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MINI REVIEW

18F-fluorodeoxyglucose positron emission tomography/computed tomography in the evaluation of clinically node-negative non-small cell lung cancer

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Abstract

One in four non-small cell lung cancer (NSCLC) patients are diagnosed at an early-stage. Following the results of the National Lung Screening Trial that demonstrated a survival benefit for low-dose computed tomography screening in high-risk patients, the incidence of early-stage NSCLC is expected to increase. Use of 18F-fluorodeoxyglucose positron emission tomography/computed tomography during initial diagnosis of these early-stage lesions has been increasing. Traditionally, positron emission tomography/computed tomography scans have been utilized for mediastinal nodal staging and to rule out distant metastases in suspected early-stage NSCLC. In clinically node-negative NSCLC, the use of sublobar resection and selective lymph node dissection has been increasing as a therapeutic option. The higher rate of locoregional recurrences after limited resection and the significant incidence of occult lymph node metastases underscores the need to further stratify clinically node-negative NSCLC in order to select patients for limited resection versus lobectomy with complete mediastinal lymph node dissection. In this report, we review the published data, and discuss the significance and potential role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography evaluation for clinically node-negative NSCLC. Consequently, the literature review demonstrates that maximum standardized uptake value is a predictive factor for occult nodal metastasis with an accuracy of 55–77%. In addition, maximum standardized uptake value is a predictor for worse overall, as well as disease-free, survival.

Introduction

Accurate staging of early-stage non-small cell lung cancer (NSCLC) guides appropriate treatment strategies for NSCLC.[1–4] The determination of ipsilateral mediastinal lymph node (N2) or any contralateral mediastinal lymph node (N3) involvement is routinely assessed by computed tomography (CT) and positron emission tomography/CT (PET/CT) scans.[5] Currently, lymph node (LN) staging is performed by invasive and non-invasive methods. Invasive methods include mediastinoscopy and endobronchial ultrasound-guided transbronchial needle aspiration,[6,7] both of which are typically performed after the results of non-invasive staging including CT and PET/CT scans. Although invasive methods have been the gold standard for mediastinal nodal diagnosis,[8] there are disadvantages, such as patient discomfort, delay to definitive treatment, cost, and risk of complications. Use of more accurate, non-invasive mediastinal nodal staging will allow the selection of only those patients who will benefit most from invasive staging. The relationship between LN size and pathological involvement has been incorporated into practice guidelines – if the short-axis diameter of a LN is <10 mm on an axial CT scan, then those nodes are considered uninvolved.[9,10] There have been previous reports that have demonstrated that this metric's false positive and false negative rates were roughly 40% and 20%, respectively.[11]

18F-fluorodeoxyglucose (FDG) PET/CT is now commonly performed and is cost-effective for non-invasive nodal staging.[12–15] 18F-FDG PET/CT scan is a functional imaging modality that can visualize biological activity of tissue through accumulation of radiolabeled FDG. When compared with normal cells, malignant cells demonstrate increased cellular uptake of glucose due to activated glycolysis.[16] FDG is a radiolabeled glucose analog that is absorbed into cells. It is then phosphorylated and generates FDG-6-phosphate, which is not dehydrogenized in the citric acid cycle.[17] This causes an accumulation of FDG-6-phosphate in malignant cells that can be identified on PET/CT scans. Thus, FDG PET/CT can be used to detect malignancies and aid in both disease staging and monitoring of therapeutic response; however, the optimal index of FDG accumulation still remains controversial.

We currently lack a standardized quantitative criterion to define an abnormal FDG avidity on PET/CT scan. In general practice, FDG avidity is represented as the highest standardized uptake value per one pixel (SUVmax) in the subject lesion, and has been reported to be useful in mediastinal nodal staging of NSCLC.[18,19] However, in patients who had undergone preoperative FDG PET/CT, the incidence of mediastinal occult nodal metastasis (ONM), which is defined as histologically proven nodal metastasis that previously showed as negative on preoperative clinical examination, ranged from 8 to 58% in various stages of NSCLC.[18,19] For thoracic surgeons, it is necessary to know the additional significance of PET/CT parameters for risk stratification of ONM and survival outcomes in early-stage NSCLC. To this end, our aim is to review previous publications that described the correlation between PET/CT parameters and ONM as well as prognosis in patients with clinically node-negative NSCLC.

