Appropriate Use Criteria for ^{18}F-FDG PET/CT in Restaging and Treatment Response Assessment of Malignant Disease

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EXECUTIVE SUMMARY

Precision medicine is evolving to include a variety of data to optimize patient care and improve outcome. Multimodality imaging is paving the way toward this goal. PET/CT with ^{18}F-FDG is now established as an important imaging modality in many clinical conditions, particularly in oncology (*1,2*). Many tumors demonstrate high glucose metabolism as one of the hallmarks of cancer (*3*). PET/CT provides combined anatomic and physiologic (glucose metabolism) information that may be used for initial diagnosis, staging, restaging, treatment response assessment, and prognosis in patients with cancer. Moreover, PET information can contribute significantly when other imaging modalities are equivocal.

This document describes the appropriate use of PET/CT* in the response assessment and restaging of patients with cancer. Our focus is on common cancers in which the use of PET/CT has been most relevant for clinical practice. Restaging is broadly defined to include the phase of the disease after initial diagnosis and treatment, which may entail local recurrence, distant metastatic disease, and assessment of response to treatments after disease recurrence. The goal of these recommendations is to guide the appropriate use of PET/CT in assessing treatment response after therapy and in evaluating imaging of patients with suspected recurrent cancer. Although the terms response assessment and restaging are frequently used in the discussion of cancer treatment, no consensus definition exists regarding the time frame that differentiates these 2 terms. Indeed, the time interval at which a patient transitions from response assessment to restaging likely varies in relation to tumor biology, therapeutic regimen, and other factors. In this work, the term *assessment of response* is taken to mean the period in which the intended target of the therapeutic regimen is being evaluated, whereas the term *restaging of disease* is taken to mean the period in which there is concern for new or progressive disease after completion of prior therapy. This document excludes "initial staging" and "surveillance." These appropriate use criteria (AUC) are intended to aid referring medical practitioners in the appropriate use of PET/CT for restaging of breast cancer, colorectal cancer, lymphoma, lung cancer, melanoma, sarcoma, and head and neck cancer.

Note: The full version of this document, including information on methodology, conflicts of interest, benefits and harms, definition of terms, list of external reviewers, and additional special commentary, is available at http://snmmi.files.cms-plus.com/Quality/jnm197988_v1.pdf.

SYSTEMATIC REVIEW

To inform the workgroup, a systematic review of the relevant evidence was commissioned by an independent group, the Pacific Northwest Evidence-based Practice Center at Oregon Health and Science University. The primary purpose was to synthesize the evidence on the accuracy and comparative accuracy of PET/CT for restaging the 7 cancer types to help inform the development of AUC.

The key research questions used to guide the systematic review were as follows (i.e., How does the diagnostic accuracy of PET/CT vary according to tumor type, grade, or stage?): In patients with specific cancers,† what is the diagnostic accuracy of PET/CT versus a reference standard (clinical and imaging follow-up, with or without pathologic diagnosis), MRI, bone scan, CT alone, or other imaging modality for evaluating treatment response, identification of tumor recurrence, or restaging? In patients with specific cancers,† what are the effects of performing PET/CT versus no PET/CT or an alternative imaging modality on quality of life, patient management,‡ and patient clinical outcomes§? In patients with specific cancers,† what is the cost effectiveness and the comparative cost of performing a restaging PET/CT versus no PET/CT or an alternative imaging modality?

The inclusion and exclusion criteria for this review were based on the study parameters established by the expert workgroup, using the PICOTS (population, intervention, comparisons, outcomes, timing, and setting) approach. Database searches were conducted on the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and OVID MEDLINE

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*This document addresses ^{18}F-FDG PET/CT only unless stated otherwise.
†Breast cancer, colon cancer, lung cancer, lymphoma, melanoma, sarcoma, and head and neck cancer.
‡Patient management includes diagnostic management and treatment management.
§Patient clinical outcomes include overall survival, event-free survival, progression-free survival, disease-specific survival, disease-free survival, skeletal-related events, or change in outcome.

(from 1946 through July 2015), supplemented by reviewing the reference lists of relevant publications.

Two reviewers independently assessed abstracts and full-text articles for inclusion and rated study quality as defined by the established PICOTS parameters. The quality (based on risk of bias) for each study was categorized as "good," "fair," or "poor" by using the predefined criteria for each study design. Specifically, Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) was used for diagnostic accuracy studies (*4*) and Assessment of Multiple Systematic Reviews (AMSTAR) for systematic reviews (*5*). The strength of overall evidence was graded as high, moderate, low, or very low by using GRADE methods, which were based on quality of evidence, consistency, directness, precision, and reporting bias.

Literature searches resulted in 2,665 potentially relevant articles. After dual review of abstracts and titles, 1,120 articles were selected for full-text dual review and 45 studies were determined to meet inclusion criteria and included in this review.

BREAST CANCER

Clinical Scenarios and AUC Scores

Clinical scenarios for the use of PET/CT and final AUC scores in breast cancer are presented in Table 1.

Scenario 1: Restaging for detection of local recurrence (Score: 8 – Appropriate). Pennant and colleagues published a metaanalysis that evaluated PET/CT for detecting recurrence in patients with a history of breast cancer (*6*). PET/CT had a significantly higher sensitivity at 95% (95% confidence interval [CI], 88%–98%) versus CT at 80% (95% CI, 65%–90%), but the increased specificity was not significant, with PET/CT at 89% (95% CI, 69%–97%) versus CT at 77% (95% CI, 50%–92%). There were no significant differences in the sensitivity or specificity of PET when compared with MRI and, in the one lesion-based study, no significant differences in the sensitivity or specificity of PET/CT when compared with MRI. Champion et al. reported the following values for the detection of breast cancer recurrence: sensitivity, 93.6%; specificity, 85.4%; positive predictive value, 96.7%; negative predictive value, 74.5%; accuracy of PET/CT, 92.1%. When compared with standard workup in 67 patients, PET/CT had higher sensitivity (94.5% vs. 33%, respectively) and higher accuracy (94% vs. 48%, respectively) (*7*). Another report indicated that the respective values for PET/CT and CT were as follows: sensitivity, 89% versus 77%; specificity, 73% versus 53%; negative predictive value, 90% versus 75%; positive predictive value, 72% versus 55% (*8*).

TABLE 1
Clinical Scenarios for Breast Cancer

Scenario no.	Description	Appropriateness	Score
1	Restaging for detection of local recurrence	Appropriate	8
2	Restaging for detection of metastases	Appropriate	7
3	Treatment response evaluation	Appropriate	7

Scenario 2: Restaging for detection of metastases (Score: 7 – Appropriate). Veit-Haibach et al. compared the value of combined PET/CT, PET+CT (viewed side by side), CT alone, and PET alone in restaging of patients with recurrent breast cancer. Overall, the tumor, node, and metastasis (TNM) stage was correctly determined in 40 of 44 patients with PET/CT, in 38 of 44 with PET+CT, in 36 of 44 with PET alone, and in 36 of 44 with CT alone. Combined PET/CT appeared to be more accurate in restaging and showed a moderate impact on therapy over PET and CT (*9*). Another study reported a sensitivity of 98.7%, specificity of 85.3%, positive predictive value of 92.5%, and negative predictive value of 97.2% in the same clinical scenario of restaging patients with known breast cancer (*10*). Yet another group reported that for recurrent lesion detection, the respective sensitivities and specificities were 84% and 100% for PET, 66% and 92% for CT, and 93% and 100% for PET/CT (*11*).

