PET Six-Month Monitoring Report 2015-2

Evidence from Primary Studies and Systematic Reviews and Recommendations from Clinical Practice Guidelines July to December 2015

R. Poon and the Program in Evidence-Based Care Disease Site Group Reviewers

Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: May 25, 2016

QUESTION

What is the role of positron emission tomography (PET) in the clinical management of patients with cancer, sarcoidosis, or epilepsy with respect to:

- Diagnosis and staging
- Assessment of treatment response
- Detection and restaging of recurrence
- Evaluation of metastasis

Outcomes of interest are survival, quality of life, prognostic indicators, time until recurrence, safety outcomes (e.g., avoidance of unnecessary surgery), and change in clinical management.

INTRODUCTION

In 2010, the Ontario PET Steering Committee (the Committee) requested that the Program in Evidence-Based Care (PEBC) provide regular updates to the Committee of recently published literature reporting on the use of PET in patients with cancer, sarcoidosis, or epilepsy. The PEBC recommended a regular monitoring program be implemented, with a systematic review of recent evidence conducted every six months. The Committee approved this proposal, and this is the 10th issue of the six-month monitoring reports. This report is intended to be a high-level, brief summary of the identified evidence, and not a detailed evaluation of its quality and relevance.

METHODS

Literature Search Strategy

Full articles and abstracts published between July and December 2015 were systematically searched through MEDLINE and EMBASE for evidence from primary studies and systematic reviews. The search strategies used are available upon request to the PEBC.

Inclusion Criteria for Clinical Practice Guidelines

Any clinical practice guidelines that contained recommendations with respect to PET were included. Study design was not a criterion for inclusion or exclusion.

Pediatric studies were included in this report and will be included in subsequent reports. The decision to include them was made by the Committee based on the formation of a Pediatric PET Subcommittee that will explore and report on indications relating to PET in pediatric cancer.

Inclusion Criteria for Primary Studies

Articles were selected for inclusion in the systematic review of the evidence if they were fully published, English-language reports of studies that met the following criteria:

1. Studied the use of 18-fluorodeoxyglucose (FDG) PET in cancer, sarcoidosis, or epilepsy in humans.
2. Evaluated the use of the following radiopharmaceutical tracers:
    - ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTATOC, ^{68}Ga DOTATATE
    - ^{18}F-choline, ^{11}C-choline (prostate cancer)
    - ^{18}F-FET ([^{18}F]fluoroethyl-L-tyrosine) (brain)
    - ^{18}F-FLT ([^{18}F]3-deoxy-^{3}F-fluorothymidine) (various)
    - ^{18}F-MISO ([^{18}F]fluoromisonidazole) (hypoxia tracer)
    - ^{18}F-FAZA ([^{18}F]fluoroazomycin arabinoside) (hypoxia tracer)
    - ^{18}F-fluoride (more accurate than bone scanning)
    - ^{18}F-flurpiridaz (cardiac)
    - ^{18}F-florbetapir (Amyvid) (dementia imaging)
    - ^{18}F-FDOPA
    - ^{68}Ga-PSMA (prostate-specific membrane antigen)
3. Published as a full article in a peer-reviewed journal.
4. Reported evidence related to change in patient clinical management or clinical outcomes, or reported diagnostic accuracy of PET compared with an alternative diagnostic modality.
5. Used a suitable reference standard (pathological and clinical follow-up) when appropriate.
6. Included ≥12 patients for a prospective study/randomized controlled trial or ≥50 patients for a retrospective study with the disease of interest.

Inclusion Criteria for Systematic Reviews

1. Reviewed the use of FDG PET/computed tomography (CT) in cancer, sarcoidosis, or epilepsy.
2. Contained evidence related to diagnostic accuracy; change in patient clinical management, clinical outcomes, or treatment response; survival; quality of life; prognostic indicators; time until recurrence; or safety outcome (e.g., avoidance of unnecessary surgery).

Exclusion Criteria

1. Letters and editorials.

RESULTS

Literature Search Results

Primary Studies and Systematic Reviews

Sixty-one studies published between July and December 2015 met the inclusion criteria. A summary of the evidence from the 61 studies can be found in **Appendix 1: Summary of studies from July to December 2015**.

Breast Cancer

Four studies met the inclusion criteria (1-4). In a prospective study involving patients with early-stage breast cancer, FDG PET/CT showed highly specific results for assessing multifocality compared with dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) (100% vs. 53%). FDG PET/CT also had a significantly higher positive predictive value (PPV) (100% vs. 50%). For the evaluation of axillary nodal involvement, sentinel lymph node biopsy offered the highest accuracy (96%), followed by FDG PET/CT (75%), diffusion-weighted imaging MRI (63%), and DCE-MRI (58%) (1). When evaluating lymph node status after neoadjuvant chemotherapy, the diagnostic accuracy in terms of the area under the receiver operating characteristic (ROC) curve of FDG PET/CT (0.532) was similar to that of MRI (0.588) but significantly lower than that of ultrasound (0.626, p=0.03) (2). For detecting bone metastases, FDG PET/CT was significantly more sensitive (93.4% vs. 84.5%; p=0.008) and more specific (99.4% vs. 89.6%, p=0.008) than ^{99m}Tc-MDP bone scintigraphy (3). In patients with locally advanced breast cancer who have no clinical or radiologic evidence of locoregional and distant disease, a prospective study reported that FDG PET/CT impacted the radiation therapy management of 20.8% of cases (4).

Esophageal Cancer

Two studies met the inclusion criteria (5,6). Pooled estimates from a meta-analysis revealed high sensitivity (96%) and moderate specificity (78%) for FDG PET or PET/CT in diagnosing recurrent esophageal cancer after treatment with curative intent (5). In the preoperative assessment of lymph node metastasis, FDG PET/CT showed a significantly better specificity and PPV than CT, when analyzed both by stations (specificity: 97.7% vs. 94.1%, p<0.01; PPV: 64.6% vs. 44.0%, p<0.01) and by cases (specificity: 81.1% vs. 34.0%, p<0.01; PPV: 78.9% vs. 53.9%, p<0.05). The sensitivity was also higher in favour of FDG PET/CT with a case-by-case analysis (75.9% vs. 55.6%, p<0.05) but comparable between the two modalities with a station-by-station analysis (6).

Gastrointestinal Cancer

Five studies met the inclusion criteria (7-11). In patients with colorectal cancer, FDG PET/CT detected distant metastases with 100% sensitivity, but specificity (69%) was substandard (7). Regarding liver metastasis detection, FDG PET/CT was less sensitive but more specific than CT or MRI on both lesion- and patient-based analyses (8). Another study evaluated the added value of a fourth FDG PET/CT scan and subsequent follow-up FDG PET/CT scans after completion of primary treatment. FDG PET/CT was able to identify recurrence or metastasis in 40.0% of scans obtained without prior clinical suspicion of disease and ruled out disease in 23.6% of scans obtained with prior clinical suspicion (9). Overall, FDG PET/CT prompted a change in treatment strategy in 9% to 42% of patients (7-9). For assessment of response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer, FDG PET/CT showed satisfactory results (pooled sensitivity: 73%; pooled specificity: 77%) (10). In patients with hepatocellular carcinoma, FDG PET/CT was significantly more sensitive than ^{99m}Tc-HDP bone scintigraphy in patient-based analysis (99.0% vs. 85.0%, p=0.042) and in region-based analysis (96.7% vs. 52.7%, p<0.001) for detecting bone metastases (11).

Genitourinary Cancer

Three studies met the inclusion criteria (12-14). A meta-analysis reported good overall sensitivity (pooled estimate: 82%) and specificity (pooled estimate: 92%) for FDG PET or FDG PET/CT in the diagnosis of urinary bladder cancer (12). Furthermore, FDG PET/CT can detect metastases with high sensitivity (89%) and PPV (90%) (13). In the staging of primary adrenal malignancy, FDG PET/CT was superior to contrast-enhanced computed tomography (CECT) for the detection and characterization of adrenal lesions (14).

Gynecologic Cancer

Five studies met the inclusion criteria (15-19). Two of the studies investigated the use of FDG PET/CT in ovarian cancer. FDG PET/CT did not provide significant advantages over multidetector CT or MRI in detecting peritoneal carcinomatosis, infiltrated lymph nodes, and basal pleural carcinomatosis (15). In relation to cancer antigen-125, FDG PET/CT identified recurrent disease in 35% of patients without increased levels of this tumour marker, which led to management changes in 41.6% of cases (16). One prospective study explored the diagnostic value of FDG PET/CT for preoperative staging in endometrial carcinoma. The authors reported a high accuracy for evaluating the presence of lymph node metastases (89% to 93%). However, detection of cervical stromal involvement was satisfactory (accuracy: 66% to 76%) (17). In the management of vulvar malignancies, FDG PET or PET/CT had a significantly lower area under the ROC curve (AUC) value than that of CT or MRI when detecting pelvic lymph node or distant metastasis (0.786 vs. 0.964, p=0.007). There was no significant difference between FDG PET or PET/CT (AUC: 0.913) and CT or MRI (AUC: 0.958) in detecting metastatic inguinal lymph nodes (18). Follow-up data from a prospective randomized trial demonstrated no survival (66.7% vs. 73.2%, p=0.417) or freedom from extrapelvic metastasis (79.3% vs. 76.1%, p=0.700) benefit for patients with cervical cancer who received pretreatment FDG PET or PET/CT compared with those who did not. Nonetheless, detection of paraaortic lymph nodes by pretreatment FDG PET or PET/CT in some patients did decrease the need for extended-field concurrent chemoradiation therapy (19).

Head and Neck Cancer

Eleven studies met the inclusion criteria (20-30). The use of FDG PET/CT to assess treatment response at three to four months postchemoradiotherapy yielded high sensitivity (90% to 100%) and specificity (84% to 89%) for detecting residual disease (20,21). Additionally, FDG PET/CT appeared to be more sensitive but less specific than MRI (20). In the follow-up of patients who underwent curative treatment, FDG PET/CT was able to diagnose subclinical recurrence with high sensitivity (96%), specificity (87%), and accuracy (89%) (22); these findings were consistent with those reported in a meta-analysis (pooled sensitivity: 92%; pooled specificity: 87%) (23). For the localization of metastatic disease, FDG PET/CT could reliably detect lymph node metastases as well as extracapsular spread (24). When compared with conventional imaging, FDG PET/CT increased the per-neck-level sensitivity by 21% (25). Moreover, FDG PET/CT was demonstrated to be more specific (pooled estimate: 90% vs. 67%, p=0.001) but less sensitive (pooled estimate: 83% vs. 96%, p=0.0014) than single-photon emission computed tomography (SPECT) for diagnosing mandibular invasion (26). Not only did FDG PET/CT improve staging, it also had a major impact on management (i.e., change in planned treatment modality or intent) in 12.5% of patients and a minor impact (i.e., intramodality changes) in 25% of patients (27). In patients with hypopharyngeal squamous cell carcinoma, FDG PET/CT was superior to CT or MRI in all diagnostic parameters on both a per-level and a per-side basis for detecting ipsilateral and contralateral lymph node metastasis. However, just accuracy and AUC on the ipsilateral level reached statistical significance (accuracy: 95.8% vs. 92.7%, p=0.02; AUC: 0.941 vs. 0.906, p=0.024) (28). FDG PET/CT was

equally effective in lymph node staging in oropharyngeal squamous cell cancer (sensitivity: 100%; specificity: 87%) (29). In differentiated thyroid carcinoma, FDG PET/CT was shown to have some value in detecting metastatic disease in patients with high serum thyroglobulin and a negative iodine-131 whole body scan (sensitivity: 84.8%; specificity 79.1%) (30).

