Journal of Nuclear Medicine, published on February 2, 2016 as doi:10.2967/jnumed.115.165480

Title: ^{18}F-Fluorodeoxyglucose PET/CT: Therapy Response Assessment Interpretation (Hopkins Criteria) and Survival Outcomes in Lung Cancer Patients

Running Head: Lung Cancer: PET/CT Therapy assessment

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Word Count: 3, 555 **Financial disclosure:** None

Abstract

The purpose of this study was to evaluate the value of a FDG-PET/CT based Hopkins interpretation system to assess the therapy response and survival in lung cancer.

Methods: This is an institutional review board approved, retrospective study. A total of 201 patients with biopsy-proven lung cancer, who had a therapy assessment FDG-PET/CT, within 6 months (mean 7.5 weeks) of completion of treatment were included. Patients were primarily treated with surgical resection, chemotherapy, radiation therapy or a combination of these treatmens. PET/CT studies were interpreted by two nuclear medicine physician and discrepancies were resolved by a third reader. The studies were scored using a qualitative 5-point scale for the primary tumor, mediastinum, distant metastatic site, if present, and overall assessment. Scores 1, 2, and 3 were considered negative and scores 4 and 5 were considered positive for residual disease. Patients were followed for a median of 12 months (up to 128 months). Kaplan-Meier plots with a Mantel-Cox log-rank test were performed considering death as the endpoint.

Results: Overall, the PET/CT studies were positive in 144 (71.6%) and negative in 57 (28.4%) of patients. There was substantial agreement between two readers (R1, R2) with K= 0.78 (P< 0.001). The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of the Hopkins scoring system were 89%, 80%, 92.8%, 71.4% and 86.7%, respectively. Overall, PET/CT resulted in

starting a new treatment plan in 70.8% of patients with positive residual disease on therapy assessment PET/CT. There was significant difference in OS between patients who were categorized as positive in comparison to those who were categorized as negative (HR= 2.12, 95% confidence interval= 1.44-3.12), which remain significant after adjustment for disease stage, prior clinical suspicion and primary treatment. Subgroup analysis according to the tumor histology showed that positive Hopkins scoring could significantly predict the OS both in small cell lung cancer (HR= 2.88, Logrank P= 0.02) and non-small cell lung cancer (HR= 2.01, Logrank P= 0.001). Similarly, there was a significant difference in OS between patients with positive and negative Hopkins score both in those who had surgical resection as part of the primary treatment (HR= 6.09, Logrank P < 0.001) and those who treated with chemotherapy +/- radiation (HR= 1.60, Logrank PP=0.02).

Conclusions: The 5-point qualitative therapy response interpretation for lung cancer has substantial inter-reader agreement, high accuracy, and could significantly predict survival in lung cancer, irrespective of tumor histology and treatment modality.

Key words: PET/CT; lung cancer; therapy assessment; survival

Introduction

Lung cancer accounts for about 13% of all cancer diagnoses in the United States. The American Cancer Society has estimated 221,200 new cases of lung cancer in the year 2015. An estimated 158,040 deaths are expected to occur due to lung cancer in 2015, accounting for about 27% of all cancer deaths, making lung cancer accountable for more deaths than any other cancer in both men and women [1, 2]. The 5-year survival rate in lung cancer patients is less than 15% [2].

Fluoro-deoxyglucose (FDG)-PET/CT is well integrated in the routine staging of lung cancer patients. The use of FDG-PET/CT could provide more accurate staging of nodal and metastatic sites compared to CT and has a high negative predictive value [3-5]. Studies have also shown that pre-operative staging PET/CT leads to change in the treatment planning, reduce the frequency of futile thoracotomies and the total number of thoracotomies [6,7]. FDG-avidity and PET-based quantitative parameters suggested as prognostic indicators of survival in patients with lung cancer both in pre-treatment and post-treatment setting [8-12]. In the post-therapy setting, a number of studies point to the usefulness of monitoring the treatment response based on decreased SUVs on serial FDG-PET imaging of the primary tumor [4, 8]. Higher volume of residual metabolically active tumor after definitive treatment appears to be associated with poorer survival [13, 14]. However, the routine use of PET/CT for response evaluation in lung cancer is currently not recommended in guideline [4].

