PET Six-Month Monitoring Report 2024-1

Evidence from Primary Studies and Meta-analyses
January to June 2024

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QUESTION

What is the role of positron emission tomography (PET) in the clinical management of patients with cancer, non-cardiac sarcoidosis, epilepsy, or dementia, fever of unknown origin (FUO), and metastases of unknown primary with respect to:

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

Outcomes of interest are:

- Change in clinical management or patient outcome (e.g., survival, quality of life, prognostic indicators, time until recurrence) or safety outcome (e.g. avoidance of unnecessary surgery).
- Diagnostic parameters (e.g., sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], accuracy)

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, epilepsy, or dementia. 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 27th 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

The methods are reported in Appendix 1: Protocol for PET 6-Month Monitoring Reports, Version 1.

RESULTS

Literature Search Results

Primary Studies and Systematic Reviews

Sixty-three studies published between January and June 2024 met the inclusion criteria. A summary of the evidence from the 63 studies can be found in Appendix 2: Summary of studies from January to June 2024.

Breast Cancer

Four studies met the inclusion criteria [1-4]. One was a phase II randomized controlled trial (RCT) [3], and the other three were retrospective trials [1,2,4]. Three studies reported on change in management [2-4], and one study reported on diagnostic outcomes [1].

The open label phase II PHERGain RCT [3] tested a chemotherapy-free, ^{18}fluorine-fluorodeoxyglucose (^{18}F-FDG)-PET-adapted strategy for the treatment of early (stages I to III invasive, operable), human epidermal growth factor receptor 2 (HER2)-positive breast cancer. Three-hundred fifty-six patients were randomly allocated either to group A (n=71) where they received docetaxel, carboplatin, trastuzumab and pertuzumab (TCHP) or group B (n=285) where they received trastuzumab with or without endocrine therapy every three weeks. PET was conducted at baseline and after two cycles of therapy (PET2). Patients who were PET2-negative continued their therapy for six more cycles; patients who were PET2-positive received six cycles of TCHP. After surgery, PET2-negative patients who did not achieve partial complete response had six more cycles of TCHP and all patients completed up to 18 cycles of trastuzumab and pertuzumab. The patient-relevant outcomes are shown in Table 1. This trial was not designed to test a between-groups comparison; therefore, differences in hazard ratios (HRs) and p values were not reported.

Francois et al. [4] in a retrospective, single institution trial, evaluated the role of FDG-PET/computed tomography (CT) in the management and staging (changes in cancer staging) of patients with stage I or IIA HER2-positive or triple-negative breast cancer.

Özdemir et al. [2] investigated the impact of PET/CT on management decision for patients with early-stage breast cancer.

The retrospective, single institution study by Sae-Lim et al. [1] tested the diagnostic performance of ^{18}F-FDG-PET/CT and breast magnetic resonance imaging (MRI) in detecting axillary lymph node metastases and the reliability in predicting axillary lymph node burden. The diagnostic outcomes for PET/CT and MRI are reported in Table 1. The combined modalities PET/CT + MRI had a PPV of 72.7%, and a NPV of 84%. Results are reported in Appendix 2.

Epilepsy

No trials were identified during this time period.

Esophageal Cancer

Two studies met the inclusion criteria [5,6].

Ohsawa et al. [5] retrospectively evaluated the associations among lymph node (LN) status using FDG-PET, lymph node status based on the reference standard (i.e., pathological examination), and prognosis in 124 patients with locally advanced esophageal squamous cell carcinoma who underwent esophagectomy after neoadjuvant chemotherapy (NCT). Patients were evaluated with PET/CT before and two to three weeks after NCT. The diagnostic parameters of PET/CT before and after NCT are reported in Table 1.

Valkema et al. [6] in a prospective, single-centre, feasibility study investigated whether ^{18}F-FDG-PET/MRI could improve tumour detection after neoadjuvant chemoradiotherapy in 21 patients with esophageal cancer. The outcomes measured were the concordance between ^{18}F-FDG-PET/MRI and the reference standard, the possibility to perform quantitative measurements, (e.g., interobserver variability and the concordance with the reference standard) and the burden for the patient of undergoing ^{18}F-FDG-PET/MRI. Two teams (Team 1 and Team 2) made of a radiologist with expertise in MRI and a nuclear medicine physician with expertise in PET independently assessed the scans. Discrepancies were resolved by discussion. Patients completed questionnaires about the burden of 18F-FDG PET/MRI; 67% were neutral of willing to undergo a similar procedure in the future, and the noise of the scanner and the duration of the procedure were reported to be the most stressful aspects of the procedure. Table 1 reports the diagnostic performance of PET/CT and PET/MRI.

Fever of Unknown Origin

A large ambispective study [7] (all the data about clinical details and history, physical examination, laboratory investigations and imaging modalities were collected retrospectively and prospectively) evaluated the potential role of 18F-FDG PET/CT for early diagnosis of the etiology of FUO and for guiding the path of investigations in the diagnostic process. A final diagnosis was reached in 219 of 573 patients (38%) and categorized into: malignant, infectious, inflammatory non infectious. PET imaging guided physicians to the site of biopsy in 104 patients to facilitate a quick diagnosis; 34.6% of these patients (36 of 104) had a conclusive diagnosis.

Gastrointestinal Cancer

Three studies met the inclusion criteria: two meta-analyses [8,9] and a prospective cohort study [10]. The meta-analyses studied the diagnostic performance of ^{18}F-FDG PET/CT in detecting preoperative lymph node status [8], and the effectiveness of NCT, comparing MRI and PET/CT in patients with rectal cancer [9]. The prospective cohort study with long-term follow-up detected a statistically significant better sensitivity of PET/CT compared with contrast-enhanced CT (CE-CT) (Table 1). No difference was found in survival, perhaps due to the small sample size.

Genitourinary Cancer

Two prospective observational studies met the inclusion criteria [11,12]. Radha et al. [11] examined, in a cross sectional study, the diagnostic accuracy of PET/CT in differentiating malignant versus benign adrenal nodules in cancer patients with suspicious adrenal nodules. Hirasawa et al. [12] evaluated the diagnostic performance of FDG-PET/CT as a screening tool for detecting renal cell carcinoma in patients with end-stage renal disease.

Gynecologic Cancer

Five studies met the inclusion criteria [13-17]. Two were meta-analyses [14,16], one was a prospective observational study [13], and two were retrospective trials [15,17]. All the

included trials reported on the diagnostic performance of PET/CT. The meta-analysis by Wilson et al., [16] compared the diagnostic accuracy of CE-CT with the accuracy of PET/CT for the detection of abdominal metastases in patients with a new or suspected diagnosis of ovarian cancer. No statistically significant difference in sensitivity between modalities ($p=0.29$) while specificity was statistically significantly better for PET/CT ($p<0.01$). The meta-analysis by Tsili et al. [14] compared the performance of multidetector CT (MDCT), MRI, including diffusion-weighted imaging, and FDG PET/CT for detecting peritoneal metastases in ovarian cancer. On a per-patient basis, MRI and FDG PET/CT had higher pooled sensitivity than MDCT ($p=0.03$, and $p<0.01$, respectively), while no statistically significant difference was detected between MRI and PET/CT ($p=0.84$). On a per-lesion analysis no differences were detected in the sensitivity estimates between MDCT and MRI and FDG PET/CT.

Elsayed et al. [13] in a prospective cross-sectional study evaluated PET/CT for the identification and localization of ovarian cancer recurrence along with the tumour marker CA-125. A retrospective trial by Van Kol et al. [15] assessed the diagnostic performance of MRI and ^{18}F-FDG-PET/CT for determining the remission status of patients with locally advanced cervical cancer. The authors concluded that the reliability of both imaging strategies for the detection of locoregional residual disease after chemoradiotherapy is limited and they did not recommend it. In another retrospective trial, Hong et al. [17] compared the diagnostic performance of the combination of MRI, enhanced CT, and 18F-FDG-PET/CT against each of the imaging modalities and concluded that the combination can accurately diagnose recurrence and metastases of ovarian cancer after surgery, and as early as possible thus improving patients' prognosis.

Head and Neck Cancer and Cancer of Unknown Primary (CUP)

Seven studies met the inclusion criteria for specific sites under the umbrella of head and neck cancers [18-24]. Two were meta-analyses [20,24] that aimed at comparing the diagnostic accuracy of CT, MRI, PET and ultrasound (US) in detecting extracapsular spread in head and neck cancers, and at comparing PET/CT and PET/MRI for the management of gliomas, respectively. One was a phase III RCT [23] that evaluated a FDG-PET-guided, dose escalated, management strategy in locally advanced head and neck squamous cell carcinoma. Two were prospective cohort studies [18,21] that aimed at assessing the diagnostic properties of 18F-FDG and molecular diagnostics in patients with indeterminate thyroid nodules [18], and at evaluating the impact of FDG-PET/CT on clinical decision making for patients with differentiated thyroid carcinoma [21]. Two were retrospective cohort studies [19,22] that aimed at evaluating the impact of PET/CT for the staging and therapeutic management [19] and the utility of the two-year post-treatment FDG-PET/CT [22] for patients with head and neck squamous cell carcinoma.

A retrospective study met the inclusion criteria [25]. Huang et al. included 62 patients with cancer of unknown primary and used ^{18}F-FDG PET/CT to detect primary cancers and to change the clinical management (.i.e., tumour staging and treatment strategies) of the patients [25]. Results are reported in Table 1.

Hematologic Cancer

Ten studies met the inclusion criteria [26-35]. Two were meta-analyses [30,35]; two were RCTs [28,29], two were comparative prospective trials [31,32], and four were comparative retrospective trials [26,27,33,34].

The meta-analysis of 15 studies by Guo et al. [30] aimed at determining the role of FDG PET/CT in the diagnosis of bone marrow involvement in patients with mature T- and natural killer-cell lymphomas (e.g., T-cell lymphomas, anaplastic large-cell lymphoma, and extranodal NK/T-cell Lymphoma). The risk of bias of the included studies was considered low. The pooled

sensitivity FDG PET/CT was 0.62 (95% confidence interval [CI], 0.48 to 0.71) and the specificity was 0.92 (95 % CI, 0.87 to 0.96). When considering the subgroup of patients with advanced disease, sensitivity and specificity dropped to 60% and 77%, respectively. Heterogeneity was significant (I^2 > 50%) during the pooled analyses.

The meta-analysis of 28, mostly retrospective, studies by Valizadeh et al. [35] compared the diagnostic performance of various imaging techniques for the diagnosis of malignant splenic lesions in lymphoma patients. PET had the highest diagnostic accuracy (area under the curve [AUC], 92%), compared with CT (AUC, 88%), MRI (AUC, 85.3%) and US (AUC, 71.3%). The pooled sensitivity of PET studies was 93% (95% CI, 80.4% to 97.7%), and the specificity was 82.8 % (95 % CI: 71.1% to 90.4%). The risk of bias of the included studies was considered high because most of the studies did not use an appropriate reference standard. Heterogeneity was significant (I^2 79% to 89%) during the pooled analyses. In the subgroup of CE-CT studies the AUC values for CE CT, MRI, US, and PET were 88.0%, 85.3%, 91.4%, and 92%, respectively, and the authors concluded that CE-CT and CT-US could be an option for patients who preferred less radiation than with PET.

One of the RCTs [28] was the long-term follow-up of the German Hodgkin Study Group HD16 trial. In this study, 1150 newly diagnosed, early-stage favourable Hodgkin lymphoma patients were randomized between standard combined-modality treatment that consisted of two cycles of **A**driamycin, **B**leomycin, **V**inblastine, **D**acarbazine (ABVD) followed by PET/CT (PET-2) and 20 Gy involved-field radiotherapy (RT) and PET-2-guided treatment where radiotherapy was omitted for PET-2 negative patients (Deauville score [DS] <3). The PET-2 guided treatment was noninferior to combined modality treatment at the 64-month follow-up for progression-free survival (PFS) (HR, 2.05; 95% CI, 1.20 to 3.51, p=0.0072).

The other RCT [29] was a secondary analysis of the FOLL12 trial; the authors evaluated the reliability of the DS in therapy response assessment and the prognostic value of the metabolic response at the end of induction (EOI) in patients with stage II-IV follicular lymphoma. Patients were randomized to standard immunochemotherapy plus rituximab versus standard immunochemotherapy versus response-adapted post-induction management. At a median follow-up of 69 months, the 5-yrs PFS in DS1–2, DS3 and DS4–5 was 74% (95% CI, 70% to 78%), 58% (95% CI, 48% to 67%, HR 1.71; p=0.001) and 36% (25% to 46%, HR 3.88; p < 0.001). The 5-year overall survival was 94% (95% CI, 92% to 96%) for the entire population, and 96% (95% CI, 94 to 97) and 82% (95% CI, 72% to 89%) in PET-negative and -positive cases at the EOI, respectively (HR, 4.48; p<0.001) with no difference between DS1–2 and DS3 patients. The ability of EOI PET to predict PFS and overall survival events at the EOI is reported in Table 1.

