUV emerged as an independent prognostic value at multivariate Cox analysis in most of them. The review also pointed out the difficulty to establish a consistent and reliable cutoff value for SUV, given the heterogeneity of clinical series, variability in the technique applied for the measurement of FDG uptake by the various Institutions, and retrospective study design. Moreover, in the majority of reviewed papers, patient's follow-up was short and dichotomised comparison was based on median or 2-year survival. A literature meta-analysis, based on 1474 patients from 13 studies (including those reported in the above discussed review), calculated an overall hazard ratio of 2.27 (95% CI: 1.70–3.02) for higher maximum SUV value, which remained substantially the same (HR 2.08, CI: 1.43–3.04) after exclusion of the studies applying "best" cutoff values.[27] A recent study testing partial volume-corrected SUVs failed to show the independent prognostic role of SUV in resectble NSCLC: poorer survival of patients with SUV more than 7 was in fact associated with tumor stage.[28] This study, however, used a different tracer (18F-FLT), which evaluates cell proliferation rather than glucose metabolism, and their conclusions may not be applicable to FDG uptake.

The intrinsic limitations of SUV are well described in the literature and include its dependency on lesions dimensions, location and motion, PET tomograph characteristics, and time delay between FDG injection and uptake measurement. Nonetheless, our study has unique clinical features: it is the first screening trial to include PET in the diagnostic protocol from the beginning of the trial, cancer patients are unselected and nearly all cases occurring in the cohort during the first 5 years were evaluable, all PET scans have been performed using the same PET scanner and analyzed by the same experienced observer (CL). As a matter of fact, a previous report on the use of PET in a CT screening trial,[24] only included 22 of 62 (35%) CT detected lung cancers.

Moreover, the follow-up was sufficiently extended (median 74 months from diagnosis) to assess long-term outcome in a reliable manner.

The choice of dividing patients in three groups corresponds to a major biologic question in lung cancer screening: to identify patients with potentially benign or indolent disease on one side, and those with very aggressive disease, escaping from early detection filter, on the opposite side. Cutoff values selected to obtain the best discriminatory power are not at all arbitrary: the SUV level of 2.5 has been considered a diagnostic threshold for malignancy, and the level of 8 represents the largest gap in the distribution of values among remaining patients. As a matter of fact, such threshold levels approached random tertile distribution.

The resulting differences in long-term survival are quite striking: $SUV_{max} \leq 2.5$ define a homogeneous population of small size (median diameter 11 mm, range 5–16), stage Ia tumors, mostly adenocarcinomas, whose 100% survival suggests an essentially nonmalignant behavior.[28] Conversely, SUV more than 8 defines a group of mostly advanced cancers (only 8% stage Ia), whose 20% survival is indicative of a highly metastatic biologic profile, despite annual CT monitoring.

If on-going randomized trials will confirm the occurrence of significant overdiagnosis, as a consequence of chest CT monitoring in heavy smokers, FDG-PET could be used to reduce the risk of unnecessary treatments, such as radical lobectomy for indolent disease, and implement targeted systemic therapies for early metastatic lung cancer.

In conclusion, our results demonstrate that, by using the present protocol, FDG-PET using SUV can predict long-term survival of screening detected lung cancer, and metabolic assessment of biologic behavior could be used in the future to improve the clinical management of CT-detected lung cancer.

ACKNOWLEDGMENTS

Supported by the Italian Ministry of Health (Ricerca Finalizzata), the Italian Association for Cancer Research (AIRC), and the European Institute of Oncology grants. The authors thank Prof. Massimo Bellomi, MD, Dr. Elvio De Fiori, MD, and Dr. Cristiano Rampinelli, MD from the Division of Radiology of the European Institute of Oncology (IEO), for the revision of spiral CT data, and Prof. Giuseppe Pelosi, from the Division of Pathology of the IEO, for the revision of pathologic diagnoses.

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