Ontario Health
Cancer Care Ontario

PET Six-Month Monitoring Report 2021-1

Evidence from Primary Studies and Systematic Reviews and Recommendations from Clinical Practice Guidelines January to June 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 21st 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 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 four studies published between January and June 2021 met the inclusion criteria. A summary of the evidence from the 104 studies can be found in **Appendix 1: Summary of studies from January to June 2021**.

Breast Cancer

Ten studies met the inclusion criteria [1-10]. Numerous studies evaluated the use of FDG PET or PET/CT in the staging of patients with breast cancer. FDG PET or PET/CT detected axillary lymph node metastases with low to moderate sensitivity (49.0% to 81.0%) but high specificity (91.0% to 94.0%) [1-4]. FDG PET or PET/CT was found to be more sensitive than magnetic resonance imaging (MRI) in one study [1] but less sensitive in another [4]. FDG PET/CT was also inadequate in accurately assessing axillary response after neoadjuvant systemic therapy [5]. Nonetheless, findings from FDG PET or PET/CT led to changed management in 18.0% to 38.8% of patients [6-9]. After curative surgery, the impact of FDG PET or PET/CT based on the proportion of management change was 44.4% [10].

Esophageal Cancer

Five studies met the inclusion criteria [11-15]. In patients treated with neoadjuvant chemotherapy or chemoradiotherapy prior to surgical resection, the authors from a meta-analysis reported a pooled sensitivity of 77.2% and a pooled specificity of 75.0% for FDG PET/CT in predicting early pathological response [11]. For detecting residual disease six to eight weeks after neoadjuvant chemoradiotherapy, diffusion-weighted MRI (85%) was found to be more accurate than FDG PET/CT (61% to 64%) [12]. In patients who underwent initial diagnosis, primary staging, restaging or follow-up due to suspected relapse, FDG PET/CT provided additional information that would impact therapeutic management in 32.9% to 37.4% of cases [13,14]. Specifically, FDG PET/CT was able to detect distant metastases in a high proportion of patients after surgical resection, thus changing the intent of management in 41.2% from salvage therapy to palliative care [15].

Gastrointestinal Cancer

Ten studies met the inclusion criteria [16-25]. In the primary staging of patients with gastric cancer, FDG PET/CT was found to be more specific (pooled estimate, 92% versus 85%) but less sensitive (pooled estimate, 49% versus 69%) than contrast-enhanced CT in the diagnosis of lymph node metastases [16]. Conversely, a retrospective study reported that FDG PET/CT upstaged 19.0% of patients by demonstrating positive lymph nodes or metastases that were previously undetected on CT [17]. FDG PET/CT showed similarly poor sensitivity (pooled estimate, 56%) but high specificity (pooled estimate, 97%) for diagnosing distant metastases [16]. For the diagnosis of recurrence, FDG PET/CT (pooled sensitivity, 81%; pooled specificity, 83%) and contrast-enhanced CT (pooled sensitivity, 82%; pooled specificity, 76%) were both moderately reliable imaging techniques [16]. In the initial staging of patients with locally advanced gall bladder cancer, 46.6% of cases were found to be upstaged to stage IV disease after FDG PET/CT [18]. Additional information provided by FDG PET/CT modified the management plan of 23.5% of patients [19]. In patients with newly diagnosed colorectal cancer, FDG PET/CT appeared to have limitations for detecting lymph node metastases (pooled sensitivity, 65%; pooled specificity, 75%) [20]. Furthermore, MRI is preferred over FDG PET/CT for evaluating colorectal cancer liver metastases (pooled sensitivity, 89% versus 62%, $p<0.001$) [21]. In the preoperative evaluation of patients with ampullary and duodenal papillary carcinoma, FDG PET/CT was more accurate than contrast-enhanced CT/MRI (88.3% versus

72.1%, p=0.007), which ultimately led to treatment decision changes in 12.8% of cases [22]. In the staging of patients with extrahepatic cholangiocarcinoma, FDG PET/CT showed lower sensitivity for identifying the primary tumour (78.6% versus 97.4% and 94.9%, respectively, p<0.001) and lymph node involvement (43.6% versus 77.6% and 74.5%, respectively, p<0.001) than either MRI or contrast-enhanced multidetector row CT. However, FDG PET/CT was more specific than both for the latter indication (95% versus 69.7% and 72.1%, respectively, p<0.001) [23]. For inguinal lymph node staging of patients with anal squamous cell carcinoma, FDG PET/CT exhibited a positive predictive value of 40% and a negative predictive value of 82% when referenced against sentinel lymph node biopsy [24]. Regarding patients with hepatocellular carcinoma, FDG PET/CT altered management in 9.9% of cases for initial staging and 21.3% of cases for restaging after prior therapy [25].

Genitourinary Cancer

Two studies met the inclusion criteria [26,27]. In the staging of patients with invasive penile squamous cell carcinoma prior to surgical treatment, FDG PET/CT appears to be more sensitive but less specific than contrast-enhanced CT in the evaluation of inguinal lymph node metastases [26]. In the primary staging of patients with high-grade prostate cancer, the sensitivity of FDG PET/CT was significantly better than that of bone scintigraphy in the assessment of bone metastases (100% versus 78.8%, p<0.05) [27].

Gynecologic Cancer

Ten studies met the inclusion criteria [28-37]. In the preoperative evaluation of women with high-risk endometrial cancer, FDG PET/CT and CT/MRI both offered very high specificity for the detection of lymph node metastases, but FDG PET/CT demonstrated superior sensitivity (63.0% to 89.0% versus 40.7% to 64.0%) [28,29], particularly in assessing paraaortic involvement [30]. Likewise, FDG PET/CT was more sensitive than CT in detecting extrauterine disease (63% versus 45%), peritoneal disease (86% versus 40%), and distant metastases (100% versus 83%). A negative FDG PET/CT scan was a significant prognostic indicator for better survival, whereas CT findings have no prognostic value [28]. In women with newly diagnosed cervical cancer, FDG PET or PET/CT or PET/MRI performed similarly to CT and MRI for detecting lymph node metastases with low sensitivity but high specificity. FDG PET or PET/CT or PET/MRI was also comparable to ultrasound and MRI in determining parametrial invasion with moderate sensitivity and high specificity [31]. In the same fashion for early-stage disease, poor sensitivity and high specificity were observed with both FDG PET/CT (sensitivity, 35%; specificity, 91%) and CT (sensitivity, 33%; specificity, 87%) in the detection of extra-cervical metastases [32]. In locally advanced cases, FDG PET or PET/CT also detected para-aortic lymph node metastases with low sensitivity (pooled estimate, 40%) but high specificity (pooled estimate, 93%) [33]. For the preoperative assessment of lymph node involvement in women with advanced epithelial ovarian cancer, FDG PET/CT showed very poor sensitivity (26.7%) but high specificity (90.9%) [34]. For the diagnosis of recurrence and metastases of ovarian cancer, FDG PET/CT (accuracy, 86.0% to 89.9%) performed better than contrast-enhanced CT (accuracy, 39.5%), and serum CA-125 (accuracy, 69.8% to 79.7%) and HE4 (accuracy, 76.8%) tumour markers [35,36]. In the preoperative lymph node staging of women with vulvar cancer, FDG PET/CT displayed a pooled sensitivity of 70% and a pooled specificity of 90% on a patient-based analysis. On a groin-based analysis, the pooled sensitivity and specificity were 76% and 88%, respectively [37].

Head and Neck Cancer

Twelve studies met the inclusion criteria [38-49]. In the staging or restaging of patients with head and neck cancer, FDG PET/CT was comparable to contrast-enhanced MRI in the

detection of distant metastases [38]. There were also insignificant differences between FDG PET/CT and PET/MRI in the N-staging of these patients [39]. In patients who underwent curative-intent treatment, FDG PET/CT detected recurrence and distant metastases with high negative predictive value but low to moderate positive predictive value [40,41]. In the work-up of patients presenting with metastatic neck nodes from unknown primary, the detection rate of FDG PET/CT for the primary site ranged from 28.5% to 40.0%; however, the false-positivity rate was substantial (9.0% to 15.0%) [42,43]. The addition of FDG PET/CT to conventional work-up in the initial staging of patients with early-stage nasopharyngeal carcinoma improved the sensitivity of detecting cervical lymph node metastases (96.6% versus 76.4%, $p<0.001$) but not for metastatic retropharyngeal lymph nodes (72.2% versus 91.1%, $p=0.004$). Information provided by FDG PET/CT modified the planned radiotherapy target volume and dose in 11.5% of patients; however, this did not translate to better survival [44]. In post-treatment response evaluation, the accuracy of FDG PET/CT using Hopkins criteria for the detection of residual nasopharyngeal carcinoma was 84.5%. Negative FDG PET/CT results were significantly correlated with greater three-year locoregional failure-free survival (96.7% versus 79.5%, $p=0.043$) and disease-free survival (84.6% versus 54.4%, $p=0.028$) [45]. In patients with oropharyngeal and hypopharyngeal squamous cell carcinoma, the diagnostic capability of pretreatment FDG PET/MRI was comparable to that of FDG PET/CT but superior to MRI for detecting synchronous cancers and distant metastases [46]. In the initial staging of patients with sinonasal tumours, FDG PET/CT or PET/MRI yielded excellent accuracies for detecting lymph node (92.3%) and distant (98.5%) metastases [47]. The utility of FDG PET/CT scans obtained three months after adjuvant therapy in patients with locally advanced oral squamous cell carcinoma was examined in one retrospective study. While the specificity of surveillance FDG PET/CT for identifying disease recurrence was high (92%), the sensitivity was only 58% [48]. In differentiated thyroid carcinoma patients with negative post-therapeutic ^{131}I whole body scan, but detectable serum thyroglobulin, a thyroglobulin doubling time of less than or equal to 2.5 years was found to optimize the diagnostic performance of FDG PET/CT for localizing sites of recurrent disease [49].

