PET Six-Month Monitoring Report 2021-2

Evidence from Primary Studies and Systematic Reviews and Recommendations from Clinical Practice Guidelines July to December 2021

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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 22nd 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 2021 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

One hundred studies published between July and December 2021 met the inclusion criteria. A summary of the evidence from the 100 studies can be found in **Appendix 1: Summary of studies from July to December 2021**.

Breast Cancer

Ten studies met the inclusion criteria [1-10]. In the preoperative staging of patients with breast cancer, FDG PET or PET/CT detected axillary lymph node metastases with a sensitivity of 77.8% to 96.2% and a specificity of 20.0% to 90.8% across multiple studies [1-4]. In the same way, ultrasound (US) demonstrated a sensitivity of 72.2% to 100% and a specificity of 0% to 75.4% [1-3], whereas magnetic resonance imaging (MRI) with or without contrast enhancement displayed a sensitivity of 72.2% to 86.6% and a specificity of 71.6% to 86.2% [1,3]. The same measures regarding US-guided fine needle aspiration for detecting axillary lymph node metastases were 91.7% and 87.5%, respectively [4]. In all studies, a significant difference in diagnostic performance was not detected between FDG PET or PET/CT and other imaging modalities. In the post-neoadjuvant chemotherapy axillary assessment, the sensitivity and specificity were 47.5% and 76.7%, respectively, for FDG PET/CT, 59.4% and 82.4%, respectively, for US, and 36.7% and 77.8%, respectively, for MRI [5]. For the detection of extra-axillary nodal metastases, US (98.2%) yielded the highest accuracy for supraclavicular nodal metastases, followed by FDG PET/CT (88.6%) and CT (61.7%) [6]. On the other hand, MRI (100%) had the highest accuracy for internal mammary nodal metastases, followed by FDG PET/CT (96.8%), US (93.2%), and CT (62.7%) [6]. In another study, FDG PET/CT upstaged 37.2% of patients by detecting more extensive nodal disease and distant metastases [7]. However, FDG PET/CT inadequately staged 22.9% of patients with grade 1 to 2 estrogen receptor-positive, clinical stage IIB/III disease [8]. For the evaluation of early response to radiation therapy, FDG PET/CT was inferior to MRI in predicting pathologic response [9]. In patients with clinically suspected recurrent disease, both FDG PET/CT (91%) and contrast-enhanced CT (90%) exhibited high accuracy for the detection of distant metastases [10].

Epilepsy

Four studies met the inclusion criteria [11-14]. In the presurgical evaluation of adult refractory epilepsy, FDG PET/MRI identified the actual resection location in seizure-free patients with a sensitivity of 95.3%, a specificity of 8.8%, and an accuracy of 65.3% [11]. Furthermore, FDG PET/MRI findings altered the therapeutic decision-making of 31.7% of cases in one study [12] and helped guide stereo-electroencephalography implantation to locate the seizure onset zone in 83.3% of cases in another (of which 73.8% achieved complete seizure-free status) [13]. Similarly in pediatric patients with normal or inconclusive MRI, the addition of FDG PET/CT impacted decision-making in 55.5% of cases [14].

Esophageal Cancer

Three studies met the inclusion criteria [15-17]. In patients undergoing neoadjuvant chemoradiotherapy, an early FDG PET or PET/CT response assessment showed moderately high sensitivity (pooled estimate, 80%) but limited specificity (pooled estimate, 54%) for a pathologic response [15]. In the randomized, phase II CALGB 80803 trial, early response assessment with FDG PET/CT after induction chemotherapy allowed non-responders to switch to the alternative chemotherapy regimen with improved pathologic complete response. PET non-responders after induction oxaliplatin, leucovorin, and fluorouracil (FOLFOX) who crossed over to carboplatin-paclitaxel (CP) achieved a pathologic complete response rate of 18.0% while those who switched

from CP to FOLFOX achieved a pathologic response rate of 20.0% [16]. In one large retrospective study with 9078 patients with nonmetastatic disease, FDG PET or PET/CT for initial staging was associated with a significantly lower risk of death as compared with those without FDG PET or PET/CT (hazard ratio, 0.74; 95% confidence interval, 0.70 to 0.79, $p<0.001$) [17].

Gastrointestinal Cancer

Ten studies met the inclusion criteria [18-27]. In the preoperative staging of colorectal cancer, the diagnostic performance of FDG PET/CT (accuracy, 73.6%), contrast-enhanced CT (accuracy, 70.0%), and contrast-enhanced MRI (accuracy, 68.6%) for detecting regional lymph node metastases were comparable [18]. However, FDG PET/CT failed to detect metastatic lymph nodes that were not evident on contrast-enhanced CT [19]. In patients with mucinous colorectal liver metastases, staging FDG PET/CT had a significant rate of false negative results for identifying hepatic and extrahepatic metastases [20]. In a multicentre RCT that compared FDG PET/CT surveillance to conventional follow-up for patients with stage II or III colorectal cancer treated with curative surgery with or without adjuvant chemotherapy, the three-year disease-free survival (74.2% versus 82.0%, respectively, $p=0.063$), five-year overall survival (83.7% versus 84.6%, respectively, $p=0.73$), and rate of surgically treated recurrence (36.2% versus 22.5%, respectively, $p=0.25$) did not differ significantly between the two groups. However, the three-year disease-free cancer survival was significantly higher in conventional follow-up than in FDG PET/CT follow-up (79.6% versus 71.0%, respectively, $p=0.038$) [21]. In patients with locally advanced rectal cancer who received neoadjuvant therapy, FDG PET/CT performed similarly to MRI [22] and digital rectal exploration plus rectoscopy [23] for the prediction of pathologic response. Prior to radiotherapy, FDG PET or PET/CT findings led to a pooled proportion of change in treatment intent or target definition of 24.8% [24]. In the staging of gallbladder cancer, FDG PET/CT was proven to be valuable in determining the TNM stage of patients [25]. Likewise for staging of gastric cancer, FDG PET/CT uncovered metastatic sites not seen on conventional imaging. Consequently, this influenced the initially planned management of 11.7% of cases [26]. As for staging of patients with hepatocellular carcinoma, FDG PET or PET/CT showed moderate specificity (pooled estimate, 80%), but suboptimal sensitivity (pooled estimate, 67%) in predicting microvascular invasion [27].

Genitourinary Cancer

Two studies met the inclusion criteria [28-29]. Results from a meta-analysis showed high sensitivity (pooled estimate, 94%) and specificity (pooled estimate, 92%) for FDG PET/CT in the detection of recurrent or residual urinary bladder cancer [28]. In patients with muscle-invasive bladder cancer receiving neoadjuvant pembrolizumab, FDG PET/CT was inadequate in evaluating pathologic lymph node involvement due to very poor sensitivity at both baseline (27.0%) and post-pembrolizumab (37.5%) scans [29].

Gynecologic Cancer

Eight studies met the inclusion criteria [30-37]. In the staging of patients with cervical cancer, FDG PET/CT detected lymph node metastases with a sensitivity of 84% to 88% and a specificity of 69% to 90% [30,31]. Overall, FDG PET/MRI performed significantly better than FDG PET/CT, CT, and MRI ($p<0.05$) [31]. In locally advanced cases treated with chemoradiotherapy, FDG PET/CT was comparable to MRI in predicting tumour response and identifying residual disease but was much more sensitive in detecting metastases (pooled estimate, 97% versus 31%, respectively) [32]. In early-stage patients who received surgery, the addition of FDG PET/CT to serum squamous cell carcinoma antigen level improved the diagnostic accuracy of detecting recurrence or metastases than either test alone [33]. For the diagnosis of ovarian or adnexal tumours, both FDG PET/CT and MRI showed similarly high diagnostic performance (area under

the curve, 0.95 for both tests) [34]. In the preoperative staging of ovarian cancer, FDG PET/CT appeared to be superior to CT [35,36] and MRI [36] in the evaluation of pelvic and para-aortic lymph node metastases. On the other hand, preoperative staging of invasive vulvar cancer with FDG PET/CT only demonstrated modest accuracy (78.4%) for assessment of groin and pelvic lymph node metastases [37].

Head and Neck Cancer

Twelve studies met the inclusion criteria [38-49]. In patients with suspected recurrence of differentiated thyroid cancer, FDG PET/CT findings modified the therapeutic approach of 42.4% to 50.0% of cases [38,39]. Specifically, FDG PET or PET/CT imaging led to significantly fewer radioiodine treatments ($p=0.016$) and trended toward more surgeries ($p=0.052$) [40]. However, this did not translate to significantly better patient survival [40]. Similarly, in patients with suspected recurrence of medullary thyroid cancer, FDG PET/CT findings influenced further management in 40.3% of cases [41]. In the pre-treatment staging of patients with head and neck squamous cell carcinoma, FDG PET/CT (89.2%), CT (83.7%) and MRI (87.0%) detected retropharyngeal lymph node metastases with similar accuracy [42]. Nonetheless, a change in the overall TNM staging or management protocol was noted in 48.4% and 71.0% of patients, respectively, as a result of information provided by FDG PET/CT [43]. Additionally, FDG PET/CT (pooled estimate, 80%) was significantly more sensitive than both CT (pooled estimate, 76%, $p=0.01$) and MRI (pooled estimate, 72%, $p<0.001$) in the detection of extranodal extension [44]. In patients with suspected recurrence of tongue carcinoma, FDG PET/CT detected recurrent or residual disease with high sensitivity (92.9%) and specificity (90.0%), leading to management changes in 29.1% of cases [45]. For oral tongue squamous cell carcinoma, surveillance FDG PET/CT discovered local recurrence with 100% sensitivity and 80.7% specificity [46]. In the staging of patients with treatment-naive squamous cell carcinoma of the oral cavity, FDG PET/CT was significantly more sensitive than contrast-enhanced CT in detecting both the primary tumours (98.4% versus 38.4%, $p<0.001$) and osseous infiltration (86.7% versus 69.0%, $p<0.05$) [47]. Furthermore, FDG PET/CT was significantly more specific than contrast-enhanced CT in detecting lymph node metastases (83.5% versus 67.0%, $p<0.01$) [47]. In comparison to MRI, FDG PET/CT was also significantly more sensitive in detecting the primary tumours (98.4% versus 69.6%, $p<0.001$) and more specific in detecting lymph node metastases (83.5 versus 62.6%, $p<0.001$) [47]. Likewise, FDG PET/CT allowed the upstaging of 11.1% of patients with treatment-naive laryngeal squamous cell carcinoma by uncovering sites of distant metastases not seen with conventional imaging (e.g., neck CT, MRI) [48]. One meta-analysis found no significant differences in diagnostic performance between FDG PET/CT and FDG PET/MRI for the detection of distant metastases in patients with oropharyngeal and hypopharyngeal squamous cell carcinoma [49].

