PET Six-Month Monitoring Report 2017-1

Evidence from Primary Studies and Systematic Reviews and Recommendations from Clinical Practice Guidelines January to June 2017

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QUESTION

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

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

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

INTRODUCTION

In 2010, the Ontario PET Steering Committee (the Committee) requested that the Program in Evidence-Based Care (PEBC) provide regular updates to the Committee of recently published literature reporting on the use of PET in patients with cancer, sarcoidosis, or epilepsy. The PEBC recommended a regular monitoring program be implemented, with a systematic review of recent evidence conducted every six months. The Committee approved this proposal, and this is the 13th issue of the six-month monitoring reports. This report is intended to be a high-level, brief summary of the identified evidence, and not a detailed evaluation of its quality and relevance.

METHODS

Literature Search Strategy

Full-text articles published between January and June 2017 were systematically searched through MEDLINE and EMBASE for evidence from primary studies and systematic reviews. The search strategies used are available upon request to the PEBC.

Inclusion Criteria for Clinical Practice Guidelines

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

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

Inclusion Criteria for Primary Studies

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

1. Studied the use of 18-fluorodeoxyglucose (FDG) PET in cancer, sarcoidosis, or epilepsy in humans.
2. Evaluated the use of the following radiopharmaceutical tracers:
    - ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTATOC, ^{68}Ga DOTATATE
    - ^{18}F-choline, ^{11}C-choline (prostate cancer)
    - ^{18}F-FET ([^{18}F]fluoroethyl-L-tyrosine) (brain)
    - ^{18}F-FLT ([^{18}F]3-deoxy-^{3}F-fluorothymidine) (various)
    - ^{18}F-MISO ([^{18}F]fluoromisonidazole) (hypoxia tracer)
    - ^{18}F-FAZA ([^{18}F]fluoroazomycin arabinoside) (hypoxia tracer)
    - ^{18}F-fluoride (more accurate than bone scanning)
    - ^{18}F-flurpiridaz (cardiac)
    - ^{18}F-florbetapir (Amyvid) (dementia imaging)
    - ^{18}F-FDOPA
    - ^{68}Ga-PSMA (prostate-specific membrane antigen)
    - ^{18}F-FACBC (fluciclovine)
3. Published as a full-text article in a peer-reviewed journal.
4. Reported evidence related to change in patient clinical management or clinical outcomes, or reported diagnostic accuracy of PET compared with an alternative diagnostic modality.
5. Used a suitable reference standard (pathological and clinical follow-up) when appropriate.
6. Included ≥12 patients for a prospective study/randomized controlled trial (RCT) or ≥50 patients (≥25 patients for sarcoma) for a retrospective study with the disease of interest.

Inclusion Criteria for Systematic Reviews

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

Exclusion Criteria

1. Letters and editorials.

RESULTS

Literature Search Results

Primary Studies and Systematic Reviews

Eighty-two studies published between January and June 2017 met the inclusion criteria. A summary of the evidence from the 82 studies can be found in **Appendix 1: Summary of studies from January to June 2017**.

Breast Cancer

Five studies met the inclusion criteria [1-5]. One meta-analysis found that magnetic resonance imaging (MRI) was more sensitive (pooled estimate, 82% versus 64%, $p<0.05$) and had a greater diagnostic odds ratio (pooled estimate, 51.28 versus 18.84, $p<0.01$) than FDG PET/CT for identifying axillary lymph node metastases [1]. In another meta-analysis of 22 studies with patients who received neoadjuvant chemotherapy, FDG PET/CT showed moderate sensitivity (pooled sensitivity, 81.9%) and specificity (pooled specificity, 79.3%) in predicting pathological response to therapy [2]. For staging patients with invasive ductal breast carcinoma, FDG PET/CT (75%) and whole-body MRI (84%) were comparably accurate [3]. In newly diagnosed estrogen receptor-positive/human epidermal growth factor receptor 2 (HER2)-negative and HER2-postive breast cancer, FDG PET/CT upstaged 13.4% and 11.8% of patients, respectively, to stage IV, by revealing unsuspected metastases [4]. Similarly in triple-negative or HER2-positive breast cancer, FDG PET/CT changed the treatment plan of 10.1% of patients in the preoperative setting and 14.3% of patients in the postoperative setting [5].

Epilepsy

One study met the inclusion criteria [6]. In a prospective study of children undergoing preoperative evaluation for medically intractable epilepsy, FDG PET/CT (91.0%) was shown to be more accurate than both dynamic contrast-enhanced MRI (57.6%, $p<0.001$) and video-electroencephalography (67.7%, $p<0.001$) in the localization of epileptic foci.

Esophageal Cancer

Two studies met the inclusion criteria [7,8]. In the diagnosis of esophageal cancer, CT perfusion appeared to have an advantage over FDG PET/CT and contrast-enhanced CT (CeCT), particularly in detecting stage I tumours [7]. For patients who underwent surgery alone or neoadjuvant therapy, FDG PET/CT (57.1%), CeCT (54.5%) and endoscopic ultrasound (EUS) (55.4%) all demonstrated poor N-staging accuracy [8].

Gastrointestinal Cancer

Eight studies met the inclusion criteria [9-16]. In colorectal cancer, preoperative FDG PET/CT had a higher specificity and accuracy than CeCT for detecting lymph node [9,10] and distant metastases [9]. However, CeCT was more sensitive than FDG PET/CT for detecting lymph node metastasis alone [9]. In patients with rising carcinoembryonic antigen (CEA) levels after curative therapy, FDG PET/CT evaluated recurrence with sensitivity of 92.7% to 94.9% and specificity of 70.6% to 95.2% [11,12]. Early postoperative FDG PET/CT impacted management changes in 14% of patients [13]. In a separate meta-analysis of 10 studies, FDG PET or PET/CT yielded a higher sensitivity for detecting disease progression after ablation therapy compared with CT (pooled estimate, 84.6% versus 53.4%, $p=0.005$). This led to a change in management in 36% to 82% of patients [14]. In squamous cell carcinoma of the anal canal, the sensitivity and specificity of FDG PET/CT to detect residual tumour after chemoradiotherapy were 92% and 85%, respectively. Relevant modifications in management occurred in 16.1% of patients as a result of post-treatment follow-up with FDG PET/CT [15].

In the staging of gastric adenocarcinoma, additional information provided by FDG PET/CT led to the upstaging of 18.7% and downstaging of 10.2% of patients [16].

Gynecologic Cancer

Seven studies met the inclusion criteria [17-23]. Four of the studies evaluated the clinical usefulness of FDG PET or PET/CT in patients previously treated for ovarian malignancy. Overall, FDG PET or PET/CT detected disease recurrence or second primary malignancy with sensitivity that ranged from 91.2% to 98.8% and specificity that ranged from 62.5% to 98.2% [17-19]. Management changes occurred in 10.5% of scans performed without clinical suspicion and recurrence was ruled out in 16.7% of scans performed with clinical suspicion [17]. Moreover, FDG PET or PET/CT altered the treatment plans of 44.1% of patients that were deemed curable as a result of CT- or MRI-detected recurrences [18]. In a separate study, the authors concluded that FDG PET/CT (97.1%) was more accurate than CT (91.2%) in assessing therapeutic response of proven omental deposits from ovarian or uterine tumours; however, there was no mention of whether this difference was statistically significant [20]. In high-risk endometrial cancer, the addition of FDG PET/CT to CT increased the sensitivity in both the abdomen (50% versus 65%, p=0.01) and pelvis (48% versus 65%, p=0.004) for detecting lymph node metastasis while preserving high specificity [21]. On the contrary, preoperative FDG PET/CT poorly predicted lymph node metastasis in patients with node-negative endometrial cancer on MRI [22]. In cervical cancer, a comparison between FDG PET or PET/CT, CT, MRI and diffuse-weighted MRI revealed that FDG PET or PET/CT had the highest specificity (pooled estimate, 98%) and diffuse-weighted MRI had the highest sensitivity (pooled estimate, 87%) for detecting lymph node metastasis [23].

Head and Neck Cancer

Twelve studies met the inclusion criteria [24-35]. In patients with oropharyngeal squamous cell carcinoma, post-treatment FDG PET/CT performed at approximately three months [24], within six months [25], and between two to three years [26] from therapy completion were all shown to be predictive of residual disease/recurrence. In nasopharyngeal carcinoma, FDG PET/CT-guided dose-painting intensity-modulated radiation therapy (IMRT) was associated with significant survival advantage over CT-based IMRT, without increasing toxicity (3-year overall survival, 91.8% versus 82.6%, p=0.049) [27]. FDG PET/CT also showed a higher sensitivity (pooled estimate, 83.7% versus 40.1%, p<0.001) and lower negative likelihood ratio (pooled estimate, 0.17 versus 0.63, p<0.001) than conventional work-ups in detecting distant metastases [28]. Three studies looked at FDG PET/CT in head and neck cancer. For the evaluation of cervical lymph node metastasis, sentinel node biopsy offered the highest accuracy (area under the curve [AUC], 0.98), followed by ultrasound (US)-guided fine-needle biopsy (AUC, 0.97), FDG PET/CT (AUC, 0.826), CT (AUC, 0.811), US (AUC, 0.807), and MRI (AUC, 0.791) [29]. In another study, no significant difference in accuracy (both by neck level and by neck side) was found between FDG PET/CT and CeCT [30]. In T staging, FDG PET/CT was more sensitive than MRI (83% versus 63%, p=0.015) [31]. With respect to differentiated thyroid cancer, patients with positive serum thyroglobulin level and negative whole-body scintigraphy after treatment would benefit from a FDG PET/CT scan for detecting recurrent disease (accuracy, 82%) [32]. However, FDG PET/CT does not appear to offer much additional value in comparison to diffuse-weighted MRI and US [33]. In salivary gland carcinomas, FDG PET/CT exhibited higher sensitivity than CT for detecting neck node metastasis (per-patient, 88.2% versus 52.9%, p=0.031; per-side, 88.9% versus 55.6%, p=0.031; per-level, 81.4% versus 46.5%, p<0.001) and could identify metastatic disease at distant sites and secondary cancer not seen on CT [34]. The authors from a retrospective study concluded that FDG PET/CT

could reliably rule out malignant cystic lesions in the neck (negative predictive value, 96%) but at the expense of a high rate of false-positive results [35].