Hematologic Cancer

Eight studies met the inclusion criteria [50-57]. For the evaluation of bone marrow involvement, one meta-analysis found that the diagnostic accuracy of FDG PET or PET/CT (area under the curve [AUC], 0.90) was comparable to that of MRI (AUC, 0.89) in patients with Hodgkin and non-Hodgkin lymphoma, but both modalities showed suboptimal sensitivity (65% and 78%, respectively) [50]. Particularly in non-Hodgkin lymphoma, FDG PET/CT also demonstrated poor sensitivity in patients with follicular lymphoma (60%) [51] and diffuse large B-cell lymphoma (DLBCL) (36%) [52]; thus, bone marrow biopsy remains necessary for definitive diagnosis. In patients with mantle cell lymphoma, the accuracy of FDG PET/CT for detecting gastric and colorectal involvement were 71.2% and 83.9%, respectively [53]. In patients with suspected primary central nervous system lymphoma, FDG PET/CT (pooled diagnostic yield, 4.9%) maybe a better alternative to contrast-enhanced CT (pooled diagnostic yield, 2.5%) for excluding systemic involvement [54]. In response assessment of advanced-stage DLBCL after four cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), interim-PET-positive patients achieved significantly worse three-year progression-free survival (PFS) (34.3% versus 78.1%, $p<0.001$) and overall survival (OS) (62.3% versus 87.1%, $p=0.03$) than interim-PET-negative patients despite receiving two additional cycles of R-CHOP [55]. In the five-year follow-up of the GHSG HD17 trial, which randomized patients with newly diagnosed, early-stage unfavourable Hodgkin lymphoma, the omission of involved-field radiotherapy for interim-PET-negative patients after two cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (eBEACOPP) plus two cycles of

doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) did not result in loss of efficacy [56]. Similarly, the final analysis of the randomized GITIL/FIL HD0607 trial demonstrated that consolidation radiotherapy could be safely omitted in advanced-stage Hodgkin lymphoma patients with a large nodal mass (≥5 cm) who obtained a negative PET scan after two and six cycles of ABVD [57].

Melanoma

Five studies met the inclusion criteria [58-62]. While the utility of FDG PET/CT is limited in the initial staging of early-stage melanoma [58,59], FDG PET/CT was able to detect asymptomatic visceral distant metastases in 25.7% of patients with locoregional recurrences [59]. Furthermore, FDG PET/MRI (sensitivity, 89.1%; specificity, 100%) appears to be comparable to FDG PET/CT (sensitivity, 92.7%; specificity, 100%) in the detection of distant metastases [60]. In patients with advanced disease, primarily not considered for surgery, FDG PET/CT results led to changes in intended management in 48.7% of cases [61]. For those who were treated with immunotherapy, baseline metabolic tumour volume ($p<0.001$), spleen to liver ratio ($p=0.001$), peak standardized uptake value ($p=0.001$), and total lesion glycolysis ($p<0.001$) parameters were all significant predictors of final response [62].

Neuro-Oncology

One study met the inclusion criteria [63]. A meta-analysis reported a pooled sensitivity of 78% and a pooled specificity of 87% for FDG PET in differentiating true glioma progression from treatment-related changes.

Non-FDG Tracers

Twenty-four studies met the inclusion criteria [63-86]. In the management of patients with neuroendocrine tumours (NETs), ^{68}Ga-DOTA PET/CT influenced decision making in 23.8% to 39.4% of cases [64,65]. For the differentiation of glioma progression from treatment-related changes, ^{18}F-FET PET with combined static and dynamic parameters (maximum tumour-to-brain ratio [TBR_{max}] + Slope) produced the highest accuracy (86%), which was a marked improvement over perfusion-weighted MRI (63%) [66]. Similarly, a meta-analysis also showed that multi-parameter analysis of ^{18}F-FET PET generated the best accuracy [63]. ^{18}F-FDOPA PET, on the other hand, performed slightly worst than ^{18}F-FET PET [63]. Several studies evaluated the use of ^{68}Ga-PSMA PET/CT or PET/MRI in prostate cancer. For initial diagnosis, pooled estimates from two meta-analyses showed a sensitivity of 90% to 97% and a specificity of 66% to 90% [67,68]. For primary staging purposes, ^{68}Ga-PSMA/^{18}F-DCFPyL PET/CT detected lymph node metastases with exceptionally high specificity (92.0% to 100%), but reduced sensitivity (15.4% to 48.3%) [69-74]. These results were on par with those of contrast-enhanced CT/MRI [69], diffusion-weighted MRI [69], and multiparametric MRI [70,72]. Conversely, ^{68}Ga-PSMA PET/CT (pooled sensitivity, 95%; pooled specificity, 100%) was found to be superior to bone scan (pooled sensitivity, 86%; pooled specificity, 87%) in the detection of bone metastases [75]. Taken together, the overall staging sensitivity ranged from 75% to 93% and specificity from 96% to 99% [68,76]. Information from ^{68}Ga-PSMA PET/CT or PET/MRI had an impact on disease management in 27.6% to 35.9% of patients [77,78]. In the biochemical recurrent setting, ^{68}Ga-PSMA PET/CT detected recurrence with an accuracy of 70% to 100% [79,80]. Subsequently, clinical management was changed in 27.6% to 68.1% of patients [80-85]. In a small prospective study of patients with hepatocellular carcinoma who were newly diagnosed or previously treated with transarterial chemoembolization, the incorporation of ^{68}Ga-PSMA PET/CT changed the treatment strategy in 33.3% of cases [86].

Pancreatic Cancer

Three studies met the inclusion criteria [87-89]. In the initial staging of patients with pancreatic ductal adenocarcinoma, the pooled proportion management changes as a result of FDG PET/CT or PET/MRI detecting lymph node (pooled sensitivity, 55%; pooled specificity, 94%) and distant (pooled sensitivity, 80%; pooled specificity, 100%) metastases was 19% [87]. For those with potentially operable disease treated with neoadjuvant therapy, FDG PET/CT upstaged 11.9% of patients who avoided noncurative surgery [88]. Results from a meta-analysis showed that FDG PET/CT (AUC, 0.92) had the highest overall accuracy for diagnosing intraductal papillary mucinous neoplasm, followed by MRI/magnetic resonance cholangiopancreatography (AUC, 0.87), diffusion-weighted MRI (AUC, 0.82), CT (AUC, 0.80), and endoscopic ultrasound (AUC, 0.79) [89].

Pediatric Cancer

Three studies met the inclusion criteria [90-92]. For the initial staging and therapy planning of patients with soft-tissue sarcoma, FDG PET/CT (sensitivity, 90%) was found to be superior to CT/MRI (sensitivity, 50%) in the detection of lymph node metastases but CT/MRI was better in the detection of lung metastases (100% versus 14%). Nonetheless, FDG PET/CT altered therapy planning in 19.2% of patients [90]. In the post-treatment evaluation of patients with Ewing sarcoma and primitive neuroectodermal tumour, FDG PET/CT (91.7%) was more accurate than multidetector CT/MRI (81.2%) in the detection of relapse and metastases. Subsequently, FDG PET/CT findings changed the course of treatment in 16.7% of patients. The PFS was significantly lower in patients with a positive PET scan in comparison to those with a negative PET scan ($p=0.001$) [91]. In patients with Hodgkin lymphoma, FDG PET/CT displayed exceptional sensitivity (pooled estimate, 95%) and specificity (pooled estimate, 97%) for the detection of bone marrow involvement [92].

Sarcoma

Three studies met the inclusion criteria [93-95]. Pooled estimates from a meta-analysis revealed high sensitivity (94%) and specificity (89%) for FDG PET/CT in the diagnosis of chondrosarcoma [93]. Likewise in another meta-analysis of patients with newly diagnosed Ewing sarcoma, FDG PET or PET/CT detected bone marrow metastases with excellent sensitivity (100%) and specificity (96%) [94]. In the restaging or post-therapy surveillance of patients with gastrointestinal stromal tumour, FDG PET/CT was shown to be highly accurate (95%) in localizing recurrences, thereby impacting clinical management in 18.0% of scans [95].

Thoracic Cancer

Six studies met the inclusion criteria [38,96-100]. In the staging or restaging of patients with non-small-cell lung carcinoma (NSCLC) for distant metastases, FDG PET/CT appeared to have a lower sensitivity (pooled estimate, 72% versus 83%) and specificity (pooled estimate, 95% versus 100%) than contrast-enhanced MRI [38]. Similarly, FDG PET or PET/CT yielded only moderate sensitivity (pooled estimate, 79%) and specificity (pooled estimate, 65%) for the prediction of occult lymph node metastases [96]. In post-treatment follow-up, FDG PET/CT (96% to 97.3%) tended to be more accurate than contrast-enhanced CT (84%) in detecting recurrent disease [97,98]. Expectedly, patients with a positive follow-up PET scan had a significantly worst OS than those with a negative follow-up PET scan (18 months versus 45 months, $p<0.0001$) [98]. The application of FDG PET/CT imaging in gamma knife radiotherapy for lung cancer patients with brain metastases improved the effective (61.5% versus 42.3%, $p=0.032$) and local (90.4% versus 75.0%, $p=0.038$) control rates, and reduced the rate of adverse events (21.2% versus 42.3%, $p=0.02$) at three months after treatment. However, the median survival times were not significantly different between patients who received FDG PET/CT and those who did not (10 months versus 10 months, $p=0.284$) [99]. In the preoperative evaluation

of patients without histological diagnosis of solitary pulmonary nodule, FDG PET/CT was highly sensitive (94.6%) but lacked specificity (23.4%) [100].

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.

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.

Genitourinary Cancer

Current Indications for Germ Cell Tumours

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

Current Eligibility Criteria for the PET MUSE Trial

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

Reviewer's Comments (Dr. Glenn Bauman)

The current recommendations for the utilization of PET/CT in genitourinary cancer remain valid and no changes are required. Nonetheless, the study by Jakobsen et al. [26] does support FDG PET/CT for staging penile cancer as an adjunct to surgical sampling. The study by Otis-Chapados et al. [27] is not convincing especially given the availability of more sensitive tracers.

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 lymphoma 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 lymphoma 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 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 (Dr. Tara Baetz)

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

Neuro-Oncology

Current Indication for Paraneoplastic Syndrome

- For the evaluation of patients with suspected paraneoplastic neurologic syndromes with negative conventional imaging, with or without positive onconeuronal antibodies.

Reviewer's Comments (Dr. Amit Singnurkar)

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

Non-FDG Tracers

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 prostate-specific antigen (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)

The meta-analysis by Lee et al. [87] and the retrospective study by Itchins et al. [88] both add to the body of evidence supporting the use of PET for staging if a patient is a candidate for potentially curative resection as determined by conventional imaging.

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

Reviewer's Comments (Dr. Amer Shammas)

The 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 (Dr. Gina Di Primio)

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

Thoracic Cancer

Current Indications for Solitary Pulmonary Nodule

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

Current Indications for NSCLC

- For initial staging of patients with NSCLC (clinical stage I–III) being considered for potentially curative therapy.
- For re-staging of patients with locoregional recurrence, after primary treatment, being considered for definitive salvage therapy.
  Note: Histological proof is not required prior to PET if there is high clinical suspicion for NSCLC (e.g., based on patient history and/or prior imaging).
  Note: PET is appropriate for patients with either histological proof of locoregional recurrence or strong clinical and radiological suspicion of recurrence who are being considered for definitive salvage therapy.

