PET Six-Month Monitoring Report 2022-1

Evidence from Primary Studies and Systematic Reviews and Recommendations from Clinical Practice Guidelines January to June 2022

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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 23rd 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 2022 were systematically searched through MEDLINE and EMBASE for evidence from primary studies and systematic reviews. The search strategies used are available upon request to the PEBC.

Inclusion Criteria for Clinical Practice Guidelines

Any clinical practice guidelines that contained recommendations with respect to PET were included. Study design was not a criterion for inclusion or exclusion.

Pediatric studies were included in this report and will be included in subsequent reports. The decision to include them was made by the Committee based on the formation of a Pediatric PET Subcommittee that will explore and report on indications relating to PET in pediatric cancer.

Inclusion Criteria for Primary Studies

Articles were selected for inclusion in the systematic review of the evidence if they were fully published, English-language reports of studies that met the following criteria:

1. Studied the use of 18-fluorodeoxyglucose (FDG) PET in cancer, sarcoidosis, or epilepsy in humans.
2. Evaluated the use of the following radiopharmaceutical tracers:
    - ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTATOC, ^{68}Ga DOTATATE
    - ^{18}F-choline, ^{11}C-choline
    - ^{18}F-FET ([^{18}F]fluoroethyl-L-tyrosine) (brain)
    - ^{18}F-FLT ([^{18}F]3-deoxy-^{3}F-fluorothymidine) (various)
    - ^{18}F-MISO ([^{18}F]fluoromisonidazole) (hypoxia tracer)
    - ^{18}F-FAZA ([^{18}F]fluoroazomycin arabinoside) (hypoxia tracer)
    - ^{18}F-fluoride (more accurate than bone scanning)
    - ^{18}F-flurpiridaz (cardiac)
    - ^{18}F-florbetapir/^{18}F-flutemetamol (dementia imaging)
    - ^{18}F-FDOPA
    - ^{68}Ga-PSMA/^{18}F-DCFPyL (prostate-specific membrane antigen)
    - ^{18}F-FACBC (fluciclovine)
3. Published as a full-text article in a peer-reviewed journal.
4. Reported evidence related to change in patient clinical management or clinical outcomes or reported diagnostic accuracy of PET compared with an alternative diagnostic modality.
5. Used a suitable reference standard (pathological and clinical follow-up) when appropriate.
6. Included ≥12 patients for a prospective study/randomized controlled trial (RCT) or ≥50 patients (≥25 patients for sarcoma) for a retrospective study with the disease of interest.

Inclusion Criteria for Systematic Reviews

1. Reviewed the use of FDG PET/computed tomography (CT) in cancer, sarcoidosis, or epilepsy.
2. Contained evidence related to diagnostic accuracy; change in patient clinical management, clinical outcomes, or treatment response; survival; quality of life; prognostic indicators; time until recurrence; or safety outcome (e.g., avoidance of unnecessary surgery).

Exclusion Criteria

1. Letters and editorials.

RESULTS

Literature Search Results

Primary Studies and Systematic Reviews

Eighty-nine studies published between January and June 2022 met the inclusion criteria. A summary of the evidence from the 89 studies can be found in **Appendix 1: Summary of studies from January to June 2022**.

Breast Cancer

Four studies met the inclusion criteria [1-4]. In the preoperative staging of patients with breast cancer, FDG PET/CT demonstrated high specificity (94.4%) but low sensitivity (54.0%) for the detection of axillary lymph node metastases [1] and did not show a clear advantage over axillary ultrasound (US) or magnetic resonance imaging (MRI) [2]. In locally advanced cases, dynamic contrast-enhanced MRI was more sensitive than FDG PET/CT in predicting pathological response after two cycles of neoadjuvant chemotherapy (100% versus 94.1%, $p<0.001$) [3]. For treatment response assessment of recurrent or de novo metastatic breast cancer, patients monitored with FDG PET/CT had significantly prolonged overall survival than those monitored with contrast-enhanced CT (hazard ratio [HR], 0.44, 95% confidence interval [CI], 0.29 to 0.68, $p=0.001$). Furthermore, FDG PET/CT-based response monitoring led to fewer treatment lines ($p<0.001$), longer duration of treatment courses ($p=0.01$), shorter time on chemotherapy ($p=0.005$), and earlier detection of first progression leading to treatment change ($p=0.03$) than contrast-enhanced CT-based response monitoring [4].

Epilepsy

Two studies met the inclusion criteria [5,6]. In the presurgical evaluation of patients with drug-resistant focal epilepsy, FDG PET findings contributed to decision making in 47.4% of cases with greater benefits in temporal lobe epilepsy than in extratemporal lobe epilepsy ($p=0.001$). For patients with temporal lobe epilepsy, MRI-negative and MRI-positive cases with concordant FDG PET-scalp video electroencephalography results had comparable one-year seizure-free outcome [5]. Moreover, FDG PET/MRI (89.0%) was more accurate than magnetoencephalography (75.3%) in localizing the epileptogenic zone that led to seizure freedom. However, the accuracy (93.2%) of combined FDG PET/MRI and magnetoencephalography was better than that of each alone [6].