The prospective cohort study by Krishna et al. [31] aimed to categorize FDG uptake in bone marrow and to correlate the FDG uptake with a bone marrow study in 42 newly diagnosed patients with lymphoma (Hodgkin 33.3%, non-Hodgkin 66.7%). Table 1 reports the sensitivity, specificity, PPV, NPV and accuracy of ^{18}F-FDG-PET/CT in predicting bone marrow involvement.

The prospective cohort study by Kumar et al. [32] aimed to pathologically validate the residual disease classified by DS in 150 lymphoma patients by using ^{18}F-FDG-PET/CT-guided metabolic core needle biopsy after first-line therapy. Diagnostic outcomes are reported in Table 1.

The four comparative retrospective trials [26,27,33,34] aimed at examining the diagnostic performance of PET/CT in assessing the bone marrow involvement and its prognostic value in patients with newly diagnosed peripheral T-cell lymphomas [26], diffuse large B-cell lymphoma [27], natural killer/T-cell lymphoma [33], and angioimmunoblastic T-cell lymphoma [34]. Diagnostic outcomes are reported in Table 1.

Melanoma

Three meta-analyses met the inclusion criteria [36-38]. Zamani-Siahkali et al. [37] described the diagnostic performance of ^{18}F-F-FDG PET in malignant melanoma at initial staging, locoregional detection, and distant metastasis diagnosis. The goal was to examine the utility of PET beyond the assessment of distant metastases and during follow-up, which, according to the authors, were current indications for its use. The included studies were published from 1998 to 2021 and included 82 patient-based datasets and 32 lesion-based datasets. In the patient-based analysis, the overall pooled sensitivity and specificity were 81% (95% CI, 73% to 87%) and 92% (95% CI, 90% to 94%), respectively, with a substantial variability among studies (I^2 for sensitivity = 92.01, and I^2 for specificity = 94.56). The authors concluded that PET had high specificity, but low sensitivity in detecting regional lymph node metastases, and it could not replace lymph node biopsy. Zhu et al. [38] focused on the diagnostic performance of PET in patients who experienced recurrence from Melanoma cancer. The 22 included, mostly retrospective, studies were published from 2010 to 2022. The results, as shown in Table 1, report a high pooled sensitivity and specificity. The variability among studies was substantial with I^2 value of 93.19% for the analysis of sensitivity and 81.52% for specificity. Mirshahvalad et al. [36], in a third systematic review and meta-analysis of 27 studies, published from 1992 to 2023, examined the diagnostic and prognostic values of ^{18}F-FDG PET in patients with uveal melanoma and its hepatic metastases. Twelve studies had data for the detection rate in primary intra-ocular tumours, and 13 studies had data for the detection of metastases. The authors reported a positive correlation between tumour size (thickness, diameter, area and volume) and ^{18}F-FDG uptake in most studies. Heterogeneity among studies was substantial for both the studies that examined the diagnostic value of PET in detecting distant metastases (for sensitivity I^2=75.99%, and for specificity I^2=70.67%,), and in those that examined the diagnostic value in detecting hepatic metastases (for sensitivity I^2=76.28%, and for specificity I^2=85.46%). Other advantages of using PET for this population is that it can show the presence second primary synchronous malignancies.

Non-FDG Tracers

Prostate-specific Membrane Antigen

Eight studies [39-46] evaluated prostate-specific membrane antigen (PSMA) PET/CT. Three were meta-analyses [39-41]; one was a phase III RCT [42]; two were prospective observational studies [43,44], and two were retrospective trials [45,46].

Among the meta-analyses, Dhar et al. [39] examined the capability of multiparametric MRI (mpMRI) and PSMA PET used alone or in combination to detect intraprostatic lesions that could be the target of dose escalation radiotherapy. The radiotracers used in the included studies were: Gallium-68 (^{68}Ga) PSMA-11, Fluorine-18 (^{18}F) DCFPyL, and 18F PSMA-1007.The diagnostic performance of PET and mpMRI are reported in Table 1; when the two modalities were combined (5 studies), pooled sensitivity was 70.3 % (95% CI, 64.1% to 75.9%), pooled specificity was 81.9% (71.9% to 88.8%), and the AUC was 0.796.

Ren et al. [40] evaluated the diagnostic ability of ^{68}Ga-PSMA-11 PET/CT and of mpMRI in detecting primary prostate cancer.

Singhal et al. [41] evaluated PSMA PET in detecting renal cell carcinoma and in clear cell renal cell carcinoma.

The Armstrong et al. [42] RCT publication reported on a secondary end point of this trial: comparison of the rate of change of treatment plan for salvage radiotherapy management between the PSMA-PET/CT and conventional imaging. Changes between the intended salvage radiotherapy plan were classified as major, minor, or no change.

Among the prospective observational trials, Tayara et al. [43]compared diagnostic properties of PSMA PET/CT with those of MRI and available nomograms in patients with intermediate to high-risk prostate cancer. PSMA PET/CT was more sensitive than MRI to assess

lymph node involvement, and MRI was better at detecting seminal vesicle involvement. mpMRI had a sensitivity, specificity, PPV and NPV, and AUC of 38.5%, 81.2%, 52.6%, 70.8%, and 0.599, respectively, for detecting extra-prostatic extension; data on PSMA PET were not reported. These data were reported by the pilot prospective study of 50 patients by Bhaler et al.[44]: the sensitivity of PSMA-PET was significantly higher than MRI (Table 1).

Among the retrospective trials, Alongi et al. [45] assessed the diagnostic properties and the impact of PSMA-PET/CT on clinical management at staging at re-staging patients with prostate cancer. Emmett et al. [46] evaluated the diagnostic accuracy of the PRIMARY score, a five-category scale developed to identify clinically significant intraprostatic malignancy on ^{68}Ga-PSMA–11 PET/CT (^{68}Ga-PSMA PET) using a combination of anatomic site, pattern, and intensity compared with another scoring system for mpMRI, the PI-RADS. The authors reported diagnostic properties of ^{68}Ga-PSMA PET and mpMRI (Table 1).

^{18}F-Fluciclovine (^{18}F-FACBC)

A meta-analysis of eight studies [47] evaluated the performance of ^{18}F-FACBC in patients with high-grade glioma.

^{18}F-fluoroestradiol (^{18}F-FES)

Gennari et al. [48] in a phase II RCT evaluated ^{18}F-FES PET/CT as a predictive tool in estrogen receptor-positive HER2-negative metastatic breast cancer.

F18-Choline

Quak et al. [49] in the APACH2 phase III RCT compared first-line F18-Choline PET/CT (FCH PET/CT) with Tc99m-sestaMIBI SPECT/CT in patients with parathyroid adenomas requiring minimally invasive parathyroidectomy. FCH PET/CT had higher sensitivity than MIBI.

^{68}Ga-DOTA-FAPI-04

Rizzo et al. [50] conducted a meta-analysis of six studies of [68Ga]Ga-radiolabeled fibroblast-activation protein inhibitors (FAPI) in head and neck cancers. The authors report a favourable diagnostic performance of the radiotracer.

6-[^{18}F]FDOPA

Suarez-Pinera et al., [51] reported their experience with 6-[18F]FDOPA PET/CT using visual and semiquantitative analyses in patients treated for primary or secondary brain cancer with suspicion of tumour recurrence or radiation necrosis. Semiquantitative analysis showed significant differences between tumour recurrence and radiation necrosis in both primary tumours and metastases. The results of the Receiver Operating Characteristic curve showed a better cut-off point to discriminate radiaton necrosis due to radiotherapy treatment. In the case of metastasis, the likelihood ratio was 1.44 with an sensitivity of 88% and a specificity of 79%, and an AUC of 0.839±0.059 (95% CI, 0.7229 to 0.955; $p<0.0001$) while in the case of primary tumours the likelihood ratio was 1.57 with a sensitivity of 100% and specificity of 93%, and an AUC of 0.975 ± 0.030 (95% CI, 0.914 to 1.03; $p<0.0017$).

^{18}F-DCFPyL

Wang et al. [52] performed a meta-analysis of 14 studies to investigate the impact of ^{18}F-DCFPyL PET/CT on changes in management of patients with prostate cancer. In meta-regression analyses, ^{18}F-DCFPyL PET/CT positivity rate was correlated with a higher proportion of patient management changes ($p=0.0023$).

Pancreatic Cancer

One study met the inclusion criteria. Karaalioglu et al. [53] conducted a retrospective analysis comparing the diagnostic performance of FDG-PET/CT with CE-CT/MRI to detect recurrence or progression of pancreaticobiliary tumours, and reported on the impact of these imaging strategies on patient management. The authors did not detect any statistically significant difference between conventional imaging and PET/CT in detecting loco-regional disease recurrence or progression. CT/MRI was more sensitive than PET/CT in detecting distant metastases ($p<0.007$).

Pediatric Cancer

Two retrospective studies were identified [54,55]. Arslantas et al. [54] compared the results of ^{18}F-FDG PET/CT with bone marrow biopsy in the initial evaluation of bone marrow involvement in newly diagnosed pediatric tumours. The authors concluded that PET/CT has a high sensitivity and specificity for assessing bone marrow involvement and recommended its use upfront. However, the results of statistical tests were not reported.

Du et al. [55] compared the diagnostic value of ^{18}F-FDG PET/CT and bone marrow biopsy and aspiration for detecting bone marrow infiltration. This was a retrospective analysis with nine-year follow-up in 103 pediatric patients of median age 9.3 years. The two procedures were concordant, and the kappa statistic was 0.779 ($p<0.001$).

Sarcoma

One study met the inclusion criteria [56]. Ko et al. [56] conducted a meta-analysis of four retrospective studies published between 2013 and 2019 comparing FDG PET/CT with MRI for the differentiation of malignant peripheral nerve sheath tumours in neurofibromatosis type 1. This meta-analysis showed substantial heterogeneity in sensitivity and specificity between studies: for PET the I^2 for sensitivity was 70.95% (95% CI, 46.40% to 95.50%), and for specificity was 93.43% (95% CI, 89.71 to 97.19) and for MRI the corresponding I^2 values were 74.61% (95% CI, 53.79 to 95.43) for sensitivity and 97.15% (95% CI, 95.89 to 98.41) for specificity.
The authors concluded that FDG PET/CT and MRI have similar, yet complementary diagnostic properties, and suggested that both imaging technologies can be used in a complementary manner.

Thoracic Cancer

Six studies met the inclusion criteria [57-62]. Two were meta-analyses [60,62], one was an RCT [58],and three were retrospective studies [57,59,61]. The meta-analysis by Zhang et al. [62] compared ^{18}F-FDG PET/CT and ^{18}F-FDG PET/MRI for lymph node metastasis staging in non-small cell lung cancer (NSCLC). Six studies and 434 patients were included. The authors concluded that the two imaging modalities have similar diagnostic properties, but note that this study had a small sample size. The meta-analysis by Li et al. [60] made the same comparison, for the diagnosis of tumour-node-metastasis staging in NSCLC. This study included all the studies of the Zhang et al. meta-analysis and two additional studies for a total of 539 patients. The results were similar between the two studies (see Table 1).

The TARGET randomized trial by de Fonseka et al. [58] compared PET/CT-guided versus CT-guided in suspected pleural thickening in 59 patients with a previous inconclusive pleural biopsy but an ongoing suspicion of pleural malignancy. The authors concluded that the data do not support the use of PET/CT for these patients.

Among the retrospective studies, Cheng et al. [57] in a very large registry study compared survival in stage I lung cancer patients who received PET/CT for staging and those who did not. No overall survival rate benefit was detected for either group. Li et al. [59], assessed the diagnostic efficiency of ^{68}Ga-FAPI–04 PET/CT for detecting lymph node metastasis in NSCLC. The authors reported an excellent diagnostic performance of ^{68}Ga-FAPI-04 PET/CT; the

metastatic lymph node detection led to a change in management in 23.08% of patients. Liu et al. [61], in a large retrospective trial, compared the diagnostic efficacy of PET/CT-aided CT-guided and routine CT-guided transthoracic needle biopsy for lung lesions. PET/CT had a better sensitivity and accuracy than CT. There was a significant interaction for lesion size particularly when diameter was larger than 3 cm (p for interaction = 0.023).

CLINICAL EXPERT REVIEW

Breast Cancer

Current Indications for Breast Cancer

Locally advanced invasive ductal breast cancer

- PET for the staging of patients with histologically confirmed clinical stage 2b or stage 3 breast cancer being considered for curative-intent combined modality treatment; and/or repeat PET on completion of neoadjuvant therapy, prior to surgery (when there is clinical suspicion of progression)
- PET for re-staging of patients with locoregional recurrence, after primary treatment, being considered for ablative or salvage therapy.

Oligometastatic invasive ductal breast cancer

- PET for staging or re-staging of patients with oligometastatic disease (4 or fewer metastases) on conventional imaging prior to radical intent or ablative therapy.

Reviewer's Comments - Dr. Muriel Brackstone

While the adaptive trial design by Perez-Garcia et al. [3] is thought provoking regarding the potential role of PET in selecting patients responding favourably to one neoadjuvant treatment over another, there currently remains insufficient data to confirm whether PET outperforms the currently used clinical examination strategies. Other retrospective studies published during this reporting time frame evaluated the sensitivity of PET in predicting axillary nodal involvement in early-stage breast cancer. PET is not more sensitive than current strategies of nodal staging. As such, there is no evidence to support a change in the role of PET in breast cancer at present. Its current role in staging of patients at diagnosis (stage IIb-III) or recurrence remains important.