Current Indication for Small Cell Lung Cancer

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

Current Indication for Mesothelioma

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

Reviewer's Comments (Dr. Donna Maziak)

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

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CONTACT INFORMATION

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APPENDIX 1: SUMMARY OF STUDIES FROM JANUARY TO JUNE 2021.

Breast Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Baran et al, 2020 [1]	Retrospective	102 patients who underwent staging prior to SLNB or ALND (locally advanced breast cancer)	FDG PET/CT	MRI	Histopathology	**Axillary lymph node metastases** Sens: 81.0% Spec: 93.2% PPV: 94.0% NPV: 78.9% +LR: 11.89 -LR: 0.20 Accu: 86.3%	**Axillary lymph node metastases** Sens: 68.6% Spec: 93.8% PPV: 96.0% NPV: 57.7% +LR: 10.97 -LR: 0.34 Accu: 76.5%	NA
Zhang et al, 2020 [2]	Meta-analysis	11 studies (1203 patients with breast cancer)	FDG PET/CT	MRI	Histopathology, imaging follow-up	**Axillary lymph node metastases** Pooled Sens: 56% Pooled Spec: 91% Pooled DOR: 12	**Axillary lymph node metastases** Pooled Sens: 55% Pooled Spec: 86% Pooled DOR: 7	NA
Kasem et al, 2021 [3]	Meta-analysis	9 studies (1486 patients with stage I-III breast cancer who underwent axillary staging)	FDG PET/CT	NA	Histopathology	**Axillary lymph node metastases** Pooled Sens: 52.2% Pooled Spec: 91.6% Pooled PPV: 77.8% Pooled NPV: 77.2% Pooled Accu: 77.3%	NA	NA
Boulc'h et al, 2021 [4]	Meta-analysis	62 patients (10374 patients with breast cancer who underwent axillary staging)	FDG PET or PET/CT	US, MRI	Histopathology	**Axillary lymph node metastases** Pooled Sens: 49% Pooled Spec: 94% Pooled DOR: 15	**Axillary lymph node metastases** ***US*** Pooled Sens: 55% Pooled Spec: 99% Pooled DOR: 112 ***MRI*** Pooled Sens: 83% Pooled Spec: 85% Pooled DOR: 28	NA
Samiei et al, 2021 [5]	Meta-analysis	13 studies (2380 patients with clinically node-positive breast cancer who received neoadjuvant systemic therapy)	FDG PET/CT	US, MRI	SLNB, ALND	**Axillary response assessment** Pooled Sens: 38% Pooled Spec: 86% Pooled PPV: 78% Pooled NPV: 49%	**Axillary response assessment** ***US*** Pooled Sens: 65% Pooled Spec: 69% Pooled PPV: 77% Pooled NPV: 50% ***MRI*** Pooled Sens: 60% Pooled Spec: 76% Pooled PPV: 78%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
							Pooled NPV: 58%	
Tawakol et al, 2020 [6]	Prospective	80 patients who underwent initial staging (breast cancer)	FDG PET/CT	Physical examination, mammography, US, CeCT	Pre- and post-PET findings	NA	NA	Findings from FDG PET/CT changed the stage (26—upstaged, 4—downstaged) and management (21—modifed radiation therapy field and/or systemic therapy, 5—surgery to neoadjuvant chemotherapy, 3—curative to palliative, 1—palliative to curative) of 37.5% (30/80) of patients.
Bhoriwal et al, 2021 [7]	Prospective	73 patients who underwent staging (locally advanced breast cancer)	FDG PET/CT	CeCT, ^{99m}Tc bone scintigraphy	Biopsy and histopathology, clinical follow-up	**Staging** Sens: 90.9% Spec: 90.0% PPV: 88.2% NPV: 92.3% Accu: 90.4%	**Staging** Sens: 71.9% Spec: 87.8% PPV: 82.1% NPV: 80.0% Accu: 80.8%	FDG PET/CT upstaged the disease in 41.1% (30/73) and downstaged the disease in 5.5% (4/73) of patients. Subsequently, a change in management plan occurred in 30.1% (22/73) of patients.
Han et al, 2021 [8]	Meta-analysis	29 studies (4276 patients with breast cancer who underwent initial staging)	FDG PET or PET/CT or PET/MRI	Mammography, US, MRI, chest x-ray, bone scan, CT	Histology, clinical and imaging follow-up	NA	NA	The pooled proportions of changes in stage and management were 25% and 18%, respectively.
Vogsen et al, 2021 [9]	Prospective	103 patients who underwent staging and treatment planning (high-risk primary breast cancer)	FDG PET/CT	Mammography with or without MRI	Biopsy, clinical and imaging follow-up, consensus from multidisciplinary conferences	**Distant metastases** Sens: 100% Spec: 95.0% PPV: 86.0% NPV: 100% Accu: 96.0% AUC: 0.99	NA	FDG PET/CT upstaged 38.8% (40/103) of patients to more advanced disease and subsequently changed the treatment of these patients.
Pak et al, 2021 [10]	Meta-analysis	13 studies (982 patients with recurrent breast cancer)	FDG PET or PET/CT	CT, MRI, bone scintigraphy, mammography, physical examination, tumour markers	Pre- and post-PET information	NA	NA	The pooled proportion of change in management as a result of FDG PET or PET/CT was 44.4%.
Esophageal Cancer								

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Foley et al, 2021 [11]	Meta-analysis	6 studies (518 patients with oesophageal adenocarcinoma who were treated with neoadjuvant chemotherapy or chemoradiotherapy prior to surgical resection)	FDG PET/CT	NA	Pathology	**Early response assessment** Pooled Sens: 77.2% Pooled Spec: 75.0%	NA	NA
Vollenbrock et al, 2021 [12]	Prospective	33 patients who underwent clinical response assessment before and 6 to 8 weeks after neoadjuvant chemoradiotherapy (locally advanced, non-metastatic oesophageal cancer)	FDG PET/CT	DWI-MRI	Histopathology	**Residual disease** Sens: 69% Spec: 29%-43% PPV: 78%-82% NPV: 20%-27% Accu: 61%-64% AUC: 0.49-0.60	**Residual disease** Sens: 92%-96% Spec: 43%-57% PPV: 86%-89% NPV: 67%-75% Accu: 85% AUC: 0.70-0.74	NA
Shashi et al, 2020 [13]	Retrospective	79 patients who underwent initial diagnosis or follow-up (esophageal cancer)	FDG PET/CT	CT, EUS	Histopathology, clinical follow-up, consensus from multidisciplinary tumour board	NA	NA	FDG PET/CT provided information that directly impacted management in 32.9% (26/79).
Reinert et al, 2021 [14]	Prospective	257 patients who underwent primary staging, restaging or follow-up due to suspected relapse (esophageal cancer)	FDG PET/CT	NA	Pre- and post-PET information	NA	NA	FDG PET/CT led to major changes in therapeutic management in 13.2% (34/257) patients (21—curative to palliative, 5—palliative to curative, 5—undecided to curative, 3—undecided to palliative). Additionally, minor changes in therapeutic management occurred in 24.1% (62/257) of cases.
Pande et al, 2020 [15]	Retrospective	68 patients who underwent	FDG PET/CT	NA	Histopathology, clinical and	**Recurrence** Sens: 98.4%	NA	Change in management was observed in 41.2%

		restaging after curative-intent surgical resection (suspected recurrence of esophageal carcinoma)			imaging follow-up	Spec: 80.0% PPV: 98.0% NPV: 80.0%		(28/68) of patients based on evidence of distant metastases seen on FDG PET/CT (28—salvage chemoradiotherapy/surgery to palliative chemotherapy/best supportive care).
Gastrointestinal 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 [16]	Meta-analysis	58 studies (9997 patients with gastric cancer)	FDG PET/CT	CeCT	Histopathology	**Lymph node metastases** Pooled Sens: 49% Pooled Spec: 92% Pooled +LR: 6.1 Pooled -LR: 0.56 Pooled DOR: 11 AUC: 0.84 **Distant metastases** Pooled Sens: 56% Pooled Spec: 97% Pooled +LR: 18.5 Pooled -LR: 0.45 Pooled DOR: 41 AUC: 0.83 **Recurrence** Pooled Sens: 81% Pooled Spec: 83% Pooled +LR: 4.8 Pooled -LR: 0.23 Pooled DOR: 21 AUC: 0.89	**Lymph node metastases** Pooled Sens: 69% Pooled Spec: 85% Pooled +LR: 4.7 Pooled -LR: 0.38 Pooled DOR: 12 AUC: 0.86 **Distant metastases** Pooled Sens: 59% Pooled Spec: 96% Pooled +LR: 15.4 Pooled -LR: 0.42 Pooled DOR: 36 AUC: 0.85 **Recurrence** Pooled Sens: 82% Pooled Spec: 76% Pooled +LR: 3.4 Pooled -LR: 0.24 Pooled DOR: 14 AUC: 0.84	NA
Bosch et al, 2020 [17]	Retrospective	105 patients who underwent pre-treatment staging (gastric adenocarcinoma)	FDG PET/CT	CT	Histology, consensus from multidisciplinary team	**Nodal involvement** Sens: 40% Spec: 73%	NA	FDG PET/CT upstaged 19.0% of patients by demonstrating previously undetected positive lymph nodes or metastases.
Patkar et al, 2020 [18]	Retrospective	103 patients who underwent initial staging (locally advanced gall bladder cancer)	FDG PET/CeCT	CeCT/MRI	Image-guided biopsy, fine needle aspiration cytology	NA	NA	FDG PET/CeCT upstaged 46.6% (48/103) of patients to stage IV disease.
Goel et al, 2020 [19]	Prospective	149 patients who underwent preoperative	FDG PET/CT	CeCT	Histopathology, imaging follow-up	**Peritoneal metastases** Sens: 66.7%	NA	Additional findings from FDG PET/CT changed the management plan in

		staging (potentially resectable gall bladder cancer)				Spec: 100% PPV: 100% NPV: 93.9% Accu: 94.5% **Liver metastases** Sens: 66.7% Spec: 100% PPV: 100% NPV: 95.7% Accu: 96.1% **Distant nodal metastases** Sens: 57.1% Spec: 78.5% PPV: 57.8% NPV: 97.3% Accu: 91.4%		23.5% (35/149) of patients (26—neoadjuvant chemotherapy to palliative chemotherapy, 9—upfront surgery to palliative chemotherapy).
Dahmarde et al, 2020 [20]	Meta-analysis	13 studies (1460 patients with newly diagnosed colorectal cancer)	FDG PET/CT	NA	Histopathology, imaging follow-up	**Lymph node metastases** Pooled Sens: 65% Pooled Spec: 75% Pooled +LR: 4.57 Pooled -LR: 0.37 Pooled DOR: 18.0 AUC: 0.86	NA	NA
Tsili et al, 2021 [21]	Meta-analysis	12 studies (536 patients with colorectal cancer liver metastases)	FDG PET/CT	CeUS, MDCT, MRI	Histopathology, intraoperative observation, clinical and imaging follow-up	**Diagnosis (patient-based)** Pooled Sens: 96% Pooled Spec: 97% **(lesion-based)** Pooled Sens: 62%*	**Diagnosis (patient-based)** ***CeUS*** Pooled Sens: 80% Pooled Spec: 97% ***MDCT*** Pooled Sens: 87% Pooled Spec: 95% ***MRI*** Pooled Sens: 87% Pooled Spec: 94% **(lesion-based)** ***CeUS*** Pooled Sens: 86% ***MDCT*** Pooled Sens: 84% ***MRI*** Pooled Sens: 89%*	NA
Wen et al, 2020 [22]	Retrospective	86 patients who underwent preoperative evaluation (ampullary and duodenal	FDG PET/CT	CeCT/CeMRI	Histopathology, clinical and imaging follow-up	**Diagnosis** Sens: 93.1% Spec: 78.6%* Accu: 88.3%*	**Diagnosis** Sens: 89.6% Spec: 35.7%* Accu: 72.1%*	FDG PET/CT affected treatment decisions in 12.8% (11/86) of patients.