Mediastinal nodal staging by means of FDG PET/CT

In a Cochrane Database Systematic Review,[19] conducted by Schmidt-Hansen *et al.*, 45 published reports of mediastinal nodal staging by 18F-FDG PET/CT were reviewed. The data were analyzed categorically according to the SUVmax cut-off value. For reports using "nodal SUVmax >background" as a threshold, the sensitivity and specificity were 77.4% (95% CI 65.3–86.1%) and 90.1% (95% CI 85.3–93.5%), respectively. The studies that used "nodal SUVmax >2.5" as a cut-off value showed that the sensitivity and specificity were 81.3% (95% CI 70.2–88.9%) and 79.4% (95% CI 70.0–86.5%), respectively. According to the authors, the mediastinal nodal staging was sufficient as a screening test regardless of the cut-off value and the wide range of sensitivity and specificity. They also reported that the relatively high heterogeneity of accuracy on mediastinal nodal staging can be affected by a range of factors, including histological type, race, and cohort size. Their analysis demonstrated that, for a given study, the proportion of participants with lung adenocarcinoma (ADC) had a significant influence on the diagnostic accuracy.[19] This phenomenon might be attributed to the relatively low FDG avidity of lung ADC compared with other NSCLC histologies.[20] By contrast, factors such as study design (prospective vs. retrospective), consecutive recruitment, and year of publication had no significant impact on the accuracy of mediastinal nodal staging by FDG PET/CT.[20]

In contrast, the third edition of the clinical practice guidelines of the American College of Chest Physicians described a "grade 2B" recommendation that invasive nodal staging is not required if LNs were evaluated as negative by CT and PET/CT scans.[21] Additionally, if mediastinal nodes were radiologically negative, invasive staging procedures were recommended only for cases with a centrally located primary tumor or positive N1 nodes.[21] The European Society of Thoracic Surgeons guidelines[22] proposed an additional criterion that the primary tumor size be >3 cm before pursuing invasive staging. Neither guideline mentions how to evaluate the FDG avidity of lymph nodes on PET/CT scans or the significance of primary tumor SUVmax in mediastinal nodal staging. This is compounded by the low-grade evidence ratings of the respective recommendations.

Primary tumor FDG accumulation as a risk factor of occult nodal metastasis

With the increased popularity of CT scans in developed nations, the detection of smaller-sized peripheral lung nodules has been increasing. Herein, sublobar resection has been proposed as a therapeutic option for a subgroup of small early-stage NSCLC.[23–26] There are three ongoing prospective randomized control trials that are comparing the outcomes of sublobar resection with lobar resection.[27] Despite this, there is still controversy on how to select less invasive NSCLC cases among clinically node-negative patients that would be appropriate for sublobar resection. Additionally, selective nodal dissection or LN sampling has been proposed as an alternative to systematic nodal dissection.[27,28] With the shift to less extensive resection, the importance of reliable nodal disease diagnosis has grown.

In the current clinical setting, FDG PET/CT is routinely used for nodal staging if a patient has a potentially resectable NSCLC. Despite several recommendations of current clinical guidelines, considerable risk of ONM in patients with negative LN FDG accumulation on preoperative examination impacts whether or not sublobar resection is an appropriate treatment option. Additionally, patients with LN metastasis should not undergo sublobar resection.

The false negative rates of intrathoracic nodes diagnosed by FDG PET/CT in patients with peripherally located clinical stage IA NSCLC have ranged from 4 to 6%.[29,30] In a prospective trial comparing FDG PET/CT with invasive nodal staging, the positive predictive value and negative predictive value of PET/CT was 64% and 95%, respectively, in patients with clinical stage I–III NSCLC.[31] These data highlight the selective utility of invasive nodal staging, as well as the need for further interpretation of FDG PET/CT information to accurately risk stratify the occurrence of ONM.

