Ontario Health
Cancer Care Ontario

PET Six-Month Monitoring Report 2020-1

Evidence from Primary Studies and Systematic Reviews and Recommendations from Clinical Practice Guidelines January to June 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 19th 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 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 (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

Sixty-eight studies published between January and June 2020 met the inclusion criteria. A summary of the evidence from the 68 studies can be found in **Appendix 1: Summary of studies from January to June 2020**.

Breast Cancer

Three studies met the inclusion criteria [1-3]. In the preoperative axillary lymph node assessment of breast cancer, FDG PET/CT displayed sensitivity that ranged from 76.0% to 85.0% and specificity that ranged from 78.0% to 97.0% [1-3]. Furthermore, FDG PET/CT identified distant metastases with high sensitivity (100%) and specificity (98.0%) [3].

Epilepsy

One study met the inclusion criteria [4]. Localization of focal cortical dysplasia on FDG PET had the highest sensitivity for seizure freedom (78.2%), followed by magnetic resonance imaging (MRI) (75.8%), and ictal single-photon emission computed tomography (SPECT) (71.8%). Localization on either one of the three imaging modalities achieved seizure freedom with a sensitivity of 97.5%.

Esophageal Cancer

Four studies met the inclusion criteria [5-8]. In previously untreated patients with esophageal cancer, FDG PET/CT's ability to detect distant metastases missed by contrast-enhanced CT led to a change in stage group in 42.1% of cases [5]. Similarly, the additional input of FDG PET/CT during radiation treatment planning modified contouring and treatment plans in 70.0% of patients [6]. In patients who received neoadjuvant chemotherapy and/or radiotherapy, two meta-analyses concluded that FDG PET or PET/CT, endoscopic ultrasound (EUS), MRI, and CT are all inadequate as single modalities for detecting residual disease or identifying complete responders [7,8].

Gastrointestinal Cancer

Seven studies met the inclusion criteria [9-15]. The role of FDG PET or PET/CT in the characterization of incidental colorectal focal FDG uptake was explored in a meta-analysis. FDG PET or PET/CT demonstrated good sensitivity (pooled estimate, 87%) and specificity (pooled estimate, 83%) for predicting malignant or premalignant lesions [9]. In patients with potentially resectable colorectal liver metastases, the addition of FDG PET or PET/CT to conventional imaging (i.e., CT, MRI) changed surgical management in 8% to 20% of cases. However, pooled data from two RCTs showed that PET or PET/CT did not significantly reduce futile laparotomies (relative risk [RR], 0.59; 95% confidence interval [CI], 0.24 to 1.47) [10]. In the post-therapeutic surveillance of colorectal cancer, FDG PET/CT was shown to be superior to contrast-enhanced CT for the detection of loco-regional recurrence and metastases [11,12]. In patients with hepatocellular carcinoma, FDG PET/CT (93.3%) was more accurate than triphasic CT (76.7%) in the evaluation of local recurrence and residual disease after transarterial chemoembolization [13]. However, FDG PET/CT was less accurate (patient-based, 69%; lesion-based, 71%) in predicting microvascular invasion and early recurrence after liver resection [14]. In the Phase II EUFURO trial, patients with adenocarcinoma in the gastro-esophageal junction, stomach or pancreas were randomized to either clinical assessment or clinical assessment plus imaging (FDG PET/CT and EUS) for follow-up after surgery. The addition of FDG PET/CT and EUS led to the detection of significantly more asymptomatic recurrences (33 versus 0, $p<0.001$) and more patients referred for chemotherapy (25 versus

14, p=0.028) within two years after surgery, but did not significantly prolong survival [15].

Gynecologic Cancer

Five studies met the inclusion criteria [16-20]. In patients with locally advanced cervical cancer, FDG PET or PET/CT was highly specific (pooled estimate, 97%) for detecting para-aortic lymph node metastases; however, sensitivity was insufficient (pooled estimate, 71%) [16]. For those deemed suitable for radical chemoradiation, FDG PET/CT upstaged 84.5% of patients and changed the treatment intent of 46.8% of cases [17]. In the preoperative evaluation of endometrial cancer, FDG PET or PET/CT detected lymph node metastases with low to moderate sensitivity (patient-based, 45.8% to 80.0%; node-based, 68.0% to 78.9%), but high specificity (patient-based, 91.1% to 96.0%; node-based, 96.0% to 98.6%) [18-20]. Furthermore, FDG PET/CT was unreliable in predicting the presence of peritoneal disease due to a high false-negative rate (62.5%) [20].

Head and Neck Cancer

Eleven studies met the inclusion criteria [21-31]. In patients with head and neck squamous cell carcinoma who underwent definitive surgery with or without postoperative radiotherapy, FDG PET/CT was found to be comparable to conventional imaging (contrast-enhanced CT and bone scintigraphy) with respect to detecting distant metastases [21]. Furthermore, FDG PET/CT after postoperative radiation has excellent prognostic value for long-term survival, where patients with a negative post-treatment scan have a significantly better three-year overall survival (OS) (89.9% versus 11.2%, p<0.001) than those with a positive scan [22]. In patients who received concurrent chemoradiotherapy prior to salvage surgery, FDG PET/CT detected residual disease with a sensitivity of 89.3% and a specificity of 76.0% [23]. Similar sensitivity (78%) and specificity (81%) were reported for FDG PET/CT in patients who received definitive radiotherapy without chemotherapy [24]. In patients with unknown primary head and neck squamous cell carcinoma, FDG PET/CT localized the primary tumour with a sensitivity of 50.9% and a specificity of 82.5% [25]. For the detection of recurrent and/or metastatic disease in differentiated thyroid cancer patients with thyroglobulin elevation and negative iodine scintigraphy, FDG PET/CT demonstrated high diagnostic sensitivity (pooled estimate, 86%) and specificity (pooled estimate, 84%) [26], while having the advantage over diffusion-weighted MRI [27]. In the differential diagnosis of benign and malignant salivary gland tumours, the diagnostic performance of FDG PET or PET/CT, US, CT, MRI, and real-time elastography were not found to be significantly different from each other [28]. Results from a meta-analysis indicated that FDG PET or PET/CT has a higher pooled sensitivity (92% versus 83%) and specificity (89% versus 78%) than MRI in the diagnosis of local recurrent and residual nasopharyngeal carcinoma [29]. For the initial staging of oral cavity squamous cell carcinoma, FDG PET/CT was more sensitive (patient-based, 69.1% versus 35.7%, p=0.001; side-based, 70.5% versus 36.4%, p<0.001; level-based, 62.1% versus 29.3%, p<0.001) but less specific (patient-based, 77.9% versus 89.0%, p=0.003; side-based, 78.7% versus 89.7%, p=0.001; neck-based, 89.2% versus 96.8%, p<0.001) than contrast-enhance CT/MRI in uncovering occult neck metastases [30]. Whereas in patients with early-stage tongue squamous cell carcinoma, FDG PET/CT displayed excellent specificity (94.9%) for detecting occult neck metastases, but sensitivity (70.6%) was substandard [31].

Hematologic Cancer

Five studies met the inclusion criteria [32-36]. For the evaluation of bone marrow involvement during pre-therapy staging, FDG PET/CT achieved the highest accuracy in diffuse large B-cell lymphoma (87.4%), followed by Hodgkin lymphoma (77.7%), other non-Hodgkin lymphoma (67.2%), and follicular lymphoma (63.0%) [32]. With respect to response

assessment, three studies investigated the role of PET-adapted treatment for newly diagnosed advanced Hodgkin lymphoma. In the five-year follow-up of the SWOG S0816 trial, interim-PET-positive patients who switched to six cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses (eBEACOPP) after two cycles of doxorubicin, vinblastine, vincristine, and dacarbazine (ABVD) had favourable progression-free survival (PFS) (63%) and OS (85%). However, these patients experienced a significantly higher rate of second malignancies (14% versus 2%, p=0.001) compared with interim-PET-negative patients who continued with four cycles of ABVD [33]. In the randomized, non-inferiority, phase 3 AHL2011 trial, interim PET after two cycles of eBEACOPP guided the switch to ABVD in early responders without significant loss in five-year OS (hazard ratio [HR], 0.94; 95% CI, 0.43 to 2.05, p=0.43), event-free survival (HR, 0.93; 95% CI, 0.69 to 1.25, p=0.31), and disease-free survival (HR, 1.10; 95% CI, 0.67 to 1.71, p=0.66) [34]. Similarly, in another trial, early de-escalation to ABVD after two cycles of eBEACOPP for PET-negative patients achieved comparable efficacy as PET-positive patients who continued with eBEACOPP, but with significantly reduced hematological and thromboembolic toxicities [35]. For all stages of newly diagnosed Hodgkin lymphoma, results from the GATLA LH-05 trial showed that the discontinuation of therapy in patients with a negative PET scan after three cycles of ABVD have excellent survival outcomes (3-year PFS, 90%; 3-year OS, 98%). The three-year PFS (65%, p<0.0001) and OS (92%, p=0.007) were significantly worse in patients with a positive PET scan who received three additional cycles of ABVD + involved-field radiation therapy or salvage treatment with ifosfamide plus carboplatin and etoposide/etoposide plus methylprednisone, cytarabine and cisplatin [36].