Hematologic Cancer

Eight studies met the inclusion criteria [36-43]. Three studies examined the clinical value of interim-PET response in patients with Hodgkin lymphoma [36-38]. In one RCT, the five-year progression-free survival (PFS) of patients with a positive interim FDG PET/CT scan after two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) improved from 77.4% for receiving additional ABVD cycles followed by involved-node radiotherapy (INRT) to 90.6% for switching to two cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone ($BEACOPP_{escalated}$) and INRT (hazard ratio, 0.42; 95% confidence interval, 0.23 to 0.74; p=0.002). Furthermore, omitting INRT from additional cycles of ABVD in patients with an interim negative scan increased the risk of relapse [36]. In another RCT, the addition of rituximab to $BEACOPP_{escalated}$ after the initial two cycles of $BEACOPP_{escalated}$ did not improve the PFS of interim-PET-positive patients [37]. In the third study, the authors concluded that end-of-treatment PET assessment more accurately predicted treatment failure than interim-PET assessment after two cycles of ABVD [38]. Two studies investigated the usefulness of FDG PET/CT to detect bone morrow involvement in patients with Hodgkin and non-Hodgkin lymphoma. Overall, the sensitivity ranged from 24.3% to 67% and the specificity ranged from 85% to 92% in patients with non-Hodgkin lymphoma, while the sensitivity ranged from 80% to 100% and the specificity ranged from 74% to 78% in patients with Hodgkin lymphoma [39,40]. In terms of response to therapy, FDG PET/CT using Deauville criteria with 4 or 5 as positive (86%) showed higher accuracy for predicting clinical outcome of patients with Hodgkin and non-Hodgkin lymphoma than FDG PET/CT using either the international Harmonization Project criteria (76%) or Deauville criteria with 3-5 as positive (84%) [41]. In newly diagnosed indolent lymphoma, FDG PET/CT changed the disease stage of 55.8% of patients, where the proportion of patients planned for active treatment was different ($p<0.0001$) before and after the scan [42]. The International Myeloma Working Group provided a number of recommendations for the optimal use of FDG PET/CT in patients with active multiple myeloma, smouldering multiple myeloma, and solitary plasmacytoma (see Appendix 1A) [43].

Melanoma

Three studies met the inclusion criteria [44-46]. FDG PET/CT was able to detect asymptomatic recurrence with high sensitivity (91% to 94.5%) and specificity (87.6% to 95%) in patients who have had resection of their primary lesion [44,45]. In patients with advanced melanoma planned for radical metastasectomy, FDG PET/CT led to minor treatment changes in 22.4% of patients and major treatment changes in 51.4% of patients [46].

Neuro-Oncology

One study met the inclusion criteria [47]. The authors from one prospective study suggested that FDG PET/CT performed better than MRI in grading glioma and that the diagnostic results of grade II and III gliomas were superior to those of grade I and IV.

Non-FDG Tracers

Seventeen studies met the inclusion criteria [48-64]. Three studies evaluated ^{11}C-choline or ^{18}F-choline PET/CT in the setting of biochemical recurrence of prostate cancer [48-50]. Due to the presence of high heterogeneity among the studies, results from a patient-based analysis (pooled sensitivity, 85.3%; pooled specificity, 32.6%) and a lesion-based analysis (pooled sensitivity, 56.2%; pooled specificity, 94.9%) showed varying sensitivity and

specificity for detecting metastatic lymph nodes [48]. In a prospective study, ^{11}C-choline PET/CT was found to be more sensitive than MRI in detecting local recurrence (83.3% versus 54.2%, p=0.03) and bone metastases (92.9% versus 78.6%, p=0.02), but no difference was seen between the two imaging modalities for detecting lymph node metastasis (81.4% versus 77.9%, p=0.65) [49]. On the other hand, ^{18}F-choline PET/CT was found to have impacted clinical management in 28.3% of patients [50]. In seven studies, ^{68}Ga-DOTA-TATE PET/CT was investigated in various malignancies. In neuroendocrine tumours (NETs), ^{68}Ga-DOTA-TATE PET/CT influenced the treatment plan of 48.1% to 50% of patients [51,52] and detected the primary site in 60.8% of patients where conventional imaging modalities failed to identify [53]. In the staging/restaging of pheochromocytomas or paragangliomas, ^{68}Ga-DOTA-TATE PET/CT had a higher lesion-based sensitivity than CeCT and MRI (93% versus 76%, p=0.042). Patient-based sensitivity for both was 93% [54]. In medullary thyroid carcinoma patients with increased calcitonin levels and negative conventional imaging after thyroidectomy, ^{68}Ga-DOTA-TATE PET/CT (accuracy, 93%) appeared to be superior to ^{111}In-octreotide SPECT/CT (accuracy, 53%) for detecting recurrence; however, no significant difference was seen due to very small sample size (15 patients) [55]. For the evaluation of intracranial meningioma, ^{68}Ga-DOTA-TATE PET/CT improved the detection of osseous involvement compared with contrast-enhanced MRI while maintaining high specificity (sensitivity, 98.5% versus 53.7%, p<0.001) [56]. In the diagnosis of indeterminate pulmonary nodules and non-neuroendocrine lung cancer, ^{68}Ga-DOTA-TATE PET/CT and FDG PET/CT were comparable in diagnostic accuracy [57]. ^{68}Ga-DOTA-TOC PET/CT was investigated in one study involving patients with metastatic NETs and unknown primary tumour. The reported true positive, false-positive, false-negative, and unconfirmed rates for identifying the primary site were 38%, 7%, 50%, and 5%, respectively [58]. Across 14 studies in a meta-analysis, 44% of patients with NETs had their management changed after undergoing ^{68}Ga-DOTA-TATE/-NOC/-TOC PET/CT [59]. Four prospective studies in prostate cancer were also identified, three with ^{68}Ga-PSMA PET/CT [60-62] and one with ^{68}Ga-PSMA-11 PET/CT or PET/MRI [63]. ^{68}Ga-PSMA PET/CT detected lymph node metastasis with sensitivities and specificities ranging from 53.3% to 64% and 85.7% to 100%, respectively [60,61]. In light of ^{68}Ga-PSMA PET/CT findings, management intent was changed in 61.5% of patients with biochemical failure and 21.3% of patients referred for primary staging [62]. Likewise, ^{68}Ga-PSMA-11 PET/CT or PET/MRI initiated a major treatment change in 53.2% of patients [63]. As for ^{18}F-DOPA PET/CT, it outperformed CeCT and MRI in the staging/restaging of patients with pheochromocytomas or paragangliomas (lesion-based sensitivity, 89% versus 76%, p=0.042) [54] and influenced the management of 57.1% of patients with medullary thyroid carcinoma [64].

Non-Small Cell Lung Cancer and Other Lung Cancer

Seven studies met the inclusion criteria [65-71]. In non-small cell lung cancer (NSCLC), FDG PET or PET/CT was more sensitive than bone scintigraphy in detecting bone metastases (97.7% versus 87.8%, respectively) [65] but less sensitive than gadolinium-enhanced MRI in diagnosing brain metastases (pooled estimate, 21% versus 77%, respectively) [66]. FDG PET or PET/CT and diffuse-weighted MRI identified lymph node metastases without significant differences between them [67]. In potentially operable NSCLC, FDG PET/CT altered the management of 37.6% of patients [68]. For those planned to undergo radiotherapy, FDG PET/CT changed the target definition of 36% of patients and changed the intent of treatment from curative to palliative in 20% of patients [69]. Furthermore, initial findings from a phase II clinical trial showed that adaptive treatment with escalated radiation dose to the FDG-avid tumour shown on mid-treatment PET improved the two-year rates of infield (82%) and overall local-regional tumour control (62%) [70]. In solitary pulmonary nodules, FDG PET/CT displayed

moderate sensitivity (pooled estimate, 82%) and specificity (pooled specificity, 81%) for differentiating malignant from benign nodules [71].

Pancreatic Cancer

One study met the inclusion criteria [72]. Results from a meta-analysis showed that FDG PET or PET/CT compare favourably to MRI, CT, EUS, and trans-abdominal US in the diagnosis of pancreatic ductal adenocarcinoma.

Pediatric Cancer

Four studies met the inclusion criteria [73-76]. In pediatric Hodgkin lymphoma, FDG PET/CT detected bone marrow involvement with high sensitivity (93.6%) and specificity (94.0%) [73]. For patients who received ABVD chemotherapy, the specificity of interim PET/CT after two cycles based on Revised International Working Group criteria (61.5%) and Deauville criteria (91.4%) were both higher than that of CeCT (40.3%, $p=0.03$ and $p<0.0001$, respectively) in predicting relapse. However, the sensitivity of interim PET/CT (Deauville criteria) was worse than that of CeCT (0% versus 75.0%, $p=0.04$). For post-treatment assessment, PET/CT (Deauville criteria) also showed better specificity than CeCT (95.7% versus 76.4%, $p=0.006$) [74]. In pediatric mature B cell non-Hodgkin lymphoma, FDG PET/CT had a higher sensitivity (89.5% versus 63.2%, $p=0.0253$), specificity (84.9% versus 58.6%, $p<0.001$), positive predictive value (45.9% versus 17.9%, $p<0.001$), and negative predictive value (98.3% versus 91.7%, $p=0.011$) than CT for evaluating residual disease, tumour response, or relapse [75]. In the pediatric and adolescent/young adult sarcoma population, FDG PET/CT was shown to be unreliable (sensitivity, 57%; specificity, 52%) in identifying nodal metastases [76].

Sarcoma

Two studies met the inclusion criteria [77,78]. FDG PET/CT displayed reliable results for confirming or ruling out recurrence (accuracy, 89%) in patients with suspected relapse of osteosarcoma [77]. In patients with gastrointestinal stromal tumors treated with chemotherapy, one meta-analysis reported a pooled sensitivity of 92% and a pooled specificity of 71% for FDG PET/CT in predicting treatment response [78].

Unknown Primary Cancer

One study met the inclusion criteria [79]. In patients with extracervical metastases from cancer of unknown primary, FDG PET/CT was found to have an overall primary tumour detection rate of 40.9%.

CLINICAL EXPERT REVIEW

Breast Cancer

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

Reviewer's Comments (Dr. Muriel Brackstone)

Five publications were published between January and July of 2017. The meta-analysis by Liang et al. [1] included 21 studies and compared PET to MRI, with axillary dissection as the reference standard. MRI was found to be significantly more sensitive than PET at detecting axillary metastases, which supports existing publications in the literature around limited sensitivity in axillary staging of breast cancer with PET.

Although the meta-analysis by Tian et al. [2] showed moderate sensitivity to detect response to neoadjuvant chemotherapy (as measured by pathological complete response at surgery), there was no imaging comparator. There was no evidence from this publication that

the sensitivity of PET/CT at detecting residual disease after neoadjuvant chemotherapy was superior to the current clinical gold standard for response to neoadjuvant chemotherapy, which remains MRI. The lack of comparison to current gold standard imaging modalities for residual disease limits the utility of this study.

The study by Catalano et al. [3] looked at staging new breast cancer patients, particularly for detecting distant metastases. This was a retrospective study of 51 patients, comparing whole body diffusion-weighted imaging, PET/MRI, and PET/CT. The reference standard was follow-up imaging and/or pathology of abnormal findings identified on these imaging modalities. WB-PET/MRI had a higher concordance to imaging for distant staging than did PET/CT (accuracy, 84% versus 75%). The retrospective design and small sample size limits any utility of this study.

