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Cancer Care Ontario

PET Six-Month Monitoring Report 2023-1

Evidence from Primary Studies and Systematic Reviews and Recommendations from Clinical Practice Guidelines January to June 2023

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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 25th 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 2023 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)
    - ^{68}Ga-FAPI
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

Seventy-three studies published between January and June 2023 met the inclusion criteria. A summary of the evidence from the 73 studies can be found in Appendix 1: Summary of studies from January to June 2023.

Breast Cancer

Five studies met the inclusion criteria [1-5]. Despite exhibiting high specificity (92.0%), FDG PET/CT was found to be insufficient for evaluating axillary response after neoadjuvant chemotherapy in clinically node-positive patients due to poor sensitivity (63.3%) [1]. In the assessment of response to first-line treatment for metastatic disease, FDG PET/CT detected first progression not seen on contrast-enhanced CT in 19.5% of patients, of which 10.3% had a subsequent change in therapy. Conversely, contrast-enhanced CT detected first progression missed by FDG PET/CT in only 1.1% of patients that led to a change in treatment. Overall, FDG PET/CT (median time, 14.9 months) detected disease progression much earlier than contrast-enhanced CT (median time, 24.3 months, $p<0.001$) [2]. Tumour response on FDG PET/CT was also significantly associated with better progression-free survival (PFS) (hazard ratio [HR], 3.49, $p<0.001$) and disease-specific survival (HR, 2.35, $p=0.008$), whereas contrast-enhanced CT failed to show any significant prognostic value [3]. FDG PET/CT was especially useful for detecting recurrent invasive lobular carcinoma and changing the management of 91.7% of these patients [4]. In patients who underwent routine surveillance after primary curative treatment, FDG PET/CT was highly accurate (98.5%) in the detection of clinically unexpected recurrence or second primary cancer. Intended management was altered as a direct result of 3.6% of scans [5].

Epilepsy

One study met the inclusion criteria [6]. A meta-analysis comprised of 23 studies showed that resection of the epileptogenic zone identified by FDG PET/magnetic resonance imaging (MRI) led to 71% of refractory patients achieving good outcome (e.g., Engel class I or International League Against Epilepsy grade 1-2) following surgery.

Esophageal Cancer

One study met the inclusion criteria [7]. In patients with gastric or esophagogastric adenocarcinomas who underwent nodal restaging after neoadjuvant therapy, FDG PET/CT (accuracy, 60.4%) underperformed in comparison to endoscopic ultrasound (US) (accuracy, 70.8%). However, positive lymph nodes on FDG PET/CT (HR, 20.91; 95% confidence interval [CI], 3.39 to 129.08, $p=0.001$) and endoscopic US (HR, 4.37; 95% CI, 1.09 to 17.54, $p=0.037$) were both significant predictors of worse disease-free survival.

Gastrointestinal Cancer

Seven studies met the inclusion criteria [8-14]. In the preoperative staging of patients with colorectal cancer, FDG PET/CT detected lymph node metastases with moderately high accuracy (80.0%) [8]. For the diagnosis of colorectal liver metastases, one prospective study found both FDG PET/MRI and MRI to be superior to FDG PET/CT [9] but a meta-analysis reported similar performance between FDG PET/CT and FDG PET/MRI [10]. Nonetheless, information obtained from FDG PET/MRI after FDG PET/CT with conventional imaging changed the treatment strategy of 9.0% of patients [9]. In patients with rectal cancer, the addition of FDG PET/CT to routine staging work-up resulted in a modified management plan of 18.2% [11]. For locally advanced cases who received neoadjuvant chemoradiotherapy, MRI outperformed FDG

PET or PET/CT in the prediction of response (area under the curve, 0.91 versus 0.85, p=0.003) [12]. In the initial staging of patients with intrahepatic cholangiocarcinoma, FDG PET/CT did not show a clear diagnostic advantage over CT or MRI regarding the ability to identify multiple tumours, macrovascular invasion, or bile duct invasion. However, FDG PET/CT was more accurate than both modalities in terms of tumour, nodes, and metastases (TNM) staging (FDG PET/CT, 75.6% versus CT, 52.2%, p=0.001 and MRI, 56.7%, p=0.007) and diagnosis of regional lymph node metastases (FDG PET/CT, 85.6% versus CT, 66.7%, p<0.01 and MRI, 75.6%, p=0.01) [13]. In patients who presented with suspicion of recurrent gallbladder cancer, FDG PET/CT had a higher sensitivity (98.8% versus 84.5%, p=0.001) and specificity (76.7% versus 46.6%, p=0.035) than tumour markers combination (carbohydrate antigen sialyl Lewis a [CA19-9] and carcinoembryonic antigen [CEA]) for confirming recurrence [14].

Genitourinary Cancer

Five studies met the inclusion criteria [15-19]. Four of the studies looked at FDG PET/CT in the evaluation of bladder cancer. For the prediction of tumour response to neoadjuvant chemotherapy, FDG PET/CT showed a pooled sensitivity of 84.0% and a pooled specificity of 75.0% [15]. In patients specifically with high-risk muscle-invasive bladder cancer, FDG PET/CT (72.0%) and contrast-enhanced CT (78.0%) showed similar accuracy for predicting complete pathological response after two to three cycles of neoadjuvant and induction therapy [16]. Likewise, FDG PET/CT (accuracy, 79.0%) and contrast-enhanced CT (accuracy, 77.0%) were comparable in the staging of lymph node metastases prior to upfront radical cystectomy with bilateral pelvic lymph node dissection [17]. In the preoperative staging of high-risk non-muscle invasive bladder cancer, additional information provided by FDG PET/CT altered the disease stage in 12.0% of patients and changed the treatment plan of 9.8% of cases [18]. In patients with contract-enhanced CT-detected solid renal mass lesions, FDG PET/CT was able to diagnosis renal cell carcinoma with good sensitivity (80.0%) but moderate specificity (75.0%) [19].

Gynecologic Cancer

Two studies met the inclusion criteria [20,21]. In the initial staging of cervical cancer, the incorporation of pre-treatment FDG PET/CT was associated with a lower risk of all-cause death in patients with stage IB-IVA disease receiving radiotherapy or concurrent chemoradiotherapy (adjusted HR, 0.88; 95% CI, 0.80 to 0.97, p=0.010) [20] but not for patients with resectable disease receiving curative surgery (adjusted HR, 1.16; 95% CI, 0.83 to 1.63, p=0.375) [21].

Head and Neck Cancer

Ten studies met the inclusion criteria [22-31]. In the initial staging of patients with head and neck squamous cell carcinoma, FDG PET/CT proved to be reliably accurate for detecting the primary tumour (89.4%), cervical lymph node metastases (85.4%), and distant metastases (87.4%). FDG PET/CT was also able to reveal the primary site in eight of 25 cases with cancer of unknown primary [22]. In post-treatment surveillance, FDG PET/CT and MRI performed comparably in the detection of locoregional recurrence or residual disease [23]. For the staging of nasopharyngeal carcinoma prior to radiotherapy or concurrent chemoradiotherapy, the integration of FDG PET/CT was associated with lower risk of all-cause death in patients with stage II (HR, 0.77; 95% CI, 0.60 to 0.99, p=0.0433), III (HR, 0.81; 95% CI, 0.69 to 0.94, p=0.0071), and IVA (HR, 0.88; 95% CI, 0.79 to 0.97, p=0.0091) disease, but not stage I (HR, 1.20; 95% CI, 0.75 to 1.93, p=0.4426) disease [24]. With respect to detecting local recurrence, FDG PET/CT offered better sensitivity (93.9% versus 79.3%, p<0.001) than MRI, while maintaining high specificity (93.8%) [25]. Likewise, FDG PET/CT improved the accuracy (75.0% versus 64.7%, p=0.022) of detecting cervical lymph node metastases over MRI in the initial staging of laryngeal

cancer [26]. In those who received definitive radiotherapy with or without chemotherapy, FDG PET/CT was unreliable in assessing local residual disease due to a high number of false positive results (positive predictive value, 33.3% to 36.0%) [27]. In oral squamous cell carcinoma, patients screened with postoperative FDG PET/CT were more likely to be diagnosed with early recurrence than those who underwent CT imaging only (16.5% versus 3.3%, p=0.0001). Interestingly, increased detection of early recurrence by FDG PET/CT translated to improved disease-free survival (p=0.026) and overall survival (OS) (p=0.047) in patients with intermediate-risk features, but not those with high-risk features [28]. The other studies examined the utility of FDG PET/CT in patients with thyroid cancer. In the preoperative staging of papillary thyroid cancer, FDG PET/CT displayed suboptimal sensitivity (42.7%) and specificity (77.7%) to be helpful in detecting cervical lymph node metastases [29]. In patients with clinical suspicion of recurrent differentiated thyroid cancer and negative ^{131}I whole body scan, FDG PET/CT was able to verify recurrence and/or metastases with an accuracy of 69.0% to 95.5% [30,31]. As a direct result, moderate to high impact on management was seen in 41.8% of cases [31].

Hematologic Cancer

One study met the inclusion criteria [32]. In the phase 2 CALGB 50801 trial that enrolled patients with bulky stage I-II classic Hodgkin lymphoma (HL), interim-PET-positive patients who switched to four cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses (eBEACOPP) coupled with involved-field radiotherapy after two cycles of doxorubicin, vinblastine, vincristine, and dacarbazine (ABVD) had excellent three-year PFS (89.7%; 95% CI, 77.2 to 100) and OS (94.4%; 95% CI, 84.4 to 100). Interim-PET-negative patients who continued with four additional cycles of ABVD achieved similarly favourable three-year PFS (93.1%; 95% CI, 87.4 to 99.1) and OS (98.6%; 95% CI, 95.9 to 100) while omitting radiation.