Our primary clinical question is whether patients at risk for ONM can be stratified based on preoperative FDG PET/CT scans. Overall, there have been only a few publications that have addressed this specific topic. A literature search was carried out through Pubmed, Medline, and the Cochrane library for studies published between January 2003 and June 2017. The subject headings "early stage" or "stage I", "positron emission tomography" or "fluorodeoxyglucose", "non-small cell lung cancer" or "non-small cell lung carcinoma", and "occult lymph node metastasis" or "occult nodal metastasis" (multiple synonyms for each term) were searched. Only studies published in English in peer-reviewed journals were included. Eligible studies include prospective or retrospective studies of lobar resection with systematic LN dissection for clinical stage I NSCLC per the seventh edition of cancer staging by the American Joint Committee on Cancer. Then, studies with <100 patients were excluded to secure study quality. As shown in Table 1, seven reports have documented the usefulness of primary tumor SUVmax for the risk stratification of mediastinal ONM using a variety of cut-off values.[32–38] Li *et al.* showed that tumor size and primary tumor SUVmax were independently associated with mediastinal ONM in patients with clinical stage I NSCLC.[36] More recently, Kaseda documented that classification of NSCLC specifically as ADC is one of the risk factors of ONM; this is in addition to primary tumor size and SUVmax.[32] When examining ONM, some studies did not include FDG PET/CT parameters, but described other predictive risk factors, such as tumor size,[39] ADC histology, and female sex.[40] All studies that included SUVmax showed a statistically significant stratification of ONM (Table 1).[32–38] In contrast, there are no reports that evaluated risk factors for N1 ONM and N2 ONM separately. It may limit further prediction on mediastinal ONM, even though Lin's report focused on only mediastinal ONM and demonstrated that SUVmax was a risk factor for mediastinal ONM.[33] Despite the limitation, primary tumor SUVmax can be utilized as a risk factor for mediastinal ONM in clinical stage I NSCLC.

It should be noted that the aforementioned reports described East Asian populations, which have been known to have a relatively greater proportion of ADC compared

Table 1 Previous studies regarding the clinical significance of 18F-fluorodeoxyglucose positron emission tomography parameters to detect nodal metastases

Author/year	No. patients (% ADC)	cStage (% cStage IA)	No. of occult nodal metastases (%)	Cut-off tumor SUV max	Findings	Accuracy
Kaseda K/2016	246 (78%)	Clinical I (58%)	N1: 13 (5.3%)N2: 18 (7.3%)	3.0	SUVmax, tumor size, and histology were risk factors of nodal metastases	55% (Sensitivity: 68% Specificity: 61%)
Lin JT/2016	284 (85%)	Clinical I (65%)	N2: 24 (8.5%)	7.3	SUVmax was risk factors of nodal metastases	77% (Sensitivity: 50% Specificity: 79%)
Nakamura H/ 2015	209 (72%)	Clinical I - III (44%)	Total: 28 (11%)	3.0	SUVmax, ly, v, and pl were risk factors of nodal metastases	55% (Sensitivity: 82% Specificity: 51%)
Miyasaka Y/ 2014	265 (76%)	Clinical I (72%)	N1: 27 (10%)N2: 24 (9.0%)	10	SUVmax and consolidation to tumor ratio were risk factors of nodal metastases	77% (Sensitivity: 49% Specificity: 83%)
Li L/2013	189 (78%)	Clinical I (71%)	N1: 30 (16%)N2: 14 (7.4%)	4.3	SUVmax and tumor size were risk factors of nodal metastases	56% (Sensitivity: 94% Specificity: 48%)
Li S/2013	129 (83%)	Clinical I (N/A)	N1: 25 (11%)N2: 49 (22%)	4.0	SUVmax was a risk factor of nodal metastases	56% (Sensitivity: 72% Specificity: 48%)
Li X/2013	144 (73%)	Clinical IA (100)	N1: 8 (5.6%)N2: 4 (2.8%)	7.25	SUVmax of primary tumor is not associated with occult nodal metastases	69% (Sensitivity: 68% Specificity: 70%)

