PET Six-Month Monitoring Report 2018-2

Evidence from Primary Studies and Systematic Reviews and Recommendations from Clinical Practice Guidelines July to December 2018

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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 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 16th 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 2018 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

Seventy-five studies published between July and December 2018 met the inclusion criteria. A summary of the evidence from the 75 studies can be found in **Appendix 1: Summary of studies from July to December 2018**.

Breast Cancer

Five studies met the inclusion criteria [1-5]. FDG PET/CT using time-of-flight and point-spread function reconstruction detected axillary lymph node metastases in T1 breast carcinoma with 92.3% sensitivity and 88.2% specificity. Additionally, distant metastatic spread was found in 13.3% of patients [1]. In newly diagnosed locally advanced breast cancer, FDG PET/CT (97%) was shown to be more accurate than conventional imaging (84%) for detecting distant metastases. FDG PET/CT upstaged 24.6% of patients and downstaged 4.9% of patients as well as modified 37.7% of treatment plans [2]. Furthermore, the sensitivity (83.2% versus 69.8%, $p<0.001$), specificity (100% versus 76.1%, $p<0.001$), and accuracy (87.6% versus 71.5%, $p<0.001$) of PET/CT in detecting bone metastases were significantly higher than that of bone scintigraphy [3]. The use of FDG PET/CT to evaluate skin-sparing mastectomy [4] and to predict pathological response [5] after neoadjuvant chemotherapy appeared to be inferior to magnetic resonance imaging (MRI).

Epilepsy

Two studies met the inclusion criteria [6,7]. The integration of PET/MRI coregistration with electroclinical data enabled the correct localization of focal cortical dysplasia type 2 in 83% of patients. Furthermore, PET/MRI coregistration prevented unnecessary invasive monitoring in 14% of MRI-negative/doubtful patients and most MRI-positive patients [6]. In terms of patients achieving a complete remission of seizures after surgical resection, FDG PET/CT showed a sensitivity of 73% to 100% and FDG PET/MRI hybrid showed a sensitivity of 63% to 89% in identifying lesions that resulted in Engel's I outcome [7].

Esophageal Cancer

Three studies met the inclusion criteria [8-10]. FDG PET/CT was shown to be significantly more sensitive (82% versus 73%, $p=0.012$) and specific (91% versus 84%, $p=0.013$) than cervical ultrasonography in the evaluation of cervical lymph node metastases [8]. Similarly, a meta-analysis reported low sensitivity (pooled estimate, 65% to 66%) and moderate to high specificity (pooled estimate, 81% to 96%) for the detection of regional nodal metastases [9]. In the restaging of patients after neoadjuvant chemoradiotherapy, FDG PET/CT detected interval metastases with moderate sensitivity (74.7%) but high specificity (93.7%) and accuracy (91.6%) [10].

Gastrointestinal Cancer

Five studies met the inclusion criteria [11-15]. For the staging of patients with advanced gastric cancer, FDG PET/CT showed poor sensitivity (29.7% to 43%) but high specificity (92.2% to 100%) for evaluating lymph node involvement [11,12]. Furthermore, FDG PET/CT and contrast-enhanced CT were comparable in detecting distant metastases with both modalities preventing unnecessary laparoscopy and/or inappropriate surgical treatment in 24% and 22% of patients, respectively [11]. In patients with obstructing colorectal cancer, FDG PET/CT demonstrated suboptimal sensitivity (lesion-based, 25.3%; patient-based, 46.1%) for detecting colonic neoplasia [13]. In the diagnosis of extrahepatic metastases or local residual/recurrent hepatocellular carcinoma, a meta-analysis reported low sensitivity (pooled

estimate, 64%) but high specificity (pooled estimate, 95%) for FDG PET or PET/CT [14]. Results from another meta-analysis showed that preoperative staging with FDG PET or PET/CT can be useful in the evaluation of primary tumour (pooled sensitivity, 80.5%; pooled specificity, 69.8%) and lymph node metastases (pooled sensitivity, 51.6%; pooled specificity, 91.4%) in patients with cholangiocarcinoma and biliary carcinoma [15].

Genitourinary Cancer

Four studies met the inclusion criteria [16-19]. In the preoperative lymph node staging of patients with newly diagnosed bladder cancer, FDG PET/CT exhibited high specificity (pooled estimate, 92%) but low sensitivity (pooled estimate, 57%) [16]. In patients with newly diagnosed high-risk prostate cancer, FDG PET/CT appeared to be more sensitive than diffusion-weighted imaging (DWI)-MRI in the identification of nodal metastases (84.6% versus 46.2%) and more specific than bone scintigraphy with regards to the evaluation of bone metastases (92.0% versus 80.0%) [17]. In patients with clinical suspicion of disease relapse after surgical resection of renal cell carcinoma, FDG PET/CT had a higher positive predictive value (PPV) than contrast-enhanced CT for detecting distant (99.1% versus 87.5%, $p<0.05$), bone (100% versus 87.5%, $p<0.05$), and soft tissue metastases (100% versus 83.3%, $p<0.05$). Conversely, FDG PET/CT had a lower sensitivity than contrast-enhanced CT for detecting lung metastases (80.6% versus 100%, $p<0.05$) [18]. The authors from a large retrospective study concluded that FDG PET/CT could be considered as second stage imaging for indeterminate adrenal lesions due to a superior specificity over unenhanced CT [19].

Gynecologic Cancer

Four studies met the inclusion criteria [20-23]. In patients with inoperable, advanced-stage cervical cancer, the addition of FDG PET/CT to MRI resulted in 18.2% of patients receiving external beam radiotherapy with para-aortic extension and 8.5% more lymph node regions requiring a boost [20]. For patients who were suspected of recurrent cervical cancer based on clinical features, elevated levels of serum tumour marker, and MRI/CT imaging, FDG PET or PET/CT revealed recurrence in 97% (pooled sensitivity) of patients and modified 57% of the therapeutic plans [21]. Similarly in patients with endometrial cancer in first remission, surveillance imaging with FDG PET/CT detected recurrence with a higher PPV than CT (86.7% versus 54.3%, $p=0.02$) [22]. In the preoperative evaluation of uterine carcinosarcoma, FDG PET/CT demonstrated superior sensitivity to MRI in detecting pelvic (63.2% versus 26.3, $p=0.008$) and para-aortic (85.7% versus 42.9%, $p=0.014$) lymph node metastases. FDG PET/CT was also highly accurate (98.2%) in uncovering distant metastases [23].

Head and Neck Cancer

Eight studies met the inclusion criteria [24-31]. In the response assessment of patients with head and neck squamous cell carcinoma, FDG PET/CT within six months after chemoradiotherapy detected residual nodal disease with a pooled sensitivity of 85% and a pooled specificity of 93% [24]. Moreover, the use of a modified physiology-based criteria system (90.3%) improved the accuracy of identifying residual disease in comparison to the use of the Hopkins criteria (72.6%) [25]. In patients with nasopharyngeal carcinoma, PET/MRI showed similar sensitivity, but higher PPV (93.1%) than both MRI (78.8%) and PET/CT (83.3%) for the assessment of distant sites [26]. For non-metastatic cases, PET/CT led to upstaging in 7.2% of patients and downstaging in 2.6% of patients when compared with MRI-based tumour staging [27]. In the diagnosis and staging of patients with laryngeal carcinoma, contrast-enhanced dual-phase FDG PET/CT was more accurate than MRI/CT for detecting primary tumour (97.8% versus 66.7%, $p<0.001$) and nodal metastases (88.9% versus 66.7%, $p=0.006$) [28]. Likewise, FDG PET/CT was more sensitive (100% versus 78.9%, $p=0.016$) and accurate

(98.3% versus 85.5%, p=0.039) than contrast-enhanced CT for detecting distant site recurrences of salivary gland carcinoma. However, no significant differences were noted for detecting loco-regional recurrences between the two imaging modalities [29]. In the assessment of early oral squamous cell carcinoma, FDG PET/CT demonstrated limited clinical benefit in detecting cervical nodal metastases and synchronous cancers [30]. Also, the addition of FDG PET/CT did not improve the diagnosis of thyroid cancer in patients with fine-needle aspiration (FNA) biopsy-derived follicular neoplasm or atypia [31].

Hematologic Cancer

Seven studies met the inclusion criteria [32-38]. Compared with contrast-enhanced CT (86.6%), FDG PET/CT (100%) improved the overall accuracy for restaging and response assessment of patients with non-Hodgkin lymphoma. This led to the modification of treatment in 11.1% of patients [32]. Alternatively, results from another prospective study showed that FDG PET/CT for response evaluation possessed a low PPV (62.5%), due to significant proportion of false-positive findings [33]. For interim-PET response assessment of patients with diffuse large B-cell lymphoma after receiving two or three cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone, using the cut-off Deauville score of 5 instead of 4/5 to define positivity, improved the PPV (from 34.9% to 71.4%) of predicting progression [34]. The use of FDG PET/CT did not offer any advantage over whole-body MRI (initial staging) [35] or contrast-enhanced CT (asymptomatic recurrence detection) [36] in patients with Hodgkin and non-Hodgkin lymphoma. However, FDG PET/CT (accuracy, 96.1%) was shown to be superior to contrast-enhanced CT (accuracy, 87.0%) for detecting extranodal extension [37]. In patients with multiple myeloma, FDG PET/CT was less sensitive (75% versus 94%, p=0.0039) than whole-body MRI in diagnosing active myelomatous tissue before treatment but more specific (86% versus 43%, p=0.0081) than whole-body MRI in detecting residual myelomatous tissue after treatment [38].