Epilepsy

Current Indications for Epilepsy

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

Reviewer's Comments

No trials were identified during this monitoring period.

Esophageal Cancer

Current Indications for Esophageal Cancer or Gastroesophageal Junction cancer

- PET for baseline staging assessment of those patients diagnosed with esophageal/Gastroesophageal junction cancer being considered for curative therapy and/or repeat PET/CT scan on completion of pre-operative/ neoadjuvant therapy, prior to surgery; or for re-staging of patients with locoregional recurrence, after primary treatment, being considered for definitive salvage therapy

Reviewer's Comments - Dr. Rebecca Wong

The paper by Valkema et al. [6] evaluated FDG-PET/MRI against FDG-PET (control). Our guide asks the question about PET, but as more evidence emerge, the question of whether PET/MRI, or other PET tracers have relevance would need to be considered. So, while the current evidence does not affect the conclusion as is defined by the guideline, we should consider thinking about asking the question whether other tracers and PET/MRI may be added. From what I know of the literature, we are not there yet but may be so in the next one or two years. I am not sure who will address whether the scope of the question need to be revisited.

Fever of Unknown Origin

Current indications for FUO

- No indications are currently issued for FUO

Reviewer's Comments – Dr. Amit Singnurkar

No immediate change based on this, but we will bank it when we find someone to do a formal review on this – we are working on this at PET Steering.

Gastrointestinal Cancer

Current Indications for PET/CT in Colorectal Cancer (apparent limited metastatic):

- PET for the staging or re-staging of patients with apparent limited metastatic disease (e.g., organ-restricted liver or lung metastases) or limited local recurrence, who are being considered for radical intent therapy

Note: as chemotherapy may affect the sensitivity of the PET scan, it is strongly recommended to schedule PET at least six weeks after last chemotherapy, if possible.

Current Indications for PET/CT in Colorectal Cancer (Recurrent)

- PET where recurrent disease is suspected on the basis of an elevated and/or rising carcinoembryonic antigen level(s) during follow-up after surgical resection but standard imaging tests are negative or equivocal

Current Indication for PET/CT in Anal Canal Cancer (staging or re-staging):

- PET for the initial staging of patients with clinical stage II-IV squamous cell carcinoma of the anal canal, or when conventional imaging is equivocal for a specific stage; or for re-staging of patients with limited recurrence, after primary treatment, being considered for definitive salvage therapy

Reviewer's Comments - Dr. Aamer Mahmud

Based on this information, I do not see a need of further review or a new recommendation.

Genitourinary Cancer
Current Indications for Genitourinary cancer
Current Indication for Bladder Cancer (muscle invasive):

- PET for the staging of patients with newly diagnosed muscle-invasive urothelial carcinoma of the bladder being considered for curative intent treatment with either radical cystectomy or radiation-based bladder preservation therapy; TNM stage T2a-T4a, N0-3, M0

Current Indications for PET/CT in Germ Cell Tumours (recurrent/persistent disease)

- PET where recurrent disease is suspected on the basis of elevated tumour marker(s) - (beta human chorionic gonadotrophin 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 Indications for PET/CT in Prostate Cancer (PSMA PET)

PSMA PET in the following patient populations:

- Initial staging of patients with a new diagnosis of high-risk prostate cancer being considered for radical (curative) therapy.

OR

- Staging of patients with recurrent prostate cancer who fall into one of the following pre-defined cohorts:
    - Post-prostatectomy node positive disease or persistently detectable prostate-specific antigen (PSA)
    - Biochemical failure post-prostatectomy
    - Biochemical failure following radical prostatectomy followed by adjuvant or salvage radiotherapy
    - Rising PSA post-prostatectomy despite salvage hormone therapy
    - Biochemical failure following treatment for oligometastatic disease
    - Biochemical failure following primary radiotherapy
    - Rising PSA and/or progression on conventional imaging despite prior second line hormone therapy or chemotherapy for castrate resistant prostate cancer
    - Where confirmation of site of disease and/or disease extent may impact clinical management over and above the information provided by conventional imaging (requires a case-by-case review)

Reviewer's Comments - Dr. Glenn Bauman

No changes to the current indications based on these publications.

Gynecologic Cancer
Current Indications for Cervical Cancer

- PET for the staging of locally advanced cervical cancer when:

- CT/MR shows positive or indeterminate pelvic nodes (>7mm and/or suspicious morphology)

OR

- CT/MR shows borderline or suspicious para-aortic

OR

- CT/MR shows suspicious or indeterminate distant metastases (e.g., chest nodules)

Current Indication for PET/CT in Gynecologic Malignancies (recurrent, prior to salvage therapy)

- PET for re-staging of patients with recurrent gynecologic malignancies under consideration for radical salvage surgery (e.g., pelvic exenteration)

Reviewer's Comments - Dr. Ji-Hyung Jang

There seems to be growing evidence that PET may potentially be useful in the ovarian cancer recurrence setting, but the study sample size remains small, and I think the actual translation to prognosis (i.e., improved survival) remains unknown.

Head and Neck Cancer and Unknown Primary
Current indication for Head and Neck Cancer

Unknown primary

- PET for the evaluation of metastatic squamous cell carcinoma in neck nodes when the primary disease site is unknown after standard radiologic and clinical investigation

***Note**: a panendoscopy is **NOT** required prior to the PET scan*

Nasopharyngeal (baseline staging)

- PET for the staging of nasopharyngeal cancer

***Note**: for cervical esophageal cancer, see* Gastrointestinal Cancers

Head & Neck node positive (baseline staging)

- PET for the baseline staging of node positive (N1-N3) head and neck cancer where PET will impact radiation therapy (e.g., radiation volume or dose)

Head and Neck (re-staging after chemoradiotherapy)

- PET to assess patients with N1-N3 metastatic squamous-cell carcinoma of the head and neck after chemoradiation (human papilloma virus negative); or who have residual neck nodes ≥1.5 cm on re-staging CT performed 10 to 12 weeks post therapy (human papilloma virus positive).

Thyroid (recurrent)

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

Anaplastic Thyroid (staging)

- PET for the staging of histologically proven anaplastic thyroid cancer with negative or equivocal conventional imaging work-up

Medullary Thyroid (staging & recurrent)

- PET for the baseline staging of histologically proven medullary thyroid cancer being considered for curative intent therapy or where recurrent disease is suspected on the basis of elevated and/or rising tumour markers (e.g., calcitonin) with negative or equivocal conventional imaging work-up

Reviewer's Comments - Dr. Amit Singnurkar

No further action based on the literature found.

Hematologic Cancer

Current Indications for PET/CT in Lymphoma

- Staging: PET for the baseline staging of patients with Hodgkin's or non-Hodgkin's lymphoma
- Interim response assessment for Hodgkin lymphoma: PET for the assessment of response in Hodgkin lymphoma following two or three cycles of chemotherapy when curative therapy is being considered
- Interim response assessment for non-Hodgkin lymphoma (pediatrics only, younger than 18 years; or 18 to 20 years old and treated at a pediatric centre): PET for the assessment of response in non-Hodgkin's lymphoma after a minimum of two cycles of chemotherapy when curative therapy is being considered
- End of therapy response assessment:
    - PET for the evaluation of residual mass(es) or lesion(s) (e.g., bone) 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
    - PET to assess response to chimeric antigen receptor T-cell therapy, 90 days post transfusion

Current Indications for Multiple Myeloma or Plasmacytoma

To evaluate the impact of PET on the management of patients with plasmacytoma or myeloma for the following indications:

- Solitary plasmacytoma: For patients with presumed solitary plasmacytoma who are candidates for curative-intent radiotherapy (to determine whether solitary or multifocal/extensive disease)
- Smoldering myeloma: Work-up of patients with smoldering myeloma (to determine whether smoldering or active myeloma)
- Nonsecretory myeloma, oligosecretory myeloma, or POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes): Baseline staging and response assessment
- Newly-diagnosed secretory multiple myeloma: Work-up of patients with newly diagnosed secretory multiple myeloma

Reviewer's Comments - Dr. Jill Dudebout

I have reviewed the papers and the only one that I think warrants discussion is the Guerra paper [29]. So technically the current indications for end-of-treatment PET scan are in patients "when further potentially curative therapy...Is being considered". That does not apply

to low-grade lymphomas such as follicular lymphoma because technically treatment indication is considered palliative; these patients will not be cured. However, I have noted in practice that already neither I myself nor my colleagues have ever had a PET scan denied for follicular lymphoma at end of treatment and it is a powerful clinical tool to guide whether further treatment such as radiation could be used to improve the response (but technically is still not curative, just for PFS). The Guerra paper shows the prognostic utility of EOI PET scan in patients with follicular lymphoma but did not go into whether certain interventions such as radiation could change the outcome. Interestingly it showed that maintenance rituximab likely could not be safely omitted in patients with a negative scan. One could argue from the prognostic value alone that it would be helpful to clinicians to approve as an indication (and in practice I believe this is already happening and would make sense to align the indications with utilization).

Melanoma

Current Indications for Melanoma

Melanoma (Staging)

PET for the staging of patients with localized "high-risk" melanoma, or for the evaluation of patients with isolated melanoma metastases when surgery or other ablative therapies are being considered.

Metastatic Melanoma (Immunotherapy)

- Baseline staging: PET for the staging of patients before starting immunotherapy; or for patients who are receiving immunotherapy and have not previously had a baseline PET
- Early response assessment: PET after two to four cycles of immunotherapy for early response assessment of patients with metastatic melanoma currently receiving immunotherapy
- End-of-therapy response assessment: PET for response assessment of patients with metastatic melanoma at end of immunotherapy

Reviewer's Comments - Dr. Nicole Look Hong

1. The three newest papers provided centre around the diagnostic performance of PET/CT (sensitivity, specificity, AUC) in relation to local, regional and/or distant metastasis. While statistically sound estimates are provided, the meta-analyses and meta regression (as appropriate) are not specifically quantitatively correlated with patient outcomes or changes in patient management. As such, it is difficult to use these as evidence to change any particular recommendations/indications within the province at this time.

2. With respect to recommendations potentially under consideration with the PET team, there are two areas where I think that PET/CT indications should be considered in melanoma and that we are working on:
    - *Surveillance* for high-risk melanoma patients (stage IIb - IIId, ± resected stage IV, ± recurrent). This is suggested in the table for the 2023-1 review.
    - *Staging and Monitoring for Merkel cell carcinoma* - this is also suggested in the 2023-1 review. The Zamani-Siahkali et al. paper [37] comments on staging. But given the use of immunotherapy in a similar way to melanoma in this disease, our clinical community thinks that early response assessment and end-of-therapy assessments (akin to the melanoma indications) would be appropriate here also. However, given the incidence of disease is so much lower than melanoma, the chance that large cohorts or trials for this patient population will become available is low.

- Both of these indications may be situations in which a PET/CT registry is appropriate to collect Ontario-specific data.
- If possible, I suggest that a targeted search for PET and Merkel cell carcinoma be done in the future in conjunction with the melanoma-site search.

3. New and emerging trends - based on current literature and emerging changes in clinical practice, I suspect these areas might come up in future literature:
    - Similar to the Mirshagahvalad paper [36], there may be more reports of PET/CT, diagnostic characteristics and clinical utility in orphan melanoma populations -- e.g., uveal melanoma, acral lentiginous melanoma, mucosal melanoma, specific mutations (e.g., BRAF, CKIT)
    - Use of PET/CT for prognostication (as suggested by the Mirshagahvalad paper [36])
    - Use of PET/CT in the neoadjuvant setting to assess early response to systemic therapy and guide surgical management

Non-FDG Tracers
Current recommendations for the use of PET/CT with non-FDG tracers:

Prostate-specific Membrane Antigen (PSMA) PET:

PSMA PET in the following patient populations:

- Initial staging of patients with a new diagnosis of high-risk prostate cancer being considered for radical (curative) therapy

OR

- Staging of patients with recurrent prostate cancer who fall into one of the following pre-defined cohorts:
    - Post-prostatectomy node positive disease or persistently detectable PSA
    - Biochemical failure post-prostatectomy
    - Biochemical failure following radical prostatectomy followed by adjuvant or salvage radiotherapy
    - Rising PSA post-prostatectomy despite salvage hormone therapy
    - Biochemical failure following treatment for oligometastatic disease
    - Biochemical failure following primary radiotherapy
    - Rising PSA and/or progression on conventional imaging despite prior second line hormone therapy or chemotherapy for castrate resistant prostate cancer
    - Where confirmation of site of disease and/or disease extent may impact clinical management over and above the information provided by conventional imaging (requires a case-by-case review)

Ga68-DOTATATE-PET and FDG-PET:
Medullary Thyroid (staging & recurrent)
PET for the baseline staging of histologically proven medullary thyroid cancer being considered for curative-intent therapy or where recurrent disease is suspected on the basis of elevated and/or rising tumour markers (e.g., calcitonin) with negative or equivocal conventional imaging work-up.