Melanoma

Three studies met the inclusion criteria [33-35]. The impact of surveillance with routine FDG PET/CT on radically treated stage IIA to IIID melanoma was examined in two retrospective studies. Application of routine FDG PET/CT detected 64.5% of all operable lesions, whereas FDG PET/CT performed only as a confirmation test detected 35.5% of all operable lesions [33]. Particularly within the first two years of surveillance, routine FDG PET/CT was associated with a greater hazard of distant recurrence than clinical examination alone (HR, 1.15; 95% CI, 1.16 to 1.96) [34]. In the initial staging of newly diagnosed Merkel cell carcinoma, FDG PET/CT upstaged 16.1% of patients with palpable lymph nodes to stage IV disease [35].

Non-FDG Tracers

Twenty-one studies met the inclusion criteria [36-56]. In one study, the diagnostic performance of ^{68}Ga-DOTA-NOC PET/CT was prospectively compared to conventional imaging (e.g., multiphasic CT, SPECT/CT, MRI) in patients with grade 1 or 2 gastroenteropancreatic NET. ^{68}Ga-DOTA-NOC PET/CT was determined to be more sensitive in the detection of primary tumour (97.8% versus 78.7%, p=0.016), lymph node metastases (97.4% versus 59.0%, p<0.001), peritoneal carcinomatosis (95.0% versus 30.0%, p<0.001), and bone metastases (100% versus 33.3%, p=0.041), while also providing higher specificity (100% versus 89.5%, p<0.001) for liver metastases. Therapeutic management was influenced by ^{68}Ga-DOTA-NOC PET/CT in 41.9% of cases [36]. ^{68}Ga-DOTA-TOC PET/CT was equally impactful in the staging or restaging of small cell lung cancer, with treatment modification in 59.0% of cases [37]. In post-treatment glioma patients, data from a meta-analysis did not show a diagnostically superior imaging technique between ^{18}F-FET PET/CT or PET/MRI and perfusion-weighted MRI with dynamic susceptibility

contrast in the differentiation of tumour progression from treatment-related abnormalities [38]. Several studies evaluated the use of ^{68}Ga-PSMA/^{18}F-DCFPyL PET/CT or PET/MRI in prostate cancer. Pooled estimates from a meta-analysis showed that ^{18}F-DCFPyL PET/CT or PET/MRI had high sensitivity (92.0%) but poor specificity (59.0%) in the diagnosis of primary prostate cancer [39]. Furthermore, ^{68}Ga-PSMA/^{18}F-DCFPyL PET/CT was equal to multiparametric MRI in the diagnosis of extracapsular extension and seminal vesical invasion [40]. For the initial staging of patients with intermediate- to high-risk prostate cancer, ^{68}Ga-PSMA PET/CT outperformed conventional MRI and CT in the detection of lymph node metastases and exceeded bone scan for skeletal metastases [41,42]. However, pelvic lymph node dissection cannot be excluded based on a negative ^{68}Ga-PSMA PET/CT due to unsatisfactory negative predictive value (NPV) (71.6%) [43]. Nonetheless, ^{68}Ga-PSMA PET/CT findings led to the addition or change of treatment modalities in 20.0% of cases [44]. With regards to response assessment after neoadjuvant chemohormonal therapy, ^{68}Ga-PSMA PET/CT based on European Association of Urology/European Association of Nuclear Medicine or Positron Emission Tomography Response Criteria In Solid Tumors 1.0 criteria was better at predicting complete remission/minimal residual disease than multiparametric MRI and nadir prostate-specific antigen (PSA) [45]. Likewise for patients with biochemically recurrent disease, ^{68}Ga-PSMA/^{18}F-DCFPyL PET/CT was more useful than multiparametric MRI in the detection of lymph node and bone metastases [46,47]. In fact, ^{18}F-DCFPyL PET/CT may render technetium 99m-methyl diphosphonate bone scintigraphy unnecessary when investigating bone metastases [48]. Taken together, management impact was seen in 33.8% to 56.4% of cases across three studies [49-51], including a phase II RCT (PSMAgRT) that reported more than one-half of the patients receiving intensified radiation therapy guided by ^{18}F-DCFPyL PET/CT [51]. ^{68}Ga-PSMA PET/CT was also examined in patients with hepatocellular carcinoma undergoing routine surveillance. The sensitivity of ^{68}Ga-PSMA PET/CT (91.0%) for diagnosing recurrent disease was comparable to MRI (87.0%) but surpassed that of CT (32.0%) [52]. In patients with digestive system tumours, ^{68}Ga-FAPI PET/CT or PET/MRI was shown to be highly sensitive in the evaluation of primary tumour lesions (pooled estimate, 97.0%) and lymph node and distant metastases (pooled estimate, 94.0%) [53]. Interestingly, ^{68}Ga-FAPI PET/CT or PET/MRI was considerably less sensitive (pooled estimate, 74.7%) for assessing lymph node metastases in gastric cancer only [54]. For the differentiation of recurrent high-grade glioma from treatment-related changes, ^{18}F-FDOPA PET/CT or PET/MRI established the highest accuracy (78.0%) when using the static parameter mean tumour-to-brain ratio with a cut-off value of 1.8 [55]. The AMYPAD-DPMS RCT investigated the clinical utility of amyloid PET in patients with subjective cognitive decline, mild cognitive impairment, or dementia. Results showed that at three-month follow-up, the proportion of patients changing etiological diagnosis after early amyloid PET (44%) was higher than those who received late amyloid PET (11%, $p<0.001$) or amyloid PET at physician's choice (29%, $p=0.002$). However, the change in cognition-specific medications was similar in the three study arms (15% for early amyloid PET, 14% for late amyloid PET, and 15% for amyloid PET at physician's choice, $p=0.97$) [56].

Pancreatic Cancer

One study met the inclusion criteria [57]. In the initial staging of patients with confirmed or suspected pancreatic cancer, FDG PET/CT findings contributed to a significant management change in 35.3% of cases.

Pediatric Cancer

One study met the inclusion criteria [58]. In children with newly diagnosed HL, FDG PET/CT provided a better assessment of bone marrow involvement than bone marrow biopsy in terms of sensitivity (100% versus 25.0%) and NPV (100% versus 94.0%).

Sarcoma

One study met the inclusion criteria [59]. For the staging of newly diagnosed Ewing sarcoma, FDG PET/CT detected bone marrow involvement with high sensitivity (92.3%) and specificity (99.4%). Given the results, the authors suggested that invasive bone marrow aspiration and biopsy should no longer be systematically performed as part of initial staging of these patients.

Thoracic Cancer

Nine studies met the inclusion criteria [60-68]. In the preoperative staging of non-small cell lung cancer (NSCLC), FDG PET/CT characterized hilar and mediastinal lymph node metastases with an accuracy of 65.9% to 81.0% across two retrospective studies [60,61]. Results from another retrospective study showed similar accuracy between FDG PET/CT and FDG PET/MRI for tumour and nodal staging, as well as the evaluation of pleural invasion [62]. In patients with unresectable NSCLC, two phase II RCTs investigated the feasibility of FDG PET/CT-guided radiotherapy treatments. In the PET-Boost trial, patients with inoperable, stage II to III disease were randomized to receive radiation dose escalation to the whole primary tumour or a PET-defined subvolume. The one-year freedom from local failure rate was 97.0% for the whole tumour group and 91.0% for the PET-subvolume group, while both groups observed a median OS of 18 months. However, both strategies led to high rates of grade 5 toxicities [63]. In the other trial, patients with unresectable, stage IIIA or IIIB disease were randomized to receive clinical target volume (CTV)-omitted or CTV-delineated intensity-modulated radiation therapy. Omitting the CTV under FDG PET/CT guidance led to lower incidence of radiation respiratory events or grade ≥3 esophagitis (11.1% versus 28.9%, p=0.035), without compromising median PFS (CTV-omitted, 9.0 months versus CTV-delineated, 10.0 months, p=0.597), median OS (31.0 months versus 26.0 months, respectively, p=0.489) or regional control times (15.0 months for both, p=0.826) [64]. For the detection of NSCLC recurrence, FDG PET/CT offered remarkable sensitivity (pooled estimate, 96.0%) and specificity (pooled estimate, 93.0%) [65]. Patients who were imaged with FDG PET/CT instead of CT before radiation therapy for oligoprogressive or recurrent disease had significant improvements in three-year OS (HR, 1.417; 95% CI, 1.32 to 1.52, p<0.0001) and three-year cancer-specific survival (HR, 1.430; 95% CI, 1.32 to 1.55, p<0.0001) [66]. For the characterization of pulmonary nodules, FDG PET/CT was comparable to diffusion-weighted MRI [67], but superior to dynamic contrast-enhanced CT when the solitary nodule is between 8 mm and 30 mm [68].

CLINICAL EXPERT REVIEW

Breast Cancer

Current Indications for Breast Cancer

- For the staging of patients with histologically confirmed clinical stage 2b or stage 3 breast cancer being considered for curative intent combined modality treatment; and/or repeat PET on completion of neoadjuvant therapy, prior to surgery (when there is clinical suspicion of progression); or for re-staging of patients with locoregional recurrence, after primary treatment, being considered for ablative or salvage therapy.
- For staging or re-staging of patients with oligometastatic disease (4 or fewer metastases) on conventional imaging prior to radical intent or ablative therapy.