Esophageal Cancer

Two studies met the inclusion criteria [7,8]. In the preoperative staging of patients with esophageal squamous cell carcinoma, FDG PET/CT was slightly more specific (99.4% versus 95.2%, $p=0.0037$) than contrast-enhanced CT in the diagnosis of hilar lymph node metastases. However, both imaging modalities displayed suboptimal sensitivity and positive predictive value (PPV) to be useful in radiotherapy planning [7]. For overall lymph node assessment, FDG PET/MRI (96.2%) was more accurate than FDG PET/CT (92.0%, $p=0.044$), MRI (86.8%, $p<0.001$), and contrast-enhanced CT (86.3%, $p<0.001$) [8].

Gastrointestinal Cancer

Five studies met the inclusion criteria [9-13]. In the management of grade 1 gastroenteropancreatic neuroendocrine tumours (NETs), FDG PET/CT findings modified the treatment plan of 52.7% of patients [9]. Results from a multicentre, prospective study revealed that FDG PET/CT had limited value in the initial staging of patients with locally advanced gastric adenocarcinoma. Treatment intent changed from curative to palliative in only 3.0% of patients based on additional FDG PET/CT findings. Conversely, laparoscopy added considerably to the staging process by changing the intent of treatment to palliative in 15.2% of patients [10]. In

the initial staging of rectal cancer patients with enlarged lateral pelvic nodes, FDG PET/contrast-enhanced CT detected additional extra-pelvic metastases in 11.4% of cases that were not evident on conventional imaging (e.g., contrast-enhanced CT, MRI). Consequently, 15.9% of management was impacted [11]. The diagnostic performance of FDG PET/CT for detecting recurrence was high (pooled sensitivity and specificity, both at 94%) in patients with colorectal cancer [12] and comparable to conventional imaging (e.g., chest radiography, abdominopelvic CT, chest CT) in asymptomatic patients with renal cell carcinoma, but with a lower radiation dose [13].

Genitourinary Cancer

Eight studies met the inclusion criteria [14-21]. In patients with muscle-invasive or high-risk non-muscle-invasive bladder cancer who have undergone initial staging, FDG PET/CT appeared to be more sensitive but less specific than contrast-enhanced CT or CT in the detection of lymph node involvement [14,15]. Overall, the addition of FDG PET/CT changed the staging of 25.9% to 42.9% of patients and enabled a treatment decision modification in 17.9% to 26.2% of cases [15-17]. For the staging of patients with penile cancer, FDG PET/CT detected pelvic and inguinal lymph node metastases with a sensitivity of 83.0% to 87.0% and a specificity of 60.0% to 88.0% [18,19]. Furthermore, FDG PET/CT had a high PPV (93.0%) for the detection of distant metastases [18]. Results from a meta-analysis showed that the diagnostic performance of FDG PET/CT (area under the ROC curve [AUC], 0.94) for the diagnosis or restaging of patients with renal cell carcinoma was comparable to that of MRI (AUC, 0.93) [20]. In patients with seminoma who underwent staging after orchiectomy, restaging after therapy, or follow-up, FDG PET/CT was superior to CT in the evaluation of active disease (accuracy, 89.0% versus 63.4%, p=0.016). Findings provided by FDG PET/CT led to a change in management in 26.8% of cases [21].

Gynecologic Cancer

Eight studies met the inclusion criteria [22-29]. In patients with precancerous endometrial lesions, FDG PET/CT diagnosed the presence of cancer with moderate sensitivity (78.3%) and specificity (79.1%) [22]. For the preoperative staging of endometrial cancer, FDG PET/CT was able to detect lymph node metastases with a sensitivity of 73.5% to 90.0% [23,24], while maintaining a low false positive rate (5.2% to 5.3%) [24]. In patients with high risk of residual disease after endometrial cancer surgery, FDG PET/CT altered the adjuvant treatment strategy in 31.0% of cases [25]. On the other hand, FDG PET/CT demonstrated subpar sensitivity (25.0% to 65.0%) [24,26,27] but high specificity [84.0% to 93.0%) [26,27] in the nodal staging of patients with cervical cancer. Nonetheless, FDG PET/CT may be a better choice over MRI with or without diffusion-weighted imaging when evaluating metastatic lymph nodes [24,26]. In the initial staging or follow-up of patients with ovarian cancer, FDG PET/CT was found to be highly sensitive (93.0%), even with low levels of CA-125 [28]. In suspected recurrent vulvar cancer, FDG PET/CT proved to be a reliable tool for assessing disease recurrence (accuracy, 98.0%) with a substantial impact on treatment decision-making (44.4% of patients) [29].

