Original Article

^{18}F-Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography Interpretation Criteria for the Assessment of Therapeutic Response in Patients with Advanced Stage of Lung Cancer: Inter-Reader Reliability, Accuracy, and Survival Outcomes

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Abstract

Aim: ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG-PET/CT) is useful in the evaluation of lung cancer (LC), both for staging and therapy assessment. However, for the evaluation of treatment response, shared criteria are not available. We proposed a 3-point score, similar to Deauville-score and compared its diagnostic accuracy with Hopkins criteria for the evaluation of treatment response in LC to validate a qualitative and simpler interpretation system. **Methods:** We retrospectively included 93 patients with advanced stage (III-IV) LC who underwent ^{18}F-FDG-PET/CT after first-line treatment. Positron emission tomography/computed tomography (PET/CT) scans were interpreted according to a 3-point scale-like Deauville score criteria (score 1 = uptake lower than blood-pool activity; score 2 = uptake higher than blood-pool but lower than liver activity; score 3 = uptake higher than liver). Inter-reader variability was assessed using percent agreement and kappa statistics. Kaplan–Meier plots with a Mantel-Cox log-rank test were performed, considering death as the endpoint. **Results:** The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of like Deauville-like score criteria were 82,76% (95% confidence interval [CI] 70.5%–91.4%), 80% (95% CI 28.3%–99%), 97.9% (95% CI 89.2%–99.6%), 28.6%(95% CI 16.38%–44.9%), and 82.5% (95% CI 70.9–90.9%), respectively. Applying Hopkins criteria score we obtained sensitivity, specificity, PPV, NPV, and accuracy of 81% [95% CI 68.6%–90.1%), 100% (95% CI 47.2–100%), 100% (95% CI %), 31.3% (95% CI 21.0%–43%), and 82.5%(95% CI 70.9%–90.9%), respectively. There was a high agreement between the two readers both using Hopkins criteria (k = 0.912) and like-Deauville-score criteria (k = 0.956). Applying 3-point-scale criteria, patients with positive PET/CT after therapy had significantly shorter lower survival (P = 0.0021). **Conclusion:** The application of 3-point scale criteria for posttherapy assessment in patients with advanced stage of LC represents an easy and reproducible method with optimal inter-observer agreement and great PPV and accuracy.

Keywords: *^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography, lung cancer, Hopkins criteria*

Introduction

Lung cancer (LC) remains the most significant solid malignancy with high cancer-related mortality. Globally, LC cases and deaths are rising and it's incidence continues to decline twice as fast in men as in women.[1] It is estimated as the most frequent cancer and cause of cancer death in men and women combined[2,3] and in women, the third most common cancer type and the second most common cause of cancer death.[2,3] It has become the most common cause of cancer death in men ages 40 and older and women ages 60 and older.[1]

The two main types of LC are small cell LC (SCLC) and non-SCLC (NSCLC); NSCLC accounts for approximately 85% of all cases of LC.[4,5] NSCLC is further divided into lung adenocarcinomas (ADC), squamous cell carcinoma (SCC), and large cell carcinoma based on their histological features.[6]

^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) is the standard modality for staging, treatment response monitoring and prognosis prediction for a variety of tumors, including NSCLC.[7,8] Measurement

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of tumor glucose metabolism as a marker of tumor activity is valuable with 18F-FDG PET-CT and it is useful not only for staging but also in the assessment of treatment's response.

PET/CT-based quantitative parameters have been proposed as reliable indicators of survival in patients with LC in both pretreatment and posttreatment settings.[9-13] In the posttherapy setting, several studies point to the usefulness of monitoring the treatment response based on decreased SUVs on serial ^{18}F-FDG PET/CT imaging of the primary tumor.[9,14] Higher volume of residual metabolically active tumor after definitive treatment appears to be associated with poorer survival.[15,16] As the changes in tumor glucose metabolism induced by chemotherapy are predictive for patient outcome, the use of ^{18}F-FDG PET/CT can help to stratify patients by probability of progression-free and overall survival.