Hematologic Cancer

Fourteen studies met the inclusion criteria (31-44). Several studies investigated the potential of FDG PET/CT to detect bone morrow involvement in patients with Hodgkin and non-Hodgkin lymphoma. While specificity of FDG PET/CT was consistently high (83.0% to 95.7%) (31-34), the reported sensitivity varied among the studies (31-35), ranging from 50.0% for a mixed population of patients with Hodgkin or non-Hodgkin lymphoma (32,33) to 100% for a population with extranodal NK/T cell lymphoma (31). Similarly, based on one systematic review, the sensitivity of FDG PET/CT (63% to 100%) and MRI (59% to 100%) for initial lymphoma staging also varied considerably (36). Regarding response assessment, interim FDG PET or PET/CT achieved less than satisfactory results for predicting treatment outcome in patients with diffuse large B-cell lymphoma after two to four cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) (37,38) but better results in patients with Hodgkin lymphoma after one to four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) or bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone (BEACOPP) (39,40). Nonetheless, patients with a negative interim PET scan have significantly higher survival rates than those with a positive interim PET scan (37-43). In chronic lymphocytic leukemia, FDG PET/CT revealed high sensitivity (87.0%) and negative predictive value (NPV) (94.0%) in identifying cases of Richter's syndrome or secondary malignancy (44).

Non-FDG Tracers

Eight studies met the inclusion criteria (45-52). Three of the studies evaluated ^{11}C-Choline PET/CT, one in bladder cancer and the other two in prostate adenocarcinoma. By patient-based analysis, ^{11}C-Choline PET/CT showed satisfactory performance for the detection of lymph node metastasis in patients with bladder cancer, providing a better specificity (90%) than sensitivity (59%) (45). In intermediate- to high-risk prostate adenocarcinoma, the best results for delineating malignant intraprostatic lesions were obtained with ^{11}C-Choline PET/CT using 60% of the maximum standardized uptake value (SUV_{60}). The Dice similarity coefficient (DSC) and Youden index (YI) of SUV_{60} were 0.59 and 0.43, respectively. Manual contouring using ^{11}C-Choline PET/CT (DSC: 0.52; YI: 0.39) was not significantly different from the automatic contouring method. However, both manual and automatic contouring using ^{11}C-Choline PET/CT were superior to manual contouring using MRI (DSC: 0.37, $p<0.001$; YI: 0.19, $p\leq0.001$) (46). For nodal staging, neither ^{11}C-Choline PET/CT (sensitivity: 8.2% to 18.9%; PPV: 50.0% to 63.6%) nor MRI (sensitivity: 9.5% to 36.1%; PPV: 40.0% to 86.7%) was shown to be useful in patients who had no evidence of lymph node involvement on CECT (47). On the contrary, PET/CT imaging with ^{68}Ga-labelled PSMA ligand HBED-CC can correctly detect recurrence in a high percentage of patients with suspected progressive prostate cancer (sensitivity: 76.6% to 88.1%; specificity: 100%) (49). The diagnostic accuracy and clinical utility of ^{18}F-Choline PET/CT in the follow-up of patients with treated low-grade glioma were demonstrated in one prospective study. Compared with advanced MRI (90.9%) and ^{201}T1-SPECT (68.8%), ^{18}F-Choline PET/CT (100%) was the most accurate for detecting or ruling out tumour activity during posttreatment follow-up. Additional information given by ^{18}F-Choline PET/CT changed the initial therapeutic approach of 72.2% of patients (48). In the diagnosis, staging and restaging of patients with pancreatic neuroendocrine tumours, ^{68}Ga-DOTA-NOC PET/CT was more specific than conventional imaging (77.7% vs. 33.3%, $p<0.0001$) (50). Among

patients with various primaries, F-DOPA PET/CT (91.9%) was found to have a superior diagnostic accuracy than perfusion-weighted MRI (75.6%) for differentiating radionecrosis from progressive brain metastases after stereotactic radiosurgery (51). Furthermore, ^{18}F-Fluoride PET or PET/CT performed significantly better than ^{99m}Tc-MDP bone scintigraphy when detecting bone metastases (pooled sensitivity: 96% vs. 88%, p=0.002; pooled specificity: 91% vs. 80%, p=0.001) (52).

Non-Small Cell Lung Cancer and Other Lung Cancer

One study met the inclusion criteria (53). Although FDG PET/CT (91.4%) and MRI (94.3%) showed comparable diagnostic accuracy for assessing primary tumour site in patients with non-small cell lung cancer (NSCLC), MRI was found to be significantly more accurate than FDG PET/CT with respect to evaluation of regional lymph node involvement (91.4% vs. 80.7%, p<0.001), assessment of presence of distant metastatic spread (98.6% vs. 90.7%, p=0.003), and clinical stage evaluation (91.4% vs. 70.7%, p<0.001).

Pancreatic Cancer

Two studies met the inclusion criteria (54,55). In diagnosing malignant pancreatic tumours, FDG PET/CT showed significantly higher sensitivity (96.0% vs. 82.0%, p=0.025), NPV (90.0% vs. 59.1%, p=0.023), and accuracy (94.3% vs. 77.1%, p=0.004) than CECT (54); whereas comparison between FDG PET/CT and serum CA19-9 levels demonstrated no significant difference (55). Likewise, FDG PET/CT and CECT performed comparably well in diagnosing peripancreatic vessel invasion or regional lymph node metastasis. However, FDG PET/CT was shown to be superior to CECT in detecting distant metastasis (sensitivity: 94.1% vs. 58.8%, p=0.015; NPV: 97.0% vs. 82.5%, p=0.049) (54).

Sarcoma

Two studies met the inclusion criteria (56,57). SUV_{max} and tumour-to-background uptake ratio on FDG PET/CT were significant predictors of survival in patients with soft tissue sarcoma (p<0.001) but not in patients with bone sarcoma (56). Pooled data (on an examination-based or lesion-based level) from a meta-analysis showed that FDG PET/CT is a useful tool for diagnosing primary bone sarcomas (sensitivity: 96%; specificity: 79%), and detecting recurrence (sensitivity: 92%; specificity: 93%), local recurrence (sensitivity: 91%; specificity: 93%), distant metastasis (sensitivity: 90%; specificity: 85%), lung metastasis (sensitivity: 83% to 88%; specificity: 89% to 98%), bone metastasis (sensitivity: 92% to 95%; specificity: 62% to 98%), and lymph node metastasis (specificity: 96%) (57).

Unknown Primary Cancer

One study met the inclusion criteria (58). FDG PET/CT detected primary site with high sensitivity (95.8%) but low specificity (66.7%) in patients presenting with malignancy of undefined primary origin.

CLINICAL EXPERT REVIEW

Breast Cancer

No recommendations currently exist for the utilization of PET/CT in breast cancer.

Reviewer's Comments (Dr. Muriel Brackstone)

The current recommendations for the utilization of PET/CT in breast cancer remain valid and no changes are required. The prospective study reported by Ergul et al. evaluated 24 patients with consecutive early-stage breast cancer over a 14-month period, seen in a single institution. All patients had FDG PET/CT scans, DCE-MRI scans, sentinel lymph node and

axillary lymph node dissection. With regards to axillary nodal staging, the most accurate staging results were obtained from the sentinel lymph node biopsy, as has been the case in previous research. Therefore, this study does not add sufficient new information to suggest that additional imaging to stage the axilla should be currently considered, particularly in light of recent trials that have suggested that positive sentinel lymph nodes in patients with early-stage breast cancer have similar outcomes when randomized to axillary dissection versus no dissection (ACOSOG Z0011).With regards to preoperative imaging to determine multifocality, both MRI and PET/CT scans had significant false positive reports, which would negatively impact the extent of surgery recommended for these patients with early disease. Therefore, although the specificity and positive predictive values were higher with FDG PET/CT compared with DCE-MRI, the overall sensitivity was 67% for FDG PET/CT versus 78% for DCE-MRI. The overall accuracy of FDG PET/CT was higher; however, the issue of false positive multifocality assessment remains and this study alone is considered insufficient to address this shortcoming. Therefore, breast assessment practices should remain as current guidelines recommend.

The study reported by You and colleagues retrospectively evaluated 139 newly diagnosed patients who underwent neoadjuvant chemotherapy and had imaging prior to and following chemotherapy. The imaging results were then correlated with histopathology. Patients underwent an axillary dissection or, for those patients who were baseline node positive, a sentinel lymph node procedure. You et al. did not report the false negative sentinel lymph node rate, which remains the most controversial aspect of sentinel lymph node staging following neoadjuvant chemotherapy for patients with biopsy-confirmed nodal positivity who become clinically node negative. Nevertheless, the greatest area under the receiver operating characteristic curve was observed in patients in the combined modality group – using all images (ultrasound, MRI, and PET/CT) – which is not practical to implement as a guideline. Given that patients will have definitive nodal staging done at surgery, these additional nodal staging imaging tests are unlikely to significantly change surgical axillary staging procedures until a prospective blinded trial is completed to confirm clinical utility.

The retrospective study reported by Teke and colleagues reviewed patients who had Tc99m bone scans and FDG PET/CT scans for staging of bony metastases. It found that PET/CT offered a higher overall accuracy, sensitivity, and specificity. A prospective, larger, and blinded confirmatory trial was performed with clinical outcome measures to demonstrate whether this higher identification of bony metastases was confirmed and translated into a clinically significant difference in care or outcome.

In a prospective study, Ng and colleagues compared FDG PET/CT staging for distant metastases with standard distant staging (CT chest/abdomen/pelvis and Tc99m bone scan) in 154 patients with locally advanced breast cancer. Among patients who had no evidence of distant metastases by standard imaging, 20% of patients were found to have imaging evidence of distant metastases or locoregional nodal extent (internal mammary nodal metastases) which resulted in a change in clinical treatment. Most of these patients do not appear to have had pathological confirmation of the disease observed only on PET/CT imaging and therefore a confirmatory study, in which the false positive rate of metastases observed only on PET/CT can be determined, should be undertaken before changing recommendations for staging to include PET/CT imaging. However, if PET/CT is to be considered as an addition to standard imaging or to replace CT chest/abdomen and pelvis, then it should be considered in only the subset of patients with locally advanced breast cancer, where the risk of distant disease is highest. A confirmatory study should be considered prior to implementing this change.

Esophageal Cancer
Current Insured Indication

- For baseline staging assessment of those patients diagnosed with esophageal cancer who are being considered for curative therapy and/or repeat PET/CT scan on completion of preoperative/neoadjuvant therapy, prior to surgery.

Current Recommendations for the Utilization of PET/CT in Esophageal Cancer

- For the staging workup of patients with esophageal cancer who are potential candidates for curative therapy, PET is recommended to improve the accuracy of M staging.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET (posttherapy or neoadjuvant therapy) for the purpose of predicting response to neoadjuvant therapy.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET for the evaluation of suspected recurrence.

Reviewer's Comments (Dr. Rebecca Wong)

Goense et al. performed a meta-analysis of the utility of PET or PET/CT in detecting recurrences after curative therapy. Eight studies were included when PET was performed in asymptomatic patients (4 studies) and for indications (4 studies). Sensitivity was high while specificity was modest. There were no equivalent data provided for the site of recurrence (i.e., local regional versus distant recurrence), nor data that described the impact of PET or PET/CT on clinical treatment decision and survival. Clinically, salvage curative therapy (e.g., salvage surgery or salvage radical chemoradiotherapy) can be considered in selected patients.

The current data would support consideration for the following change in recommendation: For patients who are candidates for radical salvage therapy in the presence of local recurrence, PET or PET/CT should be considered to exclude distant metastases.

Gastrointestinal Cancer

Current Insured Indication (Colorectal Cancer)

- Where recurrent disease is suspected on the basis of elevated and/or rising carcinoembryronic antigen level(s) during follow-up after surgical resection but standard imaging tests are negative or equivocal; or prior to surgery for liver metastases from colorectal cancer when the procedure is high-risk (e.g., multiple-staged liver resection or vascular reconstruction); or where the patient is at high risk for surgery (e.g., American Society of Anesthesiology score ≥4).