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 recommendation for the utilization of PET/CT in epilepsy remains 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 (Dr. Rebecca Wong)

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

Gastrointestinal Cancer

Current Indications for Colorectal Cancer

- For the staging or re-staging of patients with apparent limited metastatic disease (e.g., organ-restricted liver or lung metastases) or limited local recurrence, who are being considered for radical intent therapy.
  Note: as chemotherapy may affect the sensitivity of the PET scan, it is strongly recommended to schedule PET at least six weeks after last chemotherapy, if possible.
- Where recurrent disease is suspected on the basis of an elevated and/or rising CEA 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. However, based on the systematic review findings from Ko and Kim [15], it may be worthwhile to look at PET/CT for response assessment to neoadjuvant chemotherapy in bladder cancer.

Gynecologic Cancer

Current Indications for Cervical Cancer

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

Reviewer's Comments

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

Head and Neck Cancer

Current Indications for Head and Neck Cancer

- For the baseline staging of node-positive (N1-N3) head and neck cancer where PET will impact radiation therapy (e.g., radiation volume or dose).
- To assess patients with N1-N3 metastatic squamous cell carcinoma of the head and neck after chemoradiation (human papillomavirus [HPV] negative); or who have residual neck nodes ≥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 non-Hodgkin lymphoma (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 (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.

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. However, it may be optimal to consider Merkel cell carcinoma staging as an indication for PET/CT based on the data from Zijlker et al. [35].

Non-FDG Tracers

Current Indications for Gallium-68 PET/CT in Neuroendocrine Tumours

- For the evaluation of a pancreatic, small bowel or mesenteric mass with findings suggestive of a neuroendocrine tumour (NET) (e.g., hypervascular pancreatic mass, desmoplastic mesenteric mass) on conventional imaging.
- For the evaluation of extra-adrenal mass (e.g., carotid body nodule), with conventional imaging and/or elevated biomarkers suggestive of a pheochromocytoma/paraganglioma (PPGL).
- For the evaluation of patients with a genetic syndrome predisposing to NETs and a biochemical and/or morphological suspicion of a NET in whom PET results would measurably impact management.

Special Considerations for Diagnosis

- For the evaluation of patients with a suspicious mass in another anatomical location (e.g., lung) without elevated biochemical markers should be considered for further work-up and/or biopsy before the PET. PET could be considered after a failed biopsy or if a biopsy is not feasible.
- For the evaluation of patients with a pancreatic tail mass suggestive of a NET should have a Tc-99m Sulpha Colloid or Red Blood Cell scan to exclude intrapancreatic accessory spleen as both can present Ga-68 DOTATATE avid.

- For the initial staging of histologically proven well-differentiated NET (G1-G3), including unknown primary, or PPGL.
- For the initial staging of histologically proven medullary thyroid cancer being considered for curative intent therapy.

  Note: Initial staging PET scans should be requested within one year from the initial diagnosis.

  Special Considerations for Initial Staging
  - PET is not appropriate for patients with Type 1 Gastric NET, neuroendocrine carcinomas and adenocarcinomas with NET features.
  - Unless there are unique clinical and/or structural concerns, PET is not routinely appropriate for patients with diffuse idiopathic pulmonary neuroendocrine cell hyperplasia.
  - Initial staging of patients with an appendiceal NET should be considered when there are positive lymph nodes, the tumour is greater than 1 cm, and/or the tumour is invading through the serosa into the mesoappendix.
  - Initial staging of patients with medullary thyroid cancer should be considered when the patient has yet to have a thyroidectomy or following it when biomarkers are positive with negative or equivocal structural imaging.
- For the re-staging of patients with progressive NETs disease who are being considered for publicly funded peptide receptor radionuclide therapy (PRRT).

  Note: For PRRT consideration, a PET scan should be completed within 12 months. However, a more recent PET scan should be considered if there are concerning clinical features (e.g., de-differentiation).
- New baseline PET scan for patients with new metastatic disease on conventional imaging and/or clinical suspicion of de-differentiation.
- For the re-staging of patients with NETs disease when surgery (e.g., de-bulking, focal ablation, liver-directed therapy) is being considered.
- For the re-staging of patients with NETs disease where conventional imaging is negative or equivocal at the time of clinical and/or biochemical progression.
- For the re-staging of patients with medullary thyroid cancer when 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.

  Special Considerations for Routine Surveillance
  - Requests for routine surveillance when there is no clinical or biochemical suspicion of recurrence or progression are not eligible.

Current Indications for PSMA PET/CT in Prostate Cancer

- For the initial staging of patients with a new diagnosis of high-risk prostate cancer being considered for radical (curative) therapy.
- For the re-staging of patients with post-prostatectomy node-positive disease or persistently detectable PSA.
- For the re-staging of patients with biochemical failure post-prostatectomy.
- For the re-staging of patients with failure following radical prostatectomy followed by adjuvant or salvage radiotherapy.
- For the re-staging of patients with rising PSA post-prostatectomy despite salvage hormone therapy.
- For the re-staging of patients with biochemical failure following treatment for oligometastatic disease.
- For the re-staging of patients with biochemical failure following primary radiotherapy.
- For the re-staging of patients with rising PSA and/or progression on conventional imaging despite prior second line hormone therapy or chemotherapy for castrate resistant prostate cancer.
- 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. Derek Jonker)

There is insufficient evidence to recommend the utilization 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
    - 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 the initial staging of patients with histologically confirmed high grade (≥ grade 2), or ungradable, soft tissue or bone sarcomas, when conventional work-up is negative or equivocal for metastatic disease, prior to curative intent therapy.
- For re-staging of patients with suspicion of, or histologically confirmed, recurrent sarcoma (local recurrence of limited metastatic disease) when radical salvage therapy is being considered.

Current Indication for Plexiform Neurofibromas

- For patients with suspicion of malignant transformation of plexiform neurofibromas.

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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APPENDIX 1: SUMMARY OF STUDIES FROM JANUARY TO JUNE 2023.

Breast Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Memisoglu et al, 2023 [1]	Retrospective	231 patients who underwent evaluation of axillary clinical response after neoadjuvant chemotherapy (T1-4, cN1-2 breast cancer)	FDG PET/CT	NA	Histopathology	**Axillary lymph node metastases** Sens: 63.3% Spec: 92.0% PPV: 91.2% NPV: 65.7% AUC: 0.774	NA	NA
Vogsen et al, 2023 [2]	Prospective	87 patients who underwent response monitoring to first-line treatment (de novo or recurrent metastatic breast cancer)	FDG PET/CT	CeCT	Clinical or imaging follow-up	NA	NA	First progression was detected by FDG PET/CT only in 19.5% (17/87) of patients, of which 9 patients had a subsequent change in treatment. CeCT detected first progression not seen on FDG PET/CT in 1 patient (1.1%), which led to a change in management. Disease progression was detected earlier by FDG PET/CT than by CeCT (median time, 14.9 months vs. 24.3 months, p<0.001).
Vogsen et al, 2023 [3]	Prospective	87 patients who underwent response monitoring to first-line treatment (de novo or recurrent metastatic breast cancer)	FDG PET/CT	CeCT	Clinical or imaging follow-up	NA	NA	Tumour response on FDG PET/CT was significantly associated with better PFS (HR, 3.49, p<0.001) and DSS (HR, 2.35, p=0.008), whereas no association was found for tumour response on CeCT with respect to PFS (HR, 1.63, p=0.12) or DSS (HR, 1.59, p=0.20).
Bonnin et al, 2023 [4]	Retrospective	64 patients who have been previously treated	FDG PET/CT	Not specified	Histopathology, correlative clinical and imaging results	**Recurrence** Sens: 87.0% Spec: 87.0% PPV: 95.0%	NA	A change in treatment following FDG PET/CT occurred in 91.7% (44/48) of patients (29—

		(suspected recurrent invasive lobular carcinoma)				NPV: 70.0%		chemotherapy regimens introduced, 8—surgery and/or radiotherapy administered, 4—hormone therapy initiated, 3—not specified).
Lee et al, 2023 [5]	Retrospective	1681 patients (2121 scans) who underwent routine surveillance after primary curative treatment without documentation or suspicion of recurrence at conventional imaging, laboratory tests, and clinical symptoms and signs (breast cancer)	FDG PET/CT	NA	Pathology, clinical and imaging follow-up	**Recurrence or second primary cancer (scan-based)** Sens: 100% Spec: 98.5% PPV: 70.5% NPV: 100% Accu: 98.5%	NA	Intended management was changed as a direct result of 3.6% (77/2121) of scans.
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, 2023 [6]	Meta-analysis	23 studies (1292 patients who underwent refractory epilepsy resection)	FDG PET/MRI	EEG, SEEG	Follow-up	NA	NA	The proportion of patients with good outcome (Engel class I or ILAE grade 1-2) following resection of the epileptogenic zone identified by FDG PET/MRI was 71%.
Esophageal Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Amezcua-Hernandez et al, 2023 [7]	Retrospective	185 patients who underwent restaging after neoadjuvant therapy (gastric or	FDG PET/CT	EUS	Pathology	**Lymph node metastases** Sens: 27.3% Spec: 88.5% PPV: 59.0%	**Lymph node metastases** Sens: 60.0% Spec: 78.6% PPV: 73.3%	Positive lymph nodes on restaging FDG PET/CT (HR, 20.91, 95% CI, 3.39 to 129.08, p=0.001) and EUS (HR, 4.37, 95% CI, 1.09 to 17.54, p=0.037)