A qualitative therapy response assessment system that is simple and easily reproducible which can predict treatment response and outcome will be of great help in this setting. Our previous work has shown that employment of such a criterion for PET/CT therapy response assessment in patients with head and neck squamous cell carcinoma has substantial inter-reader agreement and could serve as a surrogate marker for prediction of outcome [15]. The objective of this study was to validate the 'Hopkins Criteria' for therapy response assessments for FDG-PET/CT and establish its predictive value for survival outcome in lung cancer.

Materials and methods

Eligible Patients and Follow-up

This was an Institutional Review Board approved retrospective study performed under the waiver of informed consent. The guidelines of the Health Insurance Portability and Accountability Act were followed. Two hundred and one histopathology confirmed lung cancer patients who were evaluated and treated at our institution from May 2000 to January 2013 were included. The patients were treated with surgical resection, chemotherapy, radiation therapy or a combination of any of these treatment modalities. Patients underwent a post-therapy ^{18}F-FDG-PET/CT within 24 weeks of treatment completion. The post treatment ^{18}F-FDG PET/CT studies were requested at the treating clinician's discretion for therapy response assessment. FDG-PET/CT studies performed after

24 weeks of treatment completion were considered as a follow-up study rather than a post treatment assessment and were excluded. Patients with a second primary malignancy were also excluded.

Image Analysis

Post-therapy Assessment PET/CT Interpretation Criteria (Hopkins Criteria).

The studies were scored using a qualitative 5-point scale, for the primary tumor, locoregional disease in the mediastinum and distant metastatic sites. The activity in the mediastinal blood pool was taken as background blood pool for reference. Focal ^{18}F-FDG uptake less than or equal to mediastinal blood pool was scored as 1, consistent with complete metabolic response. Focal ^{18}F-FDG uptake greater than mediastinal blood pool but less than liver was scored 2, likely complete metabolic response. Diffuse ^{18}F-FDG uptake greater than mediastinal blood pool or liver was scored 3, likely inflammatory changes. Focal ^{18}F-FDG uptake greater than liver was scored 4, likely residual tumor. Focal and intense ^{18}F-FDG uptake greater (2 to 3 times) than liver was scored 5, consistent with residual tumor (Fig. 1).

Definition of Positive and Negative PET/CT Studies.

Based on the qualitative 5-point scale, the studies were grouped as positive or negative for the primary tumor, mediastinum, and distant metastatic lesions. Overall assessment is denoted by the overall score, which is the highest score among the scores for the primary tumor, locoregional and distant metastatic

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

Reader Qualifications

The PET/CT studies were retrieved from institutional archiving system (Johns Hopkins Hospital PACS) and were reviewed using MimVista viewing platform (version 6.3.2, MimVista Software Inc., Cleveland, Ohio, USA). All images were interpreted independently by 2 board-certified nuclear medicine physicians (reader 1, reader 2) blind to patients' outcome, and scored according to the 5 point Hopkins scoring criteria (Table 1). Reader 1 (R.W) is completing a two year PET/CT fellowship after nuclear medicine board certification. Reader 2 (E. M) is a current T32 PET/CT research fellow after nuclear medicine residency and board certification. Any discrepancies were adjudicated by a third reader (R. S) who is an associate professor of Radiology, dual board-certified in Nuclear Medicine and Radiology. The final scan report were determined if all readers or 2 of the 3 readers agreed on the dichotomous classification (i.e., positive or negative scores).

Outcome Measures

Histopathologic confirmation of the lesions identified on the PET/CT, alternative imaging modalities such as CT/Magnetic Resonance Imaging (MRI) or clinical follow-up of 6 months after PET/CT were considered as the reference standard. The sensitivity and specificity, positive predictive value, negative

predictive value and accuracy of the post-therapy PET/CT assessment criteria along with 95% CIs, were calculated by constructing the 2 × 2 contingency table (cross-relating PET/CT results of the reference standards). Overall Survival (OS) was defined as the time (months) interval between the date of the post-therapy FDG-PET/CT study and the date of death. The date of the scan was recorded from the electronic medical record of each patient and the date of death was extracted from the electronic medical records or a public registry of death[16]. The survival data for patients who were alive were censored at the last follow-up date at our institution.

Statistical Analysis

Descriptive values are presented as mean [standard deviation (SD)] or median [25th, 75th range] if the data was not in a normal distribution. Categorical variables were presented as frequency (percentage). The Cohen κ coefficient (κ) was calculated to measure inter-reader agreement. Survival probabilities were generated using Kaplan–Meier survival curves and compared using the Mantel-Cox log-rank test. Uni-variate and multivariate Cox regression analyses were performed considering death as the endpoints. Subgroup analysis was performed to assess the impact of tumor histology and prior treatment on the prognostic value of Hopkins scoring. The statistical significance level was set at $p < 0.05$. Statistical analysis was performed using IBM SPSS Statistics 22.0.