Hematologic Cancer

Six studies met the inclusion criteria [50-55]. In patients with newly diagnosed diffuse large B-cell lymphoma, FDG PET/CT detected bone marrow involvement with an accuracy that ranged from 80.9% to 89.7% [50,51]. Compared with bone marrow biopsy, FDG PET/CT was considerably more sensitive (84% versus 38%, $p<0.001$) [52]. For treatment assessment after at least six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), the three-year time-to-progression of PET-positive patients who received consolidative radiotherapy did not differ significantly from that of PET-negative patients who received no further therapy (76% versus 83%, respectively, $p=0.3$), but was significantly higher than PET-positive patients who were not treated with consolidative radiotherapy (76% versus 34%, respectively, $p<0.001$) [53]. In patients with multiple myeloma, treatment response assessment with FDG PET/CT showed higher sensitivity (pooled estimate, 80% versus 25%, respectively) but

lower specificity (pooled estimate, 58% versus 83%, respectively) than MRI [54]. However, a positive FDG PET/CT scan was a significant prognostic indicator for worse progression-free survival, whereas MRI findings have no prognostic value [55].

Melanoma

Six studies met the inclusion criteria [56-61]. In the initial staging of patients with stage II and III melanoma, FDG PET/CT findings upstaged only 3.9% of cases to stage IV disease and rarely provided information that would alter clinical management [56]. Particularly, FDG PET/CT did not add any value prior to lymphoscintigraphy and sentinel lymph node biopsy in stage IIB/C patients [57]. On the contrary, staging with FDG PET/CT changed the management of 18.4% of patients with pT4b melanoma [58] and 16.0% of those with satellite or in-transit metastases, where brain MRI failed to alter treatment plan or disease stage in any patient [59]. In the follow-up of stage IV patients treated with immune checkpoint inhibitors, FDG PET/CT findings induced more management changes than contrast-enhanced CT (21.3% versus 2.5%) [60]. In patients with resected stage IIIA-D melanoma, surveillance imaging using FDG PET/CT was less specific than CT in detecting distant recurrence (78% versus 90%, p=0.003). However, the sensitivity of FDG PET/CT (94%) was higher than that of CT (76%) but the difference was not significant (p=0.1418) [61].

Non-FDG Tracers

Nineteen studies met the inclusion criteria [62-80]. ^{68}Ga-DOTA-TOC PET/CT provided added value over CT or MRI by significantly improving the sensitivity and area under the curve value for the characterization of suspected pancreatic neuroendocrine tumours (NETs) [62]. Furthermore, ^{68}Ga-DOTA-TOC/TATE/NOC PET/CT was highly effective in locating the primary site of NETs of unknown primary origin (pooled sensitivity, 82%) [63]. Overall, a major change in management was recommended for 47.4% of patients on the basis of ^{68}Ga-DOTA-TOC PET/CT findings [64]. In the initial staging of bronchopulmonary carcinoid tumours, ^{68}Ga-DOTA-NOC PET/CT changed the treatment intent of 11.8% of patients by detecting metastases to distant sites [65]. One prospective study found that neck US had a higher specificity (100% versus 70%, p=0.002) and positive predictive value (100% versus 55%, p=0.018) than ^{18}F-fluorocholine PET/CT in the nodal staging of patients with primary medullary thyroid cancer [66]. Numerous studies evaluated the utility of ^{68}Ga-PSMA PET/CT in prostate cancer. In patients with serum prostate-specific antigen (PSA) between 4 and 20 ng/ml, ^{68}Ga-PSMA PET/CT and multiparametric MRI diagnosed prostate cancer with identical accuracy (96.7%) [67]. In the preoperative staging of intermediate- to high-risk patients, ^{68}Ga-PSMA PET/CT showed a sensitivity of 37.9% to 100% and a specificity of 92.0% to 100% for detecting lymph node metastases [68-74] and was superior to whole-body MRI [73]. Moreover, bone metastases were detected by ^{68}Ga-PSMA PET/CT with high sensitivity (93.0% to 100%) and specificity (91.0% to 97.4%) as part of staging/restaging investigations [73,75]. Taken together, ^{68}Ga-PSMA PET/CT findings changed the disease stage of 36.1% of patients [76] and altered management in 31.5% to 58.7% of cases [76,77]. Results from the phase 2/3 OSPREY trial demonstrated high specificity (97.9%) but poor sensitivity (40.3%) for ^{18}F-DCFPyL PET/CT in the detection of pelvic lymph node involvement of newly diagnosed high-risk patients [78]. Conversely, ^{18}F-DCFPyL PET/CT displayed very high sensitivity (95.8%) for detecting locoregional recurrence or metastases in post-therapy patients [78]. In the latter clinical scenario, ^{18}F-DCFPyL PET/CT impacted the intended management of 40.7% of patients [79]. PET imaging with ^{18}F-FDOPA was evaluated in a small cohort of glioma patients treated with surgery and/or adjuvant radiotherapy and temozolomide. The combination of ^{18}F-FDOPA and multiparametric MRI offered the highest accuracy (96.0%) in distinguishing true recurrence from radiation necrosis, followed by ^{18}F-

FDOPA alone (84.6%), multiparametric MRI alone (77.0%), and contrast-enhanced MRI (57.7%) [80].

Pancreatic Cancer

Three studies met the inclusion criteria [81-83]. A meta-analysis reported high pooled sensitivity (84%) and specificity (95%) for FDG PET or PET/CT in the diagnosis of intraductal papillary mucinous neoplasm [81]. However, in one prospective study that only included patients considered as candidates for surgery, the diagnostic performance of FDG PET/CT was underwhelming and inferior to CT, MRI, or endoscopic US [82]. For the characterization of pancreatic and periampullary masses, FDG PET/CT showed relatively good accuracy (81.3%). Additionally, FDG PET/CT led to a change in management from curative resection to palliative therapy in 21.9% of patients by detecting distant metastases not seen on conventional imaging [83].

Pediatric Cancer

Five studies met the inclusion criteria [84-88]. Three meta-analyses evaluated the diagnostic performance of FDG PET or PET/CT in the detection of bone marrow involvement, one in newly diagnosed Hodgkin (HL) and non-Hodgkin (NHL) lymphoma [84], one in treated and newly diagnosed HL and NHL [85], and the other in neuroblastoma [86]. In all cases, FDG PET or PET/CT displayed remarkedly high sensitivity and specificity. Moreover, one retrospective study reported similarly high sensitivity (91.8%) and specificity (93.8%) for FDG PET/CT in the assessment of bone marrow involvement in patients with metastatic rhabdomyosarcoma undergoing initial staging prior to treatment [87]. However, in a mixed population of patients with various malignancies, FDG PET/CT was not as effective in identifying bone marrow involvement (sensitivity, 66%; specificity, 75%) [88].

Sarcoma

Four studies met the inclusion criteria [89-92]. One meta-analysis found that FDG PET or PET/CT can diagnose primary bone and soft tissue sarcomas with a pooled sensitivity of 89.2% and a pooled specificity of 75.1% [89]. In the initial staging of patients with osteosarcoma and Ewing sarcoma, a small prospective study could not demonstrate a difference in diagnostic performance between FDG PET/CT, whole-body MRI and skeletal scintigraphy for detecting bone metastases [90]. However, in the restaging of these patients and others with chondrosarcoma, fibrosarcoma and angiosarcoma, FDG PET/CT (90.9%) appeared to be more accurate than CT (84.8%) [91]. In another meta-analysis that looked at response assessment of patients with gastrointestinal stromal tumour undergoing molecular targeted therapy, FDG PET or PET/CT was shown to be more sensitive but less specific than CT [92].

Thoracic Cancer

Five studies met the inclusion criteria [93-97]. In the diagnosis of treatment-naive patients with non-small cell lung cancer (NSCLC), FDG PET/CT (sensitivity, 96.4%) performed superiorly to circulating tumour cells analysis (sensitivity, 75.7%) [93]. For nodal staging of patients with stage IB and IIA disease, FDG PET/CT exhibited a negative predictive value of 87% [94]. In patients with recurrent small cell lung cancer and NSCLC, FDG PET or PET/CT had a substantial impact on management (pooled estimate, 61.4%) [95]. For staging of patients with malignant pleural mesothelioma, FDG PET or PET/CT (68.7%) was less accurate than diagnostic laparoscopy (81.8%) in identifying peritoneal disease [96]. Results from a meta-analysis showed that FDG PET or PET/CT was able to differentiate thymic cancer from thymoma with a sensitivity of 89% and a specificity of 77% as well as differentiate between high-risk and low-risk thymic epithelial tumour with a sensitivity of 90% and a specificity of 81% [97].

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 Indications 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 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.

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 Indication for Bladder Cancer

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

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 (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 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.
- To assess response to chimeric antigen receptor T-cell therapy, 90 days post transfusion.

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 of patients with nonsecretory myeloma, oligosecretory myeloma, or POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes).
- For work-up of patients with newly diagnosed secretory multiple myeloma and negative or equivocal skeletal survey.

Reviewer's Comments

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

Melanoma

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.
- For the staging of patients before starting immunotherapy.
- For early response assessment of patients with metastatic melanoma currently receiving immunotherapy after two to four cycles.
- For response assessment of patients with metastatic melanoma at end of immunotherapy.

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. Patients should have elevated biochemical markers (e.g., 5-HIAA ± elevated chromogranin A) and no definitive evidence of disease on CT.
- For the staging of patients upon initial diagnosis 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.
- For patients with biochemical failure following treatment for oligometastatic disease.
- For patients with biochemical failure following primary radiotherapy.
- Where confirmation of site of disease and/or disease extent may impact clinical management over and above the information provided by conventional imaging.

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.

Pancreatic Cancer

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

Reviewer's Comments (Dr. Jim Biagi)

There is currently not enough evidence to support making appropriate recommendations for the use of PET/CT in pancreatic cancer.

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 – HL and NHL
    - Primary brain – astrocytoma, medulloblastoma, ependymoma, other
    - Reproductive – germ cell tumour
    - Sympathetic nervous system - neuroblastoma MIBG-negative
    - Other – Langerhans cell histiocytosis, melanoma of the skin, thyroid
- For the following indications:
    - Initial staging
    - Monitoring response during treatment/determine response-based therapy
    - Rule out progression prior to further therapy
    - Suspected recurrence/relapse
    - Rule out persistent disease

    - Select optimal biopsy site
- For the assessment of response in HL or NHL after a minimum of two cycles of chemotherapy when curative therapy is being considered.

