Appropriate Use Criteria for 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.

The purpose of this document is to describe the appropriate use of PET/CT* in the response assessment and restaging of patients with cancer. Our focus here 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. This phase may entail local recurrence, distant metastatic disease, and assessment of response to a variety of treatments after the disease recurs. 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. For the purposes of 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. Moreover, this document excludes "initial staging" and "surveillance." Representatives from the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the European Association of Nuclear Medicine (EANM), the American Society of Clinical Oncology (ASCO), the American College of Nuclear Medicine (ACNM), the Society for Pediatric Radiology (SPR), and the Canadian Association of Nuclear Medicine (CANM) assembled under the auspices of an autonomous workgroup to develop the following appropriate use criteria (AUC). This process was performed in accordance with the Protecting Access to Medicare Act of 2014 (*4*). This legislation requires that all referring physicians consult AUC by using a clinical decision support mechanism before ordering advanced diagnostic imaging services. These services include diagnostic MRI, CT, and nuclear medicine procedures such as PET, among other services specified by the Secretary of Health and Human Services in consultation with physician specialty organizations and other stakeholders (*4*). These 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.

INTRODUCTION

PET/CT has transformed the imaging evaluation of cancer. Large-scale planned studies such as the National Oncologic PET Registry have shown that PET/CT has a major impact on clinical management in a variety of cancers, although more data are needed to determine the advantages and disadvantages of PET/CT compared with other imaging modalities in improving various outcome measures.

There are several limitations in the existing literature regarding the utility of PET/CT in cancer. The relevant literature consists predominantly of small, retrospective studies aimed at comparing the clinical utility of PET or PET/CT with that of an established, clinically accepted modality (usually CT or MRI). Notably, although both CT and MRI have been adopted into routine clinical use in these applications, neither has been subjected to the level of scrutiny that PET/CT has undergone during the past 2 decades of efficacy analysis related to reimbursement decisions by various payers.

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Randomized trials in this arena are rare and difficult to design in an ethical fashion—use of one imaging modality does not and should not preclude the use of another more established modality in a patient undergoing clinical management of a life-threatening neoplasm. Similarly, when the efficacies of 2 modalities are being compared, both of which clearly appear to offer valuable clinical information, patient management that is truly blinded to the results may be deleterious to patient health and outcome.

Final diagnosis for individual lesions is often based on clinical observation, which typically constitutes follow-up with standardized imaging (CT and MRI). Thus, the true-positive lesions seen on PET that are most likely to be correctly classified as true positive on imaging follow-up are the very lesions for which these comparison modalities are most accurate, whereas others may be incorrectly characterized as false positive, depending on length of follow-up and interval interventions. This confirmatory bias is limited only in studies with a strict application of the reference standard, including a long follow-up, which is not always present.

In the panel's opinion, these factors led to major limitations in the initial systematic review analysis that identified sufficient numbers of relevant investigations. Therefore, the panel also conducted its own literature review, with the following parameter: primary concentration on relevant metaanalyses in the literature that addressed the use of PET and PET/CT in cancer. Several such metaanalyses have identified papers suitable for inclusion by using the same general PICOTS (population, intervention, comparisons, outcomes, timing, and setting) and Quality Assessment of Diagnostic Accuracy Studies (QUADAS) approaches initially outlined for this project. In some cases, these criteria were modified to specifically address the difficulties outlined above. For example, one of the quality assessment criteria for QUADAS is "Did patients undergo examination with the same reference standard regardless of index test result?" In many studies, such an approach would be impractical and even unsafe. For example, histopathologic confirmation of positive imaging results in such studies is generally preferable, and many such subjects went on to percutaneous or open biopsy for confirmation. It would clearly not be appropriate to submit all other patients to the same procedures. For the purposes of our analysis, the panel has included the published literature that addressed these potential limitations appropriately, rather than excluding all such data as less than ideal. The panel believes that this approach is justified, especially for clinical scenarios in which there exist large amounts of data pointing to a nearly universal conclusion, even though those data may not meet optimal "quality" standards, as long as it can be demonstrated that the data do not suffer from any demonstrable bias.

There was a specific focus on metaanalyses and large individual studies that directly compare PET or PET/CT with other modalities, the emphasis being on prospective and randomized studies, when available. The panel believes that, in most clinical scenarios, the clinical decision facing the referring physician will be "which" imaging modality to use first, rather than "whether" to image the patient at all.

Since the panel includes several experts in the field with extensive and ongoing experience in the application of PET in the clinical care of cancer patients, conclusions of the literature findings were reviewed for suitability in the clinical setting before determining a final AUC score for each category.

METHODOLOGY

Expert Workgroup Selection

The experts of this AUC workgroup were convened by the SNMMI to represent a multidisciplinary panel of health care providers with substantive knowledge in the use of PET/CT in restaging of malignancy. In addition to SNMMI members, representatives from EANM, ASCO, ACNM, SPR, and CANM were included in the workgroup. Twelve physician members were ultimately selected to participate and contribute to the resulting AUC. A complete list of workgroup participants and external reviewers can be found in Appendix A.

AUC Development

The process for AUC development was modeled after the RAND/UCLA Appropriateness Method for AUC development. It included identifying a list of relevant clinical scenarios where PET/CT scans can be used, a systematic review of evidence related to these clinical scenarios, and a systematic synthesis of available evidence followed by the development of AUC for each of the various clinical scenarios by using a modified Delphi process. Additionally, this process strove to adhere to the Institute of Medicine's standards for developing trustworthy clinical guidance. The final document was drafted on the basis of group ratings and discussions.

Scope and Development of Clinical Scenarios

To begin this process, the workgroup discussed various potential clinical scenarios for PET/CT, including possible contraindications. The scope of this workgroup was to focus on the appropriate use of PET/CT for restaging of certain cancers (breast, colorectal, lung, lymphoma, melanoma, sarcoma, and head and neck), including the assessment of treatment response and the identification of recurrent cancer, as well as the effects and comparative effects on patient management, clinical outcomes (including quality of life), and cost-effectiveness. The selected cancers do not preclude potentially appropriate use of PET/CT in restaging of other cancers. For all clinical scenarios, the relevant populations were adults (with at least 1 of the 7 cancers mentioned above), pediatric (ages newborn to 17 y), and all races or geographic locations (rural, urban, etc.).

The workgroup identified 24 clinical scenarios for the use of PET/CT in restaging of the 7 cancer types mentioned above. The clinical scenarios are intended to be as representative of the relevant patient population as possible for the development of AUC.

The resulting AUC are based on evidence regarding diagnostic accuracy and effects on clinical outcomes and clinical decision making as applied to each clinical scenario. Other factors impacting on the AUC recommendations included potential harms, such as long-term harms that may be difficult to capture, costs, availability, and patient preferences.

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 of the systematic review was to synthesize the evidence on the accuracy and comparative accuracy of PET/CT for restaging certain cancers (breast, colorectal, lung, lymphoma, melanoma, sarcoma, and head and neck) in order 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

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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 approach. Searches were conducted on the following databases: the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and OVID MEDLINE (from 1946 through July 2015). These searches were 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 the risk of bias) for each study was categorized as "good," "fair," or "poor" by using the predefined criteria for each study design. Specifically, QUADAS-2 was used for diagnostic accuracy studies (*5*), and Assessment of Multiple Systematic Reviews (AMSTAR) was used for systematic reviews (*6*). The strength of overall evidence was graded as high, moderate, low, or very low by using GRADE methods, which were based on the 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 were included in this review.