Melanoma

Two studies met the inclusion criteria [39,40]. In the post-treatment surveillance of melanoma, FDG PET/CT can detect recurrence in asymptomatic patients with high sensitivity (100%) and specificity (93.4%). In patients with clinical suspicion, a positive FDG PET/CT scan can unequivocally confirm recurrence (PPV, 100%) [39]. In the pretreatment work-up of Merkel cell carcinoma, FDG PET/CT upstaged 25.9% of patients by uncovering distant metastases or regional nodes not seen on contrast-enhanced CT. Other non-related malignancies and benign conditions were identified in 6.9% of patients. Consequently, FDG PET/CT influenced the treatment decision in 27.6% of patients [40].

Neuro-oncology

One study met the inclusion criteria [41]. FDG PET/CT (82.0%), ^{99m}Tc methionine single photon emission computed tomography/CT (79.4%) and contrast-enhanced-MRI (76.9%) showed similar diagnostic accuracy for evaluating recurrent glioma.

Non-FDG Tracers

Thirteen studies met the inclusion criteria [42-54]. Two studies evaluated the impact of ^{11}C-Choline PET/CT on prostate cancer. In radiation therapy planning, ^{11}C-Choline PET/CT caused a change in management in 48.9% of patients [42]. In the setting of biochemical relapse with serum prostate-specific antigen level below 1 ng/ml, therapy planning was altered in 16% of patients [43]. ^{11}C-Choline PET or PET/CT was also evaluated in glioma where it can differentiate tumour relapse from radiation necrosis with a pooled sensitivity of 87% and a pooled specificity of 82% [44]. PET or PET/CT imaging with ^{68}Ga-DOTA-

TATE/NOC/TOC/LAN was studied in two meta-analyses, one in recurrent medullary thyroid carcinoma and the other in metastatic pheochromocytoma and paraganglioma. ^{68}Ga-somatostatin receptor PET or PET/CT detected recurrence of medullary thyroid carcinoma at a poor rate (63.5%) [45] but outperformed FDG PET/CT in the localization of pheochromocytoma and paraganglioma [46]. One prospective study looked at ^{18}F-FACBC PET/CT in recurrent prostate cancer. Compared with multiparametric MRI, ^{18}F-FACBC PET/CT had a higher sensitivity but lower specificity for the determination of disease status in the prostate. For the detection of extraprostatic disease, ^{18}F-FACBC PET/CT had better overall diagnostic performance [47]. Several studies evaluated ^{68}Ga-PSMA PET/CT in prostate cancer. In primary staging, the sensitivity (33% to 92%) and specificity (67% to 100%) of ^{68}Ga-PSMA PET/CT varied greatly in the literature [48]. One retrospective study did show that ^{68}Ga-PSMA PET/CT provided better sensitivity (81.1% versus 64.8%, $p<0.001$) than multiparametric MRI in lesion localization [49]. For biochemical recurrence, ^{68}Ga-PSMA PET/CT findings led to a change in treatment strategy in 21.7% to 63.5% of patients [50-52]. Additionally, both ^{68}Ga-PSMA PET/CT and ^{18}F-NaF PET/CT performed superiorly to diffusion weighted MRI in diagnosing bone metastases [53]. In patients with breast cancer, ^{18}F-NaF PET/CT detected bone metastases with an accuracy of 93% and altered management in 25.4% of cases [54].

Non-Small Cell Lung Cancer and Other Lung Cancer

Eleven studies met the inclusion criteria [55-65]. FDG PET/CT is valuable for the differential diagnosis of solitary pulmonary nodules [55,56], even in patients with idiopathic pulmonary fibrosis [57]. However, specificity (34.7%) of FDG PET/CT is greatly reduced when characterizing solitary pulmonary nodules in regions known to be endemic for infectious diseases due to a high false-positive rate [58]. For the evaluation of patients with an anterior mediastinal mass, FDG PET/CT displayed a high PPV (90.1%) with a positive scan, but is unable to reliably rule out malignancy when the result is negative (NPV, 42.4%) [59]. In non-small cell lung cancer (NSCLC), FDG PET/CT showed poor overall sensitivity (33.8% to 53.8%) and moderate to high specificity (76.6% to 93.8%) for lymph node staging [60,61]. FDG PET/CT demonstrated better diagnostic results than CT, but both imaging modalities were inferior to endobronchial ultrasound-guided FNA and endoscopic ultrasound-guided FNA [61]. On the other hand, FDG PET/CT was more useful for distant metastasis staging (pooled sensitivity, 81%; pooled specificity, 96%) [62]. As for the assessment of recurrence, FDG PET/CT was found to be less specific and accurate than FDG PET/MRI (specificity, 81.0% versus 96.2%, $p<0.05$; accuracy, 84.4% versus 96.9%, $p<0.05$) and MRI with (specificity, 81.0% versus 100%, $p<0.05$; accuracy, 84.4% versus 97.9%, $p<0.05$) and without DWI (specificity, 81.0% versus 100%, $p<0.05$; accuracy, 84.4% versus 94.8%, $p<0.05$) [63]. In patients with NSCLC or small cell lung cancer (SCLC), FDG PET/CT was highly sensitive (99.2%) in detecting mediastinal lymph node metastases, but suffered from very poor specificity (13.0%) [64]. Similarly, FDG PET/CT offered minimal additional value to neck ultrasound in the staging and management of patients with suspected lung cancer who have bulky mediastinal lymphadenopathy [65].

Pancreatic Cancer

Three studies met the inclusion criteria [66-68]. FDG PET/CT was significantly more accurate than contrast-enhanced CT (68.6% versus 48.5%, $p<0.001$) in predicting lymph node metastases in resectable patients [66]. For the restaging of patients with clinical or imaging suspicion of disease progression, FDG PET/CT displayed a sensitivity, specificity, and accuracy of 85%, 84%, and 84%, respectively. Findings from FDG PET/CT influenced the therapeutic management in 30.8% of cases [67]. Similarly, the authors of a meta-analysis reported that postoperative FDG PET/CT could be of additional value in the case of suspected recurrence with equivocal or negative contrast-enhanced CT findings [68].

Pediatric Cancer

Two studies met the inclusion criteria [69,70]. In comparison with bone marrow biopsy, FDG PET/CT allowed for more accurate detection of bone marrow involvement in both non-Hodgkin lymphoma (100% versus 66.7%, p=0.001) and Hodgkin lymphoma (98.2% versus 82.3%, p=0.001) patients [69,70].

Sarcoma

Three studies met the inclusion criteria [71-73]. FDG PET/CT with maximum standardized uptake value of 8.2 achieved high specificity (92.9%) but poor sensitivity (43.8%) and accuracy (52.1%) for differentiating between malignant and benign bone and soft tissue lesions [71]. In patients with osteosarcoma, FDG PET/CT was found to be comparable to ^{99m}Tc-MDP bone scan in predicting histologic response to neoadjuvant chemotherapy [72]. Additionally, a meta-analysis reported high sensitivity and specificity for FDG PET or PET/CT in detecting bone metastases (pooled estimate, 91% and 98%, respectively) and recurrence (pooled estimate, 93% and 90%, respectively) of Ewing sarcoma family of tumours [73].

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 prospective case series by Ferdova et al. [1] is small with only 30 patients. The authors did not compare PET/CT to conventional distant staging investigations to determine whether PET/CT was superior to standard imaging.

In the prospective case series of 61 patients [2], all received both PET/CT and conventional staging bone scan and CT chest/abdomen/pelvis, as well as blood work. There appears to be a higher rate of detection of distant metastases with PET/CT; however, since each patient had all investigations without blinding, it would be difficult to avoid bias. Given that a prospective clinical trial is ongoing evaluating PET/CT versus conventional bone scan and CT chest/abdomen/pelvis (PET-ABC), determining the impact of PET/CT staging for advanced breast cancer should be deferred until the completion of this ongoing multi-centred trial.

The retrospective data from Demir et al. [3] would need to be confirmed prospectively in a larger cohort with clinical outcome implications prior to confirming the incremental value of PET/CT in breast cancer staging, which is expected to be determined in the PET-ABC trial.

The use of FDG PET/CT to evaluate skin involvement was evaluated in 30 patients by comparing serial PET/CT and MRI to determine whether patients would be eligible for skin-sparing mastectomy [4]. This study demonstrated that there was no difference in detecting residual histologically proven disease in skin after neoadjuvant chemotherapy with either the PET/CT or MRI. This finding is more likely to be related to a lack of power given the small sample size and no determinations on the clinical utility of staging can be made with this study.

