Evidence-Based PET for Thoracic Tumours

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Filippo Lococo, Alfredo Cesario,
Stefano Margaritora, and Giorgio Treglia

5.1 Introduction

Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) is a robust imaging tool that is currently used in daily clinical practice for the evaluation of thoracic malignancies. This chapter provides an overview of the current evidence-based data on the usefulness of PET/CT for the evaluation of patients with thoracic tumours including lung cancer, pleural and thymic tumours, and esophageal cancer.

5.2 Evidence-Based Data on PET in Primary Lung Tumours

Herein we reviewed recent evidence-based data on the usefulness of ^{18}F -FDG PET/CT for: (1) characterization of solitary pulmonary nodules (SPNs), (2) non-small cell lung cancer (NSCLC) staging, (3) restaging after induction therapy and systemic therapy response assessment in NSCLC, (4) radiation therapy planning, (5) diagnosis of lung cancer recurrence in NSCLC, (6) prognostic evaluation, (7) management of small cell lung cancer (SCLC).

5.2.1 Characterization of Solitary Pulmonary Nodules (SPNs)

Characterizing a SPN detected incidentally or, as is the case more recently, on CT screening for lung cancer is a major public health issue. ^{18}F -FDG PET/CT is not indicated for characterization of SPNs of less than 8 mm in diameter according to current guidelines [1]. This threshold was set to take into account the spatial resolution of PET systems, due to the significant risk of false-negative findings for small lesions. However, over the last decade, the spatial resolution of ^{18}F -FDG PET/CT has significantly increased and future analysis could verify if this threshold will be modified accordingly.

F. Lococo (✉) · A. Cesario · S. Margaritora
Department of General Thoracic Surgery, Catholic
University of the Sacred Heart, Fondazione Policlinico
A. Gemelli, Rome, Italy

G. Treglia
Clinic of Nuclear Medicine and Molecular Imaging,
Imaging Institute of Southern Switzerland, Ente
Ospedaliero Cantonale,
Bellinzona and Lugano, Switzerland

Department of Nuclear Medicine and Molecular
Imaging, Lausanne University Hospital and
University of Lausanne, Lausanne, Switzerland

Health Technology Assessment Unit, Academic
Education, Research and Innovation Area, Ente
Ospedaliero Cantonale, Bellinzona, Switzerland
e-mail: giorgio.treglia@eoc.ch

5.2.1.1 Single-Time-Point ^{18}F -FDG PET or PET/CT

In the last decade, a robust evidence has been produced on the potential use of ^{18}F -FDG PET/CT in early diagnosis of lung cancer (Table 5.1). Chien and colleagues [2] in 2013 conducted a systematic review on this topic reporting evidence of lung cancer screening programmes with ^{18}F -FDG PET, in which the estimated pooled sensitivity and specificity were 83% and 91%, respectively. At that moment, despite PET appeared to have high sensitivity and specificity as a selective screening modality, the role of primary PET screening for lung cancer remained unknown and still undefined.

Subsequently, a further systemic analysis [3] reported a very high (98.7%) pooled sensitivity of ^{18}F -FDG PET/CT in this setting while specificity was suboptimal (58.2%).

In 2016, the research team headed by Madsen [4] suggested that ^{18}F -FDG PET/CT can rule out malignancy in most SPNs due to high sensitivity

(recommendation level A) but at the same time the sensitivity of ^{18}F -FDG PET/CT in general is insufficient to rule out mediastinal lymph node metastasis (recommendation level A). Therefore, with few exceptions (lesions <1 cm and non-solid lesions), they concluded that SPNs could be presumptively considered benign if ^{18}F -FDG PET is negative. In addition, lymph node metastasis in the mediastinum cannot be ruled out on the basis of a negative ^{18}F -FDG PET/CT, and confirmative (mini)invasive staging should be performed in most patients.

More recently, a further meta-analysis [5] showed that the pooled sensitivity and specificity of ^{18}F -FDG PET/CT in characterizing SPNs were 82% and 81%, respectively, demonstrating moderate accuracy for ^{18}F -FDG PET/CT in differentiating malignant from benign SPNs.

A further meta-analysis exploring the value of ^{18}F -FDG PET/CT in the diagnosis of SPNs was reported in 2018 [6]. Pooled results indicated a sensitivity of 89% and a specificity of 70%.

Table 5.1 Main findings of included meta-analyses on the diagnostic performance of PET or PET/CT with different tracers in patients with solitary pulmonary nodules

Indication	Tracer	Authors	Year	Patients included	Pooled sensitivity (95%CI)	Pooled specificity (95%CI)
Evaluation of suspicious primary lung tumour	^{18}F -FDG (STP)	Chien et al. [2]	2013	264	83% (75–89)	91% (86–95)
		Wang et al. [3]	2015	1330	99% (N/A)	58% (N/A)
		Ruilong et al. [5]	2017	1297	82% (76–87)	81% (66–90)
		Li et al. [6]	2018	1557	89% (87–91)	70% (66–73)
		Divisi et al. [7]	2018	1463	82% (79–84)	62% (58–66)
		Basso Dias et al. [9]	2019	4224	78% (70–84)	81% (72–88)
	^{18}F -FDG (DTP)	Lin et al. [10]	2012	788	N/A	N/A
		Barger et al. [11]	2012	816	85% (82–89)	77% (72–81)
		Zhang et al. [12]	2013	415	79% (74–84)	73% (65–79)
		Zhao et al. [13]	2016	962	80% (76–84)	75% (71–79)
	^{18}F -FLT	Li et al. [14]	2015	301	81% (74–87)	70% (61–77)
		Wang et al. [15]	2015	351	80% (74–85)	82% (74–88)

95%CI 95% confidence interval, STP single-time-point PET, DTP dual-time-point PET, N/A not available

Considering the unsatisfactory results, especially in terms of specificity, the authors stated that ^{18}F -FDG PET/CT cannot replace the “gold standard” pathology by resection or biopsy.