Scenario 3: Treatment response evaluation (Score: 7 – Appropriate). This evaluation is primarily based on chemotherapy given in the neoadjuvant setting. Results may vary for immunotherapy, targeted therapy, and more advanced disease.

Cheng et al. found 17 studies (781 subjects) that fulfilled the inclusion criteria in a metaanalysis to determine the diagnostic performance of PET/CT for evaluating response to neoadjuvant chemotherapy in patients with breast cancer (*12*). The authors reported a pooled sensitivity of 85% (95% CI, 79%–89%) and a pooled specificity of 66% (95% CI, 60%–72%). The pooled likelihood ratio was 2.835 (95% CI, 1.640–4.900), the pooled negative likelihood ratio 0.221 (95% CI, 0.160–0.305), and the pooled diagnostic odds ratio 17.628 (95% CI, 7.431–41.818). The area under the curve was 0.8934. However, in a small study that enrolled 76 patients who received neoadjuvant chemotherapy, for the prediction of lymph node histopathologic response in patients with locally advanced breast cancer, the authors reported a sensitivity of 52%, specificity of 45%, positive predictive value of 50%, and negative predictive value of 47% for PET after 2 cycles and a sensitivity of 33%, specificity of 84%, positive predictive value of 67%, and negative predictive value of 56% for PET after the final cycle of chemotherapy (*13*).

COLORECTAL CANCER

Clinical Scenarios and AUC Scores

Clinical scenarios for the use of PET/CT and final AUC scores in colorectal cancer are presented in Table 2.

Scenario 1: Restaging for detection of local recurrence (Score: 7 – appropriate). For these guidelines, the panel considered "detection of local recurrence" to include recurrence within the involved colon or rectum (e.g., an anastomotic recurrence) and recurrence within adjacent soft tissue (e.g., presacral soft tissue thickening seen on CT after treatment for rectal carcinoma).

An early metaanalysis (*14*) that evaluated the efficacy of PET (before dissemination of PET/CT) included 11 articles and 366 patients with locally recurrent rectal carcinoma. The authors found an overall sensitivity of 94% and specificity of 98%, with a 29% change in management decisions. A later metaanalysis (*15*), also including only studies performed with PET (not PET/CT), found a pooled sensitivity and specificity of 94% and 94%, respectively, for local recurrence across 27 studies. A more recent metaanalysis

TABLE 2
Clinical Scenarios for Colorectal Cancer

Scenario no.	Description	Appropriateness	Score
1	Restaging for detection of local recurrence	Appropriate	7
2	Restaging for detection of metastases	Appropriate	8
3	Detection of local recurrence or metastasis in the case of rising tumor markers with negative or equivocal first-line imaging (e.g., contrast-enhanced CT or MRI)	Appropriate	8
4	Treatment response evaluation	May be appropriate	6
5	Assessment of response of metastases after chemotherapy	May be appropriate	6
6	Early assessment of metastases during chemotherapy	May be appropriate	6
7	Assessment of efficacy of neoadjuvant therapy for advanced rectal carcinoma	May be appropriate	6
8	Assessment of efficacy of localized minimally invasive therapy	May be appropriate	6

that encompassed 26 published studies that included only patients with local recurrence of colorectal cancer, or provided enough information to separate the results of local recurrences from those of metastatic disease, yielded a pooled sensitivity and specificity of PET/CT of 94% for each (*16*). Several additional metaanalyses have been published that offer interesting information, but include mixed datasets. For example, a 2011 metaanalysis compared the diagnostic performance of PET, PET/CT, CT, and MRI (*17*) in evaluating recurrent disease (local recurrence and distant disease) for patients with suspected recurrence from clinical findings or rising carcinoembryonic antigen (CEA). The authors found 14 observational studies meeting criteria for inclusion, 11 of which compared multiple modalities (12 studies evaluated PET, 5 PET/CT, 5 CT, and 1 MRI). Using receiver-operating characteristic analysis, the area under the curve of both PET and PET/CT was 0.94, compared with 0.83 for CT. In studies that directly compared PET with PET/CT, the latter showed a slightly higher diagnostic performance that was not statistically significant, but a significantly higher confidence of reader interpretation. A 2013 metaanalysis also included studies that evaluated both local recurrence and metastatic disease, but included only studies in which histopathologic diagnosis was used as a reference standard (*18*). Eleven studies that encompassed 510 patients met the inclusion criteria, including 7 that used PET and 4 that used PET/CT. The pooled sensitivity and specificity values of PET were 90% and 80%, respectively, whereas those for PET/CT were 94% and 77%, respectively. In 4 of these studies, the authors were able to directly compare PET/CT with CT, obtaining pooled sensitivity and specificity results of 94% and 93% for PET/CT, respectively, and 51% and 90% for CT, respectively.

A specific use of PET/CT reported in the literature pertaining to local recurrence is assessment for recurrence of ablated liver metastases. For this analysis, we have included this clinical scenario as a subcategory of treatment monitoring.

Overall, the panel assumes that patients being evaluated for local recurrence present with specific signs or symptoms (e.g., localized pain, equivocal abnormalities on other imaging modalities) or nonspecific indications of recurrence (e.g., rising serial CEA levels) and that the most likely next clinical step will be imaging by an advanced imaging modality. Given the generally high reported sensitivities and specificities of PET/CT relative to other modalities, with moderate strength of the data, the panel believes that PET/CT is appropriate for this indication.

Scenario 2: Restaging for detection of metastases (Score: 8 – appropriate). The panel considered "detection of metastases" to include metastases that were distant from the primary tumor. For colorectal cancer, this most commonly involved the liver, lung, and extrahepatic abdomen/pelvis, including lymph nodes.

Regarding liver metastases, an early metaanalysis that compared modalities in 61 studies (3,187 patients) found the following per-patient sensitivities: nonhelical CT, 60%; helical CT, 65%; MRI, 76%; PET (not PET/CT), 96% (*19*). Respective sensitivities on a per-lesion basis were lower for all modalities, ranging from 52% for CT to 76% for PET. A later metaanalysis included only prospective studies on detecting liver metastases in untreated colorectal cancer patients, using CT, MRI, PET, or PET/CT (*20*). Thirty-nine articles, including 3,391 patients, were assessed. The respective mean per-patient sensitivities and specificities were as follows: CT, 84% and 95%; MRI, 88% and 92%; PET, 94% and 96%. Respective per-lesion sensitivities were 74%, 80%, and 81%, with comparable specificities. The authors excluded PET/CT from the comparison analysis because of the small number of studies.