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.

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

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

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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DISCLAIMER

Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Ontario Health (Cancer Care Ontario) makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

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APPENDIX 1: SUMMARY OF STUDIES FROM JULY TO DECEMBER 2021.

Breast Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Ferahman et al, 2020 [1]	Retrospective	101 patients who underwent preoperative nodal staging (early-stage breast cancer)	FDG PET	MRI, US	SLNB	**Axillary lymph node metastases** Sens: 77.8% Spec: 90.8% PPV: 82.4% NPV: 88.1%	**Axillary lymph node metastases** ***MRI*** Sens: 72.2% Spec: 86.2% ***US*** Sens: 72.2% Spec: 75.4%	NA
Le et al, 2020 [2]	Retrospective	85 patients who are treatment naïve (unilateral primary breast cancer of at least stage T2)	FDG PET/CT	US	Cytology	**Axillary lymph node metastases** Sens: 96.2% Spec: 20.0% PPV: 95.1% NPV: 25.0% Accu: 91.8%	**Axillary lymph node metastases** Sens: 100% Spec: 0% PPV: 94.1% NPV: NA Accu: 94.1%	NA
Guney et al, 2020 [3]	Prospective	158 patients who underwent staging prior to sentinel lymph node biopsy and axillary lymph node dissection (breast cancer)	FDG PET/CT	US, CeMRI	Histopathology	**Axillary lymph node metastases** Sens: 81.9% Spec: 86.2% PPV: 87.4% NPV: 80.3% Accu: 83.9%	**Axillary lymph node metastases** ***US*** Sens: 78.7% Spec: 74.3% PPV: 78.1% NPV: 75.0% Accu: 76.7% ***CeMRI*** Sens: 86.6% Spec: 71.6% PPV: 78.0% NPV: 82.1% Accu: 79.7%	NA
Assi et al, 2021 [4]	Retrospective	268 patients who underwent nodal staging prior to sentinel lymph node biopsy and/or axillary lymph node dissection (newly diagnosed breast cancer)	FDG PET/CT	US-guided FNA	Histopathology	**Axillary lymph node metastases** Sens: 86.6% Spec: 63.5% PPV: 78.9% NPV: 75.0% Accu: 77.6%	**Axillary lymph node metastases** Sens: 91.7% Spec: 87.5% PPV: 96.8% NPV: 71.8% Accu: 90.9%	NA
Turan et al, 2021 [5]	Retrospective	171 patients who underwent post-neoadjuvant	FDG PET/CT	US, MRI	Histopathology	**Axillary lymph node metastases** Sens: 47.5%	**Axillary lymph node metastases** ***US***	NA

		chemotherapy axillary response assessment (invasive breast cancer)				Spec: 76.7% PPV: 73.1% NPV: 52.3% Accu: 60.0% AUC: 0.677	Sens: 59.4% Spec: 82.4% PPV: 82.0% NPV: 60.0% Accu: 69.2% AUC: 0.697 ***MRI*** Sens: 36.7% Spec: 77.8% PPV: 73.3% NPV: 42.4% Accu: 52.1% AUC: 0.597	
Chung et al, 2021 [6]	Retrospective	212 patients who underwent nodal staging (untreated invasive breast cancer)	FDG PET/CT	US, CT, MRI	Biopsy, imaging follow-up	**Supraclavicular nodal metastases** Sens: 86.7% Spec: 100% PPV: 100% NPV: 55.6% Accu: 88.6% **Internal mammary nodal metastases** Sens: 96.8% Spec: 100% PPV: 100% NPV: NA Accu: 96.8%	**Supraclavicular nodal metastases** ***US*** Sens: 100% Spec: 98.4% PPV: 78.2% NPV: 100% Accu: 98.2% ***CT*** Sens: 59.2% Spec: 69.6% PPV: 85.7% NPV: 35.6% Accu: 61.7% **Internal mammary nodal metastases** ***US*** Sens: 94.3% Spec: 98.8% PPV: 98.8% NPV: 99.6% Accu: 93.2% ***CT*** Sens: 62.1% Spec: 100% PPV: 100% NPV: 4.3% Accu: 62.7% ***MRI*** Sens: 100% Spec: 100% PPV: 100% NPV: NA Accu: 100%	NA
Ko et al, 2020 [7]	Retrospective	195 patients who underwent staging before	FDG PET/CT	Physical examination, mammograph	Histology, imaging follow-up	**Distant metastases** Sens: 100%	NA	FDG PET/CT upstaged 37.2% (73/196) of patients.

		beginning primary systemic therapy followed by planned surgery (stage IIA-IIIC breast cancer)		y, breast US, MRI		Spec: 94% PPV: 73%		
Iqbal et al, 2021 [8]	Retrospective	70 patients who underwent staging prior to surgery or systemic treatment (grade 1-2 estrogen receptor positive, stage IIB/III breast cancer)	FDG PET/CT	Mammography, US, MRI, CT	Pathology, clinical and/or imaging follow-up	NA	NA	FDG PET/CT correctly upstaged 10.0% (7/70) of patients but inadequately staged 22.9% (16/70) of patients (3—incorrectly downstaged, 13—incorrectly upstaged).
Bosma et al, 2021 [9]	Prospective	66 patients who underwent early response evaluation before radiation therapy and 5 weeks after radiation therapy, before surgery (low-risk breast cancer)	FDG PET/CT	MRI	Histopathology	**Pathologic response** PPV: 25.0%* NPV: 92.0%	**Pathologic response** PPV: 87.5%* NPV: 85.0%	NA
Vogsen et al, 2021 [10]	Prospective	225 patients with symptoms of first distant metastases or a biopsy-verified local recurrence (suspected recurrent breast cancer)	FDG PET/CT	CeCT	Biopsy, clinical and imaging follow-up	**Distant metastases** Sens: 100% Spec: 88% PPV: 71% NPV: 100% Accu: 91% AUC: 0.98	**Distant metastases** Sens: 96% Spec: 88% PPV: 71% NPV: 99% Accu: 90% AUC: 0.95	NA
Epilepsy								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Guo et al, 2021 [11]	Retrospective	98 patients who underwent presurgical evaluation (focal refractory epilepsy)	FDG PET/MRI	Neuropsychological examination, VEEG, brain MRI	Surgical pathology, post-surgical outcome	**Localization** Sens: 95.3% Spec: 8.8% Accu: 65.3%	NA	A total of 65.3% (64/98) patients achieved seizure freedom (Engel I) at 1-year post-surgery follow-up.

Toth et al, 2021 [12]	Prospective	60 patients who underwent presurgical evaluation (drug-resistant, focal epilepsy)	FDG PET/MRI	VEEG, cranial MRI, clinical semiology	Consensus from two multidisciplinary epilepsy surgery teams	NA	NA	FDG PET/MRI findings altered the therapeutic decision-making of 31.7% (19/60) patients (13—avoided any further invasive diagnostic procedure, 1—proved to be inoperable, 3—became eligible for resective surgery, 2—resective surgery instead of intracranial EEG).
Zhang et al, 2020 [13]	Prospective	42 patients who underwent presurgical evaluation (refractory epilepsy)	FDG PET/MRI	Clinical examination, neurologic evaluation, VEEG, MRI, MEG	Consensus from multidisciplinary team, post-surgical outcome, intracranial EEG	**Concordant with intracranial EEG** Sens: 69.0%	NA	FDG PET/MRI findings helped to navigate intracranial EEG to localize the seizure onset zone in 83.3% (35/42) patients. Complete seizure-free status (Engel I) was achieved in 73.8% (31/42) of patients.
Abdul Aziz et al, 2021 [14]	Retrospective	119 pediatric patients with normal or inconclusive MRI who underwent pre-surgical evaluation (drug resistant epilepsy)	FDG PET/CT	MRI, VEEG	Clinical follow-up	NA	NA	The addition of FDG PET/CT impacted decision making in 55.5% (66/119) of patients. Among the 25 patients who subsequently underwent epilepsy surgery, 16 achieved Engel class I outcome after a median follow-up of 20 months.
Esophageal Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Han et al, 2021 [15]	Meta-analysis	11 studies (695 patients with esophageal cancer who underwent early metabolic response assessment during neoadjuvant chemoradiotherapy)	FDG PET or PET/CT	NA	Pathology	**Pathologic response** Pooled Sens: 80% Pooled Spec: 54% AUC: 0.64	NA	NA

Goodman et al, 2021 [16]	RCT Phase II (CALGB 80803 trial)	257 patients randomly assigned 1:1 to induction FOLFOX or CP followed by early response assessment prior to chemoradiation (resectable esophageal and esophagogastric junction adenocarcinoma)	FDG PET/CT (PET non-responders crossed over to the alternative chemotherapy during chemoradiation; PET responders continued on the same chemotherapy during chemoradiation)	NA	Pathology	NA	NA	PET non-responders achieved a pathologic complete response rate of 18.0% among those who switched from FOLFOX to CP and 20.0% among those who switched from CP to FOLFOX.
Lu et al, 2021 [17]	Retrospective	9078 patients who underwent staging prior to treatment (newly diagnosed nonmetastatic esophageal cancer)	FDG PET or PET/CT (n=1765)	No FDG PET or PET/CT (n=7313)	Clinical follow-up	NA	NA	Patients who were staged with pre-treatment FDG PET or PET/CT had a significantly lower risk of death than those without pre-treatment FDG PET or PET/CT (HR=0.74, 95% CI: 0.70 to 0.79, p<0.001).
Gastrointestinal Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Guney et al, 2020 [18]	Prospective	53 patients who underwent preoperative staging (colorectal caner)	FDG PET/CT	CeCT, CeMRI	Histopathology	**Regional lymph node metastases** Sens: 88.5% Spec: 59.3% PPV: 67.6% NPV: 84.2% Accu: 73.6%	**Regional lymph node metastases** ***CeCT*** Sens: 84.2% Spec: 57.1% PPV: 64.0% NPV: 80.0% Accu: 70.0% ***CeMRI*** Sens: 93.8% Spec: 47.4% PPV: 60.0% NPV: 90.0% Accu: 68.6%	NA
Todate et al, 2021 [19]	Prospective	194 patients who underwent	FDG PET/CT	CeCT	Pathology	**Lymph node metastases**	NA	NA

