PET Six-Month Monitoring Report 2017-2

Evidence from Primary Studies and Systematic Reviews and Recommendations from Clinical Practice Guidelines July to December 2017

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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 to 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 14th 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-text articles published between July and December 2017 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)
    - ^{18}F-FACBC (fluciclovine)
3. Published as a full-text 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 (RCT) or ≥50 patients (≥25 patients for sarcoma) 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

Fifty-nine studies published between July and December 2017 met the inclusion criteria. A summary of the evidence from the 59 studies can be found in **Appendix 1: Summary of studies from July to December 2017**.

Breast Cancer

Five studies met the inclusion criteria [1-5]. For axillary lymph node staging and tumour recurrence detection, FDG PET/CT demonstrated similar diagnostic performance to ultrasound (US) and magnetic resonance imaging (MRI) [1]. A small retrospective study also showed FDG PET/CT providing minimal benefits over bone scintigraphy and CT in the detection of bone metastases [2]. Nevertheless, staging FDG PET/CT scans led to stage modification in 35.0% of patients and subsequent changes to management in 29.5% of patients [3]. In the prediction of pathological response to neoadjuvant chemotherapy, a meta-analysis reported comparable diagnostic performance between FDG PET/CT and MRI [4], while a prospective study showed that MRI was superior to FDG PET/CT for human epidermal growth factor receptor 2-positive tumours, but not estrogen receptor-positive or triple-negative tumours [5].

Esophageal Cancer

One study met the inclusion criteria [6]. The accuracy of loco-regional lymph node staging was comparable between FDG PET/CT (74.5%), CT (75.6%), and endoscopic US (EUS) (77.2%).

Gastrointestinal Cancer

Nine studies met the inclusion criteria [7-15]. Four of the studies investigated the role of FDG PET/CT in gastric cancer. In the diagnosis of gastric malignancy in patients with non-specific symptoms, the sensitivity of FDG PET/CT was similar to that of gastric endoscopy [7]. For preoperative N staging, FDG PET/CT was outperformed by both EUS (accuracy, 72.5% versus 76.2%, $p=0.02$) [8] and diffusion-weighted MRI (pooled sensitivity, 52% versus 79%, $p<0.001$) [9]. FDG PET/CT was also inferior to EUS in the restaging of lymph node involvement (accuracy, 69.0% versus 88.5%, $p<0.0001$) [8]. For evaluating recurrence, there was no significant difference in the overall diagnostic performance between contrast-enhanced CT and FDG PET/CT except for the detection of peritoneal carcinomatosis, in which contrast-enhanced CT was found to be superior (sensitivity, 96% versus 50%, $p=0.001$) [10]. In the diagnosis of patients with colorectal liver metastases, FDG PET/CT had a higher specificity (pooled estimate, 93.9% versus 73.5%, $p<0.001$) than multidetector CT but a lower sensitivity than gadoxetate disodium-enhanced MRI (pooled estimate, 74.1% versus 93.1%, $p<0.001$) [11]. In patients previously operated on for colorectal liver metastases, CT identified more pulmonary metastases in comparison to FDG PET/CT [12]. In patients with obstructive colorectal cancer whose proximal colon could not be examined by colonoscopy, FDG PET/CT showed high sensitivity (patient- and lesion-based, 100%) and specificity (patient-based, 93.9%; lesion-based, 92.6%) for the detection of synchronous invasive cancer. Despite maintaining high specificity (patient-based, 94.6%; lesion-based, 94.1%), FDG PET/CT displayed poor sensitivity for the detection of advanced adenoma (patient-based, 53.1%; lesion-based, 45.5%) [13]. In patients with locally advanced rectal cancer being assessed for neoadjuvant therapy response, dynamic contrast-enhanced MRI demonstrated the highest diagnostic accuracy (pooled estimate, 85.6%), followed by FDG PET/CT (pooled estimate, 81.8%), diffuse-weighted MRI (pooled estimate, 77.3%), and morphological MRI (pooled

estimate, 77.1) [14]. In resectable cholangiocarcinoma, the use of FDG PET/CT appears to be limited for finding metastatic lymph nodes (sensitivity, 66.7%; specificity, 78.8%) [15].

Genitourinary Cancer

Three studies met the inclusion criteria [16-18]. One prospective study compared the diagnostic performance of FDG PET/CT to that of contrast-enhanced CT in the detection of primary, recurrent and metastatic disease in renal cancer patients. FDG PET/CT appeared to provide an improvement in accuracy over contrast-enhanced CT (96% versus 88%, respectively) although no p-value was reported [16]. Another prospective study showed that FDG PET/CT is not useful in identifying pathologic complete response to neoadjuvant or induction chemotherapy for invasive bladder cancer [17]. In patients with suspected recurrent germinal cell testicular carcinoma based on conventional imaging and/or clinical data, FDG PET/CT diagnosed recurrence with high sensitivity (86.8%) and specificity (90.2%). As a result, therapeutic management was changed in 22.8% of cases [18].

Gynecologic Cancer

Four studies met the inclusion criteria [19-22]. Two of the studies compared the diagnostic capability of FDG PET/CT to MRI and sentinel lymph node mapping in cervical cancer. In early-stage disease, FDG PET/CT does not appear to offer any benefit over sentinel lymph node mapping in identifying metastatic lymph nodes [19]. In advanced-stage disease, FDG PET/CT was demonstrated to be superior to MRI for post-therapy evaluation in a patient-based analysis (area under the curve [AUC], 0.828 versus 0.618, p=0.025), and in the detection of residual local (AUC, 0.976 versus 0.850, p=0.045) and regional (AUC, 0.805 versus 0.554, p=0.014) disease [20]. In cN0 vulvar cancer patients who are unsuitable for sentinel node biopsy, preoperative FDG PET/CT offers a reliable assessment of lymph node status (accuracy, 84%) [21]. The authors from a prospective study concluded that FDG PET/CT and FDG PET/MRI both outperformed CT in restaging patients with suspected recurrence of pelvic malignancy [22].

Head and Neck Cancer

Eight studies met the inclusion criteria [23-30]. In patients with head and neck cancer treated with radiotherapy or concurrent chemoradiotherapy, FDG PET/CT was able to detect recurrent or residual disease with high accuracy (82.3% to 88.3%) [23-26]. In node-positive cases, findings from FDG PET/CT altered 6.3% of the surgical plans based on CT [27]. In patients with nasopharyngeal cancer, results from a meta-analysis showed that FDG PET/CT (pooled estimate, 83%) is more sensitive than bone scintigraphy (pooled estimate, 46%) in diagnosing bone metastases while preserving high specificity [28]. Furthermore, FDG PET/CT can differentiate MRI-negative cervical lymph nodes with high accuracy (89.2%) [29]. On the contrary, the accuracy of FDG PET/CT for identifying persistent or metastatic disease in patients with recurrent papillary thyroid cancer was worse than that of CT (58.3% versus 66.7%, p=0.025) [30].