A randomized trial of 150 patients selected for surgical resection of limited hepatic metastases compared the diagnostic accuracy of CT and that of CT plus PET (not PET/CT) with the primary outcome measure of frequency of futile laparotomies (*21*). The addition of PET to the workup decreased futile laparotomies from 45% to 28%. A more recent multicenter randomized trial of 263 patients showed only an 8% change in management and no change in survival, although the results may have been limited by a significant number of patients who had received chemotherapy up to 3 mo before imaging (*22*). A 2010 metaanalysis of studies involving multimodality imaging of known or suspected liver metastases included 21 studies of exclusively colorectal cancer patients and 4 additional studies containing predominately colorectal cancer patients (*23*). Respective sensitivity and specificity values were 63% and 98% for ultrasonography, 75% and 96% for CT, 81% and 97% for MRI, and 94% and 99% for PET (not PET/CT). A more recent metaanalysis of 18 studies of patients with known or suspected liver metastases from colorectal cancer included 12 studies (484 patients) suitable for assessment of diagnostic accuracy and 12 studies (845 patients) suitable for assessment of changes in patient management (*24*). Pooled sensitivity and specificity values for PET and PET/CT were both 93% on a per-patient basis. PET had a slightly lower sensitivity than did CT and MRI, but higher specificity, and it changed patient management by detecting extrahepatic disease in 24% of patients, with only 3.1% false-positive and 1.3% false-negative results.

Fewer articles have specifically addressed extrahepatic metastases or the general category of all metastases outside the local tumor bed. An early metaanalysis of 32 PET (non-PET/CT) studies yielded a pooled sensitivity and specificity for PET imaging of 92% and 95%, respectively, for extrahepatic metastases compared with 61% and 91%, respectively, for CT (*25*). Pooled sensitivities and specificities for hepatic metastases were 88% and 96%, respectively, for PET and 83% and 84%, respectively, for CT. A 2009 metaanalysis that included 27 PET (non-PET/CT) studies showed a pooled sensitivity and specificity for distant metastases of 91% and 83%, respectively (*15*). The corresponding values for hepatic metastases were 97% and 98%.

Although the clinical scenarios of detection of recurrence and detection of metastases often overlap, as do published data in the literature, the panel believes there are ample published data in the literature to consider PET/CT appropriate for detection of extrahepatic abdominopelvic lesions and evaluation of suspected metastases after negative or equivocal CT/MRI results, with moderate strength of the evidence.

Scenario 3: Detection of local recurrence or metastasis in the case of rising tumor markers with negative or equivocal first-line imaging (e.g., contrast-enhanced CT or MRI) (Score: 8 – appropriate). The panel feels compelled to place this indication in a separate category because of the common presentation of this clinical scenario and the relatively large amount of data in the literature on this topic. Although most such patients could be placed in 1 of the first 2 categories, many patients have no localizing symptoms or imaging results on CT or MRI to suggest a local recurrence or a site of metastases, even though active tumor is suspected on the basis of elevated or rising tumor markers (especially CEA levels). In such cases, the options are typically serial anatomic imaging or evaluation with PET/CT.

A substantial percentage of the patients included in the metaanalyses described above presented for evaluation of elevated CEA level. Serial determination of CEA levels is widely used in follow-up of colorectal cancer patients and is included in the National Comprehensive Cancer Network (NCCN) guidelines, where follow-up is suggested for at least 5 y, with imaging in cases of persistently elevated CEA levels. However, serial CEA determination has a relatively low sensitivity of 80% and specificity of 70% (*26*), and the accuracy of CT for detecting tumor recurrence in patients with a rising CEA level may be limited. A metaanalysis of 11 studies (*18*) demonstrated a sensitivity of 51% and specificity of 90% for CT in this setting. That same metaanalysis revealed pooled estimates for sensitivity and specificity of 90% and 80%, respectively, for PET and 94% and 77%, respectively, for PET/CT. In the 4 studies that directly compared CT and PET/CT, the pooled sensitivity and specificity results for CT were 51% and 90%, respectively, and for PET/CT were 94% and 93%, respectively.

From the available data, the panel believes that PET/CT, with moderate strength, is appropriate in this application. In addition, from the limited accuracy of CEA, and the clinical presumptions that earlier detection of recurrence or limited metastasis allows more targeted therapeutic options with a higher likelihood of long-term success, the panel believes that PET/CT is highly appropriate in the follow-up of such patients after negative or equivocal imaging by other modalities.

Scenario 4: Treatment response evaluation (Score: 6 – may be appropriate). Arriving at a single score for this broad indication is challenging, and perhaps misleading, because of the especially wide variety of definitions used for "treatment response evaluation" and the wide variety of approaches taken to assess treatment response with PET. Many published articles take this term to mean the assessment of efficacy of a selected treatment, performed after completion of therapy. Others use the term to define "early treatment response evaluation" (i.e., the use of PET early during the prescribed course of therapy to predict the eventual efficacy of therapy). This confusion may have been accentuated when the Centers for Medicare & Medicaid Services (CMS) lumped together 2 categories of oncologic PET reimbursement (restaging and therapy monitoring) into a single category (subsequent treatment planning). For the current purposes, the panel believes that most clinical scenarios of follow-up after treatment should be assigned to 1 of these 2 categories.

The biologic basis of PET introduces substantial potential confounding factors into these distinctions, as does the evolving nature of oncologic therapy. In addition to the well-recognized limitation of PET in detecting small volumes of residual disease after treatment, its ability to detect residual or metastatic colorectal cancer deposits soon after chemotherapy is limited by the "metabolic shutdown" of colorectal cancer tumor cells after chemotherapy administered up to several weeks (perhaps up to 3 mo) before imaging (*27*). However, the traditional standards of treatment efficacy do not universally apply to the management of advanced or metastatic colorectal cancer, which is increasingly being palliated by using targeted or cytostatic agents, rather than cytotoxic/cytocidal agents. A more appropriate clinical question in these situations might be whether early PET monitoring predicts intermediate or long-term suppression of tumor growth (and, in turn, progression-free survival or overall survival) and whether continued PET surveillance detects early release from suppression that indicates the need for alternative therapies—in parallel with the relatively well-demonstrated use of PET to assess and monitor the efficacy of imatinib mesylate (Gleevec) and similar agents in gastrointestinal stromal tumors (*28*).

One metaanalysis of 11 papers (223 patients) that evaluated various modalities after neoadjuvant therapy of colorectal liver metastases showed decreased sensitivity of both CT and PET in the neoadjuvant setting, with PET being most affected (*29*). MRI was most accurate after therapy, but no studies were available to assess pretherapy sensitivity, and 2 of the 3 included MRI studies used superparamagnetic iron-oxide contrast agents.