Ga68-DOTATATE-PET

Diagnosis:

- PET for the evaluation of a pancreatic, small bowel or mesenteric mass with findings suggestive of a neuroendocrine tumour (NET) (e.g., hypervascular pancreatic mass, desmoplastic mesenteric mass) on conventional imaging
- PET for the evaluation of extra-adrenal mass (e.g., carotid body nodule), with conventional imaging and/or elevated biomarkers suggestive of a pheochromocytoma/paraganglioma (PPGL)
- PET for a patient with a genetic syndrome predisposing to NETs and a biochemical and/or morphological suspicion of a NET in whom PET results would measurably impact management

Special Considerations for Diagnosis:

- Patients with a suspicious mass in another anatomical location (e.g., lung) without elevated biochemical markers should be considered for further work-up and/or biopsy before the PET. PET could be considered after a failed biopsy or if a biopsy is not feasible.
- Patients with a pancreatic tail mass suggestive of a NET should have a Tc-99m sulpha colloid or red blood cell scan to exclude intrapancreatic accessory spleen as both can present Ga-68 DOTATATE avid.

Initial staging:

- PET for a histologically proven well-differentiated NET (G1-G3), including unknown primary, or pheochromocytoma/paraganglioma (PPGL)
- PET for a histologically proven medullary thyroid cancer being considered for curative intent therapy

Special Considerations for Initial Staging:

- PET is not appropriate for patients with Type 1 Gastric NET, neuroendocrine carcinomas (NEC) and adenocarcinomas with NET features
- Unless there are unique clinical and/or structural concerns, PET is not routinely appropriate for patients with diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH)
- PET for the initial staging of a patient with an appendiceal NET should be considered when there are positive lymph nodes, the tumour is greater than 1 cm, and/or the tumour is invading through the serosa into the mesoappendix
- PET for the initial staging of a patient with medullary thyroid cancer should be considered when the patient has yet to have a thyroidectomy or following it when biomarkers are positive with negative or equivocal structural imaging

Re-staging:

- PET for a patient with progressive NETs disease and is being considered for publicly funded Peptide Receptor Radionuclide Therapy (PRRT)

Note: For PRRT consideration, a PET scan should be completed within 12 months; however, a more recent PET scan should be considered if there are concerning clinical features (e.g., de-differentiation)

- New baseline PET scan for patients with new metastatic disease on conventional imaging and/or clinical suspicion of de-differentiation
- *PET for a patient with NETs disease when surgery (e.g., de-bulking, focal ablation, liver-directed therapy) is being considered

- *PET for a patient with NETs disease where conventional imaging is negative or equivocal at the time of clinical and/or biochemical progression

(*): These are preliminary indications and are likely to be refined

- PET for a patient with medullary thyroid cancer when recurrent disease is suspected on the basis of elevated and/or rising tumour markers (e.g., calcitonin), with negative or equivocal conventional imaging work-up

Special considerations for routine surveillance:

- Requests for routine surveillance when there is no clinical or biochemical suspicion of recurrence or progression are not eligible

Ga68-DOTATATE PET

Neuro endocrine tumours

Diagnosis:

- PET for the evaluation of a pancreatic, small bowel or mesenteric mass with findings suggestive of a NET (e.g., hypervascular pancreatic mass, desmoplastic mesenteric mass) on conventional imaging
- PET for the evaluation of extra-adrenal mass (e.g., carotid body nodule), with conventional imaging and/or elevated biomarkers suggestive of a PPGL
- PET for a patient with a genetic syndrome predisposing to NETs and a biochemical and/or morphological suspicion of a NET in whom PET results would measurably impact management

Special Considerations for Diagnosis:

- Patients with a suspicious mass in another anatomical location (e.g., lung) without elevated biochemical markers should be considered for further workup and/or biopsy before the PET. PET could be considered after a failed biopsy or if a biopsy is not feasible
- Patients with a pancreatic tail mass suggestive of a NET should have a Tc-99m sulpha colloid or red blood cell scan to exclude intrapancreatic accessory spleen as both can present Ga-68 DOTATATE avid

Initial staging:

Note: Initial staging PET scans should be requested within 1 year from the initial diagnosis.

- PET for a histologically proven well-differentiated NET (G1-G3), including unknown primary, or PPGL
- PET for a histologically proven medullary thyroid cancer being considered for curative intent therapy

Special Considerations for Initial Staging:

- PET is not appropriate for patients with type 1 gastric NET, neuroendocrine carcinomas (NEC), and adenocarcinomas with NET features
- Unless there are unique clinical and/or structural concerns, PET is not routinely appropriate for patients with diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH)
- PET for the initial staging of a patient with an appendiceal NET should be considered when there are positive lymph nodes, the tumour is greater than 1 cm, and/or the tumour is invading through the serosa into the mesoappendix
- PET for the initial staging of a patient with medullary thyroid cancer should be considered when the patient has yet to have a thyroidectomy or following it when biomarkers are positive with negative or equivocal structural imaging

Re-staging:

- PET for a patient with progressive NETs disease and is being considered for publicly funded peptide receptor radionuclide therapy (PRRT)

Note: For PRRT consideration, a PET scan should be completed within 12 months; however, a more recent PET scan should be considered if there are concerning clinical features (e.g., de-differentiation)

- New baseline PET scan for patients with new metastatic disease on conventional imaging and/or clinical suspicion of de-differentiation
- *PET for a patient with NETs disease when surgery (e.g., de-bulking, focal ablation, liver-directed therapy) is being considered
- *PET for a patient with NETs disease where conventional imaging is negative or equivocal at the time of clinical and/or biochemical progression

(*): These are preliminary indications and are likely to be refined.

- PET for a patient with medullary thyroid cancer when recurrent disease is suspected on the basis of elevated and/or rising tumour markers (e.g., calcitonin), with negative or equivocal conventional imaging work-up

Special considerations for routine surveillance:

- Requests for routine surveillance when there is no clinical or biochemical suspicion of recurrence or progression are not eligible

Reviewer's Comments - Dr. Amit Singnurkar

No further action based on this.

Pancreatic Cancer

No indication currently exists for the utilization of PET/CT in pancreatic cancer.

Reviewer's Comments

No expert reviewed the evidence at this time.

Pediatric Cancer

Current Indications for Pediatric Cancer (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
    - 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

For the assessment of response in Hodgkin or non-Hodgkin lymphoma after a minimum of two cycles of chemotherapy when curative therapy is being considered.

Reviewer's Comments - Dr. Amer Shammas

The two articles [54,55] are about utilization PET to evaluate bone marrow at initial staging for pediatric oncology. The second paper is interesting (Du et al) and is align with growing evidence of using FDG PET for evaluation bone marrow at initial staging for Ewing Sarcoma. Our pediatric registry has already included sarcomas for initial staging.

Sarcoma

Current Indications for PET/CT in Sarcoma:

- For the initial staging of patients with histologically confirmed high grade (≥ grade 2), or ungradable, soft tissue or bone sarcomas, when conventional work-up is negative or equivocal for metastatic disease, prior to curative intent therapy.
- For re-staging of patients with suspicion of, or histologically confirmed, recurrent sarcoma (local recurrence or limited metastatic disease) when radical salvage therapy is being considered

Current Indication for PET/CT in plexiform neurofibromas:

- For patients with suspicion of malignant transformation of plexiform neurofibromas.

Reviewer's Comments - Dr. Gina Di Primio

The Meta-analysis only addresses peripheral nerve sheath tumors but is complementary to the current evidence. In a small sub-group of sarcomas (MPNST) both MRI and FDG-PET are useful.

I agree with the published conclusions; and I think it can be added as evidence to support the use of FDG-PET and MRI but not one over the other.

The study doesn't change our current recommendations.

Thoracic Cancer

Lung – non-small cell lung cancer (clinical stage I-III)

Eligibility criteria:

- PET for initial staging of patients with NSCLC (clinical stage I – III) being considered for potentially curative therapy
  OR
- for re-staging of patients with locoregional recurrence, after primary treatment, being considered for definitive salvage therapy
  OR
- for staging of patients with oligometastatic NSCLC being considered for definitive local therapy

Note: Histological proof is not required prior to PET if there is high clinical suspicion for NSCLC (e.g., based on patient history and/or prior imaging)
Note: PET is appropriate for patients with either histological proof of locoregional recurrence or strong clinical and radiological suspicion of recurrence who are being considered for definitive salvage therapy

Lung – small cell lung cancer (clinical stage I-III)

- PET for initial staging of patients with limited disease small cell lung cancer where combined modality therapy with chemotherapy and radiotherapy is being considered

Lung – solitary pulmonary nodule

- PET 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

Lung – mesothelioma

- PET for the staging of patients with histologic confirmation of malignant mesothelioma

Reviewer's Comments – Dr. Donna Maziak

The papers [57-62] do not change the indications for PET-CT scans we have established. However, ^{68}GA FAPI isotope maybe something to watch for in the future of PET scans. It is true that radiology often uses the PET scan to direct the lung biopsy to ensure the result is more fruitful (i.e., not just necrosis) but this does not apply to our indications.

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CONTACT INFORMATION

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

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Appendix 1

Protocol for PET 6-Month Monitoring Reports
Version 1 June 20, 2024

The purpose of this document is to outline the protocol for the regular monitoring of literature pertaining to the use of positron emission tomography/computed tomography (PET/CT) or positron emission tomography/magnetic resonance imaging (PET/MRI) in cancer and selected non cancer diseases. The 6-month monitoring reports serve as a means to ensure that the current PET registry and insured indications, together with the recommendation reports remain relevant, current and evidenced-based. The PEBC has a formal and standardized process (PEBC Assessment & Review Protocol) for updating guidelines and other guidance documents. However, all documents produced by the PET Steering Committee group are maintained through this regular literature protocol.

Research topic

The use of PET/CT, PET/MRI for imaging of suspected or diagnosed cancers (all cancer sites), non-cardiac sarcoidosis, epilepsy, and dementia.

Target population

Patients with suspected or diagnosed cancer(s), or epilepsy or dementia. Please note that this is not limited to those cancers with approved or insured indications or PEBC Recommendation Reports. As of 2011, non-cardiac sarcoidosis has been added to the list of disease sites. As of 2013, epilepsy has been added to the list of disease sites. Includes adults (any age) and children.

Index test/Interventions

Positron emission tomography/computed tomography with the radiopharmaceutical tracer ^{18}F- fluorodeoxy glucose (18F-FDG).

As of February 2013, the following radiopharmaceutical tracers (or probes) will be added to the monitoring reports:

- ^{18}F, 11C-Choline (prostate cancer) F18-Choline PET/CT (FCH)
- ^{18}F-FET PET ([18F]fluoroethyl)-L-tyrosine) (brain)
- ^{18}F-FLT ([18F]3-deoxy-3F-fluorothymidine) (various)
- ^{18}F-MISO (hypoxia tracer)
- ^{18}F-FAZA (hypoxia tracer)
- ^{18}F-fluoride (more accurate than bone scanning)
- ^{18}F-flurpiridaz (Cardiac)
- ^{18}F-florbetapir (Amyvid) (dementia imaging)
- ^{18}F-FDOPA
- ^{18}F-FACBC (fluciclovine)
- ^{68}Ga-PSMA/18F-DCFPyL (prostate-specific membrane antigen) 68Ga-NeoB (IS A THERANOSTIC)
- ^{68}Ga –DOTA-(NOC, TOC, TATE)
- ^{68}Ga-FAPI 68Ga-FAPI-46 ^{68}Ga-FAPI-04
- [18F]sodium fluoride ([^{18}F]NaF); [^{18}F]NaF PET/CT
- ^{68}Ga-SSA PET/CT
- ^{18}F-florbetaben PET for Abeta, ^{18}F-flortaucipir PET for tau
- ^{68}Ga-SSA PET/CT.

- [^{68}Ga]Ga-DOTA-somatostatin analogs (SSAs) for neuroendocrine tumours

Other radiopharmaceuticals not approved in Canada

- ^{11}C-METHIONINE [MET] PET
- [^{68}Ga]Ga-NOTA-(TMVP1)2
- ^{99}mTc-Methionine Single-PET
- SCANDIUM 43, SC-44, SC-47 AS THERANOSTICS)
- [^{18}F]fluoromethylcholine ([^{18}F]F-CHO
- ([^{177}Lu]Lu-PSMA) - ^{177} Lu-DOTATATE – AS RADIOTHERANOSTIC
- ^{18}F-AlF-NOTA-octreotide (18F-AlF-OC)
- ^{18}F-MK-6240 FOR ALZHEIMER'S
- [^{18}F]FAPI
- ^{68}Ga-FAP-2286
- ^{18}F-flotufolastat
- ^{18}F-florbetaben PET for Abeta, ^{18}F-flortaucipir PET for tau
- ZIRCONIUM89
- ^{223}RaCl2 or ^{177}Lu-iPSMA
- Lead-203 VMT-alpha-Neuroendocrine
- Y-90 PET
- [^{11}C] PIB) PET
- ^{18}F-fluorocholine PET/CT
- ^{18}F-PSMA-1007
- 64-Cu radiolabeled tracers (DOTATATE PET/CT
- ^{18}F-boronophenylalanine positron emission tomography (BPA-PET)
- [^{18}F]AlF-NOTA-octreotide ([18F]AlF-OC)
- ^{18}F-Florapronol, FOR ALZHEIMER'S
- [^{18}F]FAPI-42 PET/CT
- 68Ga-4D-V/Q
- [^{18}F]SiTATE [^{18}F]SiTATE, a SiFAlin tagged [Tyr3]-octreotate (TATE) PET trace
- (SSTR-PET/CT) using [^{68}Ga]-labeled tracers
- alphavbeta6-integrin PET/CT
- ^{68}Ga-Trivehexin PET/CT
- [^{18}F]fluoro-PEG-folate PET/CT [18F]fluoro-PEG6-folate

The radiopharmaceutical tracers above will be summarized in their own section within the monitoring reports. The results will be summarized in an aggregate manner to better evaluate the tracers' impact on PET/CT technology.