Hematologic Cancer

Six studies met the inclusion criteria [31-36]. Four of the studies evaluated the utility of FDG PET/CT in the staging of patients with Hodgkin lymphoma (HL) and diffuse large B-cell lymphoma (DLBCL). Overall, FDG PET/CT detected bone marrow involvement in DLBCL with sensitivity of 80% to 91.3% and specificity of 80% to 94.3% [31-33]. For HL, the sensitivity and specificity were 81% and 84%, respectively [33]. In addition, FDG PET/CT upstaged 16.0% and downstaged 5.6% of patients with HL, leading to a change in their therapeutic strategy in 6.2% of cases [34]. For interim-PET response in patients with advanced-stage HL, the survival

outcome of PET-positive patients treated with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone ($BEACOPP_{escalated}$) did not improve with the addition of rituximab [35]. However, results from another trial showed that interim-PET-positive patients would benefit from additional cycles of $BEACOPP_{escalated}$ and involved-site radiotherapy. In early-stage HL, interim-PET-positive patients were associated with worst prognosis even with additional cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine and involved-site radiotherapy [36].

Melanoma

One study met the inclusion criteria [37]. In the preoperative staging of primary cutaneous malignant melanoma, FDG PET/CT displayed high accuracy for assessing nodal (90%) and distant (95%) metastases. No significant differences in diagnostic accuracy were noted between FDG PET/CT and conventional imaging (i.e., contrast-enhanced CT and US). Overall, FDG PET/CT upstaged and impacted management in 38.6% of patients by identifying occult metastases.

Non-FDG Tracers

Twelve studies met the inclusion criteria [38-49]. Two prospective studies evaluated the diagnostic performance of ^{11}C- and ^{18}F-Choline PET/CT in prostate cancer. The region-based sensitivity (97.9% versus 72.9%, p=0.0015) and accuracy (98.6% versus 90.5%, p=0.0015) of ^{11}C-Choline PET/CT were significantly higher than those of bone scintigraphy for detecting bone involvement following treatment [38]. Conversely, the lesion-based sensitivity (75% versus 100%, p=0.031) of ^{18}F-Choline PET/CT was found to be worse than that of MRI for detecting bone metastases in patients with biochemically recurrent disease [39]. The utility of ^{68}Ga-DOTA-TOC and -TATE PET/CT in neuroendocrine tumours (NETs) were examined in several studies. ^{68}Ga-DOTA-TOC PET/CT was found to be more accurate than a conventional imaging workup (CT, MRI, EUS) in localizing the primary tumour in patients with NETs of unknown primary site (AUC, 0.941 versus 0.607, p=0.001) [40]. Similarly, ^{68}Ga-DOTA-TATE PET/CT (97%) was more accurate than ^{99m}Tc-HYNIC-TOC single-photon emission computed tomography (SPECT)/CT (79%) in detecting metastatic NETs [41]. Overall, management was altered by ^{68}Ga-DOTA-TOC or -TATE PET/CT in 14.3% to 33.8% of patients [40-42]. ^{68}Ga-PSMA PET/CT was also evaluated in prostate cancer. Results from two meta-analyses showed favourable sensitivities and specificities for ^{68}Ga-PSMA PET/CT in the staging and restaging of patients [43,44]. Furthermore, ^{68}Ga-PSMA PET/CT detected bone metastases more accurately as compared with ^{99m}Tc-DPD SPECT/CT in a patient- (AUC, 1.00 versus 0.83, p<0.05), region- (AUC, 0.99 versus 0.84, p<0.05), and lesion- (AUC, 0.99 versus 0.58, p<0.05) based analysis [45]. ^{68}Ga-PSMA PET/CT changed management in 39.0% of patients with biochemical recurrence [46]. As for ^{18}F-FACBC PET/CT, it was shown to be significantly more sensitive (87% versus 77%, p<0.01) but less specific (56% versus 99%, p<0.001) than multiparametric MRI in the detection of intraprostatic disease in patients with intermediate- to high-risk prostate cancer [47]. Two studies evaluated ^{18}F-NaF PET/CT, one in prostate cancer only [48] while the other in breast, prostate, or renal cancer [49]. Both found ^{18}F-NaF PET/CT to be better than ^{99m}Tc-HDP bone scintigraphy in detecting bone metastases. However, the clinical benefit of using ^{18}F-NaF PET/CT in the latter population is likely limited due to a low prevalence of bone metastases among those patients [49].

Non-Small Cell Lung Cancer and Other Lung Cancer

Two studies met the inclusion criteria [50,51]. The authors of a meta-analysis concluded that FDG PET/CT is able to detect adrenal metastasis in lung cancer patients with outstanding diagnostic performance (pooled sensitivity, 88.7%; pooled specificity, 90.8%) [50].

In the post-treatment follow-up of a patient cohort with predominately non-small cell lung cancer (NSCLC), FDG PET/CT outperformed chest CT in the detection of regional (sensitivity, 94.4% versus 78.6%, $p<0.05$) and distant (sensitivity, 91.9% versus 70.7%, $p<0.05$) recurrences [51].

Pancreatic Cancer

Two studies met the inclusion criteria [52,53]. FDG PET/CT was more accurate than contrast-enhanced CT for nodal (95% versus 59%, $p<0.001$) and metastatic (100% versus 83%, $p=0.01$) staging of pancreatic adenocarcinoma and resulted in a change in management in 18.5% of patients [52]. In contrast, EUS-guided fine needle aspiration had higher sensitivity (96.7% versus 53.3%, $p<0.001$) and accuracy (98.6% versus 78.9%, $p<0.001$) than FDG PET/CT for preoperative para-aortic lymph node staging in patients with pancreatobiliary cancer [53].

Pediatric Cancer

One study met the inclusion criteria [54]. FDG PET/CT demonstrated excellent sensitivity (100%) but substandard specificity (68.6%) when evaluating bone marrow infiltration in various pediatric malignancies.

Sarcoma

Two studies met the inclusion criteria [55,56]. Results from a meta-analysis showed that FDG PET/CT is a reliable imaging method for the diagnosis (pooled sensitivity, 90% to 96%; pooled specificity, 89% to 95%) and treatment response assessment (pooled sensitivity, 79%; pooled specificity, 79%) of patients with osseous and soft tissue sarcomas [55]. In the follow-up of patients with suspected recurrence of disease, FDG PET/CT showed an overall diagnostic accuracy of 91.2% and changed the management plan of 75.7% of cases [56].

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 retrospective study by Park et al. [1] suggested an improved detection of local recurrence over clinical follow-up, but only 4.3% of 142 patients developed local recurrence while five patients were found to have distant recurrence by PET/CT. The impact is too small to be clinically meaningful.

The authors from a retrospective study of 88 patients [2] noted an increased sensitivity in the detection of bony metastases using PET/CT; however, this modality was not as sensitive for osteoblastic metastases and metastases arising from low-grade mammary carcinomas. Therefore, the results of this study are insufficient to suggest a change in staging of distant metastases with PET/CT.