In a prospective study of patients with hepatic colorectal metastases referred for either immediate resection or neoadjuvant chemotherapy before resection (*30*), the relative sensitivity of PET/CT decreased from 93% in the nontreated group to 49% in the postneoadjuvant therapy group. This decrease in sensitivity could be correlated with the decreasing size of lesions after therapy and may also have been partially related to "metabolic shutdown." In addition, a significant percentage of the false-negative lesions on PET were mucinous adenocarcinomas.

One metaanalysis of 9 studies (3 PET only and 6 PET/CT) that evaluated local tumor recurrence after ablation of liver metastases showed that PET was more accurate after radiofrequency ablation (RFA) of liver metastases with an open surgical technique than with a percutaneous technique (*31*). The data also suggested that PET may be more accurate in therapy monitoring of such lesions if performed immediately after RFA, before the onset of potentially confounding inflammation.

Scenario 5: Assessment of response of metastases after chemotherapy (Score: 6 – may be appropriate). A moderate number of published papers have addressed the relationship between metabolic response of metastases to therapy, as measured by PET, and

measures of survival. A recent metaanalysis that included 7 such papers (247 patients) and addressed "event-free survival" in patients being treated for liver metastases showed a strong predictive value of response (decreased maximal standardized uptake values [SUVs]) between pre- and posttherapy PET/CT (*32*). The same analysis found 7 studies (334 similar patients) that also demonstrated a similar correlation between metabolic response after therapy and overall survival.

In general, the panel felt that this indication may be appropriate for assessment of efficacy of a completed therapeutic regimen, if the patient was a candidate for further therapy of the same or different type, depending on the result. PET/CT would be particularly appropriate if CT or MRI was inconclusive. In such cases, both the referring physician and the imaging physician should take into account the possibility of metabolic effects of recent chemotherapy, and PET/CT should be delayed as long as is practical after the last administration of chemotherapy.

Scenario 6: Early assessment of metastases during chemotherapy (Score: 6 – may be appropriate). Numerous reports have addressed the use of PET or PET/CT in early treatment monitoring during chemotherapy for metastatic colorectal carcinoma. Unfortunately, these papers generally included small numbers of patients and were extremely varied regarding treatment modality used, timing of PET imaging during therapy, PET parameter being correlated with response, and response parameter being measured.

From these reports, the panel believes that early assessment of the therapeutic effects with PET/CT may be appropriate, with relatively weak strength of evidence. In general, such imaging should be restricted to those cases in which early decisions regarding potential changes in therapy are critical because of patient condition or therapeutic toxicities, and both the referring physician and the imaging physician should take into account the potential confounding factors of metabolic shutdown and potential differences between cytocidal and cytostatic treatment modalities.

Scenario 7: Assessment of efficacy of neoadjuvant therapy for advanced rectal carcinoma (Score: 6 – may be appropriate). Likely the most investigated scenario of restaging after therapy by PET in colorectal cancer is the assessment of efficacy of neoadjuvant therapy for locally advanced rectal cancer. In this arena, the utility of PET has received mixed reviews, leading to this indication receiving a low ranking in several previous older guidelines for colorectal cancer management. However, recent metaanalyses show generally favorable results that merit reconsideration of the appropriateness of this indication.

A 2012 metaanalysis that included both PET and PET/CT papers with a QUADAS score of 10 or greater found 28 acceptable studies comprising 1,204 patients and showed a pooled sensitivity and specificity of 78% and 66%, respectively (*33*). A more recent metaanalysis that addressed only PET/CT found 34 papers (only 29 meeting criteria for full quantitative metaanalysis), including 1,526 total patients, that met inclusion criteria (*34*). The median QUADAS score was 12. Global assessment of the prediction of tumor response by PET/CT showed a sensitivity of 73% and specificity of 77%. The large sample size allowed for breakdown comparison of several methodologic options. For example, given the known limitations of PET/CT in detecting very small volumes of residual tumor, 71% of the included studies based their analysis on "major response," while 29% used "complete pathologic response." The former yielded a pooled sensitivity and specificity of 74% and 78%, respectively, whereas the latter yielded similar values of 71% and 76%, respectively. There appeared to be little difference in overall accuracies between various quantitative approaches to response determination (SUV_{max} after therapy, SUV_{max} response index, total lesion glycolysis, metabolic tumor volume), although all of these approaches tended toward higher sensitivity compared with visual analysis.

A 2016 metaanalysis (*35*) included 10 papers with high-quality scores (all 10 complied with at least 12 of 14 items on the QUADAS checklist, with a mean score of 12.7) and showed statistically significant differences in the response index and posttreatment SUV_{max} between responders and nonresponders, but with significant overlap between groups. Another metaanalysis assessed the prediction of both complete pathologic response and patient survival (*36*) and included 17 papers with a mixture of PET and PET/CT examinations. Pooled results also showed statistically significant differences in both response index and posttreatment SUV_{max} between response groups, but with significant overlap. Most, but not all, studies showed a strong association between PET response and both disease-free survival and overall survival.

There are limited direct comparisons of PET with other modalities, especially MRI. Three recent metaanalyses have shown similar accuracies of MRI for prediction of complete pathologic response (*37–39*). In a fourth recent metaanalysis with 33 studies (including MRI, PET, and PET/CT with 1,564 patients meeting the inclusion criteria), the authors concluded that diffusion-weighted MRI (DW-MRI) was superior to PET in predicting complete pathologic response (*40*). However, that analysis included 6 PET papers that used only qualitative visual analysis of response. In addition, when PET/CT studies were evaluated as a subgroup, pooled sensitivity and specificity values were 89% and 80%, respectively, versus 85% and 73%, respectively, for DW-MRI.

From the variable, but generally positive, results in the recent literature, the panel believes that PET/CT may be appropriate for this specific application, with moderate strength of the evidence. Given the current data, this application should probably be reserved for cases in which clinical factors or imaging studies raise questions regarding appropriate patient staging or management, such that evidence of response or progression on a follow-up PET/CT study would have significant likelihood of changing patient management. Such examinations will most likely be contributory if a baseline study has been performed for comparison. If there is clinical concern of distant metastatic disease that would change patient management, PET imaging in such a patient would be assigned the higher score designated for metastatic evaluation as described above.

Scenario 8: Assessment of efficacy of localized minimally invasive therapy (Score: 6 – may be appropriate). Another specific question of increasing importance is the assessment of therapeutic efficacy after localized therapy of liver metastases. For assessment of recurrence after surgical resection, the panel believes such cases would be more appropriately considered in one of the above categories for "detection of recurrence" or "detection of metastases."

A 2012 metaanalysis that evaluated PET (and PET/CT) in detecting local tumor recurrence of ablated liver metastases found 9 suitable publications for inclusion, 6 using PET/CT and 3 using PET (*31*). Sensitivity and specificity values of PET imaging for recurrence of treated metastases from colorectal carcinoma were 85% and 92%, respectively. As noted above, PET was more accurate after RFA of liver metastases with an open surgical technique than with a percutaneous one.