		esophagogastric adenocarcinoma)				NPV: 66.7% Accu: 60.4%	NPV: 66.7% Accu: 70.8%	were both significant predictors of worse DFS.
Gastrointestinal Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Soyluoglu and Ozdemir Gunay, 2023 [8]	Retrospective	50 patients who underwent preoperative staging (colorectal cancer)	FDG PET/CT	NA	Histopathology	**Lymph node metastases** Sens: 84.0% Spec: 77.0% PPV: 57.0% NPV: 59.0% Accu: 80.0%	NA	NA
Akkus Gunduz et al, 2023 [9]	Prospective	78 patients who underwent staging or restaging (colorectal cancer)	FDG PET/CT, FDG PET/MRI	MRI, US, CeCT	Histopathology, clinical and imaging follow-up	**Liver metastases** ***FDG PET/CT*** **(patient-based)** Sens: 75.6%*‡ Spec: 97.3% Accu: 85.9%‡ **(lesion-based)** ***FDG PET/CT*** Sens: 55.6%*‡ Spec: 98.5% Accu: 70.7%*‡ ***FDG PET/MRI*** **(patient-based)** Sens: 100%‡ Spec: 100% Accu: 100%‡ ***FDG PET/MRI*** **(lesion-based)** Sens: 97.2%‡ Spec: 100% Accu: 98.2%*‡	**Liver metastases** ***MRI*** **(patient-based)** Sens: 100%* Spec: 86.5% Accu: 93.5% **(lesion-based)** Sens: 100%* Spec: 80.5% Accu: 93.1%*	Information obtained from FDG PET/MRI after conventional imaging plus FDG PET/CT changed the treatment strategy of 9.0% (7/78) of patients (1—followed-up without any medical or surgical treatment, 4—surgery or locoregional treatment indicated, 2—switched to systemic therapy).
Miao et al, 2023 [10]	Meta-analysis	21 studies (2743 patients with colorectal liver metastases)	FDG PET/CT, FDG PET/MRI	NA	Histopathology, imaging follow-up	**Colorectal liver metastases** ***FDG PET/CT*** Pooled Sens: 86.0% Pooled Spec: 89.0% AUC: 0.92 ***FDG PET/MRI*** Pooled Sens: 84.0% Pooled Spec: 100% AUC: 0.89	NA	NA
Chen et al, 2023 [11]	Retrospective	357 patients who underwent initial staging (rectal cancer)	FDG PET/CT	CT, MRI, US	Biopsy, consensus from multidisciplinary meeting	NA	NA	FDG PET/CT findings led to altered management plan in 18.2% (65/357) of patients.

Gao et al, 2023 [12]	Meta-analysis	74 studies (4105 patients with locally advanced rectal cancer who received neoadjuvant chemoradiotherapy)	FDG PET or PET/CT	MRI	Histology	**Response assessment** Pooled Sens: 81.0% Pooled Spec: 75.0%* Pooled +LR: 3.29* Pooled -LR: 0.25 AUC: 0.85*	**Response assessment** Pooled Sens: 83.0% Pooled Spec: 85.0%* Pooled +LR: 5.50* Pooled -LR: 0.20 AUC: 0.91*	NA
Nishioka et al, 2022 [13]	Retrospective	90 patients who underwent initial staging (intrahepatic cholangiocarcinoma)	FDG PET/CT	CT, MRI, chest radiography, bone scintigraphy	Histopathology	**TNM staging** Accu: 75.6%* **Multiple tumours** Sens: 28.6% Spec: 100% PPV: 100% NPV: 71.4% Accu: 72.2% **Macrovascular invasion** Sens: 40.0% Spec: 97.6% PPV: 50.0% NPV: 96.5% Accu: 94.4% **Bile duct invasion** Sens: 16.7% Spec: 100% PPV: 100% NPV: 94.4% Accu: 94.4% **Regional lymph node metastases** Sens: 84.0%* Spec: 86.2% PPV: 91.3%* NPV: 83.6%* Accu: 85.6%*	**TNM staging** ***CT*** Accu: 52.2%* ***MRI*** Accu: 56.7%* **Multiple tumours** ***CT*** Sens: 48.6% Spec: 100% PPV: 100% NPV: 75.3% Accu: 80.0% ***MRI*** Sens: 51.4% Spec: 96.4% PPV: 90.0% NPV: 75.7% Accu: 78.9% **Macrovascular invasion** ***CT*** Sens: 60.0% Spec: 89.4% PPV: 25.0% NPV: 97.4% Accu: 87.8% ***MRI*** Sens: 60.0% Spec: 94.1% PPV: 37.5% NPV: 97.6% Accu: 92.2% **Bile duct invasion** ***CT*** Sens: 16.7% Spec: 98.8% PPV: 25.0% NPV: 98.8% Accu: 93.3% ***MRI*** Sens: 50.0% Spec: 98.8%	NA

							PPV: 50.0% NPV: 98.8% Accu: 95.6% **Regional lymph node metastases** ***CT*** Sens: 40.0%* Spec: 76.9% PPV: 62.5%* NPV: 67.6%* Accu: 66.7%* ***MRI*** Sens: 56.0%* Spec: 83.1% PPV: 73.7% NPV: 76.1%* Accu: 75.6%*	
Bedmutha et al, 2023 [14]	Retrospective	117 patients who received radical cholecystectomy with or without adjuvant therapy (suspected recurrent gallbladder cancer)	FDG PET/CT	Tumour markers CA19-9 and CEA	Histopathology, clinical and imaging follow-up	**Recurrence** Sens: 98.8%* Spec: 76.7%* PPV: 92.5% NPV: 95.8% Accu: 93.1%	**Recurrence** Sens: 84.5%* Spec: 46.6%* PPV: 81.6% NPV: 51.9% Accu: 74.6%	NA
Genitourinary Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Ko and Kim, 2023 [15]	Meta-analysis	5 studies (278 patients who received neoadjuvant chemotherapy for bladder cancer)	FDG PET/CT	NA	Histopathology	**Prediction of tumour response to neoadjuvant chemotherapy** Pooled Sens: 84.0% Pooled Spec: 75.0% Pooled +LR: 3.3 Pooled -LR: 0.22 Pooled DOR: 15 AUC: 0.87	NA	NA
Einerhand et al, 2023 [16]	Prospective	83 patients who underwent response assessment after 2 to 3 cycles of neoadjuvant and induction chemotherapy (high-risk muscle-	FDG PET/CT	CeCT	Histopathology	**Prediction of complete pathological response** Sens: 53.0% Spec: 75.0% PPV: 36.0% NPV: 86.0% Accu: 72.0%	**Prediction of complete pathological response** Sens: 8.0% Spec: 96.0% PPV: 33.0% NPV: 81.0% Accu: 78.0%	NA

		invasive urothelial carcinoma)						
Einerhand et al, 2023 [17]	Retrospective	237 patients who underwent staging prior to upfront radical cystectomy with bilateral pelvic lymph node dissection (muscle-invasive or high-risk T1-bladder cancer)	FDG PET/CT	CeCT	Histopathology	**Lymph node metastases** Sens: 23.0% Spec: 92.0% PPV: 42.0% NPV: 83.0% Accu: 79.0% AUC: 0.578	**Lymph node metastases** Sens: 15.0% Spec: 93.0% PPV: 33.0% NPV: 81.0% Accu: 77.0% AUC: 0.538	NA
van Ginkel et al, 2023 [18]	Retrospective	92 patients who underwent preoperative staging (high-risk non-muscle invasive bladder cancer)	FDG PET/CT	CeCT, physical examination, cystoscopy	Histopathology or cytology, clinical and imaging follow-up	**Lymph node and distant metastases** Sens: 36.0% Spec: 93.0% PPV: 64.0% NPV: 79.0% Accu: 77.0% AUC: 0.643*	**Lymph node and distant metastases *CeCT*** Sens: 12.0% Spec: 97.0% PPV: 60.0% NPV: 75.0% Accu: 74.0% AUC: 0.545*	FDG PET/CT altered the disease stage in 12.0% (11/92) of patients. Consequently, the addition of FDG PET/CT to CeCT changed the treatment plan of 9.8% (9/92) of cases (4—upfront radical cystectomy to neoadjuvant or induction chemotherapy, 2—intravesical instillations to neoadjuvant or induction chemotherapy, 2—radical cystectomy to palliative care, 1—systemic treatment to upfront radical cystectomy).
Sri Charan et al, 2022 [19]	Prospective	24 patients with CeCT detected solid renal mass lesions (renal cell carcinoma)	FDG PET/CT	CeCT	Histopathology	**Diagnosis** Sens: 80.0% Spec: 75.0% PPV: 94.1% NPV: 42.8% Accu: 79.1%	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**
Su et al, 2023 [20]	Retrospective	4167 patients who underwent staging before radiotherapy or	FDG PET/CT + CI (n=1389)	CT, CeMRI (n=2778)	Clinical follow-up	NA	NA	Pre-treatment FDG PET/CT was associated with a lower risk of all-cause death (adjusted

		concurrent chemoradiotherapy (clinical stage IB-IVA cervical cancer)						HR, 0.88, 95% CI, 0.80 to 0.97, p=0.010). The 5-year OS was also higher in patients who received pre-treatment FDG PET/CT (54.6% versus 50.1%, p<0.001).
Su et al, 2022 [21]	Retrospective	2550 patients who underwent staging before curative surgery and adjuvant treatments (clinical stage IB-IIA resectable cervical cancer).	FDG PET/CT + CI (n=520)	CT, CeMRI (n=2030)	Pathology, clinical follow-up	NA	NA	The risk of all-cause death did not differ between patients who received preoperative FDG PET/CT and those who did not (adjusted HR, 1.16, 95% CI, 0.83 to 1.63, p=0.375).
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**
Kratka et al, 2022 [22]	Prospective	198 patients who underwent initial staging (head and neck squamous cell carcinoma)	FDG PET/CT	NA	Histopathology	**Primary tumour** Sens: 90.6% Spec: 77.8% PPV: 97.6% NPV: 45.2% Accu: 89.4% **Cervical lymph node metastases** Sens: 95.8% Spec: 69.6% PPV: 82.6% NPV: 91.7% Accu: 85.4% **Distant metastases** Sens: 96.9% Spec: 85.5% PPV: 56.4% NPV: 99.3% Accu: 87.4%	NA	FDG PET/CT revealed the site of unknown primary in 32.0% (8/25) of patients.
Zhu et al, 2023 [23]	Meta-analysis	3 studies (176 patients with head and neck squamous cell carcinoma who underwent post-treatment surveillance)	FDG PET/CT	MRI	Histopathology, clinical follow-up	**Locoregional recurrence or residual disease** Pooled Sens: 68.0% Pooled Spec: 89.0%	**Locoregional recurrence or residual disease** Pooled Sens: 72.0% Pooled Spec: 85.0%	NA