The study by Ulaner et al. [4] was retrospective in design, and evaluated the upstaging rate of PET/CT for distant metastases in newly diagnosed patients who were either ER-positive/HER2-negative or HER2-positive. The reference standard was clinical staging only, which is not how patients are staged for distant disease. Among ER-positive patients, 4% of stage IIA, 14% of stage IIB and 26% of stage III patients were determined to be metastatic at diagnosis. Among HER2-positive patients, 4% of stage IIA, 14% of stage IIB and 22% of stage III patients were upstaged to metastatic (stage IV). Unfortunately, there was no standard imaging done as comparators, and follow-up imaging/biopsy was only done for lesions found on PET/CT. Therefore, true rates of clinically asymptomatic metastatic disease by stage remain unknown. This would need to be done prospectively and in a pre-registered fashion in order to avoid selection bias of patients suspected of having distant disease preferentially selected for PET/CT imaging. As a result, this limitation nullifies the utility of the study in determining the role of PET/CT for distant staging.

The study by Evangelista et al. [5] was similar to the Ulaner et al. [4] study but was prospective in nature. Two hundred and seventy-five newly diagnosed patients underwent PET/CT for distant staging. Again, there was no imaging comparator for distant staging, and the rates of upstaging were based on clinical diagnosis alone, which is not the current standard. Results showed that 6% of stage II and 24% of stage III patients were upstaged to stage IV at diagnosis prior to chemotherapy, and 11% of patients were upstaged to stage IV after neoadjuvant chemotherapy. Given the absence of a comparator, it is not possible to determine whether preselection occurred or whether these rates of upstaging are any different than those of current gold standard imaging (whole body bone scan and CT chest/abdomen/pelvis). Therefore, this study alone is insufficient to change the role of PET/CT in breast cancer staging.

Overall, none of the five studies identified have demonstrated PET/CT to be superior to current standard imaging for breast cancer diagnosis, staging or response to treatment, and there remains no evidence to suggest a change in current recommendations.

Epilepsy

Current Registry Indication

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

Current Recommendations for the Utilization of PET in Epilepsy

- ^{18}F-FDG PET is recommended for the presurgical evaluation of adult and pediatric patients with medically intractable focal or partial epilepsy in the setting of a comprehensive epilepsy surgery program within a Regional Epilepsy Surgery Centre of Excellence.

- Due to insufficient evidence, a recommendation cannot be made for or against the use of ^{18}F-FDG PET in the detection of cortical malformations in patients with intractable infantile spasms when MRI or CT fails to show structural abnormalities.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of ^{18}F-FDG PET/MRI coregistration in the presurgical evaluation of patients with medically intractable epilepsy.

Reviewer's Comments (Dr. Jorge Burneo)

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

Esophageal Cancer

Current Insured Indication

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

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

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

Reviewer's Comments (Dr. Rebecca Wong)

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

Gastrointestinal Cancer

Current Insured Indication (Colorectal Cancer)

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

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

- The routine use of PET is not recommended for the diagnosis or staging of clinical stage I to III colorectal cancers.
- PET is recommended for determining management and prognosis if conventional imaging is equivocal for the presence of metastatic disease.
- The routine use of PET is not recommended for the measurement of treatment response in locally advanced rectal cancer before and after preoperative chemotherapy.
- PET is not recommended for routine surveillance in patients with colorectal cancer treated with curative surgery who are at high risk for recurrence.

- PET is recommended to determine the site of recurrence in the setting of rising CEA levels, when a conventional work-up fails to unequivocally identify metastatic disease.
- PET is recommended in the preoperative assessment of colorectal cancer liver metastasis prior to surgical resection.

Reviewer's Comments (Dr. Anand Swaminath)

The current recommendations for the utilization of PET/CT in gastrointestinal cancer remain valid and no changes are required. The Houard et al. [15] study is interesting, but is based on retrospective data. Nevertheless, this is something to keep in mind going forward, and input from the group heading the anal canal cancer registry may be of value.

Gynecologic Cancer

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

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

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

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

Reviewer's Comments (Dr. Anthony Fyles)

The current recommendations for the utilization of PET/CT in gynecologic cancer remain valid and no changes are required. Indeed, the studies on endometrial cancer [21,22] showed PET/CT to have inadequate sensitivity for nodal staging.

Head and Neck Cancer

Current Insured Indications

- Head and neck cancer: For the evaluation of metastatic squamous cell carcinoma in neck nodes when the primary disease site is unknown after standard radiological and clinical investigation, or for the staging of nasopharyngeal cancer.
- Thyroid cancer: Where recurrent or persistent disease is suspected on the basis of an elevated and/or rising thyroglobulin level, but standard imaging studies, including I-131 scan and/or neck ultrasound, are negative or equivocal.

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

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

Reviewer's Comments (Dr. Amit Singnurkar)

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

Hematologic Cancer

Current Registry Indication (Lymphoma Staging)

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

Current Insured Indication (Lymphoma)

- For the evaluation of residual mass(es) following chemotherapy in a patient with Hodgkin or non-Hodgkin lymphoma when further potentially curative therapy (such as radiation or stem cell transplantation) is being considered; or for the assessment of response in early-stage Hodgkin lymphoma following two or three cycles of chemotherapy when chemotherapy is being considered as the definitive single modality therapy.

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

- When functional imaging is considered to be important in situations where anatomical imaging is equivocal, and/or in potentially curable cases, a FDG PET/CT scan is recommended.
- When functional imaging is considered to be important in situations where anatomical imaging is equivocal and treatment choices may be affected in limited-stage indolent lymphomas, a FDG PET/CT scan is recommended.
- An FDG PET/CT scan is recommended for the assessment of early response in early stage (I or II) Hodgkin lymphoma following two or three cycles of chemotherapy when chemotherapy is being considered as the definitive single-modality therapy, to inform completion of therapy, or to determine whether more therapy is warranted.

- In potentially curable cases, when functional imaging is considered to be important and conventional imaging is equivocal, a FDG PET/CT scan is recommended to investigate recurrence of HL or NHL.
- An FDG PET/CT scan is recommended for the evaluation of residual mass(es) following chemotherapy in a patient with Hodgkin or non-Hodgkin lymphoma when further potentially curative therapy (such as radiation or stem cell transplantation) is being considered and when biopsy cannot be safely or readily performed.
- An FDG PET/CT scan is not recommended for the routine monitoring and surveillance of lymphoma.

Reviewer's Comments

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

Melanoma

Current Registry Indication

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

Current Recommendations for the Utilization of PET/CT in Melanoma

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

Reviewer's Comments (Dr. Tara Baetz)

The two studies on surveillance scans are not strong enough to change the guidelines since neither compared to any other surveillance strategy. The Forschner et al. [46] study is very interesting and does support the registry premetastasectomy scan as only 26% of patients had the same surgical treatment as planned (30% had extensive metastases and needed to be put on systemic therapy and 19% did not have any metastases so were put back on surveillance), while the remaining patients had changes in their surgical field. This makes for a strong case as an Ontario Health Insurance Plan-funded indication.

Neuro-Oncology

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

- PET is not recommended for the determination of diagnosis or grading in gliomas.

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

Reviewer's Comments (Dr. Amit Singnurkar)

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

Non-FDG Tracers

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

Reviewer's Comments (Dr. Amit Singnurkar)

There is currently not enough evidence to support making appropriate recommendations for the use of PET/CT with non-FDG tracers. ^{18}F-PSMA and ^{68}Ga-DOTATE are currently being evaluated in Ontario as non-FDG agents. These cover the scope of many of the articles summarized in the present review. Based on the literature, there is no new non-FDG agent that requires accelerated work-up for clinical use.

NSCLC and Other Lung Cancer

Current Insured Indications

- Solitary pulmonary nodule:
    - A lung nodule for which a diagnosis could not be established by a needle biopsy due to unsuccessful attempted needle biopsy; the solitary pulmonary nodule is inaccessible to needle biopsy; or the existence of a contraindication to the use of needle biopsy.
- NSCLC:
    - Where curative surgical resection is being considered based on negative standard imaging tests; or clinical stage III NSCLC where potentially curative combined-modality therapy with radiotherapy and chemotherapy is being considered.
- Limited-disease small cell lung cancer (SCLC):
    - Where combined modality therapy with chemotherapy and radiotherapy is being considered.

Current Recommendations for the Utilization of PET/CT in SCLC

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

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

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

Reviewer's Comments (Dr. Donna Maziak)

The current recommendations for the utilization of PET/CT in lung cancer remain valid and no changes are required. It is worthwhile to note that MRI is better than PET/CT in identifying brain metastases.

Pancreatic Cancer

Current Registry Indication

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

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

- PET is not recommended for primary diagnosis of pancreatic cancer.
- PET is recommended for staging if a patient is a candidate for potentially curative surgical resection as determined by conventional staging.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET to guide clinical management based on assessment of treatment response.
- Due to insufficient evidence and lack of effective therapeutic options, PET is not recommended for clinical management of suspected recurrence, or for restaging at the time of recurrence.
- A recommendation cannot be made for or against the use of PET for staging if a solitary metastasis is identified at recurrence because there are no trials that identify the utility of PET scanning in this setting.

Reviewer's Comments (Dr. Jim Biagi)

The current recommendations for the utilization of PET/CT in pancreatic cancer remain valid and no changes are required. The meta-analysis by Toft et al. [72] does not discriminate operable from inoperable disease, and thus is of limited value. Based on the results, PET is not better than other imaging modalities to which it was compared.

Pediatric Cancer

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

- For the following cancer types (International Classification for Childhood Cancer):
    - Bone/cartilage – osteosarcoma, Ewing sarcoma
    - Connective/other soft tissue – rhabdomyosarcoma, other
    - Kidney – renal tumour
    - Liver – hepatic tumour
    - Lymphoma/post-transplant lymphoproliferative disorder – Hodgkin and non-Hodgkin lymphoma
    - Primary brain – astrocytoma, medulloblastoma, ependymoma, other
    - Reproductive – germ cell tumour
    - Sympathetic nervous system - neuroblastoma MIBG-negative
    - Other – Langerhans cell histiocytosis, melanoma of the skin, thyroid
- For the following indications:

- Initial staging
- Monitoring response during treatment/determine response-based therapy
- Rule out progression prior to further therapy
- Suspected recurrence/relapse
- Rule out persistent disease
- Select optimal biopsy site

Reviewer's Comments

A review was not completed by a clinical expert in pediatric oncology.

Sarcoma

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

Reviewer's Comments (Dr. Gina Diprimio)

The literature in the last 12 to 18 months has been convincing regarding the need to include PET/CT imaging as a staging, restaging, and recurrence surveillance modality in sarcoma.

Unknown Primary Cancer

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

Reviewer's Comments (Dr. Amit Singnurkar)

There is currently not enough evidence to support making appropriate recommendations for the use of PET/CT in unknown primary cancer. However, the study by Burglin et al. [79] is interesting and will be useful for the overall review of PET oncology indications.

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Appendix 1: Summary of studies from January to June 2017.