From the available data, the panel believes PET/CT may be appropriate for this application with relatively weak evidence, but should be reserved for patients in whom critical clinical management decisions must be made on the basis of the best possible evaluation of treatment efficacy.

LYMPHOMA

Clinical Scenarios and AUC Scores

Clinical scenarios for the use of PET/CT and final AUC scores in lymphoma are presented in Table 3.

Scenario 1: Detection of recurrent disease (Score: 8 – appropriate). Four studies evaluated the accuracy of PET/CT for detecting recurrent disease in patients treated for lymphoma (*41–44*): 2 in patients with Hodgkin lymphoma (HL) (*42,44*), 1 in patients with non-Hodgkin lymphoma (NHL) (*41*), and 1 in a mixed HL and NHL population (*43*). Sensitivity ranged from 93% to 100% and specificity from 91% to 100%. Three of the studies compared the accuracy of PET/CT to that of PET or CT alone (*41–43*). There were no clear differences between PET/CT and PET alone, although sensitivity estimates were higher in all 3 studies for PET/CT (93%–100%) than in CT alone (78%–83%). Specificity estimates for CT were inconsistent (54%–94%).

Scenario 2: Treatment response evaluation (Score: 9 – appropriate). Three studies evaluated the accuracy of PET/CT to assess treatment response in patients with lymphoma (*45–47*): 2 fair-quality studies of patients with follicular lymphomas found PET/CT to be associated with high sensitivity (100% for both studies) and specificity (100% and 99%) for detection of residual disease (*45,46*), and 1 study found that contrast-enhanced CT also had 100% sensitivity, but its specificity was much lower than that of PET at 52% (*45*). A poor-quality study of patients with diffuse large B-cell lymphoma (DLBCL) undergoing autologous stem cell transplant found a lower sensitivity for PET/CT of 53% with a specificity of 92% (*47*).

TABLE 3
Clinical Scenarios for Lymphoma

Scenario no.	Description	Appropriateness	Score
1	Detection of recurrent disease	Appropriate	8
2	Treatment response evaluation	Appropriate	9

LUNG CANCER

Clinical Scenarios and AUC Scores

Clinical scenarios for the use of PET/CT and final AUC scores in lung cancer are presented in Table 4.

Scenario 1: Restaging for detection of local recurrence (Score: 7 – appropriate). One systematic review showed a high pooled/joint sensitivity and specificity (*48*). Two studies ($n = 88$ and $n = 101$) not included in the systematic review also found that PET/CT was associated with high specificity (94% and 98%), but sensitivity estimates were inconsistent (50% and 94%, respectively) (*48,49*). This observation underlines the importance of correct patient selection, as sensitivity can be lower depending on the population studied (small lesions, etc.).

TABLE 4
Clinical Scenarios for Lung Cancer

Scenario no.	Description	Appropriateness	Score
1	Restaging for detection of local recurrence	Appropriate	7
2	Restaging for detection of metastases	Appropriate	7
3	Treatment response evaluation	Appropriate	7

Restaging after initial treatment (surgery, chemoradiotherapy, or radiotherapy): General comments. A recent metaanalysis analyzed the diagnostic efficacy of PET and PET/CT with ^{18}F-FDG compared with other imaging techniques (OITs) for detecting recurrent lung cancer (*48*). The inclusion criteria were studies of secondary lung cancer investigations that used PET or PET/CT with ^{18}F-FDG to diagnose lung cancer recurrence, considering disease as a consequence of the originally diagnosed lung cancer, regardless of whether the recurrence was local, regional, or distant. Thirteen articles and 1,035 patients were included. The studies obtained high pooled/joint sensitivity and specificity for PET/CT. Pooled sensitivity for PET, PET/CT, and OITs were 0.94, 0.90, and 0.78, respectively, and pooled specificity for PET, PET/CT, and OITs were 0.84, 0.90, and 0.80, respectively. Regarding sensitivity, lower values were associated with OITs than with PET ($P = 0.000$) and PET/CT ($P = 0.005$), and there was no significant difference between the values for PET/CT and PET ($P = 0.1$). Regarding specificity, values for PET/CT and PET were significantly higher than they were for OITs (both $P = 0.000$), with no significant difference between PET/CT and PET values ($P = 0.2$). The summary receiver operating characteristic curves showed better diagnostic accuracy associated with PET/CT than with PET and OITs. The authors concluded that PET/CT and PET were superior modalities for detecting recurrent lung cancer and that PET/CT was superior to CT (*48*).

Other studies not included in this systematic review and metaanalysis (*48*) also found that PET/CT was associated with high specificity for detecting recurrent disease after initial treatments, including homogeneous patient populations treated with surgery (*50,51*), radiotherapy (*49,52–56*), or RFA (*55,57*), as discussed below. However, another study by Jiménez-Bonilla et al. (*58*), which was not included in the metaanalysis, also evaluated a heterogeneous population, with patients in all stages of non–small cell lung cancer (NSCLC) from stage I to more advanced stages. The authors analyzed 59 suspicious lesions in 55 patients, reporting an overall sensitivity and specificity for PET/CT of 100% and 83%, respectively. PET/CT had an impact on patient management in 42 of the 59 cases (71%) of suspected recurrence.

Restaging after surgery. In their study, Toba et al. (*51*) retrospectively included 101 NSCLC patients who had undergone potentially curable operations and were followed with PET/CT at least once a year (233 PET/CT studies), selecting patients without clinical or radiologic evidence of recurrence. Eighteen (18%) asymptomatic patients had recurrent disease and 22

recurrent sites were confirmed. PET/CT correctly diagnosed recurrence in 17 of 18 (94%) patients and 21 of 22 (95%) recurrent sites. The following values were reported: sensitivity, 94.4%; specificity, 97.6%; positive predictive value, 89.5%; negative predictive value, 98.8%; accuracy, 97.0%. Additionally, PET/CT detected other previously not known diseases and allowed early appropriate treatment (*51*). In this study, all recurrent sites were located in intrathoracic or cervical fields. Although incidentally all recurrences were intrathoracic, the advantage of using PET/CT was that it demonstrated a high accuracy for detecting distant metastases.

Another study that analyzed PET/CT performance for detecting recurrent disease after initial curative surgery, also not included in the previous metaanalysis (*48*), is by Choi et al. (*50*). They included 358 patients who had undergone complete resection of NSCLC and were prospectively followed up with PET/CT and conventional methods. Recurrent disease occurred in 31% of patients. Other methods detected half of these recurrences. In the remaining patients, recurrent disease was detected with both CT and PET/CT in 51% of patients and with only PET/CT in 37%. PET/CT was false negative in 6 small or hypometabolic recurrent lesions. Because of this, the authors recommend an annual screening method that includes PET/CT and a low-dose chest CT scan (*50*). The recently published European Association of Nuclear Medicine (EANM) guidelines include an optional, but recommended, low-dose chest CT scan in the PET/CT procedure to better assess small lung lesions (*59*).