Yang et al, 2023 [24]	Retrospective	8732 patients who underwent staging prior to radiotherapy or concurrent chemoradiotherapy (stage I to IVA nasopharyngeal carcinoma)	FDG PET/CT + CI (n=4366)	US, CeMRI, chest X-ray (n=4366)	Clinical follow-up	NA	NA	Patients with stage II (HR, 0.77, 95% CI, 0.60 to 0.99, p=0.0433), III (HR, 0.81, 95% CI, 0.69 to 0.94, p=0.0071), and IVA (HR, 0.88, 95% CI, 0.79 to 0.97, p=0.0091) disease who received pre-treatment FDG PET/CT had a lower risk of all-cause death compared to those who did not receive pre-treatment FDG PET/CT. However, this association was not significant in patients with stage I disease (HR, 1.20, 95% CI, 0.75 to 1.93, p=0.4426).
OuYang et al, 2023 [25]	Retrospective	1453 and 316 patients from two cohorts who received radiotherapy (recurrent nasopharyngeal carcinoma)	FDG PET/CT	MRI, US	Histopathology, clinical and imaging follow-up	**Local recurrence (patient-based)** Sens: 93.9%* Spec: 93.8% **Regional node recurrence (node-based)** Sens: 90.9%* Spec: 85.9%	**Local recurrence *MRI* (patient-based)** Sens: 79.3%* Spec: 94.8% **Regional node recurrence *MRI* (node-based)** Sens: 67.6%* Spec: 88.2% ***US* (node-based)** Sens: 88.7% Spec: 86.9%	NA
Al-Ibraheem et al, 2023 [26]	Retrospective	68 patients who went initial staging prior to treatment (laryngeal cancer)	FDG PET/CT	Neck MRI	Histopathology	**Cervical lymph node metastases** Sens: 93.8% Spec: 58.3% PPV: 66.7% NPV: 91.3% Accu: 75.0%*	**Cervical lymph node metastases** Sens: 68.8% Spec: 61.1% PPV: 61.1% NPV: 68.8% Accu: 64.7%*	NA
Sistonen et al, 2023 [27]	Retrospective	73 patients who received definitive radiotherapy with or without chemotherapy (T2-T3 laryngeal carcinoma)	FDG PET/CT	NA	Biopsy, imaging follow-up	**Local residual disease (equivocal as positive)** Sens: 100% Spec: 75.0% PPV: 36.0% NPV: 100%	NA	NA

						Accu: 78.1% **(equivocal as negative)** Sens: 44.4% Spec: 87.5% PPV: 33.3% NPV: 91.8% Accu: 82.2%		
Yu et al, 2023 [28]	Retrospective	391 patients who underwent postoperative radiotherapy or chemoradiotherapy planning (oral squamous cell carcinoma)	FDG PET/CT (n=237)	CT (n=154)	Histology or cytology, multidisciplinary consensus based on imaging or physical exam findings	NA	NA	Postoperative PET/CT planning detected significantly more early recurrence then CT only planning (16.5% vs. 3.3%, p=0.0001). There were no significant differences in DFS (p=0.26) or OS (p=0.21) between the two groups. However, postoperative PET/CT planning was associated with improved DFS (p=0.026) and OS (p=0.047) for patients with intermediate-risk features but not high-risk features (DFS, p=0.44; OS, p=0.96).
Seo, 2023 [29]	Retrospective	234 patients who underwent preoperative staging (papillary thyroid cancer)	FDG PET/CT	NA	Pathology, clinical and imaging follow-up	**Cervical lymph node metastases (level-based)** Sens: 42.7% Spec: 77.7% PPV: 36.6% NPV: 81.9% Accu: 69.6%	NA	NA
Askar et al, 2023 [30]	Prospective	68 patients with elevated serum thyroglobulin or positive anti-thyroglobulin antibody levels and a negative ^{131}I whole-body scan after at least a single dose of radioactive iodine ablation (suspected recurrent	FDG PET/CT	^{131}I whole-body scan, serum thyroglobulin, anti-thyroglobulin antibody level	Histopathology, clinical and imaging follow-up	**Recurrence** Sens: 72.0% Spec: 57.0% PPV: 87.0% NPV: 35.0% Accu: 69.0%	NA	NA

		differentiated thyroid cancer)						
Boktor et al, 2022 [31]	Retrospective	67 patients with elevated serum thyroglobulin and negative ^{131}I whole body scan after total thyroidectomy followed by radioactive iodine ablation (suspected recurrent differentiated thyroid cancer)	FDG PET/CT	^{131}I whole-body scan, serum thyroglobulin	Histopathology, clinical or imaging follow-up	**Recurrence and/or metastases** Sens: 96.5% Spec: 94.5% PPV: 93.3% NPV: 97.2% Accu: 95.5%	NA	FDG PET/CT had a high or moderate impact on management in 41.8% (28/67) of patients (9—performed surgery, 8—referred to oncology and radiotherapy for further treatment, 2—proceeded to ^{131}I therapy, 9—change in ^{131}I therapy dose).
Hematologic Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
LaCasce et al, 2023 [32]	Prospective (Phase II CALGB 50801)	94 patients who underwent interim response assessment after 2 cycles of ABVD (bulky stage I-II classic HL)	FDG PET/CT (Interim-PET negative patients continued with 4 additional cycles of ABVD. Interim-PET positive patients switched to 4 cycles of escalated BEACOPP followed by involved-field radiotherapy)	NA	Clinical and imaging follow-up	NA	NA	The estimated HR comparing PFS of patients with positive and negative interim-PET was 1.03 (85% upper bound 2.38), which was significantly less than the null hypothesis of 4.1 (p=0.04). The 3-year PFS for patients with negative and positive interim-PET were 93.1% (95% CI, 87.4 to 99.1) and 89.7% (95% CI, 77.2 to 100), respectively. The 85% lower bound on the PFS estimate for patients with positive interim-PET was 82.9%, which was significantly higher than the null hypothesis of 40% (p<0.0001). The 3-year OS for patients with negative and positive interim-PET were 98.6% (95% CI, 95.9 to 100) and 94.4% (95% CI, 84.4 to 100), respectively.

Melanoma								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Dancheva et al, 2023 [33]	Retrospective	96 patients who underwent surveillance after radically treated first regional recurrence (recurrent stage IIA to IIID cutaneous melanoma)	FDG PET/CT + CI	US, chest X-ray, CeCT	Histology, imaging follow-up	**Recurrence** ***FDG PET/CT as part of surveillance*** Sens: 87.5% Spec: 71.4% PPV: 87.5% NPV: 71.4% Accu: 77.5% ***FDG PET/CT only for symptomatic disease or suspicious lesions*** Sens: 97.6% Spec: 100% PPV: 100% NPV: 88.9% Accu: 98.0%	NA	FDG PET/CT as part of surveillance detected 64.5% of all operable lesions whereas FDG PET/CT as a confirmation test detected only 35.5% of all operable lesions, where distant metastatic disease was prevalent.
Helvind et al, 2023 [34]	Retrospective	1480 patients who underwent surveillance with or without routine FDG PET/CT (stage IIB to IIID melanoma)	FDG PET/CT + clinical examinations (n=715)	Clinical examinations (n=765)	Clinical follow-up	NA	NA	Patients who received routine FDG PET/CT had a greater hazard of distant recurrence within the first two years of surveillance than those who only underwent clinical examinations (HR, 1.15, 95% CI, 1.16 to 1.96). After two years, the hazard of locoregional recurrence was lower for patients followed with routine FDG PET/CT (HR, 0.53, 95% CI, 0.33 to 0.84).
Zijlker et al, 2023 [35]	Retrospective	104 patients who underwent initial staging (newly diagnosed Merkel cell carcinoma)	FDG PET/CT	US with FNAC	Histopathology, clinical and imaging follow-up	**Regional lymph node metastases** Sens: 49.0% Spec: 96.0% **Distant metastases** Sens: 100% Spec: 95.0%	**Regional lymph node metastases** Sens: 40.0% Spec: 100%	For patients presented with palpable lymph nodes, FDG PET/CT upstaged 16.1% (5/31) to stage IV disease.
Non-FDG Tracers ^{68}Ga-DOTA-(TATE, NOC, TOC)								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance**	**Change in Patient Management**