		papillary carcinoma)						
Kim et al, 2020 [23]	Retrospective	234 patients who underwent staging (extrahepatic cholangiocarcinoma)	FDG PET/CT	MRI, CeMDCT	Histopathology, imaging follow-up	**Primary tumour** Sens: 78.6%* **Lymph node metastases** Sens: 43.6%* Spec: 95.0%* PPV: 85.4%* NPV: 71.5% Accu: 74.4% AUC: 0.66 **Distant metastases** Sens: 85.0% Spec: 95.8% PPV: 65.4% NPV: 98.6% Accu: 94.9% AUC: 0.90	**Primary tumour** ***MRI*** Sens: 97.4%* ***CeMDCT*** Sens: 94.9%* **Lymph node metastases** ***MRI*** Sens: 77.6%* Spec: 69.7%* PPV: 62.5%* NPV: 82.7% Accu: 72.8% AUC: 0.74 ***CeMDCT*** Sens: 74.5%* Spec: 72.1%* PPV: 64.2%* NPV: 80.8% Accu: 73.1% AUC: 0.71 **Distant metastases** ***MRI*** Sens: 92.0% Spec: 94.8% PPV: 63.2% NPV: 99.2% Accu: 94.6% AUC: 0.94 ***CeMDCT*** Sens: 80.0% Spec: 94.9% PPV: 59.3% NPV: 98.1% Accu: 93.6% AUC: 0.91	NA
Slim et al, 2020 [24]	Retrospective	69 patients without clinical evidence of inguinal lymph node involvement or with discordance between clinical evidence and imaging features (anal squamous cell carcinoma)	FDG PET/CT	SLNB	SLNB	**Inguinal metastases** Sens: 62.0% Spec: 79.0% PPV: 40.0% NPV: 82.0% AUC: 0.68	NA	NA

John et al, 2020 [25]	Retrospective	148 patients; 181 PET/CT scans for initial staging or restaging after prior therapy (hepatocellular carcinoma)	FDG PET/CT	CT, MRI	Histology, clinical and imaging follow-up, consensus from multidisciplinary tumour board	NA	NA	In patients who underwent initial staging, the incorporation of FDG PET/CT changed the BCLC and TNM staging of 5.9% (6/101) and 13.9% (14/101) of cases, respectively. Changes in management occurred in 9.9% (10/101) of cases (2—additional locoregional therapy, 6—locoregional therapy to systemic therapy, 2—change to best supportive care). In patients who demonstrated progression after prior therapy, FDG PET/CT changed the BCLC and TNM staging of 18.8% (15/80) and 21.3% (17/80) of cases, respectively. Changes in management occurred in 21.3% (17/80) of cases (8—additional locoregional therapy, 6—locoregional therapy to systemic therapy, 3—change to best supportive care). Overall, 6.6% (12/181) FDG PET/CT studies led to unnecessary follow-up tests.
Genitourinary Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Jakobsen et al, 2021 [26]	Retrospective	143 patients who underwent staging prior to surgical treatment (invasive penile	FDG PET/CT	CeCT	Histopathology, clinical and imaging follow-up	**Inguinal lymph node metastases (patient-based)** Sens: 85.4% Spec: 57.8% FN: 14.6% **(groin-based)**	**Inguinal lymph node metastases (patient-based)** Sens: 47.5% Spec: 95.8% FN: 52.5% **(groin-based)**	NA

		squamous cell carcinoma)				Sens: 88.5% Spec: 70.5% PPV: 40.0% NPV: 96.5% FN: 11.5%	Sens: 57.7% Spec: 92.7% PPV: 65.2% NPV: 90.2% FN: 42.3%	
Otis-Chapados et al, 2021 [27]	Retrospective	256 patients who underwent staging procedure prior to management (newly diagnosed high-grade prostate cancer)	FDG PET/CT	Bone scintigraphy	Biopsy, clinical and imaging follow-up	**Bone metastases** Sens: 100%* Spec: 98.7% PPV: 91.7% NPV: 100% Accu: 98.8%	**Bone metastases** Sens: 78.8%* Spec: 98.2% PPV: 86.7% NPV: 96.9% Accu: 95.7%	NA
Gynecologic Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
St. Laurent et al, 2020 [28]	Retrospective	185 patients who underwent preoperative imaging (high-risk endometrial cancer)	FDG PET/CT	CT	Histopathology, clinical and imaging follow-up	**Nodal metastases** Sens: 89% Spec: 95% PPV: 96% NPV: 95% **Extrauterine disease** Sens: 63% Spec: 92% PPV: 91% NPV: 92% **Peritoneal disease** Sens: 86% Spec: 99% PPV: 86% NPV: 99% **Distant metastases** Sens: 100% Spec: 100% PPV: 78% NPV: 100%	**Nodal metastases** Sens: 64% Spec: 95% PPV: 60% NPV: 95% **Extrauterine disease** Sens: 45% Spec: 88% PPV: 67% NPV: 88% **Peritoneal disease** Sens: 40% Spec: 97% PPV: 50% NPV: 97% **Distant metastases** Sens: 83% Spec: 99% PPV: 45% NPV: 99%	Negative PET was associated with a 5-month PFS benefit ($p<0.01$) and a 4-month OS benefit ($p<0.01$). CT findings did not associate with PFS or OS.
Nordskar et al, 2021 [29]	Retrospective	185 patients who underwent preoperative evaluation of lymph node status (endometrial cancer)	FDG PET/CT	CT/MRI	Histopathology	**Lymph node metastases** Sens: 63.0% Spec: 98.1% PPV: 85.0% NPV: 93.9% +LR: 32.5 -LR: 0.38 Accu: 93.0%	**Lymph node metastases** Sens: 40.7% Spec: 97.5% PPV: 73.3% NPV: 90.6% +LR: 16.1 -LR: 0.61 Accu: 89.2%	NA
Sallee et al, 2021 [30]	Retrospective	200 patients who underwent	FDG PET/CT	MRI	Pathology	**Para-aortic involvement**	**Para-aortic involvement**	NA

		preoperative evaluation of para-aortic involvement (high-risk endometrial cancer)				Sens: 61.8%* Spec: 89.7% PPV: 69.4% NPV: 86.1% AUC: 0.76*	Sens: 26.5%* Spec: 89.5% PPV: 48.1% NPV: 76.8% AUC: 0.58*	
Woo et al, 2020 [31]	Meta-analysis	115 studies (13,999 patients with cervical cancer)	FDG PET or PET/CT or PET/MRI	US, CT, MRI	Pathology, biopsy	**Parametrial invasion** Pooled Sens: 73% Pooled Spec: 91% AUC: 0.92 **Lymph node metastases** Pooled Sens: 57% Pooled Spec: 95% AUC: 0.88	**Parametrial invasion** ***US*** Pooled Sens: 67% Pooled Spec: 94% AUC: 0.83 ***MRI*** Pooled Sens: 71% Pooled Spec: 91% AUC: 0.91 **Lymph node metastases** ***CT*** Pooled Sens: 51% Pooled Spec: 87% AUC: 0.83 ***MRI*** Pooled Sens: 57% Pooled Spec: 93% AUC: 0.84	NA
Staley et al, 2021 [32]	Retrospective	106 patients who underwent preoperative cross-sectional imaging (early-stage cervical cancer)	FDG PET/CT	CT, MRI	Pathology	**Extra-cervical metastases** Sens: 35% Spec: 91% PPV: 55% NPV: 81%	**Extra-cervical metastases** ***CT*** Sens: 33% Spec: 87% PPV: 20% NPV: 93%	NA
Adam et al, 2020 [33]	Meta-analysis	12 studies (778 patients with locally advanced cervical cancer)	FDG PET or PET/CT	NA	Histopathology	**Pelvic lymph node metastases** Pooled Sens: 88% Pooled Spec: 93% Pooled +LR: 11.90 Pooled -LR: 0.13 **Para-aortic lymph node metastases** Pooled Sens: 40% Pooled Spec: 93% Pooled +LR: 6.08 Pooled -LR: 0.64	NA	NA
Tardieu et al, 2021 [34]	Retrospective	63 patients who underwent preoperative assessment of	FDG PET/CT	CA 125 level	Pathology	**Lymph node metastases** Sens: 26.7% Spec: 90.9%	NA	NA

		lymph node involvement (advanced epithelial ovarian cancer)				PPV: 72.7% NPV: 57.7% Accu: 60.3%		
Nawi et al, 2021 [35]	Prospective	43 patients who had undergone surgery and received adjuvant chemotherapy (suspected recurrent ovarian cancer)	FDG PET/CT	CA-125, CeCT	Histology, clinical and imaging follow-up	**Recurrence** Sens: 94.4% Spec: 90.0% PPV: 77.3% NPV: 95.2% Accu: 86.0%	**Recurrence** ***CA-125*** Sens: 50.0% Spec: 84.0% PPV: 69.2% NPV: 70.0% Accu: 69.8% ***CeCT*** Sens: 72.2% Spec: 16.0% PPV: 38.2% NPV: 44.4% Accu: 39.5%	NA
Sun et al, 2020 [36]	Retrospective	69 patients who received first cytoreductive surgery and chemotherapy (suspected recurrent ovarian cancer)	FDG PET/CT	CA-125, HE4	Pathology, cytology, clinical follow-up	**Recurrence and metastases** Sens: 90.7% Spec: 86.7% PPV: 96.1% NPV: 72.2% Accu: 89.9%	**Recurrence and metastases** ***CA-125*** Sens: 77.8% Spec: 86.7% PPV: 95.5% NPV: 52.0% Accu: 79.7% ***HE4*** Sens: 70.4% Spec: 93.3% PPV: 97.4% NPV: 48.4% Accu: 76.8%	NA
Triumbari et al, 2021 [37]	Meta-analysis	7 studies (169 patients with vulvar cancer)	FDG PET or PET/CT	NA	Histopathology, clinical follow-up	**Lymph node staging (patient-based)** Pooled Sens: 70% Pooled Spec: 90% Pooled PPV: 86% Pooled NPV: 77% Pooled DOR: 10.49 **(groin-based)** Pooled Sens: 76% Pooled Spec: 88% Pooled PPV: 70% Pooled NPV: 92% Pooled DOR: 19.43	NA	NA
Head and Neck Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance**	**Change in Patient Management**