Current Recommendations for the Utilization of PET/CT in Colorectal Cancer

- The routine use of PET is not recommended for the diagnosis or staging of clinical stage I to III colorectal cancers.
- PET is recommended for determining management and prognosis if conventional imaging is equivocal for the presence of metastatic disease.
- The routine use of PET is not recommended for the measurement of treatment response in locally advanced rectal cancer before and after preoperative chemotherapy.
- PET is not recommended for routine surveillance in patients with colorectal cancer treated with curative surgery who are at high risk for recurrence.
- PET is recommended to determine the site of recurrence in the setting of rising carcinoembryonic antigen levels, when a conventional workup fails to unequivocally identify metastatic disease.
- PET is recommended in the preoperative assessment of colorectal cancer liver metastasis prior to surgical resection.

Reviewer's Comments (Dr. Anand Swaminath)

The current recommendations for the utilization of PET/CT in gastrointestinal cancer remain valid and no changes are required. The systematic review by Maffione et al (10) on PET/CT in predicting response to neoadjuvant therapy is interesting, but the pooled sensitivity and specificity are not impressive.

Genitourinary Cancer

Current Recommendations for the Utilization of PET/CT in Testicular Cancer

- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET in the routine staging of patients with testicular cancer.
- PET is recommended for the assessment of treatment response in patients with seminoma and residual masses after chemotherapy.
- PET is not recommended for the assessment of treatment response in patients with nonseminoma.
- Due to insufficient evidence, a recommendation cannot be made for or against the routine use of PET for evaluation of recurrence.

Reviewer's Comments (Dr. Glenn Bauman)

The current recommendations for the utilization of PET/CT in genitourinary cancer remain valid and no changes are required. Aside from testicular cancer, there are currently no other indications/recommendations for the utility of FDG PET/CT in genitourinary cancers. Small series suggest the possible utility of FDG PET/CT in the diagnosis and staging of bladder cancer; however, the evidence base is currently too limited to recommend use outside of trials. Furthermore, there is a lot of evidence developing for PSMA PET agents in prostate cancer.

Gynecologic Cancer

Current Recommendations for the Utilization of PET/CT in Cervical Cancer

- PET is not recommended for diagnosis of cervical cancer.
- PET is not recommended for staging early-stage cervical cancer.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET for staging advanced-stage cervical cancer. However, ongoing studies will clarify the role of PET in advanced disease.
- PET is not recommended (following or early during therapy) for the purpose of predicting response to chemoradiation therapy.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET for evaluation of suspected recurrence.
- PET is recommended for women with recurrence who are candidates for pelvic exenteration or chemoradiation with curative intent.

Current Recommendations for the Utilization of PET/CT in Ovarian Cancer

- PET is not recommended in the diagnosis of ovarian cancer.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET in the evaluation of asymptomatic ovarian mass.
- PET is not recommended for staging of ovarian cancer.
- PET is not recommended for detecting recurrence or restaging patients not being considered for surgery.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET for patients being considered for secondary cytoreduction.

Reviewer's Comments (Dr. Anthony Fyles)

The current recommendations for the utilization of PET/CT in gynecologic cancer remain valid and no changes are required. Furthermore, the studies involving endometrial and vulvar cancer do not suggest a role for PET/CT in evaluating these tumours.

Head and Neck Cancer

Current Insured Indications

- Head and neck cancer:
    - For the evaluation of metastatic squamous cell carcinoma in neck nodes when the primary disease site is unknown after standard radiological and clinical investigation; or for the staging of nasopharyngeal cancer.
- Thyroid cancer:
    - Where recurrent or persistent disease is suspected on the basis of an elevated and/or rising thyroglobulin level, but standard imaging studies are negative or equivocal.

Current Recommendations for the Utilization of PET/CT in Head and Neck Cancer

- PET is recommended in the M and bilateral nodal staging of all patients with head and neck squamous cell carcinoma where conventional imaging is equivocal, or where treatment may be significantly modified.
- PET is recommended in all patients after conventional imaging and in addition to, or prior to, diagnostic panendoscopy where the primary site is unknown.
- PET is recommended for staging and assessment of recurrence of patients with nasopharyngeal carcinoma if conventional imaging is equivocal.
- PET is recommended for restaging patients who are being considered for major salvage treatment, including neck dissection.

Reviewer's Comments (Dr. Amit Singnurkar)

The current recommendations for the utilization of PET/CT in head and neck cancer remain valid and no changes are required.

Hematologic Cancer

Current Registry Indication (Lymphoma Staging)

- PET for the staging of Hodgkin or non-Hodgkin lymphoma being treated with curative intent:
    - For the staging of limited disease as per conventional imaging, or
    - When imaging results are equivocal for differentiating between limited- and advanced-stage disease.
- PET for apparent limited-stage nodal follicular lymphoma or other indolent non-Hodgkin lymphomas where curative radiation therapy is being considered for treatment.

Current Insured Indication (Lymphoma)

- For the evaluation of residual mass(es) following chemotherapy in a patient with Hodgkin or non-Hodgkin lymphoma when further potentially curative therapy (such as radiation or stem cell transplantation) is being considered; or for the assessment of

response in early-stage Hodgkin lymphoma following two or three cycles of chemotherapy when chemotherapy is being considered as the definitive single modality therapy.

Current Recommendations for the Utilization of PET/CT in Hematologic Cancer

- When functional imaging is considered to be important in situations where anatomical imaging is equivocal and/or in potentially curable cases, a FDG PET/CT scan is recommended.
- When functional imaging is considered to be important in situations where anatomical imaging is equivocal and treatment choices may be affected in limited-stage indolent lymphomas, a FDG PET/CT scan is recommended.
- An FDG PET/CT scan is recommended for the assessment of early response in early stage (I or II) Hodgkin lymphoma following two or three cycles of chemotherapy when chemotherapy is being considered as the definitive single modality therapy, to inform completion of therapy or to determine whether more therapy is warranted.
- In potentially curable cases, when functional imaging is considered to be important and conventional imaging is equivocal, a FDG PET/CT scan is recommended to investigate recurrence of Hodgkin lymphoma or non-Hodgkin lymphoma.
- An FDG PET/CT scan is recommended for the evaluation of residual mass(es) following chemotherapy in a patient with Hodgkin or non-Hodgkin lymphoma when further potentially curative therapy (such as radiation or stem cell transplantation) is being considered and when biopsy cannot be safely or readily performed.
- An FDG PET/CT scan is not recommended for the routine monitoring and surveillance of lymphoma.

Reviewer's Comments (Dr. Marc Freeman)

The current recommendations for the utilization of PET/CT in hematologic cancer remain valid and no changes are required.

Non-FDG Tracers

No recommendations currently exist for the utilization of PET/CT with non-FDG tracers.

Reviewer's Comments (Dr. Amit Singnurkar)

The evidence identified in this six-month review indicates a potential use for ^{68}Ga-PSMA in the restaging of recurrent prostate cancer (with elevated prostate-specific antigen level), ^{18}F-FET in differentiating radio necrosis from recurrence in treated primary brain malignancies and metastases (comparable to F-DOPA), and ^{18}F-NaF in the diagnosis of bone metastases in prostate and breast cancer where standard imaging is negative. Moreover, there is an ongoing pan-Canadian study evaluating ^{18}F-NaF.

Non-Small Cell Lung Cancer and Other Lung Cancer

Current Insured Indications

- Solitary pulmonary nodule:
    - A lung nodule for which a diagnosis could not be established by a needle biopsy due to unsuccessful attempted needle biopsy; the solitary pulmonary nodule is inaccessible to needle biopsy; or the existence of a contraindication to the use of needle biopsy.

- NSCLC:
    - Where curative surgical resection is being considered.
- Clinical stage III NSCLC:
    - Where potentially curative combined modality therapy with radical radiotherapy and chemotherapy is being considered.
- Limited-disease small cell lung cancer:
    - Where combined modality therapy with chemotherapy and radiotherapy is being considered.

Current Recommendations for the Utilization of PET/CT in Small Cell Lung Cancer

- PET is recommended for staging in patients with small cell lung cancer who are potential candidates for the addition of thoracic radiotherapy to chemotherapy.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET for the assessment of treatment response in small cell lung cancer.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET for evaluation of recurrence or restaging.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET when metastasectomy or stereotactic body radiation therapy is being contemplated for solitary metastases.

Current Recommendations for the Utilization of PET/CT in Radiation Treatment Planning for Lung Cancer

- Combination PET-CT imaging data may be used as part of research protocols in radiation treatment planning. Current evidence does not support the routine use of PET-CT imaging data in radiation treatment planning at this time outside of a research setting.

Reviewer's Comments (Dr. Donna Maziak)

The current recommendations for the utilization of PET/CT in lung cancer remain valid and no changes are required.

Pancreatic Cancer

Current Registry Indication

- For staging if the patient is a candidate for potentially curative surgical resection (pancreatectomy) as determined by conventional staging.

Current Recommendations for the Utilization of PET/CT in Pancreatic Cancer

- PET is not recommended for primary diagnosis of pancreatic cancer.
- PET is recommended for staging if a patient is a candidate for potentially curative surgical resection as determined by conventional staging.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET to guide clinical management based on assessment of treatment response.
- Due to insufficient evidence and lack of effective therapeutic options, PET is not recommended for clinical management of suspected recurrence, nor for restaging at the time of recurrence.
- A recommendation cannot be made for or against the use of PET for staging if a solitary metastasis is identified at recurrence because there are no trials that identify the utility of PET scanning in this setting.

Reviewer's Comments (Dr. Jim Biagi)

The current recommendations for the utilization of PET/CT in pancreatic cancer remain valid and no changes are required. Sun et al. (55) address the benefit of PET SUV plus CA19-9 in diagnosis, compared with benign lesions. This study does not alter the current negative PET recommendations for diagnosis of pancreatic cancer. Zhang et al. (54) demonstrated, in a case series of 70 patients, that PET/CT or contrast-enhanced CT/PET provided additional statistically significant sensitivity and NPV for staging. This study supports the one positive PET recommendation, that is, "PET is recommended for staging if a patient is a candidate for potentially curative surgical resection as determined by conventional staging."

Sarcoma

No recommendations currently exist for the utilization of PET/CT in sarcoma.

Reviewer's Comments (Dr. Gina Diprimio)

There are now findings to support the use of PET/CT and PET alone for the detection of recurrence and diagnosis of distant metastases when conventional imaging is inconclusive. The described limitations of the studies are valid (i.e., sample size too small and quality not optimal for comparison between PET/CT and conventional imaging) but finding other metastases or recurrence for bone sarcomas is important because it could mean a cure if they are resectable.

Unknown Primary Cancer

Current Recommendation for the Utilization of PET/CT in Unknown Primary Cancer

- Where the primary site of the cancer is unknown, PET is recommended in all patients after conventional imaging and in addition to, or prior to, diagnostic panendoscopy.