ADC, adenocarcinoma; ly, lymphatic invasion; N1, ipsilateral hilar nodes; N2, ipsilateral mediastinal nodes; pl, pleural invasion; SUVmax, maximum standardized uptake value; v, vascular invasion.

with other NSCLC.[41,42] Furthermore, most of the studies included non-stage IA patients, and used a variety of cut-off values for SUVmax. The SUVmax prediction accuracy may be improved if combined with additional criteria, such as tumor size and tumor location, as proposed by the American College of Chest Physicians guidelines.[21] All available literature was conducted retrospectively, which may introduce several biases including inappropriate patient selection.

Primary tumor FDG accumulation as a prognosticator

Although numerous studies have shown the prognostic significance of primary tumor FDG avidity in a variety of patient cohorts among NSCLC, there are fewer publications specifically investigating it in pathological stage IA NSCLC. A literature search was performed through Pubmed, Medline, and the Cochrane library for studies published between January 2003 and June 2017. The subject headings "early stage" or "stage I", "positron emission tomography" or "fluorodeoxyglucose", "non-small cell lung cancer" or "non-small cell lung carcinoma", and "prognostic factor" or "survival predictor" (multiple synonyms for each term) were searched. Only studies published in English in peer-reviewed journals were included. Eligible studies include prospective or retrospective studies of lobar resection with systematic lymph node dissection for stage I NSCLC per the seventh edition of cancer staging by the American Joint Committee on Cancer. Then, studies with <100 patients were excluded to secure study quality. As shown in Table 2, there are 11 available reports that analyzed the prognostic significance of FDG accumulation in resected node-negative NSCLC.[43–53] All reports, except for two, included pathological stage IB NSCLC.[43,44] All of the examined studies reported the significant association between FDG accumulation and prognosis in patients with clinically node-negative NSCLC. Kwon *et al.* reported that the risk of both disease recurrence and death increased as SUVmax of the primary tumor increased in patients with stage I NSCLC.[46] In contrast, there are no reports that have demonstrated the prognostic significance of SUVmax in a study cohort of patients with limited to stage IA NSCLC.

Additional parameters utilizing SUV values have also been applied to the study of NSCLC. Specifically, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been proposed as useful and reliable volume-based parameters of FDG accumulation in subject lesions.[54] MTV indicates the volume of metabolically active tumors using a threshold of SUV.[55] TLG is the product of MTV and associated mean SUV. Herein, both MTV and TLG can better reflect the metabolic activity of the whole tumor, whereas SUVmax only represents information of a single pixel. Recent publications have reported that higher MTV and higher TLG showed a significant association with worse overall survival or disease-free survival in patients with

Table 2 Previous studies regarding prognostic significance of 18F-fluorodeoxyglucose positron emission tomography parameters in pathological stage I non-small cell lung cancer (>100 patients)

Author/year	No. patients (% ADC)	pStage (% pStage IA)	PET parameters	Outcome	Cut-off value of PET parameters	Findings
Park SY/2015	248 (79%)	IA (100%)	SUVmax, MTV, TLG	OS, DFS	3.7 (SUVmax), 13.76 (TLG)	TLG was more strongly associated with OS and DFS compared to SUVmax and MTV
Ko KH/2015	145 (90%)	IA (100%)	SUVmax	DFS	2.5	MTV and TLG were significantly associated with OS and DFS
Domachevsky L/2015	181 (43%)	I – II (N/A)	SUVmax, MTV, TLG	OS	8.2 (SUVmax)	SUVmax was significantly associated with OS regardless of N-status
Kwon WI/2015	336 (55%)	I (59%)	SUVmax	OS, TTR	3.4, 7.2, 14.2†	Risks of both OS and TTR were significantly increase as SUVmax increased
Kim DH/2014	102 (100%)	I – II (33%)	SUVmax, MTV, TLG	DFS	6.90 (SUVmax), 10.78 (MTV), 39.68 (TLG)	SUVmax, MTV, and TLG were significantly associated with DFS
Hyun SH/2013	529 (50%)	I – II (33%)	SUVmax, MTV, TLG	DFS, OS	16 (MTV), 70 (TLG)	MTV and TLG were significantly associated with OS and DFS
Shiono S/2011	356 (73%)	I (75%)	SUVmax	DFS	4.7	SUVmax was significantly associated with DFS
Agarwal M/2010	363 (63%)	I – II (61%)	SUVmax	OS	5.9	SUVmax was significantly associated with OS
Um SW/2009	145 (48%)	I (35%)	SUVmax	DFS	13.1	SUVmax was significantly associated with DFS
Kim HR/2009	107 (44%)	I (53%)	SUVmax	OS	2.4	SUVmax was significantly associated with OS
Goodgame B/2008	136 (52%)	I (57%)	SUVmax	OS	5.5	SUVmax was significantly associated with OS

