Ontario Health
Cancer Care Ontario

PET Six-Month Monitoring Report 2020-2

Evidence from Primary Studies and Systematic Reviews and Recommendations from Clinical Practice Guidelines July to December 2020

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QUESTION

What is the role of positron emission tomography (PET) in the clinical management of patients with cancer, sarcoidosis, epilepsy, or dementia 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, 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 20th issue of the six-month monitoring reports. This report is intended to be a high-level, brief summary of the identified evidence, and not a detailed evaluation of its quality and relevance.

METHODS

Literature Search Strategy

Full-text articles published between July and December 2020 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
    - ^{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/^{18}F-flutemetamol (dementia imaging)
    - ^{18}F-FDOPA
    - ^{68}Ga-PSMA/^{18}F-DCFPyL (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-six studies published between July and December 2020 met the inclusion criteria. A summary of the evidence from the 86 studies can be found in **Appendix 1: Summary of studies from July to December 2020**.

Breast Cancer

Seven studies met the inclusion criteria [1-7]. One meta-analysis found FDG PET/CT to have better diagnostic accuracy than positron emission mammography and breast-specific gamma imaging on a per-patient basis, but not on a per-lesion basis [1]. In terms of staging and restaging, FDG PET/CT was superior to contrast-enhanced CT in the detection of primary lesion, lymph node, bone, lung, liver, and other visceral metastases [2,3]. Specifically, FDG PET/CT suggested alterations of locoregional radiation plan initially devised by contrast-enhanced CT in 18.5% of patients with inflammatory breast cancer [4]. Moreover, 17.3% patients with unilateral operable stage I and II disease were upstaged by FDG PET/CT [5]. For locally advanced cases, FDG PET/CT (accuracy, 90.0%) appeared to be more reliable than CT (accuracy, 80.0%) in the assessment of neoadjuvant chemotherapy response [6]. The five-year follow-up results of the phase II randomized AVATAXHER study showed that the addition of bevacizumab to neoadjuvant docetaxel plus trastuzumab for PET-predicted poor-responsive HER2-positive breast cancer did not improve disease-free survival [7].

Epilepsy

One study met the inclusion criteria [8]. In patients with temporal lobe epilepsy, FDG PET was able to localize the seizure onset zone with a sensitivity and specificity of 95%, where 85.5% of surgically treated cases achieved freedom from disabling seizures (Engle class I). Similarly, the sensitivity and specificity of FDG PET localization in patients with extratemporal lobe epilepsy were 80% and 95%, respectively. Consequently, Engle class I outcome was achieved in 79.2% of cases who underwent surgery.

Esophageal Cancer

Four studies met the inclusion criteria [9-12]. In the preoperative staging of esophageal cancer, FDG PET/CT exhibited high specificity (94.4% to 96.7%) but low sensitivity (28.6% to 44.4%) for diagnosing lymph node metastases in a per-station/-patient basis [9,10]. However, the sensitivity improved to 81.6% to 94.6% in a one-by-one lymph node-based analysis [9]. Surveillance FDG PET/CT detected early recurrence with an accuracy of 94.5% and uncovered second primary cancers in 1.9% of patients [11]. Overall, FDG PET/CT provided additional information that led to management changes in 32.9% of patients [12].

Gastrointestinal Cancer

Nine studies met the inclusion criteria [13-21]. In patients with hepatocellular carcinoma, preoperative FDG PET/CT with a tumour-to-normal liver standardized uptake value ratio of 1.53 showed high sensitivity (91.7%) but moderate specificity (76.4%) for predicting recurrent extrahepatic metastases [13]. In patients with rising serum alpha-fetoprotein level after surgical resection or interventional therapy, FDG PET/CT achieved similar sensitivity (95.0% to 98.0%) and specificity (72.7%) for detecting intra- and extrahepatic recurrence [14]. When compared with triphasic CT, FDG PET/CT had a superior performance in detecting residual or recurrent disease in patients who had received transarterial chemoembolization [15]. For patients with biliary tract cancer, the authors from a meta-analysis concluded that FDG PET or PET/CT is a useful tool for the initial assessment

of lymph node and distant metastases as well as for confirmation of disease relapse if diagnosis remains unclear following conventional imaging. On the contrary, FDG PET or PET/CT was unsatisfactory in the diagnosis of the primary tumour due to low specificity (pooled estimate, 51.3%). Taken as a whole, the pooled proportion of change in management as a result of FDG PET or PET/CT was 15% [16]. In another meta-analysis of patients with cholangiocarcinoma, FDG PET/CT and magnetic resonance imaging (MRI) were comparable in T staging but both had limited value in N staging. FDG PET/CT also had poor sensitivity (pooled estimate, 56%) in M staging [17]. In the follow-up of colorectal cancer, FDG PET/CT demonstrated a sensitivity of 100% and a specificity of 82.6% for the detection of recurrence regardless of serum carcinoembryonic antigen levels [18]. Furthermore, FDG PET/CT was also reliable in characterizing indeterminate lesions on contrast-enhanced CT. However, different sites of metastasis and/or recurrence showed variable accuracy results with highest for lymph nodes (100%), followed by peritoneal or mesenteric deposits (92%), liver (83%), lung (82%), and original site of primary tumour (80%) [19]. In patients with anal carcinoma, sentinel lymph node biopsy remains superior to FDG PET/CT in the staging of inguinal lymph nodes [20]. In a second retrospective study, FDG PET/CT revealed additional information to MRI that resulted in a change of stage in 13.0% of patients and led to altered management in 24.1% of cases. Despite this, FDG PET/CT failed to accurately delineate the staging of 11.1% of patients [21].

Genitourinary Cancer

Three studies met the inclusion criteria [22-24]. In patients with muscle-invasive bladder cancer, preoperative FDG PET or PET/CT has limited utility in detecting nodal metastases [22,23] but demonstrated high sensitivity (pooled estimate: 89%) and specificity (pooled estimate: 95%) for distant metastases [23]. In patients with upper tract urothelial carcinoma, FDG PET/CT characterized lymph node metastases with an accuracy of 83.9%. Presence of suspicious nodes on FDG PET/CT was associated with worst median recurrence-free survival [24].

Gynecologic Cancer

Six studies met the inclusion criteria [25-30]. FDG PET/CT was shown to have an accuracy of 79.5% for diagnosing primary lesions of cervical cancer [25] and an accuracy of 87.5% to 95.5% for diagnosing recurrent disease [25,26]. In the latter case, a positive FDG PET/CT scan was predictive of significantly worse overall survival and disease-free survival [26]. In the preoperative staging of endometrial cancer, FDG PET/CT demonstrated overall high specificity (94% to 97.2%) but low sensitivity (48% to 87%) for detecting nodal metastases [27,28]. In the restaging of ovarian cancer, FDG PET/CT (sensitivity, 94%; specificity, 75%; accuracy, 96%) can be useful for detecting recurrence in patients with elevated CA-125 levels [29]. In a meta-analysis that included various gynecological malignancies of the pelvis, the diagnostic performance of FDG PET/MRI was found to be slightly better than that of FDG PET/CT but without statistical significance [30].

Head and Neck Cancer

Eleven studies met the inclusion criteria [31-41]. Several studies looked at FDG PET/CT in the evaluation of head and neck squamous cell carcinoma. The integration of FDG PET/CT into the initial work-up changed the conventional staging of 46.3% of patients. Therapeutic decision was impacted in 19.5% of cases [31]. In patients who had undergone neck dissection, preoperative FDG PET/CT was less reliable in detecting the presence and location of regional lymph node metastases (sensitivity, 68.9%; specificity, 61.5%) [32]. Following curative-intent therapy, FDG PET/CT displayed high specificity but modest

sensitivity for identifying locoregional and distant failures [33]. However, the accuracy of FDG PET/CT in identifying treatment failures improved when performed at more than three months post-treatment as compared with imaging at less than three months [33,34]. In thyroid cancer, patients with thyroid nodules classified as EU-TIRADS 4 and no FDG uptake could be ruled out from further examination for malignancy (negative predictive value, 95.2%) [35]. For preoperative staging, FDG PET/CT demonstrated high specificity (pooled estimate, 94%) but very poor sensitivity (pooled estimate, 30%) in the detection of cervical lymph node metastases [36]. In the postoperative surveillance of intermediate- to high-risk patients, pre-ablation recombinant human thyrotropin-stimulated FDG PET/CT changed the treatment plan in 15.1% of cases [37]. In patients with hypopharyngeal carcinoma, FDG PET/MRI and FDG PET/CT provided comparable results for T and N staging [38]. In patients without enlarged lymph nodes, preoperative FDG PET/CT detected neck metastases of oral squamous cell carcinoma with a sensitivity of 83.9% and a specificity of 73.1% [39]. In cT1-2N0 tongue squamous cell carcinoma, FDG PET/CT-guided neck dissection obtained similar disease control as elective neck dissection. Thereby, surgery can be safely avoided when FDG PET/CT revealed no neck lymph node involvement [40]. In the post-treatment surveillance of patients with human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma, FDG PET/CT-detected recurrences led to meaningful salvage therapy in very few cases (1.6%) and offered no survival benefit over clinically detected recurrences [41].

Hematologic Cancer

Nine studies met the inclusion criteria [42-50]. Six of the studies evaluated the utility of FDG PET/CT in the staging of patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). When compared with diffusion-weighted imaging (DWI)-MRI, FDG PET/CT was superior in the detection of lymph node and spleen involvement [42], and overall staging accuracy [43], but was inferior in the detection of bone marrow involvement [42]. In two studies, FDG PET/CT showed that it can replace bone marrow biopsy in many cases [44,45], especially those showing multifocal uptake [45] during the evaluation of bone marrow infiltration. However, another study found that the clinical significance of FDG PET/CT remains unclear in certain pathological types [46]. In patients previously staged with contrast-enhanced CT, additional information provided by FDG PET/CT upstaged 17% and downstaged 6% of cases [47]. Specifically in patients with diffuse large B-cell lymphoma, FDG PET/CT (98.9%) also demonstrated higher accuracy than bone marrow biopsy (86.5%) in the detection of bone marrow involvement [48]. In response assessment of limited stage disease, interim-PET-positive patients who received involved field radiation therapy followed by ibritumomab tiuxetan radioimmunotherapy after three cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) achieved comparable survival outcomes as interim-PET-negative patients who continued with one additional cycle of R-CHOP [49]. In patients with mantle-cell lymphoma, FDG PET/CT permitted the upstaging of 17.2% and downstaging of 1.6% of cases, primarily by detecting sites of involvement not identified with CT. Consequently, management changes occurred in 18.9% of patients [50].