RESULTS

Patient Characteristics and Follow-up

Two hundred and one patients were included in the study (116 men, 85 women; mean age ± SD, 63 ± 11years). A history of smoking was present in 156 patients (77.6%). The histology of the primary lung malignancy was identified as small cell lung cancer in 34 patients (16.9%) and non-small cell lung cancer in 167 patients (83.1%). The demographic details of the 201 patients included in the study have been summarized in Table 1. The median follow-up of these patients was 12 months (range, 0-128 months) after completion of the post-therapy assessment PET/CT.

Time Interval of Post-therapy PET/CT

Therapy assessment FDG-PET/CT was performed between 1 and 24 weeks after completion of treatment. The average interval between the date of completion of treatment and the post treatment ^{18}F-FDG PET/CT study was 7.5 weeks (median 5 weeks, range 1 to 24). Of the 201 studies, 129 (64.2%) were performed within 8 weeks, 18 (9.0%) were performed between 8 and 12 weeks, and 54 (26.9%) were performed between 12 and 24 weeks of treatment completion. Of 201 patents with post-therapy FDG-PET/CT, 114 (56.7%) had also a baseline FDG-PET/CT prior to the initiation of treatment. There is no significant difference between the ratio of each Hopkins criteria score in patients

who had both baseline and post-therapy PET/CT scan (n= 114) compared to those with only post-therapy scan (n = 87) (trend P= 0.33)

Reader Classification of PET/CT Studies

The Cohen k coefficient (k) analysis indicates that there was substantial agreement [17] between two readers (R1, R2) with K= 0.78 (P< 0.001). Any discrepancies between the two readers (29 out of 201 studies, 14.4%) were resolved by a third reader (R3). Based on the final scores, 144 studies (71.6 %) were categorized as positive and 57 studies (28.4 %) were categorized as negative for residual disease by overall assessment. Of the positive PET/CT studies, the residual disease is identified in the primary site (89 studies, 61.8%), the mediastinum (37 studies, 25.7%), distant metastatic sites (17 studies, 11.8%) and in 1 (0.7%) study in both mediastinum and distant sites. Of the PET/CT studies that were categorized as negative, 38 studies (66.7%) were scored 1 or 2 and 19 studies (33.3%) were scored 3.

According to the original retrospective report of the FDG-PET/CT in electronic medical records, PET/CT considered as positive in 146 patients, negative in 42 patients and indeterminate in 13 patients. Considering the indeterminate studies as negative, the Cohen k coefficient analysis showed substantial agreement between original retrospective PET/CT report and Hopkins based conclusion (positive/negative) with K= 0.78 (P< 0.001).

Accuracy of the Scoring System

Six of the 201 studies (3%) did not have reference standard data for comparison required for diagnostic accuracy estimation. The reference standards were histopathology in 35.4% (69 out of 195), and clinical or alternative imaging follow-up 6 months after PET/CT in 64.6% (126 out of 195) of studies. Table 2 summarizes the 2 by 2 table. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of the scoring system were 89% (82.7 to 93.6%), 80% (66.3 to 90%), 92.8% (87.3 to 96.04%), 71.4% (58.5 to 81.6%) and 86.7%, respectively.

PET/CT results: Added Value to Prior Clinical Assessment

Of the 201 therapy assessment scans, 133 were obtained without prior clinical or imaging suspicion of progression, and 68 were obtained with prior clinical or imaging suspicion. In the context of prior clinical assessment, PET/CT identified a potential site of residual disease or metastases in 64.7% (86/ 133) of scans requested with no prior clinical suspicion, of which 95.1% (78/82, 4 missing data) confirmed through histopathology or clinical/imaging follow-up of 6 months post PET/CT study.