		staging prior to surgical resection with lymph node dissection (colorectal cancer)				Sens: 19.4% Spec: 99.5% PPV: 76.8% NPV: 93.9%		
Borello et al, 2021 [20]	Retrospective	58 patients who underwent staging prior to liver resection (mucinous colorectal liver metastases)	FDG PET/CT	MRI, intraoperative staging, total colonoscopy, CeCT	Histology, imaging follow-up	**Liver metastases (lesion-based)** Sens: 60.7% Spec: 100% **(organ-based)** Sens: 89.4% Spec: 100% **Lung metastases (organ-based)** Sens: 66.7% Spec: 95.6% **Lymph node metastases (organ-based)** Sens: 62.5% Spec: 97.8%	**Liver metastases (lesion-based)** ***MRI*** Sens: 68.6% Spec: 91.6% ***Intraoperative staging*** Sens: 89.9% Spec: 97.4%	
Monteil et al, 2021 [21]	RCT	365 patients who had undergone curative surgery with or without adjuvant chemotherapy and randomly assigned 1:1 to conventional follow-up or PET/CT follow-up (stage II or III colorectal cancer)	FDG PET/CT every 6 months and clinical exam every 3 months over 3 years (n=185)	Clinical exams, CEA measurements every 3 months, liver echography every 6 months and lung radiography or thoracoabdominal CT alternately every 12 months (n=180)	Histology, repeated imaging	**Recurrence** Sens: 88.6% Spec: 92.1% PPV: 37.9% NPV: 99.3% Accu: 91.9%	**Recurrence** Sens: 80.0% Spec: 95.9% PPV: 30.0% NPV: 89.6% Accu: 95.6%	The 3-year DFS (74.2% vs. 82.0%, respectively, p=0.063) and 5-year OS (83.7% vs. 84.6%, respectively, p=0.73) did not differ significantly between PET/CT follow-up and conventional follow-up. The rate of surgically treated recurrence also did not differ significant between the two strategies (36.2% vs. 22.5%, respectively, p=0.25). However, the 3-year DFCS was significantly higher in the conventional follow-up than in the PET/CT follow-up (79.6% vs. 71.0%, respectively, p=0.038).
Lee et al, 2021 [22]	Meta-analysis	9 studies (427 patients who received neoadjuvant treatment for	FDG PET/CT	MRI	Pathology	**Pathologic response** Pooled Sens: 79% Pooled Spec: 74% Pooled +LR: 3.1	**Pathologic response** Pooled Sens: 89% Pooled Spec: 66% Pooled +LR: 2.6	NA

		locally advanced rectal cancer)				Pooled -LR: 0.28 Pooled DOR: 11 AUC: 0.83	Pooled -LR: 0.17 Pooled DOR: 15 AUC: 0.81	
Lopez-Lopez et al, 2021 [23]	Prospective	68 patients who underwent assessment of tumour response 12 weeks after completion of neoadjuvant chemoradiation therapy (locally advanced rectal cancer)	FDG PET/CT	Digital rectal exploration + rectoscopy	Pathology	**Pathologic response** Sens: 92% Spec: 93% PPV: 98% NPV: 78% Accu: 92% **Lymph node involvement** Sens: 43% Spec: 83% PPV: 53% NPV: 76%	**Pathologic response** Sens: 96% Spec: 87% PPV: 96% NPV: 87% Accu: 94%	NA
Lee et al, 2021 [24]	Meta-analysis	12 studies (336 patients with newly diagnosed rectal cancer who underwent preoperative staging and radiotherapy target definition)	FDG PET or PET/CT	CT, MRI	Pre- and post-PET information	NA	NA	The pooled proportion of patients with a change in treatment intent or target definition was 24.8%. The PET-based GTV was significantly smaller than the conventional imaging-based GTV (SMD=-0.70; 95% CI: -1.39 to -0.01). There was no significant difference between PET-based and conventional imaging-based PTV (SMD=-0.07; 95% CI: -0.75 to 0.62).
Parida et al, 2021 [25]	Meta-analysis	8 studies (296 patients who underwent staging for gallbladder cancer)	FDG PET/CT	CT, MRI, US	Histopathology, follow-up	**T-staging** Pooled Sens: 96% Pooled Spec: 91% **N-staging** Pooled Sens: 75% Pooled Spec: 91% **M-staging** Pooled Sens: 95% Pooled Spec: 97% Pooled DOR: 248.22 AUC: 0.98	NA	NA
Debiec et al, 2021 [26]	Retrospective	111 treatment-naïve patients (gastric cancer)	FDG PET/CT	Abdominal CeCT, chest CT/X-ray, upper gastrointestinal gastroscopy	Histopathology, clinical and imaging follow-up	**Distant metastases** Sens: 76.5% Spec: 86.5% PPV: 83.0% NPV: 81.3%	NA	FDG PET/CT identified metastatic sites not seen on conventional imaging and altered initially planned management in 11.7% (13/111) of patients.

Kim and Kim, 2021 [27]	Meta-analysis	14 studies (1276 patients with hepatocellular carcinoma)	FDG PET or PET/CT	NA	Histopathology	**Microvascular invasion** Pooled Sens: 67% Pooled Spec: 80% Pooled +LR: 3.3 Pooled -LR: 0.41 Pooled DOR: 8 AUC: 0.81	NA	NA
Genitourinary Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Xue et al, 2020 [28]	Meta-analysis	7 studies (603 patients with recurrent or residual urinary bladder cancer)	FDG PET/CT	NA	Histopathology, clinical follow-up	**Recurrence or residual disease** Pooled Sens: 94% Pooled Spec: 92% Pooled +LR: 9.77 Pooled -LR: 0.09 Pooled DOR: 95.09 Q index: 0.92 AUC: 0.97	NA	NA
Marandino et al, 2021 [29]	Prospective	108 patients who underwent baseline and post-pembrolizumab prior to radical cystectomy and extend pelvic lymph node dissection (clinical T2-4aN0M0 muscle-invasive bladder cancer)	FDG PET/CT	CT, mpMRI	Histopathology	**Lymph node involvement (Baseline)** Sens: 27.0% Spec: 97.0% PPV: 57.0% NPV: 89.0% Accu: 87.0% **(Post-pembrolizumab)** Sens: 37.5% Spec: 98.0% PPV: 75.0% NPV: 90.0% Accu: 89.0%	NA	NA
Gynecologic Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Vermolen et al, 2021 [30]	Retrospective	98 patients who underwent staging prior to lymph node dissection or lymph node	FDG PET/CT	MRI	Histopathology	**Lymph node metastases (equivocal as positive)** Sens: 88% Spec: 69% PPV: 79%	NA	NA

		debulking (cervical cancer)				NPV: 81% **(equivocal as positive)** Sens: 84% Spec: 86% PPV: 89% NPV: 80%		
Zhu et al, 2021 [31]	Prospective	196 patients who underwent preoperative staging (cervical cancer)	FDG PET/CT, FDG PET/MRI	CT, MRI	Pathology	**Lymph node metastases** ***PET/CT*** Sens: 84.2%‡ Spec: 90.0%‡ Accu: 87.8%‡ ***PET/MRI*** Sens: 94.7%‡* Spec: 93.3%‡* Accu: 93.9%‡*	**Lymph node metastases** ***CT*** Sens: 68.4%* Spec: 75.0%* Accu: 72.5%* ***MRI*** Sens: 76.3%* Spec: 80.0%* Accu: 78.6%*	NA
Sanei Sistani et al, 2021 [32]	Meta-analysis	15 studies (1132 patients treated with chemoradiotherapy for locally advanced cervical carcinoma)	FDG PET/CT	MRI	Pathology	**Pathologic response** Pooled Sens: 83.5% Pooled Spec: 77.8% Pooled +LR: 4.14 Pooled -LR: 0.22 Pooled PPV: 75.0% Pooled NPV: 62.0% Pooled Accu: 80.0% Pooled DOR: 25.22 AUC: 0.80 **Residual disease** Pooled Sens: 86.0% Pooled Spec: 95.5% **Metastatic disease** Pooled Sens: 97.0% Pooled Spec: 99.0%	**Pathologic response** Pooled Sens: 82.7% Pooled Spec: 68.4% Pooled +LR: 2.92 Pooled -LR: 0.23 Pooled PPV: 85.0% Pooled NPV: 86.0% Pooled Accu: 74.0% Pooled DOR: 15.14 AUC: 0.91 **Residual disease** Pooled Sens: 73.5% Pooled Spec: 96.2% **Metastatic disease** Pooled Sens: 31.0% Pooled Spec: 98.0%	NA
Qi et al, 2021 [33]	Retrospective	246 patients who received surgery (suspected recurrent cervical cancer)	FDG PET/CT	Serum SCC-Ag	Surgical pathology, clinical and imaging follow-up	**Recurrence or metastases** Sens: 84.7% Spec: 90.8% PPV: 92.1% NPV: 82.5% AUC: 0.88	**Recurrence or metastases** Sens: 89.8% Spec: 74.3% PPV: 81.5% NPV: 85.3% AUC: 0.82	NA
Hu et al, 2021 [34]	Meta-analysis	27 studies (3730 patients with ovarian or adnexal tumours)	FDG PET/CT	MRI	Histopathology, follow-up	**Diagnosis** Pooled Sens: 94% Pooled Spec: 86% Pooled +LR: 6.7 Pooled -LR: 0.07 Pooled DOR: 95 AUC: 0.95	**Diagnosis** Pooled Sens: 92% Pooled Spec: 85% Pooled +LR: 6.1 Pooled -LR: 0.09 Pooled DOR: 67 AUC: 0.95	NA

Mimoun et al, 2021 [35]	Meta-analysis	5 studies (138 patients with epithelial ovarian cancer who underwent preoperative staging)	FDG PET/CT	CT	Histopathology	**Pelvic and para-aortic lymph node metastases** Pooled Sens: 81% Pooled Spec: 96% Pooled +LR: 22.60 Pooled -LR: 0.20 AUC: 0.97	**Pelvic and para-aortic lymph node metastases** Pooled Sens: 47% Pooled Spec: 99% Pooled +LR: 75.40 Pooled -LR: 0.54 AUC: 0.91	NA
Uysal et al, 2021 [36]	Retrospective	89 patients who underwent preoperative staging (ovarian cancer)	FDG PET/CT	CT, MRI	Histopathology	**Pelvic and para-aortic lymph node metastases** Sens: 63% Spec: 66% PPV: 70% NPV: 60% Accu: 65%	**Pelvic and para-aortic lymph node metastases** ***CT*** Sens: 62% Spec: 52% PPV: 57% NPV: 57% Accu: 57% ***MRI*** Sens: 75% Spec: 37.5% PPV: 37.5% NPV: 75% Accu: 50%	NA
Rufini et al, 2021 [37]	Retrospective	160 patients who underwent preoperative staging (invasive vulvar cancer)	FDG PET/CT	CT, US, MRI	Histopathology	**Groin and pelvic lymph node metastases** Sens: 78.9% Spec: 78.2% PPV: 61.2% NPV: 89.4% Accu: 78.4%	NA	NA
Head and Neck Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Abelleira et al, 2020 [38]	Retrospective	60 patients with biochemical incomplete or indeterminate response after total thyroidectomy and remnant ablation (differentiated thyroid cancer)	FDG PET/CT	Serum thyroglobulin, neck US, radioiodine dose whole body scanning, CT, bone scintigraphy	Histopathology, clinical follow-up	**Locoregional recurrence** Sens: 95.0% Spec: 87.5% Accu: 90.0%	NA	The therapeutic approach was modified based on FDG PET/CT findings in 50% of patients (46%—repeat surgery, 4%—administration of external beam radiotherapy).