Not dissimilar results have been reported in a further recent meta-analysis performed by Divisi and co-workers [7]. The authors concluded that despite ^{18}F -FDG PET/CT presents a fairly good diagnostic accuracy in SPNs evaluation, it should not be considered as a discriminatory test rather than a method to be included in a clinical and diagnostic pathway.

Interestingly, Deppen and co-workers [8] evaluated the accuracy of ^{18}F -FDG PET in diagnosing lung cancer comparing populations with or without a risk for endemic infectious lung disease. They observed a 16% lower average adjusted specificity in regions with endemic infectious lung disease (61%) compared with non-endemic regions (77%). On the other hand, the sensitivity did not change appreciably by endemic infection status, even after adjusting for relevant factors. On the light of these results, the authors did not suggest the use of ^{18}F -FDG PET to diagnose lung cancer in regions with endemic pulmonary infections unless an institution achieves test performance accuracy similar to that found in non-endemic regions.

Lastly, a meta-analysis investigates the diagnostic performance of ^{18}F -FDG PET/CT compared with diffusion-weighted magnetic resonance imaging (DW-MRI) for distinguishing malignant versus benign SPNs [9]. DW-MRI had a pooled sensitivity and specificity of 83% and 91%, respectively, compared with 78% and 81%, respectively, for PET/CT. The authors concluded that the diagnostic performance of DW-MRI is comparable or superior to that of ^{18}F -FDG PET/CT in the differentiation of malignant and benign pulmonary lesions.

5.2.1.2 Dual-Time-Point (DTP) PET

Several authors have also explored the potential use of a DTP ^{18}F -FDG PET in differentiating malignant from benign SPNs (Table 5.1). In 2012, a meta-analysis was performed by Lin and co-workers [10] exploring the diagnostic performance of both single-time-point (STP) and DTP

^{18}F -FDG PET techniques. Sensitivity was higher with DTP imaging at moderate levels of specificity. This potential advantage of DTP over initial STP scanning was diminished at higher levels of specificity. Although there was no clear evidence to support the routine use of DTP imaging with ^{18}F -FDG PET in the differential diagnosis of pulmonary nodules, the authors suggested as such technique may provide additional information in selected cases with equivocal results from initial scanning. Other meta-analyses [11–13] reported similar diagnostic accuracy among DTP and STP ^{18}F -FDG PET or PET/CT in the diagnosis of SPNs. According to these results, the additional value of DTP compared to STP ^{18}F -FDG-PET/CT resulted to be questionable.

5.2.1.3 ^{18}F -FLT PET for Evaluation of Pulmonary Lesions

The potential use of fluorine-18 fluorothymidine (^{18}F -FLT) PET in patients with pulmonary lesions was evaluated by two meta-analyses [14, 15] (Table 5.1), which showed that ^{18}F -FLT PET had a higher specificity but lower sensitivity compared to ^{18}F -FDG PET in the evaluation of SPNs. Therefore, the authors assumed that ^{18}F -FLT and ^{18}F -FDG together could add diagnostic confidence for pulmonary lesions.

5.2.2 NSCLC Staging

Nodal (N) and distant metastases (M) staging is one of the major prognostic factors of survival in NSCLC patients. Accurate staging of distant metastases is crucial, as the treatment strategy is directly dependent on tumour stage. Although many studies have been reported in the last decades evaluating the performance of ^{18}F -FDG PET/CT in lung cancer staging, the results among studies are still almost controversial.

5.2.2.1 N Staging

Zhao and associates [16] performed a meta-analysis about ^{18}F -FDG PET/CT for detecting mediastinal nodal metastases in patients with NSCLC. The pooled sensitivity and specificity with 95% confidence interval values (95%CI) on

a per-patient analysis were 71.9% (95%CI: 68.3–75.3%) and 89.8% (95%CI: 88.2–91.2%), respectively.

A second meta-analysis on the same issue [17] showed a pooled sensitivity of 62% for ^{18}F -FDG PET/CT (95%CI: 54–70%) and a pooled specificity of 92% (95%CI: 88–95%) on a node-based analysis. The pooled sensitivity and specificity were 67% (95%CI: 54–79%) and 87% (95%CI: 82–91%), respectively, on a patient-based analysis. Interestingly, those studies from tuberculosis endemic countries showed lower sensitivity and also lower specificity compared to non-tuberculosis endemic countries [17, 18].

Two meta-analyses were specifically limited to early-stage NSCLC cases. In detail, Wang and co-workers [19] found that the negative predictive value (NPV) of ^{18}F -FDG PET/CT for lymph nodal mediastinal metastases was 94% for T1 disease and 89% for T2 disease. Including both T1 disease and T2 disease, the NPV was 93% for mediastinal metastases and 87% for overall nodal metastases. Interestingly, adenocarcinoma histology type and high ^{18}F -FDG uptake in the primary lesion were associated with greater risk of occult nodal metastases.

Similarly, a second meta-analysis [20] focused on patients with resectable NSCLC revealed that ^{18}F -FDG PET/CT had a pooled sensitivity and specificity for N staging of 81.3% (95%CI: 70.2–88.9%) and 79.4% (95%CI: 70–86.5%), respectively. The authors assumed that accuracy of ^{18}F -FDG PET/CT in N staging was insufficient to allow management and strategy of care based on ^{18}F -FDG PET/CT findings alone.

Shen et al. [21] also investigated the diagnostic value of DTP ^{18}F -FDG PET/CT versus STP imaging for detection of mediastinal nodal metastases in NSCLC patients. Pooled sensitivity and specificity for DTP PET/CT were 85% (95%CI: 78–91%) and 75% (95%CI: 68–82%), respectively, and for STP imaging the same values were 79% (95%CI: 70–85%) and 73% (95%CI: 65–79%), respectively. The authors were very cautious in supporting the implementation of DTP imaging in routine PET protocols for mediastinal lymph node staging of NSCLC.