Finally, a meta-analysis was performed to contrast MRI and PET/CT to predict pathological response to neoadjuvant chemotherapy and found 13 studies that compared the two [5]. In this study, MRI was found to be more sensitive at predicting complete pathological response, while PET/CT was found to be more specific. The authors suggest that MRI remains superior to PET/CT for assessing residual disease after neoadjuvant chemotherapy.

In summary, these studies suggest that there is a role for PET/CT in distant staging for locally advanced disease; however, the ongoing prospective multi-centred trial will be most informative in determining the incremental benefit of PET/CT staging with information

regarding clinical impact for patients. There are insufficient data to suggest that PET/CT is superior for axillary staging, response to neoadjuvant chemotherapy, or assessment of skin involvement over standard MRI.

Epilepsy

Current Registry Indication

- For patients with medically intractable epilepsy being assessed for epilepsy surgery.

Current Recommendations for the Utilization of PET in Epilepsy

- ^{18}F-FDG PET is recommended for the presurgical evaluation of adult and pediatric patients with medically intractable focal or partial epilepsy in the setting of a comprehensive epilepsy surgery program within a Regional Epilepsy Surgery Centre of Excellence.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of ^{18}F-FDG PET in the detection of cortical malformations in patients with intractable infantile spasms when MRI or CT fails to show structural abnormalities.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of ^{18}F-FDG PET/MRI coregistration in the presurgical evaluation of patients with medically intractable epilepsy.

Reviewer's Comments (Dr. Jorge Burneo)

The current recommendations for the utilization of PET/CT in epilepsy remain valid and no changes are required. The two studies identified were not RCTs and thus the level of evidence is weak.

Esophageal Cancer

Current Insured Indications

- 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 Indications (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 Registry Indication (Anal Canal Cancer)

- For the initial staging of patients with T2-T4 squamous cell carcinoma of the anal canal with or without evidence of nodal involvement on conventional anatomical imaging.

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.

Current Recommendations for the Utilization of PET/CT in Anal Canal Cancer

- PET or PET/CT may provide added benefit to the initial staging of patients with T2-4 squamous carcinoma of the anal canal with or without evidence of nodal involvement on anatomical imaging. However, no strong evidence is currently available to justify its use as part of routine investigation, and access should be restricted to the registry-type setting.
- There is insufficient evidence to recommend the use of PET or PET/CT in the assessment of treatment response.
- There is insufficient evidence to recommend the use of PET or PET/CT for evaluation of suspected or proven recurrence.

Reviewer's Comments

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

Genitourinary Cancer

Current Insured Indications (Germ Cell Tumours)

- Where recurrent disease is suspected on the basis of elevated tumour marker(s) (beta human chorionic gonadotropin and/or alpha fetoprotein) and standard imaging tests are negative; or where persistent disease is suspected on the basis of the presence of a residual mass after primary treatment for seminoma when curative surgical resection is being considered.

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. It is worthwhile to note that the American Society of Clinical Oncology is leading a new evidence-based guideline on imaging for advanced 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

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

Head and Neck Cancer

Current Insured Indication (Unknown Primary)

- For the evaluation of metastatic squamous cell carcinoma in neck nodes when the primary disease site is unknown after standard radiological and clinical investigation.

Current Insured Indication (Nasopharyngeal Cancer)

- For the baseline staging of nasopharyngeal cancer.

Current Insured Indication (Thyroid Cancer)

- Where recurrent or persistent disease is suspected on the basis of an elevated and/or rising tumour markers (e.g., thyroglobulin) with negative or equivocal conventional imaging work-up.

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. The only area that has some potential for affecting indications is disease recurrence in head and neck squamous cell malignancies. The evidence presented is insufficient to result in a change in practice as this point but this is an area we should continue to monitor closely. The difficulty here may be different outcome measures and patient population selection in these different studies. It would be important to know whether any of this is generalizable to the Ontario practice. It is not immediately clear to me how much and at what point we do surveillance on patients post curative-intent therapy and the downstream management implications.

Hematologic Cancer

Current Registry Indication (Lymphoma)

- For the staging of patients with Hodgkin or non-Hodgkin lymphoma.

Current Registry Indications (Multiple Myeloma/Plasmacytoma)

- For patients with presumed solitary plasmacytoma who are candidates for curative intent radiotherapy; or for work-up of patients with smoldering myeloma and negative or equivocal skeletal survey; or for baseline staging and/or response assessment of nonsecretory or oligosecretory myeloma.

Current Insured Indications (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 Hodgkin lymphoma following two or three cycles of chemotherapy when chemotherapy curative therapy is being considered.

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 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.

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. The data from Poulsen et al. [40] do support staging for high-risk patients with Merkel cell carcinoma with PET/CT but this is not a standard indication.

Neuro-oncology

Current Recommendations for the use of PET/CT in Neuro-oncology

- PET is not recommended for the determination of diagnosis or grading in gliomas.
- A recommendation cannot be made for or against the use of PET for the assessment of treatment response in gliomas due to insufficient evidence.
- A recommendation cannot be made for or against the use of PET or PET/CT in the assessment of patients with recurrent gliomas due to insufficient evidence.

Reviewer's Comments (Dr. Amit Singnurkar)

The current recommendations for the utilization of PET/CT in neuro-oncology remain valid and no changes are required.

Non-FDG Tracers

Current Recommendations for Gallium-68 PET/CT in Neuroendocrine Tumours

- ^{68}Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT is recommended for the initial diagnosis of adult patients with clinical (e.g., signs, symptoms) and biochemical (e.g., markers) suspicion of neuroendocrine tumours but for whom conventional imaging is negative or equivocal or for whom biopsy is not easily obtained.
- ^{68}Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT is recommended for the staging of adult patients with localized primary neuroendocrine tumours and/or limited metastasis where definitive surgery is planned.
- ^{68}Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT is recommended for determining somatostatin receptor status and suitability for peptide receptor radionuclide therapy.
- ^{68}Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT is recommended for the staging of adult patients with neuroendocrine tumours where detection of occult disease will alter the treatment options and decision making.
- There is no recommendation regarding the use of ^{68}Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT in the assessment of treatment response for neuroendocrine tumours.
- There is no recommendation regarding the use of ^{68}Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT in the routine surveillance of neuroendocrine tumours.

Reviewer's Comments (Dr. Amit Singnurkar)

The current recommendations for the utilization of PET/CT with non-FDG tracers remain valid and no changes are required.

NSCLC and Other Lung Cancer

Current Insured Indications

- Solitary pulmonary nodule:
    - For a semi-solid or solid 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:
    - For initial staging of patients with NSCLC (clinical stage I-III) who are being considered for potentially curative therapy; or for restaging of patients with locoregional recurrence, after primary treatment, who are being considered for definitive salvage therapy.

- SCLC:
    - For initial staging of patients with limited-disease 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.

Pancreatic Cancer

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 – Hodgkin lymphoma and non-Hodgkin lymphoma
    - 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 study findings appear consistent with prior work. Staging for lymphoma seems to be the most relevant indication.

Sarcoma

Current Registry Indication

- Diagnosis (plexiform neurofibromas): for patients with suspicion of malignant transformation of plexiform neurofibromas.
- Initial Staging: for patients with high grade (≥ Grade 2), or ungradable, soft tissue or bone sarcomas, with negative or equivocal findings for nodal or distant metastases on conventional imaging, prior to curative intent therapy.
- Re-staging: for patients with history of treated sarcoma with suspicion of, or confirmed, recurrent sarcoma (local recurrence or limited metastatic disease) being considered for curative intent or salvage therapy.

Reviewer's Comments

A review was not completed by a clinical expert in sarcoma.

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Appendix 1: Summary of studies from July to December 2018.