Non-FDG Tracers

Twenty-seven studies met the inclusion criteria [37-63]. In one meta-analysis, ^{11}C-choline PET/CT was associated with a summary sensitivity of 80.9% and a summary specificity of 84.1% for detecting recurrent prostate cancer [37]. According to another meta-analysis, ^{11}C/^{18}F-choline PET/CT was able to detect bone metastases with a pooled sensitivity of 87% and a pooled specificity of 99% [38]. In patients with negative or equivocal conventional imaging (i.e., CT, bone scan) and rising prostate-specific antigen (PSA) levels after radical prostatectomy, ^{18}F-FCH PET/CT impacted planned management in significantly more cases than pelvic MRI (46.2% versus 23.9%, p<0.003) [39]. The utility of ^{68}Ga-DOTA-TATE, -TOC, and –NOC in neuroendocrine tumours (NETs) was investigated in several studies. In two retrospective reviews, ^{68}Ga-DOTA-TOC PET/CT or PET/MRI was demonstrated to be highly sensitive (92.7%) and specific (100%) for diagnosing NETs [40], while ^{68}Ga-DOTA-TATE PET/CT was shown to have altered treatment decision in 35.6% (36/101) of patients [41]. In those with metastatic NETs and unknown primary tumours, ^{68}Ga-DOTA-TATE/TOC/NOC PET/CT localized the primary site in 56% of cases which led to a 20% overall change in patient management [42]. For the specific evaluation of patients with paragangliomas, ^{68}Ga-DOTA-NOC PET/CT was found to be superior to both I-Metaiodobenzylguanidine labelled with Iodine-131 (I-131 MIBG) SPECT/CT and I-131 MIBG planar scintigraphy in terms of sensitivity (patient-based, 97.3% versus 43.2% and 36.4%, respectively, p<0.001; lesion-based, 97.7% versus 38.9% and 34.3%, respectively, p<0.001) and superior to conventional imaging (i.e., US, contrast-enhanced CT, MRI, digital subtraction angiography) in terms of specificity (lesion-based, 94.4% versus 33.3%, p=0.002) [43]. In patients with mild cognitive impairment or dementia, the addition of ^{18}F-florbetaben PET to a standardized diagnostic workup changed 17.3% of diagnoses and impacted medication plan in 6.7% (7/104) of patients [44]. Two meta-analyses assessed the diagnostic performance of ^{18}F-NaF PET/CT in the detection of bone metastases, one in prostate cancer [38] and the other in various primary tumours [45]. In both cases, ^{18}F-NaF PET/CT was demonstrated to be superior to bone scintigraphy. Likewise, three

meta-analyses evaluated ^{18}F-FACBC PET/CT in prostate cancer. On the whole, ^{18}F-FACBC PET/CT showed moderate capability in the diagnosis of primary lesions [46,47], preoperative lymph node staging [47], and detection of recurrent disease [37,47]. ^{68}Ga-PSMA PET/CT was also examined in prostate cancer. In the diagnosis of patients with total PSA levels of 0.4 to 50 ng/mL and prostate volume between 10 and 110 mL, ^{68}Ga-PSMA PET/CT showed a sensitivity of 91.7% and a specificity of 81.8% [48]. For the differentiation of high-grade intra-prostatic lesions, ^{68}Ga-PSMA PET/CT was unreliable for detecting International Society of Urological Pathology (ISUP) grade 1 prostate cancer (sensitivity, 18%), but improved remarkably for detecting ISUP grade 2 or 3 prostate cancer (sensitivity, 88%) [49]. In the initial staging of high-risk prostate cancer prior to curative-intent therapy, results from the randomized phase III proPSMA trial suggested that ^{68}Ga-PSMA PET/CT is a suitable replacement for conventional imaging. ^{68}Ga-PSMA PET/CT provided greater accuracy (area under the curve, 92% versus 65%, $p<0.0001$) for detecting pelvic nodal or distant metastases and conferred management changes more frequently (28% versus 15%, $p=0.008$) and had less equivocal findings (7% versus 23%, $p<0.001$) than combined CT and bone scanning [50]. Similar findings were reported in several observational studies. ^{68}Ga-PSMA PET/CT was better than multi-parametric MRI in the overall staging of intermediate- and high-risk prostate cancer [51], particularly in the evaluation of lymph node metastases [52], extracapsular extension [53], and the delineation of intraprostatic tumour burden [54]. However, ^{68}Ga-PSMA PET/CT and multi-parametric MRI were comparable in the detection of seminal vesicle invasion [52,53]. ^{68}Ga-PSMA PET/CT was also capable of detecting bone metastases that were not evident on bone scintigraphy [38,55]. In all, ^{68}Ga-PSMA PET/CT findings led to a treatment change in 12.6% to 18.5% of patients [54,56]. At the time of biochemical recurrence, the sensitivity (76.4% to 99%) and specificity (31.2% to 100%) of ^{68}Ga-PSMA PET/CT for disease detection varied across studies [37,57-59]. Interestingly, one prospective study found that multi-parametric MRI offered better diagnostic accuracy for the detection of local recurrence (92.3% versus 77.8%) but ^{68}Ga-PSMA PET/CT was superior for the detection of distant and lymph node metastases (90.6% versus 72.0%) [60]. Overall, ^{68}Ga-PSMA PET/CT altered the therapeutic management of 22.6% to 73.1% of patients [39,61-63].

Pediatric Cancer

One study met the inclusion criteria [64]. In the initial staging of patients with non-Hodgkin lymphoma, Hodgkin lymphoma, Ewing sarcoma, and neuroblastoma, FDG PET/CT detected bone marrow involvement with better sensitivity (90.6% vs. 53.1%) and specificity (100% vs. 87.1%) than bone marrow biopsy.

Thoracic Cancer

Three studies met the inclusion criteria [65-67]. In patients with small cell lung cancer, FDG PET/CT was demonstrated to have triggered a change of binary staging in 15% of cases [65]. In early stage non-small cell lung cancer (NSCLC), FDG PET/CT showed good overall sensitivity (93.8%) but poor specificity 62.7%) in the assessment of mediastinal lymph node involvement [66]. As for patients with subsolid nodules with a solid portion of 3 cm or smaller, FDG PET/CT was significantly less accurate than chest CT (79.9% versus 93.9%, $p<0.0001$) in detecting lymph node metastases. Likewise, FDG PET/CT has limited utility in detecting intrathoracic or distant metastases [67].

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. It is of interest to note that the study by Jayalakshmi et al. [4] included a younger population, which is not seen in previous studies.

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

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

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 carcinoembryronic 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

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

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 (human papillomavirus [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 Hodgkin or non-Hodgkin lymphoma.
- For the assessment of response in Hodgkin lymphoma 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 Hodgkin or non-Hodgkin lymphoma 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.

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, it may be prudent to discuss the study by Hofman et al. [50] at a future PET Steering Committee meeting. This is an RCT with crossover design for high-risk prostate cancer staging comparing conventional imaging to PET where significant change in management was observed with PET. Also, it is probably not worth looking at $^{11}C/^{18}F$-choline or ^{18}F-FACBC for prostate cancer given the success of ^{68}Ga-PSMA agents going forward.

Pediatric Cancer

Current Indications for Pediatric Cancer (patients must be <18 years of age)

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

- Select optimal biopsy site

Reviewer's Comments (Dr. Amer Shammas)

The current recommendations for the utilization of PET/CT in pediatric cancer 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, please visit the OH (CCO) website at https://www.cancercareontario.ca/en or contact the PEBC office at: Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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Appendix 1: Summary of studies from January to June 2020.