Lastly, two meta-analyses compared ^{18}F -FDG PET/CT and DW-MRI for detection of mediasti-

nal nodal metastases in NSCLC [22, 23] reporting similar results in terms of diagnostic accuracy among these two imaging methods.

5.2.2.2 M Staging

A meta-analysis by Li and co-workers [24] showed the excellent diagnostic performance of ^{18}F -FDG PET/CT for diagnosis of distant metastases in patients with NSCLC with a pooled sensitivity and specificity of 93% (95%CI: 88–96%) and 96% (95%CI: 95–96), respectively. Similar results were reported by Yu et al. [25] who found a pooled sensitivity of 81% (95%CI: 63–92%) and 96% (95%CI: 94–98%), respectively. A further meta-analysis on the same topic [26] demonstrated that concerning extra-thoracic metastases of NSCLC, the pooled sensitivities and specificities of ^{18}F -FDG PET/CT were 77% (95%CI: 47–93%) and 95% (95%CI: 92–97%) for all extra-thoracic metastases, whereas the same values were 91% (95%CI: 80–97%) and 98% (95%CI: 94–99%), respectively, for bone metastases. Conversely, ^{18}F -FDG PET/CT showed low sensitivity in detecting brain metastases.

Concerning the latter issue, a comparative meta-analysis MRI and ^{18}F -FDG PET/CT for the diagnosis of brain metastases in NSCLC [27] revealed that MRI had higher sensitivity (77%) than ^{18}F -FDG PET/CT (21%) for the diagnosis of brain metastases.

Chang et al. [28] found a higher sensitivity and specificity of ^{18}F -FDG PET/CT compared to bone scintigraphy (BS) in detecting bone metastases from NSCLC. A further more robust meta-analysis [29] showed that ^{18}F -FDG PET/CT is a better imaging method in terms of sensitivity and specificity compared to MRI and BS for detecting bone metastases from NSCLC, with a pooled sensitivity and specificity of 92% (95%CI: 88–95%) and 98% (95%CI: 97–98), respectively.

Finally, the diagnostic performance of ^{18}F -FDG PET/CT in detecting adrenal metastases from NSCLC was recently evaluated by Wu and co-workers [30]. The pooled sensitivity and specificity of ^{18}F -FDG PET/CT in this setting were 88.7% (95%CI: 85.2–91.7%) and 90.8% (95%CI: 87.5–93.4%), respectively, suggesting excellent performance.

5.2.3 Restaging After Induction Therapy and Prediction of Treatment Response

The ability to identify potential responders to induction treatment may improve patient selection or surgery and may help in the development of response criteria suitable for routine monitoring of response. By providing information on the metabolic activity of tumour cells, ^{18}F -FDG PET/CT has become a powerful tool in assessing treatment response. Zhang and colleagues [31] performed a meta-analysis to evaluate the value of ^{18}F -FDG PET in predicting the pathological tumour response of lung cancer to induction therapy. The authors found that ^{18}F -FDG PET could play an important role in predicting non-responders to induction therapy in cases of lung cancer: indeed, the pooled sensitivity, specificity, positive predictive value, and negative predictive value for PET-predicted response were 83% (95%CI: 76–89%), 84% (95%CI: 79–88%), 74% (95%CI: 67–81%), and 91% (95%CI: 87–94%), respectively.

A recent evidence-based article assessed the use of ^{18}F -FDG PET/CT for both assessing the efficacy of treatment response and performing post-treatment follow-up of lung cancer [32]. PET metabolic response (PERCIST criteria) has been shown to be a better predictor of histopathologic response than anatomic response metrics (WHO and RECIST criteria). ^{18}F -FDG PET/CT was indicated for treatment response assessment when it is performed within 6 months from treatment completion, though evidence for its comparative effectiveness with chest CT is still evolving.

5.2.4 Radiation Therapy Pretreatment Planning in NSCLC

^{18}F -FDG PET/CT may also increase the likelihood of correctly delineating tumour tissue before radiotherapy dose planning. In 2017, Hallqvist and colleagues [33] reported the results of a meta-analysis on the use of ^{18}F -FDG PET/CT for radiotherapy dose planning. According to

this meta-analysis, a change in target definition was 36% in patients with a former staging PET, and 43% and 26% in patients without a staging PET for NSCLC and SCLC, respectively. The corresponding summary estimates of a change in treatment intent from curative to palliative treatment were 20% and 22% and 9%, respectively. Another recent meta-analysis demonstrated that functional lung imaging, including PET, may have potential utility in radiation therapy planning and delivery [34].

5.2.5 Diagnosis of Lung Cancer Recurrence

Although there are no conclusive data to support the survival benefits of early detection or early treatment for recurrence of lung cancer, an early and accurate diagnosis of recurrence is critical to optimize therapy. A meta-analysis [35] was performed to assess the diagnostic value of ^{18}F -FDG PET and PET/CT for cases of recurrent lung cancer. In the patient-based analysis performed, ^{18}F -FDG PET and PET/CT were found to provide better detection of lung cancer recurrence compared to CT. Indeed, the pooled sensitivity for ^{18}F -FDG PET, PET/CT, and CT were 94% (95%CI: 91–97%), 90% (95%CI: 84–95), and 78% (95%CI: 71–84%), respectively while the pooled specificity for ^{18}F -FDG PET, PET/CT, and CT were 84% (95%CI: 77–89%), 90% (95%CI: 87–93%), and 80% (95%CI: 75–84%), respectively.