Melanoma

Four studies met the inclusion criteria [51-54]. In the initial staging of patients with melanoma, FDG PET/CT showed excellent sensitivity (93.3%) but inadequate specificity (60.0%) [51]. Similarly, FDG PET/CT was highly sensitive (82% to 100%) but poorly specific (14% to 93%) in the restaging of patients after primary treatment [51-53]. Nonetheless, FDG PET/CT influenced the therapeutic management of 24.3% to 28.0% of patients [52,53] with a negative scan being associated with significantly better survival [52]. In the follow-up surveillance of stage IIIB/C patients, FDG PET/CT detected asymptomatic recurrence with

high sensitivity (92.3%) and specificity (100%). The detection of early recurrence by FDG PET/CT resulted in changed management in 34.3% of patients, of whom 50% of these patients achieved a complete response or displayed no evidence of disease [54].

Non-FDG Tracers

Twenty-three studies met the inclusion criteria [23,55-76]. There is insufficient evidence to support the use of ^{11}C-choline PET/CT in the regional lymph node staging of patients with muscle-invasive bladder cancer [23]. In patients with pancreatic neuroendocrine tumours (NETs), results from one meta-analysis showed that the pooled sensitivity and specificity of ^{68}Ga-DOTA-TATE/NOC/TOC PET or PET/CT for detecting primary tumour and initial staging were 80.6% and 79.6%, respectively [55]. Similar sensitivities (73.8% to 75.8%) were reported for ^{68}Ga-DOTA-NOC PET/CT in the staging or restaging of a mixed gastroenteropancreatic NETs population [56]. In the setting of a tertiary memory clinic, amyloid PET imaging with ^{18}F-flutemetamol had a significant impact in terms of changing the initial diagnosis of 44.4% of patients and guiding 75 additional patients (increase of 218%) in receiving cholinesterase inhibitor treatment [57]. The utility of ^{68}Ga-PSMA/^{18}F-DCFPyL PET/CT in prostate cancer were evaluated in numerous studies. In patients with serum prostate-specific antigen (PSA) <50 ng/mL and/or positive digital rectal examination, ^{68}Ga-PSMA PET/CT can differentiate benign and malignant lesions with high accuracy (86%) [58]. In the staging of intermediate- to high-risk patients, ^{68}Ga-PSMA PET/CT showed a sensitivity of 63% to 80% and a specificity of 90.3% to 99.6% for detecting lymph node metastases and was better than MRI/multiparametric MRI (mpMRI) [59-62]. Similarly, ^{18}F-DCFPyL PET/CT is highly sensitive (90.9%) and can detect intraprostatic tumours missed on mpMRI [63]. Across multiple studies, the addition of ^{68}Ga-PSMA/^{18}F-DCFPyL PET/CT to conventional imaging changed the stage group of 28.6% to 36.0% of patients and influenced management in 34.8% to 39.0% of cases [64-66]. After radical prostatectomy, ^{68}Ga-PSMA PET/CT outperformed whole-body MRI in the detection of biochemical recurrence in both per-patient (detection rate, 71.4% vs. 39.3%, p=0.0167) and per-lesion analysis (detection rate, 100% vs. 23.2%, p<0.001) [67]. Likewise, ^{18}F-DCFPyL PET/CT detected recurrence in patients after prostatectomy and/or radiation therapy with high positive predictive value (86% to 92%), which modified subsequent management in 44.1% to 59.5% of cases [68-70]. For nodal staging prior to salvage lymph node dissection, ^{68}Ga-PSMA PET/CT or PET/MRI provided excellent sensitivity (72.7% to 100%) and specificity (95% to 100%) [71,72]. Overall, ^{68}Ga-PSMA PET/CT had a profound impact in various clinical indications by changing the disease stage in 68.5% of patients [73] and altering management in 57.1% to 64.1% of cases [73,74]. One study compared the capability of ^{18}F-DOPA PET/CT with conventional imaging in localizing persistent/recurrent medullary thyroid cancer. At the lesion level, ^{18}F-DOPA PET/CT (84%) had a higher detection rate than FDG PET/CT (45%), whole-body MRI (23%), and whole-body CT (32%). ^{18}F-DOPA PET/CT contributed to management changes in 19.4% of cases [75]. In patients with MRI-suspected recurrent glioblastoma, ^{18}F-FET PET using thresholds of 3.2 for tumour-to-brain ratio $(TBR)_{max}$ (99%), 1.8 for TBR_{mean} (96%), and 0.55 for biological tumour volume (98%) all achieved superb accuracy in distinguishing post-treatment changes from recurrence six months after radiotherapy [76].

Pancreatic Cancer

One study met the inclusion criteria [77]. Summary statistics from a meta-analysis showed that the overall performance of DWI-MRI and FDG PET/CT were comparable in the diagnosis of pancreatic cancer, with only a slight advantage for DWI-MRI in terms of area under the curve (0.95 vs. 0.91, p=0.015).

Sarcoma

One study met the inclusion criteria [78]. In the staging and restaging of soft-tissue sarcomas of the extremities and trunk, FDG PET/CT changed the disease stage of 15.3% of patients and altered therapy planning in 23.2% of cases.

Thoracic Cancer

Three studies met the inclusion criteria [79-81]. In patients with non-small cell lung carcinoma (NSCLC), FDG PET/CT was found to be comparable to both DWI-MRI and MRI in M staging [79] but was inferior to thoracic endosonography in mediastinal staging [80]. After treatment, FDG PET/CT was significantly more sensitive (86.9% versus 70.0%, p=0.025), more specific (73.5% versus 56.7%, p=0.048) and more accurate (82.1% versus 64.3%, p=0.013) than tumour marker testing in the detection of recurrence and/or metastases [81].

CLINICAL EXPERT REVIEW

Breast Cancer

Current Eligibility Criteria for the PET ABC Trial

- For the staging of patients with clinical stage III breast cancer.

Reviewer's Comments

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

Epilepsy

Current Indication for Epilepsy

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

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 Indications for Esophageal Cancer

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

Gastrointestinal Cancer

Current Indications for Colorectal Cancer

- 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.
- 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 Anal Canal Cancer

- For the initial staging of patients with T2-4 (or node positive) squamous cell carcinoma of the anal canal with or without evidence of nodal involvement on conventional anatomical imaging.

Reviewer's Comments (Dr. Anand Swaminath)

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

Genitourinary Cancer

Current Indications for Germ Cell Tumours

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

Current Eligibility Criteria for the PET MUSE Trial

- For the staging of patients with muscle-invasive urothelial carcinoma of the bladder.

Reviewer's Comments (Dr. Glenn Bauman)

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

Gynecologic Cancer

Current Indications for Cervical Cancer

- For the staging of locally advanced cervical cancer when CT/MRI shows positive or indeterminate pelvic nodes (>7 mm and/or suspicious morphology), borderline or suspicious para-aortic nodes, or suspicious or indeterminate distant metastases (e.g., chest nodules).
- For re-staging of patients with recurrent gynecologic malignancies under consideration for radical salvage surgery (e.g., pelvic exenteration).

Reviewer's Comments

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

Head and Neck Cancer

Current Indications for Head and Neck Cancer

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

Current Indication for Unknown Primary

- 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.

Current Indication for Nasopharyngeal Cancer

- For the staging of nasopharyngeal cancer.

Current Indications for Thyroid Cancer

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

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

Hematologic Cancer

Current Indications for Lymphoma

- For the baseline staging of patients with HL or NHL.
- For the assessment of response in HL following two or three cycles of chemotherapy when curative therapy is being considered.
- For the evaluation of residual mass(es) or lesion(s) (e.g., bone) following chemotherapy in a patient with HL or NHL when further potentially curative therapy (such as radiation or stem cell transplantation) is being considered.

Current Indications for Multiple Myeloma or Plasmacytoma

- For patients with presumed solitary plasmacytoma who are candidates for curative-intent radiotherapy (to determine whether solitary or multifocal/extensive disease).
- For work-up of patients with smoldering myeloma and negative or equivocal skeletal survey (to determine whether smoldering or active myeloma).
- For baseline staging and response assessment.

Reviewer's Comments

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

Current Indications for Melanoma

- 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.

Reviewer's Comments

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

Non-FDG Tracers

Current Indications for Gallium-68 PET/CT in NETs

- For identification of primary tumour when there is clinical suspicion of NETs and primary tumour site is unknown or uncertain.
- For the staging of patients upon initial presentation of NETs.

- For the re-staging of patients with NETs when clinical intervention is being considered.
- As a problem-solving tool in patients with NETs when confirmation of site of disease and/or disease extent may impact clinical management.

Current Indications for PSMA PET/CT in Prostate Cancer

- For patients with post-prostatectomy node-positive disease or persistently detectable PSA.
- For patients with biochemical failure post-prostatectomy.
- For patients with failure following radical prostatectomy followed by adjuvant or salvage radiotherapy.
- For patients with rising PSA post-prostatectomy despite salvage hormone therapy.

Reviewer's Comments (Dr. Amit Singnurkar)

The current recommendations for the utilization of PET/CT with non-FDG tracers remain valid and no changes are required. However, the study by Leuzy et al. [57] on the impact of amyloid PET is worth further consideration. Cholinesterase inhibitors are potent disease modulators and have been shown to delay morbidity related to dementia. This is incredibly important when considering the burden to our health system from this large and growing group of patients.

Pancreatic Cancer

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

Reviewer's Comments (Dr. Jim Biagi)

The meta-analysis by Que et al. [77] does not contribute to a change in recommendations. The diagnosis of pancreatic cancer does not mandate MRI; thus, a comparison with PET/CT does not advance the benefit of PET/CT for diagnosis.

Sarcoma

Current Indications for Sarcoma

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

Reviewer's Comments (Dr. Gina Di Primio)

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

Thoracic Cancer

Current Indications for Solitary Pulmonary Nodule

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

Current Indications for NSCLC

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

Current Indication for Small Cell Lung Cancer

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

Current Indication for Mesothelioma

- For the staging of patients with histologic confirmation of malignant mesothelioma.