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Breast Cancer								
Ozkan et al, 2019 [1]	Retrospective	192 patients who underwent initial staging (clinical stage IB-IIIA breast cancer)	FDG PET/CT	NA	Histopathology	**Axillary lymph node metastases** Sens: 78.8% Spec: 92.6% PPV: 93.3% NPV: 75.0% Accu: 83.7%	NA	NA
Mori et al, 2019 [2]	Retrospective	82 patients who underwent preoperative staging assessment (breast cancer)	FDG PET/CT with time-of-flight technique	NA	Pathology	**Axillary lymph node metastases** Sens: 85% Spec: 78% PPV: 42% NPV: 96% Accu: 79%	NA	NA
Chandra et al, 2020 [3]	Retrospective	158 patients who underwent preoperative staging (early breast cancer)	FDG PET/CT	Clinical examination, mammography	Histopathology, clinical follow-up	**Axillary lymph node metastases** Sens: 76% Spec: 97% PPV: 97% NPV: 76% Accu: 84% **Distant metastases** Sens: 100% Spec: 98% PPV: 88% NPV: 100% Accu: 99%	**Axillary lymph node metastases** Sens: 50% Spec: 94% PPV: 85% NPV: 73% Accu: 73%	NA
Epilepsy								
Jayalakshmi et al, 2019 [4]	Retrospective	188 patients who underwent epilepsy surgery (refractory epilepsy and type I or II focal cortical dysplasia)	FDG PET	Brain MRI, ictal SPECT	ILAE classification	**Seizure freedom** Sens: 78.2%	**Seizure freedom** ***Brain MRI*** Sens: 75.8% ***Ictal SPECT*** Sens: 71.8%	Localization on either PET, brain MRI or ictal SPECT achieved the highest sensitivity (97.5%) for seizure freedom.
Esophageal Cancer								
Gamal et al, 2019 [5]	Prospective	19 patients who underwent pre-operative staging (esophageal cancer)	FDG PET/CT	CeCT	Pathology	**Regional lymph node metastases** Sens: 68% Spec: 82% PPV: 68% NPV: 82%	**Regional lymph node metastases** Sens: 53% Spec: 95% PPV: 82% NPV: 80%	Compared with ceCT, PET/CT changed the stage group of 42.1% (8/19) of patients (6 upstaged, 2 downstaged).

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Accu: 79% **Distant metastases** Sens: 100% Spec: 83% PPV: 96% NPV: 100% Accu: 96%	Accu: 82% **Distant metastases** Sens: 73% Spec: 100% PPV: 100% NPV: 50% Accu: 79%	
Bhatnagar et al, 2019 [6]	Prospective	50 patients who underwent radiotherapy planning (previously untreated esophageal cancer)	FDG PET/CT	CeCT	Pre- and post-PET information	NA	NA	The addition of PET/CT changed the contouring and treatment planning of 70.0% (35/50) of patients.
Eyck et al, 2020 [7]	Meta-analysis	44 studies (patients with esophageal or esophagogastric junctional cancer who received neoadjuvant chemoradiotherapy)	FDG PET or PET/CT	Endoscopic biopsy, EUS	Histopathology	**Residual primary disease (qualitative)** Pooled Sens: 74% Pooled Spec: 52% **(SUVmax)** Pooled Sens: 69% Pooled Spec: 72% **(%ΔSUVmax)** Pooled Sens: 73% Pooled Spec: 63%	**Residual primary disease** ***Endoscopic biopsy*** Pooled Sens: 33% Pooled Spec: 95% ***EUS*** Pooled Sens: 96% Pooled Spec: 8% **Residual nodal disease** ***EUS*** Pooled Sens: 68% Pooled Spec: 57%	NA
de Gouw et al, 2019 [8]	Meta-analysis	56 studies (3625 patients with esophageal cancer who underwent restaging after neoadjuvant therapy but before surgery)	FDG PET/CT	CT, EUS, MRI	Histopathology	**Pathological complete response** Pooled Sens: 62% Pooled Spec: 73% Pooled +LR: 2.22	**Pathological complete response** ***CT*** Pooled Sens: 35% Pooled Spec: 83% Pooled +LR: 2.06 ***EUS*** Pooled Sens: 1% Pooled Spec: 99% Pooled +LR: 0.07 ***MRI*** Pooled Sens: 80% Pooled Spec: 83% Pooled +LR: 4.64	NA
Gastrointestinal Cancer								
Son and Kim, 2019 [9]	Meta-analysis	8 studies (1451 patients with incidental	FDG PET or PET/CT	NA	Colonoscopy	**Pre-malignant or malignant lesions** Pooled Sens: 87%	**NA**	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		colorectal focal FDG uptake)				Pooled Spec: 83% Pooled +LR: 5.2 Pooled –LR: 0.16 Pooled DOR: 32 AUC: 0.91		
Daza et al, 2019 [10]	Meta-analysis	13 studies (554 patients from RCTs and 2251 patients from observational studies with potentially resectable colorectal cancer liver metastases)	FDG PET or PET/CT	CT, MRI	Clinical follow-up	NA	NA	Based on two RCTs, the addition of PET or PET/CT changed surgical management in 8% of cases but did not significantly reduce futile laparotomies (RR=0.59, 95% CI, 0.24 to 1.47). Based on 8 observational studies, the addition of PET or PET/CT changed surgical management in 20% of cases while pooled data from 2 studies showed significantly reduced futile laparotomies (OR=0.51, 95% CI, 0.32 to 0.81).
Chalabi et al, 2020 [11]	Retrospective	100 patients who underwent follow-up after curative resection with or without chemoradiotherapy (suspected recurrent colorectal cancer)	FDG PET/CT	CeCT	Histopathology, cytology, clinical and imaging follow-up	**Local recurrence and metastases (lesion-based)** Sens: 95.6%* Spec: 91.4% PPV: 96.7% NPV: 88.9% Accu: 94.4%*	**Local recurrence and metastases (lesion-based)** Sens: 62.6%* Spec: 48.6% PPV: 76.0% NPV: 33.3% Accu: 58.0%*	NA
Hetta et al, 2020 [12]	Prospective	60 patients who underwent restaging and surveillance after therapy (colorectal cancer)	FDG PET/CT	CeCT	Histopathology	**Local recurrence** Sens: 95.5% Spec: 97.4% Accu: 96.7% **Hepatic metastases** Sens: 100% Spec: 100% Accu: 100% **Local nodal metastases** Sens: 100% Spec: 100% Accu: 100%	**Local recurrence** Sens: 95.0% Spec: 92.5% Accu: 93.3% **Hepatic metastases** Sens: 92.3% Spec: 95.7% Accu: 95.0% **Local nodal metastases** Sens: 77.8% Spec: 96.1% Accu: 93.3%	NA
Hetta and	Prospective	30 patients who	FDG PET/CT	Triphasic CT	Histopathology	**Local recurrence**	**Local recurrence**	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Atyia, 2020 [13]		underwent transarterial chemoembolization (hepatocellular carcinoma)			, imaging follow-up, serial AFP level monitoring	**and residual disease** Sens: 96.3% Spec: 66.7% PPV: 96.3% NPV: 66.7% Accu: 93.3%	**and residual disease** Sens: 74.0% Spec: 100% PPV: 100% NPV: 30.0% Accu: 76.7%	
Lim et al, 2019 [14]	Prospective	78 patients who underwent resection (hepatocellular carcinoma)	FDG PET/CT	CT, MRI	Histopathology, imaging follow-up	**Microvascular invasion (patient-based)** Sens: 62% Spec: 73% PPV: 53% NPV: 79% Accu: 69% **(lesion-based)** Sens: 62% Spec: 76% PPV: 53% NPV: 81% Accu: 71%	NA	NA
Bjerring et al, 2019 [15]	Phase II RCT (EUFURO)	183 patients randomized 1:1 to clinical assessment or clinical assessment plus imaging after surgery (adenocarcinomas in the GOJ, stomach or pancreas)	FDG PET/CT + EUS (n=90)	Clinical assessment (n=93)	Clinical follow-up	NA	NA	The addition of FDG PET/CT and EUS led to the detection of significantly more asymptomatic recurrences (33 vs. 0, p<0.001) and more patients referred for chemotherapy (25 vs. 14, p=0.028) within 2 years after surgery. However, FDG PET/CT and EUS did not significantly prolong the median recurrence-free survival (32 months; 95% CI, 14 to NR vs. 32 months; 95% CI, 17 to NR) or the median overall survival (46 months; 95% CI, 29 to NR vs. 36 months; 95% CI, 21 to 50).
Gynecologic Cancer								
Yu et al, 2019 [16]	Meta-analysis	14 studies (912 patients with cervical cancer)	FDG PET or PET/CT	NA	Histopathology	**Para-aortic lymph node metastases** Pooled Sens: 71%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Pooled Spec: 97% Pooled +LR: 21.53 Pooled –LR: 0.30 Pooled DOR: 70.59 AUC: 0.95		
Simonds et al, 2019 [17]	Retrospective /prospective	278 patients who underwent staging and deemed suitable for radical chemoradiation; 192 HIV-negative, 86 HIV-positive (locally advanced stage IIB-IIIB cervical cancer)	FDG PET/CT	Chest x-ray, abdominal US	Biopsy, further investigations	NA	NA	PET/CT upstaged 84.5% (235/278) of patients and changed treatment intent in 46.8% (124/268) of patients (27—to hypofractionated EBRT, 32—palliative EBRT, 65—to include extended field para-aortic node EBRT).
Hu et al, 2019 [18]	Meta-analysis	19 studies (1431 patients with endometrial cancer)	FDG PET or PET/CT	NA	Pathology	**Lymph node metastases (patient-based)** Pooled Sens: 68% Pooled Spec: 94% Pooled +LR: 9.26 Pooled –LR: 0.40 Pooled DOR: 28.81 AUC: 0.91 Q* index: 0.84 **(node-based)** Pooled Sens: 68% Pooled Spec: 96% Pooled +LR: 18.50 Pooled –LR: 0.40 Pooled DOR: 42.43 AUC: 0.82 Q* index: 0.75	NA	NA
Budak et al, 2019 [19]	Retrospective `	80 patients who underwent preoperative evaluation (endometrial cancer)	FDG PET/CT	NA	Histopathology	**Lymph node metastases (patient-based)** Sens: 80.0% Spec: 96.0% Accu: 95.0% **(node-based)** Sens: 78.9% Spec: 98.6% Accu: 97.4%	NA	NA
Stewart et al, 2019 [20]	Prospective	108 patients who underwent	FDG PET/CT	NA	Pathology	**Lymph node metastases**	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		preoperative PET/CT followed by surgery (newly diagnosed, high-risk endometrial cancer)				Sens: 45.8% Spec: 91.1% PPV: 61.1% NPV: 84.7% FNR: 54.2% **Peritoneal disease** Sens: 37.5% Spec: 97.8% PPV: 75.0% NPV: 90.0% FNR: 62.5%		
Head and Neck Cancer								
Ha et al, 2019 [21]	Prospective	95 patients who underwent restaging prior to salvage treatments (recurrent head and neck squamous cell carcinoma)	FDG PET/CT	Chest ceCT, bone scintigraphy	Histology, serial imaging follow-up	**Distant metastases (Lung)** Sens: 92.3% Spec: 100% PPV: 100% NPV: 97.2% Accu: 97.9% **(Mediastinal)** Sens: 72.7% Spec: 100% PPV: 100% NPV: 96.6% Accu: 96.8% **(Bone)** Sens: 100% Spec: 100% PPV: 100% NPV: 100% Accu: 100% **(Liver and other sites)** Sens: 100% Spec: 98.9% PPV: 66.7% NPV: 100% Accu: 98.9%	**Distant metastases (Lung)** ***Chest ceCT*** Sens: 100% Spec: 98.6% PPV: 96.3% NPV: 100% Accu: 98.9% **(Mediastinal)** ***Chest ceCT*** Sens: 72.7% Spec: 100% PPV: 100% NPV: 96.6% Accu: 96.8% **(Bone)** ***Bone scintigraphy*** Sens: 100% Spec: 98.8% PPV: 91.7% NPV: 100% Accu: 98.9%	NA
Li et al, 2019 [22]	Retrospective	82 patients who underwent response assessment following surgery and postoperative IMRT with or without	FDG PET/CT	NA	Clinical follow-up, consensus from multi-disciplinary tumour board	**Local recurrence** PPV: 100% NPV: 89.0% **Regional recurrence** PPV: 100% NPV: 89.2% **Distant metastases**	NA	The 3-year OS for patients with a negative post-treatment PET/CT was 89.9% compared to 11.2% for those with a positive PET/CT scan (p<0.001).