Among the patients who underwent PET/CT to evaluate for clinically suspected residual disease, PET/CT identified a potential site of residual disease in 85.3%

(58/ 68) of scans which were confirmed by reference standard in 94.4% (51/57, 1 missing data) . PET/CT ruled out residual disease (showed complete metabolic response to treatment) in 14.7% (10/68) of scans requested with prior clinical/imaging suspicion. (Fig. 2)

Overall, PET/CT resulted in starting a new treatment plan in 70.8% of patients (102 out of 144) with positive residual disease on post-treatment PET/CT. Of those, 26 patients (25.5%) underwent surgical tumor resection, 44 patients (43.2%) received palliative or new chemotherapeutic regimen, 24 patients (23.5%) underwent radiation therapy and 8 patients (7.8%) received combined chemo-radiation therapy. 18% of patients (26 out of 144) with positive post-treatment PET/CT did not undergo new treatment [continue the previous chemotherapy regimen or undergo watchful follow-up]. The treatment stopped in4.2% of patients (6 out of 144) because of patients' preference (4 patients) and poor tolerance to systemic therapy (2 patients). The treatment impact was unknown in 7% of patients (10 out of 144).

PET/CT Results: Therapy Assessment Score and Survival Outcome in All Patients (n=201)

The median follow-up of the study population was 12 months (range, 0-128 months) from the date of the PET/CT, and 137 (68.2%) patients died within the period of the study. The median survival in the PET positive group was 9

months (range, 0 to 119 months) and 101 (70.1%) patients died in this group. In contrast, in the PET negative group, the median survival was 37.3months (range, 2 to 128 months) (P<0.001), and 36 (63.2 %) patients died in this group. The Kaplan-Meier survival analysis showed a significant difference in the overall survival (OS) between patients who were categorized as positive by the 5-point interpretation scale, compared to those who were categorized as negative (log-rank, P <0.001), with a hazard ratio (HR) of 2.12 (95% CI, 1.44-3.12)(Fig. 3A). The result remain significant in multi-variate Cox-regression analysis after adjustment for potential confounders including disease stage, prior clinical suspicion and primary treatment modality (P = 0.002) (Table 3)

In overall assessment by the 5-point interpretation scale, a significant trend in the difference in OS between patients who were scored 1 or 2 (n=38) versus those who were scored 3 (n=19) versus those who were scored 4 or 5 (n=144) were observed (log-rank, P < 0.001) (Fig. 3B).

PET/CT results and Survival Outcomes: Impact of Tumor Histology & Treatment Modality

According to the tumor histology, 34 patients diagnosed with small cell lung cancer and 167 patients had non-small cell lung cancer. The Kaplan–Meier analysis showed a significant difference in OS of small cell lung cancer patients who had a positive PET/CT result (median survival 6.4 months, 20 deaths) and

those who had a negative result (median survival 37.3 months, 6 deaths) (log-rank, P= 0.022) with a HR of 2.88 (95%CI, 1.12- 7.39). Similarly in patients with non-small cell lung cancer, OS is significantly lower in patients with a positive PET/CT result (median survival 9.6 months, 81 deaths) compared to those with a negative PET/CT result (median survival 38.05 months, 30 deaths) (log-rank, P= 0.001) with a HR of 2.01 (95%CI: 1.31-3.07) (Fig. 4).

Among the 41 patients who had surgical resection as part of their primary treatment, 15 had negative (median survival 70.5 months, 5 deaths) and 26 had positive (median survival 7.1 months, 19 deaths) post-operative PET/CT scan. Among 160 patients who was treated with chemo or radiation therapy, post-therapy PET/CT result was negative in 42 patients (median survival 28.8 months, 31 deaths) and positive in 118 patients (median survival 9.1 months, 82 deaths). Positive Hopkins scoring could significantly predict the OS both in patients who had surgical resection as part of their primary intervention (log-rank, $P < 0.001$) and in patients who did not undergo surgery (n=160) (log-rank, P=0.025), with a HR of 6.09 (95% CI, 2.02-18.33) and 1.60 (95% CI, 06-2.43), respectively (Fig. 5).

DISCUSSION

The objective of the study was to validate the qualitative therapy response assessment PET/CT interpretation criteria (Hopkins Criteria) in lung cancer

patients and establish its diagnostic performance and predictive value for survival outcome. Our study showed that the Hopkins Criteria for post-therapy response assessment interpretation adds value to clinical assessment, results in start a new treatment in more than two-third of patients and could predict OS of with lung cancer patients.

Treatment response assessment plays a vital role in the management algorithm of patients with lung carcinoma. Studies have shown that there is a need for new strategies for therapy response assessment beyond that of established criteria such as the Response Evaluation Criteria in Solid Tumors (RECIST) and World Health Organization (WHO) criteria[18]. A uniform strategy for therapy response assessment has been of importance in the recent past. Anatomic imaging based criteria such as WHO and RECIST criteria have been shown to have limitations particularly in assessing the activity of cancer therapies that stabilize the disease.