Reviewer's Comments (Dr. Donna Maziak)

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

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Contact Information

For information about the PEBC and the most current version of all reports,
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Appendix 1: Summary of studies from July to December 2020.

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Breast Cancer								
Tadesse et al, 2020 [1]	Meta-analysis	31 studies (1069 patients with breast cancer)	FDG PET/CT	Positron emission mammography, ^{99m}Tc-MIBI BSGI	Histopathology, imaging follow-up	**Diagnosis (patient-based)** Pooled Sens: 87% Pooled Spec: 90% Pooled DOR: 93.58 AUC: 0.962 Q index: 0.907 **(lesion-based)** Pooled Sens: 91% Pooled Spec: 98% Pooled DOR: 29.31 AUC: 0.927 Q index: 0.861	**Diagnosis** ***Positron emission mammography* (patient-based)** Pooled Sens: 80% Pooled Spec: 92% Pooled DOR: 23.84 AUC: 0.885 Q index: 0.816 **(lesion-based)** Pooled Sens: 85% Pooled Spec: 94% Pooled DOR: 79.76 AUC: 0.973 Q index: 0.924 ***^{99m}Tc-MIBI BSGI* (patient-based)** Pooled Sens: 78% Pooled Spec: 79% Pooled DOR: 13.55 AUC: 0.857 Q index: 0.788 **(lesion-based)** Pooled Sens: 90% Pooled Spec: 88% Pooled DOR: 37.25 AUC: 0.937 Q index: 0.873	NA
Shawky et al, 2020 [2]	Prospective	30 patients who underwent restaging after chemotherapy and/or radiotherapy (breast cancer)	FDG PET/CT	CeCT	Histopathology, clinical and imaging follow-up	**Primary lesion** Sens: 100% Spec: 95.5% PPV: 88.9% NPV: 100% Accu: 96.7% **Lymph node metastases** Sens: 100% Spec: 80.0% PPV: 90.9% NPV: 100% Accu: 93.3% **Bone metastases**	**Primary lesion** Sens: 81.3% Spec: 90.4% PPV: 76.5% NPV: 93.0% Accu: 88.3% **Lymph node metastases** Sens: 95.0% Spec: 80.0% PPV: 90.5% NPV: 88.9% Accu: 90.0% **Bone metastases**	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Sens: 91.7% Spec: 100% PPV: 100% NPV: 94.7% Accu: 96.7% **Lung metastases** Sens: 100% Spec: 100% PPV: 100% NPV: 100% Accu: 100% **Liver metastases** Sens: 80.0% Spec: 100% PPV: 100% NPV: 96.2% Accu: 96.7% **Other visceral metastases** Sens: 88.9% Spec: 90.5% PPV: 80.0% NPV: 95.0% Accu: 90.0%	Sens: 75.0% Spec: 94.4% PPV: 90.0% NPV: 85.0% Accu: 86.7% **Lung metastases** Sens: 72.7% Spec: 73.7% PPV: 61.5% NPV: 82.4% Accu: 73.3% **Liver metastases** Sens: 40.0% Spec: 84.0% PPV: 33.3% NPV: 87.5% Accu: 76.7% **Other visceral metastases** Sens: 55.6% Spec: 95.2% PPV: 83.3% NPV: 83.3% Accu: 83.3%	
Abd-Elkader et al, 2020 [3]	Retrospective	71 patients (breast cancer)	FDG PET/CT	CeCT	Clinical and imaging follow-up	**Lymph node metastases** Sens: 100% Spec: 96.0% PPV: 91.3% NPV: 100% Accu: 97.2% **Lytic bone metastases** Sens: 100% Spec: 100% PPV: 100% NPV: 100% Accu: 100% **Sclerotic bone metastases** Sens: 100% Spec: 100% PPV: 100% NPV: 100% Accu: 100% **Hepatic metastases**	**Lymph node metastases** Sens: 85.7% Spec: 96.0% PPV: 90.0% NPV: 94.1% Accu: 93.0% **Lytic bone metastases** Sens: 89.0% Spec: 100% PPV: 100% NPV: 98.4% Accu: 98.6% **Sclerotic bone metastases** Sens: 100% Spec: 100% PPV: 100% NPV: 100% Accu: 100% **Hepatic metastases**	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Sens: 100% Spec: 100% PPV: 100% NPV: 100% Accu: 100%	Sens: 100% Spec: 95.6% PPV: 50.0% NPV: 100% Accu: 95.8%	
Jacene et al, 2020 [4]	Retrospective	81 patients who underwent initial staging prior to starting treatment (newly diagnosed inflammatory breast cancer)	FDG PET/CT	CeCT	Pathology, imaging follow-up	NA	NA	PET/CT suggested alterations of ceCT-based locoregional radiation plan in 18.5% (15/81) of patients (10—change in radiation dose, 4—change in radiation field extent, 1—change in radiation field extent and dose).
Singh et al, 2020 [5]	Prospective	156 patients who underwent initial staging without any suspicion of metastases (unilateral operable stage I and II breast cancer)	FDG PET/CT	NA	Histopathology	NA	NA	PET/CT upstaged 17.3% (27/156) of patients (6—upstaged to IIIC, 21—upstaged to IV).
Sarhan et al, 2020 [6]	Prospective	30 patients who underwent response assessment before and after neoadjuvant chemotherapy (locally advanced breast cancer)	FDG PET/CT	CT	Histopathology	**Response assessment (PERCIST 1.0)** Sens: 96.5% Spec: 75.0% PPV: 91.3% NPV: 85.7% Accu: 90.0%	**Response assessment (RECIST 1.1)** Sens: 81.8% Spec: 75.0% PPV: 90.0% NPV: 60.0% Accu: 80.0%	NA
Coudert et al, 2020 [7]	Phase II RCT (AVATAXHER)	142 patients who received two cycles of neoadjuvant docetaxel and trastuzumab and underwent a PET/CT scan before and after the first cycle (early stage HER2-positive	FDG PET/CT (PET responders continued to receive 4 more cycles whereas poor responders were randomized 2:1 to either	NA	Clinical and imaging follow-up	NA	NA	The 5-year DFS, LRFI, DDFS, and OS for PET responders were 90.5%, 94.8%, 95.5%, and 100%, respectively. The 5-year DFS, LRFI, DDFS, and OS for poor responders who received additional bevacizumab were 90.2%, 97.6%, 100%, and 95.1%, respectively. The 5-year DFS, LRFI, DDFS, and OS

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		breast cancer)	4 more cycles with or without additional bevacizumab)					for poor responders who did not receive additional bevacizumab were 76.0%, 90.9%, 86.9%, and 95.8%, respectively.
Epilepsy								
Tomas et al, 2019 [8]	Prospective	130 patients who underwent presurgical evaluation (pharmacoresistant unifocal epilepsy)	FDG PET	Semiology, MRI, EEG, intracranial EEG	Anatomoelectroclinical correlations, postsurgical outcome	Localization (Temporal lobe epilepsy) Sens: 95% Spec: 95% (Extratemporal lobe epilepsy) Sens: 80% Spec: 95%	NA	Among surgically treated temporal lobe epilepsy patients, 85.5% (53/62) achieved freedom from disabling seizures (Engel class I). Similarly, 79.2% (19/24) of extratemporal lobe epilepsy patients achieved Engle class I outcome after surgery.
Esophageal Cancer								
Yoshimura et al, 2020 [9]	Prospective	20 patients who underwent preoperative staging (esophageal cancer)	FDG PET/CT	NA	Pathology	**Lymph node metastases (station-based)** Sens: 28.6% Spec: 96.7% PPV: 44.4% NPV: 93.6% **(node-based)** Sens: 81.6-94.6% Spec: 74.3-84.6% PPV: 6.5-16.1% NPV: 99.2-99.8% AUC: 0.86-0.92	NA	NA
Li et al, 2020 [10]	Prospective	90 patients who underwent cervical nodal staging prior to esophagectomy with 3-field lymphadenectomy (esophageal squamous cell carcinoma)	FDG PET/CT	Neck US	Histology	**Cervical lymph node metastases** Sens: 44.4% Spec: 94.4% PPV: 66.7% NPV: 87.2% Accu: 84.4%	**Cervical lymph node metastases** Sens: 50.0% Spec: 90.3% PPV: 56.3% NPV: 87.8% Accu: 82.2%	NA
Kim et al, 2019 [11]	Retrospective	375 patients who underwent surveillance after definitive treatment	FDG PET/CT	Physical examination, laboratory test, chest X-ray, CT,	Pathology, imaging follow-up	**Recurrence (study-based)** Sens: 100% Spec: 94.0% PPV: 59.8%	NA	PET/CT detected unexpected second primary cancers in 1.9% (7/375) of patients.