Head and Neck Cancer

Ten studies met the inclusion criteria [30-39]. Three of the studies investigated the impact of FDG PET/CT on improving the staging and management of patients with head and neck cancer. FDG PET/CT was found to be more accurate than both contrast-enhanced CT/CT and MRI for evaluating the primary tumour [30,31]. However, FDG PET/CT was comparable to MRI for detecting mandibular invasion [32]. Overall, FDG PET/CT changed the stage of the disease in 36.4% to 46.7% of patients and influenced treatment decisions by 36.4% to 43.3% [30,31]. For the pre-treatment staging of patients with nasopharyngeal carcinoma, FDG PET/CT

was more advantage than MRI in the diagnosis of cervical lymph node metastases [33,34]. Patients staged by FDG PET/CT and MRI had significantly better five-year overall survival (95.7% versus 90.4%, p<0.001), five-year failure-free survival (85.7% versus 71.7%, p<0.001), five-year distant metastasis-free survival (93.9% versus 87.9%, p<0.001), and five-year locoregional relapse-free survival (93.0% versus 81.4%, p<0.001) than those staged by MRI alone [34]. In human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma, FDG PET/CT and contrast-enhanced CT were comparably accurate in N2 staging, but neither was able to reliably detect extranodal extension [35]. Furthermore, FDG PET/CT was superior to triple endoscopy in ruling out synchronous primary tumours [36]. In the preoperative evaluation of patients with oral squamous cell carcinoma, contrast-enhanced CT (84.0%) had the highest accuracy for the detection of bone invasion, followed by contrast-enhanced MRI (82.0%), then FDG PET/CT and panoramic radiography (both at 76.0%), and technetium-99m bone scintigraphy (72.0%) [37]. Findings from the randomized EfFECTs trial showed that FDG PET/CT-driven management of indeterminate thyroid nodules prevented futile surgery by 39.7%, without compromising on safety (p=0.17) or quality of life (p=0.11). Additionally, the proportion of management considered unbeneficial was significantly lower in the FDG PET/CT-driven group than in the diagnostic surgery group (41.8% versus 82.9%, p<0.001) [38]. In a prospective study of 20 patients with negative iodine-131 whole body scan but elevated serum thyroglobulin level after thyroidectomy, FDG PET/CT provided a better assessment of recurrent and/or metastatic differentiated thyroid cancer than CT alone [39].

Hematologic Cancer

Six studies met the inclusion criteria [40-45]. Pooled estimates (sensitivity, 87%; specificity, 85%) from one meta-analysis showed that FDG PET/CT is a reliable imaging modality in the diagnostic evaluation of patients with suspected primary central nervous system lymphoma [40]. In another meta-analysis that included patients with multiple myeloma, the pooled specificity (82% versus 57%, p<0.001) of FDG PET/CT was significantly higher than that of whole-body MRI in assessing treatment response. On the contrary, the pooled sensitivity (87% versus 64%, p=0.18) was higher for whole-body MRI but the difference was not significant [41]. For the staging of patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), FDG PET/CT detected bone marrow involvement with high sensitivity (HL, 100%; NHL, 83.3%) but low specificity (HL, 61.3%; NHL, 67.7%) [42]. In patients with lymphoblastic lymphoma who underwent treatment evaluation after allogeneic stem cell transplantation, FDG PET/CT (93.7%) was more accurate than CT (79.4%) in identifying residual disease. Moreover, a positive FDG PET/CT scan was significantly associated with a lower progression-free survival (PFS) (HR, 3.957; 95% CI, 1.839 to 8.514, p<0.001) [43]. In the response assessment of limited-stage diffuse large B-cell lymphoma after four cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), two additional cycles of CHOP may be omitted for interim-PET-negative patients without compromising efficacy [44]. In the extended follow-up of the randomized, non-inferiority, phase 3 AHL2011 trial that enrolled patients with advanced HL, interim FDG PET/CT after two cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses safely guided the switch to four cycles of doxorubicin, vinblastine, vincristine, and dacarbazine in early responders without significant loss in five-year overall survival (HR, 1.01; 95% CI, 0.50 to 2.10, p=0.53) and five-year PFS (HR, 1.07; 95% CI, 0.74 to 1.57, p=0.67) [45].