Filippi et al, 2021 [39]	Retrospective	66 patients previously treated with thyroidectomy and at least 1 cycle of radioiodine therapy (suspected recurrent differentiated thyroid cancer)	FDG PET/CT	^{131}I-WBS, US, chest X-ray, CT	Histology, clinical and imaging follow-up	**Recurrence** Sens: 84.4% Spec: 75.0% PPV: 96.1% NPV: 40.1% Accu: 83.3%	NA	Change in management occurred in 42.4% (28/66) of patients (21—submitted to surgery followed by an additional cycle of radioiodine therapy, 6—received radiotherapy, 1—received systemic therapy with lenvatinib). PET-based therapeutic decision was considered adequate in 85.7% (24/28) of cases according to decline in Tg serum by more than 50% or complete or partial metabolic response on PERCIST.
Schleupner et al, 2020 [40]	Retrospective	194 patients treated with total thyroidectomy and radioiodine remnant ablation but with persisting or rising thyroglobulin values and negative ^{131}I-scintigraphy (suspected recurrence of differentiated thyroid carcinoma)	FDG PET or PET/CT (n=149)	No PET or PET/CT (n=45)	Clinical follow-up	NA	NA	Patients who underwent FDG PET or PET/CT assessment (within first nine months) received significantly less radioiodine therapy (63.1% vs. 82.2%, p=0.016) but tended to receive more surgeries (27.5% vs. 13.3%, p=0.052) than those who did not undergo FDG PET or PET/CT assessment. However, no significant differences in overall survival (p=0.106) and event-free survival (p=0.124) were observed between the two groups.
Saponjski et al, 2020 [41]	Retrospective	67 patients with increased calcitonin or CEA levels after thyroidectomy (suspected recurrence of medullary thyroid carcinoma)	FDG PET/CT	^{99m}Tc-DMSA scintigraphy	Histopathology, follow-up	**Recurrence or metastases** Sens: 92.1% Spec: 86.2% PPV: 89.7% NPV: 89.3% Accu: 89.6%	**Recurrence or metastases** Sens: 44.4% Spec: 81.3% PPV: 57.1% NPV: 72.2% Accu: 68.0%	FDG PET/CT findings influenced the therapeutic management of 40.3% (27/67) of patients.
Kim et al, 2020 [42]	Retrospective	123 patients who underwent staging prior to	FDG PET/CT	CT, MRI	Histopathology	**Retropharyngeal lymph node metastases**	**Retropharyngeal lymph node metastases**	NA

		surgery with retropharyngeal lymph node dissection (head and neck squamous cell carcinoma)				Sens: 82.8% Spec: 93.3% PPV: 88.9% NPV: 89.4% Accu: 89.2%	***CT*** Sens: 65.1% Spec: 93.8% PPV: 84.8% NPV: 83.3% Accu: 83.7% ***MRI*** Sens: 74.4% Spec: 93.8% PPV: 86.5% NPV: 87.2% Accu: 87.0%	
Kandeel et al, 2021 [43]	Prospective	31 patients who underwent pre-treatment staging (head and neck squamous cell carcinoma)	FDG PET/CT	Physical examination, endoscopy, CT, US, MRI	Pre- and post-PET information	NA	NA	FDG PET/CT changed the overall TNM staging of 48.4% (15/31) of patients. Management protocol was modified in 71.0% (22/31) of patients (21—radiotherapy modification, 1—curative to palliative).
Abdel-Halim et al, 2021 [44]	Meta-analysis	25 studies (1995 patients with head and neck squamous cell carcinoma)	FDG PET/CT	CT, MRI, US	Histopathology	**Extranodal extension** Pooled Sens: 80%* Pooled Spec: 83% Pooled DOR: 20 AUC: 0.81	**Extranodal extension** ***CT*** Pooled Sens: 76%* Pooled Spec: 77% Pooled DOR: 10 AUC: 0.83 ***MRI*** Pooled Sens: 72%* Pooled Spec: 78% Pooled DOR: 9 AUC: 0.76 ***US*** Pooled Sens: 73% Pooled Spec: 79%	NA
Jain et al, 2020 [45]	Retrospective	110 patients who underwent restaging or post-treatment assessment (suspected recurrent tongue carcinoma)	FDG PET/CT	Not specified	Histopathology, clinical and/or imaging follow-up	**Recurrence or residual disease** Sens: 92.9% Spec: 90.0% PPV: 94.2% NPV: 87.8% Accu: 91.8%	NA	On the basis of FDG PET/CT, the management changed in 29.1% (32/110) of patients.
Ravanelli et al, 2021 [46]	Retrospective	87 patients who underwent surveillance follow-up after surgery (oral	FDG PET/CT	Clinical examination, MRI	Histology, clinical and imaging follow-up	**Local recurrence** Sens: 100% Spec: 80.7% PPV: 34.6% NPV: 100%	NA	NA

		tongue squamous cell carcinoma)						
Linz et al, 2021 [47]	Prospective	125 patients who underwent staging prior to local tumour resection with selective or complete neck dissection (newly diagnosed, treatment-naïve squamous cell carcinoma of the oral cavity)	FDG PET/CT	CeCT, MRI	Histopathology	**Primary tumour** Sens: 98.4* **Osseous infiltration** Sens: 86.7%* Spec: 91.6% PPV: 76.5% NPV: 95.6%* **Lymph node metastases (patient-based)** Sens: 82.4% Spec: 83.5%* PPV: 65.1%* NPV: 92.7%* **Lymph node metastases (side-based)** Sens: 73.6% Spec: 89.1%* PPV: 59.6%* NPV: 94.0%* **Lymph node metastases (level-based)** Sens: 58.3%* Spec: 95.8%* PPV: 37.8%* NPV: 98.1%*	**Primary tumour** ***CeCT*** Sens: 38.4%* ***MRI*** Sens: 69.6%* **Osseous infiltration** ***CeCT*** Sens: 69.0%* Spec: 90.5% PPV: 69.0% NPV: 89.6%* ***MRI*** Sens: 73.3% Spec: 90.5% PPV: 71.0% NPV: 91.5% **Lymph node metastases (patient-based)** ***CeCT*** Sens: 67.6% Spec: 67.0%* PPV: 43.4%* NPV: 84.7%* ***MRI*** Sens: 70.6% Spec: 62.6%* PPV: 41.4%* NPV: 85.1%* **Lymph node metastases (side-based)** ***CeCT*** Sens: 57.9% Spec: 76.6%* PPV: 34.9%* NPV: 89.3%* ***MRI*** Sens: 63.1% Spec: 74.3%* PPV: 34.8%* NPV: 90.3%* **Lymph node metastases (level-based)** ***CeCT*** Sens: 39.6%*	NA

							Spec: 91.8%* PPV: 17.6%* NPV: 97.2%* ***MRI*** Sens: 45.8% Spec: 92.2%* PPV: 20.6%* NPV: 97.5%*	
Albano et al, 2021 [48]	Retrospective	54 patients who underwent staging before any treatments (laryngeal squamous cell carcinoma)	FDG PET/CT	Neck CT, MRI	Histopathology, clinical or imaging follow-up	**Primary tumour** Sens: 96.3% **Cervical nodal metastases (patient-based)** Sens: 100% Spec: 85.7% PPV: 94.6% NPV: 100% Accu: 95.9% **(side-based, ipsilateral)** Sens: 96.9% Spec: 75.0% PPV: 88.9% NPV: 92.3% Accu: 89.8% **(side-based, contralateral)** Sens: 83.3% Spec: 91.4% PPV: 76.9% NPV: 94.1% Accu: 89.4%	**Primary tumour** Sens: 100% **Cervical nodal metastases (patient-based)** Sens: 91.4% Spec: 85.7% PPV: 94.1% NPV: 80.0% Accu: 89.8% **(side-based, ipsilateral)** Sens: 96.9% Spec: 87.5% PPV: 94.1% NPV: 93.3% Accu: 93.9% **(side-based, contralateral)** Sens: 50.0% Spec: 91.4% PPV: 70.0% NPV: 82.1% Accu: 79.6%	FDG PET/CT allowed the upstaging of 11.1% (6/54) patients by detecting sites of distant metastases not identified with conventional imaging.
Kave et al, 2021 [49]	Meta-analysis	9 studies (1166 patients with oropharyngeal and hypopharyngeal squamous cell carcinoma)	FDG PET/CT, FDG PET/MRI	NA	Histopathology, imaging follow-up	**Distant metastases** ***PET/CT*** Pooled Sens: 79% Pooled Spec: 88% Pooled +LR: 8.95 Pooled -LR: 0.10 Pooled PPV: 85% Pooled NPV: 95% Pooled Accu: 87% Pooled DOR: 85.51 AUC: 0.96 ***PET/MRI*** Pooled Sens: 80% Pooled Spec: 91% Pooled +LR: 9.64 Pooled -LR: 0.21 Pooled PPV: 84% Pooled NPV: 89%	NA	NA