							(Conventional Intervention)	
Lugat et al, 2023 [36]	Prospective	105 patients who underwent diagnosis, initial staging, or follow-up (confirmed or suspected grade 1 or 2 GEP-NET or suspicion of recurrence or progression)	^{68}Ga-DOTA-NOC PET/CT	Multiphasic CT, SPECT/CT, MRI	Histopathology, imaging follow-up, pre- and post-PET questionnaire	**Primary tumour** Sens: 97.9%* Spec: 81.8% PPV: 95.8% NPV: 90.0% Accu: 94.8% **Lymph node metastases** Sens: 97.4%* Spec: 98.9% PPV: 97.4% NPV: 98.5% Accu: 98.1% **Liver metastases** Sens: 97.9% Spec: 100%* PPV: 100% NPV: 98.3% Accu: 99.1% **Peritoneal carcinomatosis** Sens: 95.0%* Spec: 98.8% PPV: 95.0% NPV: 98.9% Accu: 98.1% **Bone metastases** Sens: 100%* Spec: 100% PPV: 100% NPV: 100% Accu: 100% **Other distant metastases** Sens: 100% Spec: 100% PPV: 100% NPV: 100% Accu: 100%	**Primary tumour** Sens: 78.7%* Spec: 63.6% PPV: 90.2% NPV: 41.2% Accu: 75.9% **Lymph node metastases** Sens: 59.0%* Spec: 92.4% PPV: 82.1% NPV: 79.2% Accu: 80.0% **Liver metastases** Sens: 95.8% Spec: 89.5%* PPV: 88.5% NPV: 96.2% Accu: 92.4% **Peritoneal carcinomatosis** Sens: 30.0%* Spec: 97.7% PPV: 75.0% NPV: 85.6% Accu: 84.8% **Bone metastases** Sens: 33.3%* Spec: 99.0% PPV: 75.0% NPV: 94.1% Accu: 93.3% **Other distant metastases** Sens: 71.4% Spec: 94.9% PPV: 50.0% NPV: 97.9% Accu: 93.3%	^{68}Ga-DOTA-NOC PET/CT had a therapeutic impact in 41.9% (44/105) of patients (7—more extensive surgical procedure, 2—less extensive surgical procedure, 5—modification in surveillance, 8—surgery indicated, 11—prevented unnecessary surgery, 11—initiation of systemic therapy).
Serfling et al, 2023 [37]	Retrospective	100 patients who underwent staging or restaging (SCLC)	^{68}Ga-DOTA-TOC PET/CT	CT	Pre- and post-PET information, clinical and imaging follow-up	NA	NA	Treatment was modified after ^{68}Ga-DOTA-TOC PET/CT in 59.0% (59/100) of patients (28—initiation of PRRT, 10—initiation of atezolizumab plus chemotherapy, 3—change in atezolizumab

								plus chemotherapy regimen, 3—initiation of tyrosine kinase inhibitors, 13—switched to local external beam radiation, 2—active surveillance). However, treatment modifications were not associated with prolonged OS (change to systemic treatment, HR, 95% C: 0.53 to 1.67, p=0.83; change to non-systemic treatment, HR, 0.67, 95% CI, 0.34 to 1.34, p=0.22).
^{18}F-FET								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Henssen et al, 2023 [38]	Meta-analysis	5 studies (273 treated patients with glioma)	^{18}F-FET PET/CT or PET/MRI	DSC PWI	Histology, clinical and imaging follow-up	**Distinguishing tumour progression from treatment-related abnormalities** Pooled Sens: 82.0% Pooled Spec: 85.0%	**Distinguishing tumour progression from treatment-related abnormalities** Pooled Sens: 76.0% Pooled Spec: 88.0%	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**
Pang et al, 2023 [39]	Meta-analysis	5 studies (258 patients with suspected prostate cancer)	^{18}F-DCFPyL PET/CT or PET/MRI	Digital rectal examination, transrectal US, MRI, prostate-specific antigen screening	Histopathology	**Diagnosis** Pooled Sens: 92.0% Pooled Spec: 59.0% AUC: 0.92	NA	NA
Wang et al, 2023 [40]	Meta-analysis	8 studies (416 patients with localized prostate cancer)	^{68}Ga-PSMA-11 or ^{18}F-DCFPyL or ^{68}Ga-PSMA-I/T or ^{18}F-PSMA-1007 PET/CT	mpMRI	Histopathology	**Extracapsular extension** Pooled Sens: 61.0% Pooled Spec: 74.0% **Seminal vesical invasion** Pooled Sens: 62.0% Pooled Spec: 90.0%	**Extracapsular extension** Pooled Sens: 67.0% Pooled Spec: 77.0% **Seminal vesical invasion** Pooled Sens: 60.0% Pooled Spec: 92.0%	NA

Chow et al, 2023 [41]	Meta-analysis	31 studies (2431 patients who underwent initial staging of intermediate- to high-risk prostate cancer)	^{68}Ga-PSMA-11 or ^{18}F-DCFPyL or ^{68}Ga-PSMA-I/T or ^{18}F-PSMA-1007 or ^{18}F-rhPSMA-17 PET/CT or PET/MRI	mpMRI, bone scan, CT	Histopathology, clinical or imaging follow-up	**Pelvic lymph node metastases (patient-based)** Pooled Sens: 73.2%* to 73.7%* Pooled Spec: 97.5%* to 97.8%* **(lesion-based)** Pooled Sens: 74.8%* Pooled Spec: 99.2% **Bone metastases (patient-based)** Pooled Sens: 98.0%* Pooled Spec: 96.2%*	**Pelvic lymph node metastases *mpMRI* (patient-based)** Pooled Sens: 38.9%* Pooled Spec: 82.6%* **(lesion-based)** Pooled Sens: 32.2%* Pooled Spec: 98.6% ***CT* (patient-based)** Pooled Sens: 38.5%* Pooled Spec: 83.6%* **Bone metastases *Bone scan* (patient-based)** Pooled Sens: 73.0%* Pooled Spec: 79.1%*	NA
Du et al, 2023 [42]	Retrospective	70 patients who underwent initial staging prior to neoadjuvant therapy followed by radical prostatectomy and pelvic lymph node dissection (high-risk, nonmetastatic prostate cancer)	^{68}Ga-PSMA PET/CT	MRI	Histopathology	**Lymph node metastases** Sens: 90.9% Spec: 69.5% PPV: 35.7% NPV: 97.6% Accu: 72.9%	**Lymph node metastases** Sens: 27.3% Spec: 89.8% PPV: 33.3% NPV: 97.6% Accu: 86.9%	NA
Adiyat et al, 2023 [43]	Retrospective	268 patients with a negative ^{68}Ga-PSMA PET/CT scan for metastasis prior to robotic-assisted radical prostatectomy with limited pelvic lymph node dissection (prostate cancer)	^{68}Ga-PSMA PET/CT	NA	Histopathology	**Lymph node metastases** NPV: 71.6%	NA	NA
Ong et al, 2022 [44]	Prospective	86 patients who underwent primary staging (newly diagnosed intermediate- or	^{68}Ga-PSMA PET/CT	MRI	Consensus from multidisciplinary meeting, clinical or	NA	NA	^{68}Ga-PSMA PET/CT results led to the addition or change of treatment modalities in 20.0% (16/80) of patients

		high-risk prostate cancer)			imaging follow-up			(6—progressed to androgen deprivation therapy, 5—progressed to radiation therapy, 5—progressed to chemotherapy or androgen receptor pathway inhibitor).
Ke et al, 2023 [45]	Prospective	72 patients who underwent response assessment after neoadjuvant chemohormonal therapy (high-risk, non-metastatic prostate cancer)	^{68}Ga-PSMA PET/CT	mpMRI, PSA	Pathology	**Pathologic complete remission or minimal residual disease** ***EAU/EANM*** Sens: 75.0% Spec: 95.8% PPV: 90.0% NPV: 88.5% +LR: 18.0 -LR: 0.26 ***PERCIST 1.0*** Sens: 79.2% Spec: 91.7% PPV: 82.6% NPV: 89.8% +LR: 9.50 -LR: 0.23	**Pathologic complete remission or minimal residual disease** ***mpMRI*** Sens: 58.3% Spec: 83.3% PPV: 63.6% NPV: 80.0% +LR: 3.50 -LR: 0.50 ***PSA*** Sens: 58.3% Spec: 68.8% PPV: 48.3% NPV: 76.7% +LR: 1.87 -LR: 0.61	NA
Nguyen et al, 2022 [46]	Retrospective	57 patients treated with prior therapy (biochemically recurrent prostate cancer)	^{18}F-DCFPyL PET/CT	Pelvic mpMRI	Pathology, clinical and imaging follow-up	**Local recurrence (lesion-based)** Sens: 96.0% Spec: 100% PPV: 100% NPV: 90.0% **Pelvic lymph node metastases (lesion-based)** Sens: 100%* Spec: 100% PPV: 100% NPV: 100%* **Bone metastases (lesion-based)** Sens: 100% Spec: 98.0%* PPV: 95.0%* NPV: 100%	**Local recurrence (lesion-based)** Sens: 96.0% Spec: 94.0% PPV: 98.0% NPV: 89.0% **Pelvic lymph node metastases (lesion-based)** Sens: 52.0%* Spec: 100% PPV: 100% NPV: 55.0%* **Bone metastases (lesion-based)** Sens: 86.0% Spec: 73.0%* PPV: 50.0%* NPV: 94.0%	NA
Rajwa et al, 2023 [47]	Retrospective	113 patients who underwent restaging prior to salvage radical	^{68}Ga-PSMA PET/CT	mpMRI	Histopathology	**Extraprostatic extension** Sens: 90.0% Spec: 70.0%	**Extraprostatic extension** Sens: 40.0% Spec: 94.0%	NA