The use of qualitative and quantitative PET methods to assess therapy response has gained interest in different solid tumors, wherein the ^{18}F-FDG uptake in tumor foci is compared with tracer uptake in normal structures such as the blood pool and liver [19]. This approach has been widely tested and validated in lymphoma [20, 21]. The introduction of simple qualitative criteria with good inter-reader reliability, easy reproducibility and good diagnostic performance, which can also provide prognostic information will be of immense value. Our previous work on head and neck squamous cell carcinoma patients has shown that the

interpretation criteria for therapy response assessment has substantial inter-reader agreement and could predict survival outcomes [15]. Multiple studies have shown that quantitative PET parameters provide valuable prognostic information in lung cancer [10, 13, 22, 23]. To our knowledge, the prognostic significance of qualitative PET strategies has not been clearly evaluated in lung cancer. Our study shows that there is a significant difference in the OS between patients who were categorized as positive by the 5-point interpretation scale, compared to those who were categorized as negative. This observation holds true among patient groups which undergo different treatment interventions and histology.

A common pitfall of a qualitative approach is intermediate patterns of tracer uptake. One of these patterns has been described as minimal residual uptake by Mikhaeel et al[24] in their study of 102 patients with aggressive lymphoma and showed that there was a difference in the survival between patients who were classified PET negative, PET positive and studies which demonstrated minimal residual uptake, with observed survival rates for the minimal residual uptake group falling between the PET positive and PET negative group. In routine evaluation of PET/CT studies, this classification of ^{18}F-FDG uptake which falls in the grey-zone is challenging [24]. In line with the above findings, our study has also shown a significant difference in OS between patients who were scored 1 or 2 versus score 3 versus score 4 or 5.

Recent study on locally advanced non-small cell lung cancer patients received curative chemotherapy suggested that PET/CT scan 9 months after the start of radiation therapy increased the probability of early detection of disease progression and could detect the progression in 48% of asymptomatic patients without any clinical symptom [25]. Previous studies also suggested that follow-up and surveillance PET/CT could add value to clinical assessment and excluded malignancy in about 50% and 15% of scans obtained with prior clinical suspicion, in head and neck cancer and lung cancer patients, respectively [26, 27]. This study further demonstrated the added value of therapy assessment PET/CT in lung cancer patients. PET/CT identified potential residual or metastasis in about 65% of the scans performed as a routine therapy assessment without prior clinical suspicion and excluded malignancy in about 15% of the scans performed in the presence of prior clinical or imaging suspicion.

We acknowledge a few limitations to our study. Enrollment of patients over thirteen years in a retrospective manner can be associated with inherent unavoidable biases. We did not measure any semi-quantitative parameters such as SUV_{max} or $SUV_{peak,}$ as we focused on a standardized qualitative method. This is to minimize the effect of longitudinal variability of the scans performed over a decade and to provide a simple method of qualitative therapy assessment for lung tumors. There may be underestimation of prior clinical assessment given clinical judgment was collected retrospectively and exact perspective of the treating

physician was not collected prospectively. The survival data was obtained from a public registry and the patient records at our hospital. There may be a time lag between death and the public registry update.

Conclusion:

The proposed therapy-response interpretation criteria is a simple, qualitative method with substantial inter-reader agreement, high accuracy which adds value to prior clinical assessment and can predict OS in patients with lung cancer, irrespective of the primary treatment or histology of the tumor.

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Table 1. Characteristics of the 201 patients included in the study.

Characteristic		N	(%)
Age (y)	<40	4	(2.0%)
	41-60	83	(41.3%)
	> 60	114	(56.7%)
Sex	Female	85	(42.3%)
	Male	116	(57.7%)
Race	White	142	(70.6%)
	Black	38	(18.9%)
	Other	21	(10.5%)
Histology	SCLC	34	(16.9%)
	NSCLC	167	(83.1%)
History of smoking	+	156	(77.6%)
Stage	I	23	(11.4%)
	II	16	(8.0%)
	III	67	(33.3%)
	IV	78	(38.8%)
	Unknown	17	(8.5%)
	Surgery	7	(3.5%)
	Chemotherapy	52	(25.9%)
	Radiation Therapy	11	(5.5%)
	Surgery + Chemoradiation	18	(9.0%)
	Chemoradiation	97	(48.3%)
	Surgery + Chemotherapy	16	(8.0%)
Interval between treatment and PET study	1-8 weeks	129	(64.2%)
	8-12 weeks	18	(9.0%)
	12-24 weeks	54	(26.9%)
PET/CT Results	Negative	57	(28.4%)
	Positive	144	(71.6%)
Outcome	Dead	137	(68.2%)