Rating and Scoring

In developing these AUC for PET/CT, the workgroup used the following definition of appropriateness to guide their considerations and group discussions (*7*): "The concept of appropriateness, as applied to health care, balances risk and benefit of a treatment, test, or procedure in the context of available resources for an individual patient with specific characteristics."

On reviewing the evidence summary of the systematic review, the workgroup further refined its draft clinical indications to ensure their accuracy and to facilitate consistent interpretation when scoring each indication for appropriateness. Using the evidence summary, workgroup members were first asked individually to assess the benefits and risks of PET/CT for each of the identified clinical scenarios and to provide an appropriateness score for each scenario.

Workgroup members then convened in a group setting via webinar to discuss each indication and associated scores from the first round of individual scoring. After deliberate discussion, each member independently provided his or her second round of scores for each indication. For each indication, the mode numeric score was determined and then assigned to the associated appropriate use category. For this scoring round, the group members were requested to include their expert opinion in addition to the available evidence in determining their scores. All workgroup members contributed to the final discussion and no one was forced into consensus. Once the rating process was completed, the final appropriate use ratings were summarized in a format similar to that outlined by the RAND/UCLA appropriateness method.

The workgroup scored each scenario as "appropriate," "may be appropriate," or "rarely appropriate" on a scale from 1 to 9. Scores 7–9 indicate that the use of the procedure is appropriate for the specific scenario and is generally considered acceptable. Scores 4–6 indicate that the use of the procedure may be appropriate for the specific scenario. This implies that more research is needed to classify the scenario definitively. Scores 1–3 indicate that the use of the procedure is rarely appropriate for the specific scenario and generally is not considered acceptable.

As stated by other societies that develop AUC, the division of these scores into 3 general levels of appropriateness is in part arbitrary, and the numeric designations should be viewed as a continuum. Additionally, if there was a difference in clinical opinion for a particular clinical scenario such that workgroup members could not agree on a common score, that clinical scenario was given a score of 5 to indicate a lack of agreement on appropriateness based on the available literature and their collective clinical opinion, indicating the need for additional research.

BREAST CANCER

Introduction

In the United States, breast cancer is the most common nonskin cancer and the second leading cause of cancer-related death in women (after lung cancer). Approximately 249,260 new cases of breast cancer (99% in women) and 40,890 total deaths from breast cancer (99% in women) occurred in 2016 (*8*). Breast cancer strikes women of all ages, races, ethnicities, socioeconomic strata, and geographic locales (*9*). Initial diagnosis and staging is essential in determining the choice of therapy, as well as the patient's prognosis and chances for survival (*10*).

PET/CT provides the ability to combine functional and morphologic information in a single study (*1*). The application of PET technology to a dedicated breast camera is known as positron emission mammography (PEM). PEM is the functional equivalent of conventional mammography—with a similar setup (including breast compression) and with the images displayed in the familiar mammographic format (*11*). The average acquisition time is 2–5 min with resolution capacity similar to that of PET, approximately 8 mm (*12*). The use of a conventional mammography gantry allows image co-registration with x-ray mammography and the possibility of image-guided biopsy (*13*).

PET/CT has a limited role in the diagnosis of breast cancer (*14*), but it is important in detecting locoregional (including nodal) and distant disease, in helping to plan surgical and medical treatment, in monitoring response to treatment, and in finding recurrence (*15–21*). PET also has the potential to evaluate novel treatment agents rapidly by detecting their effects on specific receptors (*17,22*) and has been shown to improve prediction of the clinical outcome in previously treated breast cancer patients (*23,24*). A retrospective study of 133 breast cancer patients evaluated with PET/CT showed that the PET results contained information on 6-mo outcome that was independent of stage or past treatment and significantly influenced patient management (*25*).

[†] 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.

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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

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. [**Table 1**]

Scenario 1: Restaging for detection of local recurrence (Score: 8 – Appropriate). Pennant and colleagues published a metaanalysis that evaluated PET/CT for the detection of recurrence in patients with a history of breast cancer (*26*). 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 increase in 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, there were also 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%; and accuracy of PET/CT, 92.1%. When compared with the standard workup available in 67 patients, PET/CT had higher sensitivity (94.5% vs. 33%, respectively) and higher accuracy (94% vs. 48%, respectively) (*27*). 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%; and positive predictive value, 72% versus 55% (*28*).

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 the 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 (*29*). 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 (*30*). 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 (*31*).

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, for targeted therapy, and in more advanced disease settings.

Cheng et al. found 17 studies (a total of 781 subjects) that fulfilled the inclusion criteria in a metaanalysis to determine the diagnostic performance of PET/CT for evaluating the response to neoadjuvant chemotherapy in patients with breast cancer (*32*). 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 (*33*).

COLORECTAL CANCER

Introduction

Colorectal cancer is the third most commonly diagnosed cancer and the third leading cause of cancer death in both men and women in the United States. The National Cancer Institute estimates that 134,490 people were diagnosed with colorectal cancer and 49,190 people died from the disease in the U.S. in 2016. The lifetime risk of developing colon cancer is approximately 4.5% for American men and women (*34*).

Because of the high risk of recurrence or metachronous metastasis in patients with colorectal carcinoma, there is great interest in noninvasive restaging and therapy monitoring. New developments in treatment options for such patients in the past several decades have increased the pressure on available imaging modalities for early detection of isolated recurrence or metastasis, exclusion of additional unsuspected disease before interventions with potentially high cost or high morbidity, and assessment of the efficacy of such therapeutic interventions. The purpose of this section of the AUC is to evaluate the appropriate use of PET/CT with FDG in restaging of patients with colorectal cancer.

Clinical Staging and Initial Management

Currently, PET/CT is not routinely used for initial staging, other than to evaluate indeterminate findings from other modalities, and initial staging is not included in the current AUC assessment.

Recurrent/Metastatic Disease: Detection and Management

Up to 60% of patients diagnosed with colorectal cancer will develop metastatic disease (*35–37*) and up to 90% of patients with metastatic disease will have unresectable disease in the liver. Approximately 30% of patients will present with synchronous liver metastases (*38,39*). Metachronous metastatic disease after locoregional treatment for colorectal cancer is more common. Despite optimal primary treatment with adequate surgery with or without adjuvant chemotherapy, around 30%–50% of patients with colon cancer will relapse and die of their disease. The liver is the most common site of metastasis and metastatic liver disease is the most common cause of death (*40,41*).

There has always been keen interest in early identification of recurrent/metastatic colorectal cancer, as operative intervention is the only potentially curative option in most cases. More recently, advances in less invasive techniques, such as radiofrequency ablation (RFA), cryoablation, radioembolization, chemoembolization, or targeted biologic agents have further increased the need for optimal

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surveillance and evaluation of suspected recurrence. Although there remains significant debate regarding surveillance strategies, it appears clear that, at present, routine surveillance of colorectal cancer patients with PET or PET/CT cannot be justified (*42*). Furthermore, for those patients diagnosed with inoperable metastatic disease, there has been an explosion of chemotherapy and targeted therapy options in recent years, with the selection and monitoring of therapeutic regimens becoming more and more complex.