						Pooled Accu: 92% Pooled DOR: 44.41 AUC: 0.92		
Hematologic Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Siti Maisarah et al, 2021 [50]	Prospective	21 patients who underwent pre-chemotherapy imaging (newly diagnosed DLBCL)	FDG PET/CT	BMB	BMB	**Bone marrow involvement** Sens: 100% Spec: 77.8% PPV: 42.9% NPV: 100% Accu: 80.9%	NA	NA
Lim et al, 2021 [51]	Retrospective	512 patients who underwent imaging prior to first-line R-CHOP (newly diagnosed DLBCL)	FDG PET/CT	BMB	BMB	**Bone marrow involvement** Sens: 59.3% Spec: 93.6% PPV: 54.7% NPV: 94.6% Accu: 89.7%	NA	NA
Kaddu-Mulindwa et al, 2021 [52]	Prospective	930 patients who underwent initial staging (aggressive B-cell NHL)	FDG PET/CT	BMB	Targeted biopsy, complementary imaging, follow-up	**Bone marrow involvement** Sens: 84%* Spec: 100% PPV: 100% NPV: 95%	**Bone marrow involvement** Sens: 38%* Spec: 100% PPV: 100% NPV: 84%	NA
Freeman et al, 2021 [53]	Retrospective	723 patients who underwent end of treatment assessment after at least 6 cycles of R-CHOP (newly diagnosed advanced-stage DLBCL)	FDG PET/CT (PET-negative patients received no further therapy while PET-positive patients were offered consolidative radiotherapy)	NA	Clinical follow-up	NA	NA	The 3-year TTP of PET-positive patients who received consolidative radiotherapy did not differ significantly from that of PET-negative patients (76% vs. 83%, respectively, p=0.3), but was significantly higher than PET-positive patients who were not treated with consolidative radiotherapy (76% vs. 34%, respectively, p<0.001). The 3-year OS were 87%, 80% and 44% for PET-negative patients, PET-positive patients treated with consolidative

								radiotherapy, and PET-positive patients not treated with consolidative radiotherapy, respectively.
Yokoyama et al, 2021 [54]	Meta-analysis	6 studies (278 patients with multiple myeloma who were given treatment)	FDG PET/CT	MRI	IMWG criteria, EBMT criteria, biopsy, clinical follow-up	**Treatment response** Pooled Sens: 80% Pooled Spec: 58% Pooled +LR: 1.8 Pooled -LR: 0.33 Pooled DOR: 6.0 Q index: 0.71 AUC: 0.77	**Treatment response** Pooled Sens: 25% Pooled Spec: 83% Pooled +LR: 1.4 Pooled -LR: 0.81 Pooled DOR: 1.7 Q index: 0.57 AUC: 0.59	NA
Mesguich et al, 2021 [55]	Prospective	27 patients who underwent evaluation of treatment response after induction chemotherapy and after ASCT (multiple myeloma)	FDG PET/CT	Whole-body MRI	Follow-up	NA	NA	Patients with a positive PET/CT, post-induction or post-ASCT, were associated with a shorter PFS (post-induction, 19 months vs. not reached, p=0.0096; post-ASCT, 18 months vs. not reached, p=0.0005). There was no significant association between whole-body MRI results and PFS at either time points.
Melanoma								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Ravichandran et al, 2020 [56]	Retrospective	258 patients who underwent perioperative staging within 3 months of initial diagnosis (stage II and III melanoma)	FDG PET/CT	NA	Histology, cross-sectional imaging follow-up	NA	NA	FDG PET/CT upstaged 3.9% (10/258) of patients to stage IV by detecting distant metastases.
Stahlie et al, 2021 [57]	Prospective	23 patients who underwent imaging prior to lymphoscintigraphy and sentinel lymph node biopsy (stage IIB/C melanoma)	FDG PET/CT	US	Histopathology	**Regional lymph node metastases** Sens: 29% Spec: 100% PPV: 100% NPV: 47%	**Regional lymph node metastases** Sens: 36% Spec: 89% PPV: 83% NPV: 47%	NA

Hardie et al, 2021 [58]	Retrospective	76 patients who underwent staging prior to considering sentinel lymph node biopsy (pT4b melanoma)	FDG PET/CT	SLNB	Consensus from multidisciplinary team meetings, FNA	NA	NA	FDG PET/CT findings led to alteration in management of 18.4% (14/76) of patients (6—directly to lymphadenectomy, 2—directly to systemic treatment, 2—directly to wide local excision alone, 4—no further treatment).
Holtkamp et al, 2020 [59]	Prospective	25 patients who underwent staging (melanoma with satellite or in-transit metastases)	FDG PET/CT	Brain MRI	Pathology, clinical and imaging follow-up	**N-staging** Sens: 58% Spec: 100% PPV: 100% NPV: 43% **M-staging** Sens: 40% Spec: 95% PPV: 67% NPV: 86%	NA	FDG PET/CT upstaged and changed the management of 16.0% (4/25) patients (1—referred for immunotherapy, 1—referred to medical oncologist, 2—therapeutic lymph node dissection). Brain MRI did not alter the treatment plan or change the disease stage in any patient.
Le Goubey et al, 2021 [60]	Retrospective	80 patients who underwent therapy monitoring of immune checkpoint inhibitors (stage IV melanoma)	FDG PET/CT	CeCT	Conclusions from multidisciplinary staff meeting	NA	NA	FDG PET/CT findings led to change in management in 21.3% (17/80) of patients (2—initiated surgery, 10—additional radiotherapy, 1—switched line of treatment, 4—additional diagnostic procedure). CeCT findings induced management changes in 2.5% (2/80) of patients (2—additional radiotherapy).
Turner et al, 2021 [61]	Retrospective	332 asymptomatic patients who completed definitive surgical treatment and underwent surveillance follow-up (stage IIIA-D melanoma)	FDG PET/CT	CT	Histopathology, clinical and/or imaging follow-up	**Distant recurrence** Sens: 94% Spec: 78%*	**Distant recurrence** Sens: 76% Spec: 90%*	NA

Non-FDG Tracers ^{68}Ga-DOTA-(TATE, NOC, TOC)								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Yoo et al, 2021 [62]	Retrospective	167 patients who underwent further evaluation (suspected pancreatic neuroendocrine neoplasms detected by CT and/or MRI)	^{68}Ga-DOTA-TOC PET/CT + CI	CT, MRI	Pathology	**Diagnosis** ***PET/CT + CT*** Sens: 92.5-96.6%* Spec: 67.6-73.5% AUC: 0.86-0.89* ***PET/CT + MRI*** Sens: 91.8-98.4%* Spec: 66.7-70.8% AUC: 0.85-0.87*	**Diagnosis** ***CT*** Sens: 74.8-87.4%* Spec: 55.9-61.8% AUC: 0.71-0.74* ***MRI*** Sens: 70.5-86.9%* Spec: 58.3% AUC: 0.67-0.75*	NA
Ma et al, 2021 [63]	Meta-analysis	10 studies (484 patients with neuroendocrine tumours of unknown primary origin)	^{68}Ga-DOTA-TOC/TATE/NOC PET/CT	NA	Histology, clinical follow-up	**Primary site** Pooled DR: 61% Pooled Sens: 82% Pooled Spec: 55% Pooled +LR: 1.9 Pooled -LR: 0.32 Pooled DOR: 6 AUC: 0.69	NA	NA
Ghobrial et al, 2020 [64]	Prospective	114 patients who underwent imaging for suspected disease progression, restaging before initiation of new therapy, measurement of disease response after therapy, evaluation of unknown primary or suspected but undiagnosed disease (known or suspected neuroendocrine tumours)	^{68}Ga-DOTA-TOC PET/CT	NA	Pre- and post-PET questionnaire, consensus from multidisciplinary tumour board	NA	NA	A major change in management was recommended in 47.4% (54/114) of patients (8—chemotherapy/biologic modifiers, 2—liver-directed therapy, 7—octreotide long acting repeatable/lanreotide, 2—palliative external beam radiotherapy, 14—PRRT, 7—primary debulking surgery, 9—observation, 4—additional imaging, 1—other supportive care).
Purandare et al, 2020 [65]	Retrospective	119 patients who underwent initial staging (bronchopulmonary carcinoid tumours)	^{68}Ga-DOTA-NOC PET/CT	NA	Histopathology, imaging follow-up	NA	NA	^{68}Ga-DOTA-NOC PET/CT changed the intent of treatment of 11.8% (14/119) of patients by detecting metastases to distant sites (12—surgery deferred, 2—additional

								radiofrequency ablation and surgical resection of hepatic metastases).
$^{11}C/^{18}F$-Choline								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Jamsek et al, 2021 [66]	Prospective	25 patients who underwent preoperative staging (newly diagnosed primary medullary thyroid cancer)	^{18}F-Fluorocholine PET/CT	Neck US	Histopathology, clinical and/or imaging follow-up	**Lymph node metastases (compartment-based)** Sens: 80% Spec: 70%* PPV: 55%* NPV: 88%	**Lymph node metastases (compartment-based)** Sens: 53% Spec: 100%* PPV: 100%* NPV: 83%	NA
^{68}Ga-PSMA/^{18}F-DCFPyL								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Soni et al, 2021 [67]	Prospective	30 patients with serum prostate-specific antigen between 4 and 20 ng/ml (suspected prostate cancer)	^{68}Ga-PSMA PET/CT	mpMRI	Biopsy	**Diagnosis** Sens: 94.4% Spec: 100% PPV: 100% NPV: 92.3% Accu: 96.7%	**Diagnosis** Sens: 100% Spec: 92.3% PPV: 94.7% NPV: 100% Accu: 96.7%	NA
Amiel et al, 2021 [68]	Retrospective	230 patients who underwent preoperative staging followed by radical prostatectomy and pelvic lymph node dissection (intermediate to high-risk prostate cancer)	^{68}Ga-PSMA-11 PET/CT	NA	Histopathology	**Regional lymph node metastases** Sens: 48.5% Spec: 95.7% PPV: 82.1% NPV: 82.2%	NA	NA
Yip et al, 2021 [69]	Meta-analysis	6 studies (476 patients with intermediate to high-risk prostate cancer who underwent initial lymph node staging prior to extended pelvic lymph node dissection)	^{68}Ga-PSMA PET/CT	mpMRI	Histopathology	**Lymph node metastases (patient-based)** Pooled Sens: 69% Pooled Spec: 93% Pooled +LR: 9.69 Pooled -LR: 0.33 Pooled DOR: 29.25 AUC: 0.94 **(lesion-based)** Pooled Sens: 58%	**Lymph node metastases (patient-based)** Pooled Sens: 37% Pooled Spec: 95% Pooled +LR: 7.52 Pooled -LR: 0.66 Pooled DOR: 11.32 AUC: 0.93 **(lesion-based)** Pooled Sens: 44%	NA