The retrospective study by Yararbas et al. [3] compared staging PET/CT with chest x-ray and abdominal ultrasound. There was no difference in the detection of bony metastases when PET/CT was compared with bone scan; therefore, all the differences were in visceral metastases not detected by chest x-ray and abdominal ultrasound. Since no comparison to standard CT chest/abdomen/pelvis was made, it is not possible to determine the incremental benefit in distant staging with PET/CT when compared with current staging standards.

It is important to note that the meta-analysis by Chen et al. [4] included 12 publications, of which only four were prospective studies. The quality of the findings from

this study will be limited by the heterogeneous nature of the pooled primary data, and should not be used to change imaging guidelines for breast cancer patients.

On the whole, there is not enough evidence to support any change in guidelines for imaging in breast cancer or for the use of PET/CT for breast cancer staging, response to treatment, or surveillance for recurrence.

Esophageal Cancer

Current Insured Indication

- For baseline staging assessment of 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 work-up 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 (post-therapy 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

A review was not completed by a clinical expert in esophageal cancer.

Gastrointestinal Cancer

Current Insured Indication (Colorectal Cancer)

- Where recurrent disease is suspected on the basis of elevated and/or rising carcinoembryonic antigen (CEA) 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 CEA levels, when a conventional work-up 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.

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.

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.

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, including I-131 scan and/or neck US, 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 HL or non-HL (NHL) 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 NHL 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 HL or NHL when further potentially curative therapy (such as radiation or stem cell transplantation) is being considered; or for the assessment of response in early-stage HL 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) HL 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 HL or NHL.
- An FDG PET/CT scan is recommended for the evaluation of residual mass(es) following chemotherapy in a patient with HL or NHL 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.

Melanoma

Current Registry Indication

- For the staging of melanoma patients with localized "high-risk" tumours with potentially resectable disease; or for the evaluation of patients with melanoma and isolated metastasis at the time of recurrence when metastasectomy is being contemplated.

Current Recommendations for the Utilization of PET/CT in Melanoma

- PET is recommended for staging of high-risk patients with potentially resectable disease.
- PET is not recommended for the diagnosis of sentinel lymph node micrometastatic disease or for staging of I, IIa, or IIb melanoma.
- The routine use of PET or PET/CT is not recommended for the diagnosis of brain metastases.
- The routine use of PET is not recommended for the detection of primary uveal malignant melanoma.
- A recommendation cannot be made for or against the use of PET for the assessment of treatment response in malignant melanoma due to insufficient evidence.
- A recommendation cannot be made for or against the use of PET for routine surveillance due to insufficient evidence.
- PET is recommended for isolated metastases at time of recurrence or when contemplating metastasectomy.

Reviewer's Comments (Dr. Tara Baetz)

The current recommendations for the utilization of PET/CT in melanoma 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)

There is currently not enough evidence to support making appropriate recommendations for the use of PET/CT with non-FDG tracers.

NSCLC 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 based on negative standard imaging tests; or clinical stage III NSCLC where potentially curative combined-modality therapy with radiotherapy and chemotherapy is being considered.
- Limited-disease small cell lung cancer (SCLC):
    - Where combined modality therapy with chemotherapy and radiotherapy is being considered.

Current Recommendations for the Utilization of PET/CT in SCLC

- PET is recommended for staging in patients with SCLC 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 SCLC.
- 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. The studies identified have not been specifically addressed in the current indications for lung cancer. The study by Wu et al. [50] is for adrenal metastasis while the retrospective study by Sheikhbahaei et al. [51] is for post-treatment follow-up.

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, or 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.

Pediatric Cancer

Current Registry Indications (patients must be <18 years of age)

- For the following cancer types (International Classification for Childhood Cancer):
    - Bone/cartilage – osteosarcoma, Ewing sarcoma
    - Connective/other soft tissue – rhabdomyosarcoma, other
    - Kidney – renal tumour
    - Liver – hepatic tumour
    - Lymphoma/post-transplant lymphoproliferative disorder – HL and NHL
    - Primary brain – astrocytoma, medulloblastoma, ependymoma, other
    - Reproductive – germ cell tumour
    - Sympathetic nervous system - neuroblastoma MIBG-negative
    - Other – Langerhans cell histiocytosis, melanoma of the skin, thyroid
- For the following indications:
    - Initial staging
    - Monitoring response during treatment/determine response-based therapy
    - Rule out progression prior to further therapy
    - Suspected recurrence/relapse
    - Rule out persistent disease
    - Select optimal biopsy site

Reviewer's Comments (Dr. David Hodgson)

The staging and response evaluation of aggressive NHL and HL with PET/CT are widely considered to be standard practice now and should be accepted as insured indications.

Sarcoma

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

Reviewer's Comments (Dr. Gina Diprimio)

A letter has been submitted on behalf of the Sarcoma Disease Site Group requesting a formal review of the literature for PET in sarcoma.

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Contact Information

For information about the PEBC and the most current version of all reports,
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Appendix 1: Summary of studies from July to December 2017.