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		chemotherapy (head and neck squamous cell carcinoma)				PPV: 100% NPV: 85.9%		
Fatehi et al, 2019 [23]	Retrospective	75 patients who underwent response assessment post concurrent chemoradiotherapy followed by salvage neck dissection with or without primary site surgery (head and neck squamous cell carcinoma)	FDG PET/CT	FNAC	Histopathology	**Predicting residual disease** Sens: 89.3% Spec: 76.0% PPV: 87.5% NPV: 79.2%	NA	NA
Arunsingh et al, 2019 [24]	Retrospective	138 patients treated with radical radiotherapy (head and neck squamous cell carcinoma)	FDG PET/CT	NA	Pathology, clinical and imaging follow-up	**Response assessment** Sens: 78% Spec: 81% PPV: 72% NPV: 85% Accu: 80%	NA	NA
Herruer et al, 2020 [25]	Retrospective	62 patients with no obvious primary on clinical examination and ceCT who underwent partial oropharyngectomy and intraoperative assessment using transoral laser microsurgery (unknown primary head and neck squamous cell carcinoma)	FDG PET/CT	Clinical examination, ceCT	Histopathology	**Localizing the primary tumour** Sens: 50.9% Spec: 82.5%	NA	NA
Qichang et al, 2019 [26]	Meta-analysis	17 studies (1195 patients with thyroglobulin elevation and	FDG PET/CT	NA	Histopathology, clinical and imaging follow-up	**Recurrence and/or metastatic disease** Pooled Sens: 86% Pooled Spec: 84%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		negative iodine scintigraphy (differentiated thyroid cancer)				Pooled +LR: 5.20 Pooled –LR: 0.17 Pooled DOR: 31.00 AUC: 0.91		
Vera et al, 2019 [27]	Prospective	40 patients with positive thyroglobulin after thyroidectomy and negative iodine-131 whole body scintigraphy (well-differentiated thyroid carcinoma)	FDG PET/CT	DW-MRI, US	Histology, cytology, clinical and imaging follow-up	**Neck recurrence (Baseline)** Sens: 46% Spec: 50% PPV: 58% NPV: 38% Accu: 48% **(6 months)** Sens: 30% Spec: 53% PPV: 30% NPV: 53% Accu: 44% **(18 months)** Sens: 11% Spec: 69% PPV: 20% NPV: 53% Accu: 45%	**Neck recurrence (Baseline)** ***DW-MRI*** Sens: 43% Spec: 29% PPV: 45% NPV: 37% Accu: 41% ***US*** Sens: 38% Spec: 55% PPV: 69% NPV: 25% Accu: 43% **(6 months)** ***DW-MRI*** Sens: 20% Spec: 60% PPV: 25% NPV: 53% Accu: 44% ***US*** Sens: 33% Spec: 75% PPV: 63% NPV: 47% Accu: 52% **(18 months)** ***DW-MRI*** Sens: 10% Spec: 82% PPV: 33% NPV: 50% Accu: 48% ***US*** Sens: NA Spec: 69% PPV: NA NPV: 47% Accu: 39%	NA
Kong et al, 2019 [28]	Meta-analysis	38 studies (2871 patients with	FDG PET or PET/CT	US, CT, MRI, real-time	Histopathology , cytology,	**Differentiating between benign**	**Differentiating between benign**	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		salivary gland tumours)		elastography	surgical findings, clinical or imaging follow-up	**and malignant tumours** Pooled Sens: 81% Pooled Spec: 89% Pooled DOR: 20 AUC: 0.88	**and malignant tumours** ***US*** Pooled Sens: 66% Pooled Spec: 92% Pooled DOR: 23 AUC: 0.91 ***CT*** Pooled Sens: 70% Pooled Spec: 73% Pooled DOR: 6 AUC: 0.77 ***MRI*** Pooled Sens: 80% Pooled Spec: 90% Pooled DOR: 38 AUC: 0.92 ***Real-time elastography*** Pooled Sens: 80% Pooled Spec: 70% Pooled DOR: 10 AUC: 0.82	
Li et al, 2019 [29]	Meta-analysis	44 studies (3369 patients with local recurrent and residual nasopharyngeal carcinoma)	FDG PET or PET/CT	MRI	Biopsy, clinical follow-up	**Local recurrence and residual disease** Pooled Sens: 92% Pooled Spec: 89% Pooled +LR: 8.46 Pooled –LR: 0.09 Pooled DOR: 95.50 AUC: 0.96	**Local recurrence and residual disease** Pooled Sens: 83% Pooled Spec: 78% Pooled +LR: 3.79 Pooled –LR: 0.22 Pooled DOR: 17.55 AUC: 0.87	NA
Bae et al, 2020 [30]	Prospective	178 patients with negative palpation findings who underwent initial staging prior to surgery (oral cavity squamous cell carcinoma)	FDG PET/CT	CeCT/MRI	Histopathology	**Occult neck metastases (patient-based)** Sens: 69.1%* Spec: 77.9%* PPV: 49.2% NPV: 89.1% Accu: 75.8% AUC: 0.780* **(neck side-based)** Sens: 70.5%* Spec: 78.7%* PPV: 48.4% NPV: 90.4%	**Occult neck metastases (patient-based)** Sens: 35.7%* Spec: 89.0%* PPV: 50.0% NPV: 81.8% Accu: 76.4% AUC: 0.649* **(neck side-based)** Sens: 36.4%* Spec: 89.7%* PPV: 50.0% NPV: 83.2%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Accu: 76.9% AUC: 0.776* **(neck level-based)** Sens: 62.1%* Spec: 89.2%* PPV: 35.0% NPV: 96.2% Accu: 86.9%* AUC: 0.813*	Accu: 77.9% AUC: 0.652* **(neck level-based)** Sens: 29.3%* Spec: 96.8%* PPV: 46.0% NPV: 93.6% Accu: 91.0%* AUC: 0.629*	
Zhao et al, 2020 [31]	Prospective	135 patients who underwent preoperative PET/CT (early stage cT1-2N0 tongue squamous cell carcinoma)	FDG PET/CT	Clinical examination, US, CT, MRI	Pathology, clinical follow-up	**Occult neck lymph node metastases** Sens: 70.6% Spec: 94.9%	NA	NA
Hematologic Cancer								
Gocer et al, 2020 [32]	Retrospective	276 patients who underwent pre-therapy staging (newly diagnosed HL and NHL)	FDG PET/CT	BMB	BMB	**Bone marrow involvement (HL)** Sens: 83.3% Spec: 76.9% PPV: 35.7% NPV: 96.7% Accu: 77.7% **(Follicular lymphoma)** Sens: 31.5% Spec: 85.1% PPV: 60.0% NPV: 63.8% Accu: 63.0% **(DLBCL)** Sens: 36.8% Spec: 96.3% PPV: 63.6% NPV: 89.6% Accu: 87.4% **(Other NHL)** Sens: 52.9% Spec: 87.5% PPV: 85.7% NPV: 56.7% Accu: 67.2%	NA	NA
Stephens et al, 2019 [33]	Prospective (SWOG	331 patients who underwent	FDG PET/CT (Interim-PET	NA	Biopsy, clinical and	NA	NA	The 5-year PFS and OS for patients with negative