5.2.6 Prognostic Evaluation in NSCLC

In their meta-analysis, Paesmans et al. [36] assessed the prognostic value of primary tumour maximum standardized uptake value (SUVmax) at ^{18}F -FDG PET for overall survival (OS) of NSCLC patients. At multivariate analysis, SUVmax was found to be independently associated with survival. The hazard ratio (HR) for SUVmax was 1.58 (95%CI: 1.27–1.96).

Despite the SUVmax represents the most widely applied semi-quantitative PET parameter

in clinical practice, volumetric PET parameters, including metabolic tumour volume (MTV) and total lesion glycolysis (TLG), have been also used to reflect disease burden and tumour aggressiveness in NSCLC. A first meta-analysis performed by Liu et al. [37] explored the prognostic value of SUVmax, MTV, and TLG on disease-free survival (DFS) and OS in surgical NSCLC patients. The pooled HRs for OS were 1.52 for SUVmax, 1.91 for MTV, and 1.94 for TLG. On the basis of these results, the authors stated that high values of SUVmax, MTV, and TLG are able to predict a higher risk of recurrence or death in patients with surgical NSCLC, suggesting the use of ^{18}F -FDG PET/CT to select patients who are at high risk of disease recurrence or death as the best candidates from aggressive treatments. Other authors [38] conducted a meta-analysis on the prognostic value of MTV and TLG in NSCLC patients. A worse prognosis was observed in patients with high MTV (HR: 2.31) and with high TLG (HR: 2.43).

Han and colleagues [39] performed a meta-analysis exploring prognostic value of texture parameters derived by ^{18}F -FDG PET in patients with lung cancer. They concluded that there is insufficient evidence to support the prognostic value of texture analysis in ^{18}F -FDG PET in lung cancer.

Another interesting application of ^{18}F -FDG PET is the ability to predict long-term results after radiation therapy. Dong and co-workers [40] explored the prognostic relevance of SUVmax at ^{18}F -FDG PET for early-stage NSCLC patients receiving stereotactic body radiation therapy (SBRT). The authors found that those NSCLC patients presenting with high levels of pre-SBRT SUVmax had poorer OS and local control and higher risk of distant metastases. These findings were confirmed by another meta-analysis [41] showing that both pre-radiotherapy and post-radiotherapy primary tumour SUVmax can predict the outcome of patients with NSCLC treated with radiotherapy.

Other authors [42] have summarized the prognostic value of early response at ^{18}F -FDG PET in NSCLC patients treated with tyrosine-kinase inhibitors (TKI). Early response of patients with

NSCLC treated with TKIs identified on ^{18}F -FDG PET was found to be associated with improved OS and progression-free survival (PFS).

5.2.7 Management of SCLC

The role of ^{18}F -FDG PET in the management of SCLC has been largely investigated in the last decades. A systematic review and meta-analysis performed by Lu et al. [43] to evaluate the diagnostic accuracy of ^{18}F -FDG PET/CT in the pre-therapeutic staging of patients with SCLC demonstrated a pooled sensitivity and specificity of 97.5% (95%CI: 94.2–99.2%) and 98.2% (95%CI: 94.9–99.6%), respectively, for the detection of extensive disease in SCLC patients. Therefore, evidence-based data suggest the role of ^{18}F -FDG PET/CT for discriminating between limited and extensive disease in SCLC.

The prognostic value of the SUVmax of primary SCLC at ^{18}F -FDG PET was recently investigated through a meta-analytic study [44]: the pooled HR for OS was 1.13 (95%CI: 1.05–1.22), thus indicating that SCLC patients with high SUVmax may have poorer prognosis.

5.3 Evidence-Based Data on PET in Pleural Tumours

Three meta-analyses assessed the role of ^{18}F -FDG PET or PET/CT in the characterization of pleural lesions [45–47], whereas meta-analyses on the role of ^{18}F -FDG PET/CT in staging, restaging, prognostic or treatment response evaluation of pleural tumours are currently lacking.

^{18}F -FDG-PET and PET/CT demonstrated to be accurate diagnostic imaging methods in the differential diagnosis between malignant and benign pleural lesions in patients with or without known cancer; nevertheless, possible sources of false-negative and false-positive results should be kept in mind [45, 46]. In patients without known cancer, sensitivity and specificity of ^{18}F -FDG-PET and PET/CT were 95% (95%CI: 92–97%) and 82% (95%CI: 76–88%), respectively [45]. In patients with known cancer, pooled sensitivity

was 86% (95%CI: 80–91%) and pooled specificity was 80% (95%CI: 73–85%) [46]. Porcel et al. in their meta-analysis [47] demonstrated that semi-quantitative PET assessment had a significantly lower sensitivity for diagnosing malignant pleural effusions than visual assessments. The pooled sensitivity and specificity of ^{18}F -FDG PET/CT using semi-quantitative interpretation for identifying malignant pleural effusions were 81% and 74%, respectively. The moderate accuracy of semi-quantitative PET assessment precludes its routine recommendation for discriminating malignant from benign pleural effusions.

5.4 Evidence-Based Data on PET in Thymic Epithelial Tumours

One meta-analysis [48] showed that ^{18}F -FDG PET may predict the WHO grade of malignancy in thymic epithelial tumours (TETs), reporting a statistically significant difference of SUVmax between the different TETs (low-grade thymomas, high-grade thymomas, and thymic carcinomas). In detail, the pooled mean difference of SUVmax between high-risk and low-risk thymomas was 1.2 (95%CI: 0.4–2.0), that between thymic carcinomas and low-risk thymomas was 4.8 (95%CI: 3.4–6.1), and that thymic carcinomas and high-risk thymomas was 3.5 (95%CI: 2.7–4.3).

Notably, meta-analyses on the role of ^{18}F -FDG PET/CT in staging, restaging, prognostic or treatment response evaluation of TETs are currently lacking.