All of these factors illustrate the growing importance of a noninvasive approach to restaging for suspected locally recurrent colorectal cancer, detection of possible metastatic disease, and monitoring of treatment efficacy. CT and MRI have become routine in such evaluations and, over the past 2 decades, PET and PET/CT have been shown to be highly effective for selected applications in this population.

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. [Table 2]

Scenario 1: Restaging for detection of local recurrence (Score: 7 – appropriate). A universal definition of local recurrence is notably absent in the literature and several studies do not clearly separate local from distant recurrent disease. The clinical scenario often encountered in practice and typically addressed in publications is referred to as "recurrence," which often includes local recurrence, regional lymph node metastasis, and distant metastasis. For the purposes of 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). It should also be noted that local recurrence is more common with rectal carcinoma than with primary lesions located elsewhere within the colon. This is predominantly due to differences in anatomy that allow for a more complete local resection and removal of the draining lymphatics elsewhere within the colon. Recent published papers regarding PET/CT for local recurrence typically do not distinguish between patients with rectal carcinoma and those with colon carcinoma.

An early metaanalysis (*43*) that evaluated the efficacy of PET (before the 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 (*44*), 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 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 (*45*). 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 (*46*) in the evaluation of recurrent disease (both local recurrence and distant disease) for patients with suspected recurrence on the basis of 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 (*47*). 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 that of assessment for recurrence of ablated liver metastases. For the purposes of 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 will present with either 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 one or another 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). As discussed, the clinical definitions of recurrence

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

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and metastasis are often blurred in colorectal cancer, and those uncertainties complicate many studies in the literature. 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%; and PET (not PET/CT), 96% (*48*). 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 the detection of liver metastases in untreated colorectal cancer patients, using CT, MRI, PET, or PET/CT (*49*). 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%; and 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 (*50*). 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 (*51*). 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 (*52*). 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 (*53*). 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 (*54*). 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 (*44*). 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, in fact, 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 a specificity of 70% (*55*), and the accuracy of CT for detecting tumor recurrence in patients with a rising CEA level may be limited. A metaanalysis of 11 studies (*47*) demonstrated a sensitivity of 51% and a 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 of 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 the detection of small volumes of residual disease after treatment, the ability of PET to detect residual or metastatic colorectal cancer deposits soon after chemotherapy has been shown to be limited by the "metabolic shutdown" of colorectal

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cancer tumor cells after chemotherapy administered up to several weeks (perhaps up to 3 mo) before imaging (*56*). This limitation is apparently related to downregulation of hexokinase activity, which may explain the suboptimal correlations between PET response and pathologic response after therapy that have been reported in the literature. Similarly, when PET was used for early treatment monitoring, most studies attempted to correlate early response prediction with PET to eventual clinical response on the basis of anatomic imaging, or to a cytocidal effect of the therapy on the basis of subsequent biopsy or resection. However, these 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 (*57*).

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 (*58*). 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 (*59*), 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 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 RFA of liver metastases with an open surgical technique than with a percutaneous technique (*60*). 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 (*61*). 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. Unsurprisingly, the reported results of the ability of early PET to predict response during therapy have been inconsistent. Larger studies with specific methodologies will be necessary, and it seems likely that differing conclusions may be drawn for different types of therapies.

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 (*62*). 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 (*63*). The median QUADAS score was 12. Global assessment of the prediction of tumor response by PET/CT showed a sensitivity of 73% and a specificity of 77%. The large sample size allowed for breakdown comparison of several different 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 (*64*) 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 the posttreatment SUV_{max} between responders and nonresponders, but with significant

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overlap between groups. Another metaanalysis assessed the prediction of both complete pathologic response and patient survival (*65*) 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.

Despite these favorable results, important questions remain, such as the optimal timing of PET/CT imaging. Interim studies performed early after initiation of therapy may prove to be more predictive than studies performed after completion of therapy, either because of a more straightforward assessment of response (evaluation of a "trend" compared with baseline, rather than more complicated analysis of "major" or "complete" response), or because of the variable influences of posttreatment inflammation, depending on the interval after therapy (*62,63*).

In addition, 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 (*66–68*). In a fourth recent metaanalysis with a total of 33 studies (including MRI, PET, and PET/CT with 1564 patients that met the inclusion criteria), the authors concluded that diffusion-weighted MRI (DW-MRI) was superior to PET in predicting complete pathologic response (*69*). 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. In most cases, routine follow-up imaging after neoadjuvant therapy appears to be noncontributory to subsequent surgical management. However, if imaging is clinically necessary, data indicate that PET/CT is at least as accurate as other modalities. 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. It should be noted that such examinations will most likely be contributory if a baseline study has been performed for comparison. Clearly, 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 that is increasing in 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 the detection of local tumor recurrence of ablated liver metastases found 9 suitable publications for inclusion, 6 using PET/CT and 3 using PET (*60*). 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 on the basis of relatively weak evidence. Further investigations will be necessary to outline the optimal clinical scenarios and optimal imaging techniques. In many cases, the clinical situation may more appropriately fit either the "detection of recurrence" or "detection of metastasis" categories. Otherwise, this application 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. From extrapolation of the data in other subcategories, it is reasonable to expect that PET/CT should have an overall accuracy greater than CT. However, both the referring physician and the imaging physician should be aware of the possible confounding factors of postintervention inflammation or metabolic shutdown in recent postchemotherapy patients.

LYMPHOMA

Introduction

Hodgkin lymphoma (HL) is a relatively uncommon malignancy that mostly affects young adults. Between 2009 and 2013, there were 2.6 new cases per 100,000 men and women per year and 0.4 deaths per 100,000 men and women per year. The 2010–2012 data showed that the lifetime risk of developing HL is approximately 0.2%, and in 2013, an estimated 193,545 people were living with this disease in the United States. In recent years, advancements in its treatment have achieved a greater than 80% cure rate, and survival at 5 y was 86.2% according to the 2006–2012 data. Survival is better for disease localized to the initial site of disease or to regional lymph nodes (>91%) and decreases with involvement of more distant sites (77%). Deaths from HL decreased by on average 2.6% per year from 2004 to 2013, new cases decreasing by on average 1.2% per year during the same period (*70*).

For non-Hodgkin lymphoma (NHL), the 2009–2013 data showed that the number of new cases was 19.5 per 100,000 per year and the number of deaths 6.0 per 100,000 per year. Approximately 2.1% of men and women will be diagnosed with NHL at some point during their lifetime, according to data from 2010 to 2012, and in 2013, an estimated 569,536 people were living with NHL in the United States. The 5-y survival rate was 86.2% according to 2006–2012 data, with survival at 5 y being better for disease localized to the original site or to regional lymph nodes (82.6 and 74.4%, respectively) than for disease that had spread to more distant sites (63.1%). Although rates for new NHL cases have not changed significantly over the last 10 y, death rates fell by on average of 2.4% each year from 2004 to 2013 (*71*).

Because of the high cure rate for both HL and NHL, long-term toxicity of available treatments has become an important consideration in the approach to the disease. Accurate staging and assessment of response to treatment have acquired a crucial role in order to deliver appropriate treatments while minimizing toxicity, particularly for the early and intermediate stages.