Restaging after stereotactic body radiation therapy (SBRT). SBRT is an established treatment option for early-stage lung cancer that causes focal changes in the lung parenchyma around the treated tumor site, most frequently as ground-glass opacities (*60,61*). Pastis et al. (*49*) analyzed the diagnostic efficacy of PET/CT for detecting local treatment failure or intrathoracic recurrences after SBRT treatment in NSCLC patients. Eighty-eight patients were included and PET/CT was done 3 mo after ending SBRT. PET/CT results were positive in 12 of 88 patients (14%), being confirmed as true positive in 8 of 12 (67%). PET/CT results were negative in 76 of 88 patients (86%), being confirmed as true negative in 68 of 76 (89%). Therefore, sensitivity was 50.0%, specificity 94.0%, positive predictive value 67.0%, and negative predictive value 89.0%. The authors concluded that a PET/CT scan 3 mo after SBRT treatment of NSCLC was specific but had a low sensitivity for detecting recurrent disease or treatment failure.

In another study that focused on lung cancer patients treated with SBRT, Zhang et al. (*56*) analyzed whether the SUVs in PET/CT after SBRT could predict local recurrence in NSCLC. The study included 128 patients with 140 biopsy-proven NSCLC tumors, in whom 506 PET/CT scans were done between 1 and 6 mo after SBRT and subsequently as clinically indicated (median follow-up 31 mo). The authors concluded that PET/CT was helpful for distinguishing SBRT-induced consolidation from local recurrence. High SUVs (>5.0) obtained more than 6 mo after SBRT for NSCLC were associated with local failure and should prompt the performance of a biopsy to rule out local recurrence (*56*). A similar study by Takeda et al. (*60*) that included 154 NSCLC patients with 214 PET/CT scans done 1 y after SBRT for detecting local recurrence reported a sensitivity and specificity of 100% and 96%–98%, respectively.

Whereas these 2 studies analyzed the performance of PET/CT studies done 6 mo to 1 y after SBRT, Van Loon et al. (*62*) reported that early PET/CT scans done 3 mo after radical (chemo-) radiotherapy with curative intent helped detect progressive disease. They prospectively included 100 patients with NSCLC who had a PET/CT scan done 3 mo after initiation of radiotherapy. Progressive disease was detected in 24 patients, only 16 with symptoms. In the subgroup of symptomatic patients, the impact on management of PET/CT was limited because no curative treatment could be offered as an alternative. However, in the asymptomatic group, in 3 of 8 patients diagnosed with progressive disease, the option of radical treatment could be offered. As progressive disease in asymptomatic patients was diagnosed with PET/CT but not CT, the authors concluded that asymptomatic patients are probably those who could profit most from an early PET/CT scan, although further studies are needed.

A frequent finding after radiotherapy is the presence of a variable and persistent ^{18}F-FDG uptake. Hoopes et al. (*63*) studied a small patient population with inoperable stage I NSCLC, reporting persistent and moderately intense ^{18}F-FDG uptake up to 2 y after SBRT treatment. This uptake could be related to inflammation and fibrosis, which is probably more persistent after SBRT than it is after conventional fractioned radiotherapy (*64*).

Restaging after RFA or microwave ablation (MWA). Besides surgery and SBRT, RFA is another option for patients with stage I NSCLC. After RFA treatment, the most frequent type of recurrence is locoregional (*65*). RFA, like SBRT, also causes ground-glass opacities in the lung parenchyma around the treated tumor site (*60,61*). Different algorithms, including PET/CT 3 to 6 mo after RFA, have been proposed in order to closely follow these patients (*55,57,65,66*), although the few studies reported had a limited number of patients. Yoo et al. (*55*) evaluated the performance of early postablation PET/CT in assessing the success of RFA for stage I NSCLC. They included 30 patients with medically inoperable stage I NSCLC who underwent 3 PET/CT scans, one at baseline, another within 4 d after RFA, and the third 6 mo after RFA. They concluded that early post-RFA PET/CT is not necessary and 6-mo post-RFA PET/CT findings correlate better with the clinical outcome at 1 y. Pou Ucha et al. (*57*) analyzed a small patient population of 7 patients, each with a single tumor lesion, who underwent RFA or MWA. CT and PET/CT were performed at baseline and follow-up, the dual time-point technique applied when necessary. PET/CT presented high accuracy and was superior to CT, although the study had methodologic limitations.

Cost-effectiveness. To date, Van Loon et al. have published the only cost-effectiveness study of NSCLC follow-up (*67*). The 100 NSCLC patients included were compared in 3 different follow-up strategies, all starting 3 mo after therapy: PET/CT, chest CT, or conventional with a chest radiograph. The authors concluded that a PET/CT 3 mo after curative intent (chemo-) radiotherapy is potentially cost-effective and is more cost-effective than CT alone. Additionally, PET/CT in asymptomatic patients appears to be equally effective and even more cost-effective (*60,67*).

Scenario 2: Restaging for detection of metastases (Score: 7 – appropriate). PET/CT has a high diagnostic performance for detecting metastases. At diagnosis, around 18%–36% of patients with NSCLC have distant metastases. Detection at initial staging is key to deciding on the most appropriate management option, as M staging has a direct impact on management and prognosis (*68*). Furthermore, in patients apparently radically treated for NSCLC, around 20% relapse because of undetected metastases at the time of initial staging (*68,69*). Metastases are usually located in the adrenal glands, bones, brain, or liver.

PET has demonstrated good performance in differentiating benign from metastatic adrenal lesions in patients with cancer (*70*), but few studies have specifically addressed this issue in lung cancer patients (*71,72*). The study that has included the most patients analyzed 113 adrenal masses detected on CT or MRI in 94 patients. PET showed a sensitivity of 98%, specificity of 90%, and accuracy of 92% for detecting metastatic disease (*72*). For bone metastases, PET is more sensitive and specific than bone scintigraphy (*69,73–75*). The best method for liver lesions is MRI, but PET is better than CT, as it detects lesions earlier and is more accurate.

A metaanalysis analyzed the diagnostic efficacy of PET/CT compared with OITs for detecting recurrent lung cancer, considering disease as a consequence of the originally diagnosed lung cancer, regardless of whether recurrence was local, regional, or distant. The authors obtained a high pooled/joint sensitivity and specificity for PET/CT, concluding that PET/CT and PET were superior modalities for detecting recurrent lung cancer and that PET/CT was superior to CT (*48*).

A metaanalysis undertaken to evaluate the performance of PET/CT for detecting distant malignancies in various cancers included 41 studies and 4,305 patients (*76*). Of these, 5 studies had data on lung cancer (*77–81*) comprising 578 patients. The pooled sensitivity was 0.91, specificity 0.96, positive likelihood ratio 25.9, and negative likelihood ratio 0.09. The authors concluded that PET/CT has an excellent diagnostic performance for detecting distant malignancies in patients with various cancers, especially in lung, breast, and head and neck cancer (*76*).