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Breast Cancer								
Park et al, 2017 [1]	Retrospective	192 patients; 142 staging scans, 349 surveillance scans (invasive lobular carcinoma, mucinous carcinoma, and tubular carcinoma)	FDG PET/CT	US, MRI	Pathology, clinical follow-up	**Axillary lymph node staging** Sens: 51.5% Spec: 94.6%* Accu: 84.7% **Local tumour recurrence** Sens: 100% Spec: 98.3%	**Axillary lymph node staging** ***US*** Sens: 42.4% Spec: 90.1% Accu: 79.2% ***MRI*** Sens: 51.5% Spec: 88.3%* Accu: 79.9% **Local tumour recurrence** ***US*** Sens: 100% Spec: 96.7%	NA
Sugihara et al, 2017 [2]	Retrospective	88 patients (suspected bone metastases from breast cancer)	FDG PET/CT	Bone scintigraphy, CT	Histology, clinical and imaging follow-up	**Bone metastases** Sens: 94%	**Bone metastases** ***Bone scintigraphy*** Sens: 89% ***CT*** Sens: 77%	NA
Yararbas et al, 2017 [3]	Retrospective	234 patients referred for staging (breast cancer)	FDG PET/CT	Physical examination, mammography, breast and axillary US, MRI	Histopathology, follow-up	NA	NA	Stage modification occurred following PET/CT in 35.0% (82/234) of patients and changed patient management in 29.5% (69/234) of cases (67— change in therapy planning, 2— radiotherapy field widened).
Chen et al, 2017 [4]	Meta-analysis	11 studies (527 patients with breast cancer)	FDG PET/CT	MRI	Histopathology	**Pathological response to NAC** Pooled Sens: 87% Pooled Spec: 85% Pooled +LR: 5.76 Pooled –LR: 0.16 Pooled DOR: 37.25 AUC: 0.93	**Pathological response to NAC** Pooled Sens: 79% Pooled Spec: 82% Pooled +LR: 4.29 Pooled –LR: 0.26 Pooled DOR: 16.43 AUC: 0.87	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Schmitz et al, 2017 [5]	Prospective	188 patients who underwent baseline and interim imaging assessment for response to NAC (stage II and III breast cancer)	FDG PET/CT	MRI	Pathology	**Pathological complete response** HER2-positive AUC: 0.543* ER-positive AUC: 0.791 Triple-negative AUC: 0.844	**Pathological complete response** HER2-positive AUC: 0.735* ER-positive AUC: 0.742 Triple-negative AUC: 0.855	NA
Esophageal Cancer								
Bunting et al, 2017 [6]	Retrospective	133 patients planned to have surgical resection (esophageal cancer)	FDG PET/CT	CT, EUS	Histopathology	**N staging** Accu: 74.5%	**N staging** ***CT*** Accu: 75.6% ***EUS*** Accu: 77.2%	NA
Gastrointestinal Cancer								
Xu et al, 2017 [7]	Retrospective	53 patients with nonspecific symptoms (gastric cancer)	FDG PET/CT	Gastric endoscopy	Pathology	**Diagnosis** Sens: 86.8%	**Diagnosis** Sens: 90.6%	NA
Redondo-Cerezo et al, 2017 [8]	Prospective	256 patients who received surgical resection (gastric cancer)	FDG PET/CT	EUS	Histology	**N staging** Sens: 50.0% Spec: 90.9% PPV: 81.8% NPV: 69.0% Accu: 72.5%* **N restaging** Sens: 41.7% Spec: 88.2% PPV: 71.4% NPV: 68.2% Accu: 69.0%*	**N staging** Sens: 78.9% Spec: 73.9% PPV: 71.4% NPV: 81.0% Accu: 76.2%* **N restaging** Sens: 83.3% Spec: 92.9% PPV: 90.9% NPV: 86.7% Accu: 88.5%*	NA
Luo et al, 2017 [9]	Meta-analysis	15 studies (1301 patients with gastric cancer)	FDG PET/CT	DWI-MRI	Pathology	**Preoperative N staging** Pooled Sens: 52%* Pooled Spec: 88% AUC: 0.66*	**Preoperative N staging** Pooled Sens: 79%* Pooled Spec: 69% AUC: 0.81*	NA
Kim et al, 2017 [10]	Retrospective	120 patients who underwent curative resection (gastric carcinoma)	FDG PET/CT	CeCT	Histopathology, clinical follow-up	**Recurrence (patient-based)** Sens: 82% Spec: 95% PPV: 94% NPV: 84% Accu: 88%	**Recurrence (patient-based)** Sens: 97% Spec: 97% PPV: 97% NPV: 97% Accu: 97%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Locoregional recurrence (lesion-based) Sens: 80% Spec: 99% PPV: 89% NPV: 98% Accu: 98% **Lymph node recurrence (lesion-based)** Sens: 88% Spec: 99% PPV: 95% NPV: 97% Accu: 97% **Liver metastasis (lesion-based)** Sens: 100% Spec: 98% PPV: 60% NPV: 100% Accu: 98% **Peritoneal carcinomatosis (lesion-based)** Sens: 50%* Spec: 100% PPV: 100% NPV: 89% Accu: 90%	**Locoregional recurrence (lesion-based)** Sens: 80% Spec: 100% PPV: 100% NPV: 98% Accu: 98% **Lymph node recurrence (lesion-based)** Sens: 92% Spec: 99% PPV: 96% NPV: 98% Accu: 98% **Liver metastasis (lesion-based)** Sens: 67% Spec: 96% PPV: 29% NPV: 99% Accu: 95% **Peritoneal carcinomatosis (lesion-based)** Sens: 96%* Spec: 100% PPV: 100% NPV: 99% Accu: 99%	
Choi et al, 2017 [11]	Meta-analysis	24 studies (patients with colorectal liver metastasis)	FDG PET/CT	MDCT, gadoxetate disodium-enhanced MRI	Pathology, intraoperative US, imaging follow-up	**Diagnosis (lesion-based)** Pooled Sens: 74.1%* Pooled Spec: 93.9%*	**Diagnosis (per-lesion based)** ***MDCT*** Pooled Sens: 82.1% Pooled Spec: 73.5%* ***Gadoxetate disodium-enhanced MRI*** Pooled Sens: 93.1%* Pooled Spec: 87.3%	NA
Lopez-Lopez et al, 2017 [12]	Prospective	57 patients for follow-up after undergoing surgery (colorectal	FDG PET/CT	CT	Histology	**Pulmonary metastases** Sens: 76% Spec: 75% PPV: 99%	**Pulmonary metastases** Sens: 90% Spec: 50% PPV: 98%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		liver metastases)				NPV: 12%	NPV: 17%	
Kim et al, 2017 [13]	Retrospective	345 patients whose proximal colon could not be examined by colonoscopy (obstructive CRC)	FDG PET/CT	Colonoscopy, CT	Pathology	**Synchronous invasive cancer (patient-based)** Sens: 100% Spec: 93.9% PPV: 41.2% NPV: 100% **(lesion-based)** Sens: 100% Spec: 92.6% PPV: 35.9% NPV: 100% **Advanced adenoma (patient-based)** Sens: 53.1% Spec: 94.6% PPV: 50.0% NPV: 95.2% **(lesion-based)** Sens: 45.5% Spec: 94.1% PPV: 51.3% NPV: 92.7%	**Synchronous invasive cancer (per-patient/lesion)** Sens: 38.5% Spec: 99.2% PPV: 71.4% NPV: 96.9%	NA
Fusco et al, 2017 [14]	Systematic review	25 studies (patients with locally advanced rectal cancer)	FDG PET/CT	MRI, DCE-MRI, DWI-MRI	TNM and tumour regression grade criteria	**Preoperative therapy response** Pooled Sens: 80.3% Pooled Spec: 83.1% Pooled PPV: 79.3% Pooled NPV: 83.9% Pooled Accu: 81.8%	**Preoperative therapy response** ***MRI*** Pooled Sens: 75.8% Pooled Spec: 78.2% Pooled PPV: 74.3% Pooled NPV: 79.6% Pooled Accu: 77.1% ***DCE-MRI*** Pooled Sens: 87.2% Pooled Spec: 84.2% Pooled PPV: 82.4% Pooled NPV: 88.5% Pooled Accu: 85.6% ***DWI-MRI*** Pooled Sens: 76.0% Pooled Spec: 79.3% Pooled PPV: 84.5% Pooled NPV: 68.9% Pooled Accu: 77.3%	NA
Ma et al,	Retrospective	66 patients	FDG	NA	Pathology	**Lymph node**	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
2017 [15]		who had hepatectomy with curative intent (cholangiocarcinoma)	PET/CT			**metastasis** Sens: 66.7% Spec: 78.8% PPV: 66.7% NPV: 78.8% AUC: 0.727		
Genitourinary Cancer								
Shaban, 2017 [16]	Prospective	25 patients (biopsy-proven renal cell carcinoma)	FDG PET/CT	CeCT	Histopathology, clinical and imaging follow-up	**Primary, recurrent, and metastatic disease** Sens: 100% Spec: 93% PPV: 100% NPV: 91% Accu: 96%	**Primary, recurrent, and metastatic disease** Sens: 100% Spec: 70% PPV: 83% NPV: 100% Accu: 88%	NA
van de Putte et al, 2017 [17]	Prospective	47 patients who received neoadjuvant or induction chemotherapy followed by radical cystectomy (cT1-4N1-3 bladder cancer)	FDG PET/CT	NA	Pathology	**Pathologic complete response** Sens: 67% Spec: 75% PPV: 75% NPV: 67% **Pathologic partial response** Sens: 92% Spec: 75% PPV: 92% NPV: 75%	NA	NA
Alongi et al, 2017 [18]	Retrospective	114 patients (suspected recurrent germinal cell testicular carcinoma based on conventional imaging and/or clinical data)	FDG PET/CT	Not specified	Pathology, comparison to other imaging modalities, clinical and imaging follow-up	**Recurrence** Sens: 86.8% Spec: 90.2% Accu: 88.4% +LR: 8.85 -LR: 0.14 Pre-test OR: 0.85 Post-test OR: 8.85	NA	PET/CT findings impacted therapeutic management in 22.8% (26/114) of cases (12—palliative to curative, 6—new chemotherapy initiated, 8—switched to wait-and-watch).
Gynecologic Cancer								
Papadia et al, 2017 [19]	Retrospective	60 patients (IA1-IIA cervical cancer)	FDG PET/CT	SLN mapping	Histopathology	**Lymph node metastasis** Sens: 68% Spec: 84% PPV: 61% NPV: 88%	**Lymph node metastasis** Sens: 93% Spec: 100% PPV: 100% NPV: 97%	NA
Su et al, 2017 [20]	Prospective	55 patients who received	FDG PET/CT	MRI	Pathology, imaging follow-	**Residual disease (patient-based)**	**Residual disease (patient-based)**	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		definitive concurrent chemoradiotherapy (FIGO stage III-IVA or positive PALN cervical squamous cell carcinoma)			up	Sens: 60% Spec: 100% PPV: 100% NPV: 87% Accu: 89% AUC: 0.828* **(region-based)** ***Local disease*** Sens: 80% Spec: 100% PPV: 100% NPV: 98% Accu: 98% AUC: 0.976* ***Regional disease*** Sens: 29% Spec: 100% PPV: 100% NPV: 91% Accu: 91% AUC: 0.805* ***PALN*** Sens: 40% Spec: 100% PPV: 100% NPV: 94% Accu: 95% AUC: 0.664 ***Distant metastases*** Sens: 57% Spec: 100% PPV: 100% NPV: 94% Accu: 95% AUC: 0.750	Sens: 27% Spec: 100% PPV: 100% NPV: 78% Accu: 80% AUC: 0.618* **(region-based)** ***Local disease*** Sens: 40% Spec: 100% PPV: 100% NPV: 94% Accu: 95% AUC: 0.850* ***Regional disease*** Sens: 0% Spec: 100% PPV: NA NPV: 87% Accu: 87% AUC: 0.554* ***PALN*** Sens: 40% Spec: 100% PPV: 100% NPV: 94% Accu: 95% AUC: 0.682 ***Distant metastases*** Sens: 14% Spec: 100% PPV: 100% NPV: 89% Accu: 89% AUC: 0.563	
Garganese et al, 2017 [21]	Prospective	47 patients who were unsuitable for sentinel node biopsy but were candidates for radical inguinal surgery (clinical N0 invasive vulvar	FDG PET/CT	CT, inguino-femoral ultrasonography, US-guided FNA	Histopathology	**Predicting nodal metastases** Sens: 56% Spec: 88% PPV: 38% NPV: 93% Accu: 84%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		cancer)						
Kirchner et al, 2017 [22]	Prospective	43 patients (suspected recurrence of pelvic malignancy; 23 ovarian, 12 cervical, 4 endometrium, 3 vulva, 1 vaginal)	FDG PET/CT, FDG PET/MRI	CT	Histopathology, imaging follow-up	**Tumour relapse (lesion-based)** ***FDG PET/CT*** Sens: 97% Spec: 83% PPV: 93% NPV: 94% Accu: 92% ***FDG PET/MRI*** Sens: 98% Spec: 83% PPV: 94% NPV: 94% Accu: 94%	**Tumour relapse (lesion-based)** Sens: 50% Spec: 58% PPV: 76% NPV:31% Accu: 53%	NA
Head and Neck Cancer								
Han et al, 2017 [23]	Retrospective	153 patients who underwent previous radiotherapy (extra-cranial head and neck cancer)	FDG PET/CT	NA	Histology	**Locoregional recurrent or residual disease** Sens: 93.0% Spec: 64.2% PPV: 80.9% NPV: 86.0% Accu: 82.3%	NA	NA
Helsen et al, 2017 [24]	Retrospective	103 patients treated with curative radiotherapy with or without chemotherapy (new or recurrent stage I-IVb head and neck squamous cell carcinoma)	FDG PET/CT	NA	Histology, clinical and imaging follow-up	**Residual disease** Sens: 91.1% Spec: 87.0% PPV: 77.3% NPV: 95.3% Accu: 88.3% **Nodal disease** Sens: 91% Spec: 93% PPV: 81% NPV: 97%	NA	NA
Riaz et al, 2017 [25]	Retrospective	93 patients with high clinical risk of residual or recurrent disease after chemoradiotherapy (head and neck cancer)	FDG PET/CT	NA	Histopathology, clinical follow-up	**Persistent disease** PPV: 88% NPV: 92% Accu: 88%	NA	NA
Van den	Prospective	125 patients	FDG	NA	Histology,	**Residual disease**	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Wyngaert et al, 2017 [26]		who received concurrent chemoradiotherapy (locoregionally advanced head and neck squamous cell carcinoma)	PET/CT		clinical and imaging follow-up	Sens: 65.2% Spec: 91.2% PPV: 62.5% NPV: 92.1% Accu: 86.4% AUC: 0.78		
Hirshoren et al, 2017 [27]	Retrospective	64 patients who underwent PET/CT prior to surgery (node-positive head and neck cutaneous squamous cell carcinoma)	FDG PET/CT	CT	Histopathology	NA	NA	PET/CT findings changed the CT-based surgical plan of 6.3% (4/64) of patients.
Xu et al, 2017 [28]	Meta-analysis	4 studies (807 patients with nasopharyngeal cancer)	FDG PET/CT	Bone scintigraphy	Histopathology, imaging follow-up	**Bone metastases** Pooled Sens: 83% Pooled Spec: 99% Pooled PPV: 61.6 Pooled NPV: 0.18 Pooled DOR: 351	**Bone metastases** Pooled Sens: 46% Pooled Spec: 98% Pooled PPV: 18.7 Pooled NPV: 0.56 Pooled DOR: 34	NA
Shen et al, 2017 [29]	Prospective	35 patients with MRI-negative cervical lymph nodes (newly diagnosed nasopharyngeal carcinoma)	FDG PET/CT	MRI	Cytopathology	**Cervical lymph node metastasis** Sens: 94.1% Spec: 85.0% PPV: 84.2% NPV: 94.4% Accu: 89.2%	NA	NA
Kang et al, 2017 [30]	Retrospective	66 patients who underwent surgery (recurrent papillary thyroid cancer)	FDG PET/CT	CT	Histopathology	**Recurrence** Sens: 38.5% Spec: 90.2% PPV: 86.3% NPV: 47.7% Accu: 58.3%*	**Recurrence** Sens: 55.0% Spec: 85.7% PPV: 86.3% NPV: 53.7% Accu: 66.7%*	NA
Hematologic Cancer								
El Karak et al, 2017 [31]	Retrospective	54 patients (DLBCL)	FDG PET/CT	BMB	BMB	**Bone marrow involvement** Sens: 80% Spec: 80% PPV: 33% NPV: 98%	NA	NA
Vishnu et al,	Retrospective	99 patients	FDG	BMAB	BMAB	**Bone marrow**	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
2017 [32]		(newly diagnosed DLBCL)	PET/CT			**involvement** Sens: 86% Spec: 86% PPV: 50% NPV: 98% Accu: 86%		
Yilmaz et al, 2017 [33]	Retrospective	486 patients (310 NHL, 176 HL)	FDG PET/CT	BMB	BMB	**Bone marrow involvement** ***HL*** Sens: 81% Spec: 84% PPV: 25.7% NPV: 98% Accu: 84% ***DLBCL*** Sens: 91.3% Spec: 94.3% PPV: 67.7% NPV: 98.8% Accu: 94%	NA	NA
Angelopoulou et al, 2017 [34]	Retrospective	162 patients who underwent initial staging (HL)	FDG PET/CT	Clinical examination, CeCT, BMB	BMB, follow-up	NA	NA	PET/CT upstaged 16.0% (26/162) and downstaged 5.6% (9/162). The therapeutic strategy was changed in 6.2% (10/162) of patients
Borchmann et al, 2017 [35]	Phase 3 RCT	1005 PET-negative patients after 2 cycles of $BEACOPP_{escalated}$ 1:1 allocation to receive either 2 or 6 additional cycles of $BEACOPP_{escalated}$; 434 PET-positive patients after 2 cycles of $BEACOPP_{escalated}$ 1:1 allocation to receive either 6	FDG PET/CT	NA	Clinical follow-up	NA	NA	For PET-negative patients, the 5-year OS was 95.4% for those who received 6 or 8 cycles of $BEACOPP_{escalated}$ and 97.7% for those who received 4 cycles of $BEACOPP_{escalated}$ (difference 2.3%, 95% CI: -0.2 to 4.9, log rank p=0.0037). For PET-positive patients, there was no significant difference in the 5-year OS between those who received 6 additional courses of $BEACOPP_{escalated}$ and those who received 6