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Breast Cancer								
Ferdova et al, 2018 [1]	Prospective	30 patients (T1 breast carcinoma)	FDG PET/CT	NA	Histology	**Axillary lymph node metastases** Sens: 92.3% Spec: 88.2% PPV: 85.7% NPV: 93.8%	NA	PET/CT detected distant metastatic spread in 13.3% (4/30) of patients.
Gajjala et al, 2018 [2]	Prospective	61 patients who underwent staging (biopsy-proven, unilateral, newly diagnosed locally advanced breast cancer)	FDG PET/CT	Serum chemistry, mammogram, ^{99m}Tc-MDP bone scan, US of the abdomen and pelvis, CeCT of the chest and upper abdomen	Histopathology, biopsy, FNAC, other imaging studies	**Distant metastases** Sens: 95% Spec: 98% PPV: 95% NPV: 98% Accu: 97%	**Distant metastases** Sens: 65% Spec: 93% PPV: 81% NPV: 84% Accu: 84%	PET/CT upstaged 24.6% (15/61) of patients (8—IIIA/B to IIIC, 7—IIIA/B to IV) and downstaged 4.9% (3/61) of patients (IV to III). PET/CT altered treatment plan in 37.7% (23/61) of patients.
Demir et al, 2017 [3]	Retrospective	50 patients (breast cancer)	FDG PET/CT	Bone scintigraphy	Histopathology, clinical or imaging follow-up	**Bone metastases** Sens: 83.2%* Spec: 100%* Accu: 87.6%*	**Bone metastases** Sens: 69.8%* Spec: 76.1%* Accu: 71.5%*	NA
Malya et al, 2018 [4]	Prospective	30 patients treated with neoadjuvant chemotherapy (locally advanced breast cancer)	FDG PET/CT	MRI	Histopathology	**Predicting skin involvement (pre-neoadjuvant chemotherapy)** Sens: 60% Spec: 80% PPV: 85.7% NPV: 50% **(post-neoadjuvant chemotherapy)** Sens: 12.5% Spec: 92.6% PPV: 66.6% NPV: 48.1%	**Predicting skin involvement (pre-neoadjuvant chemotherapy)** Sens: 100% Spec: 10% PPV: 68.9% NPV: 100% **(post-neoadjuvant chemotherapy)** Sens: 62.5% Spec: 85.7% PPV: 83.3% NPV: 66.6%	NA
Li et al, 2018 [5]	Meta-analysis	13 studies (575 patients who underwent MRI and 618 patients who underwent PET/CT after preoperative	FDG PET/CT	MRI	Pathology	**Predicting pathologic response** Pooled Sens: 77% Pooled Spec: 78% AUC: 0.84	**Predicting pathologic response** Pooled Sens: 88% Pooled Spec: 69% AUC: 0.88	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		neoadjuvant chemotherapy)						
Epilepsy								
Desarnaud et al, 2018 [6]	Retrospective	103 patients who underwent surgery for drug-resistant epilepsy (focal cortical dysplasia type 2)	FDG PET/MRI coregistration	Video-EEG, MRI	SEEG, pathology, Engel's classification	**Localization** ***MRI-positive*** Sens: 82% ***MRI-doubtful*** Sens: 87% ***MRI-negative*** Sens: 81% ***All patients*** Sens: 83%	NA	PET/MRI coregistration allowed invasive monitoring to be avoided in 14% of MRI-negative/doubtful patients and most MRI-positive patients.
Oldan et al, 2018 [7]	Retrospective	74 patients who underwent presurgical evaluation (refractory focal onset epilepsy)	FDG PET/CT or PET/MRI hybrid	Clinical semiology, video-EEG, MRI	Engel's classification	**Engel's I-III** ***FDG PET/CT*** Sens: 68-71% Spec: 25-33% PPV: 83-88% NPV: 13-14% Accu: 64% ***FDG PET/MRI hybrid*** Sens: 61-63% Spec: 24-50% PPV: 77-92% NPV: 13-14% Accu: 55-60% **Engel's I** ***FDG PET/CT*** Sens: 73-100% Spec: 25-33% PPV: 57-63% NPV: 40-100% Accu: 58-68% ***FDG PET/MRI hybrid*** Sens: 63-89% Spec: 29-33% PPV: 40-67% NPV: 40-67% Accu: 47-67%	NA	NA
Esophageal								
Goense et al, 2018 [8]	Retrospective	163 patients (newly diagnosed oesophageal cancer)	FDG PET/CT	Cervical ultrasonography	Cytopathology, clinical follow-up	**Cervical lymph node metastases** Sens: 82%* Spec: 91%*	**Cervical lymph node metastases** Sens: 73%* Spec: 84%*	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						PPV: 60% NVP: 97%	PPV: 42% NVP: 95%	
Jiang et al, 2018 [9]	Meta-analysis	19 studies (1089 patients with esophageal squamous cell carcinoma)	FDG PET/CT	NA	Pathology	**Regional lymph node metastases (patient-based)** Pooled Sens: 65% Pooled Spec: 81% Pooled +LR: 3.4 Pooled –LR: 0.44 Pooled DOR: 8 AUC: 0.80 **(nodal-based)** Pooled Sens: 66% Pooled Spec: 96% Pooled +LR: 15.2 Pooled –LR: 0.36 Pooled DOR: 43 AUC: 0.92	NA	NA
Goense et al, 2018 [10]	Retrospective	783 patients who underwent staging before and after neoadjuvant chemoradiotherapy (non-metastatic potentially resectable esophageal cancer)	FDG PET/CT	EUS, endoscopy	Histology, clinical and imaging follow-up	**Interval metastasis** Sens: 74.7% Spec: 93.7% PPV: 59.6% NPV: 96.7% Accu: 91.6%	NA	NA
Gastrointestinal Cancer								
Perlaza et al, 1018 [11]	Prospective	50 patients (locally advanced gastric adenocarcinoma)	FDG PET/CT	CeCT	Histopathology, imaging follow-up	**N staging** Sens: 43% Spec: 100% **Metastatic disease** Sens: 68% Spec: 100%	**N staging** Sens: 77% Spec: 57% **Metastatic disease** Sens: 64% Spec: 93%	PET/CT and CeCT led to the avoidance of unnecessary laparoscopy and/or inappropriate surgical treatment in 24% and 22% of metastatic patients, respectively.
Kwon et al, 2018 [12]	Retrospective	168 patients who underwent curative surgical resection (advanced gastric cancer)	FDG PET/CT	NA	Histopathology, clinical and/or imaging follow-up	**Primary tumours (pT3-4)** Sens: 73.8% Spec: 38.1% PPV: 78.2% NPV: 32.7% **Metastatic lymph nodes (pN2-3)** Sens: 29.7% Spec: 92.2% PPV: 81.1%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						NPV: 52.6%		
Hojo et al, 2018 [13]	Retrospective	93 patients who underwent surgical resection (obstructing CRC)	FDG PET/CT	Colonoscopy	Pathology	**Colonic neoplasia (lesion-based)** Sens: 25.3% PPV: 77.8% **(patient-based)** Sens: 46.1% Spec: 92.6% PPV: 81.8%	NA	NA
Liao et al, 2018 [14]	Meta-analysis	11 studies (572 patients hepatocellular carcinoma)	FDG PET or PET/CT	NA	Histopathology, clinical and imaging follow-up	**Extrahepatic metastases or local/residual recurrent disease** Pooled Sens: 64% Pooled Spec: 95% Pooled +LR: 5.32 Pooled –LR: 0.39 AUC: 0.885 Q index: 0.815	NA	NA
Hu et al, 2018 [15]	Meta-analysis	18 studies (1037 patients who underwent preoperative staging of cholangiocarcinoma)	FDG PET or PET/CT	NA	NA	**Primary tumour** Pooled Sens: 80.5% Pooled Spec: 69.8% Pooled DOR: 9.34 AUC: 0.864 **Lymph node metastases** Pooled Sens: 51.6% Pooled Spec: 91.4% Pooled DOR: 11.34 AUC: 0.858 **Distant metastases** Pooled DOR: 47.68 AUC: 0.972	NA	NA
Genitourinary Cancer								
Ha et al, 2018 [16]	Meta-analysis	14 studies (785 patients with newly diagnosed bladder cancer)	FDG PET/CT	NA	Histopathology, clinical follow-up	**Preoperative lymph node staging** Pooled Sens: 57% Pooled Spec: 92% Pooled +LR: 7.4 Pooled –LR: 0.47	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Pooled DOR: 16 AUC: 0.72		
Shen et al, 2018 [17]	Retrospective	67 patients (newly diagnosed high-risk prostate cancer)	FDG PET/CT	DWI-MRI, bone scintigraphy	Pathology, clinical and imaging follow-up	**Nodal metastases** Sens: 84.6% Spec: 96.3% PPV: 91.7% NPV: 92.9% **Bone metastases** Sens: 90.4% Spec: 92.0% PPV: 90.9% NPV: 92.0%	**Nodal metastases** ***DWI-MRI*** Sens: 46.2% Spec: 100% PPV: 100% NPV: 79.4% **Bone metastases** ***Bone scintigraphy*** Sens: 90.4% Spec: 80.0% PPV: 79.2% NPV: 90.9%	NA
Elahmadawy et al, 2018 [18]	Retrospective	96 patients with clinical suspicion of disease relapse after surgical resection (histologically proven renal cell carcinoma)	FDG PET/CT	CeCT	Histopathology, clinical and imaging follow-up	**Local recurrence** Sens: 96.0% Spec: 100% PPV: 100% NPV: 98.6% Accu: 99.0% **Distant metastases** Sens: 92.5% Spec: 99.6%* PPV: 99.1%* NPV: 96.7% Accu: 97.4% **Nodal metastases** Sens: 100% Spec: 98.2% PPV: 97.6% NPV: 100% Accu: 99.0% **Lung metastases** Sens: 80.6%* Spec: 100% PPV: 100% NPV: 91.5% Accu: 93.8% **Bone metastases** Sens: 100% Spec: 100% PPV: 100%* NPV: 100% Accu: 100% **Soft tissue**	**Local recurrence** Sens: 100% Spec: 98.6% PPV: 96.2% NPV: 100% Accu: 99.0% **Distant metastases** Sens: 93.3% Spec: 94.0%* PPV: 87.5%* NPV: 96.9% Accu: 93.8% **Nodal metastases** Sens: 92.5% Spec: 92.9% PPV: 90.2% NPV: 94.5% Accu: 92.7% **Lung metastases** Sens: 100%* Spec: 93.8% PPV: 88.6% NPV: 100% Accu: 95.8% **Bone metastases** Sens: 93.3% Spec: 97.5% PPV: 87.5%* NPV: 98.8% Accu: 96.9%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						metastases Sens: 91.2% Spec: 100% PPV: 100%* NPV: 95.4% Accu: 96.9%	**Soft tissue metastases** Sens: 88.2% Spec: 90.5% PPV: 83.3%* NPV: 93.4% Accu: 90.6%	
Adrenal Cancer								
Delivanis et al, 2018 [19]	Retrospective	379 patients (adrenal nodules)	FDG PET/CT	CT	Histopathology, histology	**Adrenal malignancy (ALR SUV_{max}>1.8)** Sens: 87% Spec: 84% PPV: 85% NPV: 86% **(Adrenal SUV_{max}>4.5)** Sens: 87% Spec: 69% PPV: 76% NPV: 83%	**Adrenal malignancy (HU>10)** Sens: 100% Spec: 33% PPV: 72% NPV: 100%	NA
Gynecologic Cancer								
Adam et al, 2018 [20]	Retrospective	88 patients undergoing (chemo)radiation with curative intent (advanced uterine cervical cancer, FIGO IB-IVA)	FDG PET/CT	MRI	Multidisciplinary tumour board, clinical follow-up	NA	NA	The addition of PET/CT to MRI resulted in a para-aortal extension of the radiotherapy field in 18.2% (16/88) of patients, or 8.5% (60/704) more lymph node regions requiring a boost.
Zhou et al, 2018 [21]	Meta-analysis	17 studies (707 patients with suspected recurrent cervical cancer)	FDG PET or PET/CT	CT/MRI	Histopathology, clinical follow-up	**Recurrence** Pooled Sens: 97% Pooled Spec: 81% AUC: 0.94	NA	PET or PET/CT modified 57% of the therapeutic plans.
Alabed et al, 2018 [22]	Retrospective	128 patients in first remission after treatment who underwent surveillance imaging (endometrial cancer)	FDG PET/CT	CT, MRI	Biopsy, imaging follow-up	**Recurrence** Sens: 92.9% Spec: 93.8% PPV: 86.7%* NPV: 96.8%	**Recurrence** ***CT*** Sens: 91.9% Spec: 91.2% PPV: 54.3%* NPV: 99.0% ***MRI or MRI+CT*** Sens: 100% Spec: 92.3% PPV: 33.3%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
							NPV: 100%	
Kim et al, 2018 [23]	Retrospective	54 patients who underwent preoperative staging (uterine carcinosarcoma)	FDG PET/CT	MRI	Pathology, imaging follow-up	**Pelvic lymph node metastases** Sens: 63.2%* Spec: 100% PPV: 100% NPV: 83.3% Accu: 87.0% **Para-aortic lymph node metastases** Sens: 85.7%* Spec: 90.0% PPV: 75.0% NPV: 94.7% Accu: 88.9% **Peritoneal seeding metastases** Sens: 59.4% Spec: 100% PPV: 100% NPV: 62.9% Accu: 75.9% **Distant metastases** Sens: 100% Spec: 97.8% PPV: 88.9% NPV: 100% Accu: 98.2%	**Pelvic lymph node metastases** Sens: 26.3%* Spec: 100% PPV: 100% NPV: 71.4% Accu: 74.1% **Para-aortic lymph node metastases** Sens: 42.9%* Spec: 97.5% PPV: 85.7% NPV: 83.0% Accu: 83.3% **Peritoneal seeding metastases** Sens: 50.0% Spec: 100% PPV: 100% NPV: 57.9% Accu: 70.4%	NA
Head and Neck Cancer								
Helsen et al, 2018 [24]	Meta-analysis	20 studies (1293 patients with head and neck squamous cell carcinoma treated with radiotherapy with or without chemotherapy or targeted agents)	FDG PET/CT	NA	Pathology, clinical follow-up	**Residual/recurrent nodal disease** Pooled Sens: 85% Pooled Spec: 93% Pooled +LR: 12.4 Pooled –LR: 0.16 Pooled DOR: 76 AUC: 0.94	NA	NA
Huang et al, 2018 [25]	Retrospective	62 patients who received concurrent chemoradiation therapy (advanced head and neck squamous cell carcinoma)	FDG PET/CT	NA	Histology	**Residual disease** ***Hopkins criteria*** Sens: 91.1% Spec: 50.0% PPV: 68.9% NPV: 82.3% Accu: 72.6% ***Physiology-based***	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						criteria Sens: 88.2% Spec: 92.9% PPV: 93.8% NPV: 86.7% Accu: 90.3%		
Chan et al, 2018 [26]	Prospective	113 patients who underwent primary tumor staging (biopsy-proven nasopharyngeal carcinoma)	FDG PET/CT, FDG PET/MRI	MRI	Histopathology, clinical and imaging follow-up	**Nodal metastases (level-based)** ***PET/CT*** Sens: 90.9% Spec: 98.3% Accu: 96.3% ***PET/MRI*** Sens: 99.5% Spec: 99.2% Accu: 99.3% **Distant metastases (lesion-based)** ***PET/CT*** Sens: 83.3% Spec: 98.8% PPV: 83.3% NPV: 98.8% Accu: 97.8% ***PET/MRI*** Sens: 90.0% Spec: 99.5% PPV: 93.1% NPV: 99.3% Accu: 98.9%	**Nodal metastases (level-based)** Sens: 94.2% Spec: 99.6% Accu: 98.2% **Distant metastases (lesion-based)** Sens: 86.7% Spec: 98.3% PPV: 78.8% NPV: 99.0% Accu: 97.6%	NA
Peng et al, 2017 [27]	Retrospective	470 patients treated with intensity-modulated radiotherapy (newly diagnosed, non-metastatic nasopharyngeal carcinoma)	FDG PET/CT	MRI	Pathology, imaging follow-up	NA	NA	PET/CT led to upstaging in 7.2% (34/470) of patients and downstaging in 2.6% (12/470) of patients.
Tatar et al, 2018 [28]	Retrospective	45 previously untreated patients (laryngeal carcinoma)	FDG PET/CT	CT/MRI	Histopathology, clinical and imaging follow-up	**Primary tumour** Sens: 100% Accu: 97.8%* **Nodal metastases** Sens: 100% Spec: 84.6% Accu: 88.9%* **TNM staging**	**Primary tumour** Sens: 93.3% Accu: 66.7%* **Nodal metastases** Sens: 100% Spec: 69.2% Accu: 66.7%* **TNM staging**	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Accu: 86.7%*	Accu: 46.7%*	
Lee et al, 2018 [29]	Retrospective	58 patients who underwent restaging after definitive treatment (recurrent salivary gland carcinoma)	FDG PET/CT	CeCT	Histopathology, imaging follow-up	**Local recurrence** Sens: 82.4% Spec: 95.1% PPV: 87.5% NPV: 92.9% Accu: 91.4% **Regional recurrence** Sens: 88.2% Spec: 95.1% PPV: 88.2% NPV: 95.1% Accu: 93.1% **Distant site recurrence** Sens: 100%* Spec: 95.0% PPV: 97.4% NPV: 100% Accu: 98.3%*	**Local recurrence** Sens: 94.1% Spec: 97.6% PPV: 94.1% NPV: 97.6% Accu: 96.6% **Regional recurrence** Sens: 76.5% Spec: 95.1% PPV: 86.7% NPV: 90.7% Accu: 89.7% **Distant site recurrence** Sens: 78.9%* Spec: 95.0% PPV: 96.8% NPV: 70.4% Accu: 85.5%*	NA
Yamaga et al, 2018 [30]	Retrospective	205 patients (early oral squamous cell carcinoma, cT1-2N0M0)	FDG PET/CT	Clinical examination, CT of the head and neck and chest, MRI, cervical US	Pathology, clinical follow-up	**Cervical nodal metastases** Sens: 32.3% Spec: 77.6% Accu: 70.7%	NA	PET/CT detected 8 (6.8%) synchronous cancers but missed 6 (2.9%) synchronous cancers.
Nguyen et al, 2018 [31]	Prospective	108 patients planned for surgery (FNAB-derived follicular neoplasm or atypia)	FDG PET/CT	Clinical examination, US	Histology	**Diagnosis of thyroid cancer** Sens: 79% Spec: 32% PPV: 31% NPV: 79%	NA	NA
Hematologic Cancer								
Elshafey et al, 2018 [32]	Prospective	45 patients who underwent treatment response assessment after 4 cycles of chemotherapy (NHL)	FDG PET/CT	CeCT	Follow-up	**Restaging and response assessment** Sens: 97.7% Spec: 66.6% PPV: 97.7% NPV: 66.6% Accu: 100%	**Restaging and response assessment** Sens: 82.2% Spec: 66.6% PPV: 97.7% NPV: 20.0% Accu: 86.6%	PET/CT modified the treatment in 11.1% (5/45) of patients (2—added involved-field radiation, 2—reinforced chemotherapy protocol, 1—added stem cell implantation).
Radhakrishnan et al, 2018 [33]	Prospective	17 patients who underwent interim response, end-of-therapy response	FDG PET/CT	NA	Histopathology	**Residual disease** PPV: 62.5%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		and recurrence assessment (pathologically proven NHL)						
Kim et al, 2018 [34]	Retrospective	150 patients who underwent interim response assessment after 2 or 3 cycles of R-CHOP and end of treatment response assessment (DLBCL)	FDG PET/CT	NA	Clinical and imaging follow-up	**Prediction of progression (interim assessment)** ***DC with 4 and 5 as positive*** Sens: 38.5% Spec: 74.8% PPV: 34.9% NPV: 77.6% AUC: 0.57 ***DC with 5 as positive*** Sens: 25.6% Spec: 96.4% PPV: 71.4% NPV: 78.7% AUC: 0.61	NA	With DC score of 4 or 5 as positive, there was no significant difference in 2-year PFS between patients with negative interim-PET and those with positive interim-PET (77.6% vs. 65.1%, p=0.069). With DC score of 5 as positive, patients with positive interim-PET showed inferior 2-year PFS then those with negative interim-PET (28.6% vs. 78.7%, HR=5.975; 95% CI: 1.500 to 23.795, p<0.0001).
Wang et al, 2018 [35]	Meta-analysis	8 studies (338 patients with lymphoma)	FDG PT/CT	WB-MRI	Pathology, bone marrow biopsy, clinical and imaging follow-up	**Staging** **HL and aggressive NHL** Pooled Accu: 98% **Indolent NHL** Pooled Accu: 87%	**Staging** **HL and aggressive NHL** Pooled Accu: 98% **Indolent NHL** Pooled Accu: 96%	NA
Garcia Vicente et al, 2018 [36]	Retrospective	90 patients in complete remission (30 HL, 60 NHL)	FDG PET/CT	CeCT	Histopathology, clinical and imaging follow-up	**Recurrence** Sens: 50% Spec: 88% PPV: 17% NPV: 97%	**Recurrence** Sens: 50% Spec: 91% PPV: 20% NPV: 98%	NA
Attalla et al, 2018 [37]	Retrospective	50 patients (14 HL, 36 NHL)	FDG PET/CT	CT	Histopathology, clinical and imaging follow-up	**Extranodal extension** Sens: 97.2% Spec: 80.0% PPV: 98.6% NPV: 66.7% Accu: 96.1%	**Extranodal extension** Sens: 88.9% Spec: 60.0% PPV: 97.0% NPV: 27.3% Accu: 87.0%	NA
Basha et al, 2018 [38]	Prospective	56 patients referred for pre-therapeutic evaluation; 22 patients returned for post-therapeutic assessment (newly	FDG PET/CT	WB-MRI	Bone marrow aspiration and biopsy	**Active myelomatous tissue at diagnosis** Sens: 75%* Spec: 80% PPV: 87%	**Active myelomatous tissue at diagnosis** Sens: 94%* Spec: 80%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		diagnosed multiple myeloma)				NPV: 64% Accu: 77% **Residual myelomatous tissue after treatment** Sens: 75% Spec: 86%* PPV: 75% NPV: 86% Accu: 82%	PPV: 89% NPV: 89% Accu: 89% **Residual myelomatous tissue after treatment** Sens: 75% Spec: 43%* PPV: 43% NPV: 75% Accu: 55%	
Melanoma								
Lee et al, 2018 [39]	Retrospective	76 patients who underwent initial treatment; 92 scans for routine surveillance and 51 scans for suspicious recurrence (melanoma)	FDG PET/CT	Physical examination, MRI, US, CT, bone scan	Histology, clinical or imaging follow-up	**Recurrence** ***Routine surveillance*** Sens: 100% Spec: 93.4% PPV: 76.2% NPV: 100% Accu: 94.6% ***Clinical suspicion*** Sens: 78.0% Spec: 100% PPV: 100% NPV: 52.6% Accu: 82.4%	NA	NA
Poulsen et al, 2018 [40]	Prospective (Phase II)	58 patients who underwent a pre-treatment scan (Merkel cell carcinoma)	FDG PET/CT	CeCT	Cytology, clinical and imaging follow-up	**Staging** Sens: 94.7% Spec: 88.2% PPV: 94.7% NPV: 88.2% +LR: 8.05 -LR: 0.06	NA	PET/CT influenced the treatment decision in 27.6% (16/58) of patients. Upstaging occurred in 25.9% (15/58) of patients due to the detection of distant metastases or regional nodes that were not seen on CeCT. Other non-related malignancies and benign conditions were identified by PET/CT in 6.9% (4/58) of patients.
Neuro-Oncology								
Arora et al, 2018 [41]	Prospective	39 previously treated patients (suspected	FDG PET/CT	^{99m}Tc Methionine SPECT/CT, CE-	Histopathology, clinical and imaging follow-	**Recurrence** Sens: 82.8% Spec: 80.0%	**Recurrence** ***^{99m}Tc Methionine***	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		recurrent glioma)		MRI	up	PPV: 92.3% NPV: 61.5% Accu: 82.0%	***SPECT/CT*** Sens: 75.9% Spec: 90.0% PPV: 95.6% NPV: 56.2% Accu: 79.4% ***CE-MRI*** Sens: 87.1% Spec: 30.0% PPV: 79.4% NPV: 42.9% Accu: 76.9%	
Non-FDG Tracers $^{11}C/^{18}F$-Choline								
D'Agostino et al, 2018 [42]	Prospective	135 patients who underwent staging or restaging before planning the radiotherapy course (prostate cancer)	^{11}C-Choline PET/CT	CT, MRI, bone scan, PSA level	Consensus	NA	NA	The indication to radiotherapy was modified in 48.9% (66/135) of patients on the basis of ^{11}C-Choline PET/CT results (23—excluded from radiotherapy, 43—change in radiotherapy prescription).
Gomez-de la Fuente et al, 2018 [43]	Retrospective	50 patients (biochemical relapse of prostate cancer with serum PSA <1 ng/ml)	^{11}C-Choline PET/CT	NA	Biopsy, imaging follow-up	NA	NA	Therapy planning was changed following ^{11}C-Choline PET/CT in 16% (8/50) of patients (2—received prostatic bed EBRT, 2—received prostatic bed and pelvic lymph nodes EBRT, 1—change in hormone therapy plus neck and pelvic lymph nodes EBRT, 1—received hormone therapy, 1—received radical prostatectomy, prostatic bed EBRT and surgery plus chemotherapy of the sigmoid cancer, 1—changed to prostatic bed EBRT only, lymph node chains were not treated).
Gao et al,	Meta-analysis	5 studies (118	^{11}C-Choline	NA	Pathology,	**Differentiate**	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
2018 [44]		patients with glioma treated with radiation therapy with or without chemotherapy)	PET or PET/CT		clinical follow-up	**between tumour relapse and radiation necrosis** Pooled Sens: 87% Pooled Spec: 82% Pooled +LR: 4.90 Pooled –LR: 0.16 Pooled DOR: 35.50 AUC: 0.9170 Q* index: 0.8499		
^{68}Ga-DOTA-(TATE, NOC, TOC, LAN)								
Treglia et al, 2017 [45]	Meta-analysis	9 studies (152 patients with recurrent medullary thyroid carcinoma)	^{68}Ga-DOTA-TATE/NOC/TOC/LAN PET or PET/CT	Somatostatin receptor SPECT/CT, US, CT, MRI, FDG PET or PET/CT, ^{123}I-MIBG scintigraphy, ^{99m}Tc-(V)DMSA, F-DOPA PET/CT, bone scintigraphy	Pathology, imaging or clinical/biochemical/imaging follow-up	**Recurrence** Pooled DR: 63.5%	NA	NA
Kan et al, 2018 [46]	Meta-analysis	17 studies (629 patients with known or suspected metastatic pheochromocytomas and/or paragangliomas)	^{68}Ga-DOTA-TATE/NOC/TOC PET/CT, FDG PET/CT	NA	Histopathology, biochemical biomarkers, clinical follow-up, all available imaging	**Diagnosis** ***^{68}Ga-DOTA-TATE/NOC/TOC*** Pooled Sens: 95% Pooled Spec: 87% AUC: 0.88 ***FDG PET/CT*** Pooled Sens: 85% Pooled Spec: 55% AUC: 0.78	NA	NA
^{18}F-FACBC								
Akin-Akintayo et al, 2018 [47]	Prospective	24 patients who underwent non-prostatectomy definitive surgery (suspected recurrent prostate cancer)	^{18}F-FACBC PET/CT	mpMRI	Histology, clinical follow-up, consensus from multidisciplinary truth panel	**Recurrence** ***Prostate*** Sens: 100% Spec: 11.1% PPV: 61.9% NPV: 100% Accu: 63.6% ***Extraprostatic*** Sens: 87.5% Spec: 90.0% PPV: 87.5% NPV: 90.0% Accu: 88.9%	**Recurrences** ***Prostate*** Sens: 15.4-38.5% Spec: 55.6-77.8% PPV: 50.0-55.6% NPV: 38.5-38.9% Accu: 40.9-45.5% ***Extraprostatic*** Sens: 50.0-75.0% Spec: 70.0-80.0% PPV: 57.1-75.0% NPV: 63.6-80.0% Accu: 61.1-77.8%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
^{68}Ga-PSMA								
Corfield et al, 2018 [48]	Systematic review	5 studies (216 patients who underwent primary staging for high-risk prostate cancer)	^{68}Ga-PSMA PET/CT	NA	Histopathology	**Metastatic disease (lesion-based)** Sens: 33-92% Spec: 82-100% PPV: 84-100% NPV: 69-98% **(patient-based)** Sens: 64-91% Spec: 67-99% PPV: 83-96% NPV: 80-96%	NA	NA
Berger et al, 2018 [49]	Retrospective	50 patients who underwent radical prostatectomy (newly diagnosed prostate cancer or a rising PSA following definitive radiotherapy)	^{68}Ga-PSMA PET/CT	mpMRI	Histopathology	**Index lesion Localization** Sens: 81.1%* Spec: 84.6% PPV: 89.2% NPV: 74.2% **Pelvic lymph node spread** Sens: 50.0% Spec: 91.5% PPV: 20.0% NPV: 97.7% **Multifocal disease** Sens: 88.9% Spec: 40.0% PPV: 93.0% NPV: 28.6% **Seminal vesicle invasion** Sens: 11.1% Spec: 92.7%	**Index lesion Localization** Sens: 64.8%* Spec: 82.7% PPV: 85.4% NPV: 60.0% **Multifocal disease** Sens: 10.0% Spec: 10.0% PPV: 14.3% NPV: 6.9% **Seminal vesicle invasion** Sens: 75.0% Spec: 95.0%	NA
Frenzel et al, 2018 [50]	Retrospective	106 patients; 120 scans for radiotherapy planning due to staging of primary disease, biochemical relapse, or known metastatic disease (prostate cancer)	^{68}Ga-PSMA PET/CT	CT	Consensus from interdisciplinary team	NA	NA	^{68}Ga-PSMA PET/CT findings altered the radiotherapy regime of 45.8% (55/120) of cases.
Zacho et al, 2018 [51]	Prospective	70 patients with PSA level of ≥0.2 ng/mL after radical	^{68}Ga-PSMA PET/CT	NA	Histopathology, pre- and post-PET forms	NA	NA	Results of the ^{68}Ga-PSMA PET/CT caused a definite change in management in