Quantitative assessments of ^{18}F-FDG PET/CT imaging are useful in the study of patient's outcome, however, even qualitative evaluation may add value to clinical assessment and it can be easily and immediately understood both by referring physicians and clinicians. It is mandatory to find a way to make as better reproducible as possible qualitative assessments of ^{18}F-FDG PET/CT imaging and the aim of our study was to find a basic and clearly method which can validate qualitative imaging assessments making it replicable and useful for patients outcome analysis.

A positron emission tomography/computed tomography (PET/CT)-based visual interpretation system, Hopkins criteria, has been previously accepted to assess therapy response and survival in head and neck SCC and even in LC.[17] Our aim was to compare the reproducibility and the accuracy of Hopkins criteria with a new proposed Deauville-like score criteria for the evaluation of treatment response in advanced stage LC.

Methods

Our study was a retrospective, single-center cohort analysis, including patients with LC who underwent 18F-FDG PET/CT scans for posttherapy assessment. According to histopathologic results we selected advanced stage of LC at diagnosis (III or IV stage) which were assessed after different treatments strategies from September 2014 to January 2020.

18F-FDG PET/CT was performed in all cases with a glucose level lower than 150 mg/dL. An activity of 3.5–4.5 MBq/Kg of 18F-FDG was administered intravenously and images were acquired at least 60+/-10 min after injection from the skull base to the mid-thigh on a Discovery ST and 690 PET/CT tomographs (General Electric Company-GE-Milwaukee, WI, USA) with standard parameters (CT: 80 mA, 120 Kv without contrast; 2.5–4 min per bed-PET-step of 15 cm); the reconstruction was performed in a 256 × 256 matrix and 60 cm field of view.

Patients were asked to void before imaging acquisition, no oral or intravenous contrast agents were used during 18F-FDG-PET; a written consent was obtained before the studies.

Visual analysis was carried out by two nuclear medicine physicians (MG, DA) with experience in this field, who were blinded to all other patient data. When in doubt, a third nuclear medicine physician (FB) with high experience helped in the assessment of PET/CT scans. They analyzed PET/CT images using the 5-points Hopkins score,[17] as follows:

- Score 1: focal ^{18}F-FDG uptake less than or equal to mediastinal blood pool
- Score 2: focal ^{18}F-FDG uptake greater than mediastinal blood pool but less than liver
- Score 3: Diffuse ^{18}F-FDG uptake greater than mediastinal blood pool or liver
- Score 4: Focal ^{18}F-FDG uptake greater than liver
- Score 5: Focal and intense ^{18}F-FDG uptake greater (2–3 times) than liver.

Scores 1, 2, and 3 were considered negative and scores 4 and 5 were considered positive for residual tumor.

Moreover, to simplify images interpretation and to reduce the operator-dependent evaluation, we proposed a 3-points evaluation similar to Deauville score (called Deauville-like score) regarding the comparison with the liver and the blood-pool but based on only three points; qualitative assessment of ^{18}F-FDG uptake in the primary tumor lesion is described as:

- Score 1: uptake lower than blood-pool activity
- Score 2: uptake higher than blood-pool but lower than liver
- Score 3: uptake higher than liver.

Scores 1 and 2 were considered negative and scores 3 were considered positive for residual tumor.

Visual activity in the mediastinal blood pool and in the liver is taken as the background blood pool for reference. Overall assessment is denoted by overall score, which is the highest score among the scores for the primary tumor, locoregional and distant metastasis lesions, if present.

Reference standard

A combination of clinical/imaging follow-up (CT and/or subsequent PET/CT) for a median period of 16 months after restaging 18F-FDG PET/CT and/or histopathology (when available) was taken as reference standard. Because histopathological confirmation of all lesions was not ethically and clinically feasible, histopathology was available only for 6 studies. Lesions demonstrating increase in size on radiologic follow-up examinations and/or increase in 18F-FDG uptake on subsequent PET/CT were considered as true positive; also lesions showing response to therapy were taken as true positive. Instead, lesions not showing any change or decrease in size and/or 18F-FDG uptake without any treatment were considered as false positive.