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		(esophageal cancer)		barium contrast esophagography, esophagogastroduodenoscopy, US		NPV: 100% +LR: 16.7 -LR: 0 Accu: 94.5%		
Shashi et al, 2020 [12]	Retrospective	79 patients at initial diagnosis or recurrent disease (esophageal cancer)	FDG PET/CT	CT, EUS	Histopathology, consensus from multidisciplinary tumour board	NA	NA	PET/CT provided additional information and changed management in 32.9% (26/79) of patients.
Gastrointestinal Cancer								
Morio et al, 2020 [13]	Retrospective	67 patients who underwent preoperative examination (hepatocellular carcinoma)	FDG PET/CT	CeCT	Histopathology	**Recurrent extrahepatic metastases (TNR ≥ 1.53)** Sens: 91.7% Spec: 76.4% PPV: 45.8% NPV: 97.7% Accu: 79.1% AUC: 0.869	NA	NA
Ali et al, 2020 [14]	Prospective	100 patients with a rising serum AFP level surgical resection or interventional therapy (hepatocellular carcinoma)	FDG PET/CT	Serum AFP level	Histopathology, clinical and imaging follow-up	**Recurrence (patient-based)** Sens: 95.0% Spec: 72.7% PPV: 92.5% NPV: 80.0% Accu: 90.0% **(lesion-based)** Sens: 98.0% Spec: 72.7% PPV: 97.0% NPV: 80.0% Accu: 95.6%	NA	NA
Gomaa et al, 2020 [15]	Not specified	46 patients who received transarterial chemoembolization as a locoregional treatment (hepatocellular carcinoma)	FDG PET/CT	Triphasic CT	Clinical and imaging follow-up	**Local residual or recurrence** Sens: 100% Spec: 66.7% PPV: 89.5% NPV: 100% Accu: 91.3%	**Local residual or recurrence** Sens: 82.0% Spec: 66.7% PPV: 87.5% NPV: 57.1% Accu: 78.2%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Lamarca et al, 2019 [16]	Meta-analysis	47 studies (2125 patients with biliary tract cancer)	FDG PET or PET/CT	NA	Pathology, imaging follow-up	**Primary tumour** Pooled Sens: 91.7% Pooled Spec: 51.3% Pooled +LR: 1.79 Pooled -LR: 0.22 Pooled DOR: 11.01 AUC: 0.87 **Lymph node metastases** Pooled Sens: 88.4% Pooled Spec: 69.1% Pooled +LR: 2.18 Pooled -LR: 0.24 Pooled DOR: 11.36 AUC: 0.85 **Distant metastases** Pooled Sens: 85.4% Pooled Spec: 89.7% Pooled +LR: 8.78 Pooled -LR: 0.21 Pooled DOR: 44.42 AUC: 0.93 **Relapse** Pooled Sens: 90.1% Pooled Spec: 83.5% Pooled +LR: 4.30 Pooled -LR: 0.13 Pooled DOR: 42.90 AUC: 0.96	NA	The pooled proportion of change in management as a result of PET or PET/CT was 15%
Huang et al, 2020 [17]	Meta-analysis	32 studies (1626 patients who underwent staging of cholangiocarcinoma)	FDG PET/CT	MRI	Histopathology	**T staging** Pooled Sens: 91% Pooled Spec: 85% Pooled +LR: 5.88 Pooled –LR: 0.11 Pooled DOR: 53.04 AUC: 0.94 **N staging** Pooled Sens: 52% Pooled Spec: 92%* Pooled +LR: 10.22 Pooled –LR: 0.52 Pooled DOR: 11.90 AUC: 0.77 **M staging** Pooled Sens: 56% Pooled Spec: 95%	**T staging** Pooled Sens: 90% Pooled Spec: 84% Pooled +LR: 5.51 Pooled –LR: 0.12 Pooled DOR: 44.79 AUC: 0.93 **N staging** Pooled Sens: 64% Pooled Spec: 69%* Pooled +LR: 2.03 Pooled –LR: 0.53 Pooled DOR: 3.83 AUC: 0.69	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Pooled +LR: 11.53 Pooled –LR: 0.48 AUC: 0.90		
Milardovic et al, 2020 [18]	Retrospective	50 surgically treated patients with normal or elevated CEA (suspicion of recurrent colorectal cancer)	FDG PET/CT	CEA	Histopathology, clinical follow-up	**Recurrence** Sens: 100% Spec: 82.6% PPV: 87.1% NPV: 100%	**Recurrence** Sens: 48.1% Spec: 82.6% PPV: 76.5% NPV: 57.6%	NA
Marashdeh et al, 2020 [19]	Retrospective	67 patients with indeterminate lesions on ceCT during surveillance (colorectal cancer)	FDG PET/CT	Clinical evaluation, CEA lab levels, ceCT	Biopsy or imaging follow-up	**Peritoneal or mesenteric deposits** Sens: 100% Spec: 83% PPV: 83% NPV: 100% Accu: 92% **Liver metastases** Sens: 82% Spec: 83% PPV: 82% NPV: 83% Accu: 83% **Lymph node metastases** Sens: 100% Spec: 100% PPV: 100% NPV: 100% Accu: 100% **Local recurrence** Sens: 100% Spec: 60% PPV: 71% NPV: 100% Accu: 80% **Lung metastases** Sens: 100% Spec: 67% PPV: 71% NPV: 100% Accu: 82%	NA	NA
De Nardi et al, 2019 [20]	Retrospective	63 patients with clinically	FDG PET/CT	Endoscopy, pelvic MRI,	SLNB	**Inguinal lymph node staging**	NA	There were no significant differences in OS (55

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		negative inguinal lymph nodes (anal squamous cell carcinoma)		endoanal US, total body CT		Sens: 22.2% Spec: 82.6% PPV: 33.3% NPV: 73.1% Accu: 65.6%		months vs. 41 months; p=0.652) and DFS (48 months vs. 38 months; p=0.992) between patients who showed inguinal uptake on PET/CT and those who did not.
Manafi-Farid et al, 2020 [21]	Retrospective	54 patients who underwent pretreatment staging (anal carcinoma)	FDG PET/CT	MRI	Other imaging modalities, imaging follow-up	NA	NA	PET/CT resulted in upstaging in 9.3% (5/54) and downstaging in 3.7% (2/54) of patients. However, PET/CT led to erroneous upstaging in 1.9% (1/54) and downstaging in 9.3% (5/54). Nonetheless, PET/CT changed treatment approach in 24.1% (13/54) of patients (6—change in radiation field, 4—change in radiation field and dose, 2—change in radiation dose, 1—switched to palliative therapy).
Genitourinary Cancer								
Dason et al, 2020 [22]	Retrospective	185 patients without suspicious nodes on CT who underwent cystectomy and pelvic lymph node dissection (muscle invasive urothelial bladder cancer)	FDG PET/CT	CeCT	Pathology	**Lymph node metastases (patient-based)** Sens: 7.1%-23.0% Spec: 89.4%-95.0% PPV: 25.0%-37.5% NPV: 74.5%-82.7% **(region-based)** Sens: 9.0%-10.0% Spec: 98.5%-99.0% PPV: 20.0%-33.3% NPV: 91.3%-96.6%	NA	NA
Fonteyne et al, 2020 [23]	Meta-analysis	19 studies (1041 newly diagnosed muscle invasive bladder cancer)	FDG PET or PET/CT	NA	Histology, imaging follow-up	**Regional lymph node staging** Pooled Sens: 58% Pooled Spec: 89% Pooled +LR: 5.62 Pooled -LR: 0.48 Pooled DOR: 11.90	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Distant metastasis staging Pooled Sens: 89% Pooled Spec: 95% Pooled +LR: 23.70 Pooled -LR: 0.13 Pooled DOR: 236.00		
Voskuilen et al, 2020 [24]	Retrospective	117 patients who underwent preoperative lymph node staging (upper tract urothelial carcinoma)	FDG PET/CT	NA	Histopathology	**Lymph node metastases** Sens: 82.4% Spec: 84.4% PPV: 66.7% NPV: 92.7% Accu: 83.9%	NA	Median recurrence-free survival was significantly worse in patients with positive PET/CT than in those with a negative PET/CT (16 months vs. 36 months; p=0.03).
Gynecologic Cancer								
Tan et al, 2020 [25]	Retrospective	71 patients who underwent initial diagnosis or postoperative follow-up (cervical cancer)	FDG PET/CT	NA	Pathology, clinical and imaging follow-up	**Diagnosis** Sens: 86.7% Spec: 55.6% Accu: 79.5% **Recurrence or metastases** Sens: 100% Spec: 93.8% Accu: 87.5%	NA	NA
Peng et al, 2020 [26]	Retrospective	88 patients with or without elevated serum SCC-Ag levels after primary treatment (suspicion of recurrent cervical cancer)	FDG PET/CT	SCC-Ag levels	Histopathology, clinical and imaging follow-up	**Recurrence** Sens: 98.2% Spec: 90.9%* Accu: 95.5%*	**Recurrence** Sens: 87.3% Spec: 57.6%* Accu: 76.1%*	Patients with positive PET/CT had a significantly lower OS (35.1% vs. 90.3%; p<0.001) and DFS (26.3% vs. 90.3%; p<0.001) than those with negative PET/CT.
Crivellaro et al, 2020 [27]	Not specified	167 patients who underwent nodal staging prior to surgical treatment with or without SLNB (endometrial cancer)	FDG PET/CT	NA	Histopathology	**Pelvic lymph node metastases (without SLNB)** Sens: 87% Spec: 94% PPV: 70% NPV: 98% Accu: 93% **(with SLNB)** Sens: 48% Spec: 97% PPV: 87% NPV: 85%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Accu: 85%		
Jose et al, 2020 [28]	Prospective	94 patients who underwent preoperative staging (endometrial cancer)	FDG PET/CT	MRI	Histopathology	**Lymph node metastases** Sens: 72.7% Spec: 97.2% PPV: 88.9% NPV: 92.1% Accu: 91.5%	**Lymph node metastases** Sens: 54.6% Spec: 94.4% PPV: 75.0% NPV: 87.2% Accu: 85.1%	NA
Cengiz et al, 2019 [29]	Retrospective	52 patients who underwent restaging due to elevation of CA-125 levels after surgery and chemotherapy or radiotherapy (ovarian cancer)	FDG PET/CT	CA-125 levels	Histopathology, clinical and imaging follow-up	**Recurrence** Sens: 94% Spec: 75% PPV: 98% NPV: 50% Accu: 96%	NA	NA
Virarkar et al, 2020 [30]	Meta-analysis	9 studies (patients with gynecological malignancies of the pelvis)	FDG PET/CT, FDG PET/MRI	NA	Histopathology, clinical and imaging follow-up	**Malignancy (patient-based)** ***FDG PET/CT*** Pooled Sens: 62.6% Pooled Spec: 91.6% Pooled DOR: 17 AUC: 0.84 ***FDG PET/MRI*** Pooled Sens: 73.3% Pooled Spec: 91.2% Pooled DOR: 28 AUC: 0.85 **(lesion-based)** ***FDG PET/CT*** Pooled Sens: 81.5% Pooled Spec: 86.6% Pooled DOR: 26 AUC: 0.91 ***FDG PET/MRI*** Pooled Sens: 84.7% Pooled Spec: 89.3% Pooled DOR: 44 AUC: 0.92	NA	NA
Head and Neck Cancer								
Leclere et al, 2020 [31]	Retrospective	477 patients who underwent initial staging (newly diagnosed head	FDG PET/CT	Clinical examination, panendoscopy, CT, MRI	Multidisciplinary team meeting, clinical follow-up	NA	NA	PET/CT downstaged 11.7% (56/477) and upstaged 34.6% (165/477) of patients. Patient management was