Reviewer's Comments (Dr. Amit Singnurkar)

The current recommendation for the utilization of PET/CT in unknown primary cancer remains valid and no change is required.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Contact Information

For information about the PEBC and the most current version of all reports,
please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

REFERENCES

1. Ergul N, Kadioglu H, Yildiz S, Yucel SB, Gucin Z, Erdogan EB, et al. Assessment of multifocality and axillary nodal involvement in early-stage breast cancer patients using 18F-FDG PET/CT compared to contrast-enhanced and diffusion-weighted magnetic resonance imaging and sentinel node biopsy. Acta Radiol. 2015;56(8):917-23.
2. You S, Kang DK, Jung YS, An YS, Jeon GS, Kim TH. Evaluation of lymph node status after neoadjuvant chemotherapy in breast cancer patients: comparison of diagnostic performance of ultrasound, MRI and 18F-FDG PET/CT. Br J Radiol. 2015;88(1052):20150143.
3. Teke F, Teke M, Inal A, Kaplan MA, Kucukoner M, Aksu R, et al. Significance of hormone receptor status in comparison of 18F -FDG-PET/CT and 99mTc-MDP bone scintigraphy for evaluating bone metastases in patients with breast cancer: single center experience. Asian Pac J Cancer Prev. 2015;16(1):387-91.
4. Ng SP, David S, Alamgeer M, Ganju V. Impact of pretreatment combined (18)F-fluorodeoxyglucose positron emission tomography/computed tomography staging on radiation therapy treatment decisions in locally advanced breast cancer. Int J Radiat Oncol Biol Phys. 2015;93(1):111-7.
5. Goense L, van Rossum PS, Reitsma JB, Lam MG, Meijer GJ, van Vulpen M, et al. Diagnostic performance of 18F-FDG PET and PET/CT for the detection of recurrent esophageal cancer after treatment with curative intent: a systematic review and meta-Analysis. J Nucl Med. 2015;56(7):995-1002.
6. Karashima R, Watanabe M, Imamura Y, Ida S, Baba Y, Iwagami S, et al. Advantages of FDG-PET/CT over CT alone in the preoperative assessment of lymph node metastasis in patients with esophageal cancer. Surg Today. 2015;45(4):471-7.
7. Wasserberg N, Purim O, Bard V, Kundel Y, Gordon N, Groshar D, et al. Early postoperative 18F-FDG PET/CT in high-risk stage III colorectal cancer. Clin Nucl Med. 2015;40(4):e222-7.
8. Maffione AM, Lopci E, Bluemel C, Giammarile F, Herrmann K, Rubello D. Diagnostic accuracy and impact on management of (18)F-FDG PET and PET/CT in colorectal liver metastasis: a meta-analysis and systematic review. Eur J Nucl Med Mol Imaging. 2015;42(1):152-63.
9. Marcus C, Marashdeh W, Ahn SJ, Taghipour M, Subramaniam RM. 18F-FDG PET/CT and Colorectal Cancer: Value of Fourth and Subsequent Posttherapy Follow-up Scans for Patient Management. J Nucl Med. 2015;56(7):989-94.
10. Maffione AM, Marzola MC, Capirci C, Colletti PM, Rubello D. Value of (18)F-FDG PET for predicting response to neoadjuvant therapy in rectal cancer: systematic review and meta-analysis. AJR Am J Roentgenol. 2015;204(6):1261-8.
11. Seo HJ, Kim GM, Kim JH, Kang WJ, Choi HJ. 18F-FDG PET/CT in hepatocellular carcinoma: detection of bone metastasis and prediction of prognosis. Nucl Med Commun. 2015;36(3):226-33.
12. Zhang H, Xing W, Kang Q, Chen C, Wang L, Lu J. Diagnostic value of [18F] FDG-PET and PET/CT in urinary bladder cancer: a meta-analysis. Tumour Biol. 2015;36(5):3209-14.
13. Ozturk H. Detecting metastatic bladder cancer using 18F-fluorodeoxyglucose positron-emission tomography/computed tomography. Cancer Res Treat. 2015;47(4):834-43.
14. Cistaro A, Niccoli Asabella A, Coppolino P, Quartuccio N, Altini C, Cucinotta M, et al. Diagnostic and prognostic value of 18F-FDG PET/CT in comparison with morphological imaging in primary adrenal gland malignancies - a multicenter experience. Hell J Nucl Med. 2015;18(2):97-102.

15. Schmidt S, Meuli RA, Achtari C, Prior JO. Peritoneal carcinomatosis in primary ovarian cancer staging: comparison between MDCT, MRI, and 18F-FDG PET/CT. Clin Nucl Med. 2015;40(5):371-7.
16. Evangelista L, Palma MD, Gregianin M, Nardin M, Roma A, Nicoletto MO, et al. Diagnostic and prognostic evaluation of fluorodeoxyglucose positron emission tomography/ computed tomography and its correlation with serum cancer antigen-125 (CA125) in a large cohort of ovarian cancer patients. J Turk Ger Gynecol Assoc. 2015 01 Sep;16(3):137-44.
17. Husby JA, Reitan BC, Biermann M, Trovik J, Bjorge L, Magnussen IJ, et al. Metabolic tumor volume on 18F-FDG PET/CT improves preoperative identification of high-risk endometrial carcinoma patients. J Nucl Med. 2015;56(8):1191-8.
18. Lin G, Chen CY, Liu FY, Yang LY, Huang HJ, Huang YT, et al. Computed tomography, magnetic resonance imaging and FDG positron emission tomography in the management of vulvar malignancies. Eur Radiol. 2015;25(5):1267-78.
19. Lin SY, Tsai CS, Chang YC, Ng KK, Chang TC, Kao WH, et al. The role of pretreatment FDG-PET in treating cervical cancer patients with enlarged pelvic lymph node(s) shown on MRI: a Phase 3 randomized trial with long-term follow-up. Int J Radiat Oncol Biol Phys. 2015;92(3):577-85.
20. Schouten CS, de Graaf P, Alberts FM, Hoekstra OS, Comans EF, Bloemena E, et al. Response evaluation after chemoradiotherapy for advanced nodal disease in head and neck cancer using diffusion-weighted MRI and 18F-FDG-PET-CT. Oral Oncol. 2015;51(5):541-7.
21. Slevin F, Subesinghe M, Ramasamy S, Sen M, Scarsbrook AF, Prestwich RJ. Assessment of outcomes with delayed (18)F-FDG PET-CT response assessment in head and neck squamous cell carcinoma. Br J Radiol. 2015;88(1052):20140592.
22. Robin P, Abgral R, Valette G, Le Roux PY, Keromnes N, Rousset J, et al. Diagnostic performance of FDG PET/CT to detect subclinical HNSCC recurrence 6 months after the end of treatment. Eur J Nucl Med Mol Imaging. 2015;42(1):72-8.
23. Sheikhbahaei S, Taghipour M, Ahmad R, Fakhry C, Kiess AP, Chung CH, et al. Diagnostic accuracy of follow-up FDG PET or PET/CT in patients with head and neck cancer After definitive treatment: a systematic review and meta-analysis. AJR Am J Roentgenol. 2015;205(3):629-39.
24. Dequanter D, Shahla M, Aubert C, Deniz Y, Lothaire P. Prognostic value of FDG PET/CT in head and neck squamous cell carcinomas. Onco Targets Ther. 2015 26 Aug;8:2279-83.
25. Sun R, Tang X, Yang Y, Zhang C. (18)FDG-PET/CT for the detection of regional nodal metastasis in patients with head and neck cancer: a meta-analysis. Oral Oncol. 2015;51(4):314-20.
26. Li C, Sheng S, Men Y, Sun H, Xia H, Li L. Emission computed tomography for the diagnosis of mandibular invasion by head and neck cancers: a systematic review and meta-analysis. J Oral Maxillofac Surg. 2015;73(9):1875.e1-11.
27. Arias F, Chicata V, Garcia-Velloso MJ, Asin G, Uzcanga M, Eito C, et al. Impact of initial FDG PET/CT in the management plan of patients with locally advanced head and neck cancer. Clin Transl Oncol. 2015;17(2):139-44.
28. Shin NY, Lee JH, Kang WJ, Koh YW, Sohn B, Kim J. Clinical usefulness of [18F]FDG PET-CT and CT/MRI for detecting nodal metastasis in patients with hypopharyngeal squamous cell carcinoma. Ann Surg Oncol. 2015;22(3):994-9.
29. Sadick M, Weiss C, Piniol R, Frey S, Hoermann K, Schoenberg SO, et al. 18F-fluorodeoxyglucose uptake level-based lymph node staging in oropharyngeal squamous cell cancer--role of molecular marker expression on diagnostic outcome. Oncol Res Treat. 2015;38(1-2):16-22.

30. Elboga U, Karaoglan H, Sahin E, Kalender E, Demir HD, Basibuyuk M, et al. F-18 FDG PET/CT imaging in the diagnostic work-up of thyroid cancer patients with high serum thyroglobulin, negative I-131 whole body scan and suppressed thyrotropin: 8-year experience. Eur Rev Med Pharmacol Sci. 2015;19(3):396-401.
31. Zhou Z, Chen C, Li X, Li Z, Zhang X, Chang Y, et al. Evaluation of bone marrow involvement in extranodal NK/T cell lymphoma by FDG-PET/CT. Ann Hematol. 2015;94(6):963-7.
32. Kim HY, Kim JS, Choi DR, Kim HS, Kwon JH, Jang GD, et al. The clinical utility of FDG PET-CT in evaluation of bone marrow involvement by lymphoma. Cancer Res Treat. 2015;47(3):458-64.
33. Cho SF, Chang CC, Liu YC, Chang CS, Hsiao HH, Liu TC, et al. Utilization of 18F-FDG PET/CT as a staging tool in patients with newly diagnosed lymphoma. Kaohsiung J Med Sci. 2015;31(3):130-7.
34. Cetin G, Cikrikcioglu MA, Ozkan T, Karatoprak C, Ar MC, Eskazan AE, et al. Can positron emission tomography and computed tomography be a substitute for bone marrow biopsy in detection of bone marrow involvement in patients with Hodgkin's or Non-Hodgkin's lymphoma? Turk J Haematol. 2015 04 Aug;32(3):213-9.
35. Chen-Liang TH, Martin-Santos T, Jerez A, Senent L, Orero MT, Remigia MJ, et al. The role of bone marrow biopsy and FDG-PET/CT in identifying bone marrow infiltration in the initial diagnosis of high grade non-Hodgkin B-cell lymphoma and Hodgkin lymphoma. Accuracy in a multicenter series of 372 patients. Am J Hematol. 2015;90(8):686-90.
36. Regacini R, Puchnick A, Shigueoka DC, Iared W, Lederman HM. Whole-body diffusion-weighted magnetic resonance imaging versus FDG-PET/CT for initial lymphoma staging: systematic review on diagnostic test accuracy studies. Sao Paulo Med J. 2015;133(2):141-50.
37. Sun N, Zhao J, Qiao W, Wang T. Predictive value of interim PET/CT in DLBCL treated with R-CHOP: meta-analysis. Biomed Res Int. 2015;2015:648572.
38. Swinnen LJ, Li H, Quon A, Gascoyne R, Hong F, Ranheim EA, et al. Response-adapted therapy for aggressive non-Hodgkin's lymphomas based on early [18F] FDG-PET scanning: ECOG-ACRIN Cancer Research Group study (E3404). Br J Haematol. 2015;170(1):56-65.
39. Rigacci L, Puccini B, Zinzani PL, Biggi A, Castagnoli A, Merli F, et al. The prognostic value of positron emission tomography performed after two courses (INTERIM-PET) of standard therapy on treatment outcome in early stage Hodgkin lymphoma: A multicentric study by the fondazione italiana linfomi (FIL). Am J Hematol. 2015;90(6):499-503.
40. Adams HJ, Nievelstein RA, Kwee TC. Prognostic value of interim FDG-PET in Hodgkin lymphoma: systematic review and meta-analysis. Br J Haematol. 2015;170(3):356-66.
41. Sauter CS, Matasar MJ, Meikle J, Schoder H, Ulaner GA, Migliacci JC, et al. Prognostic value of FDG-PET prior to autologous stem cell transplantation for relapsed and refractory diffuse large B-cell lymphoma. Blood. 2015;125(16):2579-81.
42. Simontacchi G, Filippi AR, Ciammella P, Buglione M, Saieva C, Magrini SM, et al. Interim PET after two ABVD cycles in early-stage Hodgkin lymphoma: outcomes following the continuation of chemotherapy plus radiotherapy. Int J Radiat Oncol Biol Phys. 2015;92(5):1077-83.
43. Zhu D, Xu XL, Fang C, Ji M, Wu J, Wu CP, et al. Prognostic value of interim 18F-FDG-PET in diffuse large B cell lymphoma treated with rituximab-based immune-chemotherapy: A systematic review and meta-analysis. Int J Clin Exp Med. 2015 30 Sep;8(9):15340-50.
44. Mauro FR, Chauvie S, Paoloni F, Biggi A, Cimino G, Rago A, et al. Diagnostic and prognostic role of PET/CT in patients with chronic lymphocytic leukemia and progressive disease. Leukemia. 2015;29(6):1360-5.