Comparator(s) or reference test(s)

Any of the conventional imaging or treatment methods associated with the disease site.

Appropriate reference standards are histopathology, or clinical- or imaging follow-up done with PET or (more often) with some other types of imaging. They usually use conventional imaging*.
*Conventional imaging: SPECT, Biomarkers, physical examination, or anything that is not PET

Outcome

- Diagnostic parameters (e.g., sensitivity, specificity, PPV, NPV, accuracy),
- Change in clinical management or patient outcome (e.g. survival, quality of life, prognostic indicators, time until recurrence) or safety outcome (e.g. avoidance of unnecessary surgery).

Literature Search database(s)

EMBASE, MEDLINE, and Guideline Developers (e.g., ASCO, SIGN, etc.). The literature search strategies for EMBASE and MEDLINE can be found in Appendix 1a and 1b, respectively. The literature search strategies have been amended as of February 2013 to become non-radiopharmaceutical tracer specific. Prior to this the search strategies were focused only on ^{18}F-FDG as the sole radiopharmaceutical tracer under evaluation.

Study design(s)

Clinical practice guidelines; systematic reviews; randomized controlled trial or quasi-randomized controlled trial or non-randomized controlled trial or controlled before and after study or prospective cohort study or historically controlled trial or nested case-control study or case-control study and retrospective study.

Study inclusion criteria

- Prospective or retrospective comparative studies evaluating the use of PET/CT in primary cancer, non-cardiac sarcoidosis, epilepsy, or dementia.
- Single arm studies are included if the addition of PET/CT would influence the diagnosis. For example, the population would be patients with negative CT or MRI or no clinical suspicion of metastases, but PET/CT was able to detect metastases missed by conventional imaging with a sensitivity, specificity and accuracy of a certain percentage. In this case, even though it is a single arm study, the information provided by PET/CT is very useful.
- Study not duplicated or superseded by a later study with the same purpose from the same institution
- Study reported numeric data on at least one objective outcome of interest
- Study with ≥12 patients for prospective study and ≥50 patients for retrospective (≥25 for sarcoma) study with the disease site of interest
- Study used a suitable reference standard (histopathologic and/or clinical and imaging follow-up) when appropriate

Exclusion criteria

- Studies of cardiac populations
- Studies of populations that do not have cancer
- Animal studies
- PET-only studies (we are interested in PET/CT or PET MRI studies)

- Narrative reviews, commentaries, editorials
- Studies published outside of the 6-month period of interest

Time frame (search period)

- Six-month intervals (January to June and July to December)

Reviews of included studies

Once the literature has been screened, the research coordinator will summarize the included studies into tables based on disease sites. The research coordinator will then send the table and full-text copies of the studies to assigned representatives from the PET Steering Committee. These committee members will then evaluate whether the current literature should be reviewed by a member of a disease site group (DSG). If the literature is deemed eligible for review the DSG representative (or a team from the DSG) will review the literature and indicate whether or not the new literature warrants an in-depth review as to how PET/CT is utilized in the disease site. The reviews from the PET Steering Committee members and the DSG representatives will be consolidated in the six-month monitoring report. The research coordinator along with the assigned reviewers will make a concerted effort to ensure new evidence from all the disease sites is reviewed. However, it is possible that one or more disease sites will not be reviewed due to slow turnaround time.

Finalization

All six-month monitoring reports will receive final copy editing prior to web posting to the Cancer Care Ontario webpage (https://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=75520). The reports will be presented to the committee members at a scheduled PET Steering Committee meeting to signify the completion of the document. Barring any unexpected circumstances, the reports should be completed within six months from the end of each search period.

Appendix 1A
EMBASE Search Strategy (Amended February, 2013)

1. Tomography, Emission-Computed/ or (positron adj emission adj tomography).ti,ab. or PET.ti,ab. or positron emission tomography/ or PET-CT.ti,ab. or PET$CT.ti,ab.
2. (pet or petscan$ or pet ct).ti,ab.
3. Tomography, Emission-Computed/
4. emission.ti,ab.
5. (tomograph or tomographs or tomographic$ or tomogrpahy or tomographies).ti,ab.
6. 4 and 5
7. 2 or 3 or 6
8. exp neoplasm/ or neoplasm staging/ or cancer$.ti,ab. or tumor$.ti,ab. or tumour$.ti,ab. or carcinoma$.ti,ab. or neoplasm$.ti,ab. or staging.ti,ab. or metastas$.ti,ab. or metastatic.ti,ab. or exp neoplasm metastasis/ or exp neoplastic processes/ or neoplastic process$.ti,ab. or adenocarcinoma$.ti,ab. or sarcoid$.ti,ab. or epilepsy$.ti,ab.
9. 1 and 8
10. limit 9 to (english language and yr="2012" and dd=20120701-20121231)**
11. (comment or editorial or letter or case reports).pt.
12. 10 not 11
13. (integrative research review$ or research integration or (methodologic$ adj10 review$) or (methodologic$ adj10 overview$) or (quantitativ$ adj10 review$) or (quantitativ$ adj10 overview$) or (quantitativ$ adj10 synthes$) or (systematic adj10 review$) or (systematic adj10 overview$) or (metaanal or meta anal$)).ti,ab. or meta-analysis/
14. (review-tutorial or review-academic or review).pt. or (pooling or pooled analys$ or mantel heanszel$).ti,ab.
15. (peto$ or der simonian or dersimonian or fixed effect$).ti,ab.
16. 13 or 14
17. 12 and 16
18. 12 not 16
19. (conference or conference proceeding or conference proceeding$ or conference paper or conference paper$ or discussion or discussion$ or in brief or invited comment or invited comment$).ti,ab.
20. 17 not 19
21. 18 not 19

** - *publication dates will change based on the timeframe of the 6-month monitoring report.*

Appendix 1B
MEDLINE Search Strategy (Amended February, 2013)

1. Tomography, Emission-Computed/ or (positron adj emission adj tomography).ti,ab. or PET.ti,ab. or PET-FDG.ti,ab. or positron emission tomography/ or PET-CT.ti,ab. or PET$CT.ti,ab.
2. (pet or petscan$ or pet ct).ti,ab.
3. Tomography, Emission-Computed/
4. emission.ti,ab.
5. (tomograph or tomographs or tomographic$ or tomogrpahy or tomographies).ti,ab.
6. 4 and 5
7. 2 or 3 or 6
8. exp neoplasm/ or neoplasm staging/ or cancer$.ti,ab. or tumor$.ti,ab. or tumour$.ti,ab. or carcinoma$.ti,ab. or neoplasm$.ti,ab. or staging.ti,ab. or metastas$.ti,ab. or metastatic.ti,ab. or exp neoplasm metastasis/ or exp neoplastic processes/ or neoplastic process$.ti,ab. or adenocarcinoma$.ti,ab. or sarcoid$.ti,ab. or epilepsy$.ti,ab.
9. 1 and 8
10. limit 9 to (english language and yr="2012")
11. (comment or editorial or letter or case report).pt.
12. 10 not 11
13. (integrative research review$ or research integration or (methodologic$ adj10 review$) or (methodologic$ adj10 overview$) or (quantitativ$ adj10 review$) or (quantitativ$ adj10 overview$) or (quantitativ$ adj10 synthes$) or (systematic adj10 review$) or (systematic adj10 overview$) or (metaanal or meta anal$)).ti,ab. or meta-analysis/
14. (review-tutorial or review-academic or review).pt. or (pooling or pooled analys$ or mantel heanszel$).ti,ab.
15. (peto$ or der simonian or dersimonian or fixed effect$).ti,ab.
16. 13 or 14
17. 12 and 16
18. 12 not 16
19. (conference or conference proceeding or conference proceeding$ or conference paper or conference paper$ or discussion or discussion$ or in brief or invited comment or invited comment$).ti,ab.
20. 17 and 19
21. 17 not 19
22. (201207: or 201208: or 201209: or 201210: or 201211: or "201212").ed.**
23. 20 and 22
24. 21 and 22

** - *publication dates will change based on the timeframe of the 6-month monitoring report*

Appendix 2: Summary of included studies from January to June 2024.

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
Breast Cancer								
Perez-Garcia et al, 2024 [3]	Phase II RCT (PHERGain trial)	356 patients randomly assigned 1:4 to receive either TCHP or PET-based adapted strategy after 2 cycles of neoadjuvant therapy (HER2-positive, stage I-IIIA invasive, operable breast cancer)	FDG PET/CT (After 2 cycles of HP with or without endocrine therapy, PET-responders continued with 6 more cycles of HP with or without endocrine therapy, while PET-non-responders switched to 6 cycles of TCHP) (n=285)	6 cycles of TCHP (n=71)	NA	NA	NA	The 3-year invasive DFS rate for patients who received PET-based adapted strategy was 94.8% (95% CI, 91.4 to 97.1), and 98.3% in the TCHP group (95% CI 95.1-100). The 3-year EFS rate was 93.5% (90.7-96.5) in the PET-adapted group and 98.4% (95.3-100) in the TCHP group. The 3-year OS rate was 98.5% (97.1-100 in the PET adapted group and 98.4 (95.3-100) in the TCHP group. Incidences of treatment-related grade 3-4 toxicities (33% in the PET-adapted versus 62% in the TCHP group) and serious adverse events (14% versus 28% respectively) were lower among patients in the PET-adapted strategy group.
Sae-Lim et al, 2024 [1]	Retrospective, single institution	265 patients who underwent preoperative staging (primary operable breast cancer)	FDG PET/CT	MRI	Histopathology	**Axillary lymph node metastases** Sens: 53.4%* Spec: 82.1%* PPV: 65.5% NPV: 73.5% Accu: 70.9%	**Axillary lymph node metastases** Sens: 71.8%* Spec: 67.8%* PPV: 56.0% NPV: 80.8% Accu: 69.2%	NA
Ozdemir et al, 2024 [2]	Retrospective	81 patients who underwent initial staging	FDG PET/CT	US, mammography, MRI, CT	Consensus from breast cancer tumour board	NA	NA	FDG PET/CT impacted treatment decision in 19.7% (16/81) of patients (11—neoadjuvant

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
		(early-stage breast cancer)						treatment to surgery, 5— surgery to neoadjuvant treatment).
Francois et al, 2024 [4]	Retrospective, single institution	287 female patients with clinical stage I or IIA, HER2+, or TNBC.	^{18}F-FDG-PET/CT for cancer staging prior to any surgical or systemic treatment (n=287)	NA	Histopathology	NA	NA	The results of PET changed the treatment plan for 52 (18%) of patients. *Inter-modality* (i.e., Change in planned treatment): 7 patients (2%) – switched from curative to palliative intent. *Intra-modality* (i.e., Modification in dose/site/strategy of a previously indicated treatment, due to discovery of locoregional lymph node involvement: Revision of surgical or radiation procedures): 45 patients (16%)
Dementia								
Lindhout et al, 2024 [63]	Retrospective (register-based cohort)	13,312 patients diagnosed with dementia	PET/SPECT	CT/MRI, neurophysiologic examination, EEG, CSF testing	NA	NA	NA	Time to poor outcome (i.e., institutionalization in long-term facility or death). Patients who had PET/SPECT during the diagnostic phase had a higher risk of experiencing a poor outcome (RR 1.09, 95% CI 1.02-1.17). Median time to poor outcome was 3.2 years (or 1157 days, 95% CI 1090-1261) for those who had a PET/SPECT and 3.5 year (or 1274 days, 95% CI 1218-1341) for control patients that did not.