Melanoma

Three studies met the inclusion criteria [46-48]. The utility of routine FDG PET/CT in the surveillance of asymptomatic patients with stage IIB to III cutaneous melanoma was investigated in two retrospective studies. Despite FDG PET/CT having an impact on

management in 14.5% of patients, false-positive findings prompted unnecessary additional investigations in 12.3% of cases [46]. In the other study, FDG PET/CT also yielded a high false-positive rate (PPV, 32.0%), which led to further diagnostic work-up with few remarkable findings [47]. Similarly, a high number of false-positive results (PPV, 39.0%) were observed in the FDG PET/CT follow-up of patients with high-risk malignant melanoma treated with adjuvant immunotherapy [48].

Non-FDG Tracers

Twenty-four studies met the inclusion criteria [49-72]. In patients with suspected pheochromocytoma and paraganglioma, ^{68}Ga-DOTA-TATE PET/CT had higher lesion-based sensitivity than ^{131}I-MIBG scintigraphy for both primary tumour (94.0% versus 75.0%, p=0.005) and metastatic disease (82.0% versus 52.0%, p<0.0001). ^{68}Ga-DOTA-TATE PET/CT was also more sensitive than contrast-enhanced CT when detecting metastatic disease (82.0% versus 48.0%, p<0.0001) [49]. Authors from another study concluded that the supplementation of ^{68}Ga-DOTA-TOC PET to MRI at three-month postoperative follow-up improved the detection of residual meningioma [50]. The capability of ^{18}F-FCH PET/CT to identify malignancy in thyroid nodules with indeterminate cytology was investigated in one prospective study. While ^{18}F-FCH PET/CT offered high negative predictive value (NPV) (94.0% to 96.0%) for ruling out malignancy, it has very poor PPV (28.0% to 29.0%). Nevertheless, ^{18}F-FCH PET/CT would have hypothetically reduced the number of unnecessary surgeries by 39.3% [51]. In patients with clinically suspected prostate cancer, the combined application of ^{68}Ga-PSMA PET/CT with biparametric MRI [52] or multiparametric MRI [53] improved the sensitivity of diagnosing prostate lesions than either MRI alone. In the primary staging of patients with intermediate- to high-risk prostate cancer, ^{68}Ga-PSMA PET/CT or PET/MRI detected lymph node metastases with low to moderate sensitivity (29.0% to 75.0%) but high specificity (84.0% to 100%) across multiple studies [54-61]. A recent meta-analysis that examined the diagnostic accuracy of PET/CT with any PSMA tracer for primary nodal staging also produced similar results (pooled sensitivity, 58.0%; pooled specificity, 95.0%) [62]. For the detection of extraprostatic extension (AUC, 0.79 versus 0.59, p=0.002) and seminal vesicle invasion (AUC, 0.84 versus 0.63, p=0.001) multiparametric MRI performed better than ^{68}Ga-PSMA PET/CT [63]. Overall, information provided by ^{68}Ga-PSMA PET/CT changed the treatment strategy of 10.0% to 43.1% of patients [64,65]. In the setting of biochemically recurrent disease, one prospective multicentre study confirmed the high PPV of ^{68}Ga-PSMA PET/CT or PET/MRI in identifying recurrence in the prostate/prostate bed (83.0%), pelvic lymph nodes (72.0%), and soft-tissue (88.0%) and bone (83.0%) lesions [66], while another multicentre study (IAEA-PSMA trial) demonstrated substantial influence of ^{68}Ga-PSMA PET/CT on disease management (56.8% of cases) [67]. Equally impactful, ^{18}F-DCFPyL PET/CT changed the planned management of 58.0% to 63.9% of patients with biochemical failure [68,69]. In patients with suspected glioma, ^{18}F-FACBC PET/CT was shown to have a high PPV (88.0%) for diagnosing tumour area not visualized by contrast-enhanced MRI, and thus modifying the extent of planned tumour resection in 47.2% of cases [70]. On the other hand, ^{18}F-FET PET/MRI demonstrated a high NPV (89.0%) for ruling out malignancy in untreated patients, which contributed to 32.8% of overall change in management. ^{18}F-FET PET/MRI was even more beneficial in differentiating between tumour progression and treatment-related changes (accuracy, 93.0%) by altering the clinical management of 52.7% of patients [71]. In terms of grade III or IV glioma alone, ^{18}F-FET PET/CT with a tumour-to-white matter ratio cut-off of 2.5 can be a viable imaging protocol for differentiating late recurrence from post-treatment changes (sensitivity, 89.7%; specificity, 81.8%) [72].

Pancreatic Cancer

One study met the inclusion criteria [73]. FDG PET/CT (accuracy, 94.0%) outperformed serum CA19-9 (accuracy, 74.9%), contrast-enhanced CT (accuracy, 81.2%), and contrast-enhanced MRI (accuracy, 81.7%) in the diagnosis of pancreatic lesions.