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Breast Cancer								
Liang et al, 2017 [1]	Meta-analysis	21 studies (1905 patients with early breast cancer)	FDG PET/CT	MRI	ALND, SLNB	**Axillary lymph node metastasis** Pooled Sens: 64%* Pooled Spec: 93% Pooled DOR: 18.84* AUC: 0.88 Q test: 0.81	**Axillary lymph node metastasis** Pooled Sens: 82%* Pooled Spec: 93% Pooled DOR: 51.28* AUC: 0.94 Q test: 0.88	NA
Tian et al, 2017 [2]	Meta-analysis	22 studies (1119 breast cancer patients who received neoadjuvant chemotherapy)	FDG PET/CT	NA	Pathology	**Predicting pathological response** Pooled Sens: 81.9% Pooled Spec: 79.3% Pooled +LR: 3.96 Pooled –LR: 0.23 Pooled DOR: 17.35 AUC: 0.87	NA	NA
Catalano et al, 2017 [3]	Retrospective	191 patients (newly diagnosed invasive ductal carcinoma of the breast)	FDG PET/CT	DWI-MRI	Pathology, imaging follow-up	**Staging** Accu: 75%	**Staging** Accu: 84%	NA
Ulaner et al, 2017 [4]	Retrospective	483 patients; (newly diagnosed stage I-IIIC ER+/HER2- and HER2+ breast cancer)	FDG PET/CT	Physical exam, mammography, breast US, if available, breast MRI and/or surgical findings,	Histology, imaging follow-up	NA	NA	FDG PET/CT demonstrated unsuspected metastases in 13.4% (32/238) of ER+/HER2- patients and 11.8% (29/245) of HER2+ patients, upstaging them to stage IV.
Evangelista et al, 2017 [5]	Prospective	275 patients who underwent PET/CT before or after surgery (stage I-III, triple-negative or HER2+ breast cancer)	FDG PET/CT	Clinical examination, mammography, breast US, if available, breast MRI or surgical findings	Pathology, imaging follow-up	NA	NA	In the preoperative setting, PET/CT provided additional diagnostic information in 28.2% (42/149) of patients and a change in treatment was reported in 10.1% (15/149) of patients (12—systemic treatment, 2—systemic + local treatment, 1—enlarged surgical

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
								approach). In the postoperative setting, PET/CT changed the treatment strategies in 14.3% (18/126) of patients (8—additional external beam radiotherapy, 3—further surgery, 7—more aggressive systemic treatment or local and system therapies).
Epilepsy								
Wang et al, 2017 [6]	Prospective	166 pediatric patients undergoing preoperative evaluation (medically-intractable epilepsy)	FDG PET/CT	DCE-MRI, VEEG	Intraoperative electrocorticography	**Localization of epileptic foci** Accu: 91.0%*	**Localization of epileptic foci** ***DCE-MRI*** Accu: 57.6%* ***VEEG*** Accu: 67.7%*	NA
Esophageal Cancer								
Genc et al, 2016 [7]	Prospective	33 patients (pathologically confirmed esophageal cancer)	FDG PET/CT	CT perfusion, CeCT	Histopathology	**Diagnosis** Sens: 87.9% Spec: 0% PPV: 93.6% NPV: 0%	**Diagnosis** ***CT perfusion*** Sens: 100% Spec: 100% PPV: 100% NPV: 100% ***CeCT*** Sens: 93.4% Spec: 0% PPV: 93.9% NPV: 0%	NA
Foley et al, 2017 [8]	Retrospective	112 patients who underwent surgery alone or neoadjuvant therapy (esophageal or gastro-esophageal tumour)	FDG PET/CT	CeCT, EUS	Histopathology	**N-staging** Sens: 35.3% Spec: 90.9% Accu: 57.1%	**N-staging** ***CeCT*** Sens: 39.7% Spec: 77.3% Accu: 54.5% ***EUS*** Sens: 42.6% Spec: 75.0% Accu: 55.4%	NA
Gastrointestinal Cancer								
Lee et al, 2017 [9]	Retrospective	220 patients who underwent staging prior to curative	FDG PET/CT	CeCT	Pathology	**Lymph node metastasis** Sens: 43.5%* Spec: 83.6%*	**Lymph node metastasis** Sens: 58.7%* Spec: 64.8%*	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		surgery (CRC)				PPV: 65.6% NPV: 67.3% Accu: 66.8%* **Distant metastasis** Sens: 78.6% Spec: 93.7%* PPV: 45.8% NPV: 98.5% Accu: 92.7%*	PPV: 54.5% NPV: 68.6% Accu: 62.3%* **Distant metastasis** Sens: 78.6% Spec: 86.9%* PPV: 28.9% NPV: 98.4% Accu: 86.4%*	
Sasaki et al, 2017 [10]	Retrospective	370 patients who underwent surgical resection (CRC)	FDG PET/CT	CeCT	Histopathology	**Lymph node metastasis** Sens: 56.8% Spec: 90.4% PPV: 84.6% NPV: 69.3% Accu: 74.2%	**Lymph node metastasis** Sens: 38.4% Spec: 95.5% PPV: 90.6% NPV: 57.5% Accu: 65.0%	NA
Vallam et al, 2017 [11]	Retrospective	104 patients who had undergone curative resection of the primary tumour and had become disease free after surgery (non-metastastic CRC with rising CEA levels)	FDG PET/CT (follow-up surveillance)	Clinical examination, serum CEA levels, complete haematological and liver function tests, CeCT, colonoscopy	Cytology or histopathology, clinical and imaging follow-up	**Recurrence** Sens: 92.7% Spec: 95.2% PPV: 96.2% NPV: 90.9%	NA	NA
Yu et al, 2017 [12]	Retrospective	56 patients with rising CEA levels after curative therapy and had not received any other radiological examinations previously (CRC)	FDG PET/CT	NA	Pathology, imaging follow-up	**Relapse** Sens: 94.9% Spec: 70.6% PPV: 88.1% NPV: 85.7% Accu: 87.5%	NA	NA
Fehr et al, 2017 [13]	Retrospective	50 patients who had undergo a complete	FDG PET/CT	CT scan of chest, abdomen, and pelvis	Biopsy, CEA serum level, imaging follow-up	NA	NA	Early postoperative PET/CT led to management changes in 14% (7/50) of patients (6—

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		resection (pT1-4, pN2, cM0 CRC)						initiated palliative chemotherapy or immunochemotherapy, 1— watch and wait + palliative chemotherapy).
Samim et al, 2017 [14]	Meta-analysis	10 studies (304 patients with colorectal liver metastases or liver metastasis from other tumour sites)	FDG PET or PET/CT	CT	Histopathology, clinical and imaging follow-up	**Disease progression after ablation therapy** Pooled Sens: 84.6%* Pooled Spec: 92.4%	**Disease progression after ablation therapy** Pooled Sens: 53.4%* Pooled Spec: 95.7%	Across 3 studies, PET or PET/CT changed management in 36% to 82% of patients.
Houard et al, 2017 [15]	Retrospective	87 patients treated with chemoradiotherapy (biopsy-proven squamous cell cancer of the anal canal)	FDG PET/CT (1 to 8 months post-treatment)	CT, MRI	Histology, clinical and imaging follow-up	**Residual disease** Sens: 92% Spec: 85% PPV: 72% NPV: 96.4%	NA	PET/CT changed patient management in 16.1% (14/87) of cases (8— salvage surgery, 2— triggered chemotherapy, 1—treated with radiofrequency, 1—avoided unnecessary biopsy, 2— unneeded biopsy). The 2-year PFS was 96% for patients with CMR and 28% for those without CMR ($p<0.0001$). The 2-year CSS was 100% for patients with CMR and 59% for those without CMR ($p<0.0001$).
Serrano et al, 2016 [16]	Retrospective	166 patients (biopsy-proven gastric adenocarcinoma)	FDG PET/CT	CeCT	Histopathology, chart review, subsequent radiologic or nuclear imaging	NA	NA	In comparison to CeCT, PET/CT upstaged 18.7% (31/166) and downstaged 10.2% (17/166) of patients.
Gynecologic Cancer								
Han et al, 2016 [17]	Retrospective	268 patients; 416 PET/CT scans (previously treated for ovarian malignancy)	FDG PET/CT	CT, MRI, CA125	Histology, imaging and clinical follow-up	**Recurrence or second primary malignancy** Sens: 98.8% Spec: 98.2% PPV: 93.1% NPV: 99.7% Accu: 98.3%	NA	Changes in management occurred in 10.5% (38/362) PET/CT scans performed without clinical suspicion (19—salvage or palliative chemotherapy, 14— debulking surgery and chemotherapy, 2— additional radiotherapy, 3—surgery). Disease