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
Esophageal Cancer								
Valkema et al, 2024 [6]	Prospective	21 patients who underwent restaging after neoadjuvant chemoradiotherapy (esophageal cancer)	FDG PET/CT; FDG PET/MRI	NA	Histopathology, clinical follow-up	**Primary residual disease** ***FDG PET/CT*** Sens: 86% Spec: 14%-57% PPV: 67%-80% NPV: 33%-67% Accu: 61%-76% ***FDG PET/MRI*** Sens: 36%-78% Spec: 14%-43% PPV: 56%-65% NPV: 25% Accu: 38%-57% **Locoregional residual disease** ***FDG PET/CT*** Sens: 17%-33% Spec: 46%-85% PPV: 22%-33% NPV: 60%-69% Accu: 42%-63% ***FDG PET/MRI*** Sens: 17%-33% Spec: 62%-85% PPV: 29%-33% NPV: 67%-69% Accu: 53%-63%	NA	NA
Ohsawa et al, 2024 [5]	Retrospective	124 patients who underwent preoperative assessment of lymph node status (esophageal squamous cell carcinoma)	FDG PET/CT	NA	Pathology	**Lymph node metastases** ***Pre-neoadjuvant chemotherapy* (patient-based)** Sens: 81.2% Spec: 43.6% Accu: 64.5% **(station-based)** Sens: 51.6% Spec: 96.0% Accu: 92.1% ***Post-neoadjuvant chemotherapy* (patient-based)** Sens: 47.8% Spec: 96.4%	NA	NA

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
						Accu: 69.4% **(station-based)** Sens: 28.2% Spec: 99.5% Accu: 93.1%		
Fever of unknown origin (FUO)								
Khan et al, 2024 [7]	Ambispective	573 patients with FUO	FDG PET/CT	NA	Histopathology	NA	NA	Guiding the biopsy site: 36 of 104 patients (34.6%) Providing a diagnosis: 219 of 573 (38%)
Gastrointestinal Cancer								
Ma et al, 2024 [8]	Meta-analysis	15 studies (1209 patients with rectal cancer)	FDG PET/CT	NA	Not specified	**Lymph node metastases (patient-based)** Pooled Sens: 56.0% Pooled Spec: 88.0% AUC: 0.75 **(node-based)** Pooled Sens: 65.0% Pooled Spec: 96.0% AUC: 0.90	NA	NA
Aymard et al, 2024 [10]	Prospective	48 patients who underwent presurgical staging (presumed localized colon cancer)	FDG PET/CT	CeCT, colonoscopy	Histopathology, imaging follow-up	**Primary tumour (lesion-based)** Sens: 94.0%* Spec: 87.0% PPV: 92.0% NPV: 89.0% **Lymph node metastases (patient-based)** Sens: 33.0% Spec: 90.0% PPV: 67.0% NPV: 70.0%	**Primary tumour (lesion-based)** ***CeCT + colonoscopy*** Sens: 78.0%* Spec: 97.0% PPV: 98.0% NPV: 73.0% **Lymph node metastases (patient-based)** ***CeCT*** Sens: 22.0% Spec: 84.0% PPV: 44.0% NPV: 65.0%	NA
Zhao et al, 2024 [9]	Meta-analysis	6 studies (396 locally progressive rectal cancer patients who	FDG PET/CT	MRI	Pathology	**Pathologic complete response** Pooled Sens: 78.0% Pooled Spec: 71.0% AUC: 0.80	**Pathologic complete response** Pooled Sens: 76.0% Pooled Spec: 74.0% AUC: 0.81	NA

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
		underwent assessment of treatment response after neoadjuvant chemoradiotherapy)						
Genitourinary Cancer								
Radha et al, 2024 [11]	Prospective	124 patients who underwent adrenal imaging (suspicious adrenal nodules)	FDG PET/CT	NA	Histopathology	**Diagnosis** Sens: 89.7% Spec: 86.6% PPV: 92.1% NPV: 82.9% Accu: 88.6%	NA	NA
Hirasawa et al, 2024 [12]	Prospective	150 patients with end-stage renal disease	FDG PET/CT	NA	Histopathology of the surgical specimen Histopathology of the needle biopsy specimen Clinical follow-up	**Diagnosis** Sens: 100% Spec: 93.9% NPV:100%	NA	NA
Gynecologic Cancer								
van Kol et al, 2023 [15]	Retrospective	145 patients who underwent response assessment of chemoradiotherapy (locally advanced cervical cancer)	FDG PET/CT	MRI	Histology, clinical follow-up, consensus from multidisciplinary team	**Locoregional residual disease** Sens: 63.0% Spec: 76.2% PPV: 55.8% NPV: 81.1%	**Locoregional residual disease** Sens: 63.3% Spec: 68.2% PPV: 47.7% NPV: 80.2%	NA
Elsayed et al, 2024 [13]	Prospective	27 patients who underwent follow-up after surgical treatment with or without chemotherapy (suspected recurrent ovarian cancer)	FDG PET/CT	CA-125 tumour markers	Histopathology, clinical or imaging follow-up	**Recurrence** Sens: 91.3% Spec: 75.0% PPV: 95.4% NPV: 60.3% Accu: 88.9%	**Recurrence** Sens: 62.5% Accu: 64.0%	NA

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
Wilson et al, 2024 [16]	Meta-analysis	15 studies (918 patients who underwent initial staging of ovarian cancer)	FDG PET/CT	CeCT	Histopathology, clinical follow-up	**Abdominal metastases** Pooled Sens: 87.0% Pooled Spec: 90.0%*	**Abdominal metastases** Pooled Sens: 82.0% Pooled Spec: 72.0%*	NA
Tsili et al, 2024 [14]	Meta-analysis	33 studies (2025 patients with primary or recurrent ovarian cancer)	FDG PET/CT	MDCT, MRI	Histopathology, clinical and/or imaging follow-up	**Peritoneal metastases (patient-based)** Pooled Sens: 93.7%* Pooled Spec: 91.5% Pooled DOR: 84.15 AUC: 0.97 **(region-based)** Pooled Sens: 58.3% Pooled Spec: 92.6% AUC: 0.89	**Peritoneal metastases (patient-based)** ***MDCT*** Pooled Sens: 79.7%* Pooled Spec: 92.1% Pooled DOR: 29.55 AUC: 0.91 ***MRI*** Pooled Sens: 82.7% Pooled Spec: 90.3% Pooled DOR: 93.95 AUC: 0.96 **(region-based)** ***MDCT*** Pooled Sens: 70.1% Pooled Spec: 90.2% AUC: 0.92 ***MRI*** Pooled Sens: 92.6% Pooled Spec: 90.3% AUC: 0.96	NA
Hong et al, 2024 [17]	Retrospective	95 patients with ovarian cancer who had undergone surgical treatment	FDG PET/CT	MRI, enhanced CT	Histopathology after the second operation	**Recurrence and metastases** Sens: 90.14% Spec: 70.83%[a] Accu: 85.26 PPV: 90.14 NPV: 70.83 [a]p<0.05 vs enhanced CT	**MRI** Sens: 87.32% Spec: 45.83% Accu: 76.84% PPV: 82.67% NPV: 55.00% **Enhanced CT** Sens: 85.92% Spec:41.67% Accu: 74.74% PPV: 82.67% NPV: 50.00% **Combination** Sens: 97.18%[ab] Spec: 95.83%[abc] Accu: 96.84%[abc] PPV: 98.57%[abc] NPV: 92.00%[ab]	NA

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
							[a]p<0.05 vs. enhanced CT, [b]p<0.05 vs. MRI, [c]p<0.05 vs. 18F-FDG PET/CT	
Head and Neck								
de Koster et al, 2024 [18]	Prospective (EfFECTS trial)	115 patients who underwent preoperative workup (cytologically indeterminate thyroid nodules)	FDG PET/CT	Molecular diagnostics	Histopathology, imaging follow-up	**Malignancy** Sens: 93.0% Spec: 41.0%* PPV: 36.0% NPV: 95.0%	**Malignancy** Sens: 80.0% Spec: 69.0%* PPV: 48.0% NPV: 91.0%	NA
Vogel et al, 2024 [21]	Prospective	98 patients who underwent initial staging, restaging for therapy control or follow-up for suspected relapse (differentiated thyroid cancer)	F-FDG PET/CT	NA	Pre- and post-PET questionnaires	NA	NA	Prior to FDG PET/CT, only 19.4% (19/98) of patients had an established treatment plan. With knowledge of FDG PET/CT findings, the proportion of patients with a well-defined treatment plan increased to 91.8% (90/98). Of those patients with an existing plan, FDG PET/CT results modified the therapeutic approach in 31.6% (6/19) (1—watchful waiting to radioiodine treatment, 2—further radioiodine treatment to follow-up, 3—radioiodine therapy to surgery or tyrosine kinase inhibitor).
Garcia-Curdi et al, 2024 [19]	Retrospective	169 patients who underwent initial staging (head and neck squamous cell carcinoma)	FDG PET/CT	CeCT	Histology, clinical follow-up	**Primary tumour** Sens: 95.8% Spec: 99.0% PPV: 98.6% NPV: 97.0% **Cervical lymph node metastases** Sens: 89.7% Spec: 99.0% PPV: 98.4%	**Primary tumour** Sens: 85.4% Spec: 67.5% PPV: 74.5% NPV: 80.6% **Cervical lymph node metastases** Sens: 66.2% Spec: 89.4% PPV: 79.6%	NA

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
						NPV: 93.5% **Distant metastases** Sens: 96.2% Spec: 96.5% PPV: 83.3% NPV: 99.3%	NPV: 80.9% **Distant metastases** Sens: 60.7% Spec: 98.6% PPV: 89.5% NPV: 92.7%	
Mair et al, 2024 [20]	Meta-analysis	28 studies (3378 patients with head and neck cancer)	FDG PET/CT	CT, MRI, US	Histopathology	**Extracapsular spread** Pooled Sens: 80.0% Pooled Spec: 93.0% Pooled +LR: 12.3 Pooled -LR: 0.21 Pooled DOR: 57.75	**Extracapsular spread** ***CT*** Pooled Sens: 63.0% (95% CI, 0.53-0.73) Pooled Spec: 85.0% (95% CI, 0.74-0.91) Pooled +LR: 4.33 Pooled -LR: 0.425 Pooled DOR: 10.1 ***MRI*** Pooled Sens: 83.0% (95% CI, 0.71-0.90) Pooled Spec: 85.0% (95% CI, 0.73-0.92) Pooled +LR: 5.7 Pooled -LR: 0.19 Pooled DOR: 29.18 ***US*** Pooled Sens: 80.0% (95% CI, 0.68-0.88) Pooled Spec: 84.0% (95% CI, 0.74-0.91) Pooled +LR: 4.83 Pooled -LR: 0.23 Pooled DOR: 20.69	NA
Zhang et al, 2024 [22]	Retrospective	154 patients with asymptomatic head and neck squamous cell carcinoma	FDG PET/CT	NA	Histopathology or follow-up imaging investigations	Sens: 100% Spec: 100% Accu: 100% PPV: 100% NPV: 100%	NA	NA
de Leeuw et al, 2024 [23]	RCT (Phase III), the ARTFORCE study	226 patients with T3-4-N0-3-M0 locally advanced head and neck squamous cell carcinoma	FDG PET/CT	NA	NA	NA	NA	PET-guided vs. conventional radiotherapy: PFS at 2 years: 68.6 % (95 % CI 60.4–77.9 %) vs. 66.9% (58.8–76.3%), HR 1.06 (0.70-1.61), p=0.78

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
								OS at 2 years: 80.7% (73.6–88.4%) vs. 79.3% (72.2–87.2%), HR 0.93 (0.59-1.47), p=0.76 Toxicity at 2 years Grade ≥2 xerostomia 10.3% vs. 14.1%, p=0.63; OR 0.70, 95% CI 0.23–2.04 Grade ≥3 dysphagia 6.4% vs. 3.8 % p=0.72; OR 1.71, 0.32–11.39)
Al-Lami et al, 2024 [24]	Systematic review and meta-analysis of comparative studies	9 studies with 373 patients with glioma	FDG PET/CT	PET/MRI	Not reported	PET/CT Sens: 61.2% (95% CI 46.4 – 74.2), p=0.0009 Spec: 83.2% (95% CI 67.3 – 92.3), p=0.231	PET/MRI: Sens: 85.5% (95% CI 76.2 – 91.6) p=0.538 Spec: 65.9% (95% CI 43.4 - 83.0) p=0.841	NA
Hematology								
Guo et al, 2024 [30]	Meta-analysis	15 studies (1989 patients with mature T- and natural killer-cell lymphoma)	FDG PET/CT	BMB	BMB, imaging follow-up	**Bone marrow involvement** Pooled Sens: 62.0% Pooled Spec: 92.0% Pooled +LR: 5.81 Pooled -LR: 0.50 Pooled DOR: 14.35 AUC: 0.85	NA	NA
Valizadeh et al, 2024 [35]	Meta-analysis	28 studies (2358 patients with lymphoma or focal splenic lesion)	FDG PET or PET/CT	CeCT/CT, CeMRI, MRI, CeUS, US	Histopathology, clinical and/or imaging follow-up	**Malignant spleen lesions or splenic involvement** Pooled Sens: 93.0% Pooled Spec: 82.8% AUC: 0.920	**Malignant spleen lesions or splenic involvement** ***CeCT/CT*** Pooled Sens: 73.6% Pooled Spec: 89.2% AUC: 88% ***CeMRI*** Pooled Sens: 81.4% Pooled Spec: 94.2% AUC: 85.3% ***MRI*** Pooled Sens: 60.8% Pooled Spec: 92.8% AUC: 70.3% ***CeUS***	NA