Pediatric Cancer

Three studies met the inclusion criteria [74-76]. In the staging of patients with neuroblastoma and rhabdomyosarcoma, FDG PET/CT detected bone marrow involvement with a sensitivity of 97.0% to 100% and a specificity of 83.9% to 86.1% [74,75]. In childhood central nervous system tumours, the addition of ^{18}F-FET PET to MRI significantly increased the accuracy of discriminating tumour from non-tumour lesions in both treated (91% versus 81%, p=0.044) and untreated (96% versus 90%, p=0.0001) patients. Information provided by ^{18}F-FET PET altered the treatment plan of 7.9% of scans [76].

Sarcoma

Three studies met the inclusion criteria [77-79]. In patients with clinically suspected or detected uterine mass, FDG PET or PET/CT showed good sensitivity (pooled estimate, 88%) and specificity (pooled estimate, 83%) for differentiating between uterine leiomyomas and uterine sarcomas [77]. FDG PET/CT was also shown to be useful in the staging of Kaposi sarcoma with an accuracy that ranged from 83% on a per patient basis to 92% on a per lesion basis [78]. In the staging and surveillance of bone and soft tissue sarcoma, 14.8% of patients had significant FDG PET/CT findings that altered the clinical course [79].

Thoracic Cancer

Eight studies met the inclusion criteria [80-87]. In the diagnosis of patients with suspected lung cancer, the addition of FDG PET/CT-guided transthoracic biopsy increased the sensitivity of predicting malignancy from 74.5% to 96.0% [80]. In non-small cell lung cancer (NSCLC), FDG PET/CT had better sensitivity (90.5% versus 75.0%, p=0.04) and specificity (60.5% versus 43.6%, p=0.01) for mediastinal nodal staging when compared with contrast-enhanced CT, but no significant differences when compared with endobronchial US/transbronchial needle aspirate. Although FDG PET/CT changed the staging and management of 17.5% of patients, 29.8% would have been incorrectly staged at the same time [81]. FDG PET/CT was less beneficial in the staging of patients with T1 part-solid lung adenocarcinoma, where it initiated further investigations in 3.4% cases but did not change any of the final management plans [82]. Conversely, surveillance FDG PET/CT showed excellent sensitivity (98.9%) and specificity (98.1%) for detecting clinically unsuspected recurrence after curative therapy [83]. For the initial staging of patients with small-cell lung cancer, both FDG PET/MRI and whole-body MRI outperformed FDG PET/CT in T staging (p=0.004 for both comparisons) and overall TNM staging (p=0.004 and p=0.001, respectively). In N and M staging, FDG PET/CT and PET/MR were both significantly more accurate than conventional imaging (e.g., MRI, CT, bone scintigraphy) [84]. In the staging of patients with thymic epithelial tumours, FDG PET/MRI (84.4%) but not FDG PET/CT (78.1%) was found to be superior to conventional examination (e.g., MRI or CT with contrast enhancement, bone scintigraphy) (71.9%, p=0.008 versus FDG PET/MRI) [85]. As for restaging, FDG PET/CT displayed outstanding sensitivity (100%) and moderate specificity (76.7%) in detecting recurrence [86]. Lastly, findings from the SPUtNIk trial indicated that FDG PET/CT is more accurate than dynamic contrast-enhanced CT in the characterization of solitary pulmonary nodules (AUC, 0.77 versus 0.62, p<0.001) [87].

CLINICAL EXPERT REVIEW

Breast Cancer

Current Eligibility Criteria for the PET ABC Trial

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

Reviewer's Comments

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

Epilepsy

Current Indications for Epilepsy

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

Reviewer's Comments (Dr. Jorge Burneo)

The current 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 carcinoembryonic antigen level(s) during follow-up after surgical resection but standard imaging tests are negative or equivocal.

Current Indication for Anal Canal Cancer

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

Reviewer's Comments

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. The meta-analysis by Lee et al. [19] supports the use of FDG PET/CT in the staging of penile cancer and may be worthwhile to consider developing a guideline for this disease site.

Gynecologic Cancer

Current Indications for Cervical Cancer

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

Reviewer's Comments

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

Head and Neck Cancer

Current Indications for Head and Neck Cancer

- For the baseline staging of node-positive (N1-N3) head and neck cancer where PET will impact radiation therapy (e.g., radiation volume or dose).
- To assess patients with N1-N3 metastatic squamous cell carcinoma of the head and neck after chemoradiation (HPV negative); or who have residual neck nodes equal to or greater than 1.5 cm on re-staging CT performed 10 to 12 weeks post therapy (HPV positive).

Current Indication for Unknown Primary

- For the evaluation of metastatic squamous cell carcinoma in neck nodes when the primary disease site is unknown after standard radiologic and clinical investigation.
  Note: a panendoscopy is not required prior to the PET scan.

Current Indication for Nasopharyngeal Cancer

- For the staging of nasopharyngeal cancer.