†Multiple group comparison. ADC, adenocarcinoma; DFS, disease-free survival; MTV, metabolic tumor volume; OS, overall survival; PET, positron emission tomography; SUVmax, standardized uptake value; TLG, total lesion glycolysis; TTR, time to recurrence.

node-negative NSCLC.[44,45,48,49] Additionally, in a report by Shiono,[56] the SUV index (a ratio of primary tumor SUVmax to liver SUV mean) was a significant prognostic indicator for stage IA NSCLC. In this situation, the SUV index can minimize the influence of factors that can affect FDG uptake, such as histology and race, even though there is limited published evidence about this in surgically-resected NSCLC. These parameters have been reported in a limited number of studies, thus they should be further investigated for validation.

FDG-PET parameters of evaluation

The 5-year overall survival of patients with resected pathological stage IA NSCLC ranges from 70 to 85%.[57–60] Given that invasion size can be a determinant of aggressiveness and recurrence in small-sized NSCLC, it is reasonable to assume that volumetric parameters, such as MTV and TLG, can be helpful in differentiating non-invasive tumors from invasive tumors among stage IA NSCLC. Despite this, the most appropriate segmentation method to measure MTV and TLG remains controversial. Furthermore, volumetric parameters, such as MTV and TLG, are limited by the fact that the SUV of some subcentimeter tumors cannot be detected by PET scans due to constraints in spacial resolution.[61]

The advantage of these parameters of FDG accumulation is that they are readily available preoperative prognosticators. Despite SUVmax possibly having limited predictive ability for ONM, it can be useful for risk stratification of ONM in patients with NSCLC who were diagnosed as node-negative based on both chest CT and FDG PET/CT scans. Thus, it is required to improve predictiveness for ONM by using other FDG-PET parameters or in combination with other clinical factors including tumor size. For primary tumors with a high SUVmax, invasive nodal staging might be required to investigate ONM preoperatively. Diagnostic accuracy may be improved by including the additional criteria of tumor size and tumor location. A majority of tumors with lower SUVmax can be treated by upfront resection and systematic nodal dissection. Among them, a subgroup of patients with small-sized tumors and a lower SUVmax may be candidates for sublobar resection. In contrast, there is no consensus on the appropriate cut-off value of primary tumor SUVmax to differentiate tumors without ONM as well as recurrence in clinical stage I NSCLC, because no prospective study has demonstrated a specific cut-off value so far. Furthermore, further investigations are required to clarify the most appropriate parameter of FDG accumulation for risk stratification in clinical stage IA NSCLC, because SUVmax can be affected by many factors, including tumor histology,[62,63] race,[64] blood sugar,[65–68] and inflammation.[69,70]

Ongoing randomized trials investigating the survival outcome of sublobar resection showed comparable prognosis with lobectomy in clinical stage IA NSCLC. A better part of the plan is the more appropriate selection of candidates based on FDG PET/CT scans. There are still hurdles that we face regarding the application of the current findings into clinical practice, and further studies will shed light on an optimal management strategy based on FDG PET/CT evaluation in potentially resectable NSCLC.

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