PET/CT imaging represents an important tool in the management of HLs and NHLs for initial disease staging and for subsequent response assessment at completion of treatment. HL is invariably FDG-avid and PET is universally accepted as a primary tool for staging and restaging of HL. In a study that included 766 patients with a diagnosis of lymphoma, all 233 cases of HL demonstrated FDG avidity. In NHL, PET imaging should be reserved for tumor subtypes that have a high or at least a moderate degree of FDG uptake, such as diffuse large B-cell lymphomas (DLBCL), follicular lymphomas, most T-cell lymphomas, nodal marginal zone lymphomas, Burkitt's lymphomas, and mantle cell lymphomas, all of which

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present FDG avidity (*72*). PET seems to be less sensitive for extranodal marginal zone lymphomas, which present FDG avidity in 54%–67% of cases, depending on the location. Among the T-cell lymphomas, the primary cutaneous anaplastic and the enteropathy-type variants have lower FDG avidity (40% and 67%, respectively) and the role of PET is therefore more limited (*72*).

PET positivity at the end of treatment is a significant negative risk factor in patients with early-stage and advanced HL, with survival being significantly better for those with negative PET scans (95%) than for those with positive scans (69%) (*73,74*). Subsequent treatment failure was lower and progression-free survival better for patients with negative PET scans at the end of treatment (*75*).

Standardized systems have been developed for the visual assessment of response to treatment with PET/CT. The Deauville criteria developed for HL (*76*) and the Lugano criteria developed for both HL and NHL (*77*) have both adopted a 5-point scale to assess response to treatment, using mediastinal and liver activity as a reference. A score of 4 or 5 is assigned to lesions with FDG uptake above liver activity and is universally accepted as PET-positive residual disease during or after treatment.

Clinical Scenarios and AUC Scores

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

Scenario 1: Detection of recurrent disease (Score: 8 – appropriate). Four studies evaluated the accuracy of PET/CT for the detection of recurrent disease in patients treated for lymphoma (*78–81*): 2 in patients with HL (*79,81*), 1 in patients with NHL (*78*), and 1 in a mixed HL and NHL population (*80*). 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 (*78–80*). 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 (*82–84*): 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 (*82,83*), and 1 study found that contrast-enhanced CT also had 100% sensitivity, but its specificity was much lower than that of PET at 52% (*82*). 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% (*84*).

Surveillance

Although survival rates have dramatically improved in recent years, relapses still occur in approximately 30%–50% of HL and NHL cases with adverse characteristics or advanced disease after first-line therapy (*85,86*). In a metaanalysis, the sensitivity and specificity values of PET in identifying disease relapse for HL were 50%–100% and 67%–100%, respectively, and for NHL were 33%–77% and 82%–100%, respectively, irrespective of the presence of a residual mass on CT (*87*). More than 60% of relapses from HL and aggressive NHL are diagnosed clinically, especially for aggressive NHL and cases with extranodal involvement. HL relapses are more commonly detected by PET scans because of clinically silent disease, although no survival benefit was found with PET (*88*). In summary, survival does not appear to be affected by mode of detection of recurrent lymphoma or the frequency of imaging. The low positive predictive value associated with follow-up PET scans negates their clinical value in identifying patients who would benefit from additional treatment (*89*).

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

Introduction

Lung cancer represents around 13.3% of all new cancer cases, and it is estimated that it will be the cause of 26.5% of all cancer-related deaths, with only around 17.7% of all lung cancer patients surviving 5 y from the initial diagnosis. Smoking is widely recognized as the leading cause of lung cancer (*90*). Between 2009 and 2013, there were 57.3 new cases per 100,000 men and women per year and 46.0 deaths per 100,000 men and women per year. The lifetime risk of developing lung cancer is approximately 6.6% for men and women, based on 2010–2012 data (*90*). In 2013, there were an estimated 415,707 people living with lung and bronchus cancer in the United States. Cancer stage at diagnosis determines treatment options and has a strong influence on length of survival. In general, if the cancer is found only in the part of the body where it started, it is considered localized (sometimes referred to as stage I). If it has spread to a different part of the body, the stage is regional or distant. The earlier that lung and bronchus cancer is caught, the better chance a person has of surviving 5 y after being diagnosed. For lung and bronchus cancer, 15.7% of cases are diagnosed at the local stage, and the 5-y survival for localized lung and bronchus cancer is 55.2%. Rates for new lung and bronchus cancer cases have been falling on average by 1.8% each year over the last 10 y, and death rates have been falling on average by 2.2% each year over 2004–2013 (*90*).

Classification

Non–small cell lung cancer (NSCLC) represents 85%–90% of lung cancer (*91*) and includes 3 main types: squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. The first 2 types account for around 80% of all lung cancers worldwide. Squamous cell carcinomas are predominantly associated with smoking and usually present as large tumors in the center of the lung (*92,93*). In contrast, adenocarcinomas are frequently located in the periphery of the lung and are divided into 4 categories: (a) preinvasive lesions, including 2 subtypes, atypical adenomatous hyperplasia and adenocarcinoma in situ (≤3 cm, formerly bronchioloalveolar carcinoma [BAC], which can be nonmucinous, mucinous, or mixed mucinous/nonmucinous); (b) minimally invasive adenocarcinoma (≤3 cm lepidic predominant tumor with ≤ 5 mm invasion) that can be nonmucinous, mucinous, or mixed mucinous/nonmucinous; (c) invasive adenocarcinoma, including lepidic predominant (formerly nonmucinous BAC pattern with > 5 mm invasion), acinar predominant, papillary predominant, micropapillary predominant, and solid predominant; and (d) variants of invasive adenocarcinoma: invasive mucinous adenocarcinoma (including formerly mucinous BAC),

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colloid, fetal (low and high grade), and enteric. It is worth highlighting that in 2011 the International Association for the Study of Lung Cancer (IASLC) and other societies jointly revised and updated the classification for adenocarcinoma of the lung. Since then, the denomination BAC has no longer been used, being replaced by the last 4 entities listed (in situ pulmonary adenocarcinoma, minimally invasive adenocarcinoma, and the 2 invasive adenocarcinomas) (*94*).

Diagnosis

The imaging diagnosis of patients with lung cancer includes chest x-ray, CT, PET, bone scintigraphy and, in neuroendocrine tumors, somatostatin receptor scintigraphy (*93*). CT has been the gold standard imaging technique for many decades, but it has limitations because it relies exclusively on morphologic aspects.

PET/CT has been extensively studied in lung cancer and there is evidence showing its utility for characterizing solitary pulmonary nodules (*95*), staging (*96*), guiding therapy (*97*), monitoring treatment response (*98*), and predicting outcome (*99*). Its economic utility has also been demonstrated in a cost-effectiveness analysis for some of these indications (*93,100*).

Epidemiology of Recurrence

Lung cancer recurs after surgery in 30%–75% of patients (*101*). As in other cancers, after initial treatment (surgery, radiotherapy), it is challenging to differentiate recurrence from postsurgical changes if using CT alone, as many benign processes (atelectasis, consolidations, and radiation-induced fibrosis) are difficult to differentiate from locoregional recurrence (*102,103*). PET/CT has a great advantage, as it differentiates metabolically active from inactive areas. However, it can yield false-positive results from active inflammation, especially in the acute postoperative or postradiotherapy phase, although this characteristic of FDG is now being used in the diagnosis of infection and inflammation, demonstrating a good diagnostic performance (*104*).