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
	S0816)	interim response assessment after 2 cycles of ABVD (advanced-stage HL)	negative patients continued with 4 additional cycles of ABVD. Interim-PET positive patients switched to 6 cycles of escalated BEACOPP)		imaging follow-up			interim-PET were 76% and 96%, respectively. The 5-year PFS and OS for patients with positive interim-PET who received escalated BEACOPP were 63% and 85%, respectively. Patients treated with escalated BEACOPP reported a significantly higher rate of second malignancies than those who received ABVD (14% vs. 2%; p=0.001).
Casasnovas et al, 2019 [34]	Phase III RCT (AHL2011)	821 randomized 1:1 to either standard treatment with 4 cycles of escalated BEACOPP or PET-driven treatment (newly diagnosed advanced HL)	FDG PET/CT (for the PET-driven treatment group, PET-positive patients after 2 cycles of escalated BEACOPP continued with 2 more cycles while PET-negative patients switched to ABVD for 2 cycles)	NA	Clinical follow-up	NA	NA	The 5-year PFS in the PET-driven group was non-inferior to that of the standard group (85.7% vs. 86.2%; HR=1.08; 95% CI, 0.74 to 1.60; non-inferiority=0.65). The 5-year OS was 95.2% in the standard group and 96.4% in the PET-driven group (HR=0.94; 95% CI, 0.43 to 2.05; p=0.43). The 5-year event-free survival was 76.8% in the standard group and 78.6% in the PET-driven group (HR=0.93; 95% CI, 0.69 to 1.25; p=0.31). The 5-year disease-free survival was 89.9% in the standard group and 90.0% in the PET-driven group (HR=1.10; 95% CI, 0.67 to 1.71; p=0.66).
Dlugosz-Danecka et al, 2019 [35]	Retrospective	188 patients who underwent response assessment after 2 cycles of escalated BEACOPP	FDG PET/CT (interim-PET negative patients switched to 4 cycles of ABVD while	NA	Clinical follow-up	NA	NA	The 10-year PFS and OS for patients with interim-negative PET were 87.2% and 95%, respectively. The 10-year PFS and OS for patients with interim-positive PET were 55.3%

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		(previously untreated, advanced-stage HL)	interim-PET positive patients continued with 4 additional cycles of escalated BEACOPP; consolidation IFRT was allowed in patients with stage IIBX)					and 72.3%, respectively. Grade 3 or 4 febrile neutropenia (53.2% vs. 5.0%; p<0.001), anemia (74.5% vs. 7.8%; p<0.001), thrombocytopenia (34.0% vs. 5.0%; p<0.001), and pulmonary embolism (6.4% vs. 0%; p=0.02) occurred significantly more in patients with interim-positive PET.
Pavlovsky et al, 2019 [36]	Prospective (GATLA LH-05)	377 patients who underwent response assessment after 3 cycles of ABVD (newly diagnosed stage I-IV classical HL)	FDG PET/CT (interim-PET negative patients received no further therapy while interim-PET positive patients received 3 additional cycles of ABVD + IFRT or salvage treatment with ICE/ESHAP)	NA	Clinical follow-up	NA	NA	The 3-year PFS (90% vs. 65%; p<0.0001) and OS (98% vs. 92%; p=0.007) for patients with interim-negative PET were significantly higher than those with interim-positive PET.
Non-FDG Tracers $^{11}C/^{18}F$-Choline								
Sathianathen et al, 2019 [37]	Meta-analysis	21 studies (3202 patients with evidence of biochemical recurrent prostate cancer)	^{11}C-Choline PET/CT	NA	Histopathology, further imaging and/or clinical follow-up	**Recurrence (patient-based)** Pooled Sens: 80.9% Pooled Spec: 84.1% Pooled +LR: 5.4 Pooled -LR: 0.24 Pooled DOR: 25.2	NA	NA
Zhou et al, 2019 [38]	Meta-analysis	24 studies (1732 patients with prostate cancer)	$^{11}C/^{18}F$-Choline PET/CT	MRI, bone scintigraphy	Histopathology, biopsy, imaging findings,	**Bone metastases (patient-based)** Pooled Sens: 87% Pooled Spec: 99%	**Bone metastases (patient-based)** ***MRI*** Pooled Sens: 91%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
					clinical follow-up	Pooled DOR: 504.16 AUC: 0.99 **(lesion-based)** Pooled Sens: 80%	Pooled Spec: 96% Pooled DOR: 242.63 AUC: 0.98 ***Bone scintigraphy*** Pooled Sens: 86% Pooled Spec: 95% Pooled DOR: 114.44 AUC: 0.95 **(lesion-based)** ***MRI*** Pooled Sens: 81% Bone scintigraphy Pooled Sens: 68%	
Emmett et al, 2019 [39]	Prospective	91 patients with rising PSA levels after radical prostatectomy and negative or equivocal CT and bone scan who were being considered for salvage radiotherapy (recurrent prostate cancer)	^{18}F-FCH PET/CT	CT, bone scan, pelvic MRI	Biopsy, targeted treatment response, pre- and post-PET questionnaire	**Extraprostatic fossa disease** Sens: 47.8% Spec: 97.0% PPV: 91.7% NPV: 73.9%	**Extraprostatic fossa disease** Sens: 19.0% Spec: 97.0% PPV: 80.0% NPV: 66.0%	^{18}F-FCH PET/CT changed patient management more often than pelvic MRI (46.2% vs. 23.9%, p<0.003).
^{68}Ga-DOTA-(TATE, NOC, TOC)								
Chan et al, 2019 [40]	Retrospective	90 patients with 110 lesions (NETs)	^{68}Ga-DOTA-TOC PET/CT or PET/MRI	NA	Biopsy	**Diagnosis (lesion-based)** Sens: 92.7% Spec: 100%	NA	NA
Crown et al, 2020 [41]	Retrospective	101 patients (moderately or well-differentiated NETs)	^{68}Ga-DOTA-TATE PET/CT	CT, MRI, ^{111}In-pentetreotide	Pre- and post-PET information	NA	NA	^{68}Ga-DOTA-TATE PET/CT altered management in 35.6% (36/101) of patients (14—initiated systemic therapy, 4—biopsy cancelled, 3—hepatic surgery altered or hepatic ablation added, 4—surgery deferred, 11—influenced decision regarding the use of PRRT and somatostatin analogs).
De Dosso et	Meta-analysis	12 studies (383	^{68}Ga-DOTA-	Somatostatin	Histology,	**Localization**	NA	The pooled proportion of