		prostatectomy (radiorecurrent prostate cancer)				PPV: 64.0% NPV: 92.0% Accu: 77.0% **Lymph node metastases** Sens: 27.0% Spec: 100% PPV: 100% NPV: 84.0% Accu: 85.0%	PPV: 83.0% NPV: 66.0% Accu: 70.0% **Lymph node metastases** Sens: 14.0% Spec: 50.0% PPV: 6.0% NPV: 72.0% Accu: 43.0%	
Wilson et al, 2023 [48]	Retrospective	91 patients who underwent staging or restaging (intermediate-to-high-risk or biochemically recurrent prostate cancer)	^{18}F-DCFPyL PET/CT	^{99m}Tc-MDP bone scintigraphy	Pathology, clinical follow-up	**Bone metastases (lesion-based)** Sens: 100% Spec: 97.0% PPV: 93.0% NPV: 100%	**Bone metastases (lesion-based)** Sens: 89.0% Spec: 91.0% PPV: 80.0% NPV: 95.0%	NA
Pozdnyakov et al, 2023 [49]	Meta-analysis	34 studies (3680 patients with biochemically recurrent prostate cancer)	^{68}Ga-PSMA or ^{18}F-DCFPyL PET/CT or PET/MRI	NA	Pre- and post-PET information	NA	NA	The pooled proportion of change in patient management after ^{68}Ga-PSMA or ^{18}F-DCFPyL PET/CT or PET/MRI was 56.4%.
Arafa et al, 2023 [50]	Retrospective	235 patients who underwent initial staging, evaluation of biochemical recurrence, or restaging of metastatic disease (prostate cancer)	^{18}F-DCFPyL PET/CT	NA	Pre- and post-PET information	NA	NA	^{18}F-DCFPyL PET/CT impacted the management of 33.8% (53/157) of patients.
Petit et al, 2023 [51]	Phase II RCT (PSMAgRT trial)	262 patients randomized 1:1 to ^{18}F-DCFPyL PET/CT or standard-of-care imaging prior to radiotherapy (high-risk, recurrent, or oligometastatic prostate cancer)	^{18}F-DCFPyL PET/CT + CI (n=125)	CT, MRI, bone scan (n=137)	Clinical follow-up	NA	NA	The addition of ^{18}F-DCFPyL PET/CT led to the intensification of radiotherapy in 52.0% (65/125) of patients.
Wong et al, 2023 [52]	Prospective	19 patients who underwent routine surveillance	^{68}Ga-PSMA PET/CT	MRI, CT, serum AFP	Histology, clinical follow-up	**Diagnosis or recurrence (lesion-based)** Sens: 91.0%	**Diagnosis or recurrence *MRI* (lesion-based)**	NA

		(suspected or treated hepatocellular carcinoma)				Spec: 70.0% PPV: 71.0% NPV: 90.0%	Sens: 87.0% Spec: 73.0% PPV: 76.0% NPV: 85.0% ***CT*** **(lesion-based)** Sens: 32.0% Spec: 100% PPV: 100% NPV: 64.0% ***Serum AFP*** **(lesion-based)** Sens: 45.0% Spec: 88.0% PPV: 83.0% NPV: 54.0%	
^{68}Ga-FAPI								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Huang et al, 2023 [53]	Meta-analysis	18 studies (524 patients with digestive system tumours)	^{68}Ga-FAPI PET/CT or PET/MRI	NA	Histopathology, imaging follow-up	**Diagnosis (patient-based)** Pooled Sens: 98.0% **(lesion-based)** **Primary tumour** Pooled Sens: 97.0% **Lymph node and distant metastases** Pooled Sens: 94.0%	NA	NA
Rizzo et al, 2023 [54]	Meta-analysis	8 studies (147 patients with gastric cancer)	^{68}Ga-FAPI PET/CT or PET/MRI	NA	Not specified	**Regional lymph node metastases** Pooled Sens: 74.7% Pooled Spec: 89.0% Pooled +LR: 4.38 Pooled -LR: 0.16 Pooled DOR: 25.68	NA	NA
^{18}F-DOPA								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Rozenblum et al, 2023 [55]	Retrospective	106 patients who received radiotherapy (suspected recurrent high-grade glioma)	^{18}F-FDOPA PET/CT or PET/MRI	MRI	Histopathology, clinical and imaging follow-up	**Differentiating tumour progression from treatment-related changes** ***TBR_{max} of 2.6*** Sens: 75.0%	NA	NA

						Spec: 77.0% Accu: 75.0% AUC: 0.78 ***TBR_{mean} of 1.8*** Sens: 82.0% Spec: 71.0% Accu: 78.0% AUC: 0.79 ***TSR_{max} of 1.4*** Sens: 79.0% Spec: 71.0% Accu: 76.0% AUC: 0.76 ***TSR_{mean} of 1.0*** Sens: 69.0% Spec: 80.0% Accu: 73.0% AUC: 0.74 ***MTV of 4.88 cm^3*** Sens: 59.0% Spec: 80.0% Accu: 66.0% AUC: 0.71 ***TTP of 8.0 min*** Sens: 50.0% Spec: 71.0% Accu: 56.0% AUC: 0.56 ***Slope of -0.05 h^{-1}*** Sens: 68.0% Spec: 63.0% Accu: 67.0% AUC: 0.65		
Amyloid								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Altomare et al, 2023 [56]	RCT (AMYPAD-DPMS trial)	794 patients randomized to receive either early amyloid PET (<1 month), late amyloid PET (6-10 months), or amyloid PET at physician's choice in the diagnostic work-up (subjective	^{18}F-flutemetamol or ^{18}F-florbetaben PET	NA	Clinical follow-up	NA	NA	The proportion of patients with very high diagnostic confidence (>90%) after 3 months was higher for those who received early amyloid PET (40%, 95% CI, 34% to 46%) or amyloid PET at physician's choice (37%, 95% CI, 31% to 43%) than those who received late amyloid PET (11%, 95%

		cognitive decline, mild cognitive impairment, or dementia)						CI, 8% to 16%, p<0.001 for both comparisons). After 3 months, the proportion of patients changing etiological diagnosis after early amyloid PET (44%) was higher than those who received late amyloid PET (11%, p<0.001) or amyloid PET at physician's choice (29%, p=0.002). Change in cognition-specific medications was similar in the 3 groups (15% for early amyloid PET, 14% for late amyloid PET, and 15% for amyloid PET at physician's choice, p=0.97).
Pancreatic Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Power and Larcos, 2023 [57]	Retrospective	51 patients who underwent initial staging (confirmed or suspected pancreatic cancer)	FDG PET/CT	CT, MRI, US, endoscopic retrograde cholangiopancreatography, magnetic retrograde cholangiopancreatography, endoscopic US, core biopsy, fine needle aspiration, diagnostic laparoscopy	Consensus from multidisciplinary team, pre- and post-PET information	NA	NA	FDG PET/CT findings altered management plans in 35.3% (18/51) of patients (3—prompted further investigation and/or biopsy, 5—change to curative therapy, 10—curative to palliative).
Pediatric Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**

Arslantas et al, 2023 [58]	Retrospective	54 patients who underwent pre-treatment staging (newly diagnosed HL)	FDG PET/CT	BMB	Histology, imaging follow-up	**Bone marrow involvement** Sens: 100% Spec: 100% PPV: 100% NPV: 100%	**Bone marrow involvement** Sens: 25.0% Spec: 100% PPV: 100% NPV: 94.0%	NA
Sarcoma								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Guinot et al, 2023 [59]	Retrospective	180 patients who underwent initial staging (Ewing sarcoma)	FDG PET/CT	Bone marrow aspiration and biopsy	Cytology and histology	**Bone marrow involvement** Sens: 92.3% Spec: 99.4% PPV: 92.3% NPV: 99.4%	NA	NA
Thoracic Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Prisadov et al, 2023 [60]	Retrospective	359 patient who underwent preoperative staging (NSCLC)	FDG PET/CT	Thoracic CT, bronchoscopy	Histopathology	**Mediastinal lymph node metastases** Sens: 47.4% Spec: 90.1% Accu: 81.0%	NA	NA
Damirov et al, 2023 [61]	Retrospective	138 patients who underwent staging prior to lung resection and radical lymphadenectomy (confirmed or suspected NSCLC)	FDG PET/CT	NA	Histopathology	**Hilar and mediastinal lymph node metastases** Sens: 59.1% Spec: 69.1% PPV: 47.3% NPV: 78.3% Accu: 65.9% AUC: 0.625	NA	NA
Wang et al, 2023 [62]	Retrospective	52 patients who underwent initial thoracic staging (NSCLC)	FDG PET/CT, FDG PET/MRI	NA	Pathology	**T staging** ***FDG PET/CT*** Accu: 82.7% ***FDG PET/MRI*** Accu: 84.6% **N staging** ***FDG PET/CT*** Accu: 88.5% ***FDG PET/MRI*** Accu: 88.5% **Pleural invasion** ***FDG PET/CT*** Sens: 64.0%	NA	NA