45. Ceci F, Bianchi L, Graziani T, Castellucci P, Pultrone C, Eugenio B, et al. 11C-choline PET/CT and bladder cancer: lymph node metastasis assessment with pathological specimens as reference standard. Clin Nucl Med. 2015;40(2):e124-8.
46. Chang JH, Lim Joon D, Davis ID, Lee ST, Hiew CY, Esler S, et al. Comparison of [(11)C]choline positron emission tomography with T2- and diffusion-weighted magnetic resonance imaging for delineating malignant intraprostatic lesions. Int J Radiat Oncol Biol Phys. 2015;92(2):438-45.
47. Van den Bergh L, Lerut E, Haustermans K, Deroose CM, Oyen R, Isebaert S, et al. Final analysis of a prospective trial on functional imaging for nodal staging in patients with prostate cancer at high risk for lymph node involvement. Urol Oncol. 2015;33(3):109.e23-31.
48. Gomez-Rio M, Testart Dardel N, Santiago Chinchilla A, Rodriguez-Fernandez A, Olivares Granados G, Luque Caro R, et al. 18F-Fluorocholine PET/CT as a complementary tool in the follow-up of low-grade glioma: diagnostic accuracy and clinical utility. Eur J Nucl Med Mol Imaging. 2015;42(6):886-95.
49. Afshar-Oromieh A, Avtzi E, Giesel FL, Holland-Letz T, Linhart HG, Eder M, et al. The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 2015;42(2):197-209.
50. Sharma P, Arora S, Dhull VS, Naswa N, Kumar R, Ammini AC, et al. Evaluation of (68)Ga-DOTANOC PET/CT imaging in a large exclusive population of pancreatic neuroendocrine tumors. Abdom Imaging. 2015;40(2):299-309.
51. Cicone F, Minniti G, Romano A, Papa A, Scaringi C, Tavanti F, et al. Accuracy of F-DOPA PET and perfusion-MRI for differentiating radionecrotic from progressive brain metastases after radiosurgery. Eur J Nucl Med Mol Imaging. 2015;42(1):103-11.
52. Shen CT, Qiu ZL, Han TT, Luo QY. Performance of 18F-fluoride PET or PET/CT for the detection of bone metastases: a meta-analysis. Clin Nucl Med. 2015;40(2):103-10.
53. Ohno Y, Koyama H, Yoshikawa T, Takenaka D, Seki S, Yui M, et al. Three-way comparison of whole-body MR, coregistered whole-body FDG PET/MR, and integrated whole-body FDG PET/CT imaging: TNM and stage assessment capability for non-small cell lung cancer patients. Radiology. 2015;275(3):849-61.
54. Zhang J, Zuo CJ, Jia NY, Wang JH, Hu SP, Yu ZF, et al. Cross-modality PET/CT and contrast-enhanced CT imaging for pancreatic cancer. World J Gastroenterol. 2015;21(10):2988-96.
55. Sun Y, Duan Q, Wang S, Zeng Y, Wu R. Diagnosis of pancreatic cancer using 18F-FDG PET/CT and CA19-9 with SUVmax association to clinical characteristics. J BUON. 2015;20(2):452-9.
56. Andersen KF, Fuglo HM, Rasmussen SH, Petersen MM, Loft A. Semi-quantitative calculations of primary tumor metabolic activity using F-18 FDG PET/CT as a predictor of survival in 92 patients with high-grade bone or soft tissue sarcoma. Medicine. 2015;94(28):e1142.
57. Liu F, Zhang Q, Zhu D, Li Z, Li J, Wang B, et al. Performance of positron emission tomography and positron emission tomography/computed tomography using fluorine-18-fluorodeoxyglucose for the diagnosis, staging, and recurrence assessment of bone sarcoma: a systematic review and meta-analysis. Medicine. 2015;94(36):e1462.
58. Jain A, Srivastava M, Pawaskar A, Shelley S, Elangovan I, Jain H, et al. Contrast-enhanced [18F] fluorodeoxyglucose-positron emission tomography-computed tomography as an initial imaging modality in patients presenting with metastatic malignancy of undefined primary origin. Indian J Nucl Med. 2015 01 Jul;30(3):213-20.

59. You JJ, Cline KJ, Gu CS, Pritchard KI, Dayes IS, Gulenchyn KY, et al. (18)F-fluorodeoxyglucose positron-emission tomography-computed tomography to diagnose recurrent cancer. Br J Cancer. 2015;112(11):1737-43.
60. Lee JW, Lee JH, Cho A, Yun M, Lee JD, Kim YT, et al. The performance of contrast-enhanced FDG PET/CT for the differential diagnosis of unexpected ovarian mass lesions in patients with nongynecologic cancer. Clin Nucl Med. 2015;40(2):97-102.
61. Tatci E, Ozmen O, Dadali Y, Biner IU, Gokcek A, Demirag F, et al. The role of FDG PET/CT in evaluation of mediastinal masses and neurogenic tumors of chest wall. Int J Clin Exp Med. 2015 30 Jul;8(7):11146-52.

Appendix 1: Summary of studies from July to December 2015.

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
Breast Cancer								
Ergul et al., 2015 (1)	Prospective	24 patients (early-stage breast cancer; stage I or II)	FDG PET/CT	DCE-MRI, DW-MRI, SNB	Histopathology, ALND	**Multifocality** Sens: 67% Spec: 100% PPV: 100% NPV: 83% Accuracy: 88% **Axillary nodal involvement** Sens: 67% Spec: 89% PPV: 91% NPV: 62% Accuracy: 75%	**Multifocality** ***DCE-MRI*** Sens: 78% Spec: 53% PPV: 50% NPV: 80% Accuracy: 63% **Axillary nodal involvement** ***DCE-MRI*** Sens: 47% Spec: 78% PPV: 78% NPV: 47% Accuracy: 58% ***DW-MRI*** Sens: 40% Spec: 100% PPV: 100% NPV: 50% Accuracy: 63% ***SNB*** Sens: 93% Spec: 100% PPV: 100% NPV: 90% Accuracy: 96%	NA
You et al., 2015 (2)	Retrospective	139 patients who underwent neoadjuvant chemotherapy before surgery (breast cancer)	FDG PET/CT	US, MRI	Histopathology	**Axillary lymph node metastasis** Sens: 22% Spec: 85% PPV: 80% NPV: 28% AUC: 0.532*	**Axillary lymph node metastasis** ***US*** Sens: 50% Spec: 77% PPV: 84% NPV: 38% AUC: 0.626* ***MRI*** Sens: 72% Spec: 54% PPV: 80% NPV: 44% AUC: 0.588	NA
Teke et al.,	Retrospective	62 patients	FDG	^{99m}Tc-MDP	Clinical or	**Bone metastasis**	**Bone metastasis**	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
2015 (3)		(breast cancer)	PET/CT	bone scintigraphy	imaging follow-up	***(Per-lesion basis)*** Sens: 93.4%* Spec: 99.4%* PPV: 98.6% NPV: 97.1% Accuracy: 97.6%	***(Per-lesion basis)*** Sens: 84.5%* Spec: 89.6%* PPV: 77.9% NPV: 93.1% Accuracy: 88.1%	
Ng et al., 2015 (4)	Prospective	154 patients (locally advanced breast cancer with no clinical or radiologic evidence of distant metastases on conventional imaging)	FDG PET/CT	CT of the chest, abdomen, and pelvis; whole-body bone scan	Biopsy, imaging follow-up	NA	NA	PET/CT imaging resulted in a change in management plans in 20.8% (32/146) of patients (17—curative to palliative and adjuvant radiation therapy was omitted due to detection of distant metastatic disease, 15—change in radiation therapy field design due to detection of locoregional nodal disease outside conventional radiation therapy fields).
Esophageal Cancer								
Goense et al., 2015 (5)	Meta-analysis	8 studies (486 patients with esophageal cancer who were previously treated with curative intent)	FDG PET or PET/CT	NA	Histopathology, clinical and imaging follow-up	**Recurrence** Pooled Sens: 96% Pooled Spec: 78%	NA	NA
Karashima et al., 2015 (6)	Retrospective	107 patients who underwent esophagectomy with lymph node dissection (esophageal cancer)	FDG PET/CT	CT	Histopathology	**Lymph node metastasis** ***(Per-station basis)*** Sens: 39.0% Spec: 97.7%* PPV: 64.6%* ***(Per-patient basis)*** Sens: 55.6%* Spec: 81.1%* PPV: 78.9%*	**Lymph node metastasis** ***(Per-station basis)*** Sens: 43.4% Spec: 94.1%* PPV: 44.0%* ***(Per-patient basis)*** Sens: 75.9%* Spec: 34.0%* PPV: 53.9%*	NA
Gastrointestinal Cancer								
Wasserberg et al., 2015 (7)	Retrospective	91 patients who underwent early postoperative PET/CT (high-risk stage III CRC)	FDG PET/CT	CeCT	Biopsy, imaging follow-up	**Distant metastases** Sens: 100% Spec: 69% PPV: 37% NPV: 100%	NA	PET/CT upstaged 15% (14/91) of patients prompting a change in treatment strategy (7—received palliative chemotherapy with bevacizumab, 5—underwent curative metastasectomy,