						Pooled Spec: 99% Pooled +LR: 80.79 Pooled -LR: 0.43 Pooled DOR: 189.05 AUC: 0.99	Pooled Spec: 99% Pooled +LR: 57.00 Pooled -LR: 0.56 Pooled DOR: 101.24 AUC: 0.99	
Peng et al, 2020 [70]	Meta-analysis	10 studies (701 patients with intermediate to high-risk prostate cancer who underwent preoperative lymph node staging)	^{68}Ga-PSMA PET/CT	NA	Pathology	**Lymph node metastases** Pooled Sens: 84% Pooled Spec: 95% Pooled +LR: 17.19 Pooled -LR: 0.17 Pooled DOR: 100 AUC: 0.97	NA	NA
Wang et al, 2021 [71]	Meta-analysis	9 studies (640 patients with prostate cancer who underwent pelvic lymph node staging prior to radical prostatectomy)	^{68}Ga-PSMA-11 PET/CT	mpMRI	Histopathology	**Pelvic lymph node metastases** Pooled Sens: 71% Pooled Spec: 92% AUC: 0.92	**Pelvic lymph node metastases** Pooled Sens: 40% Pooled Spec: 92% AUC: 0.82	NA
Meijer et al, 2021 [72]	Retrospective	434 patients who underwent initial staging prior to robot-assisted laparoscopic radical prostatectomy and extended pelvic lymph node dissection (localized prostate cancer)	^{68}Ga-PSMA-11 or ^{18}F-DCFPyL or ^{18}F-PSMA-1007 PET/CT	mpMRI	Histopathology	**Pelvic lymph node metastases** Sens: 37.9% Spec: 94.1% PPV: 64.3% NPV: 84.4%	NA	NA
Van Damme et al, 2021 [73]	Retrospective	134 patients who underwent staging or restaging (81 newly diagnosed prostate cancer at high risk for metastases; 53 biochemical recurrence after curative treatment)	^{68}Ga-PSMA PET/CT	Whole-body MRI	Histopathology, clinical and imaging follow-up	**Staging (Bone metastases)** Sens: 93% Spec: 95% PPV: 81% NPV: 98% AUC: 0.94 **(Lymph node metastases)** Sens: 100% Spec: 96% PPV: 93% NPV: 100% AUC: 0.98* **(Visceral metastases)**	**Staging (Bone metastases)** Sens: 100% Spec: 97% PPV: 87% NPV: 100% AUC: 0.99 **(Lymph node metastases)** Sens: 67% Spec: 100% PPV: 100% NPV: 86% AUC: 0.83* **(Visceral metastases)**	NA

						Sens: 100% Spec: 99% PPV: 75% NPV: 100% AUC: 0.99 **Restaging (Bone metastases)** Sens: 100% Spec: 91% PPV: 86% NPV: 100% AUC: 0.96 **(Lymph node metastases)** Sens: 87% Spec: 100% PPV: 100% NPV: 90% AUC: 0.94 **(Visceral metastases)** Sens: 100% Spec: 100% PPV: 100% NPV: 100% AUC: 1.00	Sens: 100% Spec: 100% PPV: 100% NPV: 100% AUC: 1.00 **Restaging (Bone metastases)** Sens: 100% Spec: 91% PPV: 86% NPV: 100% AUC: 0.96 **(Lymph node metastases)** Sens: 79% Spec: 97% PPV: 95% NPV: 85% AUC: 0.88 **(Visceral metastases)** Sens: 60% Spec: 100% PPV: 100% NPV: 96% AUC: 0.80	
Gultekin et al, 2020 [74]	Prospective	51 patients who underwent staging prior to radical prostatectomy with or without extended lymph node dissection (non-metastatic prostate cancer)	^{68}Ga-PSMA PET/CT	NA	Histopathology	**Intraprostatic tumour localization** Sens: 58.2% Spec: 75.3% PPV: 84.4% NPV: 44.0% Accu: 63.4% **Extracapsular extension** Sens: 68.4% Spec: 75.0% PPV: 61.9% NPV: 80.0% Accu: 72.6% **Seminal vesicle involvement** Sens: 63.6% Spec: 92.3% PPV: 70.0% NPV: 90.0% Accu: 86.0% **Lymph node metastases**	NA	NA

						Sens: 50.0% Spec: 100% PPV: 100% NPV: 88.0% Accu: 89.3%		
Caglar et al, 2020 [75]	Retrospective	95 patients who underwent primary staging or restaging (prostate cancer)	^{68}Ga-PSMA PET/CT	Bone scintigraphy	Clinical and imaging follow-up	**Bone metastases** Sens: 98.2% Spec: 97.4% PPV: 98.2% NPV: 97.4%	**Bone metastases (equivocal scans as positive)** Sens: 94.6% Spec: 56.4% PPV: 75.7% NPV: 88.0% **(equivocal scans as negative)** Sens: 75.0% Spec: 94.9% PPV: 95.5% NPV: 72.5% **(equivocal scans excluded)** Sens: 93.3% Spec: 91.7% PPV: 95.5% NPV: 88.0%	NA
Al-Ibraheem et al, 2021 [76]	Retrospective	108 patients who underwent staging or restaging for definitive radiation therapy planning (prostate cancer)	^{68}Ga-PSMA PET/CT	Bone scan, CT, pelvic MRI	Consensus from multidisciplinary panel	NA	NA	^{68}Ga-PSMA PET/CT changed the disease stage of 36.1% (39/108) of patients (24 upstaged, 15 downstaged). Radiation planning was altered in 31.5% (34/108) of patients (27—change in radiation field, 7—stereotactic body radiotherapy added to oligometastatic sites).
Artigas et al, 2021 [77]	Retrospective	184 patients treated with radical prostatectomy with or without adjuvant or salvage radiotherapy (biochemically recurrent, hormone-sensitive prostate cancer)	^{68}Ga-PSMA-11 PET/CT	NA	Histology, imaging and/or clinical follow-up, consensus from multidisciplinary meeting	NA	NA	The clinical management changed after ^{68}Ga-PSMA-11 PET/CT in 58.7% (108/184) of patients (32—androgen deprivation therapy to metastasis-directed therapy, 33—salvage radiotherapy to metastasis-directed therapy, 5—salvage radiotherapy to androgen deprivation therapy, 32—androgen deprivation

								therapy to active surveillance, 6—salvage radiotherapy to active surveillance).
Pienta et al, 2021 [78]	Prospective (Phase 2/3 OSPREY trial)	385 patients who underwent staging or restaging (268 newly diagnosed high-risk prostate cancer planned for radical prostatectomy with pelvic lymph node dissection; 117 with suspected recurrent/metastatic prostate cancer on conventional imaging)	^{18}F-DCFPyL PET/CT	CT, MRI	Histopathology	**Primary tumour** Sens: 98.0% PPV: 100% **Pelvic lymph node metastases** Sens: 40.3% Spec: 97.9% PPV: 86.7% NPV: 83.2% **Locoregional recurrence or metastases** Sens: 95.8% PPV: 81.9%	**Primary tumour** Sens: 35.9% PPV: 100% **Pelvic lymph node metastases** Sens: 42.6% Spec: 65.1% PPV: 28.3% NPV: 77.8%	NA
Meijer et al, 2021 [79]	Retrospective	253 patients who underwent restaging after robot-assisted radical prostatectomy or external beam radiation therapy (biochemically recurrent, hormone-sensitive prostate cancer)	^{18}F-DCFPyL PET/CT	NA	Pre- and post-PET information	NA	NA	^{18}F-DCFPyL PET/CT findings changed the intended management of 40.7% (103/253) of patients (8—local treatment to locoregional treatment, 13—local treatment to metastasis-directed radiotherapy, 9—local treatment to systemic treatment, 13—systemic treatment to local treatment, 39—systemic treatment to locoregional treatment, 21—systemic treatment to metastasis-directed radiotherapy).
^{18}F-FDOPA								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Jena et al, 2021 [80]	Prospective	26 patients previously treated with surgery and/or	^{18}F-FDOPA PET or PET/mpMRI	CeMRI, mpMRI	Histopathology, clinical or imaging follow-up	**Recurrence** ***^{18}F-FDOPA PET*** Sens: 81.0% Spec: 100%	**Recurrence** ***CeMRI*** Sens: 52.4% Spec: 80.0%	NA

		adjuvant radiotherapy and temozolomide (suspected recurrent glioma)				PPV: 100% NPV: 55.6% Accu: 84.6% ***^{18}F-FDOPA PET/mpMRI*** Sens: 95.0% Spec: 100% PPV: 100% NPV: 80.0% Accu: 96.0%	PPV: 91.7% NPV: 28.6% Accu: 57.7% ***mpMRI*** Sens: 81.0% Spec: 60.0% PPV: 89.5% NPV: 42.9% Accu: 77.0%	
Pancreatic Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Kim and Kim, 2021 [81]	Meta-analysis	14 studies (752 patients with intraductal papillary mucinous neoplasm)	FDG PET or PET/CT	NA	Histopathology, clinical and imaging follow-up	**Diagnosis** Pooled Sens: 84% Pooled Spec: 95% Pooled +LR: 17.4 Pooled -LR: 0.17 Pooled DOR: 101 AUC: 0.93	NA	NA
Regenet et al, 2020 [82]	Prospective	99 patients considered as candidates for surgery (suspected intraductal papillary mucinous neoplasms)	FDG PET/CT	CT, MRI, endoscopic US	Histopathology	**Diagnosis** Sens: 54.2% Spec: 76.0% PPV: 41.9% NPV: 83.8%	**Diagnosis** ***CT*** Sens: 20.0% Spec: 83.3% PPV: 33.3% NPV: 71.4% ***MRI*** Sens: 33.3% Spec: 95.2% PPV: 66.7% NPV: 83.3% ***Endoscopic US*** Sens: 45.5% Spec: 82.8% PPV: 50.0% NPV: 80.0%	NA
Reddy et al, 2021 [83]	Prospective	32 patients who had radiologically detected lesion (pancreatic and periampullary masses)	FDG PET/CT	US, CT, MRI	Pathology	**Diagnosis** Sens: 92.0% Spec: 42.8% PPV: 85.2% NPV: 60.0% Accu: 81.3%	NA	FDG PET/CT detected additional distant metastases not seen on conventional imaging and subsequently changed the management from curative resection to palliative therapy in 21.9% (7/32) of patients.
Pediatric Cancer								