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
al, 2019 [42]		patients with metastatic NETs and unknown primary)	TATE/TOC/NOC PET/CT	receptor scintigraphy	imaging or clinical/biochemical follow-up	Pooled DR: 56%		change in patient management due to ^{68}Ga-DOTA-TATE/TOC/NOC PET/CT was 20%.
Arora et al, 2019 [43]	Prospective	90 patients referred for staging or restaging (suspected or histology proven paraganglioma)	^{68}Ga-DOTA-NOC PET/CT	I-131 MIBG SPECT/CT, I-131 MIBG planar scintigraphy, US, CeCT, MRI, digital subtraction angiography	Histopathology, combination of characteristic imaging findings, biochemical parameters, and imaging follow-up	**Staging or restaging (patient-based)** Sens: 97.3%* Spec: 93.7% PPV: 98.6% NPV: 88.2% Accu: 96.6% **(lesion-based)** Sens: 97.7%* Spec: 94.4%* PPV: 99.2% NPV: 85.0% Accu: 97.3%	**Staging or restaging (patient-based)** ***I-131 MIBG SPECT/CT*** Sens: 43.2%* Spec: 100% PPV: 100% NPV: 27.5% Accu: 53.3% ***I-131 MIBG planar scintigraphy*** Sens: 36.4%* Spec: 100% PPV: 100% NPV: 25.4% Accu: 47.7% **(lesion-based)** ***I-131 MIBG SPECT/CT*** Sens: 38.9%* Spec: 100% PPV: 100% NPV: 18.3% Accu: 46.3% ***I-131 MIBG planar scintigraphy*** Sens: 34.3%* Spec: 100% PPV: 100% NPV: 17.3% Accu: 42.2% ***US, CeCT, MRI, and digital subtraction angiography*** **(lesion-based)** Sens: 94.5% Spec: 33.3%* PPV: 89.7% NPV: 50.0% Accu: 86.1%	NA
Amyloid								
Spallazzi et	Prospective	104 patients who	^{18}F-	Neurological	Consensus	NA	NA	^{18}F-florbetaben PET