5.5 Evidence-Based Data on PET in Esophageal Tumours

5.5.1 Staging

The real and unquestionable additional diagnostic value of ^{18}F -FDG PET/CT in comparison to conventional imaging methods is in evaluating distant metastases (M staging) of esophageal cancer [49], whereas recent evidence-based articles have addressed the performance of ^{18}F -FDG

PET/CT for detecting lymph nodal metastases (N staging).

Jiang et al. [50] found that the pooled sensitivity and specificity estimates of ^{18}F -FDG PET/CT for detecting regional lymph nodal metastases at staging were 66% (95%CI: 51–78%) and 96% (95%CI: 92–98%), respectively. The corresponding values on a per-patient analysis were 65% (95% CI: 49–78%) and 81% (95%CI: 69–89%), respectively. Overall, ^{18}F -FDG PET/CT has a moderate to low sensitivity and a high to moderate specificity for detection of regional nodal metastases in esophageal cancer. Therefore, extending the extent of lymph node dissection or radiotherapy target volume is necessary after the diagnosis of regional nodal metastases by ^{18}F -FDG PET/CT.

In another meta-analysis [51], Hu et al. evaluated the diagnostic performance of ^{18}F -FDG PET/CT for the assessment of preoperative lymph node metastases in patients with esophageal cancer. In patients without neoadjuvant treatment, ^{18}F -FDG PET/CT had a pooled sensitivity and specificity of 57% (95%CI: 45–69%) and 91% (95%CI: 85–95), respectively. In patients who received neoadjuvant treatment, ^{18}F -FDG PET/CT had a pooled sensitivity and specificity of 53% (95%CI: 35–70%) and 96% (95%CI: 86–99%), respectively. Therefore, ^{18}F -FDG PET/CT has a high specificity but a low sensitivity; thus, it cannot accurately detect the lymph nodal involvement in patients with esophageal cancer.

Shi et al. [52] also demonstrated that ^{18}F -FDG PET/CT had lower sensitivity and accuracy for detection of regional nodal metastases in patients with esophageal cancer before surgery. The pooled sensitivity and specificity were 62% (95%CI: 40–79%) and 96% (95%CI: 93–98%), respectively, on a per-station analysis; the corresponding values on a per-patient analysis were 55% (95%CI: 34–74%) and 76% (95%CI: 66–83%), respectively.

In this setting, cervical ultrasonography has very limited additional diagnostic value as supplement to a negative ^{18}F -FDG PET/CT in the detection of cervical lymph node metastases during the initial staging of patients with esophageal cancer, as demonstrated by Goense et al. [53].

5.5.2 Restaging

Restaging after neoadjuvant therapy aims to reduce the number of patients undergoing oesophagectomy in case of distant (interval) metastases. Kroese et al. [54] assessed the diagnostic performance of ^{18}F -FDG PET or PET/CT for the detection of distant interval metastases after neoadjuvant therapy in patients with esophageal cancer. The pooled proportion of patients in whom true distant interval metastases were detected by ^{18}F -FDG PET or PET/CT at restaging was 8% (95%CI: 5–13%). The pooled proportion of patients in whom false-positive distant findings were detected by ^{18}F -FDG PET or PET/CT at restaging was 5% (95%CI: 3–9%). In conclusion, ^{18}F -FDG PET or PET/CT at restaging after neoadjuvant therapy for esophageal cancer can considerably impact on treatment decision-making. However, pathological confirmation of suspected lesions is needed.

Cong et al. [55] assessed the value of ^{18}F -FDG PET or PET/CT for response prediction of primary tumour in patients with esophageal cancer during (group A) or after (group B) neoadjuvant chemoradiotherapy. The pooled sensitivity and specificity were 85% (95%CI: 76–91%) and 59% (95%CI: 48–69%), respectively, in group A. The equivalent values were 67% (95%CI: 60–73%) and 69% (95%CI: 63–74%), respectively, in group B. Interestingly, the pooled sensitivity was 90% in the studies that enrolled patients with esophageal squamous cell carcinoma merely in group B. According to the present data, ^{18}F -FDG PET/CT should not be used routinely to guide treatment strategy in esophageal cancer patients, but an additional value is expected in patients with esophageal squamous cell carcinoma treated with neoadjuvant chemoradiotherapy.

Goense et al. [56] assessed the diagnostic performance of ^{18}F -FDG PET or PET/CT for diagnosing recurrent esophageal cancer after initial treatment with curative intent. Pooled estimates of sensitivity and specificity for ^{18}F -FDG PET and PET/CT in this setting were 96% (95%CI: 93–97%) and 78% (95%CI: 66–86%), respec-

tively. Therefore, ^{18}F -FDG PET and PET/CT are reliable imaging modalities with a high sensitivity and moderate specificity for detecting recurrent esophageal cancer after treatment with curative intent. However, histopathologic confirmation of PET/CT-suspected lesions is required, because a considerable false-positive rate is noticed.

5.5.3 Predictive and Prognostic Value

Han et al. [57] performed a meta-analysis on the prognostic value of volumetric parameters (MTV and TLG) derived from pretreatment ^{18}F -FDG PET/CT in patients with esophageal cancer. The pooled HRs of MTV and TLG for OS were 2.26 (95%CI: 1.73–2.96) and 2.23 (95%CI: 1.73–2.87), respectively. Regarding event-free survival, the pooled HRs of MTV and TLG were 2.03 (95%CI: 1.66–2.49) and 2.57 (95%CI: 1.82–3.62), respectively. Therefore, in patients with esophageal cancer, MTV and TLG derived from pretreatment ^{18}F -FDG PET are significant prognostic factors.

Schollaert et al. [58] performed a meta-analysis on the predictive value of ^{18}F -FDG PET for assessing DFS and OS in esophageal and oesophagogastric junction cancer after neoadjuvant chemoradiation therapy. The pooled HRs for complete metabolic response versus no response were 0.51 for OS (95%CI: 0.4–0.64) and 0.47 for DFS (95%CI: 0.38–0.57), respectively. Therefore, metabolic response on ^{18}F -FDG PET is a significant predictor of long-term survival.