Current Indications for Thyroid Cancer

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

Reviewer's Comments (Dr. Amit Singnurkar)

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

Hematologic Cancer

Current Indications for Lymphoma

- For the baseline staging of patients with HL or NHL.
- For the assessment of response in HL following two or three cycles of chemotherapy when curative therapy is being considered.
- For the evaluation of residual mass(es) or lesion(s) (e.g., bone) following chemotherapy in a patient with HL or NHL when further potentially curative therapy (such as radiation or stem cell transplantation) is being considered.
- To assess response to chimeric antigen receptor T-cell therapy, 90 days post transfusion.

Current Indications for Multiple Myeloma or Plasmacytoma

- For patients with presumed solitary plasmacytoma who are candidates for curative-intent radiotherapy (to determine whether solitary or multifocal/extensive disease).
- For work-up of patients with smoldering myeloma and negative or equivocal skeletal survey (to determine whether smoldering or active myeloma).
- For baseline staging and response assessment of patients with nonsecretory myeloma, oligosecretory myeloma, or POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes).
- For work-up of patients with newly diagnosed secretory multiple myeloma and negative or equivocal skeletal survey.

Reviewer's Comments

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

Melanoma

Current Indications for Melanoma

- For the staging of patients with localized "high-risk" melanoma, or for the evaluation of patients with isolated melanoma metastases, when surgery or other ablative therapies are being considered.
- For the staging of patients before starting immunotherapy.
- For early response assessment of patients with metastatic melanoma currently receiving immunotherapy after two to four cycles.
- For response assessment of patients with metastatic melanoma at end of immunotherapy.

Reviewer's Comments

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

Non-FDG Tracers

Current Indications for Gallium-68 PET/CT in NETs

- For identification of primary tumour when there is clinical suspicion of NETs and primary tumour site is unknown or uncertain. Patients should have elevated biochemical markers (e.g., 5-HIAA ± elevated chromogranin A) and no definitive evidence of disease on CT.
- For the staging of patients upon initial diagnosis of NETs.
- For the re-staging of patients with NETs when clinical intervention is being considered.
- As a problem-solving tool in patients with NETs when confirmation of site of disease and/or disease extent may impact clinical management.

Current Indications for PSMA PET/CT in Prostate Cancer

- For patients with post-prostatectomy node-positive disease or persistently detectable 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. The emerging tracer ^{68}Ga-FAPI will be valuable to look at in future reports.

Pancreatic Cancer

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

Reviewer's Comments

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

Pediatric Cancer

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

- For the following cancer types (International Classification for Childhood Cancer):
    - Bone/cartilage – osteosarcoma, Ewing sarcoma
    - Connective/other soft tissue – rhabdomyosarcoma, other
    - Kidney – renal tumour
    - Liver – hepatic tumour
    - Lymphoma/post-transplant lymphoproliferative disorder – HL and NHL
    - Primary brain – astrocytoma, medulloblastoma, ependymoma, other
    - Reproductive – germ cell tumour
    - Sympathetic nervous system - neuroblastoma MIBG-negative
    - Other – Langerhans cell histiocytosis, melanoma of the skin, thyroid
- For the following indications:
    - Initial staging

    - Monitoring response during treatment/determine response-based therapy
    - Rule out progression prior to further therapy
    - Suspected recurrence/relapse
    - Rule out persistent disease
    - Select optimal biopsy site
- For the assessment of response in HL or NHL after a minimum of two cycles of chemotherapy when curative therapy is being considered.

Reviewer's Comments (Dr. Amer Shammas)

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

Sarcoma

Current Indications for Sarcoma

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

Reviewer's Comments (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 2022.

Breast Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Kong and Choi, 2021 [1]	Retrospective	221 patients who underwent preoperative staging (early invasive breast cancer)	FDG PET/CT	NA	Histopathology	**Axillary lymph node metastases** Sens: 54.0% Spec: 94.4% PPV: 79.0% NPV: 84.0% Accu: 83.0%	NA	NA
Aktas et al, 2022 [2]	Retrospective	336 patients who underwent nodal staging with or without neoadjuvant chemotherapy (breast cancer)	FDG PET/CT	AUS, MRI	Histopathology or cytopathology	**Axillary lymph node metastases** Sens: 78.0% Spec: 53.0% PPV: 56.2% NPV: 51.4% Accu: 72.5%	**Axillary lymph node metastases** ***AUS*** Sens: 83.0% Spec: 62.0% PPV: 59.2% NPV: 54.8% Accu: 79.1% ***MRI*** Sens: 86.1% Spec: 75.0% PPV: 68.5% NPV: 51.6% Accu: 85.3%	NA
Sobhi et al, 2022 [3]	Prospective	25 patients who underwent response assessment after two cycles of neoadjuvant chemotherapy (locally advanced breast cancer)	FDG PET/CT	DCE-MRI	Pathology	**Predicting pathological response** Sens: 94.1%* Spec: 25.0% PPV: 72.7% NPV: 66.7%	**Predicting pathological response** Sens: 100%* Spec: 12.5% PPV: 70.8% NPV: 100%	NA
Naghavi-Behzad et al, 2022 [4]	Retrospective	227 patients who underwent treatment response assessment (recurrent or de novo metastatic breast cancer)	FDG PET/CT	CeCT	Clinical follow-up	NA	NA	Patients monitored with FDG PET/CT had significantly longer OS than those monitored with CeCT (HR=0.44, 95% CI: 0.29 to 0.68, p=0.001). Additionally, FDG PET/CT-based response monitoring led to fewer treatment lines (p<0.001), longer duration of treatment