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		prostatectomy or a rise of ≥2.0 ng/mL above the PSA nadir value after radiation therapy (biochemical relapse of prostate cancer)						21.7% (15/69) patients and guided the choice of treatment in another 21.7% (15/69) of patients.
Mattiolli et al, 2018 [52]	Retrospective	125 patients with negative conventional imaging (biochemical recurrence of prostate cancer)	^{68}Ga-PSMA PET/CT	Pelvic US, bone scintigraphy, pelvic MRI, CT of the abdomen	Biopsy, clinical follow-up	NA	NA	^{68}Ga-PSMA PET/CT led to a treatment change in 63.5% (66/104) of patients.
Zacho et al, 2018 [53]	Prospective	68 patients treated with curative intent (biochemical recurrence of prostate cancer)	^{68}Ga-PSMA PET/CT	DW-MRI	All available imaging and clinical follow-up	**Bone metastases (patient-based)** Sens: 80% Spec: 98-100% PPV: 89-100% NPV: 97% AUC: 0.89-0.90* **(lesion-based)** Sens: 56% PPV: 100%	**Bone metastases (patient-based)** Sens: 25-38% Spec: 87-92% PPV: 30-33% NPV: 89-90% AUC: 0.59-0.62* **(lesion-based)** Sens: 25% PPV: 20%	NA
^{18}F-NaF								
Zacho et al, 2018 [53]	Prospective	68 patients treated with curative intent (biochemically recurrent prostate cancer)	^{18}F-NaF PET/CT	DW-MRI	All available imaging and clinical follow-up	**Bone metastases (patient-based)** Sens: 90% Spec: 90-98% PPV: 60-90% NPV: 98% AUC: 0.90-0.94* **(lesion-based)** Sens: 81% PPV: 76%	**Bone metastases (patient-based)** Sens: 25-38% Spec: 87-92% PPV: 30-33% NPV: 89-90% AUC: 0.59-0.62* **(lesion-based)** Sens: 25% PPV: 20%	NA
Broos et al, 2018 [54]	Retrospective	118 patients (breast cancer)	^{18}F-NaF PET/CT	CeCT	Histology, clinical, biochemical and imaging follow-up	**Bone metastases** Sens: 96% Spec: 91% PPV: 89% NPV: 97% Accu: 93%	NA	^{18}F-NaF PET/CT scan results led to a change in patient management in 25.4% (30/118) of patients (23—changes in medication, 6—received palliative radiotherapy, 1—treated with samarium-153 therapy).
Non-Small Cell Lung Cancer and other Lung Cancer								