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		and neck squamous cell carcinoma)						modified (medium and high impact) in 19.5% (93/477) of cases.
LeRose et al, 2020 [32]	Retrospective	84 patients who underwent presurgical workup or post-treatment surveillance (head and neck squamous cell carcinoma)	FDG PET/CT	NA	Histopathology	**Regional lymph node metastases** Sens: 68.9% Spec: 61.5% PPV: 67.4% NPV: 63.2%	NA	NA
Wong et al, 2019 [33]	Meta-analysis	24 studies (2627 patients with head and neck squamous cell carcinoma who underwent surveillance following definitive treatment)	FDG PET/CT	NA	Histopathology, clinical and imaging follow-up	**Local failure** Pooled Sens: 85% Pooled Spec: 92% Pooled PPV: 64% Pooled NPV: 97% Pooled Accu: 91% AUC: 0.95 **Regional failure** Pooled Sens: 78% Pooled Spec: 95% Pooled PPV: 65% Pooled NPV: 97% Pooled Accu: 93% AUC: 0.99 **Locoregional and distant failure** Pooled Sens: 81% Pooled Spec: 91% Pooled PPV: 69% Pooled NPV: 95% Pooled Accu: 89% AUC: 0.94	NA	PET/CT performed >3 months showed significantly higher sensitivity (87% vs. 60%; p=0.02) and specificity (93% vs. 84%; p<0.001) than PET/CT performed ≤3 months for local failure.
Breik et al, 2020 [34]	Retrospective	140 treated with curative intent and no clinical signs of treatment failure (head and neck cancer)	FDG PET/CT	MRI	Biopsy, clinical or imaging follow-up	**Recurrence or metastases (3 months post-treatment)** Sens: 100% Spec: 69.6% PPV: 36.4% NPV: 100% **(6 months post-treatment)** Sens: 93.3% Spec: 86.7%	**Recurrence or metastases (3 months post-treatment)** Sens: 50.0% Spec: 86.2% PPV: 14.3% NPV: 97.4% **(6 months post-treatment)** Sens: 100% Spec: 83.3%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						PPV: 53.9% NPV: 98.7%	PPV: 25.0% NPV: 100%	
Trimboli et al, 2019 [35]	Retrospective	93 patients with US assessment of EU-TIRADS 4 or 5 (thyroid nodule ≥1cm)	FDG PET/CT	Neck US	Histology	**Malignancy** **EU-TIRADS 4** Sens: 87.5% Spec: 50.0% PPV: 25.9% NPV: 95.2% +LR: 1.75 -LR: 0.25 **EU-TIRADS 5** Sens: 96.3% Spec: 61.1% PPV: 78.8% NPV: 91.7% +LR: 2.48 -LR: 0.06	NA	NA
Kim and Kim, 2020 [36]	Meta-analysis	9 studies (759 patients with thyroid cancer who underwent preoperative lymph node staging)	FDG PET/CT	NA	Histopathology	**All cervical lymph node metastases** Pooled Sens: 30% Pooled Spec: 94% Pooled +LR: 3.2 Pooled –LR: 0.6 Pooled DOR: 5.5 AUC: 0.84 **Central lymph node metastases** Pooled Sens: 28% Pooled Spec: 87% Pooled +LR: 6.1 Pooled –LR: 0.65 Pooled DOR: 9.5 AUC: 0.79 **Lateral lymph node metastases** Pooled Sens: 56% Pooled Spec: 94% Pooled +LR: 7.6 Pooled –LR: 0.51 Pooled DOR: 15.1 AUC: 0.67	NA	NA
Rendl et al, 2020 [37]	Retrospective	73 patients who underwent pre-ablation rhTSH-stimulated PET/CT	FDG PET/CT	I-131 WBS	Histology, clinical follow-up	NA	NA	PET/CT changed the treatment plan in 15.1% (11/73) of patients (9—additional surgery, 2—initiated tyrosine

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		(intermediate-to-high risk differentiated thyroid cancer)						kinase inhibitor therapy).
Huang et al, 2020 [38]	Prospective	20 patients who underwent staging (hypopharyngeal carcinoma)	FDG PET/CT, FDG PET/MRI	MRI	Histology	**T staging (lesion-based)** ***PET/CT*** Accu: 63.6% ***PET/MRI*** Accu: 81.8% **N staging (level-based)** ***PET/CT*** Sens: 76.5% Spec: 98.3% PPV: 92.8% NPV: 93.6% ***PET/MRI*** Sens: 88.2% Spec: 98.2% PPV: 93.7% NPV: 96.7%	**T staging (lesion-based)** Accu: 72.7% **N staging (level-based)** Sens: 64.7% Spec: 94.7% PPV: 78.6% NPV: 90.0%	NA
Niu et al, 2020 [39]	Retrospective	78 patients without large palpable lymph nodes who underwent evaluation of neck status prior to primary tumour resection and neck dissection (oral squamous cell carcinoma)	FDG PET/CT	NA	Histopathology	**Neck metastases (neck side-based)** Sens: 83.9% Spec: 73.1% PPV: 59.1% NPV: 90.7% Accu: 76.5%	NA	NA
Zhu et al, 2020 [40]	Retrospective	235 patients who were surgically treated (cT1-2N0 tongue squamous cell carcinoma)	FDG PET/CT-guided neck dissection (n=66)	Elective neck dissection without preoperative PET/CT (n=169)	Histopathology	NA	NA	There was no significant difference in 5-year RC rate between patients who received preoperative PET/CT and those who did not (86% vs. 87%, respectively; p=0.731). Likewise, the 5-year DSS rates were not significantly different between the two groups

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
								(93% vs. 90%, respectively; p=0.583).
Corpman et al, 2019 [41]	Retrospective	233 patients who underwent treatment assessment and subsequent surveillance after completion of treatment (HPV-associated oropharyngeal squamous cell carcinoma)	FDG PET/CT	Physical examination, patient symptoms	Histopathology, clinical follow-up	**Recurrence (study-based)** ***Treatment assessment*** Sens: 100% Spec: 59.9% PPV: 13.4% NPV: 100% ***Subsequent surveillance*** Sens: 100% Spec: 72.4% PPV: 8.1% NPV: 100%	NA	The use of post-treatment PET/CT led to meaningful salvage treatment in 1.6% (3/188) of cases. There was no significant difference in OS between recurrences detected by surveillance PET/CT and those detected clinically (p=0.76).
Hematologic Cancer								
Kharuzhyk et al, 2020 [42]	Prospective	92 patients who underwent initial staging prior to treatment (47 HL; 45 NHL)	FDG PET/CT	DWI-MRI	Biopsy, follow-up	**Lymph node involvement (node-based)** Sens: 96.4%* Spec: 99.8% PPV: 99.7% NVP: 97.1% Accu: 98.2% AUC: 0.98* **Lung involvement (patient-based)** Sens: 86.7% Spec: 98.7% PPV: 92.9% NVP: 97.4% Accu: 96.7% AUC: 0.93 **Spleen involvement (patient-based)** Sens: 100%* Spec: 100% PPV: 100% NVP: 100% Accu: 100% AUC: 1.00* **Bone marrow involvement (patient-based)** Sens: 64.5%*	**Lymph node involvement (node-based)** Sens: 92.8%* Spec: 99.1% PPV: 98.9% NVP: 94.3% Accu: 96.3% AUC: 0.96* **Lung involvement (patient-based)** Sens: 73.3% Spec: 98.7% PPV: 91.7% NVP: 95.0% Accu: 94.6% AUC: 0.89 **Spleen involvement (patient-based)** Sens: 54.8%* Spec: 98.3% PPV: 94.4% NVP: 80.6% Accu: 83.3% AUC: 0.77* **Bone marrow involvement (patient-based)** Sens: 87.1%*	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Spec: 87.3% PPV: 74.1% NVP: 81.4% Accu: 79.1% AUC: 0.76* **Other organs involvement (patient-based)** Sens: 66.7% Spec: 98.6% PPV: 92.3% NVP: 92.4% Accu: 92.4% AUC: 0.83	Spec: 96.4% PPV: 93.1% NVP: 93.0% Accu: 93.0% AUC: 0.92* **Other organs involvement (patient-based)** Sens: 77.8% Spec: 98.6% PPV: 93.3% NVP: 94.8% Accu: 94.6% AUC: 0.88	
Gamal et al, 2020 [43]	Prospective	32 newly diagnosed patients (22 HL; 10 NHL)	FDG PET/CT	Whole-body DWI-MRI with background signal suppression	Histopathology, clinical and imaging follow-up	**Staging** Sens: 96% Spec: 100% PPV: 100% NPV: 80% Accu: 97%	**Staging** Sens: 93% Spec: 76% PPV: 96% NPV: 61% Accu: 91%	NA
Kandeel et al, 2020 [44]	Retrospective	138 patients who underwent initial staging prior to treatment (50 HL; 88 DLBCL)	FDG PET/CT	BMB	BMB, imaging follow-up	**Bone marrow involvement** **HL** Sens: 87.5%* Spec: 100% PPV: 100% NPV: 94.4%* Accu: 96.0%* **DLBCL** Sens: 66.7% Spec: 89.7% PPV: 76.9% NPV: 83.9% Accu: 81.8%	**Bone marrow involvement** **HL** Sens: 50.0%* Spec: 100% PPV: 100% NPV: 81.0%* Accu: 84.0%* **DLBCL** Sens: 68.8% Spec: 100% PPV: 100% NPV: 84.9% Accu: 88.6%	PET/CT upstaged 8.7% (12/138) of patients to stage IV but no change in treatment plan in any of these cases.
Elamir et al, 2020 [45]	Prospective	145 patients who underwent initial staging or imaging prior to new line of therapy (57 NHL; 88 HL)	FDG PET/CT	BMB	BMB, imaging follow-up, local biopsy, targeted MRI, CT changes	**Bone marrow involvement** Sens: 95.6% Spec: 98.0% PPV: 95.6% NPV: 98.0% Accu: 97.2%	**Bone marrow involvement** Sens: 46.7% Spec: 100% PPV: 100% NPV: 80.6% Accu: 83.4%	NA
Xiao-Xue et al, 2020 [46]	Retrospective	153 patients who underwent initial staging (15 HL; 138 NHL)	FDG PET/CT	BMB	BMB	**Bone marrow involvement** Sens: 54.3% Spec: 80.5% Accu: 74.5%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Zytoon et al, 2020 [47]	Retrospective	100 untreated patients who underwent initial assessment and staging (66 NHL; 32 HL)	FDG PET/CT	CeCT	Clinical monitoring, other imaging findings, iliac crest bone marrow biopsy	**Lymph node involvement (lesion-based)** Sens: 97.5% Spec: 94.0% Accu: 98.0% **Splenic involvement (lesion-based)** Sens: 95.2% Spec: 98.0% Accu: 99.0% **Bone marrow involvement (lesion-based)** Sens: 93.7% Spec: 96.0% Accu: 99.0% **Extranodal involvement (lesion-based)** Sens: 94.0% Spec: 96.2% Accu: 99.5%	**Lymph node involvement (lesion-based)** Sens: 83.1% Spec: 94.0% Accu: 89.6% **Splenic involvement (lesion-based)** Sens: 87.6% Spec: 86.6% Accu: 76.0% **Bone marrow involvement (lesion-based)** Sens: 88.6% Spec: 86.2% Accu: 75.0% **Extranodal involvement (lesion-based)** Sens: 80.0% Spec: 88.6% Accu: 95.9%	PET/CT upstaged 17% (17/100) of patients and downstaged 6% (6/100) of patients.
Al-Sabbagh et al, 2020 [48]	Retrospective	89 patients who underwent pre-therapy staging (large B-cell lymphoma)	FDG PET/CT	BMB	BMB, guided biopsy, imaging follow-up	**Bone marrow involvement** Sens: 95.8% Spec: 100% PPV: 100% NPV: 98.5% -LR: 0.04 Accu: 98.9%	**Bone marrow involvement** Sens: 50.0% Spec: 100% PPV: 100% NPV: 84.4% -LR: 0.5 Accu: 86.5%	NA
Persky et al, 2020 [49]	Prospective	132 patients underwent response assessment after 3 cycles of R-CHOP (previously untreated, nonbulky, stage I/II DLBCL)	FDG PET/CT (interim-PET negative patients continued with 1 additional cycle of R-CHOP while interim-PET positive patients received IFRT	NA	Clinical and imaging follow-up	NA	NA	The 5-year PFS and OS were similar between patients with positive interim-PET (86% and 85%, respectively) and those with negative interim-PET (89% and 91%, respectively).