								courses (p=0.01), and shorter time on chemotherapy (p=0.005) than CeCT-based response monitoring. FDG PET/CT detected first progression 4.7 months earlier than CeCT, leading to treatment change (p=0.03).
Epilepsy								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Steinbrenner et al, 2022 [5]	Retrospective	951 patients who underwent presurgical evaluation (drug-resistant focal epilepsy)	FDG PET	MRI, scalp video EEG	Consensus from multidisciplinary meetings, seizure outcome 1 year after surgery (ILAE classification)	NA	NA	FDG PET findings contributed to decision-making in 47.4% (396/836) of patients (78—recommended resection, 187—helped to plan electrode placement in intracranial EEG, 131—excluded from surgery). FDG PET was most beneficial in patients with temporal lobe epilepsy compared to those with extratemporal epilepsy (58% vs. 44%, respectively, p=0.001). Among temporal lobe epilepsy cases, seizure-freedom 1 year after surgery did not differ significantly between patients with negative MRI and scalp video EEG-PET concordance and those with positive MRI and scalp video EEG-PET concordance (65% vs. 68%, respectively, p=0.48).
Guo et al, 2022 [6]	Retrospective	73 patients with negative or focal lesion on MRI who underwent	FDG PET/MRI	Physical examination, symptomatology, scalp EEG,	Engel I surgical outcome	**Lobar localization** ***FDG PET/MRI*** Sens: 90.6% Spec: 77.8%	**Lobar localization** ***MEG*** Sens: 76.5% Spec: 66.7%	NA

		presurgical evaluation (refractory temporal lope epilepsy)		video EEG, MRI, MEG		Accu: 89.0% ***FDG PET/MRI +*** ***MEG*** Sens: 100% Spec: 44.4% Accu: 93.2%	Accu: 75.3%	
Esophageal Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Chu et al, 2022 [7]	Retrospective	174 patients who underwent staging prior to radical lymphadenectomy and esophagectomy (esophageal squamous cell carcinoma)	FDG PET/CT	CeCT	Pathology	**Hilar lymph node metastases** Sens: 0% Spec: 99.4%* PPV: 0% NPV: 95.4% Accu: 94.8%	**Hilar lymph node metastases** Sens: 12.5% Spec: 95.2%* PPV: 11.1% NPV: 95.8% Accu: 91.4%	NA
Wang et al, 2022 [8]	Prospective	35 untreated patients who underwent preoperative assessment (resectable esophageal squamous cell carcinoma)	FDG PET/CT, FDG PET/MRI	MRI, CeCT	Pathology	**Primary tumour staging** ***PET/MRI*** Accu: 85.7% **Lymph node metastases (station-based)** ***PET/CT*** Sens: 52.2%‡* Spec: 96.8%* PPV: 66.7% NPV: 94.3% Accu: 92.0%‡ AUC: 0.745‡* ***PET/MRI*** Sens: 78.3%‡* Spec: 98.4%* PPV: 85.7%* NPV: 97.4%* Accu: 96.2%‡* AUC: 0.883‡*	**Primary tumour staging** ***MRI*** Accu: 77.1% ***CeCT*** Accu: 51.4% **Lymph node metastases (station-based)** ***MRI*** Sens: 47.8%* Spec: 91.5%* PPV: 40.7%* NPV: 93.5% Accu: 86.8%* AUC: 0.697 ***CeCT*** Sens: 21.7%* Spec: 94.2%* PPV: 31.3%* NPV: 90.8%* Accu: 86.3%* AUC: 0.580*	NA
Gastrointestinal Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**