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Hou et al, 2018 [55]	Retrospective	88 patients (pulmonary nodules)	FDG PET/CT	High-resolution CT	Pathology, clinical follow-up	**Differentiate between malignant and benign nodules** Sens: 91.7% Spec: 62.5% Accu: 78.4%	**Differentiate between malignant and benign nodules** Sens: 83.3% Spec: 70.0% Accu: 77.3%	NA
Evangelista et al, 2018 [56]	Retrospective	355 patients (SPN)	FDG PET/CT	CT	Histopathology, imaging follow-up	**Malignancy** Sens: 85.6% Spec: 85.7% PPV: 86% NPV: 85.2% Accu: 85.6%	NA	NA
Lee et al, 2018 [57]	Retrospective	55 patients with idiopathic pulmonary fibrosis (SPN sized 8-30 cm)	FDG PET/CT	Chest CT	Histopathology	**Differential diagnosis of SPN** Sens: 98% Spec: 86% PPV: 95% NPV: 92% Accu: 92%	NA	NA
Purandare et al, 2017 [58]	Retrospective	191 patients (SPNs)	FDG PET/CT	NA	Histopathology	**Malignancy (SUV_{max} of 2.5)** Sens: 94.4% Spec: 34.7% PPV: 81.9% NPV: 66.6% Accu: 79.5%	NA	NA
Proli et al, 2018 [59]	Retrospective	134 patients who underwent surgery (anterior mediastinal mass)	FDG PET/CT	NA	Histopathology	**Differentiate between malignant and benign masses** Sens: 82.7% Spec: 58.3% PPV: 90.1% NPV: 42.4% AUC: 0.63	NA	NA
Bustos Garcia de Castro et al, 2017 [60]	Retrospective	113 patients who underwent surgery (NSCLC)	FDG PET/CT	NA	Pathology	**Lymph node staging (tumour-based)** Sens: 53.8% Spec: 76.6% PPV: 38.9% NPV: 85.7% +LR: 2.30 -LR: 0.60 Accu: 71.7%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						(lymph node station-based) Sens: 34.1% Spec: 91.2% PPV: 24.6% NPV: 94.3% +LR: 3.87 -LR: 0.72 Accu: 86.7%		
Frechet et al, 2018 [61]	Retrospective	997 patients operated on with curative intent (NSCLC)	FDG PET/CT	CT, EBUS-FNA, EUS-FNA	Pathology, biopsy	**Hilar lymph nodes staging** Sens: 39.7%* Spec: 80.3%* PPV: 35.2% NPV: 83.2% **Mediastinal lymph nodes staging** Sens: 33.8%* Spec: 93.8%* PPV: 30.6%* NPV: 94.6%	**Hilar lymph nodes staging** ***CT*** Sens: 17.0%* Spec: 94.7%* PPV: 46.8% NPV: 80.5% **Mediastinal lymph nodes staging** ***CT*** Sens: 18.9%* Spec: 94.9% PPV: 23.8% NPV: 93.2% ***EBUS-FNA*** Sens: 72.7%* Spec: 100%* PPV: 100%* NPV: 92.6% ***EUS-FNA*** Sens: 51.9% Spec: 100%* PPV: 100%* NPV: 87.5%	NA
Yu et al, 2018 [62]	Meta-analysis	10 studies (1333 patients with NSCLC)	FDG PET/CT	NA	Pathology and/or imaging follow-up	**Distant metastases** Pooled Sens: 81% Pooled Spec: 96% Pooled +LR: 22.9 Pooled –LR: 0.20 Pooled DOR: 117 AUC: 0.97	NA	NA
Ohno et al, 2017 [63]	Prospective	96 patients (completely resected NSCLC)	FDG PET/CT, FDG PET/MRI	DWI-MRI, MRI, brain MRI, CE-CT, bone scintigraphy	Pathology, clinical and imaging follow-up, consensus by multidisciplinar	**Recurrence** ***PET/CT*** Sens: 100% Spec: 81.0%*† PPV: 53.1% NPV: 100%	**Recurrence** ***DWI-MRI*** Sens: 88.2% Spec: 100%* PPV: 100% NPV: 97.5%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
					y panels	Accu: 84.4%*‡ AUC: 0.92*‡ ***PET/MRI*** Sens: 100% Spec: 96.2%‡ PPV: 85.0% NPV: 100% Accu: 96.9%‡ AUC: 0.99‡	Accu: 97.9%* AUC: 0.99* ***MRI*** Sens: 70.6% Spec: 100%* PPV: 100% NPV: 94.0% Accu: 94.8%* AUC: 0.93 **Brain MRI, CE-CT, bone scintigraphy** Sens: 70.6% Spec: 87.3%‡ PPV: 54.5% NPV: 93.2% Accu: 84.4%‡ AUC: 0.91‡	
Lee et al, 2018 [64]	Retrospective	247 patients with suspicious lymph node involvement (194 NSCLC; 53 SCLC)	FDG PET/CT	Chest CT	EBUS-TBNA, cytopathology	**Mediastinal lymph node metastases** Sens: 99.2% Spec: 13.0% PPV: 69.9% NPV: 88.9% Accu: 70.8% AUC: 0.561	**Mediastinal lymph node metastases** Sens: 88.8% Spec: 44.6% PPV: 76.1% NPV: 66.7% Accu: 74.0% AUC: 0.667	NA
Ahmed et al, 2018 [65]	Retrospective	123 patients with evidence of mediastinal lymphadenopathy on CT (27 SCLC; 96 NSCLC)	FDG PET/CT	CT, neck US	Cytology or histology	**Cervical lymphadenopathy** Sens: 87.5% Spec: 81.1% PPV: 50.0% NPV: 96.8%	NA	PET/CT provided additional overall clinical stage information in 8.9% (4/45) of patients and led to a change in management in 2.2% (1/45) of patients.
Pancreatic Cancer								
Kim et al, 2018 [66]	Retrospective	70 patients who underwent radical surgery (pancreatic cancer)	FDG PET/CT	CeCT	Pathology, clinical follow-up	**Lymph node metastases** Sens: 61.0%* Spec: 79.3% PPV: 80.7%* NPV: 59.0%* Accu: 68.6%*	**Lymph node metastases** Sens: 25.0%* Spec: 84.6% PPV: 71.4%* NPV: 42.3%* Accu: 48.5%*	NA
Albano et al, 2018 [67]	Retrospective	52 patients with clinical or imaging suspicion of disease progression (pancreatic cancer)	FDG PET/CT	US, CT, MRI, bone scan	Clinical and imaging follow-up	**Recurrence** Sens: 85% Spec: 84% PPV: 90% NPV: 76%	NA	PET/CT influenced the therapeutic management of 30.8% (16/52) of patients (5—palliative to curative, 11—switched to