Table 2. Diagnostic Accuracy Estimation of the five-point Qualitative Post-therapy Assessment Scoring System (Hopkins Criteria) for lung cancer follow up

	Disease Positive	**Disease Negative**	**Total**
PET/CT positive	129	10	139
PET/CT negative	16	40	56
Total	145	50	195

Table 3. Uni-variate and multi-variate Cox-regression analysis.

	Overall survival	
	Hazard Ratio	**P-value**
Uni-variate analysis		
Positive Hopkins criteria	2.12 (1.44-3.11)	<0.001
Age	1.00 (0.99, 1.02)	0.40
Sex	1.11 (0.79, 1.56)	0.53
Race	0.80 (0.61, 1.04)	0.09
Smoking	0.89 (0.57, 1.40)	0.63
Time interval between treatment and PET study	1.02 (0.99, 1.04)	0.17
Prior clinical suspicious	1.44 (1.01, 2.04)	0.04
Disease stage	1.17 (1.01, 1.35)	0.04
Treatment	1.57 (1.01, 2.44)	0.05
Tumor histology	0.70 (0.45, 1.07)	0.09
Multi-variate analysis*		
Positive Hopkins criteria	1.86 (1.25, 2.78)	0.002

*after adjustment for disease stage, prior clinical suspicion and primary treatment modality

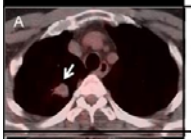
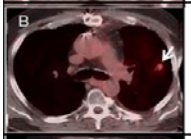
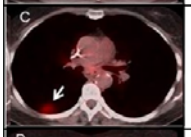
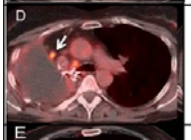
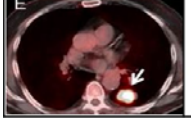
	Score	Description	
	1	^{18}F-FDG uptake less than mediastinal blood pool consistent with complete metabolic response	Negative
	2	Focal ^{18}F-FDG uptake greater than mediastinal blood pool but less than liver, consistent with likely complete metabolic response	
	3	Diffuse ^{18}F-FDG uptake greater than mediastinal blood pool or liver consistent with probable inflammation	
	4	Focal ^{18}F-FDG uptake greater than liver consistent with likely residual disease	Positive
	5	Focal and intense ^{18}F-FDG uptake consistent with residual disease	

FIGURE 1. Five-point Qualitative Post-therapy Assessment Scoring System (Hopkins Criteria) for lung cancer