Statistical analysis

All statistical analysis was performed using MedCalc Software version 17.1 for Windows (Ostend, Belgium). The descriptive analysis of categorical variables comprised the calculation of simple and relative frequencies. The numeric variables were described as mean, minimum, and maximum.

Inter-reader variability was assessed using percent agreement and kappa statistics. Kaplan-Meier plots with a Mantel-Cox log-rank test were performed, considering death as the endpoint.

A $P \leq 0.05$ was considered as statistically significant.

Using the final diagnosis as a reference, sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy were calculated based on Bayes's law, with 95% confidence intervals.

OS was calculated from the date of baseline 18F-FDG PET/CT to the date of death from any cause or to the date of last follow-up. Survival curves were plotted according to the Kaplan–Meier method and differences between groups were analyzed by using a two-tailed log-rank test. Cox regression was used to estimate the hazard ratio and its confidence interval (CI).

Results

Population features

In our study, 63 patients with biopsy-proven LC were included (37 men and 26 women) and the main clinical characteristics are described in Table 1. Some patients underwent more than one ^{18}F-FDG-PET/CT evaluation during follow-up period, to evaluate therapy response. Of the total number of 93 ^{18}F-FDG-PET/CT scans analyzed, the most common histological types of LC evaluated were ADC and SCC, 31 and 15 patients, respectively, but there were also 15 patients with SCLC, 1 patient with poorly-differentiated carcinoma and 1 patient with ADC plus microcitoma. The patients received different therapies in our center as they were treated with surgical resection, chemotherapy (CHT), radiation therapy (RT), or a combination of any of these treatment modalities; particularly nine patients received surgery and chemotherapy, six patients surgery, chemotherapy and radiotherapy, 16 patients both chemo-and radiotherapy (1 of them had a relapse after therapy), 26 patients only CHT, 4 patients only RT, and finally one patient received all the treatment modalities and gamma-knife therapy.

PET/CT evaluation were applied at least after 4 weeks from chemotherapy treatment and 12 weeks after radiotherapy and patients were followed up for a median of 18.5 months (range 2–139 months).

Table 1: Main patients characteristics

Characteristics	*n* (%)
Sex	
Women	26/63 (41)
Men	37/63 (59)
Median age (years)	61.5
≤60	19 (30)
>60	44 (70)
History of smoking or exposition (+)	33/63 (52)
Histology	
Adenocarcinoma	31/63 (49)
Squamous cell carcinoma	15/63 (24)
Small cell LC	15/63 (24)
Poorly-differentiated carcinoma	1/63 (1)
Adenocarcinoma + microcitoma	1/63 (1)
Treatment	
SR + CHT + RT	6/63 (10)
SR + CHT	9/63 (14)
SR + RT	1/63 (2)
CHT + RT	16/63 (25)
RT	4/63 (6)
CHT	26/63 (41)
SR + CHT + RT + gammaKnife	1/63 (2)
PET/CT results	
Negative	23/93 (25)
Positive	70/93 (75)

SR: Surgery, CHT: Chemotherapy, RT: Radiotherapy, PET/CT: *Positron emission tomography*-computed tomography, LC: Lung cancer

The sensitivity, specificity, PPV, NPV, and accuracy of like Deauville-like score criteria were 82.76% (95% confidence interval [CI] 70.5%–91.4%), 80% (95% CI 28.3%–99%), 97.9% (95% CI 89.2%–99.6%), 28.6% (95% CI 16.38%–44.9%), and 82.5% (95% CI 70.9%–90.9%), respectively. Instead applying the Hopkins criteria score, we obtained sensitivity, specificity, PPV, NPV, and accuracy of 81% [95% CI 68.6%–90.1%), 100% (95% CI 47.2%–100%), 100% (95% CI %), 31.3% (95% CI 21.0%–43%), and 82.5% (95% CI 70.9%–90.9%), respectively [Table 2].