						Spec: 95.0% PPV: 78.0% NPV: 91.0% AUC: 0.79 ***FDG PET/MRI*** Sens: 82.0% Spec: 98.0% PPV: 90.0% NPV: 95.0% AUC: 0.90		
Cooke et al, 2023 [63]	RCT (Phase II ARTFORCEPET -Boost trial)	107 patients randomized 1:1 to receive radiation dose escalation to either whole primary tumour or PET-defined subvolume within the primary tumour (inoperable stage II-III NSCLC)	PET-subvolume (n=53)	Whole tumour (n=54)	Clinical and imaging follow-up	NA	NA	The 1-year FFLF rate was 97.0% for the whole tumour group and 91.0% for the PET-subvolume group. The median OS was 18 months for both groups. Acute and late ≥3 adverse events occurred in 42.6% and 22.2% of patients in the whole tumour group, respectively. In the PET-subvolume group, acute and late ≥3 adverse events occurred in 37.7% and 32.1% of patients, respectively.
Cui et al, 2023 [64]	RCT (Phase II trial)	90 patients randomized 1:1 to receive either CTV-omitted or CTV-delineated IMRT regimen (unresectable stage IIIA or IIIB NSCLC)	CTV-omitted under FDG PET/CT guidance (n=45)	CTV-delineated (n=45)	Clinical and imaging follow-up	NA	NA	The incidence of radiation respiratory events or grade ≥3 esophagitis was significantly lower in the CTV-omitted group (11.1% vs. 28.9%, p=0.035). The median PFS (9.0 months vs. 10.0 months, respectively, p=0.597), OS (31.0 months vs. 26.0 months, respectively, p=0.489), and regional control times (15.0 months vs. 15.0 months, p=0.826) did not differ significantly between the two groups.
Chen et al, 2023 [65]	Meta-analysis	20 studies (1973 patients with NSCLC)	FDG PET/CT	NA	Histopathology	**Recurrence** Pooled Sens: 96.0% Pooled Spec: 93.0% Pooled +LR: 13.2	NA	NA

						Pooled -LR: 0.04 Pooled DOR: 310 AUC: 0.98		
Sterbis et al, 2023 [66]	Retrospective	5017 patients who underwent restaging prior to subsequent radiation therapy (oligoprogressive or recurrent NSCLC)	FDG PET/CT (n=2829)	CT (n=2188)	Clinical follow-up	NA	NA	Patients who received CT rather than FDG PET/CT before subsequent radiation therapy had a lower 3-year OS (HR, 1.417, 95% CI, 1.32 to 1.52, p<0.0001) and 3-year cancer-specific survival (HR, 1.430, 95% CI, 1.32 to 1.55, p<0.0001).
Liu et al, 2023 [67]	Meta-analysis	10 studies (871 patients with 948 pulmonary nodules)	FDG PET/CT	Diffusion-weighted MRI	Histology, imaging follow-up	**Diagnosis (nodule-based)** Pooled Sens: 82.0% Pooled Spec: 81.0% Pooled +LR: 4.22 Pooled -LR: 0.22 Pooled DOR: 15.77 AUC: 0.87	**Diagnosis (nodule-based)** Pooled Sens: 85.0% Pooled Spec: 91.0% Pooled +LR: 9.58 Pooled -LR: 0.17 Pooled DOR: 54.46 AUC: 0.94	NA
Gilbert et al, 2022 [68]	Prospective	312 patients with nodule of ≥8 mm and ≤30 mm (solitary pulmonary nodule)	FDG PET/CT	Dynamic CeCT	Histology, clinical and imaging follow-up	**Malignant diagnosis** Sens: 79.1% Spec: 81.8% PPV: 87.3%% NPV: 71.2% Accu: 80.1% AUC: 0.80*	**Malignant diagnosis** Sens: 95.3% Spec: 29.8% PPV: 68.2% NPV: 80.0% Accu: 69.9% AUC: 0.62*	NA
Various Sites								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Zhang et al, 2023 [69]	Meta-analysis	10 studies (1042 patients with various cancers)	FDG PET/CT, FDG PET/MRI	NA	Pathology, imaging follow-up	**Distant metastases** ***FDG PET/CT*** Pooled Sens: 81.0% Pooled Spec: 97.0% Pooled +LR: 23.1 Pooled -LR: 0.20 AUC: 0.95 ***FDG PET/MRI*** Pooled Sens: 87.0% Pooled Spec: 97.0% Pooled +LR: 25.1 Pooled -LR: 0.13 AUC: 0.98	NA	NA

Darweesh et al, 2023 [70]	Prospective	30 patients who underwent staging, management, and follow-up (malignant tumours suspected to have peritoneal carcinomatosis)	FDG PET/CT	NA	Histopathology, clinical and imaging follow-up	**Peritoneal carcinomatosis** Sens: 76.2% Spec: 88.9% PPV: 94.1% NPV: 61.5% Accu: 80.0% AUC: 0.910	NA	NA
Mirshahvalad et al, 2023 [71]	Meta-analysis	43 studies (1278 patients with various primary tumours)	FDG PET/CT, FDG PET/MRI	NA	Histopathology, imaging follow-up	**Malignant pulmonary lesions** ***FDG PET/CT*** Pooled Sens: 99.0% Pooled Spec: 99.0% Pooled +LR: 112.7 Pooled -LR: 0.01 Pooled DOR: 7913 AUC: 1.00 ***FDG PET/MRI*** Pooled Sens: 96.0% Pooled Spec: 100% Pooled +LR: 384.3 Pooled -LR: 0.04 Pooled DOR: 8821 AUC: 1.00	NA	NA
Boulu et al, 2023 [72]	Retrospective	144 patients with serum C-reactive protein level >15 mg/L on 2 or more occasions at least 3 weeks apart, with or without fever (inflammatory syndrome of undetermined origin)	FDG PET/CT	Tumour markers, CT, fibroscopy, colonoscopy, bone marrow biopsy, echocardiography, temporal artery biopsy, dental X-ray	Clinical follow-up	**Diagnosis** Sens: 68.6% Spec: 73.8% PPV: 86.4% NPV: 50.8%	NA	FDG PET/CT was determined to be useful for making a diagnosis in 38.9% (56/144) of patients. The median time interval between FDG PET/CT and a confirmed diagnosis was 30.5 days.
Bae, 2023 [73]	Retrospective	91 patients with symptoms and fever that persisted for >3 weeks (classical fever of unknown origin)	FDG PET/CT	NA	Clinical follow-up	NA	NA	Patients who underwent FDG PET/CT evaluation when final diagnosis was neoplasm had a shorter length of hospital stay than those who did not receive FDG PET/CT (mean, 11.4 days versus 36.0 days, p=0.02). However, FDG PET/CT lengthened the hospital stay in patients

	diagnosed with infection (mean, 21.1 days versus 11.1 days, p=0.022).

*p<0.05

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

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; Accu, accuracy; AFP, alpha-fetoprotein; AMYPAD-DPMS, Amyloid Imaging to Prevent Alzheimer's Disease Diagnostic and Patient Management Study; AUC, area under the curve; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; BMB, bone marrow biopsy; CA19-9, carbohydrate antigen sialyl Lewis a; CEA, carcinoembryonic antigen; CeCT, contrast-enhanced computed tomography; CeMRI, contrast-enhanced magnetic resonance imaging; CI, confidence interval; CT, computed tomography; CTV, clinical target volume; DFS, disease-free survival; DOR, diagnostic odds ratio; DSC, dynamic susceptibility contrast; DSS, disease-specific survival; EAU/EANM, European Association of Urology and European Association of Nuclear Medicine; EEG, electroencephalography; EUS, endoscopic ultrasound; ^{18}F, fluorine-18; ^{18}F-DCFPyL (2-(3-{1-carboxy-5-[(6-18F-fluoropyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid; ^{8}F-DOPA, 18-fluoro-3,4-dihydroxyphenylalnine; FDG, fluorodeoxyglucose; ^{18}F-FET, O-(2[^{18}F]-fluoroethyl)-L-tyrosine; FFLF, freedom from local failure; FFS, failure-free survival; FIGO, Federation of Gynecology and Obstetrics; FNAC, fine needle aspiration cytology; ^{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-FAPI, Gallium 68–labeled fibroblast activation protein (FAP) inhibitor; ^{68}Ga-PSMA, Gallium-68-labelled prostate-specific membrane antigen; GEP-NET, gastroenteropancreatic neuroendocrine tumours; HL, Hodgkin lymphoma; HR, hazard ratio; ^{131}I, Iodine-131; ILAE, International League Against Epilepsy; IMRT, intensity-modulated radiation therapy; –LR, negative likelihood ratio; +LR, positive likelihood ratio; mpMRI, multiparametric magnetic resonance imaging; MRI, magnetic resonance imaging; MTV, metabolic tumour volume; NA, not applicable; NPV, negative predictive value; NSCLC, non-small-cell lung carcinoma; OS, overall survival; PERCIST, Positron Emission Tomography Response Criteria in Solid Tumors; PET, positron emission tomography; PFS, progression-free survival; PPV, positive predictive value; PSA, prostate-specific antigen; PSMAgRT, PSMA-PET/CT-Guided Intensification of Radiation Therapy; PWI, perfusion weighted magnetic resonance imaging; PSA, prostate-specific antigen; SCLC, small-cell lung carcinoma; SEEG, stereoelectroencephalography; Sens, sensitivity; Spec, specificity; SPECT, single-photon emission CT; TBRmax, maximal tumour-to-background [18F]FET uptake; TBRmean, mean tumour-to-background [18F]FET uptake^{99m}Tc, Technetium 99m; ^{99m}Tc-MDP, Technetium 99m-methyl diphosphonate; TNM, tumour, nodes, and metastases; TSRmax, maximal tumour-to-striatum [18F]FET uptake; TSRmean, mean tumour-to-striatum [18F]FET uptake; TTP, time-to-peak; US, ultrasonography