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
								2—started neoadjuvant treatment and scheduled for surgery).
Maffione et al., 2015 (8)	Systematic review and meta-analysis	18 studies (1059 patients with CRC)	FDG PET/CT	MRI, CT	Histopathology, clinical and radiological follow-up	**Liver metastases** ***(Per-patient basis)*** Mean Sens: 93% Mean Spec: 81% ***(Per-lesion basis)*** Mean Sens: 66% Mean Spec: 86%	**Liver metastases** ***(Per-patient basis)*** ***MRI*** Mean Sens: 100% Mean Spec: 70% ***CT*** Mean Sens: 98% Mean Spec: 70% ***(Per-lesion basis)*** ***MRI*** Mean Sens: 89% Mean Spec: 81% ***CT*** Mean Sens: 79% Mean Spec: 67%	PET/CT findings resulted in a change in management in 9% to 42% (mean: 24%) of patients.
Marcus et al., 2015 (9)	Retrospective	73 patients; 313 fourth and subsequent follow-up PET/CT scans (colorectal cancer)	FDG PET/CT	NA	Histopathology, imaging or clinical follow-up, electronic medical records	NA	NA	PET/CT identified recurrence or metastasis in 40.0% (61/165) of scans obtained without prior clinical suspicion of disease and ruled out disease in 23.6% (35/148) of scans obtained with prior suspicion of disease. PET/CT resulted in management change after 34.2% (107/313) of scans (75—initiation of new treatment, 25—change in treatment, 7—treatment stopped).
Maffione et al., 2015 (10)	Systematic review and meta-analysis	34 studies (1526 patients with locally advanced rectal cancer treated with neoadjuvant chemotherapy)	FDG PET/CT	NA	Pathology	**Pathologic response** Pooled Sens: 73% Pooled Spec: 77% Pooled +LR: 3.09 Pooled –LR: 0.37 AUC: 0.83	NA	NA
Seo et al., 2015 (11)	Retrospective	67 patients (hepatocellular carcinoma)	FDG PET/CT	^{99m}Tc-HDP bone scintigraphy	Pathology, serial imaging	**Bone metastasis** ***(Per-patient basis)*** Sens: 99.0%* ***(Per-region basis)*** Sens: 96.7%*	**Bone metastasis** ***(Per-patient basis)*** Sens: 85.0%* ***(Per-region basis)***	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
							Sens: 52.7%*	
Genitourinary Cancer								
Zhang et al., 2015 (12)	Meta-analysis	10 studies (433 patients with bladder lesions)	FDG PET or PET/CT	NA	Histopathology, clinical follow-up	**Diagnosis** Pooled Sens: 82% Pooled Spec: 92% +LR: 6.80 –LR: 0.27 DOR: 25.18 AUC: 0.93	NA	NA
Ozturk, 2015 (13)	Retrospective	79 patients (suspected metastatic bladder cancer)	FDG PET/CT	CT, MRI	Histopathology, clinical follow-up	**Metastatic disease** Sens: 89% Spec: 78% PPV: 90% NPV: 75% Accuracy: 86%	NA	NA
Cistaro et al., 2015 (14)	Retrospective	68 patients (histologically confirmed primary adrenal malignancy)	FDG PET/CT	CeCT	Histology, imaging, and clinical follow-up	**Characterizing adrenal malignancies** Sens: 75% Spec: 100% PPV: 100% NPV: 63% Accuracy: 82%	**Characterizing adrenal malignancies** Sens: 59% Spec: 100% PPV: 100% NPV: 27% Accuracy: 65%	NA
Gynecological Cancer								
Schmidt et al., 2015 (15)	Prospective	15 patients (ovarian cancer and suspected peritoneal carcinomatosis)	FDG PET/CT	MDCT, MRI	Histopathology, surgical exploration	**Peritoneal carcinomatosis** Sens: 95% Spec: 96% PPV: 98% NPV: 92% Accuracy: 96% AUC: 0.96 **Infiltrated lymph nodes** Sens: 93% Spec: 95% AUC: 0.96 **Basal pleural carcinomatosis** AUC: 1.00	**Peritoneal carcinomatosis** ***MDCT*** Sens: 96% Spec: 92% PPV: 95% NPV: 94% Accuracy: 95% AUC: 0.94 **Peritoneal carcinomatosis** ***MRI*** Sens: 98% Spec: 84% PPV: 91% NPV: 96% Accuracy: 93% AUC: 0.90 **Infiltrated lymph nodes** ***MDCT*** Sens: 77% Spec: 98% AUC: 0.88	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
							MRI Sens: 100% Spec: 98% AUC: 1.00 **Basal pleural carcinomatosis** ***MDCT*** AUC: 0.92 ***MRI*** AUC: 0.67	
Evangelista et al., 2015 (16)	Retrospective	125 patients (ovarian cancer)	Whole body FDG PET/CT	CA-125	Histopathology, clinical and radiological follow-up	**Recurrence** Sens: 98.6% Spec: 77.8% PPV: 97.1% NPV: 87.5% Accuracy: 96.1% **Therapy response assessment** Sens: 98.6% Spec: 77.8% PPV: 97.1% NPV: 87.5% Accuracy: 96.1%	**Recurrence** Sens: 73.9% Spec: 88.9% PPV: 98.1% NPV: 30.8% Accuracy: 75.6% **Therapy response assessment** Sens: 63.6% Spec: 83.3% PPV: 70.0% NPV: 78.9% Accuracy: 75.9%	The addition of PET/CT changed the management of 41.6% (52/125) of patients.
Husby et al., 2015 (17)	Prospective	129 patients (endometrial carcinoma)	FDG PET/CT	NA	Histopathology	**Cervical stroma involvement** Sens: 25% to 33% Spec: 74% to 87% PPV: 49% to 65% NPV: 85% to 86% Accuracy: 66% to 76% **Lymph node metastasis** Sens: 77% to 85% Spec: 91% to 96% PPV: 62% to 76% NPV: 97% to 98% Accuracy: 89% to 93%	NA	NA
Lin et al., 2015 (18)	Prospective	23 patients (primary or recurrent vulvar malignancies)	FDG PET or PET/CT	CT or MRI	Pathology, clinical follow-up	**Metastatic inguinal lymph nodes** Sens: 92% Spec: 91% PPV: 85% NPV: 95% Accuracy: 91% AUC: 0.913 **Pelvic lymph node**	**Metastatic inguinal lymph nodes** Sens: 92% Spec: 100% PPV: 100% NPV: 96% Accuracy: 97% AUC: 0.958 **Pelvic lymph node**	PET or PET/CT findings had a positive impact in 4 scans (1—upstaged with additional pancreas metastasis, 1—confirmed negative distant metastasis, 1—ruled out CT-defined false-positive lesions, 1—identified an additional

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET) or distant metastasis Sens: 100% Spec: 57% PPV: 33% NPV:100% Accuracy: 65% AUC: 0.786*	Diagnostic Accuracy (CI) or distant metastasis Sens: 100% Spec: 93% PPV: 75% NPV: 100% Accuracy: 94% AUC: 0.964*	Change in Patient Management lesion in the right upper lung) and a negative impact in 3 scans (2—false-positve findings leading to unnecessary surgery, 1—false-negative finding leading to undertreatment).
Lin et al., 2015 (19)	RCT (second analysis)	129 patients with MRI-detected enlarged pelvic node(s) but negative para-aortic lymphadenopathy (cervical cancer)	FDG PET or PET/CT	MRI (no PET)	Biopsy, whenever accessible	NA	NA	During the 4-year additional follow-up period, no new patients experienced late events of treatment failure. There were no significant differences in terms of 8-year actual rates of OS (66.7% vs. 73.2%; p=0.417) and 8-year freedom from extrapelvic metastasis after primary chemoradiation therapy (79.3% vs. 76.1%; p=0.700) between the PET arm and the control arm.
Head and Neck								
Schouten et al., 2015 (20)	Retrospective	73 patients (advanced staged head and neck squamous cell carcinoma after completion of chemoradiotherapy)	FDG PET/CT	DW-MRI	Histopathology, follow-up	**Residual nodal disease** Sens: 100% Spec: 84% PPV: 25% NPV: 100%	**Residual nodal disease** Sens: 60% Spec: 93% PPV: 38% NPV: 97%	NA
Slevin et al., 2015 (21)	Retrospective	105 patients (definitive nonsurgical treatment for locally advanced head and neck squamous cell carcinoma)	FDG PET/CT	NA	Pathology, clinical or imaging follow-up	**4-month posttreatment response assessment** ***Primary disease*** Sens: 90% Spec: 89% PPV: 47% NPV: 99% ***Nodal disease*** Sens: 91% Spec: 89% PPV: 53% NPV: 99%	NA	NA
Robin et al.,	Prospective	116 patients	Whole	Inspection and	Histopathology,	**Recurrence**	NA	PET/CT detected

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
2015 (22)		with no findings suggestive of recurrence at 6 months follow-up (head and neck squamous cell carcinoma)	body FDG PET/CT	palpation of all anatomical subsites of the head and neck, endoscopy	imaging follow-up	Sens: 96% Spec: 87% PPV: 65% NPV: 99% Accuracy: 89%		subclinical recurrence in 19% (22/116) of patients.
Sheikhbahaei et al., 2015 (23)	Systematic review and meta-analysis	23 studies; 2247 scans (curatively treated patients with head and neck cancer)	FDG PET or PET/CT	NA	Histopathology, clinical or imaging follow-up	**Local recurrence** Pooled Sens: 91% Pooled Spec: 89% **Regional recurrence** Pooled Sens: 88% Pooled Spec: 95% **Distant metastasis and/or second primary tumour** Pooled Sens: 93% Pooled Spec: 97% **All recurrence** Pooled Sens: 92% Pooled Spec: 87%	NA	NA
Dequanter et al., 2015 (24)	Retrospective	54 patients (head and neck squamous cell carcinomas)	FDG PET/CT	CT, MRI, panendoscopy	Pathology	**Cervical lymph node metastasis** ***(SUV_{max} of 4.05)*** Sens: 92% Spec: 88% AUC: 0.96 **Extracapsular spread** ***(SUV_{max} of 4.15)*** Sens: 83% Spec: 88% AUC: 0.86	NA	NA
Sun et al., 2015 (25)	Meta-analysis	24 studies (1270 patients with head and neck cancer)	FDG PET/CT	CT, MRI, CT/MRI	Histopathology	**Regional nodal metastasis** ***(Per-level basis)*** Pooled Sens: 84% Pooled Spec: 96% Pooled +LR: 22.2 Pooled –LR: 0.17 Pooled DOR: 130 ***(Per-side basis)*** Pooled Sens: 84% Pooled Spec: 83% Pooled +LR: 5.1 Pooled –LR: 0.20	**Regional nodal metastasis** ***(Per-level basis)*** Pooled Sens: 63% Pooled Spec: 96% Pooled +LR: 16.8 Pooled –LR: 0.38 Pooled DOR: 44	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
						Pooled DOR: 25.9 AUC: 0.90 ***(Per-patient basis)*** Pooled Sens: 91% Pooled Spec: 87% Pooled +LR: 7.2 Pooled –LR: 0.11 Pooled DOR: 68 AUC: 0.93		
Li et al., 2015 (26)	Systematic review and meta-analysis	17 studies (668 patients with head and neck cancer who had undergone mandibulectomy)	FDG PET/CT	SPECT	Pathology	**Mandibular invasion** Pooled Sens: 83%* Pooled Spec: 90%* Pooled +LR: 5.69 Pooled –LR: 0.23 Pooled DOR: 41.24 AUC: 0.93	**Mandibular invasion** Pooled Sens: 96%* Pooled Spec: 67%* Pooled +LR: 2.51 Pooled –LR: 0.11 Pooled DOR: 28.50 AUC: 0.91	NA
Arias et al., 2015 (27)	Retrospective	72 patients (locally advanced head and neck cancer)	FDG PET/CT	CT	Histology	NA	NA	PET/CT changed the stage of 37.5% (27/71) of patients. Major changes in management plan occurred in 12.5% (9/71) of patients (6—detection of distant metastases, 3—migration to stage IV) and minor changes in 25% (18/72) of patients (16—upgraded N stage, 2—migration to T4).
Shin et al., 2015 (28)	Prospective	72 patients who underwent primary tumour resection and neck dissection (hypopharyngeal SCC)	FDG PET/CT	CT/MRI	Histopathology	**Nodal metastasis** ***Ipsilateral (side-by-side basis)*** Sens: 92.2% Spec: 95.2% PPV: 97.9% NPV: 83.3% Accuracy: 93.1% AUC: 0.937 ***(level-by level basis)*** Sens: 89.1% Spec: 99.0% PPV: 97.6% NPV: 95.1% Accuracy: 95.8%* AUC: 0.941* ***Contralateral (side-by-side basis)*** Sens: 66.7%	**Nodal metastasis** ***Ipsilateral (side-by-side basis)*** Sens: 90.2% Spec: 85.7% PPV: 93.9% NPV: 78.3% Accuracy: 88.9% AUC: 0.880 ***(level-by-level basis)*** Sens: 84.8% Spec: 96.4% PPV: 91.8% NPV: 93.1% Accuracy: 92.7%* AUC: 0.906* ***Contralateral (side-by-side***	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
						Spec: 100% PPV: 100% NPV: 89.2% Accuracy: 91.1% AUC: 0.833 ***Contralateral (level-by-level basis)*** Sens: 60.0% Spec: 98.4% PPV: 81.8% NPV: 95.4% Accuracy: 94.4% AUC: 0.792	***basis)*** Sens: 58.3% Spec: 97.0% PPV: 87.5% NPV: 86.5% Accuracy: 86.7% AUC: 0.777 ***Contralateral (level-by-level basis)*** Sens: 53.3% Spec: 96.1% PPV: 61.5% NPV: 94.6% Accuracy: 91.6% AUC: 0.747	
Sadick et al., 2015 (29)	Prospective	33 patients (oropharyngeal squamous cell cancer)	FDG PET/CT	US	Histology	**Nodal staging** Sens: 100% Spec: 87% PPV: 93% NPV: 100%	NA	NA
Elboga et al., 2015 (30)	Prospective	90 patients with elevated serum Tg levels and a negative I-131 WBS (differentiated thyroid carcinoma)	FDG PET/CT	I-131 WBS	Histopathology, cytology, serum Tg measurements, clinical and radiological follow-up	**Metastatic disease** Sens: 84.8% Spec: 79.1% PPV: 91.1% NPV: 73.3%	NA	NA
Hematology								
Zhou et al., 2015 (31)	Retrospective	55 patients (extranodal NK/T cell lymphoma)	FDG PET/CT	BMB	Pathology	**Bone marrow involvement** Sens: 100% Spec: 86.0% PPV: 41.7% NPV: 100% Accuracy: 87.3%	NA	NA
Kim et al., 2015 (32)	Retrospective	94 patients (8 HL, 86 NHL)	FDG PET/CT	BMB	BMB	**Bone marrow involvement** Sens: 50.0% Spec: 95.7% PPV: 80.0% NPV: 84.8% +LR: 11.7	NA	NA
Cho et al., 2015 (33)	Retrospective	185 patients (newly diagnosed lymphoma)	FDG PET/CT	BMB	Pathology	**Bone marrow involvement** Sens: 50.0% Spec: 91.6%	NA	PET/CT findings resulted in the upstaging of 9.2% (17/185) of patients.