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
			followed by ibritumomab tiuxetan radioimmunotherapy)					
Albano et al, 2019 [50]	Retrospective	122 patients who underwent staging (mantle-cell lymphoma)	FDG PET/CT	CT, GI endoscopy, bone marrow biopsy	Bone marrow biopsy, GI endoscopy	**Gastrointestinal involvement** Sens: 64% Spec: 91% PPV: 69% NPV: 90% Accu: 85% LR+: 7.55 LR-: 0.39 **Bone marrow involvement** Sens: 52% Spec: 98% PPV: 97% NPV: 65% Accu: 74% LR+: 29.9 LR-: 0.49	NA	PET/CT permitted the upstaging of 17.2% (21/122) and downstaging of 1.6% (2/122) of patients. PET/CT affected subsequent management in 18.9% (23/122) (21—switched to more aggressive chemotherapy, 2—avoided unnecessary invasive therapies).
Melanoma								
El-Shourbagy et al, 2020 [51]	Retrospective	50 patients who underwent staging or restaging (malignant melanoma)	FDG PET/CT	NA	Histopathology, clinical and imaging follow-up	**Staging** Sens: 93.3% Spec: 60.0% PPV: 88.2% NPV: 75.0% Accu: 85.7% **Recurrence** Sens: 100% Spec: 66.7% PPV: 88.9% NPV: 100% Accu: 90.9% **Distant metastases** Sens: 100% Spec: 66.7% PPV: 93.8% NPV: 100% Accu: 94.4%	NA	NA
Albano et al, 2020 [52]	Retrospective	74 patients who underwent restaging after surgical	FDG PET/CT	Not specified	Histology, clinical and imaging follow-up	**Recurrence** Sens: 82% Spec: 93% PPV: 88%	NA	PET/CT influenced the therapeutic management in 24.3% (18/74) of patients (4—radiotherapy

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		resection (suspicion of recurrent cutaneous melanoma)				NPV: 89% Accu: 89% AUC: 0.87		to chemotherapy, 2—added radiotherapy, 4—added chemotherapy, 5—initiated surgery, 3—added lymph-node dissection). The 2-year PFS (90% vs. 46%, p<0.05) and OS (76% vs. 39%, p<0.05) were significantly longer for patients with a negative scan than a positive one.
Mahajan et al, 2020 [53]	Retrospective	100 patients who underwent restaging after treatment (recurrent cutaneous squamous cell carcinoma)	FDG PET/CT	CT/MRI	Histopathology, clinical and imaging follow-up	**Recurrence (lesion-based)** Sens: 99% Spec: 14% PPV: 94% NPV: 67% Accu: 94%	**Recurrence (lesion-based)** Sens: 92% Spec: 12% PPV: 94% NPV: 10% Accu: 87%	PET/CT resulted in overall management change in 28.0% (28/100) of patients (16—intramodality changes or addition of modality, 12—intermodality change).
Stahlie et al, 2020 [54]	Prospective	35 asymptomatic patients who underwent follow-up surveillance after complete surgical resection (stage IIIB or IIIC melanoma)	FDG PET/CT	Physical examination, serum S100B and lactate dehydrogenase levels	Pathology, sequential imaging, clinical follow-up	**Recurrence** Sens: 92.3% Spec: 100% PPV: 100% NPV: 98.9%	NA	PET/CT changed management by detecting early recurrence in 34.3% (12/35) of patients, of whom 6 achieved a complete response or displayed no evidence of disease.
Non-FDG Tracers								
^{11}C-Choline								
Fonteyne et al, 2020 [23]	Meta-analysis	3 studies (109 newly diagnosed muscle invasive bladder cancer)	^{11}C-Choline PET/CT	NA	Histology, imaging follow-up	**Regional lymph node staging** Pooled Sens: 51% Pooled Spec: 80% Pooled +LR: 2.68 Pooled -LR: 0.63 Pooled DOR: 4.69	NA	NA
^{68}Ga-DOTA-(TATE, NOC, TOC)								
Bauckneht et al, 2020 [55]	Meta-analysis	38 studies (1143 patients with pancreatic neuroendocrine	^{68}Ga-DOTA-TATE/NOC/TOC PET or PET/CT	NA	Histopathology, imaging follow-up	**Primary lesion and initial staging (patient-based)** Pooled DR: 80.6%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		tumours)				Pooled Sen: 79.6% Pooled Spec: 95.0% Pooled +LR: 5.76 Pooled -LR: 0.20 Pooled DOR: 35.6 **(lesion-based)** Pooled DR: 92.1%		
Sharma et al, 2020 [56]	Retrospective	56 patients with known or unknow primary (gastroenteropancreatic neuroendocrine tumours)	^{68}Ga-DOTA-NOC PET/CT	CeCT + CT enterography	Histopathology, imaging follow-up	**Primary site (patient-based)** Sens: 56.5% Accu: 56.5% **(lesion-based)** Sens: 71.4% Accu: 66.7% **Staging or restaging (patient-based)** Sens: 75.8% Accu: 75.8% **(lesion-based)** Sens: 73.8% Accu: 67.4%	**Primary site (patient-based)** Sens: 56.5% Accu: 56.5% **(lesion-based)** Sens: 57.7% Accu: 44.1% **Staging or restaging (patient-based)** Sens: 72.7% Accu: 72.7% **(lesion-based)** Sens: 73.2% Accu: 52.6%	NA
Amyloid								
Leuzy et al, 2019 [57]	Prospective	207 patients with an uncertain diagnosis (mild cognitive impairment, Alzheimer's disease, non-Alzheimer's disease, dementia not otherwise specified, and subjective cognitive decline)	^{18}F-flutemetamol PET, FDG PET/CT	Neuropsychological testing, CT, MRI, CSF sampling, apolipoprotein E genotyping, electroencephalography, speech/language testing	Consensus from multidisciplinary meeting, pre- and post-PET information	NA	NA	PET led to a change in diagnosis in 44.4% (92/207) of patients with 75 additional patients (increase of 218%) receiving cholinesterase inhibitor treatment.
^{68}Ga-PSMA/^{18}F-DCFPyL								
Chandra et al, 2020 [58]	Retrospective	64 patients with raised serum PSA (<50 ng/ml) and/or positive digital rectal examination (suspected	^{68}Ga-PSMA PET/CT	Serum PSA, digital rectal examination, MRI	Biopsy	**Diagnosis** Sens: 74% Spec: 92% PPV: 85% NPV: 86% Accu: 86%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		prostate cancer)						
Dekalo et al, 2019 [59]	Retrospective	59 patients who underwent radical prostatectomy and pelvic lymph node dissection (intermediate or high-risk prostate cancer)	^{68}Ga-PSMA-11 PET/CT	NA	Histopathology	**Seminal vesicle invasion** Sens: 58% Spec: 96% PPV: 78% NPV: 90% AUC: 0.77 **Lymph node involvement** Sens: 67% Spec: 98% PPV: 67% NPV: 98% AUC: 0.82	NA	NA
Wu et al, 2020 [60]	Meta-analysis	13 studies (1597 patients with intermediate- or high-risk prostate cancer)	^{68}Ga-PSMA PET/CT	MRI	Histopathology	**Lymph node metastases** Pooled Sens: 65% Pooled Spec: 94% Pooled +LR: 10.6 Pooled -LR: 0.37 Pooled DOR: 29 AUC: 0.92	**Lymph node metastases** Pooled Sens: 41% Pooled Spec: 92% Pooled +LR: 4.9 Pooled -LR: 0.65 Pooled DOR: 8 AUC: 0.83	NA
Tu et al, 2020 [61]	Meta-analysis	11 studies (904 patients with intermediate- or high-risk prostate cancer who underwent preoperative lymph node staging)	^{68}Ga-PSMA PET/CT	NA	Histopathology	**Lymph node staging (patient-based)** Pooled Sens: 63% Pooled Spec: 93% Pooled PPV: 79% Pooled NPV: 84% Pooled +LR: 8.7 Pooled -LR: 0.39 Pooled DOR: 22 AUC: 0.91 **(node-based)** Pooled Sens: 70% Pooled Spec: 99% Pooled PPV: 85% Pooled NPV: 97% Pooled +LR: 50.7 Pooled –LR: 0.30 Pooled DOR: 167 AUC: 0.96	NA	NA
Kulkarni et al, 2020 [62]	Retrospective	51 patients who underwent primary lymph	^{68}Ga-PSMA PET/CT	mpMRI	Histopathology	**Lymph node metastases (patient-based)**	**Lymph node metastases (patient-based)**	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		node staging prior to definitive surgical treatment (intermediate- and high-risk prostate cancer)				Sens: 80.0% Spec: 90.3% PPV: 84.2% NPV: 87.5% Accu: 86.3% **(lesion-based)** Sens: 69.2% Spec: 99.6% PPV: 87.1% NPV: 98.7% Accu: 98.4%	Sens: 43.7% Spec: 78.9% PPV: 45.7% NPV: 63.6% Accu: 62.8% **(lesion-based)** Sens: 32.2% Spec: 98.5% PPV: 52.6% NPV: 96.7% Accu: 95.5%	
Gaur et al, 2020 [63]	Prospective	26 patients; 44 tumours with evidence of disease on CT and bone scanning (high-risk localized prostate cancer)	^{18}F-DCFPyL PET/CT	mpMRI	Histopathology	**Intraprostatic tumour localization (lesion-based)** DR: 80.0% Sens: 90.9%	**Intraprostatic tumour localization (lesion-based)** DR: 88.4% Sens: 86.4%	NA
Basha et al, 2019 [64]	Prospective	173 patients with no prior treatment (newly diagnosed prostate cancer)	^{68}Ga-PSMA-11 PET/CT	CT, MRI	Histopathology	**Diagnosis** Sens: 96%	NA	PET/CT upstaged 17.9% (20/112) of patients and downstaged 10.7% (12/112) of patients.
Parikh et al, 2020 [65]	Prospective Phase II	100 previously untreated patients who underwent initial staging (prostate cancer)	^{18}F-DCFPyL PET/CT	^{99m}Tc-MDP bone scan, CT, MRI	National Comprehensive Cancer Network criteria, pre- and post-PET information	NA	NA	PET/CT changed the stage group of 36.0% (36/100) of patients (28 upstaged, 8 downstaged). In total, 39.0% (39/100) of patients had a change in pre-specified treatment recommendations.
Tarr et al, 2020 [66]	Prospective	46 patients without evidence of metastatic disease who underwent pre-operative staging (high-risk prostate cancer)	^{68}Ga-PSMA PET/CT	MRI, bone scintigraphy	Pathology, consensus from multidisciplinary team	NA	NA	The addition of ^{68}Ga-PSMA PET/CT to conventional imaging changed the stage group of 32.6% (15/46) of patients (9—upstaged, 6—downstaged). Subsequent management was changed in 34.8% (16/46) of patients (12—intermodality change, 4—intramodality change).