Recurrence of NSCLC may be classified as locoregional recurrence or distant metastases, the latter being the most common form of NSCLC recurrence (*102*). Depending on the initial stage at diagnosis and on the treatment applied, metastatic recurrence comprises 39%–65.5% of all recurrences (*105*), whereas around 30% of recurrences are locoregional. Locoregional recurrence is located within the treated hemithorax, usually presenting as nodules that involve the surgically treated area or the area treated with RFA or microwave ablation (MWA), as well as within other thoracic structures (bronchial stump, pleura, chest wall, and lymph nodes) (*102,103*). Moreover, apart from recurrences, new primary lung cancer is also reported in 1%–2% of NSCLC patients per year after initial radical therapy (*106*).

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. [Table 4]

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

Scenario 1: Restaging for detection of local recurrence (Score: 7 – appropriate). One systematic review showed a high pooled/joint sensitivity and specificity (*107*). 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) (*107,108*). This observation underlines the importance of correct patient selection, as sensitivity can be lower depending on the population studied (small lesions, etc.).

Restaging after initial treatment (surgery, chemoradiotherapy, or radiotherapy): General comments. A recent metaanalysis analyzed the diagnostic efficacy of PET and PET/CT with FDG compared with other imaging techniques (OITs) for the detection of recurrent lung cancer (*107*). The inclusion criteria were studies of secondary lung cancer investigations that used PET or PET/CT with 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 the detection of recurrent lung cancer and that PET/CT was superior to CT (*107*). Regarding the role of PET/CT in the detection of local recurrence, one of the limitations of this study is that data for the disease were pooled regardless of whether the recurrence was local, regional, or distant. Another limitation was that a subgroup analysis was not performed that considered different initial treatments.

Other studies not included in this systematic review and metaanalysis (*107*) also found that PET/CT was associated with high specificity for the detection of recurrent disease after initial treatments, including homogeneous patient populations treated with surgery (*109,110*), radiotherapy (*108,111–115*), or RFA (*114,116*), as discussed below. However, another study by Jiménez-Bonilla et al. (*117*), which was not included in the metaanalysis, also evaluated a heterogeneous population, with patients in all stages of 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. (*110*) retrospectively included 101 NSCLC patients who had undergone potentially curable operations and were followed with a 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.

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PET/CT correctly diagnosed recurrence in 17 of the 18 (94%) patients and 21 of the 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%; and accuracy, 97.0%. Additionally, PET/CT detected other previously not known diseases and allowed early appropriate treatment (*110*). 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 the performance of PET/CT for detecting recurrent disease after initial curative surgery, also not included in the previous metaanalysis (*107*), is that by Choi et al. (*109*). 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 (*109*). The recently published EANM guidelines include an optional, but recommended, low-dose chest CT scan in the PET/CT procedure to better assess small lung lesions (*118*).

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 (*102,119*). Pastis et al. (*108*) 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 the detection of recurrent disease or treatment failure. They recommend CT (every 6 mo for the first 2 y and every year thereafter) (*120*) instead of PET/CT in this situation, whereas they state that PET/CT should be reserved for cases with suspected metastatic disease, to evaluate new abnormalities found on CT, or for subsequent follow-up when the inflammation due to the radiation therapy has subsided (*108*).

In another study that focused on lung cancer patients treated with SBRT, Zhang et al. (*115*) 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 (*115*). A similar study by Takeda et al. (*112*) that included 154 NSCLC patients with 214 PET/CT scans done 1 y after SBRT for the detection of 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. (*113*) 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 of them with symptoms. In the subgroup of symptomatic patients, the impact on the 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 FDG uptake. Hoopes et al. (*111*) studied a small patient population with inoperable stage I NSCLC, reporting persistent and moderately intense 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 (*121*).

Restaging after RFA or 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 (*122*). RFA, like SBRT, also causes ground-glass opacities in the lung parenchyma around the treated tumor site (*102,119*). Different algorithms, including PET/CT 3 to 6 mo after RFA, have been proposed in order to closely follow these patients (*114,116,122,123*), although the few studies that have been reported have a limited number of patients. Yoo et al. (*114*) 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. (*116*) 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 (*124*). 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 (*102,124*).

Scenario 2: Restaging for detection of metastases (Score: 7 – appropriate). PET/CT has a high diagnostic performance for the detection of metastases. At the moment of diagnosis of NSCLC, around 18%–36% of patients have distant metastases. The detection of these metastases at initial staging is key to deciding on the most appropriate management option, as M staging has a direct impact on management and prognosis (*125*). Furthermore, in patients apparently radically treated for NSCLC, around 20% relapse because of

the presence of undetected metastases at the time of initial staging (*94,125*). 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 (*126*), but few studies have specifically addressed this issue in lung cancer patients (*127,128*). 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 (*128*). For bone metastases, PET is more sensitive and specific than bone scintigraphy (*94,129–131*). The best method for liver lesions is MRI, but PET is better than CT, as it detects lesions earlier and is more accurate. MRI is also the best method for brain metastases, as PET is limited because of the high physiologic FDG uptake in the normal brain. Other non-FDG tracers must be considered for brain metastases.

A metaanalysis analyzed the diagnostic efficacy of PET/CT compared with OITs for the detection of recurrent lung cancer, considering disease as a consequence of the originally diagnosed lung cancer, regardless of whether the 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 the detection of recurrent lung cancer and that PET/CT was superior to CT (*107*).

In a metaanalysis in which the authors evaluated the performance of PET/CT for the detection of distant malignancies in various cancers, 41 studies and 4,305 patients were included (*132*). Of these, 5 studies had data on lung cancer (*133–137*) 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 the detection of distant malignancies in patients with various cancers, especially in lung cancer, breast cancer, and head and neck cancer (*132*).

Scenario 3: Treatment response evaluation (Score: 7 – appropriate). Personalized medicine is based on tailoring treatments to the individual patient. To accomplish this, it is of utmost importance to have tools that provide early and precise assessment of response to therapy (*138,139*). Traditionally, tumor response has been assessed by comparing the tumor size on CT before and after treatment, previously in 2 dimensions (*140*) and more recently in 1 dimension (RECIST) (*141*). PET provides functional information and detects metabolic changes earlier than morphologic changes. Early assessment of response can be of great value to patients with cancer, in particular lung cancer. A large proportion of patients undergo treatments that are toxic and expensive with no response, when there are second-line treatments available (*142*). 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 (*142*). 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 (*118*). One of the methodologic aspects that needs to be standardized in the response assessment studies is the best timing of PET/CT, which has not yet been standardized. If performed too early, PET/CT might overestimate FDG uptake because glucose metabolism might be present in cells that are lethally damaged and because there are inflammatory processes in the responding tissues (*142*). If done too late, other problems might appear, such as late evaluation of response or the risk of tumor repopulation. In summary, large-scale trials are needed that apply strict methodologic standardization.

In patients with locally advanced lung cancer who undergo multimodality treatment, correct restaging after induction therapy is needed (*142*). 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 the evaluation of 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 (*143–145*). 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 a 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 (*146*). 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% (*143–145*) than do those who have residual N2 disease (*147*). Therefore, identifying patients who are N2 negative after completion of their neoadjuvant therapy is a critical component for patient selection for thoracotomy (*146*). 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 (*148,149*), 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% (*148,150*). 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 (*151*) 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 the management decisions. The prospective study by Cerfolio et al. concluded that repeat integrated PET/CT is superior to repeat CT for the restaging of patients with N2 stage IIIa NSCLC after neoadjuvant chemoradiotherapy (*146*).