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET) PPV: 63.6% NPV: 86.2%	Diagnostic Accuracy (CI)	Change in Patient Management
Cetin et al., 2015 (34)	Retrospective	161 patients (61 HL, 100 aggressive NHL)	FDG PET/CT	BMB	BMB	**Bone marrow involvement** ***HL*** Sens: 71.4% Spec: 87.0% PPV: 41.7% NPV: 95.0% Accuracy: 85.2% ***Aggressive NHL*** Sens: 51.7% Spec: 83.0% PPV: 55.5% NPV: 80.8% Accuracy: 74.0%	NA	NA
Chen-Liang et al., 2015 (35)	Retrospective	372 patients (140 HL, 232 High-grade B-cell NHL)	FDG PET/CT	BMB	Pathology	**Bone marrow infiltration** ***HL*** Sens: 96.8% NPV: 99.0% Accuracy: 99.3 ***High-grade B-cell NHL*** Sens: 52.7% NPV: 81.7% Accuracy: 84.1%	**Bone marrow infiltration** ***HL*** Sens: 32.3% NPV: 83.8% Accuracy: 85.0% ***High-grade B-cell NHL*** Sens: 77.6% NPV: 90.2% Accuracy: 90.7%	NA
Regacini et al., 2015 (36)	Systematic review	6 studies (116 patients with HL, NHL, and DLBCL)	FDG PET/CT	WB-MRI	Physical examination, laboratory and histological results, BMB, clinical and imaging follow-up	**Staging** Sens: 63% to 100%	**Staging** Sens: 59% to 100%	NA
Sun et al., 2015 (37)	Meta-analysis	6 studies (605 patients newly diagnosed with DLBCL and treated with R-CHOP)	FDG PET/CT (interim-PET performed after 2 to 4 cycles)	NA	Follow-up	**Prognosis** Pooled Sens: 52.4% Pooled Spec: 67.8% Pooled +LR: 1.78 Pooled –LR: 0.71 Pooled DOR: 3.23 AUC: 0.699	NA	NA
Swinnen et al., 2015 (38)	Prospective (E3404 trial)	80 patients received 4 cycles of R-CHOP chemotherapy with	FDG PET/CT (PET-positive patients received 4	NA	Clinical and imaging follow-up	**Progression-free at 2 years** ***Midtreatment PET*** NPV: 75% ***End-of-treatment PET***	NA	The 2-, 3-, and 4-year PFS rates were 42%, 33%, and 33%, respectively, for midtreatment PET-positive patients and 76%, 71%, and 71%, respectively, for

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
		midtreatment PET scan performed during cycle 3 (DLBCL)	cycles of R-ICE and PET-negative patients received 2 more cycles of R-CHOP)			NPV: 79%		midtreatment PET-negative patients. The 2-, 3-, and 4-year OS rates were 77%, 69%, and 69%, respectively, for midtreatment PET-positive patients and 93%, 93%, and 90%, respectively, for midtreatment PET-negative patients.
Rigacci et al., 2015 (39)	Retrospective	246 patients treated with 4 cycles of ABVD and involved-field radiotherapy (newly diagnosed HL stage IA to IIA with or without bulky disease)	FDG PET/CT (interim-PET after 2 courses of ABVD)	NA	Follow-up	**Predicting treatment outcome** ***Deauville criteria*** Sens: 68% Spec: 97% PPV: 73% NPV: 96% Accuracy: 94% ***IHP criteria*** Sens: 65.5% Spec: 92% PPV: 53% NPV: 95% Accuracy: 89%	NA	The 2-year PFS rates for interim-PET negative and positive patients were 97% and 30%, respectively (p=0.000).
Adams et al., 2015 (40)	Systematic review and meta-analysis	10 studies (1389 patients with HL)	FDG PET or PET/CT (interim-PET performed between 1 and 4 cycles)	NA	Biopsy, histology, clinical and imaging follow-up	**Predicting treatment failure** Pooled Sens: 70.8% Pooled Spec: 89.9% AUC: 0.877	NA	NA
Sauter et al., 2015 (41)	Retrospective	129 patients who were chemosensitive to salvage chemotherapy and proceeding to HDT-ASCT (relapsed and refractory DLBCL)	FDG PET/CT	NA	Follow-up	NA	NA	At 3 years, patients with a Deauville response of 1 to 3 to salvage chemotherapy experienced significantly better PFS (77% vs. 49%; p<0.001) and OS rates (86% vs. 54%; p<0.001), compared with patients with a Deauville response of 4.
Simontacchi et al., 2015 (42)	Retrospective	257 patients treated with ABVD chemotherapy and radiation therapy (stage I to II HL)	FDG PET (interim-PET after 2 cycles of ABVD)	NA	Follow-up	NA	NA	Using a Deauville score cutoff of 3, the 5-year PFS rate was 98.1% for PET-negative patients and 83.7% for PET-positive patients (p=0.0001). The 5-year OS rates were 98.5% and 93.0%

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
								for PET-negative and PET-positive patients, respectively (p=0.029). Using a Deauville score cutoff of 4, the 5-year PFS rate was 97.7% for PET-negative patients and 78.6% for PET-positive patients (p=0.0001). The 5-year OS rates were 98.6% and 89.3% for PET-negative and PET-positive patients, respectively (p=0.002).
Zhu et al., 2015 (43)	Systematic review and meta-analysis	11 studies (1081 patients with DLBCL treated with rituximab-based immunochemotherapy)	FDG PET/CT (interim-PET performed between second and fourth cycle)	NA	Follow-up	NA	NA	The PFS in patients with a positive interim PET result was significantly shorter than in those with a negative result. Pooled HR=2.96 (95% confidence interval: 2.25 to 3.89). The interim-PET negative patients also had a significantly higher complete remission rate compared with the interim-PET positive patients. Pooled RR=5.53 (95% confidence interval: 2.59 to 11.80).
Mauro et al., 2015 (44)	Retrospective	90 patients (chronic lymphocytic leukemia)	FDG PET/CT	NA	Histology	**Diagnosis of Richter's syndrome or second malignancy** ***(SUV_{max} of ≥5)*** Sens: 87.0% Spec: 71.2% PPV: 51.3% NPV: 94.0%	NA	NA
Non-FDG Tracers $^{11}C/^{18}F$-Choline								
Ceci et al., 2015 (45)	Retrospective	59 patients with bladder cancer (39 staging, 20 restaging)	^{11}C-Choline PET/CT	US, CeCT, MRI	Histology	**Lymph node metastasis** Sens: 59% Spec: 90% PPV: 71% NPV: 84% Accuracy: 81%	NA	NA
Chang et al.,	Prospective	21 patients	^{11}C-	T2W/DW-MRI	Histopathology	**IPL delineation**	**IPL delineation**	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
2015 (46)		who were suitable for radical prostatectomy (prostate adenocarcinoma)	Choline PET/CT			***SUV_{40}*** Sens: 94% Spec: 38% DSC: 0.52 YI: 0.32 ***SUV_{50}*** Sens: 85% Spec: 56% DSC: 0.58 YI: 0.41 ***SUV_{60}*** Sens: 72% Spec: 71% DSC: 0.59* YI: 0.43* ***SUV_{70}*** Sens: 57% Spec: 82% DSC: 0.56 YI: 0.39 ***SUV_{80}*** Sens: 38% Spec: 89% DSC: 0.46 YI: 0.26 ***Manual contour*** Sens: 53% Spec: 86% DSC: 0.52* YI: 0.39*	***Manual contour*** Sens: 28% Spec: 92% DSC: 0.37* YI: 0.19*	
Van den Bergh et al., 2015 (47)	Prospective	75 patients (localized, biopsy-confirmed prostate adenocarcinoma)	^{11}C-Choline PET/CT	DW MRI	Histopathology	**Nodal staging** ***(Per-patient basis)*** Sens: 18.9% Spec: 89.5% PPV: 63.6% NPV: 53.1% Accuracy: 54.7% ***(Per-region basis)*** Sens: 8.2% Spec: 98.8% PPV: 50.0% NPV: 88.3% Accuracy: 87.5%	**Nodal staging** ***(Per-patient basis)*** Sens: 36.1% Spec: 94.7% PPV: 86.7% NPV: 61.0% Accuracy: 66.2% ***(Per-region basis)*** Sens: 9.5% Spec: 98.0% PPV: 40.0% NPV: 88.3% Accuracy: 86.9%	NA
Gomez-Rio et al., 2015 (48)	Prospective	18 patients (indeterminate clinical and/or radiological	^{18}F-Choline PET/CT	aMRI, ^{201}T1-SPECT	Histology, consensus diagnosis	**Tumour activity** Sens: 100% Spec: 100% Accuracy: 100%	**Tumour activity** ***aMRI*** Sens: 100% Spec: 50%	Results from ^{18}F-Choline PET/CT led to modification of the therapeutic intention suggested by routine