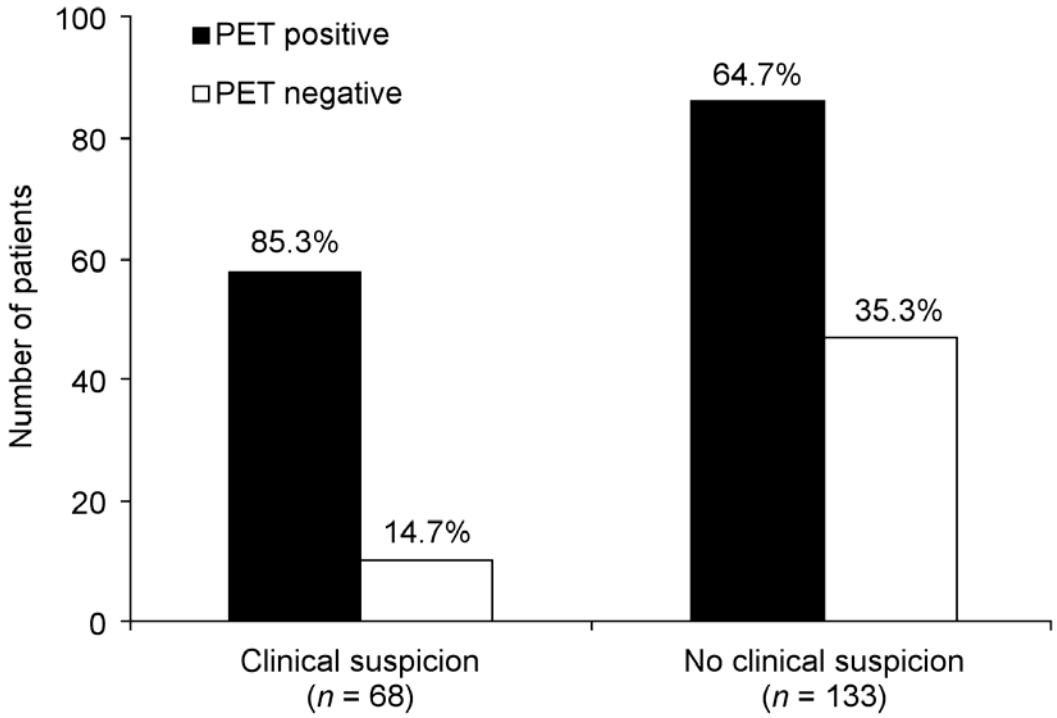


FIGURE 2. Added value of PET/CT to clinical assessment. PET/CT was helpful in excluding tumors in 14.7% (10/68) of scans ordered with clinical or imaging suspicion of recurrence and identifying recurrence in 64.7% (86/ 133) of scans ordered with no prior clinical or imaging suspicion.

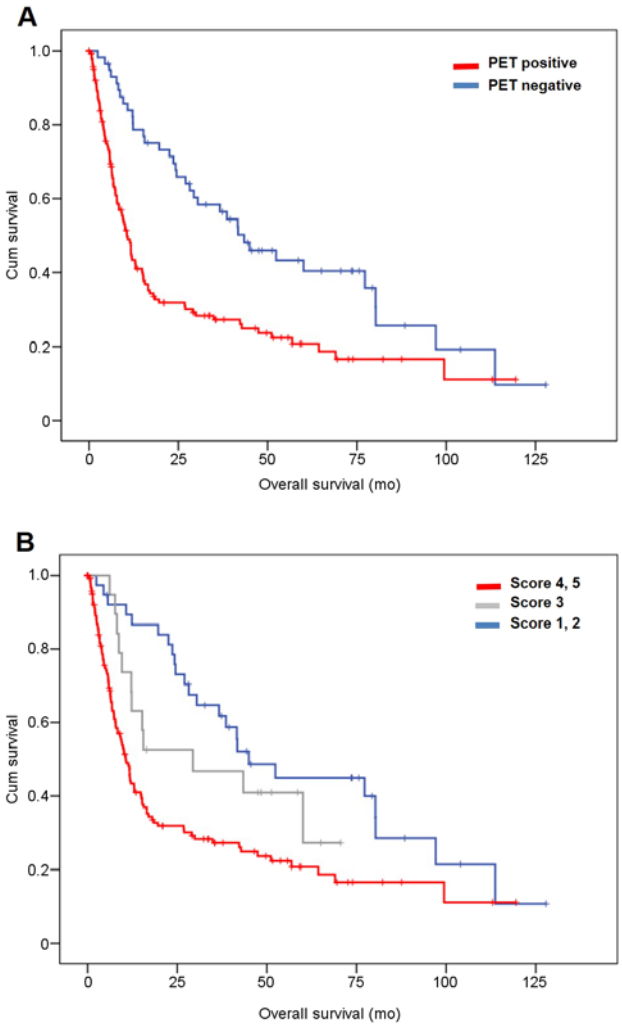


FIGURE 3. Kaplan-Meier survival plot by PET/CT 5-point interpretation criteria: (A) OS (months) between patients who were categorized as positive (red line) and negative (blue line) differed significantly [n= 201; log-rank P < 0.001; HR: 2.12 (95%CI: 1.44-3.12)] (B) OS (months) differed significantly between patients who were scored as 4 or 5 (red line) versus 3 (grey line) versus 1 or 2 (blue line) by the 5-point post-therapy interpretation criteria [log-rank P <0.001].