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Li et al, 2021 [84]	Meta-analysis	9 studies (1640 patients with newly diagnosed HL and NHL)	FDG PET/CT	BMB	BMB, follow-up	**Bone marrow involvement** Pooled Sens: 97% Pooled Spec: 99% Pooled +LR: 79.9 Pooled -LR: 0.03 Pooled DOR: 2414.6 AUC: 1.00	NA	NA
Hu et al, 2021 [85]	Meta-analysis	8 studies (1417 patients with HL and NHL)	FDG PET/CT	BMB	BMB, imaging follow-up	**Bone marrow infiltration** Pooled Sens: 95% Pooled Spec: 95% AUC: 0.99	NA	NA
Sun et al, 2021 [86]	Meta-analysis	7 studies (127 patients with neuroblastoma)	FDG PET or PET/CT	BMB	BMB	**Bone metastases or bone marrow involvement** Pooled Sens: 87% Pooled Spec: 96% Pooled +LR: 21.3 Pooled -LR: 0.14 Pooled DOR: 157 AUC: 0.97	NA	NA
Mercolini et al, 2021 [87]	Retrospective	114 patients who underwent initial staging prior to treatment (metastatic rhabdomyosarcoma)	FDG PET/CT	Bone scintigraphy	BMB/BMA	**Bone marrow involvement** Sens: 91.8% Spec: 93.8%	NA	NA
Tezol et al, 2020 [88]	Retrospective	75 patients who underwent staging before the initiation of systemic therapy (23 HL, 20 NHL, 11 neuroblastoma, 10 Ewing sarcoma, 6 Langerhans cell histiocytosis, 5 rhabdomyosarcoma)	FDG PET/CT	BMB	BMB	**Bone marrow involvement** Sens: 66% Spec: 75% PPV: 60% NPV: 80%	NA	NA
Sarcoma								

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Younis et al, 2020 [89]	Meta-analysis	21 studies (1198 patients with primary bone and soft tissue sarcomas)	FDG PET or PET/CT	NA	Histopathology	**Diagnosis and grading** Pooled Sens: 89.2% Pooled Spec: 75.1% AUC: 0.88	NA	NA
Aryal et al, 2021 [90]	Prospective	54 patients who underwent initial staging (24 osteosarcoma; 30 Ewing sarcoma)	FDG PET/CT	Whole-body MRI, ^{99m}Tc-MDP skeletal scintigraphy	Consensus from multidisciplinary team, imaging follow-up	**Bone metastases (osteosarcoma)** Sens: 100% Spec: 100% PPV: 100% NPV: 100% **(Ewing sarcoma)** Sens: 88% Spec: 100% PPV: 100% NPV: 96%	**Bone metastases (osteosarcoma)** ***Whole-body MRI*** Sens: 83% Spec: 94% PPV: 83% NPV: 94% ***^{99m}Tc-MDP skeletal scintigraphy*** Sens: 67% Spec: 78% PPV: 50% NPV: 88% **(Ewing sarcoma)** ***Whole-body MRI*** Sens: 88% Spec: 95% PPV: 88% NPV: 95% ***^{99m}Tc-MDP skeletal scintigraphy*** Sens: 50% Spec: 95% PPV: 80% NPV: 84%	NA
Abdella et al, 2021 [91]	Prospective	33 patients with primary malignant bone tumours who underwent assessment of treatment response or routine follow-up (12 osteosarcoma, 6 chondrosarcoma, 8 Ewing sarcoma, 5 fibrosarcoma, 2 angiosarcoma)	FDG PET/CT	CT	Histopathology, imaging follow-up	**Restaging** Sens: 94.4% Spec: 86.7% PPV: 89.5% NPV: 92.8% Accu: 90.9%	**Restaging** Sens: 88.2% Spec: 81.2% PPV: 83.3% NPV: 86.6% Accu: 84.8%	NA

Yokoyama et al, 2021 [92]	Meta-analysis	4 studies (91 patients treated with molecular targeted therapy for GIST)	FDG PET or PET/CT	CT	Clinical follow-up	**Treatment response** Pooled Sens: 89% Pooled Spec: 65% Pooled +LR: 1.9 Pooled -LR: 0.23 Pooled DOR: 5.8 Q index: 0.74 AUC: 0.81	**Treatment response** Pooled Sens: 52% Pooled Spec: 92% Pooled +LR: 3.0 Pooled -LR: 0.66 Pooled DOR: 4.9 Q index: 0.66 AUC: 0.71	NA
Thoracic Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Zhang et al, 2021 [93]	Retrospective	309 treatment-naïve patients (NSCLC)	FDG PET/CT	Circulating tumour cells	Histopathology	**Diagnosis** Sens: 96.4%	**Diagnosis** Sens: 75.7%	NA
Buero et al, 2021 [94]	Retrospective	76 patients who underwent pulmonary resection with systematic nodal sampling (stage IB and IIA NSCLC)	FDG PET/CT	Chest CT	Surgical pathology	**Nodal metastases** NPV: 87%	NA	NA
Yoon and Pak, 2021 [95]	Meta-analysis	8 studies (523 patients with recurrent SCLC and NSCLC)	FDG PET or PET/CT	CT, MRI, US, bone scan, x-ray, tumour marker	Pre- and post-PET information	NA	NA	The pooled rate of management change was 61.4%.
Ripley et al, 2021 [96]	Retrospective	187 patients who underwent staging (malignant pleural mesothelioma)	FDG PET or PET/CT	Diagnostic laparoscopy	Pathology	**Peritoneal disease** Sens: 25.0% Spec: 77.5% PPV: 18.4% NPV: 83.6% Accu: 68.7%	**Peritoneal disease** Sens: 71.0% Spec: 84.0% PPV: 46.8% NPV: 93.6% Accu: 81.8%	NA
Kim et al, 2022 [97]	Meta-analysis	14 studies (691 patients with thymic epithelial tumour)	FDG PET or PET/CT	NA	Histopathology	**Differentiation between thymic cancer and thymoma** Pooled Sens: 89% Pooled Spec: 77% Pooled +LR: 3.9 Pooled -LR: 0.14 Pooled DOR: 28 AUC: 0.92 **Differentiation between low-risk and high-risk thymic epithelial tumour**	NA	NA

						Pooled Sens: 90% Pooled Spec: 81% Pooled +LR: 4.7 Pooled -LR: 0.12 Pooled DOR: 38 AUC: 0.91		
Various Sites								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Zhou et al, 2021 [98]	Prospective	70 patients with solid malignancies (suspicious liver lesions)	FDG PET/CT, FDG PET/MRI	NA	Histopathology, clinical and imaging follow-up	**Liver metastases (patient-based)** ***PET/CT*** Sens: 76.8% Spec: 85.7% PPV: 95.6% NPV: 48.0% Accu: 78.6% ***PET/MRI*** Sens: 98.2% Spec: 100% PPV: 100% NPV: 93.3% Accu: 98.6% **(lesion-based)** ***PET/CT*** Sens: 35.2% Spec: 85.7% PPV: 97.2% NPV: 8.6% Accu: 38.6% ***PET/MRI*** Sens: 98.0% Spec: 100% PPV: 100% NPV: 75.0% Accu: 98.1%	NA	The therapeutic strategies of 41.4% (29/70) of patients needed reconsideration after additional FDG PET/MRI (13—change in clinical staging, 14—change in surgical planning, 2—change in diagnosis).
Soni et al, 2021 [99]	Retrospective	83 patients with extracervical metastases (carcinoma of unknown primary)	FDG PET/CT	Physical examination, US, CT, MRI	Histopathology, clinical or imaging follow-up	**Primary site** DR: 39% Sens: 89% Spec: 85% PPV: 82% NPV: 91% Accu: 87%	NA	NA
Woo et al, 2021 [100]	Meta-analysis	38 studies (2795 patients with cancer of unknown primary)	FDG PET or PET/CT	CT, MRI	Pathology, pre- and post-PET information	**Primary site** Pooled DR: 35% **Additional metastases** Pooled DR: 25%	NA	The pooled proportion of patients with a change in management was 35%.

*p<0.05
‡Significant difference with PET/MRI (p<0.05)
Abbreviations: Accu, accuracy; ASCT, autologous stem cell transplant; AUC, area under the curve; BMA, bone marrow aspirate; BMB, bone marrow biopsy; DLBCL, diffuse large B-cell lymphoma; CEA, carcinoembryonic antigen; CeCT, contrast-enhanced computed tomography; CeMRI, contrast-enhanced magnetic resonance imaging; CI, confidence interval; CP, carboplatin-paclitaxel; CT, computerized tomography; DFCS, disease-free cancer survival; DFS, disease-free survival; DLBCL, diffuse large B-cell lymphoma; DOR, diagnostic odds ratio; DR, detection rate; EBMT, European Society for Blood and Marrow Transplant; EEG, electroencephalography;^{18}F-DCFPyL, (2s)-2-[[(1S)-1-carboxy-5-[(6-(^{18}F)fluoranylpyridine-3-carbonyl)amino]pentyl]carbamoylamino]pentanedioic acid; FDG, fluorodeoxyglucose; ^{18}F-FDOPA, ^{18}F-fluorodeoxyglucose; FNA, fine needle aspiration; ^{18}F-NaF, ^{18}F-sodium fluoride; FOLFOX, oxaliplatin, leucovorin, and fluorouracil; ^{18}F-PSMA, Fluorine-18-labelled prostate-specific membrane antigen; ^{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-PSMA, Gallium-68-labelled prostate-specific membrane antigen; ^{68}Ga-PSMA-11, Gallium-68-labelled prostate-specific membrane antigen 11; GIST, gastrointestinal stromal tumour; GTV, gross tumour volume; HL, Hodgkin lymphoma; HR, hazard ratio; IMWG, International Myeloma Working Group; ^{131}I-WBS, radioiodine whole body scan; +LR, positive likelihood rate; -LR, negative likelihood rate; MEG, magnetoencephalography; mpMRI, multi-parametric magnetic resonance imaging; MRI, magnetic resonance imaging; NA, not applicable; NHL, non-Hodgkin lymphoma; NPV, negative predictive value; NSCLC, non-small-cell lung carcinoma; OS, overall survival; OSPREY, A PrOspective Phase 2/3 Multi-Center Study of 18F-DCFPyL PET/CT Imaging in Patients With PRostate Cancer: Examination of Diagnostic AccuracY; PERCIST, PET Response Criteria In Solid Tumor; PET, positron emission tomography; PFS, progression-free survival; PPV, positive predictive value; PRRT, peptide-receptor radionuclide therapy; PTV, planning target volume; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RCT, randomized controlled trial; SCC-Ag, serum squamous cell carcinoma antigen; SCLC, small cell lung cancer; Sens, sensitivity; SLNB, sentinel lymph node biopsy; SMD, standard mean difference; Spec, specificity; ^{99m}Tc-DMSA, technetium 99m dimercaptosuccinic acid; ^{99m}Tc-MDP, technetium-99m-labelled methylene diphosphonate; Tg, thyroglobulin; TNM, tumour, node, metastasis; TTP, time to progression; US, ultrasound; VEEG, video-electroencephalography; vs, versus; WBS, whole body scan