							(Conventional Intervention)	
Li et al, 2020 [38]	Meta-analysis	4 studies (511 patients with head and neck cancer)	FDG PET/CT	CeMRI	Histology, imaging follow-up	**Distant metastases** Pooled Sens: 82% Pooled Spec: 97% Pooled +LR: 23.9 Pooled -LR: 0.19	**Distant metastases** Pooled Sens: 81% Pooled Spec: 98% Pooled +LR: 36.5 Pooled -LR: 0.20	NA
Slouka et al, 2020 [39]	Retrospective	90 patients who underwent preoperative staging (head and neck cancer)	FDG PET/CT, FDG PET/MRI	NA	Histopathology	**N staging** ***PET/CT*** Sens: 94.7% Spec: 46.7% PPV: 81.8% NPV: 77.8% OR: 15.8 ***PET/MRI*** Sens: 88.5% Spec: 63.6% PPV: 85.2% NPV: 70.0% OR: 13.4	NA	NA
Risor et al, 2020 [40]	Retrospective	279 patients who underwent surveillance scan after curative-intended radiotherapy (suspected recurrent head and neck cancer)	FDG PET/CT	Clinical examination	Histopathology, imaging follow-up	**Recurrence** Sens: 80.0-89.1% Spec: 78.6-89.7% PPV: 50.5-65.7% NPV: 94.8-96.7%	NA	There was a significant difference in time to recurrence between patients with PET-positive and PET-negative results ($p<0.001$).
Jung et al, 2020 [41]	Prospective	225 patients who underwent primary surgery, with or without postoperative radiotherapy or chemoradiotherapy (advanced-stage head and neck squamous cell carcinoma)	FDG PET/CT	NA	Biopsy, imaging follow-up	**Local recurrence** PPV: 71.8% NPV: 99.3% **Regional recurrence** PPV: 82.1% NPV: 99.3% **Distant metastases** PPV: 68.2% NPV: 99.3%	NA	NA
Huasong et al, 2021 [42]	Meta-analysis	16 studies (724 patients with head and neck squamous cell carcinoma of unknown primary)	FDG PET/CT	Endoscopy, CeCT/CT, CeMRI/MRI	Histopathology	**Occult primary tumour** Pooled DR: 40% Pooled FP: 9%	NA	NA

Sarma et al, 2021 [43]	Retrospective	63 patients with one or more palpable neck nodes (cancer of unknown primary)	FDG PET/CT	NA	Histopathology, clinical follow-up	**Primary site** DR: 28.5% FP: 15.0% Sens: 78.2% Spec: 85.0% PPV: 75.0% NPV: 87.1%	NA	NA
Xiao et al, 2021 [44]	Retrospective	1003 patients who underwent initial staging prior to radical therapy (stage I-II nasopharyngeal carcinoma)	FDG PET/CT + conventional workup (n=218)	MRI, chest radiograph, liver US, bone scintigraphy (n=785)	Histopathology, imaging follow-up	**Retropharyngeal lymph node metastases** Sens: 72.2%* Spec: 88.5% PPV: 78.1% NPV: 84.8%* **Cervical lymph node metastases** Sens: 96.6%* Spec: 72.9%* PPV: 71.1%* NPV: 96.9%*	**Retropharyngeal lymph node metastases** ***MRI*** Sens: 91.1%* Spec: 90.6% PPV: 84.7% NPV: 94.7%* **Cervical lymph node metastases** ***MRI*** Sens: 76.4%* Spec: 96.1%* PPV: 93.2%* NPV: 85.5%*	FDG PET/CT modified the planned target volume and dose in 11.5% (25/218) of patients (15 upstaged and 10 downstaged). There were no significant differences in 5-year OS (p=0.17), LRFS (p=0.928), RRFS (p=0.409), PFS (p=0.288), and DMFS (p=0.267) between patients who underwent additional FDG PET/CT and those who underwent conventional workup only.
Liu et al, 2020 [45]	Retrospective	116 patients who underwent post-treatment response evaluation (nasopharyngeal cancer)	FDG PET/CT	NA	Histopathology, clinical and imaging follow-up	**Residual disease** Sens: 73.7% Spec: 86.6% PPV: 51.9% NPV: 94.4% Accu: 84.5%	NA	The 3-year LRFFS (95.7% vs. 79.5%; p=0.043) and DFS (84.6% vs. 54.4%; p=0.028) were significantly higher in negative-PET patients than in positive-PET patients.
Yeh et al, 2020 [46]	Prospective	198 patients who agreed to receive chemoradiation (oropharyngeal and hypopharyngeal squamous cell carcinoma)	FDG PET/CT, FDG PET/MRI	MRI	Histology, imaging follow-up	**Synchronous cancers and distant metastases** ***PET/CT*** **(patient-based)** Sens: 65.5% Spec: 93.0% PPV: 78.3% NPV: 87.5% Accu: 85.4% AUC: 0.917 **(site-based)** Sens: 69.9%* Spec: 99.1% PPV: 81.7% NPV: 98.3% Accu: 97.6%	**Synchronous cancers and distant metastases (patient-based)** Sens: 58.2%* Spec: 96.5% PPV: 86.5% NPV: 85.7% Accu: 85.9% AUC: 0.905* **(site-based)** Sens: 57.8%* Spec: 99.6% PPV: 88.9% NPV: 97.7% Accu: 97.4%	NA

						PET/MRI **(patient-based)** Sens: 69.1%* Spec: 95.8% PPV: 86.4% NPV: 89.0% Accu: 88.4% AUC: 0.930* **(site-based)** Sens: 73.5%* Spec: 99.6% PPV: 91.0% NPV: 98.5% Accu: 98.2%		
Meerwein et al, 2020 [47]	Retrospective	65 patients who underwent initial staging (primary malignant sinonasal tumours)	FDG PET/CT or PET/MRI	CT, MRI	Biopsy, clinical and imaging follow-up	**Lymph node metastases** Sens: 100% Spec: 91.7% PPV: 50.0% NPV: 100% Accu: 92.3% **Distant metastases** Sens: 100% Spec: 98.3% PPV: 87.5% NPV: 100% Accu: 98.5%	NA	NA
Qian et al, 2020 [48]	Retrospective	220 patients who underwent surveillance scan 3 months after adjuvant therapy (stage III, IVA, or IVB oral squamous cell carcinoma)	FDG PET/CT	NA	Biopsy, clinical and imaging follow-up	**Recurrence** Sens: 58% Spec: 92% PPV: 85% NPV: 73%	NA	Among the 37 patients with biopsy-confirmed progression who underwent salvage therapy, 10.8% (4/37) of patients were found to be without evidence of disease at last follow-up.
Albano et al, 2021 [49]	Retrospective	113 patients with negative post-therapeutic ^{131}I-WBS but positive serum thyroglobulin (differentiated thyroid carcinoma)	FDG PET/CT	^{131}I-WBS, serum thyroglobulin	Histopathology, clinical and imaging follow-up	**Recurrence** Sens: 92% Spec: 94% PPV: 97% NPV: 87% +LR: 16.15 -LR: 0.08 Accu: 93%	NA	NA
Hematologic 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, 2020 [50]	Meta-analysis	5 studies (386 patients with NHL or HL)	FDG PET or PET/CT	MRI	BMB	**Bone marrow involvement** Pooled Sens: 65% Pooled Spec: 90% Pooled +LR: 6.4 Pooled -LR: 0.39 Pooled DOR: 16 AUC: 0.90	**Bone marrow involvement** Pooled Sens: 78% Pooled Spec: 86% Pooled +LR: 5.6 Pooled -LR: 0.26 Pooled DOR: 22 AUC: 0.89	NA
St-Pierre et al, 2020 [51]	Retrospective	548 patients who underwent staging (newly diagnosed follicular lymphoma)	FDG PET/CT	BMB	BMB	**Bone marrow involvement** Sens: 60% Spec: 80%	NA	NA
Saiki et al, 2021 [52]	Retrospective	84 patients who underwent staging before initiation of treatment (newly diagnosed DLBCL)	FDG PET/CT	BMB	BMB	**Bone marrow involvement** Sens: 36% Spec: 87% PPV: 50% NPV: 79%	NA	NA
Skrypets et al, 2021 [53]	Retrospective	79 patients who underwent staging of gastrointestinal involvement (mantle cell lymphoma)	FDG PET/CT	Esophagogastroduodenoscopy, colonoscopy	Biopsy	**Gastric involvement** Sens: 61.5% Spec: 74.4% PPV: 44.4% NPV: 85.3% Accu: 71.2% **Colorectal involvement** Sens: 81.8% Spec: 85.0% PPV: 75.0% NPV: 89.5% Accu: 83.9%	NA	NA
Park et al, 2021 [54]	Meta-analysis	9 studies (1040 patients with suspected primary CNS lymphoma)	FDG PET/CT	ceCT	Histopathology, imaging follow-up	**Systemic lymphoma involvement** Pooled DR: 4.9% Pooled FP: 5.3% **Incidental secondary malignancy** Pooled DR: 3.1%	**Systemic lymphoma involvement** Pooled DR: 2.5%	NA
Jin et al, 2021 [55]	Prospective	53 patients who underwent interim response assessment after 4 cycles of R-CHOP (advanced-stage DLBCL)	FDG PET/CT (Interim-PET negative patients received 2	NA	Clinical follow-up	NA	NA	Patients with negative interim-PET had a significantly better 3-year PFS (78.1% vs. 34.3%; p<0.001) and OS (87.1% vs. 62.3%; p=0.03)

			additional cycles of R-CHOP. Interim-PET positive patients received 4 additional cycles of R-CHOP)					than those with a positive interim-PET.
Borchmann et al, 2021 [56]	Phase III RCT (GHSG HD17)	1100 patients randomly assigned 1:1 to either standard combined-modality treatment or PET-guided treatment that consisted of omitting IFRT for those patients with negative PET after 2 cycles of eBEACOPP and 2 cycles of ABVD (newly diagnosed, early-stage unfavourable HL)	FDG PET/CT	NA	Clinical follow-up	NA	NA	The 5-year PFS was 97.3% in the standard combined-modality treatment group and 95.1% in the PET-guided treatment group (HR=0.523; 95% CI: 0.226 to 1.211). The difference was 2.2%, which excluded the predefined non-inferiority margin of 8%.
Gallamini et al, 2020 [57]	Phase II RCT (GITIL/FIL HD 0607)	296 patients with both a negative PET after 2 and 6 cycles of ABVD were randomly assigned 1:1 to receive consolidation radiotherapy or no further treatment (advanced-stage HL with a large nodal mass)	FDG PET/CT	NA	Clinical follow-up	NA	NA	The 6-year PFS was 92% in patients treated with consolidation therapy and 90% in patients with no further treatment (p=0.48). The 6-year OS was 99% in patients treated with consolidation therapy and 98% in patients with no further treatment (p=0.61).
Melanoma								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**