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
								recurrence was ruled out in 16.7% (9/54) of PET/CT scans performed with clinical suspicion.
Chou et al, 2017 [18]	Prospective	73 patients who had completed primary cytoreductive surgery and standard adjuvant chemotherapy; 92 PET scans (ovarian cancer)	FDG PET or PET/CT	CT, MRI	Pathology, imaging follow-up	**Suspicious lesions detected on post-therapy CT or MRI** Sens: 91.2% Spec: 62.5% PPV: 91.2% NPV: 62.5%	NA	In 34 patients with CT- or MRI-detected recurrences that were deemed curable, PET/CT scans led to altered treatment plans in 44.1% (15/34) of the patients (10—additional salvage treatment, 5—curative treatment to palliation).
Xu et al, 2017 [19]	Meta-analysis	49 studies (3065 patients with recurrent or metastatic ovarian cancer)	FDG PET/CT	NA	Histopathology, clinical follow-up	**Recurrence or metastasis** Pooled Sens: 92% Pooled Spec: 91% Pooled +LR: 6.97 Pooled –LR: 0.09 Pooled DOR: 88.45 AUC: 0.956 Q test: 0.899	NA	NA
Kassem, 2017 [20]	Prospective	34 patients who underwent surgical intervention, chemotherapy, radiotherapy or combined treatment (proven omental deposits from ovarian or uterine tumours)	FDG PET/CT	CT	Histopathology, clinical and imaging follow-up	**Assessment of therapeutic response** Sens: 96.9% Spec: 100% Accu: 97.1%	**Assessment of therapeutic response** Sens: 93.6% Spec: 66.7% Accu: 91.2%	NA
Atri et al, 2017 [21]	Prospective	49 patients who are appropriate surgical candidates (primary, previously	FDG PET/CT	CT	Pathology	**Lymph node metastasis** ***Abdomen*** Sens: 65%* Spec: 88% AUC: 0.78 ***Pelvis***	**Lymph node metastasis** ***Abdomen*** Sens: 50%* Spec: 93% AUC: 0.74 ***Pelvis***	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		untreated high-risk endometrial cancer)				Sens: 65%* Spec: 93% AUC: 0.82*	Sens: 48%* Spec: 89% AUC: 0.73*	
Park et al, 2017 [22]	Retrospective	362 patients with negative lymph node on preoperative MRI and subsequently underwent lymph node dissection (endometrial cancer)	FDG PET/CT	MRI	Pathology	**Lymph node metastasis (patient-based)** Sens: 18.5% Spec: 94.0% PPV: 93.5% NPV: 20.0% Accu: 88.4% **(station-based)** Sens: 16.3% Spec: 98.8% PPV: 98.0% NPV: 25.0% Accu: 96.9%	NA	NA
Liu et al, 2017 [23]	Meta-analysis	67 studies (patients with cervical cancer)	FDG PET or PET/CT	CT, MRI, DWI-MRI	Surgery, biopsy	**Lymph node metastasis (patient-based)** Pooled Sens: 76% Pooled Spec: 94% Pooled +LR: 13.2 Pooled –LR: 0.25 Pooled DOR: 52 AUC: 0.95* **(region- or node-based)** Pooled Sens: 55%* Pooled Spec: 98%* Pooled +LR: 26.2* Pooled –LR: 0.46* Pooled DOR: 57 AUC: 0.90*	**Lymph node metastasis** ***CT*** **(patient-based)** Pooled Sens: 59% Pooled Spec: 91% Pooled +LR: 6.5 Pooled –LR: 0.45 Pooled DOR: 14 AUC: 0.90* ***MRI*** Pooled Sens: 59% Pooled Spec: 90% Pooled +LR: 5.8 Pooled –LR: 0.45 Pooled DOR: 13 AUC: 0.80* **(region- or node-based)** ***CT*** Pooled Sens: 50% Pooled Spec: 92% Pooled +LR: 6.1 Pooled –LR: 0.54 Pooled DOR: 11 AUC: 0.83* ***MRI*** Pooled Sens: 47%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
							Pooled Spec: 96% Pooled +LR: 12.0 Pooled –LR: 0.55 Pooled DOR: 22 AUC: 0.88 ***DWI-MRI*** Pooled Sens: 87%* Pooled Spec: 83%* Pooled +LR: 5.2* Pooled –LR: 0.15* Pooled DOR: 34 AUC: 0.92	
Head and Neck Cancer								
Bird et al, 2016 [24]	Retrospective	146 patients treated with primary definitive radiotherapy (stage III/IV histologically confirmed oropharyngeal squamous cell carcinoma)	FDG PET/CT	Clinical examination	Histology, clinical and imaging follow-up	**Local recurrence** Sens: 100% Spec: 94.2% PPV: 52.9% NVP: 100% **Regional recurrence** Sens: 87.5% Spec: 93.1% PPV: 60.9% NPV: 98.4%	NA	NA
Taghipour et al, 2017 [25]	Retrospective	110 patients who underwent therapy assessment within 6 months after completion of primary treatment (biopsy-proven oropharyngeal squamous cell carcinoma)	FDG PET/CT	CeCT	Histopathology, clinical and imaging follow-up	**Residual disease** **Primary site** Sens: 75.0% Spec: 91.5% PPV: 25.0% NPV: 99.0% Accu: 90.9% **Ipsilateral neck** Sens: 60.0% Spec: 97.1%* PPV: 50.0%* NPV: 98.1% Accu: 95.5% **Contralateral neck** Sens: 100% Spec: 98.1% PPV: 50.0% NPV: 100% Accu: 98.2% **Distant metastasis** Sens: 100% Spec: 98.1%	**Residual disease** **Primary site** Sens: 75.0% Spec: 90.6% PPV: 23.1% NPV: 99.0% Accu: 90.0% **Ipsilateral neck** Sens: 80.0% Spec: 66.7%* PPV: 10.3%* NPV: 98.6% Accu: 67.3% **Contralateral neck** Sens: 100% Spec: 94.4% PPV: 25.0% NPV: 100% Accu: 94.5%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						PPV: 50.0% NPV: 100% Accu: 98.2%		
Hobelmann et al, 2017 [26]	Retrospective	95 patients treated with primary transoral robotic surgery (biopsy-proven oropharyngeal squamous cell carcinoma)	FDG PET/CT	NA	Biopsy, clinical and imaging follow-up	**Residual disease or recurrence** **2 years post-treatment** Sens: 100% Spec: 77% PPV: 19% NPV: 100% **2.5 years post-treatment** Sens: 86% Spec: 76% PPV: 33% NPV: 98% **3 years post-treatment** Sens: 86% Spec: 71% PPV: 35% NPV: 96%	NA	NA
Liu et al, 2017 [27]	Retrospective	213 patients (locoregional advanced nasopharyngeal carcinoma)	FDG PET/CT-guided dose painting-IMRT (n=101)	CT-based IMRT (n=112)	Clinical follow-up	NA	NA	Compared with CT-based IMRT, PET/CT-guided dose painting-IMRT significantly improved CRR (99.0% vs. 92.9%; p=0.037), 3-year LFFS (98.8% vs. 91.3%; p=0.032), LRFFS (97.2% vs, 91.2%; p=0.049), DMFS (92.9% vs. 87.4%; p=0.041), DFS (87.9% vs. 82.9%; p=0.02), and OS (91.8% vs. 82.6%; p=0.049). There were no significant differences in the incidence of grade 3-4 acute and late toxic effects between the two groups.
Xu et al, 2017 [28]	Meta-analysis	10 studies (1774 patients with nasopharyngeal carcinoma)	FDG PET/CT	Conventional work-ups	Biopsy, clinical and imaging follow-up	**Distant metastases** Pooled Sens: 83.7%* Pooled Spec: 97.7% Pooled +LR: 36.42 Pooled –LR: 0.17*	**Distant metastases** Pooled Sens: 40.1%* Pooled Spec: 97.8% Pooled +LR: 16.85 Pooled –LR: 0.63*	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						AUC: 0.980* Q test: 0.937*	AUC: 0.914* Q test: 0.846*	
Liao et al, 2016 [29]	Meta-analysis	73 studies (patients with cN0 head and neck cancer)	FDG PET/CT	CT, MRI, US, US-FNA, SNB	Histopathology, follow-up	**Cervical lymph node metastasis** Pooled Sens: 48.3% Pooled Spec: 86.2% AUC: 0.826	**Cervical lymph node metastasis** ***CT*** Pooled Sens: 47.0% Pooled Spec: 88.9% AUC: 0.811 ***MRI*** Pooled Sens: 56.6% Pooled Spec: 82.5% AUC: 0.791 ***US*** Pooled Sens: 63.3% Pooled Spec: 79.1% AUC: 0.807 ***US-FNA*** Pooled Sens: 56.4% Pooled Spec: 100% AUC: 0.97 ***SNB*** Pooled Sens: 84.9% Pooled Spec: 100% AUC: 0.98	NA
Cho et al, 2017 [30]	Retrospective	73 patients who underwent neck dissection; 579 neck levels; 116 neck sides (head and neck squamous cell carcinoma)	FDG PET/CT	CeCT	Histopathology	**Cervical lymph node metastasis (neck level-based)** Sens: 69% Spec: 86%* PPV: 44% NPV: 94% Accu: 83% **(neck side-based)** Sens: 94%* Spec: 56%* PPV: 64% NPV: 92%* Accu: 73%	**Cervical lymph node metastasis (neck level-based)** Sens: 53% Spec: 91%* PPV: 49% NPV: 92% Accu: 85% **(neck side-based)** Sens: 66%* Spec: 76%* PPV: 70% NPV: 73%* Accu: 72%	NA
Chaput et al, 2017 [31]	Prospective	35 patients (histologically proven T1-T2 head and neck squamous cell carcinoma)	FDG PET/CT	MRI	Histology	**T staging** Sens: 83%*	**T staging** Sens: 63%*	NA
Qiu et al, 2017 [32]	Retrospective	82 patients with negative	FDG PET/CT	131I-WBS and/or 131I-SPECT/CT,	Surgical pathology,	**Recurrence** Sens: 84%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		Tg, negative 131I-WBS at first postablation and progressively increased TgAb level (differentiated thyroid cancer)		neck US	histopathology, imaging follow-up	Spec: 72% PPV: 92% NPV: 57% Accu: 82%		
Vera et al, 2017 [33]	Prospective	40 patients with positive Tg and negative WBS after total thyroidectomy (well-differentiated thyroid cancer)	FDG PET/CT	DW-MRI, neck US	Histology, clinical and imaging follow-up	**Recurrence** **Baseline follow-up** Sens: 46% Spec: 50% PPV: 58% NPV: 38% Accu: 48% **6-month follow-up** Sens: 30% Spec: 53% PPV: 30% NPV: 53% Accu: 44% **18-month follow-up** Sens: 30% Spec: 53% PPV: 30% NPV: 53% Accu: 44%	**Recurrence** **Baseline follow-up** ***DW-MRI*** Sens: 43% Spec: 29% PPV: 45% NPV: 37% Accu: 41% ***Neck US*** Sens: 38% Spec: 55% PPV: 69% NPV: 25% Accu: 43% **6-month follow-up** ***DW-MRI*** Sens: 20% Spec: 60% PPV: 25% NPV: 53% Accu: 44% ***Neck US*** Sens: 33% Spec: 75% PPV: 63% NPV: 47% Accu: 52% **18-month follow-up** ***DW-MRI*** Sens: 38% Spec: 55% PPV: 69% NPV: 25% Accu: 43% ***Neck US*** Sens: NA	