Lastly, Zhu et al. [59] performed a meta-analysis on the prognostic significance of SUVmax on ^{18}F -FDG PET/CT in patients with localized oesophagogastric junction cancer receiving neoadjuvant chemotherapy/chemoradiation therapy. Significant prognostic values of SUVmax before and during therapy in localized oesophagogastric junction cancer were not found. Conversely, relative changes in ^{18}F -FDG-uptake after therapy are significant prognostic markers for OS and DFS.

References

- MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. *Radiology*. 2017;284(1):228–43.
- Chien CR, Liang JA, Chen JH, Wang HN, Lin CC, Chen CY, et al. [(18)F]Fluorodeoxyglucose-positron emission tomography screening for lung cancer: a systematic review and meta-analysis. *Cancer Imaging*. 2013;13(4):458–65.
- Wang HQ, Zhao L, Zhao J, Wang Q. Analysis on early detection of lung cancer by PET/CT scan. *Asian Pac J Cancer Prev*. 2015;16(6):2215–7.
- Madsen PH, Holdgaard PC, Christensen JB, Højlund-Carlsen PF. Clinical utility of F-18 FDG PET-CT in the initial evaluation of lung cancer. *Eur J Nucl Med Mol Imaging*. 2016;43(11):2084–97.
- Ruifeng Z, Daohai X, Li G, Xiaohong W, Chunjie W, Lei T. Diagnostic value of 18F-FDG-PET/CT for the evaluation of solitary pulmonary nodules: a systematic review and meta-analysis. *Nucl Med Commun*. 2017;38(1):67–75.
- Li ZZ, Huang YL, Song HJ, Wang YJ, Huang Y. The value of 18F-FDG-PET/CT in the diagnosis of solitary pulmonary nodules: a meta-analysis. *Medicine*. 2018;97(12):e0130.
- Divisi D, Barone M, Bertolaccini L, Zaccagna G, Gabriele F, Crisci R. Diagnostic performance of fluorine-18 fluorodeoxyglucose positron emission tomography in the management of solitary pulmonary nodule: a meta-analysis. *J Thorac Dis*. 2018;10(Suppl 7):S779–89.
- Deppen SA, Blume JD, Kensinger CD, Morgan AM, Aldrich MC, Massion PP, et al. Accuracy of FDG-PET to diagnose lung cancer in areas with infectious lung disease: a meta-analysis. *JAMA*. 2014;312(12):1227–36.
- Basso Dias A, Zanon M, Altmayer S, Sartori Pacini G, Henz Concatto N, Watte G, et al. Fluorine 18-FDG PET/CT and diffusion-weighted MRI for malignant versus benign pulmonary lesions: a Meta-analysis. *Radiology*. 2019;290(2):525–34.
- Lin YY, Chen JH, Ding HJ, Liang JA, Yeh JJ, Kao CH. Potential value of dual-time-point ¹⁸F-FDG PET compared with initial single-time-point imaging in differentiating malignant from benign pulmonary nodules: a systematic review and meta-analysis. *Nucl Med Commun*. 2012;33(10):1011–8.
- Barger RL Jr, Nandalur KR. Diagnostic performance of dual-time 18F-FDG PET in the diagnosis of pulmonary nodules: a meta-analysis. *Acad Radiol*. 2012;19(2):153–8.
- Zhang L, Wang Y, Lei J, Tian J, Zhai Y. Dual time point 18FDG-PET/CT versus single time point 18FDG-PET/CT for the differential diagnosis of pulmonary nodules: a meta-analysis. *Acta Radiol*. 2013;54(7):770–7.
- Zhao M, Ma Y, Yang B, Wang Y. A meta-analysis to evaluate the diagnostic value of dual-time-point F-fluorodeoxyglucose positron emission tomography/computed tomography for diagnosis of pulmonary nodules. *J Cancer Res Ther*. 2016;12(Suppl):C304–8.
- Li XF, Dai D, Song XY, Liu JJ, Zhu YJ, Xu WG. Comparison of the diagnostic performance of 18F-fluorothymidine versus 18F-fluorodeoxyglucose positron emission tomography on pulmonary lesions: a meta analysis. *Mol Clin Oncol*. 2015;3(1):101–8.
- Wang Z, Wang Y, Sui X, Zhang W, Shi R, Zhang Y, et al. Performance of FLT-PET for pulmonary lesion diagnosis compared with traditional FDG-PET: a meta-analysis. *Eur J Radiol*. 2015;84(7):1371–7.
- Zhao L, He ZY, Zhong XN, Cui ML. (18)FDG-PET/CT for detection of mediastinal nodal metastasis in non-small cell lung cancer: a meta-analysis. *Surg Oncol*. 2012;21(3):230–6.
- Pak K, Park S, Cheon GJ, Kang KW, Kim IJ, Lee DS, et al. Update on nodal staging in non-small cell lung cancer with integrated positron emission tomography/computed tomography: a meta-analysis. *Ann Nucl Med*. 2015;29(5):409–19.
- Liao CY, Chen JH, Liang JA, Yeh JJ, Kao CH. Meta-analysis study of lymph node staging by 18 F-FDG PET/CT scan in non-small cell lung cancer: comparison of TB and non-TB endemic regions. *Eur J Radiol*. 2012;81(11):3518–23.
- Wang J, Welch K, Wang L, Kong FM. Negative predictive value of positron emission tomography and computed tomography for stage T1-2N0 non-small-cell lung cancer: a meta-analysis. *Clin Lung Cancer*. 2012;13(2):81–9.
- Schmidt-Hansen M, Baldwin DR, Hasler E, Zamora J, Abaira V, Roqué I Figuls M. PET-CT for assessing mediastinal lymph node involvement in patients with suspected resectable non-small cell lung cancer. *Cochrane Database Syst Rev*. 2014;(11):CD009519.
- Shen G, Hu S, Deng H, Jia Z. Diagnostic value of dual time-point 18 F-FDG PET/CT versus single time-point imaging for detection of mediastinal nodal metastasis in non-small cell lung cancer patients: a meta-analysis. *Acta Radiol*. 2015;56(6):681–7.
- Wu LM, Xu JR, Gu HY, Hua J, Chen J, Zhang W, et al. Preoperative mediastinal and hilar nodal staging with diffusion-weighted magnetic resonance imaging and fluorodeoxyglucose positron emission tomography/computed tomography in patients with non-small-cell lung cancer: which is better? *J Surg Res*. 2012;178(1):304–14.
- Shen G, Lan Y, Zhang K, Ren P, Jia Z. Comparison of 18F-FDG PET/CT and DWI for detection of mediastinal nodal metastasis in non-small cell lung cancer: a meta-analysis. *PLoS One*. 2017;12(3):e0173104.
- Li J, Xu W, Kong F, Sun X, Zuo X. Meta-analysis: accuracy of 18FDG PET-CT for distant metastasis staging in lung cancer patients. *Surg Oncol*. 2013;22(3):151–5.
- Yu B, Zhu X, Liang Z, Sun Y, Zhao W, Chen K. Clinical usefulness of 18F-FDG PET/CT for