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Accu: 84% AUC: 0.84 +LR: 5.3 -LR: 0.17		a wait-and-watch approach).
Daamen et al, 2018 [68]	Meta-analysis	7 studies (333 patients with resected pancreatic ductal adenocarcinoma)	FDG PET/CT	CeCT	Histology, imaging follow-up	**Recurrence** Pooled Sens: 88% Pooled Spec: 89%	**Recurrence** Pooled Sens: 70% Pooled Spec: 80%	NA
Pediatric Cancer								
Chen et al, 2018 [69]	Retrospective	93 children and adolescents (newly diagnosed NHL)	FDG PET/CT	BMB	Directed biopsy, supplementary radiological studies, or imaging follow-up	**Bone marrow involvement** Sens: 95% Spec: 98% PPV: 97% NPV: 96%	**Bone marrow involvement** Sens: 56% Spec: 100% PPV: 100% NPV: 74%	NA
Badr et al, 2018 [70]	Retrospective	140 pediatric patients (113 HL; 27 NHL)	FDG PET/CT	BMB	Pathology, clinical and imaging follow-up	**Bone marrow involvement** **HL** Sens: 100%* Spec: 97.7% PPV: 92.6%* NPV: 100%* Accu: 98.2%* **NHL** Sens: 100%* Spec: 100% PPV: 100% NPV: 100%* Accu: 100%*	**Bone marrow involvement** **HL** Sens: 32.0%* Spec: 100% PPV: 100%* NPV: 83.8%* Accu: 82.3%* **NHL** Sens: 42.9%* Spec: 100% PPV: 100% NPV: 61.9%* Accu: 66.7%*	NA
Sarcoma								
Miwa et al, 2018 [71]	Retrospective	122 patients (bone and soft tissue lesions)	FDG PET/CT	NA	Histopathology	**Differentiate between malignant and benign lesions (SUV_{max} of 8.2)** Sens: 43.8% Spec: 92.9% PPV: 96.8% NPV: 25.2% Accu: 52.1%	NA	NA
Lee et al, 2018 [72]	Retrospective	62 patients treated with neoadjuvant chemotherapy and complete resection of the primary	FDG PET/CT	^{99m}Tc-MDP bone scan	Histology	**Histologic response (Δ%SUV_{max} of ≤-49.0%)** Sens: 80.0%	**Histologic response (Δ%T/NT_{max} of ≤-12.5%)** Sens: 83.3%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		tumour (osteosarcoma)				Spec: 81.3% AUC: 0.829	Spec: 75.0% AUC: 0.772	
Huang et al, 2018 [73]	Meta-analysis	23 studies (524 patients with Ewing sarcoma family of tumours)	FDG PET or PET/CT	NA	Not specified	**Primary lesions (lesion-based)** Pooled Sens: 86% Pooled Spec: 80% Pooled +LR: 3.92 Pooled –LR: 0.19 Pooled DOR: 29.22 Q index: 0.847 AUC: 0.915 **Recurrence (examination-based)** Pooled Sens: 93% Pooled Spec: 90% Pooled +LR: 8.53 Pooled –LR: 0.09 Pooled DOR: 109.98 Q index: 0.913 AUC: 0.966 **Lung metastases (examination-based)** Pooled Sens: 72% Pooled Spec: 97% Pooled +LR: 13.51 Pooled –LR: 0.38 Pooled DOR: 60.55 Q index: 0.886 AUC: 0.947 **Bone metastases (examination-based)** Pooled Sens: 91% Pooled Spec: 98% Pooled +LR: 26.60 Pooled –LR: 0.15 Pooled DOR: 347.37 Q index: 0.949 AUC: 0.986	NA	NA
Various Sites								
Gupta et al,	Retrospective	193 patients with	FDG PET/CT	NA	Pathology,	**Malignant lesions**	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
2017 [74]		proven or suspected malignancy			clinical and imaging follow-up	Sens: 97.8% Spec: 43% PPV: 82.4% NPV: 87.5% Accu: 83.1%		
Park et al, 2018 [75]	Retrospective	103 patients with no known malignancies (abnormal bone lesions radiologically suspected as cancer metastasis)	FDG PET/CT	CT, MRI, US, bone scan, mammogram	Biopsy, comprehensive analysis of clinical, laboratory, imaging, and endoscopy results	**Primary cancer** Sens: 61.3% Spec: 60.7% Accu: 61.2%	NA	NA