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
							Pooled Sens: 91.1% Pooled Spec: 85.7% AUC: 91.4% ***US*** Pooled Sens: 68.0% Pooled Spec: 83.9% AUC: 71.3%	
Fuchs et al, 2024 [28]	RCT (long-term follow-up of the HD16 trial)	1150 patients who underwent interim-PET response evaluation after 2 cycles of ABVD (newly diagnosed early-stage favourable HL)	FDG PET/CT	NA	Clinical follow-up	NA	NA	For PET-negative patients, the 5-year PFS was 94.2% for those who received combined-modality treatment and 86.7% for those who received ABVD only (HR, 2.05; 95% CI, 1.20 to 3.51, p=0.0072). The 5-year OS were 98.3% and 98.8%, respectively, p=0.14.
Guerra et al, 2024 [29]	RCT, phase III	729 follicular lymphoma patients with stage III-IV disease	FDG PET/CT (end of induction PET [EOI])	NA	Clinical follow-up	Ability of PET to predict PFS events: Sens: 38.0% Spec: 92.8% PPV: 50.0% NPV: 88.8% Accu: 84.1% Ability of PET to predict OS events: Sens: 51.7% Spec: 89.6% PPV: 20.3% NPV: 97.3% Accu: 87.7%	NA	Prognostic value of PET: PFS at 5 years PET +: 36% PET -: 71%
Krishna et al, 2024 [31]	Prospective	42 patients who underwent initial staging (newly diagnosed HL and NHL)	FDG PET/CT	BMA/BMB	BMA/BMB, imaging follow-up	**Bone marrow involvement** Sens: 86.6% Spec: 77.7% PPV: 68.4% NPV: 91.3% Accu: 80.9%	NA	NA
Kumar et al. 2024 [32]	Prospective	150 patients with lymphoma	FDG PET/CT	NA	Histopathology (150 patients)	**Nodal sites:** Sens: 95.4% NPV: 81.2% Diagnostic yield: 96.2% **Extra-nodal sites:**	NA	NA

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
						Sens: 98.3% NPV: 87.5% Diagnostic yield: 98.5%		
Doma et al, 2024 [27]	Retrospective	145 patients who underwent staging prior to start of treatment (stage II-IV DLBCL)	FDG PET/CT	BMB	Histopathology, imaging follow-up	**Bone marrow involvement** Sens: 88.4% Spec: 100% PPV: 100% NPV: 95.3% Accu: 96.5%	**Bone marrow involvement** Sens: 41.9% Spec: 100% PPV: 100% NPV: 46.8% Accu: 61.5%	NA
Chen and Zhao et al, 2024 [26]	Retrospective	201 patients who underwent initial staging (newly diagnosed peripheral T-cell lymphoma)	FDG PET/CT	NA	BMB	**Bone marrow involvement** Sens: 43.2% Spec: 90.2% PPV: 50.0% NPV: 87.6% Accu: 81.6%	NA	NA
Lee et al, 2024 [33]	Retrospective	193 patients who underwent initial staging (extranodal natural killer/T-cell lymphoma)	FDG PET/CT	BMB	BMB	**Bone marrow involvement** Sens: 30.4% Spec: 99.0%	NA	NA
Liang et al, 2024 [34]	Retrospective	84 patients who underwent pretreatment staging (newly diagnosed angioimmunoblastic T-cell lymphoma)	FDG PET/CT	BMB	BMB, imaging follow-up	**Bone marrow involvement** Sens: 40.0% Spec: 100% PPV: 100% NPV: 75.0%	**Bone marrow involvement** Sens: 76.7% Spec: 100% PPV: 100% NPV: 88.5%	NA
Melanoma								
Zamani-Siahkali et al, 2024 [37]	Meta-analysis	100 studies (10403 patients with melanoma)	FDG PET or PET/CT or PET/MRI	NA	Histopathology, follow-up, further imaging	**Regional lymph node metastases (patient-based)** Pooled Sens: 56.0% Pooled Spec: 97.0% AUC: 0.93 **(lesion-based)** Pooled Sens: 38.0% Pooled Spec: 98.0% **Distant metastases (patient-based)** Pooled Sens: 88.0%	NA	NA

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
						Pooled Spec: 94.0% AUC: 0.97 **(lesion-based)** Pooled Sens: 84.0% Pooled Spec: 93.0%		
Zhu et al, 2024 [38]	Meta-analysis	22 studies (2214 patients with suspected melanoma recurrence)	FDG PET/CT	NA	Histopathology, clinical follow-up	**Recurrence** Pooled Sens: 91.0% Pooled Spec: 91.0% AUC: 0.95	NA	NA
Mirshahvalad et al, 2024 [36]	Meta-analysis	27 studies (1075 patients with uveal melanoma)	FDG PET or PET/CT	NA	Not specified	**Primary intra-ocular tumour** Pooled Sens: 45.0% **Distant metastases** Pooled Sens: 96.0% Pooled Spec: 100% **Hepatic metastases** Pooled Sens: 95.0% Pooled Spec: 100% **Metastatic disease** Pooled Sens: 96.0% Pooled Spec: 100%	NA	NA
Thoracic Cancer								
de Fonseka et al, 2024 [58]	RCT (TARGET trial)	59 patients with a previous inconclusive pleural biopsy were randomized (1:1) to receive either CT-guided biopsy or PET/CT followed by CT-guided biopsy (suspected pleural malignancy)	FDG PET/CT + CT-guided biopsy (n=30)	CT-guided biopsy (n=29)	Biopsy, follow-up	**Diagnosis** Sens: 81.0% (54-96) NPV: 73.0%	**Diagnosis** Sens: 79.0% (54-94) NPV: 64.0%	The proportion of pleural malignancy correctly identified (RR, 1.03; 95% CI, 0.83 to 1.29, p=0.77), the number of invasive procedures undertaken to confirm diagnosis (IRR, 0.93; 95% CI, 0.56 to 1.55, p=0.78), the number of hospital visits (IRR, 1.30; 95% CI, 0.54 to 3.13, p=0.56), and survival (HR, 1.04; 95% CI, 0.39 to 2.75, p=0.94) were similar between the two groups. However, the median time to pleural malignancy diagnosis was longer for patients who received FDG PET/CT (92 days) compared to those who did not (35 days) (subHR,

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
								0.65; 95% CI, 0.32 to 1.33, p=0.24).
Zhang et al, 2024 [62]	Meta-analysis	6 studies (434 NSCLC patients who underwent pretreatment staging)	FDG PET/CT; FDG PET/MRI	NA	Pathology	**Lymph node metastases** ***FDG PET/CT*** Pooled Sens: 78.0% (0.59-0.90) Pooled Spec: 87.0% (0.72-0.94) Pooled Accu: 81.0% (0.71-0.90) ***FDG PET/MRI*** Pooled Sens: 84.0% (0.68-0.93) Pooled Spec: 87.0% (0.80-0.92) Pooled Accu: 84.0% (0.75-0.92)	NA	NA
Li et al, 2024 [60]	Meta-analysis	8 studies (539 patients who underwent initial staging of NSCLC)	FDG PET/CT; FDG PET/MRI	NA	Histopathology, imaging follow-up	**T staging** ***FDG PET/CT*** Pooled Sens: 90.0% (81–96) Pooled Spec: 97.0% (89–100) ***FDG PET/MRI*** Pooled Sens: 88.0% (78–94) Pooled Spec: 95.0% (87–99) **N staging** ***FDG PET/CT*** Pooled Sens: 70.0% (63–76) Pooled Spec: 92.0% (88–95) AUC: 0.90 ***FDG PET/MRI*** Pooled Sens: 71.0% (65–77) Pooled Spec: 91.0% (87–94) AUC: 0.88 **M staging** ***FDG PET/CT*** Pooled Sens: 79.0% (62–91)	NA	NA

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
						Pooled Spec: 94.0% (90–97) AUC: 0.96 ***FDG PET/MRI*** Pooled Sens: 82.0% (70–91) Pooled Spec: 96.0% (93–98) AUC: 0.94		
Li et al.b 2024 [59]	Retrospective	91 patients with NSCLC who underwent PET/CT for the detection of lymph node involvement	68Ga-FAPI-04 PET/CT	Conventional imaging	Histopathology imaging follow-up	**Diagnosis - station-based** Sens: 72.00% Spec: 93.10% Acc: 89.36% **Lesion-based:** Sens: 58.06% Spec: 94.79% Acc: 91.60% **For differentiating lymph node metastases using an SUVmax of 4.815 as the optimal cutoff:** Sens: 62.96% Spec: 96.70% Diagnosis: PPV: 67.74%, p=0.727 Acc for TNM stage: 82.42%, p=0.029 Diagnosis: PPV: 61.29% Acc for TNM stage: 68.13%	Diagnosis: PPV: 61.29% Acc for TNM stage: 68.13%	Change in treatment management: 21 patients (23.08%, 21/91) Primary tumors found: 4 patients (4.39%) Therapeutic regimens changed: 17 patients (18.68%)
Liu et al, 2024 [61]	Retrospective	458 patients who underwent CT-guided transthoracic needle biopsy with or without PET/CT (suspicious lung lesions)	FDG PET/CT + CT-guided transthoracic needle biopsy (n=227)	CT-guided transthoracic needle biopsy (n=231)	Histopathology, imaging follow-up	**Diagnosis** Sens: 95.7%[a] Spec: 100% PPV: 100% NPV: 79.5% Accu: 96.3%[b] [a]p=0.035 [b]p=0.048	**Diagnosis** Sens: 90.1%[a] Spec: 100% PPV: 100% NPV: 69.1% Accu: 91.9%[b]	Change in treatment management: 21 patients (23.08%, 21/91); Primary tumours found: 4 patients (4.39%) Therapeutic regimens changed: 17 patients (18.68%)
Cheng et al, 2024 [57]	Retrospective	5298 patients who underwent preoperative	FDG PET/CT (n=2649)	No FDG PET/CT (n=2649)	Clinical follow-up	NA	NA	There was no significant difference in 5-year survival rate between

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
		staging (clinical stage I lung cancer)						patients who received FDG PET/CT and those who did not (79.8% versus 78.2%, p=0.6528; HR, 0.99; 95% CI, 0.84 to 1.16, p=0.9105).
Pancreatic Cancer								
Karaalioglu et al, 2024 [53]	Retrospective	70 patients who underwent posttreatment follow-up (recurrent pancreaticobiliary neoplasms)	FDG PET/CT	CeCT/ceMRI	Biopsy, imaging follow-up	**Recurrence/progression of local disease** Sens: 76.6% Spec: 92.5% PPV: 88.5% NPV: 84.1% AUC: 0.846 **Recurrence/progression of local lymph nodes** Sens: 77.8% Spec: 96.2% PPV: 87.5% NPV: 92.6% AUC: 0.870 **Recurrence/progression of distant organ involvement** Sens: 80.7%* Spec: 76.9% PPV: 93.9% NPV: 47.6% AUC: 0.788	**Recurrence/progression of local disease** Sens: 90.0% Spec: 95.0% PPV: 93.1% NPV: 92.7% AUC: 0.925 **Recurrence/progression of local lymph nodes** Sens: 88.9% Spec: 96.2% PPV: 88.9% NPV: 96.2% AUC: 0.925 **Recurrence/progression of distant organ involvement** Sens: 96.5%* Spec: 61.5% PPV: 91.7% NPV: 80.0% AUC: 0.790	FDG PET/CT had a major impact on management in 8.6% (6/70) of patients.
Pediatric Cancer								
Du et al, 2024 [55]	Retrospective	103 patients who underwent initial staging (newly diagnosed Ewing sarcoma)	FDG PET/CT	NA	BMB/BMA Cytology, histology	**Bone marrow involvement** Sens: 100% Spec: 95.8% PPV: 66.7% NPV: 100% Accu: 96.1%	NA	NA
Arslantas et al, 2024 [54]	Retrospective	64 patients who underwent initial staging (newly diagnosed	FDG PET/CT	BMB	Histopathology	**Bone marrow involvement** Sens: 95.6% Spec: 100% PPV: 100%	**Bone marrow involvement** Sens: 60.8% Spec: 100% PPV: 100%	NA

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
		neuroblastoma, Hodgkin and non-Hodgkin lymphoma, Ewing sarcoma and rhabdomyosarcoma)				NPV: 97.6%	NPV: 82.0%	
Non-FDG Tracers								
PSMA								
Dhar et al, 2024 [39]	Meta-analysis	42 studies (1276 patients with newly diagnosed prostate adenocarcinoma)	^{68}Ga-PSMA-11 or ^{18}F-DCFPyL or ^{18}F−PSMA-1007 PET/CT or PET/MRI	mpMRI	Histopathology	**Intraprostatic tumour (12 studies)** Pooled Sens: 75.7% Pooled Spec: 87.1% AUC: 0.889	**Intraprostatic tumour (13 studies)** Pooled Sens: 64.7% Pooled Spec: 86.4% AUC: 0.852	NA
Ren et al, 2024 [40]	Meta-analysis	16 studies (1227 patients with prostate cancer)	^{68}Ga-PSMA-11 PET/CT	mpMRI	Histopathology, imaging follow-up	**Primary tumour** Pooled Sens: 87.0% Pooled Spec: 80.0% AUC: 0.89	**Primary tumour** Pooled Sens: 84.0% Pooled Spec: 74.0% AUC: 0.83	NA
Singhal et al, 2024 [41]	Meta-analysis	11 studies (260 patients who underwent staging or restaging of renal cell carcinoma)	^{68}Ga-PSMA-11 or ^{18}F-DCFPyL or ^{18}F−PSMA-1007 or ^{68}Ga-P16-093 PET/CT	CT	Histopathology, imaging follow-up	**Local disease (patient-based)** Pooled Sens: 87.2% Pooled Spec: 100% **(lesion-based)** Pooled Sens: 88.9% Pooled Spec: 100% **Metastatic disease** Pooled Sens: 92.0% Pooled Spec: 96.9% **Recurrent disease** Pooled Sens: 100% Pooled Spec: 100%	**Local disease (patient-based)** Pooled Sens: 93.3% Pooled Spec: 96.8% **(lesion-based)** Pooled Sens: 94.4% Pooled Spec: 96.8% **Metastatic disease** Pooled Sens: 96.0% Pooled Spec: 66.7% **Recurrent disease** Pooled Sens: 66.7% Pooled Spec: 95.0%	NA
Armstrong et al, 2024 [42]	RCT, Phase III	193 patients with prostate cancer planning to receive salvage radiotherapy	^{68}Ga-PSMA-11 PET/CT	fluciclovine-PET CT, Bone scan MRI No imaging	Histopathology	NA	NA	Major change in Salvage radiotherapy management: Control group vs. PSMA-11 group 22.4% vs 45.1% (95% CI 9-35%, p=0.002 Minor changes: 0% vs. 7%;