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
							Spec: 69% PPV: NA NPV: 47% Accu: 39%	
Park et al, 2017 [34]	Prospective	67 patients who received a staging workup and subsequently underwent surgery with or without postoperative radiotherapy/chemoradiotherapy (salivary gland carcinoma)	FDG PET/CT	CeCT, chest CT	Pathology, biopsy	**Neck node metastasis (patient-based)** Sens: 88.2%* Spec: 91.9% PPV: 83.3% NPV: 94.4% Accu: 90.7% AUC: 0.874* **(neck side-based)** Sens: 88.9%* Spec: 91.9% PPV: 83.3% NPV: 94.4% Accu: 90.7% AUC: 0.868* **(neck level-based)** Sens: 81.4%* Spec: 94.4% PPV: 77.8% NPV: 95.5% Accu: 91.9% AUC: 0.870* **Distant metastasis to thoracic cavity** Sens: 100% Spec: 95.2% PPV: 57.1% NPV: 100% Accu: 95.5% **Secondary cancer** Sens: 100% Spec: 96.9% PPV: 50.0% NPV: 100% Accu: 97.0%	**Neck node metastasis *CeCT* (patient-based)** Sens: 52.9%* Spec: 94.6% PPV: 81.8% NPV: 81.4% Accu: 81.5% AUC: 0.759* **(neck side-based)** Sens: 55.6%* Spec: 94.9% PPV: 83.3% NPV: 82.2% Accu: 84.2% AUC: 0.742* **(neck level-based)** Sens: 46.5%* Spec: 98.3% PPV: 87.0% NPV: 88.5% Accu: 88.3% AUC: 0.737* ***Chest CT*** **Distant metastasis to thoracic cavity** Sens: 75.0% Spec: 95.2% PPV: 50.0% NPV: 98.4% Accu: 94.0% **Secondary cancer** Sens: 0% Spec: 100% PPV: NA NPV: 97.0% Accu: 97.0%	NA
Abadi et al, 2017 [35]	Retrospective	58 patients (a single cervical cyst)	FDG PET/CT	NA	Histopathology, follow-up	**Differentiate between malignant and benign lesions** Sens: 95%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Spec: 61% PPV: 56% NPV: 96% Accu: 72%		
Hematologic Cancer								
Andre et al, 2017 [36]	RCT	1950 patients who underwent interim-PET response evaluation after 2 cycles of ABVD; 1:1 allocation (previously untreated stage I and II supradiaphragmatic HL)	FDG PET/CT (PET-positive patients switched to 2 cycles of BEACOPPesc and INRT, PET-negative patients received 2 or 4 additional ABVD cycles minus INRT)	NA	Clinical follow-up	NA	NA	In PET-positive patients, the 5-year PFS improved from 77.4% for standard ABVD + INRT to 90.6% for intensification to BEACOPPesc + INRT (HR=0.42; 95% CI: 0.23 to 0.74; p=0.002). The 5-year OS rates were 89.3% and 96.0% for ABVD + INRT and BEACOPPesc + INRT, respectively (HR=0.45; 95% CI: 0.19 to 1.07; p=0.062). In PET-negative patients, the 5-year PFS favored ABVD + INRT in both favorable risk (99.0% vs. 87.1%; HR=15.8; 95% CI: 3.8 to 66.1) and unfavorable risk patients (92.1% vs. 89.6%; HR=1.45; 95% CI: 0.8 to 2.5), noninferiority of ABVD only could not be demonstrated.
Borchmann et al, 2017 [37]	Phase 3 RCT	440 PET-positive patients after 2 cycles of BEACOPPescalated 1:1 allocation to receive either additional 6 courses of BEACOPPescalated or 6 courses of BEACOPPescalated plus rituximab	FDG PET/CT	NA	Clinical follow-up	NA	NA	The 3-year PFS was 91.4% for patients in the BEACOPPescalated group and 93.0% for those in the BEACOPPescalated plus rituximab group (difference 1.6%, 95% CI: -4.0-7.3; log rank p=0.99). There was no significant difference in 3-year OS between the two groups (96.5 vs. 94.4, respectively; p=0.31).

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		(newly diagnosed, advanced stage HL)						
Mesguich et al, 2016 [38]	Retrospective	76 patients who underwent interim-PET assessment after 2-4 cycles of ABVD and end-of-treatment evaluation (HL)	FDG PET/CT	NA	Biopsy, clinical and imaging follow-up	**Predicting treatment failure** ***Interim-liver*** Sens: 46.7% Spec: 85.2% PPV: 43.8% NPV: 86.7% Accu: 77.6% ***Interim-mediastinum*** Sens: 80.0% Spec: 32.8% PPV: 22.6% NPV: 87.0% Accu: 42.1% ***End-of-treatment*** Sens: 80.0% Spec: 93.4% PPV: 75.0% NPV: 95.0% Accu: 90.8%	NA	The 5-year PFS was significantly worst for patients with positive end-of-treatment PET than for patients with negative end-of-treatment PET (23% vs. 96%; p<0.001).
Ujjani et al, 2016 [39]	Retrospective	149 patients with newly diagnosed lymphoma (58 DLBCL, 57 FL, 34 HL)	FDG PET/CT	BMB	BMB	**Bone marrow involvement** ***DLBCL*** Sens: 60% Spec: 92% Accu: 86% ***FL*** Sens: 67% Spec: 85% Accu: 77% ***HL*** Sens: 100% Spec: 74% Accu: 76%	NA	NA
Oner et al, 2017 [40]	Prospective	172 treatment naïve patients (64 HL, 108 NHL)	FDG PET/CT	BMB	BMB	**Bone marrow involvement** ***HL*** Sens: 80.0% Spec: 78.0% PPV: 23.5% NPV: 97.9%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						NHL Sens: 24.3% Spec: 90.1% PPV: 56.3% NPV: 69.6%		
Fallanca et al, 2016 [41]	Retrospective	101 patients who underwent early restaging after treatment (35 HL, 66 NHL)	FDG PET/CT	NA	Multidisciplinary team case notes, imaging follow-up	**Response assessment (end of treatment)** ***IHPC*** Sens: 97% Spec: 67% PPV: 57% NPV: 98% Accu: 76% ***DC with 3-5 as positive*** Sens: 97% Spec: 76% PPV: 64% NPV: 98% Accu: 84% ***DC with 4 and 5 as positive*** Sens: 92% Spec: 87% PPV: 74% NPV: 92% Accu: 86%	NA	NA
Metser et al, 2017 [42]	Prospective	197 patients being considered for curative radiation therapy (newly diagnosed indolent lymphoma)	FDG PET/CT	CT	Follow-up, data linkage	NA	NA	PET/CT changed the disease stage of 55.8% (110/197) of patients (72—upstaged, 10—downstaged, 28—required further evaluation to confirm disease extent). The change in proportion of patients planned for active treatment before and after PET/CT was significant ($p<0.0001$).
Cavo et al, 2017 [43]	Systematic review and consensus guideline	Patients with multiple myeloma and other plasma cell disorders	FDG PET/CT	MRI, x-ray, CT, MIBI	Consensus statement by the International Myeloma Working	**Active multiple myeloma** • PET/CT should be considered as part of the initial investigations in patients with newly diagnosed multiple myeloma because it provides information useful for prognostication and allows to more carefully assess the bulk of the disease, particularly in patients with extramedullary sites of the disease; assessing the bulk of the disease		