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 studies, and mixed treatments in the remaining studies (*152*). 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

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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

Introduction

Malignant melanoma arises from melanocytes, pigment-producing cells derived from the neural crest and distributed throughout the body. Most melanomas arise from the skin surfaces and are associated with UV exposure. According to 2014 American Cancer Society SEER data (*153*), an estimated 76,100 new cases of melanoma are diagnosed in the U.S. each year, resulting in 9,710 deaths from the disease.

In the melanoma patient population, there is a close link between survival and the extent of disease at the time of presentation and diagnosis. Tumors confined to the superficial layers of the skin are treated surgically and usually have a good prognosis. Deeper tumor involvement, locoregional disease (nodal metastases or in-transit disease), and distant metastases are associated with poorer prognosis and are often treated with a combination of locally directed efforts and systemic therapy.

TNM staging of melanoma according to the American Joint Committee on Cancer is based on the following features: depth of invasion (in mm), ulceration, nodal or lymphatic spread, and distant metastases. Also considered are the number of lymph nodes involved, the size of disease in a lymph node (whether micro- or macroscopic), and serum lactate dehydrogenase (LDH) levels. In examining these criteria, it becomes obvious that imaging plays an important role in the staging of melanoma, but by no means provides enough information for comprehensive assessment. For this reason, imaging (particularly with PET/CT) in patients with newly diagnosed melanoma is reserved for those with evidence of advanced disease. In a metaanalysis of pooled data from 14 studies that examined the role of PET imaging in patients with melanoma, PET was found to have a sensitivity of 88% and a specificity of 82% for detection of disease (*154*). A second metaanalysis that compared the role of PET/CT with CT alone found superior disease detection with PET (*155*).

Imaging has a stronger role in evaluating disease in patients with known disease, in determining the efficacy of treatment during therapy, or in determining whether disease has recurred after completion of therapy. For the development of this document, the panel reviewed publications regarding the use of PET/CT imaging in melanoma for detection of recurrent disease and treatment response evaluation in the setting of both impaired and nonimpaired renal function.

Clinical Scenarios and AUC Scores

Clinical scenarios for the use of PET/CT and final AUC scores in melanoma are presented in Table 5. [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 a specificity of 93% for detection of malignant melanoma recurrence (*156*). A large metaanalysis representing 74 separate studies that pooled the results of multimodality imaging in 10,528 patients (*155*) found that PET/CT had the best performance for the detection of recurrent disease, with a sensitivity of 86% and a specificity of 91%. In comparison, CT was found to have 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 a 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 (*157*). 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

Introduction

Sarcoma, including osteosarcoma, the Ewing sarcoma family of tumors, rhabdomyosarcoma, and soft tissue sarcoma (including leiomyosarcoma, fibroblastic sarcoma, and liposarcoma), comprises less than 0.2% of all cancers and approximately 20% of all childhood solid tumors. Soft tissue sarcomas account for 7% of all childhood cancers and approximately 1% of adult tumors. Sarcoma often presents with metastatic disease at diagnosis that can include pulmonary and skip bony lesions; soft tissue sarcomas may metastasize through hematogenous dissemination and rarely to nodes. Risk factors for sarcoma include prior external beam irradiation and exposure to certain chemicals and are linked to diseases that involve genetic predisposition to cancer. The diagnosis of this cancer occurs mostly in people who are less than 20 y old, and 12.5% of patients younger than 20 die from this disease annually. The overall median age at diagnosis is 43 y and the median age at death is 64 y. This cancer type accounts for approximately 0.3% of all annual cancer deaths. The 5-y survival rate is approximately 67% and the overall survival rate is approximately 64% (*158,159*).

Clinical Scenarios and AUC Scores

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

Scenario 1: Restaging for detection of local recurrence (Score: 7 – appropriate). PET/CT has better sensitivity and specificity for detection of recurrent disease than does conventional imaging or bone scintigraphy. In a metaanalysis by Liu et al. (*160*) for local recurrence, 4 trials showed 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 (*161*), one fair-quality study with 833 PET/CT studies of 206 patients with stage II–intravenous osteosarcoma after treatment with surgery and chemotherapy identified a sensitivity of 95% and a specificity of 98% for detection of metastatic disease. The comparative sensitivity for bone scan was 76%, although there was similar specificity for detection of metastases. In the metaanalysis by Liu et al.,

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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

they cited 5 trials involving 1,001 pooled lesions for detection of distant metastases in bone sarcoma with a sensitivity of 90% and a specificity of 85% (*160*). 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 (*160,162*). Gabriel and Rubello stated that FDG PET/CT can be helpful to confirm the presence of isolated pulmonary metastases in patients with soft tissue sarcoma. They also stated that FDG PET/CT has 80%–90% sensitivity and specificity for detection of metastases (*163*).

Scenario 3: Treatment response evaluation (Score: 8 – appropriate). Bone sarcomas exhibit an increased rate of glycolysis and thus PET/CT studies have been used to assess bone sarcoma. 18-FDG uptake in heterogeneous tumors can be correlated to the aggressiveness of the tumor and the pathologic grade and can be 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 (*160,164–166*).

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 (*163*). 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

Introduction

In the United States, an estimated 55,000 new head and neck cancer cases and approximately 12,000 deaths occur each year. Head and neck squamous cell carcinoma accounts for 90% of head and neck cancers. The overall 5-y survival rate for all stages is approximately 60%, which depends on several factors, the most important of which is disease stage and association with human papilloma virus (*167*).

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. [**Table 7**]

Scenario 1: Restaging for detection of local recurrence (Score: 7 – appropriate). A recent metaanalysis (*168*) that included 23 studies constituting a total of 2,247 PET/CT examinations established a pooled sensitivity of 0.92 (95% CI, 0.90–0.94) and a specificity of 0.87 (95% CI, 0.82–0.91) for follow-up PET/CT in the detection of recurrence. The pooled sensitivity was 0.95 (95% CI, 0.91–0.97) and the 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, at a sensitivity of 0.92 (95% CI, 0.85–0.96) and a specificity of 0.91 (95% CI, 0.78–0.96). In the management of these patients for 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 sensitivity of 84.6% and a specificity of 94.9% for detection of distant metastases (*169*).

Scenario 3: Treatment response evaluation (Score: 7 – appropriate). In a metaanalysis of 51 studies comprising 2,335 patients, Gupta and colleagues (*170*) evaluated the diagnostic performance of a posttreatment PET/CT scan. The impact of timing of posttreatment PET/CT 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%; and positive predictive value, 58.6% and 52.1%. In scans performed at ≥ 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 (*171*) performed a metaanalysis of 27 studies to evaluate the effectiveness of PET in the detection of 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 the sensitivity was significantly higher for scans performed > 10 wk after conventional radiation therapy than for those performed at < 10 wk after therapy ($P = 0.002$).

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

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PET/CT findings in posttherapy assessment are time and therapy dependent. An increase in 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 (*172*) proposed new standardized interpretation criteria for the assessment of therapy response for head and neck cancers on the basis of 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 as follows: score 1 (complete metabolic response, FDG uptake less than that of IJV), score 2 (likely complete metabolic response, focal 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 FDG uptake). Scores 1, 2, and 3 are considered negative and scores 4 and 5 are considered 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%).