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
								No change 77.6% vs. 54.9% IN a multivariable logistic regression model testing the variables PSA, grade group, NCCN risk group and randomization arm, OR 3.6 (95% CI 1.8-7.0, p<0.001 for the randomization arm (PSMA-PET)
Tayara et al, 2024 [43]	Prospective, single centre	74 patients who underwent initial staging prior to radical prostatectomy with pelvic lymph node dissection (newly diagnosed intermediate-to-high-risk prostate cancer)	^{68}Ga-PSMA-11 PET/CT	mpMRI	Histopathology	**Lymph node metastases** Sens: 65.0% Spec: 90.7% PPV: 73.3% NPV: 87.7% AUC: 0.779 **Seminal vesicle involvement** Sens: 30.0% Spec: 87.0% PPV: 46.2% NPV: 77.0% AUC: 0.585	**Lymph node metastases** Sens: 55.0% Spec: 75.9% PPV: 45.8% NPV: 82.1% AUC: 0.655 **Seminal vesicle involvement** Sens: 65.4% Spec: 89.6% PPV: 77.3% NPV: 82.7% AUC: 0.775	NA

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
Bahler et al, 2024 [44]	Prospective pilot, single arm	50 patients at intermediate or high risk prostate cancer who were scheduled for prostatectomy	68Ga-PSMA-11 PET/CT	Multiparametric (mp) MRI	Whole-mount histopathology (WMH)	Extraprostatic extension along the posterior neurovascular bundle: Sens: 86% Spec: 73% PPV: 46% NPV: 95% Area under ROC: 0.80 Seminal vesicle invasion: Sens: 0.50% Spec: 0.93% PPV: 0.63% NPV: 0.88% Area under ROC: 0.71 Lymph node involvement: Sens: 0.44% Spec: 0.98% PPV: 0.80% NPV: 0.89% Area under ROC: 0.71	Extraprostatic extension along the posterior neurovascular bundle: Sens: 57% (p=0.03) Spec: 77% PPV: 40% NPV: 87% Area under ROC: 0.67 Seminal vesicle invasion: Sens: 1.00% (p=0.03) Spec: 1.00% PPV: 1.00% NPV: 1.00% Area under ROC: 1.00, (p<0.01) Lymph node involvement: Sens: 0.00% (p=0.05) Spec: 0.98% PPV: 0.00% NPV: 0.82% Area under ROC: 0.51, (p=0.03)	Surgeons' predictions of correct nerve-sparing approach: With PSMA-PET and MRI: 74% With MRI alone: 65% (p=0.01)
Alongi et al., 2024 [45]	Retrospective	80 patients with prostate cancer who needed staging or re-staging	^{18}F-PSMA-1007	NA	Clinical follow-up with CT and bone scan	In the whole group: Sens: 75% Spec: 95.2% NPV: 75% PPV: 95% Accur: 91.2% AUC: 0.851 At Staging (n=31): Sens: 77.6% Spec: 89.5% NPV: 77.6% PPV: 89.5% Accur: 85.7%	NA	Impact on clinical management: 57.5% At staging: PET led to overstaging in 51% (16/31), and understaging in 12.9% (4/31) of the patients At re-staging: PET led to overstaging in 53% (26/49), and understaging in 20.4% (10/49) of the patients.

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
						Area under ROC: 0.87 At Re-staging (n=49): Sens: 66.7% Spec: 92.9% NPV: 85.7% PPV: 81.3% Accur: 82.6% Area under ROC: 0.79		
Emmett et al, 2024 [46]	Retrospective	227 patients who underwent imaging prior to initial prostate biopsy (clinically significant prostate cancer)	^{68}Ga-PSMA PET/CT	mpMRI	Histopathology	**Diagnosis (PRIMARY score)** Sens: 86% Spec: 76% PPV: 88% NPV: 72%	**Diagnosis (PI-RADS score)** Sens: 89% Spec: 74% PPV: 88% NPV: 76%	NA
^{18}F-FACBC								
Castello et al, 2023 [47]	Meta-analysis	8 studies (113 patients with glioma)	^{18}F-FACBC PET/CT or PET/MRI	CeMRI	Histology, clinical or imaging follow-up	**Differentiating between high- and low-grade glioma** Pooled Sens: 91.6% Pooled Spec: 66.4% **Differentiating between high-grade recurrence and post-treatment changes** Pooled Sens: 93.3% Pooled Spec: 75.9%	NA	NA
^{18}F-FES								
Gennari et al, 2024 [48]	RCT phase II	147 endocrine-resistant patients with ERD/HER2-negative metastatic breast cancer treated with single agent endocrine	^{18}F-FES CT/PET	NA	Conventional diagnostic and staging procedures as clinically indicated	NA	NA	PFS ^{18}F-FES CT/PET SUV $\geq$2 in patients treated with ET: median 18.0 months (95% CI 11.2-23.1 months). In patients with SUV < 2 randomized to arm A, median 12.4 months (95% CI 3.1-59.6 months) vs. 23.0 months (95% CI 7.7-

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
		therapy (ET) (Arm A) vs. chemotherapy (Arm B)						30.0 months) in patients treated in arm B. (HR=0.71, 95% CI 0.3-1.7). At 24 months, the PFS rate was 40.2% (95% CI 31.1% to 49.2%) in patients with ^{18}F-FES SUV ≥2, 33.3% (95% CI 10.3% to 58.8%) in Arm A, and 48.6% (95% CI 21.9% to 70.3%) in arm B. OS Median not reached in patients with SUV≥2 treated in Arm A, and 28.2 months (95% CI 14.2 months-not estimable [NE]) in patients with SUV <2 randomized to arm A versus 52.8 months (95% CI 16.2 months-NE) in arm B (HR 0.97, 95% CI 0.3-3.1).
F18-Choline								
Quak et al, 2024 [49]	RCT Phase III APACH2 trial	57 adult patients with primary hyperparathyroidism due to parathyroid adenomas who were treated with minimally invasive parathyroidectomy	F18-Choline PET/CT – first line	MIBI SPECT/CT first line	Clinical and imaging follow-up	FCH1 n=29 Sens: 82% (95% CI, 62%-93%) PPV: 92% (95% CI, 72%-99%)	MIBI1 n=28 63% (95% CI, 42%-80%) PPV: 100% (95% CI, 77%-100%)	Normocalcemia 1 month after positive first-line imaging-guided minimally invasive: FCH1: 23 of 27 patients (85%) MIBI1: 14 of 25 patients (56%)
^{68}Ga-DOTA-FAPI-04								
Rizzo et al, 2023 [50]	Meta-analysis	6 studies (82 patients with head and neck cancer)	^{68}Ga-DOTA-FAPI-04 PET/CT	NA	Not specified	**Lymph node metastases** Pooled Sens: 90.1% Pooled Spec: 84.3%	NA	NA

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
						Pooled +LR: 3.84 Pooled -LR: 0.01 Pooled DOR: 55.34		
6-[^{18}F]F DOPA								
Suarez-Pinera et al, 2024 [51]	Retrospective	62 patients with brain lesions which could be tumours or radionecrosis (RNC)	6-[^{18}F] FDOPA	NA	Clinical and radiological follow-up	**Metastases identification:** Sens: 49% **Primaries identification:** Sens: 72% **For visual and semi-quantitative interpretation of FDOPA:** Metastases: Sens: 96% Spec: 72% Primaries: Sens: 94% Spec: 80%	NA	NA
^{18}F-DCFPyL								
Wang et al, 2024 [52]	Meta-analysis	14 studies (3078 patients with prostate cancer	^{18}F-DCFPyL PET/CT	CT, MRI, bone scan	Pre- and post-PET questionnaires, multidisciplinary meeting	NA	NA	Management changes, due to ^{18}F-DCFPyL PET/CT, pooled proportions: Patients with biochemical recurrent disease 49.6% (95% CI, 38.8%-60.4%) Primary staging, 22.3% (95% CI, 15.5% - 29.0%)
Sarcoma								
Ko and Kim, 2024 [56]	Meta-analysis	4 studies (117 patients with peripheral nerve sheath tumours)	FDG PET/CT	MRI	Histopathology	**Malignancy** Pooled Sens: 99.0% Pooled Spec: 53.0% Pooled +LR: 2.1 Pooled -LR: 0.02 Pooled DOR: 115 AUC: 0.945	**Malignancy** Pooled Sens: 85.0% Pooled Spec: 85.0% Pooled +LR: 5.7 Pooled -LR: 0.17 Pooled DOR: 34 AUC: 0.889	NA
Metastases of Unknown Primary								
Huang et al, 2024 [25]	Retrospective	62 patients who did not receive	FDG PET/CT	CT, MRI, US	Histopathology	**Primary tumour** Sens: 67.7%	NA	FDG PET/CT altered the tumour staging of 54.8%

Citation	Study Type	Population	PET Type	Conventional intervention (Conv. Int.)	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conv. Int.)	Change in Patient Management
		prior treatment (cancer of unknown primary)						(34/62) of patients. Subsequently, changes in treatment strategies occurred in 21.0% (13/62) of cases.

Abbreviations: ^{18}F = Fluorine 18; ^{18}F-DCFPyL = Piflufolastat F-18; ^{18}F-FACBC = 18F-Fluciclovine; ^{18}F-FES = ^{18}F-Fluoroestradiol; ^{68}Ga-FAPI-04 = Gallium-68 Fibroblast Activation Protein Inhibitor-04; ABVD = a chemotherapy regimen that includes doxorubicin (A), bleomycin (B), vinblastine (V) and dacarbazine (D); Accu = accuracy; AUC = Area under the curve; BMA = Bone Marrow Aspiration; BMB = Bone Marrow Biopsy; CA-125 = Cancer Antigen 125; CeCT = Contrast-enhanced Computed Tomography; CeMRI = Contrast-enhanced Magnetic Resonance Imaging; CeUS = Contrast-enhanced ultrasound; CI = confidence Interval; Conv. Int. = conventional intervention; CSF = cerebrospinal fluid; CT = Computed tomography; DCFPyL = 2-(3-(1-Carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl)-ureido)-pentanedioic acid; DFS = disease-free survival; DLBCL = Diffuse large B-cell lymphoma; DOR = Diagnostic Odd Ratio; EEG = Electroencephalogram; EFS = Event-free survival; ERD/HER2- = Estrogen Receptor-Deficient / Human Epidermal Growth Factor Receptor 2-Negative; ET = Endocrine Therapy; FCH1 = F18-choline; F-FDG = FDG = Fluorodeoxyglucose; FDOPA = Fluorodopa; FUO = Fever of unknown origin; HER2 = human epidermal growth factor receptor 2; HL = Hodgkin lymphoma; HP = a chemotherapy regimen that includes Trastuzumab (H) and Pertuzumab (P); HR = Hazard Ratio; IRR = Incidence Rate Ratio; +LR = Positive Likelihood Ratio; -LR = Negative Likelihood Ratio; MDCT = Multi-detector computed tomography; MIBI = Methoxyisobutylisonitrile; mpMRI = multiparametric MRI; MRI = Magnetic resonance imaging; NA = Not Applicable; NHL = Non-Hodgkin lymphoma; NPV = Negative Predictive Value; NR = No Record; NSCLC = Non-small cell Lung Cancer; OR = Odds ratio; OS = overall survival; PET = positron emission tomography; PFS = Progression-Free Survival; PI-RADS = Prostate Imaging Reporting and Data System; PPV = Positive Predictive Value; PSMA = Prostate-Specific Membrane Antigene; RCT = Randomized Controlled Trial; RNC = radionecrosis; RR = Relative Risk; Sens = sensitivity; Spec = Specificity; SPECT = Single Proton Emission Computed Tomography; subHR = Sub distribution Hazard Ratio; SUV = Standardized uptake value; SUVmax = Maximum Standardized Uptake Value; TCHP = a chemotherapy regimen that includes Docetaxel (T), Carboplating (C), Trastuzumab (H) and Pertuzumab (P); TNBC = Triple-negative Breast Cancer; TNM = Tumour, Node, Metastases; US = Ultrasound; WMH = Whole-mount histopathology;