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		additional courses of $BEACOPP_{escalated}$ or 6 additional courses of $BEACOPP_{escalated}$ plus rituximab (newly diagnosed, advanced stage HL)						additional courses of $BEACOPP_{escalated}$ plus rituximab (96.4% vs. 93.9%, respectively; p=0.25).
Dann et al, 2017 [36]	Prospective	355 patients; early HL received 2 cycles of ABVD and advanced HL with IPS 0-2 received 2 cycles of ABVD and those with IPS ≥3 received 2 cycles of $BEACOPP_{escalated}$ prior to interim PET assessment (early and advanced HL)	FDG PET/CT (PET-positive early HL received 2× or 4× ABVD + ISRT and PET-negative early HL received ISRT or 2× ABVD + ISRT; PET-positive advanced HL received 4× $BEACOPP_{escalated}$ + ISRT and PET-negative advanced HL received 4× ABVD)	NA	Clinical and imaging follow-up	NA	NA	In early HL, the 5-year PFS for interim PET-positive patients was significantly worse than that of interim PET-negative patients (88.7% vs. 69.2%, p=0.008). The 5-year OS was 100% and 95%, respectively. In advanced HL, there was no significant difference in the 5-year PFS between interim PET-positive and interim PET-negative patients (68.4% vs. 80.8%, respectively, p=0.07). The 5-year OS was 91.4% and 97.8%, respectively.
Melanoma								
Chandra et al, 2017 [37]	Prospective	70 patients (primary cutaneous malignant	FDG PET/CT	CeCT, US	Histopathology, clinical and imaging follow-up	**N staging** Sens: 86% Spec: 96% PPV: 97%	**N staging** ***CeCT*** Sens: 77% Spec: 96%	PET/CT upstaged and impacted management in 38.6% (27/70) of patients by identifying