BENEFITS AND HARMS OF IMPLEMENTING THE AUC GUIDANCE

It has been suggested that doing the right test for a given indication is a laudable goal. At the same time, in an era in which insurance companies derive unwavering policies from AUC guidance, the impact of broad-sweeping statements may be loss of the ability of clinicians to exercise judgment and to "choose right" for their patient. This AUC guidance is just that, guidance based on the available literature and expertise in the field. We recognize that there are exceptions to our suggestions. Further, as the technology and protocols evolve, so, too, will the indications for the studies being acquired. We hope that this document will help clarify the current state of PET/CT in restaging malignant disease and will be updated as new investigations expand the scope of our practice.

QUALIFYING STATEMENTS

Study/Evidence Limitations

There are several limitations of the existing literature on the diagnostic accuracy of PET/CT for restaging of malignant disease, many of which are outlined in the Introduction and in the Scope and Development of Clinical Scenarios sections above. Several of these limitations were particularly apparent when rigorous inclusion criteria were applied to the systematic literature review.

Much of the PET literature comprises small retrospective studies that assess the accuracy of FDG PET or PET/CT in lesion detection or overall staging/restaging in patients with various cancers, typically with comparison of PET techniques to other routinely used imaging techniques, such as CT or MRI. However, patient populations are often heterogeneous and standards for assessing "truth" in such cases often necessarily depend on clinical follow-up or further imaging follow-up, rather than histologic proof. Randomized or truly blinded trials that assess the accuracy of PET/CT are nearly impossible to conduct in an ethical fashion, since the results of advanced imaging has assumed such tremendous importance in the management of cancer patients. Use of one imaging modality does not preclude the use of another, and, in the case of PET versus an alternative technique, each may provide information critical to patient management that should not be withheld from the treating physician. "Work-up" bias or "confirmatory" bias can be difficult to avoid under such circumstances.

In addition, it is difficult to infer the current value of a rapidly evolving technology from data acquired years previously. Technologic and protocol changes are leading to improved image quality, and studies based on older equipment and protocols may provide misleading results. A significant percentage of published data available for the current analysis addresses standalone PET, rather than PET/CT, which typically shows greater accuracy in oncologic studies. The recent promulgation of time-of-flight PET, PET/MR, and PET/CT protocols, which use intravenous CT contrast, may improve sensitivity and specificity for the detection of oncologic disease, but, as yet, have little associated literature. Such reasons may explain variations between the current recommendations and those currently available from official agencies in several different countries regarding the use of PET/CT in oncology, as most such reviews are at least 5-y-old and are, therefore, of decreasing applicability.

A confounding issue for clinical PET research for the past several decades has been that oncologic practitioners have been quick to recognize the clinical value of PET and have incorporated it into patient management before optimal scientific investigations have been completed. Indeed, although PET/CT is often relied on to assess treatment response and has become part of the NCCN guidelines in certain instances, we found only 1 good-quality review, and the reference standards in the included studies in that review varied from pathologic findings to alternative imaging and clinical follow-up. Moreover, we found only 1 good-quality and 8 fair-quality pertinent diagnostic accuracy studies.

As a result, the panel also conducted its own literature review, with a focus on relevant metaanalyses and large individual studies in the literature that addressed the use of PET and PET/CT in malignancy. Decades of extensive clinical experience also played a role in our assessment of the appropriateness of PET/CT in many scenarios. Ultimately, since the panel included several experts in the field with extensive and ongoing experience in the application of PET in the clinical care of oncology patients, the conclusions from the literature were reviewed for suitability in the clinical setting before a final AUC score for each category was determined.

Special Commentary

The pregnancy status of women of child-bearing age should be determined. Radiation exposure to the fetus from PET/CT is low and may be decreased further with special attention to protocol (i.e., minimizing the amount of radiotracer administered and the exposure related to CT). In addition, good hydration may be helpful. Ultimately, the physician involved in the care of the patient and fetus should weigh the benefits of the scan against the potential risks of radiation exposure. Of note, no known harmful effects from PET/CT have been identified in a pregnant patient or fetus.

The main source of potential radiation exposure to a breast-feeding infant is likely to be from the close proximity to the breast (external) rather than ingestion of milk (internal). In patients reluctant to discontinue breast-feeding, expression of breast milk and bottle-feeding by a third party could help to minimize radiation

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exposure to the infant. The 110-min physical half-life of ^{18}F and the low excretion of FDG into breast milk support the use of PET as the preferred oncologic imaging procedure in nursing mothers if imaging cannot otherwise be avoided (*173*).

Radiation Dose

According to models recommended in the International Commission on Radiological Protection Publication (ICRP) 106, administering 444 MBq of ^{18}F FDG would impart an approximate effective dose of 8.4 mSv to an adult male, 10.7 mSv to an adult female, and 16.4 mSv to a 10-y-old (*174*). The critical organ is the bladder. In adults, the suggested maximum and minimum amount of ^{18}F FDG administered is 740 MBq and 370 MBq, respectively. Often an empiric dose of 555 MBq or less is used, although generally a weight-based approach is preferred for calculating the amount of radioactivity administered when possible. In children, the suggested amount of ^{18}F FDG administered is 3.7–5.2 MBq/kg, with a minimum of 26 MBq. Some practitioners may choose to set a fixed maximum activity equal to 70 times the recommended weight-based administered activity or approximately 370 MBq (*175*). Typically, the effective dose estimate for the CT portion of the study is less than 10 mSv, although this can vary depending on the protocol being used.

IMPLEMENTATION OF THE AUC GUIDANCE

To develop broad-based multidisciplinary clinical guidance documents, SNMMI has been working with several medical specialty societies. This collaboration will foster the acceptance and adoption of this guidance by other specialties.

SNMMI has developed a multipronged approach to disseminate the AUC to all relevant stakeholders—referring physicians, nuclear medicine physicians, and patients. The dissemination and implementation tactics will be a mix of outreach and educational activities and will be targeted to each of these audiences.

SNMMI will also create detailed case studies for members and referring physicians and make the cases available via online modules and webinars. These cases will cover the appropriate clinical scenarios for the use of PET/CT, as well as some cases in which the results of PET/CT are equivocal.

Related resources such as the systematic review supporting the development of this AUC, a list of upcoming education events, factsheets, and other didactic materials will be made available on the SNMMI webpage dedicated to PET/CT AUC. Live sessions will be held at the SNMMI annual and midwinter meetings and at the relevant societal meetings of referring physicians to highlight the importance of this AUC. The society also aims to create a mobile application for this AUC for both Apple and Android platforms. Mobile applications are becoming increasingly popular in the health care industry and can be used to push updates to all users.

In addition to these activities, SNMMI will also undertake patient-focused outreach to provide education on how AUC can play an invaluable role in achieving a more accurate diagnosis.