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
al, 2019 [44]		underwent a standardized diagnostic workup for cognitive disorders (mild cognitive impairment and dementia)	florbetaben PET	and physical examination, blood tests, MRI, comprehensive neuropsychological assessment	from multidisciplinary meeting, pre- and post-PET information			changed the initial diagnosis of 17.3% (18/104) of patients and impacted medication plan in 6.7% (7/104) of patients.
18F-NaF								
Zhou et al, 2019 [38]	Meta-analysis	24 studies (1732 patients with prostate cancer)	^{18}F-NaF PET/CT	MRI, bone scintigraphy	Histopathology, biopsy, imaging findings, clinical follow-up	**Bone metastases (patient-based)** Pooled Sens: 96% Pooled Spec: 97% Pooled DOR: 673.67 AUC: 0.99 **(lesion-based)** Pooled Sens: 97%	**Bone metastases (patient-based)** ***MRI*** Pooled Sens: 91% Pooled Spec: 96% Pooled DOR: 242.63 AUC: 0.98 ***Bone scintigraphy*** Pooled Sens: 86% Pooled Spec: 95% Pooled DOR: 114.44 AUC: 0.95 **(lesion-based)** ***MRI*** Pooled Sens: 81% ***Bone scintigraphy*** Pooled Sens: 68%	NA
Liu et al, 2019 [45]	Meta-analysis	7 studies (368 patients bone metastases)	^{18}F-NaF PET/CT	^{99m}Tc-MDP bone scintigraphy	Histopathology, clinical or imaging follow-up	**Bone metastases (equivocal results as negative)** Pooled Sens: 88%* Pooled Spec: 96% Pooled +LR: 14.68 Pooled –LR: 0.16 Pooled DOR: 159.56 AUC: 0.978 Q index: 0.934 **(equivocal results as positive)** Pooled Sens: 92%* Pooled Spec: 92%* Pooled +LR: 8.40 Pooled –LR: 0.12 Pooled DOR: 105.41 AUC: 0.969 Q index: 0.918	**Bone metastases (equivocal results as negative)** Pooled Sens: 65%* Pooled Spec: 91% Pooled +LR: 7.34 Pooled –LR: 0.40 Pooled DOR: 22.14 AUC: 0.873 Q index: 0.804 **(equivocal results as positive)** Pooled Sens: 71%* Pooled Spec: 77%* Pooled +LR: 2.67 Pooled –LR: 0.41 Pooled DOR: 8.33 AUC: 0.800 Q index: 0.736	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
^{18}F-FACBC								
Bin et al, 2020 [46]	Meta-analysis	9 studies (363 patients with prostate cancer)	^{18}F-FACBC PET/CT	NA	Not specified	**Primary lesions and metastases** Pooled Sens: 88% Pooled Spec: 73% Pooled +LR: 3.3 Pooled –LR: 0.17 Pooled DOR: 20 AUC: 0.86	NA	NA
Kim and Lee, 2019 [47]	Meta-analysis	13 studies (563 patients with prostate cancer)	^{18}F-FACBC PET/CT or PET/MRI	NA	Not specified	**Diagnosis** Pooled Sens: 87% Pooled Spec: 84% Pooled +LR: 5.3 Pooled –LR: 0.16 Pooled DOR: 34 AUC: 0.92 **Preoperative lymph node staging** Pooled Sens: 56% Pooled Spec: 98% Pooled +LR: 19.3 Pooled –LR: 0.48 Pooled DOR: 44 **Recurrence** Pooled Sens: 79% Pooled Spec: 69% Pooled +LR: 2.5 Pooled –LR: 0.3 Pooled DOR: 9 AUC: 0.75	NA	NA
Sathianathen et al, 2019 [37]	Meta-analysis	21 studies (3202 patients with evidence of biochemical recurrent prostate cancer)	^{18}F-FACBC PET/CT	NA	Histopathology, further imaging and/or clinical follow-up	**Recurrence (patient-based)** Pooled Sens: 79.7% Pooled Spec: 61.9% Pooled +LR: 2.1 Pooled –LR: 0.36 Pooled DOR: 8.0 **(lesion-based)** Pooled Sens: 62.7% Pooled Spec: 69.8%	NA	NA
^{68}Ga-PSMA								
Zhang et al, 2019 [48]	Retrospective	58 patients with total PSA levels of 0.4-50 ng/ml and prostate volume between 10 and	^{68}Ga-PSMA PET/CT	TRUS-guided biopsy	Histopathology, clinical and imaging follow-up	**Diagnosis** Sens: 91.7% Spec: 81.8% PPV: 89.2% NPV: 85.7%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		110 ml (suspected prostate cancer)				AUC: 0.867		
Scheltema et al, 2019 [49]	Retrospective	54 patients who underwent imaging prior to radical prostatectomy (intermediate-grade, ISUP grades 2 or 3, prostate cancer)	^{68}Ga-PSMA PET/CT	mpMRI	Histopathology	**Diagnosis** **ISUP grade 1** Sens: 18% Spec: 97% PPV: 63% NPV: 79% AUC: 0.57 **ISUP grade 2 or 3** Sens: 88% Spec: 93% PPV: 85% NPV: 95% AUC: 0.91	**Diagnosis** **ISUP grade 1** **(PI-RADS 3-5 as positive)** Sens: 10% Spec: 91% PPV: 25% NPV: 76% AUC: 0.50 **(PI-RADS 4-5 as positive)** Sens: 7% Spec: 98% PPV: 50% NPV: 77% AUC: 0.52 **ISUP grade 2 or 3** **(PI-RADS 3-5 as positive)** Sens: 68% Spec: 91% PPV: 75% NPV: 87% AUC: 0.79 **(PI-RADS 4-5 as positive)** Sens: 56% Spec: 97% PPV: 88% NPV: 84% AUC: 0.76	NA
Hofman et al, 2020 [50]	Phase III RCT (proPSMA)	302 patients randomized 1:1 to conventional imaging or PET/CT before curative-intent surgery or radiotherapy (high-risk prostate cancer)	^{68}Ga-PSMA-11 PET/CT	CT, bone scan	Histopathology, clinical and imaging follow-up	**Pelvic nodal or distant metastases** Sens: 85% Spec: 98% Accu: 94% AUC: 92%*	**Pelvic nodal or distant metastases** Sens: 38% Spec: 91% Accu: 75% AUC: 65%*	^{68}Ga-PSMA-11 PET/CT conferred management change more frequently (28% vs. 15%, p=0.008) and had less equivocal findings (7% vs. 23%, p<0.001) than conventional imaging.
Pallavi et al, 2020 [51]	Prospective	35 patients who were planned for radical	^{68}Ga-PSMA-11 PET/CT	mpMRI	Surgical histopathology	**Staging** Sens: 86.2% Spec: 94.7%	**Staging** Sens: 68.6% Spec: 89.1%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		prostatectomy (intermediate- and high-risk prostate cancer)						
van Leeuwen et al, 2019 [52]	Retrospective	140 patients who were candidates for radical prostatectomy with ePLND (intermediate- and high-risk prostate cancer)	^{68}Ga-PSMA PET/CT	mpMRI	Histopathology	**Seminal vesicle invasion** Sens: 46% Spec: 93% PPV: 74% NPV: 80% **Lymph node metastases** Sens: 53% Spec: 88% PPV: 71% NPV: 76%	**Seminal vesicle invasion** Sens: 65% Spec: 95% PPV: 85% NPV: 86% **Lymph node metastases** Sens: 14% Spec: 99% PPV: 88% NPV: 67%	NA
Chen et al, 2020 [53]	Retrospective	54 patients without lymph node or bone metastases who underwent primary staging prior to radical prostatectomy (prostate cancer)	^{68}Ga-PSMA PET/CT	mpMRI	Pathology	**Extracapsular extension** Sens: 78%* Spec: 94% PPV: 97% NPV: 67% **Seminal vesicle invasion** Sens: 75% Spec: 95% PPV: 82% NPV: 93%	**Extracapsular extension** Sens: 54%* Spec: 94% PPV: 95% NPV: 48% **Seminal vesicle invasion** Sens: 67% Spec: 93% PPV: 72% NPV: 91%	The addition of ^{68}Ga-PSMA PET/CT converted 18.5% (10/54) of patients from nerve-sparing surgery to non-nerve sparing surgery.
Bettermann et al, 2019 [54]	Prospective	17 patients who underwent delineation of intraprostatic tumour burden prior to prostatectomy (prostate cancer)	^{68}Ga-PSMA-11 PET/CT	mpMRI	Histopathology	**Gross tumour volume delineation (quadrant-based)** Sens: 86.0% Spec: 87.0% Accu: 86.5%	**Gross tumour volume delineation (quadrant-based)** Sens: 58.0% Spec: 94.0% Accu: 74.7%	NA
Zhou et al, 2019 [38]	Meta-analysis	24 studies (1732 patients with prostate cancer)	^{68}Ga-PSMA PET/CT	MRI, bone scintigraphy	Histopathology, biopsy, imaging findings, clinical follow-up	**Bone metastases (patient-based)** Pooled Sens: 97% Pooled Spec: 100% Pooled DOR: NA AUC: 1.00 **(lesion-based)** Pooled Sens: 88%	**Bone metastases (patient-based)** ***MRI*** Pooled Sens: 91% Pooled Spec: 96% Pooled DOR: 242.63 AUC: 0.98 ***Bone scintigraphy*** Pooled Sens: 86% Pooled Spec: 95%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
							Pooled DOR: 114.44 AUC: 0.95 **(lesion-based)** ***MRI*** Pooled Sens: 81% Bone scintigraphy Pooled Sens: 68%	
Zacho et al, 2020 [55]	Retrospective	112 patients who underwent primary staging (newly diagnosed intermediate- to high-risk prostate cancer)	^{68}Ga-PSMA PET/CT	^{99m}Tc bone scintigraphy	All available imaging results, clinical/laboratory and imaging follow-up	**Bone metastases (equivocal results as negative)** Sens: 100% Spec: 96% PPV: 81% NPV: 100% **(equivocal results as negative)** Sens: 100% Spec: 93% PPV: 74% NPV: 100%	NA	NA
van Kalmthout et al, 2020 [56]	Prospective	103 patients who were at greater than 10% MSKCC risk for lymph node metastasis and considered candidates for ePLND (newly diagnosed prostate cancer and negative bone scintigraphy)	^{68}Ga-PSMA PET/CT	Bone scintigraphy	Histopathology, clinical follow-up	**Lymph node metastases (patient-based)** Sens: 41.5% Spec: 90.9% PPV: 77.3% NPV: 67.6% **(template-based)** Sens: 35.1% Spec: 96.4% PPV: 64.5% NPV: 89.0%	NA	^{68}Ga-PSMA PET/CT findings led to a treatment change in 12.6% (13/103) of patients (6—ePLND template extended, 6—ePLND cancelled, 1—ADT and radiotherapy administered following ePLND).
Sathianathen et al, 2019 [37]	Meta-analysis	21 studies (3202 patients with evidence of biochemical recurrent prostate cancer)	^{68}Ga-PSMA PET/CT	NA	Histopathology, further imaging and/or clinical follow-up	**Recurrence (lesion-based)** Pooled Sens: 76.4% Pooled Spec: 99.8%	NA	NA
Lawhn-Heath et al, 2019 [57]	Prospective	72 patients who underwent radiation therapy or prostatectomy (biochemically recurrent prostate cancer)	^{68}Ga-PSMA-11 PET/CT	CT, MRI	Histopathology, clinical and imaging follow-up	**Recurrence** Sens: 89.1% Spec: 31.2% PPV: 90.6% NPV: 24.7%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Hope et al, 2019 [58]	Meta-analysis	20 studies (522 patients with prostate cancer)	^{68}Ga-PSMA-11 PET/CT	NA	Pathology	**Staging** Pooled Sens: 74% Pooled Spec: 96% Pooled PPV: 93% Pooled NPV: 85% Pooled Accu: 86% **Restaging** Pooled Sens: 99% Pooled Spec: 76% Pooled PPV: 99% Pooled NPV: 76% Pooled Accu: 98%	NA	NA
Hamed et al, 2019 [59]	Prospective	188 patients with rising PSA serum levels after definitive primary therapy (prostate cancer)	^{68}Ga-PSMA PET/CT	NA	Histopathology, clinical and imaging follow-up	**Recurrence** Sens: 98.8% Spec: 100% PPV: 100% NPV: 91.3% Accu: 98.8%	NA	NA
Radzina et al, 2020 [60]	Prospective	32 patients treated with radical prostatectomy and/or radiotherapy (biochemically recurrent prostate cancer)	^{68}Ga-PSMA-11 PET/CT	mpMRI, bone scintigraphy	Histopathology, additional radiological examination, follow-up, opinion on multidisciplinary team meeting	**Local recurrence** Sens: 63.6% Spec: 73.7% PPV: 58.3% NPV: 77.8% Accu: 77.8% **Lymph node metastases** Sens: 83.3% Spec: 80.0% PPV: 80.0% NPV: 100% Accu: 90.6% **Bone metastases** Sens: 83.3% Spec: 92.0% PPV: 71.4% NPV: 95.8% Accu: 71.0%	**Local recurrence** ***mpMRI*** Sens: 90.9% Spec: 94.7% PPV: 90.9% NPV: 94.7% Accu: 92.3% **Lymph node metastases** Sens: 41.7% Spec: 94.4% PPV: 83.3% NPV: 70.8% Accu: 72.0% **Bone metastases** ***Bone scintigraphy*** Sens: 50.0% Spec: 84.0% PPV: 42.8% NPV: 87.5% Accu: 77.4%	NA
Emmett et al, 2019 [39]	Prospective	91 patients with rising PSA levels after radical prostatectomy and negative or equivocal CT and	^{68}Ga-HBED-CC PSMA-11 PET/CT	CT, bone scan, pelvic MRI	Biopsy, targeted treatment response, pre- and post-PET questionnaire	**Extraprostatic fossa disease** Sens: 66.7% Spec: 100% PPV: 100% NPV: 50.0%	**Extraprostatic fossa disease** Sens: 19.0% Spec: 97.0% PPV: 80.0% NPV: 66.0%	^{68}Ga-HBED-CC PSMA-11 PET/CT changed the management of 22.6% (7/31) of patients.