According to Hopkins Criteria, 9 examinations resulted as score1, 6 as score 2, 13 as score 3, 20 as score 4, and finally, 45 were classified as score 5. According Deauville-like criteria, 13 PET/CT examinations were classified as score 1, 12 as score 2, and 68 as score3. According to Deauvile-like criteria, 48 examinations resulted finally as true positive, 1 as false positive, 10 as false negative, and 4 as true negative. According to Hopkins criteria, 47 PET/CT were finally classified as true positive, 11 as false negative, and 5 as true negative.

There was a high agreement between the two readers both using Hopkins criteria (k = 0.912) and like Deauville score criteria (k = 0.956).

Table 2: Comparison of the accuracy between the two interpretation criteria

	Percentage (95% CI)	
	Deauville-like score	Hopkins score
Sensitivity	82.76 (70.5-91.4)	81 (68.6-90.1)
Specificity	80 (28.3-99)	100 (47.2-100)
PPV	97.9 (89.2-99.6)	100
NPV	28.6 (16.38-44.9)	31.3 (21-43)
Accuracy	82.5 (70.9-90.9)	82.5 (70.9-90.9)

CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

Survival analysis

After a median follow-up of 16 months (range 1–51 months), 40 patients died and among them, 34 had a positive Hopkins score evaluation and the same number of positive Deauville-like score assessment.

The remaining 23 patients were alive at the last follow-up time; about them, 14 had a positive PET/CT according to Hopkins criteria, while 16 according to Deauville-like criteria.

Applying Deauville-like criteria, patients with positive PET/CT after therapy had significantly shorter lower survival compared to negative scan (P = 0.0036); while applying Hopkins criteria, the difference was almost significant (P = 0.052) [Figure 1].

Discussion

After the initial diagnosis of NSCLC, accurate TNM staging of LC is crucial for determining appropriate therapy. Most patients with stages I to II NSCLC benefit from surgical resection, whereas patients with more advanced disease are candidates for nonsurgical treatment. Conventional clinical staging is most often performed with CT of the thorax and upper abdomen. Nevertheless, CT imaging has limited sensitivity for microscopic metastatic disease and is frequently unable to discriminate between mediastinal lymph nodes that are enlarged owing to malignancy and those that are enlarged owing to benign reactive hyperplasia.[18-22] In contrast, ^{18}F-FDG PET/CT has been shown to have greater sensitivity for the detection of metabolically active malignant disease and can lead to changes in initial staging and treatment plans for NSCLC when used in combination with conventional work-up.[21,23]

18F-FDG is a nonspecific tracer which is taken up in any process with increased glucose consume and due its nonspecificity, many conditions may affect a correct interpretation and final diagnosis.

To avoid this possibility, quantitative parameters have been wildly approved with SUV parameters evaluation in the pre-and posttherapy settings; monitoring a decreasing value of SUV of the main lesions helps to understand tumor's evolution and its probably response to therapy. According to previous different studies, ^{18}F-FDG PET/CT has been approved as a standard modality for staging, treatment response monitoring, and prognosis prediction for many tumors, including NSCLC.

As quantitative parameters assessment is useful in the interpretation of PET/CT scans, even qualitative analysis may add value in the final response as it is immediately understood even by physicians and clinicians. However, standardized criteria are lacking.

Our aim was to seek interpretation criteria that could be objective, reproducible, and easily understood by both referring physicians and clinicians.