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		melanoma)				NPV: 80% Accu: 90% **M staging** Sens: 87% Spec: 100% PPV: 100% NPV: 93% Accu: 95%	PPV: 97% NPV: 70% Accu: 84% ***US*** Sens: 75% Spec: 88% PPV: 91% NPV: 66% Accu: 80% M staging ***CeCT*** Sens: 70% Spec: 100% PPV: 100% NPV: 87% Accu: 90%	clinically occult nodal/distant metastasis.
Non-FDG Tracers $^{11}C/^{18}F$-Choline								
Kitajima et al, 2017 [38]	Prospective	21 patients (prostate cancer)	^{11}C-Choline PET/CT	Bone scintigraphy	Clinical and imaging follow-up	**Bone metastases (patient-based)** Sens: 90.9% Spec: 90.0% PPV: 90.9% NPV: 90.0% Accu: 90.5% AUC: 0.968 **(region-based)** Sens: 97.9%* Spec: 99.0% PPV: 97.9% NPV: 99.0% Accu: 98.6%* AUC: 0.999*	**Bone metastases (patient-based)** Sens: 81.8% Spec: 90.0% PPV: 90.0% NPV: 81.8% Accu: 85.7% AUC: 0.823 **(region-based)** Sens: 72.9%* Spec: 99.0% PPV: 97.2% NPV: 88.3% Accu: 90.5%* AUC: 0.839*	NA
Huysse et al, 2017 [39]	Prospective	64 patients (biochemically relapsed prostate cancer)	^{18}F-Choline PET/CT	MRI	Clinical follow-up	**Bone metastases (patient-based)** Sens: 87% Spec: 100% PPV: 100% NPV: 96% **(lesion-based)** Sens: 75%* Spec: 100% PPV: 100% NPV: 90%	**Bone metastases (patient-based)** Sens: 100% Spec: 96% PPV: 88% NPV: 100% **(lesion-based)** Sens: 100%* Spec: 93% PPV: 86% NPV: 100%	NA
^{68}Ga-DOTA-(TATE, TOC)								
Chen et al,	Prospective	36 patients	^{68}Ga-	CT, MRI, EUS	Histopathology,	**Primary tumour**	**Primary tumour**	^{68}Ga-DOTA-TOC PET/CT