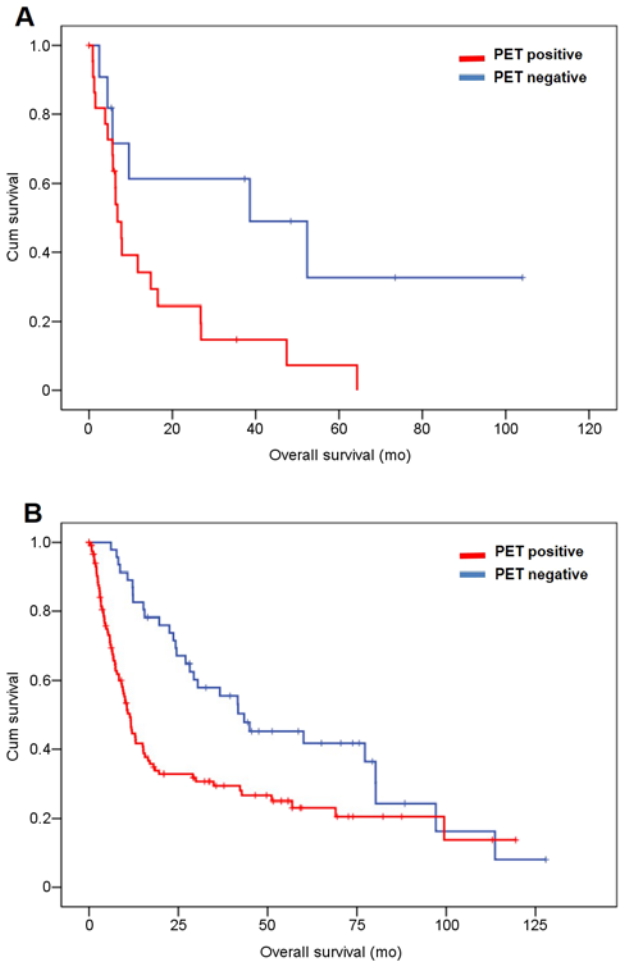


FIGURE 4. Kaplan-Meier survival plot by PET/CT result and tumor histology: OS (months) between patients who were PET positive (red line) and PET negative (blue line) were significantly different between patients with small cell lung cancer (A) [n= 34; log-rank P = 0.022; HR: 2.88 (95%CI:1.12- 7.39)] and those with non-small cell lung cancer (B) [n= 167; log-rank P = 0.001; HR: 2.01 (95%CI:1.31-3.07)].

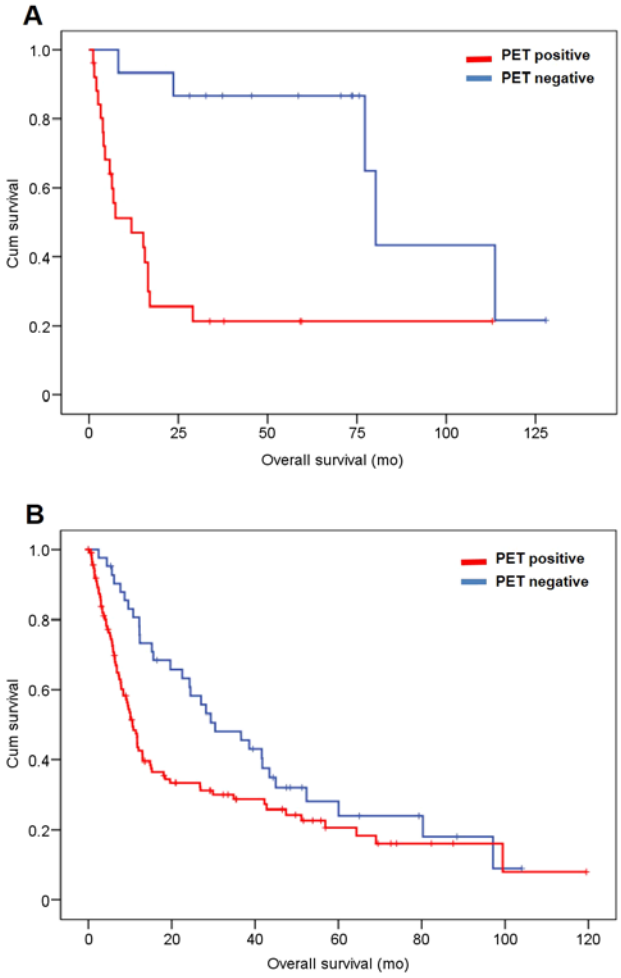


FIGURE 5. Kaplan-Meier survival plot by PET/CT result and treatment: OS (months) between patients who were PET positive (red line) and PET negative (blue line) were significantly different between patients who were treated with surgical resection as part of the primary intervention (A) [n= 41; log-rank P < 0.001; HR: 6.09 (95%CI: 2.02-18.33)] and those who did not have surgical resection as part of the primary intervention (B) [n= 160; log-rank P = 0.025; HR: 1.60 (95%CI:1.06-2.43)].