Cheng et al, 2021 [58]	Retrospective	92 patients who underwent initial staging (cutaneous melanoma)	FDG PET/CT	NA	Histopathology	**Regional nodal metastases** Sens: 34.6% Spec: 95.4% PPV: 88.2% +LR: 7.62 -LR: 0.68 Accu: 78.2%	NA	NA
Aviles Izquierdo et al, 2020 [59]	Retrospective	83 patients who underwent staging or restaging (stage I-III melanoma)	FDG PET/CT	SLNB	Histology	**Staging prior to SLNB** Sens: 5.0% Spec: 72.5% PPV: 15.3% NPV: 44.0% **Staging with positive SLNB** Sens: 62.5% Spec: 80.0% PPV: 83.3% NPV: 57.0% **Skin metastases** Sens: 50.0% Spec: 0% PPV: 88.0% NPV: 0% **Nodal locoregional recurrence** Sens: 50.6% Spec: 38.1% PPV: 69.9% NPV: 25.2%	NA	In patients with locoregional recurrences, FDG PET/CT revealed asymptomatic visceral distant metastases in 25.7% (9/35) of cases.
Berzaczy et al, 2020 [60]	Prospective	22 patients who underwent initial staging or restaging (melanoma)	FDG PET/CT, FDG PET/MRI	NA	Histopathology, previous and/or follow-up imaging	**Distant metastases (region-based)** ***PET/CT*** Sens: 92.7% Spec: 100% ***PET/MRI*** Sens: 89.1% Spec: 100%	NA	NA
Olthof et al, 2020 [61]	Prospective	119 patients; 201 PET/CT scans characterization of unclear lesions, routine follow-up or therapy response evaluation (advanced melanoma)	FDG PET/CT	CT, MRI, US, tumour marker	Pre- and post-PET information, clinical follow-up	NA	NA	FDG PET/CT results led to changes in intended management in 48.7% (98/201) of cases (77—major, 21—minor).

Ayati et al, 2021 [62]	Meta-analysis	24 studies (1146 patients with metastatic melanoma who were treated with immunotherapy)	FDG PET/CT	NA	Clinical and imaging follow-up	**Predicting treatment response (change in SUV_{max})** Pooled Sens: 71% Pooled Spec: 40% **(early PECRIT and PERCIMT)** Pooled Sens: 94% Pooled Spec: 84% **(early EORTC and PERCIST)** Pooled Sens: 64% Pooled Spec: 80% **(late PERCIMT)** Pooled Sens: 92% Pooled Spec: 76% **(late EORTC)** Pooled Sens: 67% Pooled Spec: 77%	NA	Baseline FDG PET/CT parameters MTV ($p<0.001$), SLR ($p=0.001$), SUL/SUV_{peak} ($p=0.001$), and TLG ($p<0.001$) were all significant predictors of OS.
Neuro-Oncology								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Cui et al, 2021 [63]	Meta-analysis	15 studies (patients with suspected recurrence of glioma)	FDG PET	NA	Histopathology, clinical and imaging follow-up	**Differentiating tumour progression from treatment-related changes** Pooled Sens: 78% Pooled Spec: 87% Pooled DOR: 23 AUC: 0.90	NA	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**
Anderson et al, 2020 [64]	Retrospective	63 patients who underwent prior imaging (neuroendocrine tumours)	^{68}Ga-DOTA-TATE PET/CT	CT, MRI, Octreoscan, ^{131}I-MIBG, FDG PET/CT	Imaging follow-up	NA	NA	^{68}Ga-DOTA-TATE PET/CT impacted the therapeutic management plan in 23.8% (15/63) of patients (7—refeeral and/or initiation of PRRT, 1—initiated octreotide analog, 1—initiated

								chemotherapy, 5—change in planned extent of surgery, 1—cancelled surgery).
Cuthbertson et al, 2021 [65]	Retrospective	183 patients with 224 scans for diagnosis and staging, detecting recurrence or determining eligibility for PRRT (clinically suspected or histologically confirmed pancreatic NETs)	^{68}Ga-DOTA PET/CT	Biochemical testing, CT/MRI, EUS	Histopathology, consensus from multidisciplinary team	NA	NA	^{68}Ga-DOTA PET/CT influenced management in 39.4% (85/216) of cases.
^{18}F-FET								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Steidl et al, 2021 [66]	Retrospective	104 patients with MRI findings suspicious for progressive disease according to RANO (grade II-IV glioma)	^{18}F-FET PET or PET/MRI	PWI-DWI	Histopathology, clinical and imaging follow-up	**Differentiating tumour progression from treatment-related changes (TBR_{max} > 1.95)** Sens: 70% Spec: 60% PPV: 88% NPV: 32% Accu: 68% **(Slope < 0.69 SUV/h)** Sens: 84% Spec: 62% PPV: 90% NPV: 50% Accu: 80% **(TBR_{max} + Slope)** Sens: 96% Spec: 43% PPV: 87% NPV: 75% Accu: 86%	**Differentiating tumour progression from treatment-related changes ($rCBV_{max}$ > 2.85)** Sens: 54% Spec: 100% PPV: 100% NPV: 36% Accu: 63%	NA
Cui et al, 2021 [63]	Meta-analysis	15 studies (patients with suspected	^{18}F-FET PET	NA	Histopathology, clinical and imaging follow-up	**Differentiating tumour progression from**	NA	NA

		recurrence of glioma)				**treatment-related changes (TBR_{max} > 1.95 to 3.52)** Pooled Sens: 88% Pooled Spec: 78% Pooled DOR: 26 AUC: 0.86 **(TBR_{mean} > 1.52 to 2.98)** AUC: 0.90 **(TTP < 20 to 45 min)** Pooled Sens: 80% Pooled Spec: 67% Pooled DOR: 8 AUC: 0.81 **(multi-parameter)** Pooled Sens: 88% Pooled Spec: 79% Pooled DOR: 26 AUC: 0.91		
^{18}F-FDOPA								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Cui et al, 2021 [63]	Meta-analysis	3 studies (patients with suspected recurrence of glioma)	^{18}F-FDOPA PET	NA	Histopathology, clinical and imaging follow-up	**Differentiating tumour progression from treatment-related changes (TBR_{max} or visual)** Pooled Sens: 85% Pooled Spec: 70% Pooled DOR: 13 AUC: 0.85	NA	NA
^{68}Ga-PSMA								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Satapathy et al, 2021 [67]	Meta-analysis	7 studies (389 patients with suspected prostate cancer)	^{68}Ga-PSMA PET/CT	Serum PSA testing, digital rectal examination, transrectal US	Histopathology	**Diagnosis** Pooled Sens: 97% Pooled Spec: 66% Pooled PPV: 2.86 Pooled NPV: 0.05 Pooled DOR: 61 AUC: 0.91	NA	NA

Matushita et al, 2021 [68]	Meta-analysis	34 studies (4532 patients with prostate cancer)	^{68}Ga-PSMA PET/CT or PET/MRI	NA	Histopathology, clinical follow-up, change in PSA values	**Diagnosis** Pooled Sens: 90% Pooled Spec: 90% **Staging** Pooled Sens: 93% Pooled Spec: 96% AUC: 0.97 **Restaging** Pooled Sens: 76% Pooled Spec: 42% AUC: 0.73	NA	NA
Petersen et al, 2020 [69]	Prospective	20 patients who underwent staging prior to definitive radiotherapy (newly diagnosed intermediate- or high-risk prostate cancer)	^{68}Ga-PSMA PET/CT	MRI/CeCT, DWI-MRI	Histopathology	**Lymph node metastases (patient-based)** Sens: 38.5% Spec: 100% PPV: 100% NPV: 46.7% Accu: 60.0% **(region-based)** Sens: 15.4% Spec: 97.1% PPV: 57.1% NPV: 82.3% Accu: 80.9%	**Lymph node metastases** ***MRI/CeCT*** **(patient-based)** Sens: 7.7% Spec: 100% PPV: 100% NPV: 36.8% Accu: 40.0% **(region-based)** Sens: 0% Spec: 99.1% PPV: 0% NPV: 80.0% Accu: 79.4% ***DWI-MRI*** **(patient-based)** Sens: 36.4% Spec: 83.3% PPV: 80.0% NPV: 41.8% Accu: 52.9% **(region-based)** Sens: 17.4% Spec: 96.6% PPV: 57.1% NPV: 81.6% Accu: 80.0%	NA
Franklin et al, 2021 [70]	Retrospective	233 patients who underwent preoperative staging (prostate cancer)	^{68}Ga-PSMA PET/CT	mpMRI	Histopathology	**Pelvic lymph node metastases** Sens: 48.3% Spec: 92.0% PPV: 66.7% NPV: 84.3%	**Pelvic lymph node metastases** Sens: 22.4% Spec: 94.9% PPV: 59.1% NPV: 78.7%	NA
Jansen et al, 2021 [71]	Prospective	117 patients who underwent lymph node staging prior to robot-assisted radical	^{18}F-DCFPyL PET/CT	NA	Histopathology	**Pelvic lymph node metastases (patient-based)** Sens: 41.2% Spec: 94.0%	NA	NA

		prostatectomy with extended pelvic lymph node dissection (intermediate- or high-risk prostate cancer)				PPV: 53.8% NPV: 90.4% **(template-based)** Sens: 34.7% Spec: 97.7% PPV: 44.4% NPV: 96.6%		
Frumer et al, 2020 [72]	Retrospective	89 patients who underwent staging prior to radical prostatectomy with pelvic lymph node dissection (intermediate- or high-risk prostate cancer)	^{68}Ga-PSMA PET/CT	mpMRI	Histology	**Lymph node invasion** Spec: 94.8% NPV: 89.0% AUC: 0.60	**Lymph node invasion** Spec: 94.8% NPV: 86.9% AUC: 0.52	NA
Klingenberg et al, 2021 [73]	Retrospective	177 patients who underwent primary staging prior to radical prostatectomy with pelvic lymph node dissection (newly diagnosed, high-risk prostate cancer)	^{68}Ga-PSMA PET/CT	NA	Histopathology	**Lymph node metastases** Sens: 30.6% Spec: 96.5% PPV: 68.8% NPV: 84.5% Accu: 83.1%	NA	NA
Kopp et al, 2020 [74]	Retrospective	90 patients who underwent primary staging prior to radical prostatectomy with extended pelvic lymph node dissection (at least intermediate-risk prostate cancer)	^{68}Ga-PSMA PET/CT	NA	Histopathology	**Lymph node metastases (patient-based)** Sens: 43.8% Spec: 96.0% PPV: 70.0% NPV: 88.8% **(side-based)** Sens: 42.9% Spec: 95.6% PPV: 56.3% NPV: 92.7% **(region-based)** Sens: 47.6% Spec: 98.9% PPV: 66.7% NPV: 97.5%	NA	NA
Zhao et al, 2021 [75]	Meta-analysis	4 studies (318 patients with prostate cancer)	^{68}Ga-PSMA PET/CT	Bone scan	Pathology, clinical and imaging follow-up	**Bone metastases** Pooled Sens: 97% Pooled Spec: 100% Pooled +LR: 88.45	**Bone metastases** Pooled Sens: 86% Pooled Spec: 87% Pooled +LR: 6.67	NA