APPENDIX A: WORKGROUP MEMBERS AND EXTERNAL REVIEWERS

WORKGROUP

The members of the workgroup are Hossein Jadvar, MD, PhD, MPH, MBA, University of Southern California, Los Angeles, CA (SNMMI); Patrick M. Colletti, MD, University of Southern California, Los Angeles, CA (ACNM); Roberto Delgado-Bolton, MD, PhD, Hospital San Pedro, University of La Rioja, Logroño, La Rioja, Spain (EANM); Giuseppe Esposito, MD, MBA, Georgetown University Hospital, Washington, DC (SNMMI); Landis Griffeth, MD, PhD, Baylor University Medical Center, Dallas, TX (SNMMI); Bernd J. Krause, MD, Rostock, Germany (EANM); Andrei Horia Iagaru, MD, FACNM, Stanford University Medical Center, Stanford, CA (SNMMI); Helen Ruth Nadel, MD, FRCPC, British Columbia Children's Hospital, Vancouver, BC, Canada (SNMMI, SPR, CANM); David Quinn, MBBS, PhD, FRACP, FACP, USC Norris Comprehensive Cancer Center, Los Angeles, CA (ASCO); Eric Rohren, MD, PhD, The University of Texas, Houston, TX (SNMMI); Rathan M. Subramaniam, MD, PhD, MPH, FACNM, The Johns Hopkins University, Baltimore, MD (ACNM); and Katherine Zukotynski, MD, FRCPC, McMaster University, Hamilton, ON, Canada (SNMMI).

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SNMMI

The supporting staff from SNMMI are Sukhjeet Ahuja, MD, MPH, Director, Evidence & Quality Department, and Julie Kauffman, Program Manager, Evidence & Quality Department.

APPENDIX B: DEFINITION OF TERMS AND ACRONYMS [AQ1]

ACNM: American College of Nuclear Medicine
ASCO: American Society of Clinical Oncology
AUC: appropriate use criteria
BAC: bronchioloalveolar carcinoma
CANM: Canadian Association of Nuclear Medicine
CEA: carcinoembryonic antigen
Chemotherapy (*176*): The use of synthetic or naturally occurring chemicals for the treatment of diseases. It is particularly used to refer to the use of chemical-based agents to treat cancer. Chemotherapy may also include agents that enhance immune function or alter hormonal activity.
CI: confidence interval
CT: computed tomography
EANM: European Association of Nuclear Medicine
FDG (*177*): A fludeoxyglucose F 18 injection is used to help diagnose cancer, heart disease, and epilepsy. It is used in a procedure called a positron emission tomography (PET) scan as a radiopharmaceutical.
HL: Hodgkin lymphoma
Lymphoma (*178*): A cancer of part of the immune system called the lymph system. There are many types of lymphoma such as Hodgkin lymphoma (*179*) and non-Hodgkin lymphoma (*178*).

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Melanin (*180*): Pigment produced by the skin or melanocyte cells that give the skin a darker hue.

Melanocytes (*181*): Pigment-producing cells in the skin of humans and other vertebrates.

Melanoma (*182*): The most serious type of skin cancer.

Metastasis (*183*): The spread of cancer from one part of the body to another. A tumor formed by cells that have spread is called a "metastatic tumor" or a "metastasis." The metastatic tumor contains cells that are like those in the original (primary) tumor. The plural form of metastasis is metastases (meh-TAS-tuh-SEEZ).

MRI: magnetic resonance imaging

MWA: microwave ablation

NHL: non-Hodgkin lymphoma

NSCLC: non-small cell lung cancer

OIT: other imaging technique

PEM: positron emission mammography

PET scan (*184*): "A positron emission tomography (PET) scan is a type of imaging test. It uses a radioactive substance called a tracer to look for disease in the body. A PET scan shows how organs and tissues are working. This is different than magnetic resonance imaging (MRI) and computed tomography (CT), which show the structure of, and blood flow to and from organs. Many places have machines that combine the PET and CT images, so that only one exam is performed."

PICOTS: population, intervention, comparison, outcome, timing, and setting

QUADAS: Quality Assessment of Diagnostic Accuracy Studies

Radiation therapy (*185*): A cancer treatment that uses high doses of radiation to kill cancer cells and stop them from spreading. The radiation may be external, from special machines, or internal, from radioactive substances. The type of radiation therapy depends on many factors, including the type of cancer; the size of the cancer; the cancer's location in the body; how close the cancer is to normal tissues that are sensitive to radiation; how far into the body the radiation needs to travel; and the patient's general health and medical history.

Restaging (*186*): A reevaluation of the extent of disease, after a round of treatment, that provides the basis for ongoing management.

RFA: radiofrequency ablation

Sarcoma (*187*): A malignant or cancerous tumor that occurs in the connective tissues of the body, including the bones, cartilage, tendons, and soft tissues.

SBRT: restaging after stereotactic body radiation therapy

SNMMI: Society of Nuclear Medicine and Molecular Imaging

SPR: Society for Pediatric Radiology

SUV: standardized uptake value

TNM: tumor, node, and metastasis (stage)

APPENDIX C: DISCLOSURES AND CONFLICTS OF INTEREST (COIs)

SNMMI rigorously attempted to avoid any actual, perceived, or potential COIs that might have arisen as a result of an outside relationship or personal interest on the part of the workgroup members or external reviewers. Workgroup members were required to provide disclosure statements of all relationships that might be perceived as real or potential COIs. These statements were reviewed and discussed by the workgroup chair and SNMMI staff and were updated and reviewed by an objective third party at the beginning of every workgroup meeting or teleconference. The disclosures for workgroup members can be found in Table 1C. A COI was defined as a relationship with industry—including consulting, speaking, research, and other nonresearch activities—that exceeds $5,000 in funding over the previous or upcoming 12-month period. In addition, if an external reviewer was either the principal investigator of a study or another key member of the study personnel, that person's participation in the review was considered likely to present a COI. All reviewers were asked about any potential COI. A COI was also considered likely if an external reviewer or workgroup member was either the principal investigator or a key member of a study directly related to the content of this AUC. All external reviewers were asked about any potential COI.

APPENDIX D: PUBLIC COMMENTARY

The workgroup solicited information from all communities through the SNMMI website and through direct solicitation of SNMMI members. The comments and input helped to shape the development of these AUC on the appropriate use of FDG PET/CT for clinical indications of the detection of malignant disease.

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TABLE 1C
Relationships with Industry and Other Entities

Workgroup member	Reported relationships
Colletti, Patrick	• None
Delgado-Bolton, Roberto	• None
Esposito, Giuseppe	• GE, clinical trial agreement for Parkinson disease
Griffeth, Landis	• None
Iagaru, Andrei	• None
Jadvar, Hossein	• None
Krause, Bernd	• Bayer Pharma AG, research grant for oncology • TauRx Therapeutics, research grant for neurology • Amgen, research grant for oncology
Nadel, Helen	• None
Quinn, David	• Dendreon, honorarium for advisory board on prostate cancer therapy • Astellas, honorarium for advisory board on prostate cancer therapy • Astellas Farma Brasil, honorarium for advisory board on prostate cancer therapy • Janssen Cilag Brasil, honorarium for advisory board on prostate cancer therapy • Pfizer Australia, honorarium for teaching renal cancer therapy
Rohren, Eric	• None
Subramaniam, Rathan	• None
Zukotynski, Katherine	• None

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Director; Michelle Bruno, MPH, Manager) and from the Pacific Northwest Evidence-Based Practice Center of Oregon Health and Science University (Roger Chou, MD, FACP, Director; Miranda Pappas, MA, Project Manager, Research Associate).

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[AQ1] Please add citations for Appendix B, C, and D in text where suitable