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
					Group	with PET/CT also applies to patients with relapsed or refractory multiple myeloma. (Grade B) • In patients with newly diagnosed multiple myeloma, with or without extramedullary disease, and more than three focal lesions, PET/CT identifies subgroups of patients with unfavourable outcomes; controversies exist about the prognostic role of SUV_{max}. (Grade B) • PET/CT is now the preferred technique for evaluating and monitoring response to therapy; metabolic changes assessed by PET/CT provide an earlier evaluation of response compared with MRI. (Grade A) • PET/CT should be coupled with sensitive bone marrow-based assays as part of minimal residual disease detection inside and outside the bone marrow. (Grade B) **Smouldering multiple myeloma** • Patients who meet the diagnostic criteria for smouldering multiple myeloma and have one or more lytic lesions on PET/CT should be defined as having multiple myeloma that requires immediate therapy. (Grade A) • PET/CT is recommended to distinguish smouldering multiple myeloma from active multiple myeloma if whole-body X-ray is negative and whole-body MRI is unavailable. (Grade A) **Solitary plasmacytoma** • Patients with focal lesions on PET but without underlying lytic lesions on the CT part of PET/CT are at high risk of progression to active multiple myeloma. (Grade B) • Patients with suspected solitary plasmacytoma, either extramedullary plasmacytoma or solitary bone plasmacytoma without symptoms or signs suggestive of cord compression, should receive PET/CT to unequivocally confirm the diagnosis, provided whole-body MRI is unavailable. (Grade A)		
Melanoma								
Madu et al, 2017 [44]	Prospective	18 asymptomatic patients with a normal S100B; 32 surveillance scans (resected stage IIIB and IIIC melanoma)	FDG PET/CT	S100B, physical examination	Pathology, clinical and imaging follow-up	**Recurrence** Sens: 91% Spec: 95% PPV: 91% NPV: 95%	NA	NA
Lawal et al, 2017 [45]	Retrospective	144 patients in whom all malignant lesions had been surgically	FDG PET/CT	NA	Histology, imaging follow-up	**Asymptomatic recurrence** Sens: 94.5% Spec: 87.6% Accu: 89.6%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		excised; 313 PET/CT scans (histologically confirmed malignant melanoma)						
Forschner et al, 2017 [46]	Prospective	107 patients planned for radical metastasectomy (advanced melanoma)	FDG PET/CT	CT, MRI, US, tumour marker	Clinical follow-up	NA	NA	PET/CT resulted in minor changes in 22.4% (24/107) of patients (10—enlargement of surgical field, 10—reduction of surgical field, 2—surgery at another site, 2—radiofrequency ablation without surgery) and major changes in 51.4% (55/107) of patients (20—watching, 25—allocated to systemic treatment, 7—allocated to systemic treatment and palliative surgery, 2—allocated to palliative radiotherapy, 1—performed isolated extremity perfusion). The estimated 1- and 2-year OS of patients treated by complete metastasectomy were 90% and 79%, respectively. The estimated 1-year and 2-year OS of patients treated with systemic therapy were 72% and 61%, respectively.
Neurology-Oncology								
Song et al, 2016 [47]	Prospective	70 patients (primary gliomas or suspected gliomas)	FDG PET/CT	MRI	Pathology, follow-up	**Grading** ***Grade I*** Sens: 80.6% Spec: 78.5% Accu: 79.8% ***Grade II*** Sens: 86.4% Spec: 87.9% Accu: 85.7% ***Grade III***	**Grading** ***Grade I*** Sens: 76.3% Spec: 72.4% Accu: 75.6% ***Grade II*** Sens: 82.9% Spec: 86.3% Accu: 84.7% ***Grade III***	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Sens: 87.7% Spec: 88.4% Accu: 86.9% ***Grade IV*** Sens: 82.1% Spec: 79.5% Accu: 78.6%	Sens: 86.3% Spec: 87.4% Accu: 85.1% ***Grade IV*** Sens: 79.6% Spec: 76.5% Accu: 77.2%	
Non-FDG Tracers **$^{11}C/^{18}F$-Choline**								
Evangelista et al, 2016 [48]	Meta-analysis	9 studies (361 prostate cancer patients with biochemical recurrence after primary treatments and underwent salvage lymphadenectomy)	11C/18F-Choline PET/CT	NA	Pathology	**Pathological lymph nodes (patient-based)** Pooled Sens: 85.3% Pooled Spec: 32.6% Pooled PPV: 75.0% Pooled NPV: 49.6% Pooled +LR: 1.21 Pooled –LR: 0.46 Pooled DOR: 2.84 **(lesion-based)** Pooled Sens: 56.2% Pooled Spec: 94.9% Pooled PPV: 85.8% Pooled NPV: 82.5% Pooled +LR: 11.2 Pooled –LR: 0.48 Pooled DOR: 30.9%	NA	NA
Wieder et al, 2017 [49]	Prospective	57 patients (suspected recurrence of prostate cancer)	11C-Choline PET/CT	DWI-MRI	Biopsy and histopathology, clinical and imaging follow-up	**Local recurrence** Sens: 83.3%* Spec: 93.9% PPV: 90.9% NPV: 88.6% Accu: 89.5% AUC: 0.993* **Lymph node metastasis** Sens: 81.4% Spec: 99.7% PPV: 97.9% NPV: 97.3% Accu: 97.4% AUC: 0.945 **Bone metastases** Sens: 92.9%* Spec: 98.4% PPV: 91.5%	**Local recurrence** Sens: 54.2%* Spec: 81.8% PPV: 68.4% NPV: 71.1% Accu: 70.1% AUC: 0.729* **Lymph node metastasis** Sens: 77.9% Spec: 87.5% PPV: 52.8% NPV: 96.5% Accu: 88.2% AUC: 0.905 **Bone metastases** Sens: 78.6%* Spec: 87.5% PPV: 52.9%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						NPV: 98.7% Accu: 97.6% AUC: 0.984	NPV: 96.5% Accu: 88.2% AUC: 0.925	
Gauvin et al, 2017 [50]	Retrospective	60 patients initially treated with curative intent (biochemical recurrence of prostate cancer)	18F-Choline PET/CT	CT, MRI, bone scan	Histology, clinical and imaging follow-up, consensus from blinded non-treating physicians	NA	NA	PET/CT changed the clinical management plan in 28.3% (17/60) of patients (7—watchful waiting to treatment, 4—treatment to watchful waiting, 6 modified therapeutic strategy).
68Ga-DOTA-(TATE, NOC, TOC)								
Calais et al, 2017 [51]	Prospective	96 patients (suspected or histologically proven NET)	68Ga-DOTA-TATE PET/CT	NA	Electronic chart review	NA	NA	68Ga-DOTA-TATE PET/CT resulted in intended management changes in 50% (48/96) of patients. These changes were implemented in 75% (36/48) of patients.
Panagiotidis et al, 2017 [52]	Retrospective	104 patients (histologically proven NETs)	68Ga-DOTA-TATE PET/CT	FDG PET/CT	Histology	NA	NA	68Ga-DOTA-TATE PET/CT affected the management plan in 48.1% (50/104) of patients (5—active surveillance, 9—surgery, 8—chemotherapy, 14—PRRT, 1—everolimus, 11—somatostain analogs, 2—liver-directed surgery). FDG PET/CT affected the management plan in 21.2% (22/104) of patients (4—active surveillance, 10—chemotherapy, 5—surgery, 1—radiofrequency ablation, 2—somatostatin analogs).
Sampathirao and Basu, 2017 [53]	Retrospective	51 patients (metastatic NET with unknown primary)	68Ga-DOTA-TATE PET/CT	US, CT/CeCT, MRI, EUS, FDG PET/CT	Histopathology, further correlative imaging	**Staging** Sens: 96.9%	**Staging** ***US*** Sens: 43.0% ***CT/CeCT*** Sens: 57.8% ***FDG PET/CT*** Sens: 51.6%	68Ga-DOTA-TATE PET/CT detected the primary in 60.8% (31/51) of patients in which conventional imaging modalities failed to conclusively diagnose.
Archier et al, 2016 [54]	Prospective	30 patients (pheochromocytomas or	68Ga-DOTA-TATE PET/CT	CeCT, MRI	Histology, consensus	**Staging or restaging (patient-based)** Sens: 93%	**Staging or restaging (patient-based)** Sens: 93%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		paragangliomas at initial diagnosis or relapse)				**(lesion-based)** Sens: 93%*	**(lesion-based)** Sens: 76%*	
Yamaga et al, 2017 [55]	Prospective	15 patients with increased calcitonin levels and or imaging evidence of metastases after total thyroidectomy with lymph node dissection (medullary thyroid carcinoma)	68Ga-DOTA-TATE PET/CT	111In-octreotide SPECT/CT, chest/abdominal/ bone/neck CT, neck US, neck/abdominal/ mediastinal/bone MRI, bone scan	Histopatholog y, biochemical, clinical and imaging follow-up, correlation with all imaging modalities	**Recurrence** Sens: 100% Accu: 93%	**Recurrence** ***111In-octreotide SPECT/CT*** Sens: 46% Accu: 53% ***CT/US/MRI/Bone scan*** Sens: 100% Accu: 93%	NA
Kunz et al, 2017 [56]	Retrospective	82 patients (confirmed or suspected intracranial meningioma)	68Ga-DOTA-TATE PET/CT	CE-MRI	Pathology	**Osseous involvement** Sens: 98.5%* Spec: 86.7% +LR: 7.39 -LR: 0.02 AUC: 0.932	**Osseous involvement** Sens: 53.7%* Spec: 93.3% +LR: 8.06 -LR: 0.50 AUC: 0.773	NA
Walker et al, 2017 [57]	Prospective	30 patients; 31 lesions (newly, diagnosed, untreated lung cancer or indeterminate pulmonary nodules)	68Ga-DOTA-TATE PET/CT	FDG PET/CT	Pathology, imaging follow-up	**Diagnosis** Sens: 73.3% Spec: 93.8% PPV: 91.7% NPV: 78.9% Accu: 83.5%	**Diagnosis** Sens: 93.3% Spec: 81.3% PPV: 82.4% NPV: 92.9% Accu: 87.3%	NA
Menda et al, 2017 [58]	Prospective	40 patients (histologically proven NET metastases and an unknown primary)	68Ga-DOTA-TOC PET/CT	CT and/or MRI of the abdomen-pelvis	Histology, clinical and imaging follow-up	**Primary tumour site** TP: 38% FP: 7% FN: 50% Unconfirmed: 5%	NA	NA
Barrio et al, 2017 [59]	Meta-analysis	14 studies (1561 patients with neuroendocrine tumours)	68Ga-DOTA-TATE or 68Ga-DOTA-NOC or 68Ga-DOTA-TOC PET/CT	Bone scan, US, MRI, CT, octreoscan, and FDG PET/CT	Pre-scan and post-scan therapy recommendati ons	NA	NA	Across the studies, 68Ga-DOTA-TATE or 68Ga-DOTA-NOC or 68Ga-DOTA-TOC PET/CT findings resulted in management changes in 44% of the patients.

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
68Ga-PSMA								
van Leeuwen et al, 2017 [60]	Prospective	30 patients suitable for radical prostatectomy with an extended pelvic lymph node dissection (biopsy-proven intermediate- to high-risk prostate cancer)	68Ga-PSMA PET/CT	NA	Histopathology	**Lymph node metastasis (patient-based)** Sens: 64% Spec: 95% PPV: 88% NPV: 82% **(side-based)** Sens: 56% Spec: 98% PPV: 90% NPV: 86% **(region-based)** Sens: 54% Spec: 99% PPV: 92% NPV: 94% **(node-based)** Sens: 58% Spec: 100% PPV: 94% NPV: 98%	NA	NA
Obek et al, 2017 [61]	Prospective	51 patients with negative 99mTc-MDP bone scan and scheduled to undergo radical prostatectomy and extended lymph node dissection (high-risk and very high-risk nonmetastatic prostate cancer)	68Ga-PSMA PET/CT	99mTc-MDP bone scan, MRI or CT	Histopathology	**Lymph node metastasis** Sens: 53.3% Spec: 85.7% PPV: 61.5% NPV: 81.0% Accu: 76.0%	**Lymph node metastasis** ***MRI or CT*** Sens: 25.0% Spec: 76.3% Accu: 72.7%	NA
Roach et al, 2017 [62]	Prospective	420 patients referred for either primary staging or restaging/biochemical failure (histological diagnosis of	68Ga-PSMA PET/CT	CT, MRI, bone scintigraphy	Pre- and post-PET questionnaire	**NA**	**NA**	In patients referred for primary staging, 68Ga-PSMA PET/CT detected additional local, nodal, and metastatic disease in 13.9% (15/108), 25.0% (27/108), and 6.5% (7/108) of patients, respectively.

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		prostate cancer)						As a consequence, management intent was changed in 21.3% (23/108) of patients. In patients with biochemical failure, 68Ga-PSMA PET/CT detected additional local, nodal, and metastatic disease in 31.7% (99/312), 43.3% (135/312), and 19.6% (61/312) of patients, respectively. Management intent was changed in 61.5% (192/312) of patients.
Hope et al, 2017 [63]	Prospective	126 patients with biochemical recurrence following definitive local therapy (prostate cancer)	68Ga-PSMA-11 PET/CT or PET/MRI	CT, bone scan, MRI, 18F-NaF PET,	Pre- and post-PET questionnaire	**NA**	**NA**	68Ga-PSMA-11 PET/CT or PET/MRI resulted in a major change in 53.2% (67/126) of patients (40—targeted treatment, 12—systemic treatment, 10—active surveillance, 5—others).
18F-DOPA								
Archier et al, 2016 [54]	Prospective	30 patients (pheochromocytomas or paragangliomas at initial diagnosis or relapse)	18F-FDOPA PET/CT	CeCT, MRI	Histology, consensus	**Staging or restaging (patient-based)** Sens: 97% **(lesion-based)** Sens: 89%*	**Staging or restaging (patient-based)** Sens: 93% **(lesion-based)** Sens: 76%*	NA
Golubic et al, 2017 [64]	Prospective	28 patients with increasing levels of calcitonin after primary surgical procedure and negative conventional imaging findings (medullary thyroid carcinoma)	18F-DOPA PET/CT	US, CT, FNAC, bone scintigraphy, 99mTc EDDA/HYNIC-TOC scintigraphy	Histology, clinical follow-up	**NA**	**NA**	18F-DOPA PET/CT findings led to a change in management in 57.1% (16/28) patients (7—neck dissection, 2—additional FNAC, 5—radiotherapy, 2—chemotherapy).

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Non-Small Cell Lung Cancer and Other Lung Cancer								
Rodrigues et al, 2016 [65]	Retrospective	164 patients (14 SCLC, 143 NSCLC, 7 unknown)	FDG PET/CT	Bone scintigraphy	Autopsy, histology, clinical and imaging follow-up	**Bone metastases** Sens: 97.7% Spec: 100% Accu: 99.4%	**Bone metastases** Sens: 87.8% Spec: 97.5% Accu: 94.2%	NA
Li et al, 2017 [66]	Meta-analysis	5 studies (307 NSCLC, 442 lung adenocarcinoma, 203 all types)	FDG PET or PET/CT	Gadolinium-enhanced MRI	Histopathology, imaging follow-up	**Brain metastases** Pooled Sens: 21% Pooled Spec: 100% Pooled +LR: 184.7 Pooled –LR: 0.79 Pooled DOR: 235 AUC: 0.98	**Brain metastases** Pooled Sens: 77% Pooled Spec: 99% Pooled +LR: 149.6 Pooled –LR: 0.23 Pooled DOR: 657 AUC: 0.97	NA
Shen et al, 2017 [67]	Meta-analysis	43 studies (patients with NSCLC; 21,058 lymph nodes)	FDG PET or PET/CT	DWI	Histopathology, clinical follow-up	**Lymph node metastasis** Pooled Sens: 65% Pooled Spec: 93% Pooled +LR: 8.46 Pooled –LR: 0.38 Pooled DOR: 25.18 AUC: 0.88	**Lymph node metastasis** Pooled Sens: 72% Pooled Spec: 97% Pooled +LR: 13.15 Pooled –LR: 0.32 Pooled DOR: 46.11 AUC: 0.79	NA
Kung et al, 2017 [68]	Retrospective	186 patients (potentially operable NSCLC)	FDG PET/CT	CT thorax	Histological, radiological, and surgical findings	NA	NA	Overall change in management occurred in 37.6% (70/186) of patients (65—avoided futile surgery, 5—further neoadjuvant treatment or investigation).
Hallqvist et al, 2017 [69]	Meta-analysis	36 studies (2333 NSCLC/SCLC patients who underwent dose planning for thoracic radiation with curative intent)	FDG PET/CT	CT	Departmental treatment planning metrics	NA	NA	In NSCLC, dose planning based on PET/CT changed the target definition of 36% of patients with a staging PET/CT and 43% of patients without a staging PET/CT. The proportion of patients with a change in treatment intent from curative to palliative treatment was 20% for those with a staging PET/CT and 22% for those without a staging PET/CT. In SCLC, 26% of patients had a change in target definition and 9% of patients had a change in