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
2017 [40]		(clinically suspected NET and NET of unknown primary site)	DOTA-TOC PET/CT, FDG PET/CT		clinical follow-up	***^{68}Ga-DOTA-TOC PET/CT*** Sens: 88% Spec: 100% Accu: 94% AUC: 0.941* ***FDG PET/CT*** Sens: 41% Spec: 100% Accu: 72% AUC: 0.706	Sens: 53% Spec: 68% Accu: 61% AUC: 0.607*	findings modified the treatment plan of 33.3% (12/36) of patients (5—switched to watchful waiting, 4—recommended systemic or combination therapy, 3—underwent surgery).
Kunikowska et al, 2017 [41]	Prospective	68 patients (metastatic NET)	^{68}Ga-DOTA-TATE PET/CT	99mTc-HYNIC-TOC SPECT or SPECT/CT	Clinical and imaging follow-up	**Malignancy** Sens: 100% Spec: 85% PPV: 97% NPV: 100% Accu: 97%	**Malignancy** Sens: 82% Spec: 69% PPV: 92% NPV: 47% Accu: 79%	^{68}Ga-DOTA-TATE PET/CT changed clinical decision making in 33.8% (23/68) of patients.
Lawal et al, 2017 [42]	Retrospective	203 patients (NET and other Grade I and II SSTR tumours)	^{68}Ga-DOTA-TATE PET/CT	CeCT	Histology, imaging follow-up	**Staging or restaging or suitability for PRRT or recurrence or primary site of tumour** Sens: 94.2% Spec: 91.9% PPV: 95.6% NPV: 89.5% Accu: 96.6%	NA	Management was altered by ^{68}Ga-DOTA-TATE PET/CT in 14.3% (29/203) of patients.
^{68}Ga-PSMA								
Von Eyben et al, 2016 [43]	Meta-analysis	15 studies (1256 patients with prostate cancer)	^{68}Ga-PSMA PET/CT or PET/MRI	NA	Pathology	**Initial staging** **Primary tumour (lesion-based)** Pooled Sens: 70% Pooled Spec: 84% Pelvic lymph node metastasis **(patient-based)** Pooled Sens: 61% Pooled Spec: 97% **Restaging** **Pelvic lymph node metastasis** Sens: 87-93% Spec: 93-100%	NA	NA
Perera et al, 2016 [44]	Meta-analysis	5 studies (220 patients with advanced	^{68}Ga-PSMA PET/CT	NA	Histopathology	**Lymph node metastasis (patient-based)**	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		prostate cancer)				Pooled Sens: 86% Pooled Spec: 86% AUC: 0.91 **(lesion-based)** Pooled Sens: 80% Pooled Spec: 97% AUC: 0.95		
Janssen et al, 2017 [45]	Retrospective	54 patients (prostate cancer)	^{68}Ga-PSMA PET/CT	^{99m}Tc-DPD-SPECT/CT	Clinical and imaging follow-up	**Bone metastases (patient-based)** Sens: 100% Spec: 100% AUC: 1.00* **(region-based)** Sens: 97.7% Spec: 100% AUC: 0.99* **(lesion-based)** Sens: 97.4% Spec: 100% AUC: 0.99*	**Bone metastases (patient-based)** Sens: 82.8% Spec: 84.0% AUC: 0.83* **(region-based)** Sens: 69.4% Spec: 98.3% AUC: 0.84* **(lesion-based)** Sens: 46.2% Spec: 69.2% AUC: 0.58*	NA
Afaq et al, 2017 [46]	Retrospective	100 patients (biochemical recurrence of prostate cancer)	^{68}Ga-PSMA PET/CT	NA	Pathology, when available	NA	NA	^{68}Ga-PSMA PET/CT findings altered management in 39.0% (39/100) of patients.
^{18}F-FACBC								
Jambor et al, 2017 [47]	Prospective	26 patients scheduled for radical robot-assisted prostatectomy (intermediate- to high-risk prostate cancer)	^{18}F-FACBC PET/CT	mpMRI	Histopathology	**Intraprostatic disease** Sens: 87%* Spec: 56%* Accu: 72% AUC: 0.72*	**Intraprostatic disease** Sens: 77%* Spec: 99%* Accu: 88% AUC: 0.88*	NA
^{18}F-NaF								
Wondergem et al, 2017 [48]	Retrospective	226 patients who underwent primary staging (histopathologically or clinically proven prostate cancer)	^{18}F-NaF PET/CT	^{99m}Tc-HDP bone scintigraphy	Clinical, biochemical and imaging follow-up	**Bone metastases** Sens: 96.8-100% Spec: 97.6-100% PPV: 98.4-100% NPV: 95.3-100% Accu: 98.1-99.0%	**Bone metastases** Sens: 84.2-94.7% Spec: 72.0-100% PPV: 61.0-100% NPV: 93.2-96.7% Accu: 79.2-95.0%	NA
Lofgren et al,	Prospective	117 patients	^{18}F-NaF	^{99m}Tc-HDP planar	Histology,	**Bone metastases**	**Bone metastases**	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
2017 [49]		with clinical suspicion of bone metastases (62 prostate cancer, 54 breast cancer, 1 renal cancer)	PET/CT	bone scintigraphy, ^{99}mTc-HDP SPECT/CT	clinical and imaging follow-up	***^{18}F-NaF PET/CT*** Sens: 80.0% Spec: 97.9% PPV: 85.7% NPV: 96.9% Accu: 95.5%	***^{99}mTc-HDP planar bone scintigraphy*** Sens: 64.3% Spec: 96.5% PPV: 75.0% NPV: 94.3% Accu: 91.9% ***^{99}mTc-HDP SPECT/CT*** Sens: 60.0% Spec: 92.8% PPV: 56.3% NPV: 93.8% Accu: 88.4%	
NSCLC and Other Lung Cancer								
Wu et al, 2017 [50]	Meta-analysis	9 studies (707 patients with lung cancer)	FDG PET/CT	NA	Histopathology, clinical and imaging follow-up	**Adrenal metastasis (lesion-based)** Pooled Sens: 88.7% Pooled Spec: 90.8% Pooled +LR: 8.55 Pooled –LR: 0.09 Pooled DOR: 96.83 AUC: 0.962 Q test: 0.908	NA	NA
Sheikhbahaei et al, 2017 [51]	Retrospective	275 treated patients; 423 scans (251 NSCLC, 24 SCLC)	FDG PET/CT	Chest CT	Histopathology, clinical and imaging follow-up	**Local recurrence** Sens: 96.0% Spec: 82.1% PPV: 81.2% NPV: 96.2% Accu: 88.3% **Regional recurrence** Sens: 94.4%* Spec: 87.1% PPV: 77.8% NPV: 97.0%* Accu: 89.5% **Distant recurrence** Sens: 91.9%* Spec: 87.1% PPV: 75.8% NPV: 96.0%* Accu: 88.5%	**Local recurrence** Sens: 95.4% Spec: 83.0% PPV: 81.9% NPV: 95.8% Accu: 88.6% **Regional recurrence** Sens: 78.6%* Spec: 88.9% PPV: 77.3% NPV: 89.7%* Accu: 85.6% **Distant recurrence** Sens: 70.7%* Spec: 88.4% PPV: 73.1% NPV: 87.2%* Accu: 83.0%	NA
Pancreatic Cancer								
Santhosh et al, 2017 [52]	Prospective	54 patients (pancreatic	FDG PET/CT	CeCT	Histopathology	**Nodal staging** Sens: 89%	**Nodal staging** Sens: 33%	PET/CT findings changed the