Scenario 3: Treatment response evaluation (Score: 7 – appropriate). Traditionally, tumor response has been assessed by comparing the tumor size on CT before and after treatment, previously in 2 dimensions (*82*) and more recently in 1 dimension (RECIST) (*83*). PET provides functional information and detects metabolic changes earlier than morphologic changes. Early assessment of response to therapy can help tailor treatments in order to continue them in responding patients and to discontinue them and change to second-line treatments in nonresponders. Current evidence in this setting shows that PET/CT response is probably earlier and more accurate than CT response (*84*). However, an important issue to be resolved is the standardization of the methodology. The EANM has recently updated the PET/CT procedure guidelines for tumor imaging, focusing on harmonization so that the methodology and results will be comparable worldwide (*59*).

In patients with locally advanced lung cancer who undergo multimodality treatment, correct restaging after induction therapy is needed (*84*). In NSCLC stage IIIa-N2, a favorable outcome after surgery and a combined treatment modality highly depends on pathologic downstaging or clearance of all tumor in the mediastinal lymph nodes after the induction phase. CT has limitations in evaluating response to induction treatment because small-sized lymph nodes can still harbor metastatic disease, whereas large nodes can be caused by inflammatory factors or scarring (*85–87*). Several studies have analyzed the role of PET in this clinical setting with good results.

One fair-quality study of patients with stage IIIa NSCLC with biopsy-proven N2 disease who underwent neoadjuvant chemoradiotherapy and subsequent restaging ($n = 93$) found that PET/CT was associated with a sensitivity of 62% and specificity of 88% in identifying N2 disease. The proportion of patients with correct stage classification, compared with pathologic staging, was greater with PET/CT than with CT across tumor stages 0 through IV, though differences were statistically significant only for stage 0 and stage I (*88*). Other studies have shown that patients who are downstaged via neoadjuvant therapy and then undergo resection have a significantly longer 5-y survival rate of 40%–50% (*85–87*) than do those who have residual N2 disease (*89*). Therefore, identifying patients who are N2 negative after completion of their neoadjuvant therapy is a critical component for patient selection for thoracotomy (*88*). However, correctly identifying responding from nonresponding patients remains a challenge. Most patients with pathologically diagnosed N2 disease have undergone mediastinoscopy. Repeat mediastinoscopy is difficult, often inaccurate (*90,91*), and potentially dangerous, in particular after radiotherapy. Furthermore, studies have shown a high false-negative rate of repeat mediastinoscopy after neoadjuvant therapy, with a range of 25%–42% (*90,92*). Fine-needle aspiration guided by endoscopic ultrasound has been used as a restaging method with a reported accuracy of 83% in one study with a small patient population ($n = 19$) after neoadjuvant chemoradiotherapy. The main problems of this technique are that it does not allow adequate visualization of the lower paratracheal nodes (*93*) and is available in only a few centers. In summary, the surgeon often has the clinical stage assessed only by repeat PET/CT or CT to back up management decisions. The prospective study by Cerfolio et al. concluded that repeat integrated PET/CT is superior to repeat CT for restaging of patients with N2 stage IIIa NSCLC after neoadjuvant chemoradiotherapy (*88*).

A metaanalysis published in 2012 analyzed the value of PET and CT in predicting the pathologic tumor response of NSCLC after neoadjuvant therapy. The pathologic outcome was the gold standard. Thirteen studies and 414 patients were included with different neoadjuvant treatments: chemoradiotherapy in 5 studies, chemotherapy in 2, and mixed treatments in the remainder (*94*). For prediction of response with PET, the pooled sensitivity was 83%, specificity 84%, positive predictive value 74%, and negative predictive value 91%. The predictive value of PET in NSCLC patients with pathologic response was significantly higher than that of CT ($P < 0.05$). However, the limitations of the metaanalysis included the heterogeneity of the studies, the mixed pathologic types, and their retrospective design. Taking into account these limitations, the authors concluded that PET is useful for predicting patients with NSCLC who would be nonresponders to neoadjuvant therapy, and it has better predictive value than that of CT for evaluating pathologic documented responses.

MELANOMA

Clinical Scenarios and AUC Scores

Clinical scenarios for the use of PET/CT and final AUC scores in melanoma are presented in Table 5.

Scenario 1: Detection of recurrent disease (Score: 9 – appropriate). The systematic review identified one fair-quality study ($n = 90$) that found that PET/CT was associated with a sensitivity of 87% and specificity of 93% for detecting malignant melanoma recurrence (*95*). A large metaanalysis representing 74 separate studies that pooled the results of multimodality imaging in 10,528 patients (*96*) found that PET/CT had the best performance for detecting recurrent disease, with a sensitivity of 86% and specificity of 91%. In comparison, CT had values of 63% for sensitivity and 78% for specificity. The utility of ultrasound was limited to evaluation of recurrence in the local site or regional nodal basin.

TABLE 5
Clinical Scenarios for Melanoma

Scenario no.	Description	Appropriateness	Score
1	Restaging for detection of recurrent disease	Appropriate	9
2	Treatment response evaluation	Appropriate	7

Scenario 2: Treatment response evaluation (Score: 7 – appropriate). One fair-quality study ($n = 97$) found that PET/CT was associated with a sensitivity of 92% (95% CI, 83%–97%) and specificity of 59% (95% CI, 41%–76%) for distinguishing patients with a complete response after isolated limb infusion chemotherapy for stage IIIb or IIIc malignant melanoma (*97*). As in other malignancies, functional imaging with PET/CT can often differentiate residual viable tumor from treatment-related scarring and fibrosis, and it may serve as an imaging biomarker for therapy response.

SARCOMA

Clinical Scenarios and AUC Scores

Clinical scenarios for the use of PET/CT and final AUC scores in sarcoma are presented in Table 6.

Scenario 1: Restaging for detection of local recurrence (Score: 7 – appropriate). PET/CT has better sensitivity and specificity for detecting recurrent disease than does conventional imaging or bone scintigraphy. In a metaanalysis by Liu et al. (*98*) for local recurrence, 4 trials showed ^{18}F-FDG PET/CT had 91% sensitivity and 93% specificity. In soft tissue sarcoma, PET/CT has a high negative predictive value in excluding disease in enlarged lymph nodes.