						Pooled -LR: 0.05 Pooled DOR: 1468.33 AUC: 0.997	Pooled -LR: 0.19 Pooled DOR: 36.23 AUC: 0.884	
Perera et al, 2020 [76]	Meta-analysis	5 studies (244 patients with high-risk and advanced prostate cancer)	^{68}Ga-PSMA-11 PET/CT or PET/MRI	NA	Histopathology	**Primary staging (patient-based)** Pooled Sens: 77% Pooled Spec: 97% AUC: 0.97 **(lesion-based)** Pooled Sens: 75% Pooled Spec: 99% AUC: 0.97	NA	NA
Donswijk et al, 2020 [77]	Retrospective	64 patients who underwent staging (newly diagnosed intermediate- and high-risk prostate cancer)	^{68}Ga-PSMA PET/CT	MRI, CT, bone scintigraphy	Histopathology, clinical and imaging follow-up, consensus from multidisciplinary tumour board	NA	NA	With additional information from ^{68}Ga-PSMA PET/CT, the N status was upstaged in 23.4% (15/64) and downstaged in 9.4% (6/64) of patients. Moreover, the M status was upstaged in 12.5% (8/64) and downstaged in 23.4% (15/64) of patients. Subsequent management was changed in 35.9% (23/64) of cases (9—undecided to curative, 6—undecided to palliative, 6—palliative to curative, 2—curative to palliative).
Ferraro et al, 2020 [78]	Retrospective	116 patients who underwent staging (newly diagnosed intermediate or high-risk prostate cancer)	^{68}Ga-PSMA PET/CT or PET/MRI	CT, MRI, bone scan	Consensus from multidisciplinary tumour board	NA	NA	^{68}Ga-PSMA PET/CT or PET/MRI had an impact on disease management in 27.6% (32/116) of patients (15—change in therapy modality, 17—change in modality detail).
Pfister et al, 2020 [79]	Retrospective	142 patients who underwent staging prior to salvage radical prostatectomy (recurrent prostate cancer)	^{68}Ga-PSMA PET/CT	CT, bone scintigraphy	Histopathology	**Local recurrence (patient-based)** Sens: 100% Spec: NA PPV: 100% NPV: NA Accu: 100% **(lobe-based)** Sens: 80.7% Spec: 66.7%	NA	NA

						PPV: 94.7% NPV: 32.0% Accu: 79.0% **Lymph node metastases (patient-based)** Sens: 28.6% Spec: 100% PPV: 100% NPV: 72.2% Accu: 75.0% **(node-based)** Sens: 34.8% Spec: 100% PPV: 100% NPV: 97.5% Accu: 97.6%		
Fourquet et al, 2021 [80]	Retrospective	278 patients previously treated with curative intent and no known history of distant metastases (biochemically recurrent prostate cancer)	^{68}Ga-PSMA-11 PET/CT	NA	Histology, other imaging, follow-up imaging, PSA evolution, consensus from multidisciplinary meetings	**Recurrence (equivocal as positive)** Sens: 73% Spec: 57% Accu: 71% **(equivocal as negative)** Sens: 70% Spec: 70% Accu: 70%	NA	^{68}Ga-PSMA-11 PET/CT impacted disease management in 58.3% (162/278) of patients. The treatment was considered effective in 89.0% (138/155) of patients when guided by ^{68}Ga-PSMA-11 PET/CT versus 60.8% (62/102) when not guided by ^{68}Ga-PSMA-11 PET/CT ($p<0.001$).
Liu et al, 2021 [81]	Meta-analysis	11 studies (1580 patients with biochemical recurrent prostate cancer)	^{68}Ga-PSMA-11 PET/CT or PET/MRI, ^{18}F-DCFPyL PET/CT, ^{18}F-DCFBC PET/CT	Bone scintigraphy, mpMRI, MRI, CT, X-ray, ^{18}F-NaF PET/CT, ^{18}F-Fluciclovine PET/CT	Pre- and post-PET questionnaires, consensus from multidisciplinary oncology committee	NA	NA	The pooled overall proportion of management change was 61%.
Fendler et al, 2020 [82]	Prospective	382 patients who received prior therapy (biochemically recurrent prostate cancer)	^{68}Ga-PSMA PET/CT or PET/MRI	MRI, CT, FDG or ^{18}F-NaF PET, bone scan, biopsy, others not specified	Pre- and post-PET questionnaires	NA	NA	^{68}Ga-PSMA PET/CT or PET/MRI led to an intended management change in 68.1% (260/382) of patients (176 major change, 84 minor change). Furthermore, 150 and 73 diagnostic tests were prevented and triggered, respectively after ^{68}Ga-

								PSMA PET/CT or PET/MRI .
Deandreis et al, 2020 [83]	Prospective	223 patients who are eligible for salvage therapy (biochemically recurrent hormone-sensitive prostate cancer)	^{68}Ga-PSMA-11 PET/CT	Serum PSA, choline PET/CT	Histopathology, clinical and imaging follow-up, consensus from multidisciplinary tumour board	**Recurrence (patient-based)** DR: 39.9% **Local recurrence (region-based)** DR: 23.3% **Distant recurrence (region-based)** DR: 16.6%	NA	^{68}Ga-PSMA-11 PET/CT changed the clinical management of 34.5% (77/223) of patients.
Diao et al, 2021 [84]	Meta-analysis	20 studies (2026 patients with biochemically recurrent prostate cancer)	^{68}Ga-PSMA PET/CT or PET/MRI	Serum PSA	Pre- and post-PET information	NA	NA	The pooled proportion of patients with management change as a result of ^{68}Ga-PSMA PET/CT or PET/MRI was 53%.
Bottke et al, 2021 [85]	Retrospective	76 patients with PSA ≤0.5 ng/ml after radical prostatectomy planned for salvage radiotherapy (biochemically recurrent prostate cancer)	^{68}Ga-PSMA-11 PET/CT	NA	Pre- and post-PET information	NA	NA	^{68}Ga-PSMA-11 PET/CT led to changes in radiotherapy target volume in 27.6% (21/76) of patients.
Kunikowska et al, 2021 [86]	Prospective	15 patients who are newly diagnosed or previously treated with TACE (hepatocellular carcinoma)	^{68}Ga-PSMA-11 PET/CT	CeCT/MRI	Histopathology	NA	NA	^{68}Ga-PSMA-11 PET/CT changed the treatment strategy in 33.3% (5/15) of patients (4—disqualified from surgery, 1—disqualified from TACE).
Pancreatic Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Lee et al, 2020 [87]	Meta-analysis	10 studies (852 patients with pancreatic ductal adenocarcinoma who underwent initial staging)	FDG PET/CT or PET/MRI	NA	Histopathology, imaging follow-up	**Lymph node metastases** Pooled Sens: 55% Pooled Spec: 94% Pooled +LR: 9.87 Pooled -LR: 0.47 Pooled DOR: 2.11 AUC: 0.88 **Distant metastases**	NA	The pooled proportion of patients who underwent management changes following FDG PET/CT was 19%.

						Pooled Sens: 80% Pooled Spec: 100% Pooled +LR: 215.30 Pooled -LR: 0.20 Pooled DOR: 1084.20 AUC: 0.92		
Itchins et al, 2020 [88]	Retrospective	115 patients treated with neoadjuvant therapy (potentially operable pancreatic ductal adenocarcinoma)	FDG PET/CT	CT, MRI, CA19-9 blood marker	Pathology, multidisciplinary team consensus	NA	NA	FDG PET/CT upstaged 11.9% (13/109) of patients during neoadjuvant therapy and thus avoided noncurative surgery.
Liu et al, 2021 [89]	Meta-analysis	28 studies (1812 patients with intraductal papillary mucinous neoplasm)	FDG PET/CT	CT, DWI, EUS, MRI/MRCP	Histopathology	**Diagnosis** Pooled Sens: 80% Pooled Spec: 90% Pooled DOR: 35 AUC: 0.92	**Diagnosis** ***CT*** Pooled Sens: 70% Pooled Spec: 78% Pooled DOR: 8 AUC: 0.80 ***DWI*** Pooled Sens: 72% Pooled Spec: 97% Pooled DOR: 88 AUC: 0.82 ***EUS*** Pooled Sens: 60% Pooled Spec: 80% Pooled DOR: 6 AUC: 0.79 ***MRI/MRCP*** Pooled Sens: 76% Pooled Spec: 83% Pooled DOR: 16 AUC: 0.87	NA
Pediatric Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Elmanzalawy et al, 2020 [90]	Retrospective	26 patients who underwent initial staging and therapy planning (soft-tissue sarcoma)	FDG PET/CT	CT/MRI	Histopathology, clinical and imaging follow-up, consensus from multidisciplinary tumour board	**Lymph node metastases** Sens: 90% Spec: 81% PPV: 75% NPV: 93% **Lung metastases** Sens: 14% Spec: 100%	**Lymph node metastases** Sens: 50% Spec: 63% PPV: 45% NPV: 67% **Lung metastases** Sens: 100% Spec: 89%	FDG PET/CT altered therapy planning in 19.2% (5/26) of patients (3—additional surgical resection of nodal metastasis, 1—expanded radiation field, 1—radiation therapy omitted).