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Sawicki et al, 2019 [67]	Prospective	28 patients with PSA levels ≥0.2 ng/ml who had undergone radical prostatectomy with or without pelvic lymphadenectomy (biochemical recurrent prostate cancer)	^{68}Ga-PSMA PET/CT	Whole-body MRI	Histopathology, clinical and imaging follow-up	**Recurrence (patient-based)** DR: 71.4%* **(lesion-based)** DR: 100%*	**Recurrence (patient-based)** DR: 39.3%* **(lesion-based)** DR: 23.2%*	NA
Liu et al, 2020 [68]	Prospective	79 patients who underwent restaging after radiation therapy (recurrent prostate cancer)	^{18}F-DCFPyL PET/CT	CT, bone scan, mpMRI	Biopsy, pre- and post-PET questionnaire	**Prostatic recurrence** Sens: 86% Spec: 67% PPV: 92%	**Prostatic Recurrence** Sens: 93% Spec: 100% PPV: 100%	PET/CT changed the staging of 44.3% (35/79) of patients (27 upstaged, 8 downstaged). A change in planned management occurred in 59.5% (47/79) of cases (19—avoided unnecessary therapy, 15—initiated therapy, 3—added systemic therapy, 3—added directed salvage therapy, 3—changed to directed salvage therapy alone, 2—changed to systemic therapy alone, 1—directed salvage therapy to systemic therapy, 1—systemic therapy to directed salvage therapy).
Lindenberg et al, 2020 [69]	Prospective	77 patients with rising PSA level and negative bone scan and/or CT after prostatectomy and/or radiation therapy (biochemically recurrent prostate cancer)	^{18}F-DCFPyL PET/CT	CT, bone scan, mpMRI	Histopathology	**Recurrence (lesion-based)** Sens: 69% Spec: 91% PPV: 86%	**Recurrence (lesion-based)** ***mpMRI*** Sens: 69% Spec: 74% PPV: 69%	The addition of ^{18}F-DCFPyL PET/CT to mpMRI improved the PPV by 38% (p=0.02). ^{18}F-DCFPyL PET/CT also depicted more pelvic lymph nodes than did mpMRI (128 vs. 23 nodes).
Chausse et al, 2020 [70]	Retrospective	93 previously treated patients	^{18}F-DCFPyL PET/CT	MRI, CT, bone scan	Histopathology, clinical or	NA	NA	^{18}F-DCFPyL PET/CT led to a change in management

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		with rising PSA and negative or equivocal conventional imaging (biochemically recurrent prostate cancer)			imaging follow-up, consensus from tumour board			in 44.1% (41/93) of patients (8—therapy intensification, 7—reduced interventions, 26—adrogen-deprivation therapy to stereotactic body radiotherapy).
Abufaraj et al, 2019 [71]	Prospective	65 patients who underwent lymph node staging prior to salvage lymph node dissection (biochemical recurrent prostate cancer)	^{68}Ga-PSMA-11 PET/CT or PET/MRI	NA	Histopathology	**Lymph node metastases (region-based)** ***Right pelvic*** Sens: 94.6% Spec: 96.4% PPV: 97.2% NPV: 93.1% Accu: 95.4% ***Left pelvic*** Sens: 100% Spec: 96.4% PPV: 97.4% NPV: 100% Accu: 98.5% ***Presacral*** Sens: 90.9% Spec: 97.7% PPV: 95.2% NPV: 95.5% Accu: 95.4% ***Retroperitoneal*** Sens: 72.7% Spec: 100% PPV: 100% NPV: 94.7% Accu: 95.4%	NA	NA
Kimura et al, 2020 [72]	Systematic review and meta-analysis	14 studies (462 prostate cancer patients who experienced a biochemical recurrence after primary treatment prior to salvage lymph node dissection)	^{68}Ga-PSMA PET/CT or PET/MRI	NA	Histopathology	**Lymph node metastases (patient-based)** PPV: 69.6%-93.3% **(lesion-based)** Pooled Sens: 84% Pooled Spec: 97% Pooled +LR: 30.3 Pooled –LR: 0.16 Pooled DOR: 189 AUC: 0.98	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						(Field-based) Pooled Sens: 82% Pooled Spec: 95% Pooled +LR: 15.8 Pooled –LR: 0.19 Pooled DOR: 82 AUC: 0.89		
Sonni et al, 2020 [73]	Prospective	197 patients who underwent presurgical staging or restaging of definitive treatment (prostate cancer)	^{68}Ga-PSMA-11 PET/CT	CT, bone scan	Biopsy, pre- and post-PET questionnaire	NA	NA	^{68}Ga-PSMA PET/CT changed the disease stage in 68.5% (135/197) of patients and impacted management in 57.1% (104/182) of cases (29—systemic to focal, 9—focal to systemic, 13—change in systemic, 19—change in focal, 19—switched to active surveillance, 1—active surveillance to androgen deprivation therapy, 5—systemic to combined therapy, 2—focal to combined therapy, 4—combined therapy to focal, 3—combined therapy to systemic).
Bianchi et al, 2019 [74]	Prospective	276 patients who underwent radical prostatectomy as the primary treatment (biochemical recurrent prostate cancer)	^{68}Ga-PSMA PET/CT	NA	Consensus from multidisciplinary team	NA	NA	PET/CT led to a major treatment change in 64.1% (177/276) of patients (49—palliative to curative, 20—curative to palliative, 22—palliative to surveillance, 66—curative to surveillance, 14—surveillance to curative, 6—surveillance to palliative). A minor clinical impact was observed in 2.5% (7/276) of patients (4—more aggressive/extended approach, 3—less aggressive/extended approach).

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
^{18}F-DOPA								
Terroir et al, 2019 [75]	Prospective	36 patients with elevated postoperative serum calcitonin levels (medullary thyroid cancer)	^{18}F-DOPA PET/CT, FDG PET/CT	Whole-body MRI, whole-body CT, neck US	Pathology, concordance between two imaging modalities, follow-up	**Persistent or recurrent disease (patient-based)** ***^{18}F-DOPA PET/CT*** DR: 64% ***FDG PET/CT*** DR: 40% **(lesion-based)** ***^{18}F-DOPA PET/CT*** DR: 84%‡* ***FDG PET/CT*** DR: 45%‡	**Persistent or recurrent disease (patient-based)** ***Whole-body MRI*** DR: 40% ***Whole-body CT*** DR: 48% ***Neck US*** DR: 31% **(lesion-based)** ***Whole-body MRI*** DR: 23%* ***Whole-body CT*** DR: 32%*	^{18}F-DOPA PET/CT contributed to changes in treatment management in 19.4% (7/36) of patients.
^{18}F-FET								
Bashir et al, 2019 [76]	Retrospective	146 patients; 168 PET scans, who received first-line radiotherapy or chemoradiotherapy or second-line chemotherapy (MRI-suspected recurrent glioblastoma)	^{18}F-FET PET	MRI	Histopathology, clinical or imaging follow-up	**Differentiating between post-treatment changes and recurrence (study-based)** ***TBRmax with threshold of 3.2*** Sens: 99% Spec: 94% PPV: 99% NPV: 94% Accu: 99% AUC: 0.97 ***TBRmean with threshold of 1.8*** Sens: 96% Spec: 94% PPV: 99% NPV: 71% Accu: 96% AUC: 0.98 ***BTV with threshold of 0.55*** Sens: 98% Spec: 94% PPV: 99% NPV: 83% Accu: 98% AUC: 0.96	NA	NA
Pancreatic Cancer								