- the detection of distant metastases in patients with non-small cell lung cancer at initial staging: a meta-analysis. *Cancer Manag Res.* 2018;10:1859–64.
26. Wu Y, Li P, Zhang H, Shi Y, Wu H, Zhang J, et al. Diagnostic value of fluorine 18 fluorodeoxyglucose positron emission tomography/computed tomography for the detection of metastases in non-small-cell lung cancer patients. *Int J Cancer.* 2013;132(2):E37–47.
 27. Li Y, Jin G, Su D. Comparison of gadolinium-enhanced MRI and 18FDG PET/PET-CT for the diagnosis of brain metastases in lung cancer patients: a meta-analysis of 5 prospective studies. *Oncotarget.* 2017;8(22):35743–9.
 28. Chang MC, Chen JH, Liang JA, Lin CC, Yang KT, Cheng KY, et al. Meta-analysis: comparison of F-18 fluorodeoxyglucose-positron emission tomography and bone scintigraphy in the detection of bone metastasis in patients with lung cancer. *Acad Radiol.* 2012;19(3):349–57.
 29. Qu X, Huang X, Yan W, Wu L, Dai K. A meta-analysis of ¹⁸FDG-PET-CT, ¹⁸FDG-PET, MRI and bone scintigraphy for diagnosis of bone metastases in patients with lung cancer. *Eur J Radiol.* 2012;81(5):1007–15.
 30. Wu Q, Luo W, Zhao Y, Xu F, Zhou Q. The utility of 18F-FDG PET/CT for the diagnosis of adrenal metastasis in lung cancer: a PRISMA-compliant meta-analysis. *Nucl Med Commun.* 2017;38(12):1117–24.
 31. Zhang C, Liu J, Tong J, Sun X, Song S, Huang G. 18F-FDG-PET evaluation of pathological tumour response to neoadjuvant therapy in patients with NSCLC. *Nucl Med Commun.* 2013;34(1):71–7.
 32. Sheikhbahaei S, Mena E, Yanamadala A, Reddy S, Solnes LB, Wachsmann J, et al. The value of FDG PET/CT in treatment response assessment, follow-up, and surveillance of lung cancer. *AJR Am J Roentgenol.* 2017;208(2):420–33.
 33. Hallqvist A, Alverbratt C, Strandell A, Samuelsson O, Björkander E, Liljegren A, et al. Positron emission tomography and computed tomographic imaging (PET/CT) for dose planning purposes of thoracic radiation with curative intent in lung cancer patients: a systematic review and meta-analysis. *Radiother Oncol.* 2017;123(1):71–7.
 34. Bucknell NW, Hardcastle N, Bressel M, Hofman MS, Kron T, Ball D, et al. Functional lung imaging in radiation therapy for lung cancer: a systematic review and meta-analysis. *Radiother Oncol.* 2018;129(2):196–208.
 35. He YQ, Gong HL, Deng YF, Li WM. Diagnostic efficacy of PET and PET/CT for recurrent lung cancer: a meta-analysis. *Acta Radiol.* 2014;55(3):309–17.
 36. Paesmans M, Garcia C, Wong CY, Patz EF Jr, Komaki R, Eschmann S, et al. Primary tumour standardised uptake value is prognostic in nonsmall cell lung cancer: a multivariate pooled analysis of individual data. *Eur Respir J.* 2015;46(6):1751–61.
 37. Liu J, Dong M, Sun X, Li W, Xing L, Yu J. Prognostic value of 18F-FDG PET/CT in surgical non-small cell lung cancer: a Meta-analysis. *PLoS One.* 2016;11(1):e0146195.
 38. Im HJ, Pak K, Cheon GJ, Kang KW, Kim SJ, Kim IJ, et al. Prognostic value of volumetric parameters of (18)F-FDG PET in non-small-cell lung cancer: a meta-analysis. *Eur J Nucl Med Mol Imaging.* 2015;42(2):241–51.
 39. Han S, Woo S, Suh CH, Kim YJ, Oh JS, Lee JJ. A systematic review of the prognostic value of texture analysis in 18F-FDG PET in lung cancer. *Ann Nucl Med.* 2018;32(9):602–10.
 40. Dong M, Liu J, Sun X, Xing L. Prognostic significance of SUVmax on pretreatment 18 F-FDG PET/CT in early-stage non-small cell lung cancer treated with stereotactic body radiotherapy: a meta-analysis. *Acta Radiol.* 2018;59(9):1082–90.
 41. Na F, Wang J, Li C, Deng L, Xue J, Lu Y. Primary tumor standardized uptake value measured on F18-Fluorodeoxyglucose positron emission tomography is of prediction value for survival and local control in non-small-cell lung cancer receiving radiotherapy: meta-analysis. *J Thorac Oncol.* 2014;9(6):834–42.
 42. Ma J, Wu X, Li J, Wang Z, Wang Y. Prognostic value of early response assessment using (18F)FDG-PET in patients with advanced non-small cell lung cancer treated with tyrosine-kinase inhibitors. *J Investig Med.* 2017;65(5):935–41.
 43. Lu YY, Chen JH, Liang JA, Chu S, Lin WY, Kao CH. 18F-FDG PET or PET/CT for detecting extensive disease in small-cell lung cancer: a systematic review and meta-analysis. *Nucl Med Commun.* 2014;35(7):697–703.
 44. Zhu D, Wang Y, Wang L, Chen J, Byanju S, Zhang H, et al. Prognostic value of the maximum standardized uptake value of pre-treatment primary lesions in small-cell lung cancer on 18F-FDG PET/CT: a meta-analysis. *Acta Radiol.* 2018;59(9):1082–90.
 45. Treglia G, Sadeghi R, Annunziata S, Lococo F, Cafarotti S, Bertagna F, et al. Diagnostic accuracy of 18F-FDG-PET and PET/CT in the differential diagnosis between malignant and benign pleural lesions: a systematic review and meta-analysis. *Acad Radiol.* 2014;21(1):11–20.
 46. Treglia G, Sadeghi R, Annunziata S, Lococo F, Cafarotti S, Prior JO, et al. Diagnostic performance of fluorine-18-fluorodeoxyglucose positron emission tomography in the assessment of pleural abnormalities in cancer patients: a systematic review and a meta-analysis. *Lung Cancer.* 2014;83(1):1–7.
 47. Porcel JM, Hernández P, Martínez-Alonso M, Bielsa S, Salud A. Accuracy of fluorodeoxyglucose-PET imaging for differentiating benign from malignant pleural effusions: a meta-analysis. *Chest.* 2015;147(2):502–12.
 48. Treglia G, Sadeghi R, Giovannella L, Cafarotti S, Filosso P, Lococo F. Is (18)F-FDG PET useful in predicting the WHO grade of malignancy in thymic epithelial tumors? A meta-analysis. *Lung Cancer.* 2014;86(1):5–13.
 49. Marzola MC, De Manzoni G, Grassetto G, Cordiano C, Al-Nahhas A, Alavi A, et al. Extended staging