Scenario 2: Restaging for detection of metastases (Score: 7 – appropriate). In the Oregon Health and Science University systematic review (*99*), one fair-quality study with 833 PET/CT studies of 206 patients with stage II–IV osteosarcoma after treatment with surgery and chemotherapy identified a sensitivity of 95% and specificity of 98% for detecting metastatic disease. The comparative sensitivity for bone scan was 76%, although there was similar specificity for detecting metastases. In the metaanalysis by Liu et al., they cited 5 trials involving 1,001 pooled lesions for detecting distant metastases in bone sarcoma with a sensitivity of 90% and specificity of 85% (*98*). The early detection and management of metastatic disease could improve survival. Detection of pulmonary metastases was not as good as detection of nonpulmonary metastatic lesions. This result could relate to the size of the lesions able to be detected by PET on free breathing studies and to the CT scan technique used for PET/CT studies (*98,100*). Gabriel and Rubello stated that ^{18}F-FDG PET/CT can be helpful to confirm the presence of isolated pulmonary metastases in patients with soft tissue sarcoma. They also stated that ^{18}F-FDG PET/CT has 80%–90% sensitivity and specificity for detection of metastases (*101*).

TABLE 6
Clinical Scenarios for Sarcoma

Scenario no.	Description	Appropriateness	Score
1	Restaging for detection of local recurrence	Appropriate	7
2	Restaging for detection of metastases	Appropriate	7
3	Treatment response evaluation	Appropriate	8

Scenario 3: Treatment response evaluation (Score: 8 – appropriate). Because bone sarcomas exhibit an increased rate of glycolysis, PET/CT studies have been used to assess them. ^{18}F-FDG uptake in heterogeneous tumors can be correlated to the aggressiveness of the tumor and the pathologic grade and used to localize the best biopsy site. SUV before and after chemotherapy can suggest a histologic response with an SUV2:1 of < 0.5 or an SUV2 of < 2.5 (*98,102–104*).

Soft tissue sarcoma lesions with a high SUV have indicated poorer prognosis, albeit no cutoff value has been confirmed. A 35% reduction in SUV after the first cycle of chemotherapy has been suggested as a histologic response marker in soft tissue sarcoma. A 60% reduction in SUV when scans are compared before and after completing neoadjuvant chemotherapy in high-grade soft tissue sarcoma showed 100% sensitivity and 71% specificity for histologic response assessment. Classification by the European Organization for Research and Treatment of Cancer (EORTC) described 25% sensitivity and 100% specificity (*101*). Similar to that for bone sarcoma, a reduction of 40% in SUV for soft tissue sarcoma was a predictor of response and lower risk of recurrent disease and death after treatment with both complete resection and chemotherapy. In contrast, a higher risk of recurrence was found in patients with soft tissue sarcoma lesions at diagnosis with an SUV of greater than 6.0 and an SUV reduction of less than 40% after treatment.

HEAD AND NECK CANCER

Clinical Scenarios and AUC Scores

Clinical scenarios for the use of PET/CT and final AUC scores in head and neck cancer are presented in Table 7.

Scenario 1: Restaging for detection of local recurrence (Score: 7 – appropriate). A recent metaanalysis (*105*) that included 23 studies constituting 2,247 PET/CT examinations established a pooled sensitivity of 0.92 (95% CI, 0.90–0.94) and specificity of 0.87 (95% CI, 0.82–0.91) for follow-up PET/CT in the detecting recurrence. Pooled sensitivity was 0.95 (95% CI, 0.91–0.97) and specificity 0.78 (95% CI, 0.70–0.84) for scans performed 4–12 mo after treatment. Estimates for scans performed at more than 12 mo after treatment were similar, with a sensitivity of 0.92 (95% CI, 0.85–0.96) and specificity of 0.91 (95% CI, 0.78–0.96). In managing the detection of local recurrence, direct laryngoscopic techniques and physical examination remain key aspects, followed by PET/CT or other imaging as important adjuncts in detecting recurrence in lymph node and more distant sites.

Scenario 2: Restaging for detection of metastases (Score: 9 – appropriate). A metaanalysis consisting of 27 studies established a

TABLE 7
Clinical Scenarios for Head and Neck Cancer

Scenario no.	Description	Appropriateness	Score
1	Restaging for detection of local recurrence	Appropriate	7
2	Restaging for detection of metastases	Appropriate	9
3	Treatment response evaluation	Appropriate	7

sensitivity of 84.6% and specificity of 94.9% for detection of distant metastases (*106*).

Scenario 3: Treatment response evaluation (Score: 7 – appropriate). In a metaanalysis of 51 studies comprising 2,335 patients, Gupta and colleagues (*107*) evaluated the diagnostic performance of a posttreatment PET/CT scan. The impact of its timing was also assessed before and after 12 wk. The respective values of PET/CT reported for primary site and neck nodes were as follows: pooled sensitivity, 79.9% and 72.7%; specificity, 87.5% and 87.6%; negative predictive value, 95.1% and 94.5%; positive predictive value, 58.6% and 52.1%. In scans performed at $\geq$ 12 wk compared with those done at $<$ 12 wk, sensitivity was higher in primary tumor (91.9% vs. 73.6%, respectively, $P = 0.12$) and neck nodes (90.4% vs. 62.5%, respectively, $P < 0.001$). Similarly, Isles and colleagues (*108*) performed a metaanalysis of 27 studies to evaluate the effectiveness of PET in detecting recurrence or residual head and neck squamous cell carcinoma after conventional radiation therapy. They reported a pooled sensitivity of 94%, specificity of 82%, positive predictive value of 75%, and negative predictive value of 95%. Considering the effect of the timing of scans, the authors indicated that sensitivity was significantly higher for scans performed $>$ 10 wk than for those performed $<$ 10 wk after conventional radiation therapy ($P = 0.002$).

PET/CT findings in posttherapy assessment are time and therapy dependent. An increase in ^{18}F-FDG uptake occurs in recently radiated tissues, which may last 12 to 16 wk. So that a balance can be ensured between the disadvantages of early and late imaging, the first posttreatment PET/CT scan to assess therapy response is recommended at least 12 wk after radiation therapy to minimize radiation-related inflammatory uptake and at least 3 wk (before the next cycle) after completion of chemotherapy.

Marcus and colleagues (*109*) proposed new standardized interpretation criteria for assessing therapy response for head and neck cancers from the results of a posttherapy PET/CT scan (Hopkins criteria). Therapy response is assessed from the intensity (compared with internal jugular vein [IJV] and liver activity) and pattern (focal or diffuse) of PET uptake in primary tumor and neck nodes and categorized into 5 scores: score 1 (complete metabolic response, ^{18}F-FDG uptake less than that of IJV), score 2 (likely complete metabolic response, focal ^{18}F-FDG uptake greater than that of IJV and less than that of liver), score 3 (likely postradiation inflammation, diffuse uptake greater than that of IJV or liver), score 4 (likely residual tumor, focal uptake greater than that of liver), and score 5 (residual tumor, focal and intense ^{18}F-FDG uptake). Scores 1, 2, and 3 are considered negative and scores 4 and 5 positive for residual tumor. This qualitative assessment scoring system was shown to have substantial interrater reliability (κ = 0.69–0.79) and high specificity (92.2%) and negative predictive value (91.1%).

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