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
		findings of tumour activity during standard follow-up after treatment for low-grade glioma)					Accuracy: 90.9% ***^{201}T1-SPECT*** Sens: 69.2% Spec: 66.7% Accuracy: 68.8%	surveillance (clinical and aMRI) in 72.2% (13/18) of patients.
^{68}Ga-PSMA								
Afshar-Oromieh et al., 2015 (49)	Retrospective	319 patients (suspected progressive prostate cancer)	^{68}Ga-PSMA-HBED-CC PET/CT	CT, MRI	Histology when available	**Recurrence** ***(Per-lesion basis)*** Sens: 76.6% Spec: 100% PPV: 100% NPV: 91.4% ***(Per-patient basis)*** Sens: 88.1%	NA	NA
^{68}Ga-DOTANOC								
Sharma et al., 2015 (50)	Retrospective	141 patients (histologically confirmed and/or clinically suspected pancreatic NET)	^{68}Ga-DOTANOC PET/CT	CT, US, MRI, EUS, ERCP, bone scintigraphy	Histopathology, imaging and clinical follow-up, biochemical markers	**Primary or metastatic tumours** Sens: 83.1% Spec: 77.7%* PPV: 96.9% NPV: 35.0% Accuracy: 82.5%	**Primary or metastatic tumours** Sens: 87.0% Spec: 33.3%* PPV: 91.7% NPV: 23.0% Accuracy: 81.3%	NA
F-DOPA								
Cicone et al., 2015 (51)	Prospective	42 patients treated with stereotactic radiosurgery (50 brain metastases from various primaries)	F-DOPA PET/CT	Perfusion-weighted MRI	Histology, imaging and clinical follow-up	**Differentiating radionecrosis from tumour progression** ***($SUVL_{max}$/$Bkgr_{max}$ with cut-off value of 1.59)*** Sens: 93.3% Spec: 90.9% Accuracy: 91.9% AUC: 0.924	**Differentiating radionecrosis from tumour progression** ***(rCBV with cut-off value of 2.14)*** Sens: 86.7% Spec: 68.2% Accuracy: 75.6% AUC: 0.808	NA
^{18}F-Fluoride								
Shen et al., 2015 (52)	Meta-analysis	11 studies (613 patients with various oncologic diseases)	^{18}F-Fluoride PET or PET/CT	^{99m}Tc-MDP bone scintigraphy	Histopathology, imaging, and clinical follow-up	**Bone metastases** Pooled Sens: 96%* Pooled Spec: 91%* Pooled +LR: 12.6 Pooled –LR: 0.05 Pooled DOR: 341 AUC: 0.986	**Bone metastases** Pooled Sens: 88%* Pooled Spec: 80%* Pooled +LR: 3.32 Pooled –LR: 0.21 Pooled DOR: 20 AUC: 0.902	NA
NSCLC								
Ohno et al., 2015 (53)	Prospective	140 patients (NSCLC)	FDG PET/CT	MRI	Pathology, initial and follow-up	**Primary tumour** Accuracy: 91.4% **Regional lymph**	**Primary tumour** Accuracy: 94.3% **Regional lymph**	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
					imaging, surgical treatment	**node involvement** Accuracy: 80.7%* **Distant metastatic spread** Accuracy: 90.7%* **Clinical stage evaluation** Accuracy: 70.7%*	**node involvement** Accuracy: 91.4%* **Distant metastatic spread** Accuracy: 98.6%* **Clinical stage evaluation** Accuracy: 91.4%*	
Pancreatic Cancer								
Zhang et al., 2015 (54)	Retrospective	70 patients (pancreatic lesions)	FDG PET/CT	CECT	Histopathology, clinical follow-up	**Diagnosis** Sens: 96.0%* Spec: 90.0% PPV: 96.0% NPV: 90.0%* Accuracy: 94.3%* **Peripancreatic vessel invasion** Sens: 93.3% Spec: 93.8% PPV: 93.3% NPV: 93.8% Accuracy: 93.5% **Regional lymph node metastasis** Sens: 89.5% Spec: 91.7% PPV: 94.4% NPV: 84.6% Accuracy: 90.3% **Distant metastasis** Sens: 94.1%* Spec: 97.0% PPV: 94.1% NPV: 97.0%* Accuracy: 96.0%	**Diagnosis** Sens: 82.0%* Spec: 65.0% PPV: 85.4% NPV: 59.1%* Accuracy: 77.1%* **Peripancreatic vessel invasion** Sens: 93.3% Spec: 93.8% PPV: 93.3% NPV: 93.8 Accuracy: 93.5% **Regional lymph node metastasis** Sens: 63.2% Spec: 91.7% PPV: 92.3% NPV: 61.1% Accuracy: 74.2% **Distant metastasis** Sens: 58.8%* Spec: 100% PPV: 100% NPV: 82.5%* Accuracy: 86.0%	NA
Sun et al., 2015 (55)	Retrospective	91 patients (suspected pancreatic cancer)	FDG PET/CT	CA19-9	Pathology, cytology	**Diagnosis** Sens: 67.5% Spec: 72.7% PPV: 94.7% NPV: 23.5% Accuracy: 68.1% AUC: 75.9%	**Diagnosis** Sens: 75.0% Spec: 81.8% PPV: 96.8% NPV: 31.0% Accuracy: 75.8% AUC: 85.7%	NA
Sarcoma								
Andersen et al., 2015 (56)	Retrospective	92 patients underwent pretreatment FDG PET/CT scan (37 BS, 55	FDG PET/CT	NA	Histopathology	**Predictor of survival** ***Bone sarcoma (SUV$_{max}$ of 11.6)*** Sens: 58.3	NA	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
		STS)				Spec: 72.0 AUC: 0.630 ***(T/B ratio of 8.0)*** Sens: 66.7 Spec: 66.0 AUC: 0.593 ***Soft tissue sarcoma (SUV_{max} of 17.7)*** Sens: 58.6 Spec: 88.5 AUC: 0.797* ***(T/B ratio of 7.2)*** Sens: 89.7 Spec: 61.5 AUC: 0.787*		
Liu et al., 2015 (57)	Systematic review and meta-analysis	42 studies (1530 patients with primary bone sarcoma)	FDG PET/CT	NA	Histopathology, follow-up	**Diagnosis** ***(Per-lesion basis)*** Pooled Sens: 96% Pooled Spec: 79% **Recurrence** ***(Per-examination basis)*** Pooled Sens: 92% Pooled Spec: 93% Pooled +LR: 10.26 Pooled –LR: 0.11 Pooled DOR: 113.12 **Local recurrence** ***(Per-examination basis)*** Pooled Sens: 91% Pooled Spec: 93% Pooled +LR: 10.89 Pooled –LR: 0.12 Pooled DOR: 96.69 **Distant metastasis** ***(Per-lesion basis)*** Pooled Sens: 90% Pooled Spec: 85% Pooled +LR: 5.16 Pooled –LR: 0.15 Pooled DOR: 33.87 **Lung metastasis** ***(Per-examination basis)*** Pooled Sens: 88% Pooled Spec: 98% Pooled +LR: 23.71	NA	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
						Pooled –LR: 0.15 Pooled DOR: 249.48 ***(Per-lesion basis)*** Pooled Sens: 83% Pooled Spec: 89% Pooled +LR: 9.75 Pooled –LR: 0.20 Pooled DOR: 52.05 **Bone metastasis** ***(Per-examination basis)*** Pooled Sens: 92% Pooled Spec: 98% Pooled +LR: 46.23 Pooled –LR: 0.10 Pooled DOR: 566.19 ***(Per-lesion basis)*** Pooled Sens: 95% Pooled Spec: 62% Pooled +LR: 2.43 Pooled –LR: 0.08 Pooled DOR: 30.64 **Lymph node metastasis** ***(Per-examination basis)*** Pooled Spec: 96%		
Unknown Primary								
Jain et al., 2015 (58)	Prospective	163 patients (malignancy of undefined primary origin)	FDG PET/CT	NA	Histopathology, further investigations, follow-up	**Primary site** Sens: 95.8% Spec: 66.7% PPV: 88.3% NPV: 85.7%	NA	NA
Various Sites								
You et al., 2015 (59)	Prospective	101 patients with clinical suspicion of recurrent cancer (56 NSCLC, 19 breast cancer, 10 ovarian cancer, 6 oesophageal cancer, 6 lymphoma, 4 head and neck cancer)	FDG PET/CT	X-ray, US, CT, MRI, nuclear medicine bone scan	All available source documents, follow-up	NA	NA	Planned management was changed in 53% (52/99) of patients after findings on PET/CT (38—no treatment to treatment, 9—clinical or imaging follow-up to biopsy, 2—imaging to clinical follow-up, 3—biospy to clinical or imaging follow-up).

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
Lee et al., 2015 (60)	Retrospective	72 patients who showed unexpected ovarian lesions on PET (33 colorectal cancer, 20 breast cancer, 19 gastric cancer)	FDG PET/CT	NA	Histopathology	**Malignant ovarian lesions** ***PET/ldCT with SUV_{max} of 2.5 (Per-patient basis)*** Sens: 84.9% Spec: 84.2% Accuracy: 84.7% ***(Per-lesion basis)*** Sens: 80.5% Spec: 81.0% Accuracy: 80.6% ***PET/CECT with SUV_{max} of 2.5 (Per-patient basis)*** Sens: 98.1% Spec: 78.9% Accuracy: 91.7% ***(Per-lesion basis)*** Sens: 95.1% Spec: 76.2% Accuracy: 91.3%	NA	NA
Tatci et al., 2015 (61)	Retrospective	88 patients (mediastinal and chest wall lesions)	FDG PET/CT	NA	Pathology	**Malignancy** Sens: 90.0% Spec: 55.2% PPV: 50.9% NPV: 91.4% Accuracy: 67.0%	NA	NA

Abbreviations: +LR: positive likelihood ratio; -LR: negative likelihood ratio; ^{11}C-Choline: carbon 11 choline; ^{18}F-Choline: fluorine 18 fluoromethylcholine; ^{68}Ga-DOTANOC: gallium-68 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid 1-Nal3-octreotide; ^{68}Ga-PSMA-HBED-CC: gallium-68 Glu-urea-Lys(Ahx) N,N'-bis [2-hydroxy-5-(carboxyethyl)benzyl] ethylenediamine-N,N'-diacetic acid; ^{99m}Tc-HDP: 99m-Tc hydroxydiphosphonate; ^{99m}Tc-MDP: 99mTc-methylene diphosphonate; ^{201}T1-SPECT: Thallium-201 single-photon emission computed tomography; ABVD: adriamycin, bleomycin, vinblastine, dacarbazine; ALND: axillary lymph node dissection; aMRI: advanced MRI; AUC: area under curve; BMB: bone marrow biopsy; BS: bone sarcoma; CA19-9: cancer antigen 19-9; CA-125: cancer antigen 125; CeCT: contrast-enhanced CT; CI: conventional intervention; CRC: colorectal cancer; CT: computed tomography; DCE-MRI: dynamic contrast-enhanced MRI; DLBCL: diffuse large B-cell lymphoma; DOR: diagnostic odds ratio; DSC: dice similarity coefficient; DW-MRI: diffusion-weighted MRI; ERCP: endoscopic retrograde cholangio-pancreatography; EUS: endoscopic US; F-DOPA: 6-[18F]-fluoro-L-3,4-dihydroxyphenylalanine; FDG: fluorodeoxyglucose; HDT-ASCT: high dose chemotherapy plus autologous stem cell transplantation; HL: Hodgkin lymphoma; HR: hazard ratio; I-131 WBS: iodine-131 whole body scintigraphy; IHP: International Harmonization Project; IPL: intraprostatic lesions; ldCT: low-dose computed tomography; MDCT: multidetector CT; MRI: magnetic resonance imaging; NA: not available; NET: neuroendocrine tumour; NHL: non-Hodgkin lymphoma; NK/T-cell: natural killer/T-cell; NPV: negative predictive value; NSCLC: non-small cell lung carcinoma; OS: overall survival; PET: positron emission tomography; PFS: progression-free survival; PPV: positive predictive value; rCBV: relative cerebral blood volume; R-CHOP: rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, prednisolone; RCT: randomized controlled trial; R-ICE: rituximab, ifosfamide, carboplatin, etoposide; RR: relative risk; SCC: squamous cell carcinoma; Sens: sensitivity; SNB: sentinel node biopsy; Spec: specificity; SPECT: single-photon emission computed tomography; STS: soft tissue sarcoma; SUV: standardized uptake value; SUV_{max}: maximum standardized uptake value; $SUVL_{max}/Bkgr_{max}$: maximum lesion to maximum background uptake ratio; T/B: tumour-to-background; T2W: tier-2 weighted; Tg: thyroglobulin; US: ultrasound; WB-MRI: whole-body MRI; YI: Youden index

*$p<0.05$