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		bone scan who were being considered for salvage radiotherapy (recurrent prostate cancer)						
Schmidt-Hegemann et al, 2019 [61]	Retrospective	172 patients who underwent staging or restaging before radiotherapy (prostate cancer)	^{68}Ga-PSMA PET/CT	CT	Consensus pre- and post-PET information	NA	NA	^{68}Ga-PSMA PET/CT and CT findings resulted in an intensification of treatment in 62.2% (107/172) and 39.5% (68/172) of patients, respectively.
Rousseau et al, 2019 [62]	Prospective	52 patients with PSA level ≤1.5 ng/mL and normal or equivocal pelvic mpMRI and bone scan after radical prostatectomy (occult biochemical relapse of prostate cancer)	^{68}Ga-PSMA PET/CT	Pelvic mpMRI, bone scan	Clinical follow-up, pre- and post-scan decisions from multidisciplinary meetings	NA	NA	^{68}Ga-PSMA PET/CT changed the therapeutic management of 73.1% (38/52) of patients.
Muller et al, 2019 [63]	Retrospective	223 patients who underwent staging (recurrent prostate cancer)	^{68}Ga-PSMA-11 PET/CT or PET/MRI	PSA levels, initial tumour stage, resection margins, previous treatment according to guidelines	Clinical follow-up, pre- and post-PET information	NA	NA	^{68}Ga-PSMA-11 PET/CT or PET/MRI changed management in 60.1% (122/203) of patients.
Pediatric Cancer								
Yagci-Kupeli et al, 2019 [64]	Retrospective	94 newly diagnosed patients who underwent initial staging (36 NHL, 27 HL, 16 Ewing sarcoma, 15 neuroblastoma)	FDG PET/CT	BMB	Histopathology, follow-up studies	**Bone marrow involvement** Sens: 90.6% Spec: 100% PPV: 100% NPV: 95.4%	**Bone marrow involvement** Sens: 53.1% Spec: 87.1% PPV: 94.4% NPV: 80.6%	NA
Thoracic Cancer								
Martucci et	Meta-analysis	6 studies (277	FDG PET/CT	CT, bone	Histology,	NA	NA	PET/CT changed the

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
al, 2020 [65]		patients with SCLC)		scintigraphy	further imaging, clinical or biochemical follow-up			overall stage of 15% of patients.
Smith et al, 2019 [66]	Retrospective	234 patients who underwent non-invasive imaging prior to surgical staging by video-assisted mediastinoscopy (NSCLC)	FDG PET/CT	Video-assisted mediastinoscopy	Histopathology	**Mediastinal lymph node involvement** Sens: 93.8% Spec: 62.7% PPV: 57.1% NPV: 95.1%	NA	NA
Suh et al, 2020 [67]	Retrospective	855 patients who underwent preoperative staging (subsolid NSCLC with a solid portion diameter of 3cm or smaller on CT)	FDG PET/CT	Chest CT	Pathology	**Lymph node metastases** Sens: 44.0%* Spec: 81.5%* PPV: 9.6% NPV: 97.0% Accu: 79.9%* **Intrathoracic or distant metastases** Sens: 0% Spec: 99.3% PPV: 0% NPV: 99.7% Accu: 99.0%	**Lymph node metastases** Sens: 12.0%* Spec: 97.5%* PPV: 17.7% NPV: 96.1% Accu: 93.9%* **Intrathoracic or distant metastases** Sens: 0% Spec: 99.8% PPV: 0% NPV: 99.7% Accu: 99.5%	NA
Various Sites								
Wu et al, 2019 [68]	Retrospective	97 Chinese patients who underwent percutaneous core-needle biopsy followed by tumour resection (bone tumours and tumour-like lesions)	FDG PET/CT-guided biopsy	CT-guided biopsy	Surgical histopathology	**Diagnosis** Accu: 97.6%*	**Diagnosis** Accu: 76.4%*	There was no significant difference in complication rate between PET/CT-guided biopsy and CT-guided biopsy ($p>0.05$). However, a significant difference in the average cost of bone biopsy was noted between the two groups ($p<0.001$).

*$p<0.05$

Abbreviations: ABVD, adriamycin, bleomycin, vinblastine, and dacarbazine combination therapy; **Accu**, accuracy; **ADT**, androgen deprivation therapy; **AFP**, alfa feto protein; **AUC**, area under the curve; **BEACOPP**, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; **BMB**, bone marrow biopsy; **^{11}C-Choline**, carbon-11-choline contrast; **CeCT**, contrast-enhanced computed tomography; **CI**, confidence interval; **CT**, computed tomography; **DLBCL**, diffuse large B-cell lymphoma; **DOR**, duration of response; **DR**, detection rate; **DWI-MRI**, diffusion-weighted magnetic resonance imaging; **EBRT**, external beam radiotherapy; **ePLND**, extended pelvic lymph node dissection; **ESHAP**, etoposide plus methylprednisone, cytarabine and cisplatin; **EUS**, Endoscopic ultrasound; **^{18}F-Choline**, fluoromethylcholine; **FDG**, fluorodeoxyglucose; **^{18}F-FACBC**, anti1-amino-3-(18)F-fluorocyclobutane-1-carboxylic acid; **^{18}F-FCH**, ^{18}F-fluorocholine; **^{18}F-FDG**, fluorine-18-fluorodeoxyglucose; **FNAC**, fine needle aspiration cytology; **^{18}F-**

NaF, fluorine 18–sodium fluoride; **^{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; **GOJ,** gastro-esophageal junction; **HIV**, human immunodeficiency virus; **HL**, Hodgkin lymphoma; **HR**, hazard ratio; **ICE**, ifosfamide plus carboplatin and etoposide; **IFRT**, involved-field radiation therapy; **ILAE**, International League Against Epilepsy; **IMRT**, intensity-modulated radiation therapy; **ISUP**, International Society of Urological Pathology; **I-131-MIBG**, I-Metaiodobenzylguanidine labelled with Iodine-131; **+LR**, positive likelihood ratio; **-LR**, negative likelihood ratio; **mpMRI**, multi-parametric magnetic resonance imaging; **MRI**, magnetic resonance imaging; **MSKCC**, Memorial Sloan Kettering Cancer Center; **99mTc**, technetium; **99mTc-MDP**, technetium 99m-methyl diphosphonate; **NA**, not applicable; **NETs**, neuroendocrine tumours; **NHL**, non-Hodgkin lymphoma; **NPV**, negative predictive value; **NR**, not reported; **NSCLC**, non-small-cell lung carcinoma; **OR**, odds ratio; **OS**, overall survival; **PET**, positron emission tomography; **PFS**, progression free survival; **PI-RADS**, Prostate Imaging Reporting and Data System; **PPV**, positive predictive value; **PRRT**, peptide receptor radionuclide therapy; **PSA**, prostate specific antigen; **RCT**, randomized controlled trial; **RR**, relative risk; Sens, sensitivity; **SCLC**, small cell lung cancer; **Spec**, specificity; **SPECT**, single-photon emission computed tomography; **SUV**, standardized uptake value; **US**, ultrasound; **vs**, versus