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
								treatment intent.
Kong et al, 2017 [70]	Prospective (Phase 2)	42 patients requiring daily fractionated radiotherapy (inoperable or unresectable stage II-III NSCLC)	FDG PET/CT	NA	Clinical follow-up	NA	NA	Adapting radiotherapy-escalated radiation dose to the FDG-avid tumour on midtreatment PET improved the rates of infield and overall local regional tumour controls at 2 years to 82% and 62%, respectively. The 2- and 5-year OS were 52% and 30%, respectively.
Ruilong et al, 2017 [71]	Meta-analysis	12 studies (1297 patients with 1301 SPNs)	FDG PET/CT	NA	Histopathology, clinical and imaging follow-up	**Differentiating malignant from benign SPNs** Pooled Sens: 82% Pooled Spec: 81% Pooled +LR: 4.3 Pooled –LR: 0.22 Pooled DOR: 17.58 AUC: 0.87	NA	NA
Pancreatic Cancer								
Toft et al, 2017 [72]	Meta-analysis	52 studies (5399 patients with suspected pancreatic ductal adenocarcinoma)	FDG PET or PET/CT	MRI, CT, EUS, TAUS	Histology, clinical follow-up	**Diagnosis** Pooled Sens: 89% Pooled Spec: 70% Pooled Accu: 84%	**Diagnosis** ***MRI*** Pooled Sens: 93% Pooled Spec: 89% Pooled Accu: 90% ***CT*** Pooled Sens: 90% Pooled Spec: 87% Pooled Accu: 89% ***EUS*** Pooled Sens: 91% Pooled Spec: 86% Pooled Accu: 89% ***TAUS*** Pooled Sens: 88% Pooled Spec: 94% Pooled Accu: 91%	NA
Pediatric Cancer								
Hassan et al, 2017 [73]	Retrospective	784 patients (histologically proven HL)	FDG PET/CT	BMB	BMB	**Bone marrow involvement** Sens: 93.6% Spec: 94.0% PPV: 53.0% NPV: 99.4%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Bakhsi et al, 2017 [74]	Prospective	57 patients who underwent interim response assessment after 2 cycles of ABVD and end of treatment assessment (HL)	FDG PET/CT	CeCT	Clinical and imaging follow-up	**Interim assessment** **RIW criteria** Sens: 25.0% Spec: 61.5%* PPV: 4.7% NPV: 91.4% **Deauville criteria** Sens: 0%* Spec: 91.4%* PPV: 0% NPV: 91.4% **Post-treatment assessment** **RIW criteria** Sens: 25.0% Spec: 88.0% PPV: 14.2% NPV: 93.6% **Deauville criteria** Sens: 25.0% Spec: 95.7%* PPV: 33.3% NPV: 94.1%	**Interim assessment** Sens: 75.0%* Spec: 40.3%* PPV: 8.8% NPV: 95.4% **Post-treatment assessment** **RIW criteria** Sens: 25.0% Spec: 76.4%* PPV: 7.6% NPV: 92.8%	NA
Abdel Rahman et al, 2016 [75]	Retrospective	115 patients; 152 scans (newly diagnosed mature B cell NHL)	FDG PET/CT	CT	Follow-up	**Residual disease, tumour response or relapse** Sens: 89.5%* Spec: 84.9%* PPV: 45.9%* NPV: 98.3%*	**Residual disease, tumour response or relapse** Sens: 63.2%* Spec: 58.6%* PPV: 17.9%* NPV: 91.7%*	NA
Wagner et al, 2017 [76]	Prospective	28 pediatric and adolescents and young adults patients (soft tissue sarcoma)	FDG PET/CT	CT, MRI	SLNB	**Lymph node metastasis** Sens: 57% Spec: 52% PPV: 29% NPV: 79%	**Lymph node metastasis** ***CT*** Sens: 100% Spec: 71% PPV: 50% NPV: 100% ***MRI*** Sens: 67% Spec: 64% PPV: 50% NPV: 78%	NA
Sarcoma								
Angelini et al, 2017 [77]	Retrospective	37 patients (suspected relapse of	FDG PET/CT	Clinical examination, CT, MRI	Histology, clinical follow-up,	**Recurrence (patient-based)** Sens: 91%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		osteosarcoma)			correlative imaging, biopsy	Spec: 75% PPV: 97% NPV: 50% Accu: 89% **(site-based)** **Local relapse** Sens: 96% Spec: 100% PPV: 100% NPV: 93% Accu: 97% **Lung metastasis** Sens: 80% Spec: 100% PPV: 100% NPV: 88% Accu: 92% **Lymph nodes and distant metastases** Sens: 100% Spec: 95% PPV: 94% NPV: 100% Accu: 97%		
Hassanzadeh-Rad et al, 2016 [78]	Meta-analysis	9 studies (187 patients with GIST treated with chemotherapy)	FDG PET/CT	NA	Follow-up	**Prediction of treatment response** Pooled Sens: 92% Pooled Spec: 71%	NA	NA
Unknown Primary Cancer								
Burglin et al, 2017 [79]	Meta-analysis	20 studies (1942 patients with extracervical metastases from cancer of unknown primary)	FDG PET/CT	Laboratory tests, CeCT, MRI, pan-endoscopies for head and neck cancer	Biopsy, clinical and imaging follow-up	**Primary tumour** Pooled DR: 40.9%	NA	NA
Various Sites								
Birk Christensen et al, 2017 [80]	Retrospective	581 patients who underwent PET/CT as part of the radiotherapy planning (71 lung, 207 head	FDG PET/CT	NA	Consensus, subsequent imaging or biopsy	NA	NA	PET/CT provided additional diagnostic information that resulted in a major change in treatment strategy in 10.8% (63/581) of patients.

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		and neck, 103 upper GI, 102 lower GI, 41 gynecological, 57 other)						
Ali and Hamed, 2017 [81]	Prospective	273 patients underwent initial staging before treatment (138 lung, 57 esophagus, 28 head and neck, 17 lymphoma, 13 GU, 6 stomach, 3 melanoma, 11 other)	FDG PET/CT	Conventional staging work-up according to site and cell type of primary tumour	Histopathology	**Second primary cancer (patient-based)** Sens: 89.2%* PPV: 56.5% **(lesion-based)** PPV: 36.1%	**Second primary cancer** Sens: 23.1%*	NA
Garcia Vicente et al, 2017 [82]	Meta-analysis	16 studies (793 patients PNS)	FDG PET or PET/CT	CT	Pathology, clinical and radiological follow-up	**Malignancy** Pooled Sens: 87% Pooled Spec: 86% AUC: 0.91	**Malignancy** Pooled Sens: 44% Pooled Spec: 82% AUC: 0.52	NA

Abbreviations: +LR: positive likelihood ratio; -LR: negative likelihood ratio**;** ^{11}C-choline: carbon-11 choline; ^{18}F-Choline : fluorine-18 choline; ^{18}F-FLT: fluorine-18 2',3'-dideoxy-3'-fluoro-2-thiothymidine; 18F-DOPA: fluorine-18-L-dihydroxyphenylalanine; 68Ga-DOTA-TATE: gallium-68-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-1-Nal3-octreotide; 68Ga-PSMA: ^{68}Ga-PSMA: gallium-68-labeled prostate-specific membrane antigen ligand with chelator HBED-CC; ^{99m}Tc: technetium-99m; ^{131}I: iodine-131; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine combination chemotherapy; Accu: accuracy/staging accuracy; ALND: axillary lymph node dissection; AUC: area under the curve; BEACOPPesc: bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone escalated regimen; BMB: bone marrow biopsy; CA125: cancer antigen 125; CEA: carcinoembryonic antigen; CeCT: contrast-enhanced computed tomography; CI: confidence interval; CMR: complete metabolic response; CRC: colorectal cancer; CRR: complete response rate; CT perfusion: computed tomography perfusion; DFS: disease-free survival; DC: Deauville Criteria; DCE-MRI: dynamic contrast-enhanced magnetic resonance imaging; DLBCL: diffuse large B-cell lymphoma; DMFS: distant metastasis-free survival; DOR: diagnostic odds-ratio; DR: detection rate; DWI-MRI: diffusion-weighted magnetic resonance imaging; ER+/HER2-: estrogen receptor-positive/ human epidermal growth factor receptor 2 negative; EUS: endoscopic ultrasound**;** FDG: 2-fluoro-2-deoxy-D-glucose or fluorodeoxyglucose; FL: follicular lymphoma; FNAC: fine-needle aspiration cytology; GI: gastrointestinal; GIST: gastrointestinal stromal tumors; GU: genitourinary; HER2+: human epidermal growth factor receptor 2 positive; HL: Hodgkin's lymphoma; HR: hazard ratio; IHPC: International Harmonization Project Criteria; IMRT: intensity-modulated radiation therapy; INRT: involved-node radiotherapy; LFFS: local failure-free survival; MDP: methylene diphosphonate; MIBI: Sestamibi Technetium-99m bone marrow scanning; MRI: Magnetic Resonance Imaging; NA: not applicable/not available; NET: neuroendocrine tumour; NHL: non-Hodgkin lymphoma; NPV: negative predictive value; NSCLC: non-small cell lung cancer; OS: overall survival; PET/CT: positron-emission tomography/computed tomography; PFS: progression-free survival; PNS: paraneoplastic neurological syndromes; PPV: positive predictive value; PRRT: peptide receptor radionuclide therapy; Q-test: Cochrane Q Statistic; RIW: Revised International Working Group; S100B: S100 calcium-binding protein B; SCLC: small cell lung cancer; Sens: sensitivity; SLNB: sentinel lymph node biopsy; SNB: sentinel node biopsy; Spec: specificity; SPECT: single photon emission computed tomography; SPN: solitary pulmonary nodule; SUV: standard uptake value; TAUS: transabdominal ultrasound; Tg: thyroglobulin; TgAb: antithyroglobulin antibody; US: ultrasound; US-FNA: ultrasound-guided fine-needle aspiration**;** VEEG: video electroencephalography**;** WBS: whole body scintigraphy

*$p<0.05$