						PPV: 100% NPV: 76%	PPV: 78% NPV: 100%	
Sobic Saranovic et al, 2020 [91]	Retrospective	48 patients who underwent post-treatment evaluation (clinical suspicion of recurrent and/or metastatic Ewing sarcoma and Primitive neuroectodermal tumour)	FDG PET/CT	MDCT/MRI	Histopathology, clinical follow-up	**Relapse and metastases** Sens: 93.7% Spec: 87.5% PPV: 93.7% NPV: 87.5% Accu: 91.7%	**Relapse and metastases** Sens: 90.0% Spec: 70.6% PPV: 84.3% NPV: 75.0% Accu: 81.2%	FDG PET/CT findings changed the course of treatment in 16.7% (8/48) of patients (3—new surgery followed by radiotherapy, 5—more aggressive chemotherapy). The PFS was significantly lower in patients with positive PET findings in comparison to those with negative PET findings (p=0.001).
Kim and Kim, 2021 [92]	Meta-analysis	7 studies (1265 patients with HL)	FDG PET/CT	NA	BMB	**Bone marrow involvement** Pooled Sens: 95% Pooled Spec: 97% Pooled +LR: 37.8 Pooled -LR: 0.05 Pooled DOR: 732 AUC: 0.98	NA	NA
Sarcoma								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Zhang et al, 2020 [93]	Meta-analysis	7 studies (270 patients with suspected chondrosarcoma)	FDG PET/CT	NA	Histopathology, clinical and imaging follow-up	**Diagnosis** Pooled Sens: 94% Pooled Spec: 89% Pooled +LR: 8.27 Pooled -LR: 0.07 Pooled DOR: 113.0 AUC: 0.92	NA	NA
Campbell et al, 2021 [94]	Meta-analysis	4 studies (142 patients with newly diagnosed Ewing sarcoma)	FDG PET or PET/CT	BMB	BMB	**Bone marrow metastases** Pooled Sens: 100% Pooled Spec: 96% Pooled PPV: 75% Pooled NPV: 100%	NA	NA
Albano et al, 2020 [95]	Retrospective	54 patients who underwent restaging or post-therapy surveillance (suspected recurrent or	FDG PET/CT	CT, MRI, US	Histopathology, clinical and imaging follow-up	**Recurrence (study-based)** Sens: 89% Spec: 97% PPV: 93% NPV: 96% Accu: 95%	NA	FDG PET/CT had a positive impact on clinical management in 18.0% (18/100) of scans (8—local therapy to systemic therapy, 3—initiated specific

		asymptomatic GIST)						therapy, 7—remained in watch-and-wait approach).
Thoracic 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, 2020 [38]	Meta-analysis	6 studies (779 patients with NSCLC)	FDG PET/CT	CeMRI	Histology, imaging follow-up	**Distant metastases** Pooled Sens: 72% Pooled Spec: 95% Pooled +LR: 13.5 Pooled -LR: 0.30	**Distant metastases** Pooled Sens: 83% Pooled Spec: 100% Pooled +LR: 400.8 Pooled -LR: 0.17	NA
Seol et al, 2021 [96]	Meta-analysis	14 studies (3535 patients with NSCLC)	FDG PET or PET/CT	NA	Histology	**Occult lymph node metastases** Pooled Sens: 79% Pooled Spec: 65% Pooled +LR: 2.3 Pooled -LR: 0.32 Pooled DOR: 7 AUC: 0.77	NA	NA
Toba et al, 2021 [97]	Retrospective	187 patients who had undergone potentially curative operation (NSCLC)	FDG PET/CT	Physical examination, chest radiograph, tumour marker measurement , chest CT, brain MRI	Histology, clinical and imaging follow-up	**Recurrence** Sens: 97.9% Spec: 97.1% PPV: 92.0% NPV: 99.3% Accu: 97.3%	NA	NA
Gamal et al, 2021 [98]	Prospective	63 patients treated with curative or palliative treatment (potentially resectable NSCLC)	FDG PET/CT	CeCT	Histopathology, clinical and imaging follow-up	**Residual or recurrent disease** Sens: 100% Spec: 92% PPV: 92% NPV: 100% Accu: 96%	**Residual or recurrent disease** Sens: 72% Spec: 95% PPV: 94% NPV: 79% Accu: 84%	Patients with a negative follow-up PET had a significantly longer median OS than those with a positive follow-up PET (45 months vs. 18 months; p<0.0001).
He et al, 2020 [99]	Retrospective	104 patients treated with gamma knife radiotherapy with or without PET/CT (lung cancer with brain metastases)	FDG PET/CT (n=52)	No FDG PET/CT (n=52)	Follow-up	NA	NA	At 3 months after treatment, the effective rate (61.5% vs. 42.3%; p=0.032) and local control rate (90.4% vs. 75.0%; p=0.038) were significantly higher in patients with PET/CT than in those without. However, the median survival times (10

								months for both; p=0.284) were not significantly different between the two groups. The incidence rate of acute and chronic adverse events (21.2% vs. 42.3%; p=0.02) were significantly lower in patients with PET/CT than in those without.
Honguero Martinez et al, 2021 [100]	Retrospective	305 patients who underwent surgical resection (undiagnosed solitary pulmonary nodule)	FDG PET/CT	Physical examination, routine laboratory tests, ECG, chest X-ray, CT, spirometry, pulmonary diffusion capacity test, fibreoptic bronchoscopy	Pathology	**Diagnosis** Sens: 94.6% Spec: 23.4% PPV: 87.1% NPV: 44.0% Accu: 83.6%	NA	NA
Various Sites								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Li et al, 2020 [101]	Retrospective	124 patients who did not receive prior chemotherapy and/or radiation therapy (hepatic metastatic carcinoma of unknown primary)	FDG PET/CT	NA	Histopathology, clinical and imaging follow-up	**Primary site** Sens: 88.8% Spec: 52.9% PPV: 91.4% NPV: 40.0% Accu: 83.1%	NA	NA
Reinert et al, 2020 [102]	Prospective	155 patients who underwent primary staging, restaging or lesion characterization (cancer of unknown primary)	FDG PET/CT, ^{68}Ga-DOTA-TATE PET/CT	CT, MRI	Histology, pre- and post-PET questionnaires	NA	NA	Intended therapeutic management was revised in 45.8% (71/155) after PET/CT (22—initiated palliative therapy, 12—initiated curative therapy, 2—started watchful waiting, 5—curative to palliative, 30—other minor changes).

Nikolova et al, 2021 [103]	Retrospective	53 patients with lymph node metastases (cancer of unknown primary)	FDG PET/CT	Physical examination, serum tumour marker test, chest X-ray, CT, MRI, mammography, cervical US, endoscopy	Histopathology, clinical follow-up	**Primary site** Sens: 73% Spec: 89% Accu: 81% AUC: 0.80	NA	FDG PET/CT modified the treatment plan of 49.1% (26/53) of patients (15—avoided unnecessary surgery, 8—avoided unnecessary systemic procedures, 3—other changes).
Mohamed et al, 2021 [104]	Prospective	39 patients with brain metastases at initial presentation (cancer of unknown primary)	FDG PET/CT	NA	Histopathology, clinical and imaging follow-up	**Primary site** Sens: 79% Spec: 95% Accu: 87%	NA	There was no significant difference (p=0.217) in median OS between patients with an identified primary tumour (12 months) and those with unidentified primary tumour (13 months).

*p<0.05

Abbreviations: Accu, accuracy; ALND, axillary lymph node dissection; AUC, area under the curve; BCLC, Barcelona Chronic Liver Cancer; BMB, bone marrow biopsy; CA19-9, carbohydrate antigen 19-9; CA-125, carbohydrate antigen 125; CeCT, contrast-enhanced computed tomography; CeMDCT, contrast-enhanced multidetector row computed tomography; CeMRI, contrast-enhanced magnetic resonance imaging; CeUS, contrast-enhanced ultrasound; CT, computerized tomography; DFS, disease-free survival; DLBCL, diffuse large B-cell lymphoma; DMFS, distant metastasis-free survival; DOR, diagnostic odds ratio; DR, detection rate; DWI, diffusion weighted imaging; eBEACOPP, escalated doses of etoposide, cyclophosphamide and doxorubicin, and regular doses of bleomycin, vincristine, procarbazine, and prednisone; EORTC, European Organization for Research and Treatment of Cancer; EUS, Endoscopic ultrasound; ^{18}F-DCFBC, N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]4-^{18}F-fluorobenzyl-L-cysteine; ^{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; ^{18}F-FET, O-(2[^{18}F]-fluoroethyl)-L-tyrosine; FN, false negative; ^{18}F-NaF, ^{18}F-sodium fluoride; FP, false positive; ^{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; GHSG, German Hodgkin Study Group; GIST, gastrointestinal stromal tumour; HE4, human epididymis protein 4; HL, Hodgkin lymphoma; HR, hazard ratio; ^{13}I, 131-Iodine; IFRT, involved-field radiation therapy; ^{131}I-MIBG, ^{131}I-meta-iodobenzylguanadine; +LR, positive likelihood rate; -LR, negative likelihood rate; LRFFS, locoregional failure-free survival; LRFS, local relapse-free survival; MDCT, multidetector computed tomography; mpMRI, multi-parametric magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; ^{99}mTc, technetium 99m; MTV, metabolic tumour volume; NA, not applicable; NET, neuroendocrine tumours; NHL, non-Hodgkin lymphoma; NPV, negative predictive value; NSCLC, non-small-cell lung carcinoma; OS, overall survival; PECRIT, PET/CT criteria for early prediction of response to immune checkpoint inhibitor therapy; PERCIMT, compared efficacy of EORTC with PET response evaluation criteria for immunotherapy; PERCIST, PET Response Criteria In Solid Tumor; PET, positron emission tomography; PFS, progression-free survival; PPV, positive predictive value; PRRT, peptide-receptor radionuclide therapy; PSA, prostate specific antigen; PWI, perfusion-weighted imaging; RANO, Response Assessment in Neuro-Oncology; $rCBV_{max}$, maximum relative cerebral blood volume; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RCT, randomized controlled trial; RRFS, regional recurrence-free survival; Sens, sensitivity; SLNB, sentinel lymph node biopsy; SLR, spleen to liver ratio; Spec, specificity; SUL/SUV_{peak}, peak of standardized uptake value; SUV_{max}, maximum standardized uptake value; TACE, transarterial chemoembolization; TBRmax, maximum tumour-to-brain ratio; TBRmean, mean tumour-to-brain ratio; TLG, total lesion glycolysis; TNM, tumour, node, metastasis; TTP, time-to-peak; US, ultrasound; vs, versus; WBS, whole body scan