- of oesophageal cancer using FDG-PET—a critical appraisal. *Eur J Radiol.* 2012;81(1):21–30.
50. Jiang C, Chen Y, Zhu Y, Xu Y. Systematic review and meta-analysis of the accuracy of 18F-FDG PET/CT for detection of regional lymph node metastasis in esophageal squamous cell carcinoma. *J Thorac Dis.* 2018;10(11):6066–76.
 51. Hu J, Zhu D, Yang Y. Diagnostic value of 18F-fluorodeoxyglucose positron-emission tomography/computed tomography for preoperative lymph node metastasis of esophageal cancer: a meta-analysis. *Medicine.* 2018;97(50):e13722.
 52. Shi W, Wang W, Wang J, Cheng H, Huo X. Meta-analysis of 18FDG PET-CT for nodal staging in patients with esophageal cancer. *Surg Oncol.* 2013;22(2):112–6.
 53. Goense L, Meziani J, van Rossum PSN, Wessels FJ, Meijer GJ, Lam MGEH, et al. Limited additional value of cervical ultrasonography over a negative 18F-FDG PET/CT for diagnosing cervical lymph node metastases in patients with esophageal cancer: a systematic review and meta-analysis. *Nucl Med Commun.* 2018;39(7):645–51.
 54. Kroese TE, Goense L, van Hillegersberg R, de Keizer B, Mook S, Ruurda JP, et al. Detection of distant interval metastases after neoadjuvant therapy for esophageal cancer with 18F-FDG PET(CT): a systematic review and meta-analysis. *Dis Esophagus.* 2018;31(12).
 55. Cong L, Wang S, Gao T, Hu L. The predictive value of 18F-FDG PET for pathological response of primary tumor in patients with esophageal cancer during or after neoadjuvant chemoradiotherapy: a meta-analysis. *Jpn J Clin Oncol.* 2016;46(12):1118–26.
 56. Goense L, van Rossum PS, Reitsma JB, Lam MG, Meijer GJ, van Vulpen M, et al. Diagnostic performance of ¹⁸F-FDG PET and PET/CT for the detection of recurrent esophageal cancer after treatment with curative intent: a systematic review and meta-analysis. *J Nucl Med.* 2015;56(7):995–1002.
 57. Han S, Kim YJ, Woo S, Suh CH, Lee JJ. Prognostic value of volumetric parameters of pretreatment 18F-FDG PET/CT in esophageal cancer: a systematic review and meta-analysis. *Clin Nucl Med.* 2018;43(12):887–94.
 58. Schollaert P, Crott R, Bertrand C, D'Hondt L, Borghet TV, Krug B. A systematic review of the predictive value of (18)FDG-PET in esophageal and esophagogastric junction cancer after neoadjuvant chemotherapy on the survival outcome stratification. *J Gastrointest Surg.* 2014;18(5):894–905.
 59. Zhu W, Xing L, Yue J, Sun X, Sun X, Zhao H, et al. Prognostic significance of SUV on PET/CT in patients with localised esophagogastric junction cancer receiving neoadjuvant chemotherapy/chemoradiation: a systematic review and meta-analysis. *Br J Radiol.* 2012;85(1017):e694–701.

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