*p<0.05

‡Significant difference with PET/MRI (p<0.05)

Abbreviations: +LR: positive likelihood ratio; -LR: negative likelihood ratio; ^{11}C-choline: carbon-11 choline; ^{18}F-Choline: fluorine-18 choline; ^{18}F-NaF: ^{18}F-sodiumfluoride; ^{68}Ga-PSMA: ^{68}Gallium prostate-specific membrane antigen; 99mTc-MDP: Technetium 99m-methyl diphosphonate; Accu: accuracy; AI: accuracy index; AUC: area under the curve; BMB: bone marrow biopsy; CeCT: contrast-enhanced computed tomography; CI: confidence interval; CRC: colorectal cancer; CT: computed tomography; DLBCL: diffuse large B-cell lymphoma; DOR: diagnostic odds-ratio; 68Ga-DOTA-(TATE, TOC): gallium-68-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-1-Nal3-octreotide; DR: detection rate; DW-MRI or DWI: diffusion-weighted magnetic resonance imaging; EBRT: external beam radiation therapy; EBUS: endobronchial ultrasound-guided; EEG: electroencephalogram; EUS: endoscopic ultrasound-guided; FDG: 2-fluoro-2-deoxy-D-glucose or fluorodeoxyglucose; F-FACBC: fluciclovine (18F) or anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid; FIGO: International Federation of Gynecology and Obstetrics; FNA: fine-needle aspiration; FNAB: fine-needle aspiration biopsy; FNAC: fine-needle aspiration cytology; HL: Hodgkin's lymphoma; mL: millilitre; mm: millimetre; mpMRI: multiparametric MRI; MRI: magnetic resonance imaging; NA: not applicable/not available; ng: nanogram; NHL: non-Hodgkin lymphoma; NPV: negative predictive value; NSCLC: non-small cell lung cancer; PET: positron-emission tomography; PFS: progression-free survival; PPV: positive predictive value; PSA: prostate-specific antigen; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; SCLC: small cell lung cancer; SEEG: stereoelectroencephalography; Sens: sensitivity; Spec: specificity; SPECT: single photon emission computed tomography; SPN: solitary pulmonary nodule; SUV_{max}: maximum standardized uptake value; US: ultrasound, WB: whole body