Treatment response assessment plays a vital role in the management algorithm of patients with lung carcinoma. Beyond the established anatomic imaging-based criteria such as the Recist and World Health Organization criteria,[24] which have some limitations, particularly in assessing the activity of cancer therapies that stabilize disease, new uniform strategy for therapy response is needed. Previous studies have shown that qualitative PET parameters provide valuable prognostic information in LC.[11,15,17,25,26]

Taking examples from Hopkins criteria, previously accepted for LC, and Deauville-score accepted for treatment response, especially in lymphoma,[27] and recently approved in inflammatory diseases as in endocarditis,[28] we propose a simpler three-points score which can be easily used by referring physicians in PET/CT assessment and equally easily understood by clinicians in the evaluation of lung patients response to therapy.

A common pitfall of a qualitative approach is intermediate patterns of tracer uptake, where it is not easy to correctly define certain positive or negative results and this classification in the gray zone is still challenging. Our aim was to identify a simpler score, with only three points of evaluation which may help and facilitate images interpretation and makes easily reproducible images interpretation between readers.

According to Deauville-like criteria, still positive PET/CT after therapy has the same accuracy, when compared to Hopkins criteria, to predict patient's survival; its added value is a simpler strategy in the evaluation which may simplify and help clinicians's assessment. A three-points scale may be more immediate in the qualitative assessments of images, as it excludes doubts in case of inflammatory disease or uncertain uptake.

Deauville-like three points scale has a better sensitivity than Hopkins criteria, while has an almost comparable PPV and a low NPV as well.

Even using Deauville-like 3-points scale, positive PET/CT after therapy has a great value in the assessment of patients

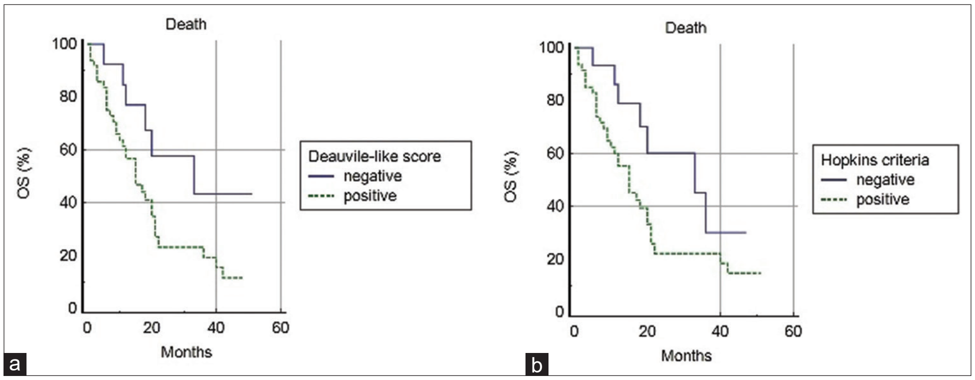

Figure 1: Kaplan–Meier survival plot by positron emission tomography/computed tomography after treatment. Overall survival (OS) between patients according Deauville-like criteria (a) and Hopkins criteria (b)

survival, as it reveals shorter lower outcome [Figure 1]. Applying Deauville-like criteria, patients with positive PET/CT after therapy had significantly lower survival compared to negative scan (P = 0.0036); while applying Hopkins criteria, the difference was almost significant (P = 0.052).

Deauville-like three-points scale may add useful information to clinicians in the evaluation of posttreatment response, as this approach has been widely tested and validated in different solid tumors, such as in lymphoma. Simplifying referring physicians evaluation, comparing tracer uptake in tumor foci and in normal structures such as blood pool or liver, could be a simple, qualitative and reliable interpretation system with great accuracy.

Our study has several limitations, like the relatively low sample of patients included and the retrospective design of the study, and the heterogeneity of patients included (histology, treatment). It would be useful a further large multicenter study to validate the proposed method.

Conclusion

The use of 3-point scale criteria similar to Deauville score for posttherapy assessment in patients with advanced stage of LC represents an easy and reproducible method with s high inter-observer agreement, PPV, and accuracy; moreover, it is easily understood by referring physicians.

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Conflicts of interest

There are no conflicts of interest.

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