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Que et al, 2020 [77]	Meta-analysis	26 studies (1377 patients with pancreatic cancer)	FDG PET/CT	DWI-MRI	Biopsy	**Diagnosis** Pooled Sens: 88% Pooled Spec: 78% Pooled +LR: 4.07 Pooled -LR: 0.16 Pooled DOR: 20.65 AUC: 0.91*	**Diagnosis** Pooled Sens: 93% Pooled Spec: 86% Pooled +LR: 6.53 Pooled -LR: 0.08 Pooled DOR: 44.07 AUC: 0.95*	NA
Sarcoma								
Annovazzi et al, 2020 [78]	Retrospective	282 patients; 345 PET/CT scans, who underwent initial staging or disease restaging (soft-tissue sarcomas of the extremities and trunk)	FDG PET/CT	MRI, CT	Histopathology, imaging follow-up	**Relapse (patient-based)** Sens: 95.4% (eqv as pos), 90.8% (eqv as neg) Spec: 82.6% (eqv as pos), 95.6% (eqv as neg) **Lung metastases (patient-based)** Sens: 86.0% Spec: 96.7% PPV: 97.7% NPV: 80.6% Accu: 90.0% **(lesion-based)** Sens: 74.1% Spec: 97.7% PPV: 99.3% NPV: 46.2% Accu: 78.5% **Bone metastases (patient-based)** Sens: 100% Spec: 100% PPV: 100% NPV: 100% Accu: 100% **(lesion-based)** Sens: 100% Spec: 100% PPV: 100% NPV: 100% Accu: 100% **Lymph node metastases (patient-based)** Sens: 96.0%	**Bone metastases *CT* (patient-based)** Sens: 69.2% Spec: NA PPV: 94.7% NPV: NA Accu: 66.7% **(lesion-based)** Sens: 48.8% Spec: NA PPV: 97.5% NPV: NA Accu: 48.2% **Lymph node metastases *CT* (patient-based)** Sens: 56.0% Spec: 10.0% PPV: 60.9% NPV: 8.3% Accu: 42.9%	PET/CT changed the pretreatment TNM staging group in 15.3% (26/170) of patients (19 upstaged, 7 downstaged). Therapy planning was altered in 23.2% (80/345) of cases.

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Spec: 50.0% PPV: 82.8% NPV: 83.3% Accu: 82.9%		
Thoracic Cancer								
Machado Medeiros et al, 2020 [79]	Meta-analysis	4 studies (553 patients with NSCLC)	FDG PET/CT	DWI-MRI, MRI	Histopathology, imaging follow-up	**M staging** Pooled Sens: 83% Pooled Spec: 93% Pooled PPV: 91% Pooled NPV: 83% Pooled +LR: 11.7 Pooled -LR: 0.19 Pooled DOR: 62 AUC: 0.95	**M staging** ***DWI-MRI*** Pooled Sens: 78% Pooled Spec: 91% Pooled PPV: 88% Pooled NPV: 79% Pooled +LR: 8.7% Pooled -LR: 0.24 Pooled DOR: 35 AUC: 0.93 ***MRI*** Pooled Sens: 92% Pooled Spec: 92% Pooled PPV: 90% Pooled NPV: 90% Pooled +LR: 10.8% Pooled -LR: 0.09 Pooled DOR: 117 AUC: 0.93	NA
Chrysikos et al, 2020 [80]	Prospective	130 patients who underwent diagnosis and staging (potentially operable NSCLC)	FDG PET/CT	EBUS/EUS-b, chest CT	Histology	**Mediastinal lymph node staging** Sens: 92.2% Spec: 43.9%* PPV: 64.8%* NPV: 83.3% Accu: 72.7%	**Mediastinal lymph node staging** ***EBUS/EUS-b*** Sens: 93.8% Spec: 100%* PPV: 100%* NPV: 93.4% Accu: 96.7%	NA
Mu et al, 2020 [81]	Prospective	95 patients who underwent imaging and tumour marker examination after treatment (NSCLC)	FDG PET/CT	CEA and CYFRA21-1 levels	Histopathology, clinical and imaging follow-up	**Recurrence and/or metastases** Sens: 86.9%* Spec: 73.5%* PPV: 82.8%* NPV: 80.7%* Accu: 82.1%*	**Recurrence and/or metastases** Sens: 70.0%* Spec: 56.7%* PPV: 68.3%* NPV: 41.4%* Accu: 64.3%*	NA
Various Sites								
Yoo et al, 2020 [82]	Retrospective	74 patients with suspected bone metastases (cancer of unknown primary)	FDG PET/CT	NA	Histopathology, clinical or imaging follow-up	**Primary site** DR: 84.2%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Budak and Yanarates, 2020 [83]	Retrospective	100 patients with bone metastases (cancer of unknown primary)	FDG PET/CT	NA	Histopathology, clinical follow-up	**Primary site** DR: 72% Sens: 84.7% Spec: 46% Accu: 79%	NA	NA
van't Sant et al, 2020 [84]	Meta-analysis	24 studies (2302 patients with newly diagnosed gastrointestinal or ovarian cancer)	FDG PET or PET/CT	CT, DWI-MRI or MRI	Histopathology, surgical findings, clinical and imaging follow-up	**Peritoneal metastases (region-based)** Pooled Sens: 79% Pooled Spec: 90% Pooled DOR: 36.5	**Peritoneal metastases** ***CT*** **(region-based)** Pooled Sens: 68% Pooled Spec: 88% Pooled DOR: 15.9 **(patient-based)** Pooled Sens: 70% Pooled Spec: 94% Pooled DOR: 33.5 ***DWI-MRI or MRI*** **(region-based)** Pooled Sens: 91% Pooled Spec: 85% Pooled DOR: 63.3	NA
Zidan et al, 2020 [85]	Prospective	30 patients with extra cranial malignancies (18 unknown primary; 5 lung cancer; 3 breast cancer; 2 melanoma; 1 renal cell carcinoma; 1 papillary thyroid carcinoma)	FDG PET/CT	CeCT	Clinical and imaging follow-up	**Brain metastases** Sens: 78.1% Spec: 92.7% PPV: 83.3% NPV: 90.0% Accu: 88.0%	**Brain metastases** Sens: 81.3% Spec: 94.1% PPV: 86.7% NPV: 91.4% Accu: 90.0%	NA
Zytoon et al, 2020 [86]	Prospective	175 patients with proven or suspected metastatic lesions (cancer of unknown primary)	FDG PET/CT	NA	Histopathology, clinical and imaging follow-up	**Primary site** Sens: 100% Spec: 93.3% PPV: 95.2% NPV: 100% Accu: 97.1%	NA	NA

*$p<0.05$

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

Abbreviations: Accu, accuracy; AFP, alfa feto protein; AUC, area under the curve; BMB, bone marrow biopsy; BSGI, breast-specific gamma imaging; BTV, biological tumour volume; CA-125, cancer antigen 125; ^{11}C-choline, carbon-11-choline contrast; CEA, carcinoembryonic antigen; CeCT, contrast-enhanced computed tomography; CSF, cerebral spinal fluid; CT, computerized tomography; cT1-2N0, clinical early stage; CYFRA21-1, cytokeratin 19 fragment; DDFS, distant disease-free survival; DFS, disease-free survival;

DLBCL, diffuse large B-cell lymphoma; DOR, diagnostic odds ratio; DR, detection rate; DSS, disease-specific survival; DWI-MRI, diffusion-weighted magnetic resonance imaging; EEG, electroencephalogram; EBUS/EUS-b, endobronchial ultrasound/transesophageal bronchoscopic ultrasound; EUS, Endoscopic ultrasound; EU-TIRADS, European Thyroid Imaging Reporting and Data Systems; ^{18}F-DCFPyL, (2s)-2-[[(1S)-1-carboxy-5-[(6-(^{18}F)fluoranylpyridine-3-carbonyl)amino]pentyl]carbamoylamino]pentanedioic acid; FDG, fluorodeoxyglucose; ^{18}F-DOPA, fluoro dihydroxyphenylalanine; ^{18}F-FET, O-(2[^{18}F]-fluoroethyl)-L-tyrosine; ^{68}Ga-DOTA-NOC, Gallium-68-1,4,7,10-tetraazacyclododecane-1,4,7,10-tet-raacetic acid-1-Nal3-octreotide; ^{68}Ga-DOTA-TATE, Gallium-68-dodecanetetraacetic acid-Tyr3-octreotate; ^{68}Ga-DOTA-TOC, Gallium-68-edotretide; ^{68}Ga-HBED-CC PSMA-11/ ^{68}Ga-PSMA-11, Gallium-68-labelled prostate-specific membrane antigen 11; GI, gastrointestinal; HER2, human epidermal growth factor receptor 2; HL, Hodgkin lymphoma; HPV, human papillomavirus; IFRT, involved-field radiation therapy; +LR, positive likelihood ratio; -LR, negative likelihood ratio; LFRI, local relapse-free interval; mpMRI, multi-parametric magnetic resonance imaging; MRI, magnetic resonance imaging; 99mTc-MIBI, technetium sestamibi; 99mTc-MDP, technetium 99m-methyl diphosphonate; NA, not applicable; NHL, non-Hodgkin lymphoma; NPV, negative predictive value; NSCLC, non-small-cell lung carcinoma; OS, overall survival; PERCIST, PET Response Criteria In Solid Tumor; PET, positron emission tomography; PFS, progression-free survival; PPV, positive predictive value; PSA, prostate specific antigen; RC, regional control; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RCT, randomized controlled trial; RECIST, Response Evaluation Criteria In Solid Tumors; rhTSH, recombinant human thyrotropin; SCC-Ag, serum squamous cell carcinoma antigen; Sens, sensitivity; SLNB, sentinel lymph node biopsy; Spec, specificity; TBRmax, maximum tumour-to-background ratio; TBRmean, mean tumour-to-background ratio; TNM, tumour, node, metastasis; TNR, tumour-to-normal liver standardized uptake value ratio; US, ultrasound; vs, versus; WBS, whole body scan