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		adenocarcinoma)				Spec: 100% PPV: 100% NPV: 90% Accu: 95%* **Metastatic staging** Accu: 100%*	Spec: 84% PPV: 67% NPV: 60% Accu: 59%* **Metastatic staging** Sens: 73% Spec: 87% PPV: 69% NPV: 89% Accu: 83%*	management in 18.5% (10/54) of patients.
Kurita et al, 2016 [53]	Prospective	52 patients without apparent distant metastases (pancreatobiliary cancer)	FDG PET/CT	MDCT, EUS, EUS-FNA	Histopathology	**Para-aortic lymph node metastasis (lesion-based)** Sens: 53.3%* Spec: 97.6% PPV: 94.1% NPV: 74.1% Accu: 78.9%*	**Para-aortic lymph node metastasis (lesion-based)** ***EUS-FNA*** Sens: 96.7%* Spec: 100% PPV: 100% NPV: 97.5% Accu: 98.6%*	NA
Pediatric Cancer								
Zapata et al, 2017 [54]	Retrospective	69 patients (7 rhabdomyosarcoma, 7 Ewing sarcoma, 20 neuroblastoma, 18 HL, 17 NHL)	FDG PET/CT	BMB	BMB	**Bone marrow involvement** Sens: 100% Spec: 68.6% PPV: 52.9% NPV: 100% Accu: 76.8%	NA	NA
Sarcoma								
Muheremu et al, 2017 [55]	Meta-analysis	16 studies (883 patients with osseous and soft tissue sarcoma)	FDG PET/CT	NA	Histopathology, clinical and imaging follow-up	**Diagnosis (patient-based)** Pooled Sens: 90% Pooled Spec: 89% AUC: 0.944 **(lesion-based)** Pooled Sens: 96% Pooled Spec: 95% AUC: 0.967 **Response to neoadjuvant therapy** Pooled Sens: 79% Pooled Spec: 79% AUC: 0.871	NA	NA
Kassem et al, 2017 [56]	Prospective	37 patients (suspected recurrence of	FDG PET/CT	NA	Histopathology, clinical and imaging follow-	**Recurrence** Sens: 90% Spec: 100%	NA	PET/CT findings led to a change in management plan in 75.7% (28/37) of

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		soft tissue sarcoma)			up	PPV: 100% NPV: 70% Accu: 91.2%		patients (5—initiated radiotherapy, 7—received chemoradiotherapy, 8—limb-sparing surgeries, 8—surgeries followed by or preceded adjuvant radiotherapy).
Various Sites								
Delivanis et al, 2017 [57]	Retrospective	353 patients (adrenal masses)	FDG PET/CT	Unenhanced CT	Pathology, clinical and imaging follow-up, surgical information	**Malignancy** ***SUVmax > 1.8*** Sens: 87% Spec: 84% PPV: 85% NPV: 86% ***SUVmax > 4.5*** Sens: 87% Spec: 69% PPV: 76% NPV: 83%	**Malignancy** ***HU > 10*** Sens: 100% Spec: 33% PPV: 72% NPV: 100%	NA
Sheikhbahaei et al, 2017 [58]	Meta-analysis	12 studies (528 patients with clinically suspected neurologic paraneoplastic syndromes)	FDG PET or PET/CT	NA	Histopathology, imaging follow-up	**Underlying malignancy** Pooled Sens: 89% Pooled Spec: 83% Pooled +LR: 4.47 Pooled –LR: 0.25 Pooled DOR: 26.99 AUC: 0.915 Q test: 0.848	NA	NA
Wang et al, 2017 [59]	Retrospective	128 patients who are being considered for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (peritoneal metastases)	FDG PET/CT	CT, MRI	Histopathology, clinical and imaging follow-up	NA	NA	PET/CT provided definitive answers for 36.3% (33/91) of patients with indeterminate lesions on CT/MRI (10—confirmed for surgery, 8—had surgery without hyperthermic intraperitoneal chemotherapy, 15—avoided unnecessary surgery and referred for palliative therapy).

Abbreviations: +LR: positive likelihood ratio; -LR: negative likelihood ratio; ^{11}C-choline: carbon-11 choline; ^{18}F-Choline: fluorine-18 choline; ^{18}F-FACBC: ^{18}F fluciclovine; ^{18}F-NaF: 18F-sodium fluoride; 68Ga-DOTA-(TATE, TOC): gallium-68-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-1-Nal3-octreotide; ^{68}Ga-PSMA: ^{68}Ga-PSMA: gallium-68-labeled

prostate-specific membrane antigen ligand with chelator HBED-CC; ^{99m}Tc: technetium-99m; ^{131}I: iodine-131; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine combination chemotherapy; Accu: accuracy/staging accuracy; AUC: area under the curve; $BEACOPP_{escalated}$: bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone escalated regimen; BMB: bone marrow biopsy; BMAM: bone marrow aspirate/biopsy; CeCT: contrast-enhanced computed tomography; CI: confidence interval; CRC: colorectal cancer; DCE-MRI: dynamic contrast-enhanced magnetic resonance imaging; DLBCL: diffuse large B-cell lymphoma; DOR: diagnostic odds-ratio; DWI-MRI: diffusion-weighted magnetic resonance imaging; ER+: estrogen receptor-positive; EUS: endoscopic ultrasound; FIGO: International Federation of Gynecology and Obstetrics; FDG: 2-fluoro-2-deoxy-D-glucose or fluorodeoxyglucose; FNAC: fine needle aspiration cytology; HER2+: human epidermal growth factor receptor 2 positive; HL: Hodgkin's lymphoma; IPS: international prognostic score; ISRT: involved site radiation therapy; MDCT: multi-detector row computed tomography; MRI: Magnetic Resonance Imaging; NA: not applicable/not available; NAC: neoadjuvant chemotherapy; NET: neuroendocrine tumour; NHL: non-Hodgkin lymphoma; NPV: negative predictive value; NSCLC: non-small cell lung cancer; OR: odds ratio; OS: overall survival; PALN: pelvic/para-aortic lymph node; PET: positron-emission tomography; PFS: progression-free survival; PPV: positive predictive value; SCLC: small cell lung cancer; Sens: sensitivity; SLN: sentinel lymph node; SSTR: somatostatin receptor; Spec: specificity; SPECT: single photon emission computed tomography; US: ultrasound

*$p<0.05$