Magi et al, 2022 [9]	Retrospective	55 patients who underwent assessment of disease aggressiveness at the time of initial diagnosis or evaluation due to evidence of disease progression (G1 GEP NETs)	FDG PET/CT	NA	Clinical follow-up, consensus from multidisciplinary teams	NA	NA	FDG PET/CT modified the therapeutic management of 52.7% (29/55) of patients.
Gertsen et al, 2021 [10]	Prospective	394 patients who underwent initial staging (locally advanced, clinically curable gastric adenocarcinoma)	FDG PET/CT	Laparoscopy	Biopsy, clinical and imaging follow-up, multidisciplinary consensus	**Distant metastases** Sens: 33% Spec: 97% PPV: 63% **Peritoneal metastases** Sens: 7% Spec: 100% PPV: 100%	**Peritoneal metastases** Sens: 82% Spec: 78% PPV: 43%	FDG PET/CT findings resulted in a change from curative to palliative treatment intent in 3.0% (12/394) of patients. Laparoscopy findings changed the intent of treatment to palliative in 15.2% (60/394) of patients.
Agrawal et al, 2022 [11]	Prospective	44 patients with enlarged lateral pelvic nodes who underwent staging (treatment naïve rectal cancer)	FDG PET/CeCT	CeCT, MRI	Pathology, clinical or imaging follow-up	NA	NA	FDG PET/CeCT upstaged 11.4% (5/44) of patients by detecting additional extra-pelvic metastases and treatment plan was changed in 15.9% (7/44) of cases.
Liu et al, 2022 [12]	Meta-analysis	29 studies (2011 patients with recurrent colorectal cancer)	FDG PET/CT	NA	Histology, biopsy	**Recurrence** Pooled Sens: 94% Pooled Spec: 94% Pooled +LR: 15.93 Pooled -LR: 0.06 Pooled DOR: 156.72 AUC: 0.97	NA	NA
Park et al, 2022 [13]	Retrospective	343 who underwent surgery and postoperative surveillance (renal cell carcinoma)	FDG PET/CT	Chest radiography, abdominopelvic CT, chest CT	Pathology, clinical follow-up	**Recurrence (patient-based)** Sens: 92.3% Spec: 97.0% PPV: 80.0% NPV: 99.0% Accu: 96.5% **(lesion-based)** Sens: 94.2% Spec: 81.8% PPV: 97.0% NPV: 69.2% Accu: 92.5%	**Recurrence (patient-based)** Sens: 89.7% Spec: 97.7% PPV: 83.3% NPV: 98.7% Accu: 96.8% **(lesion-based)** Sens: 79.7% Spec: 54.6% PPV: 88.7% NPV: 30.0% Accu: 76.3%	NA

Genitourinary Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Moussa et al, 2021 [14]	Retrospective	300 patients who underwent lymph node staging prior to radical cystectomy (bladder cancer)	FDG PET/CT	CeCT	Histopathology	**Pelvic lymph node metastases** Sens: 40.3%* Spec: 79.5%* PPV: 61.4% NPV: 62.3% Accu: 62.0% +LR: 1.97 -LR: 0.75 DOR: 2.62	**Pelvic lymph node metastases** Sens: 13.4%* Spec: 86.7%* PPV: 45.0% NPV: 55.4% Accu: 54.0% +LR: 1.01 -LR: 0.99 DOR: 1.02	NA
Bertolaso et al, 2022 [15]	Retrospective	130 patients who underwent staging prior to cystectomy and lymph node dissection (muscle invasive bladder cancer)	FDG PET/CT	CT	Pathology	**Lymph node involvement (before neoadjuvant chemotherapy)** Sens: 80.8% Spec: 54.2% FPR: 56.3% FNR: 13.5% **(after neoadjuvant chemotherapy)** Sens: 60.0% Spec: 89.7% FPR: 33.3% FNR: 13.3%	**Lymph node involvement (before neoadjuvant chemotherapy)** Sens: 26.9% Spec: 83.1% FPR: 58.8% FNR: 27.9% **(after neoadjuvant chemotherapy)** Sens: 10.0% Spec: 100% FPR: 0% FNR: 23.7%	FDG PET/CT findings enabled a treatment decision modification in 26.2% (34/130) of patients (12—therapeutic intensification, 22—therapeutic de-escalation).
Coskun et al, 2022 [16]	Retrospective	70 patients who underwent preoperative staging (bladder cancer)	FDG PET/CT	MRI or CT	Pathology	NA	NA	The addition of FDG PET/CT upstaged 30.0% (21/70) of patients to stage IV and downstaged 12.9% (9/70) of patients from stage IV.
Voskuilen et al, 2022 [17]	Retrospective	711 patients who underwent staging (invasive urothelial bladder cancer)	FDG PET/CT	CeCT	Consensus from multidisciplinary discussions	NA	NA	FDG PET/CT findings changed the clinical stage of 25.9% (184/711) of patients (181 upstaged, 3 downstaged). Consequently, the recommended treatment strategy changed in 17.9% (127/711) of patients (50—upfront local therapy to neoadjuvant or induction

								chemotherapy before local treatment, 65—curative to palliative, 2—palliative to curative, 10—treatment change due to second primary malignancy).
Ottenhof et al, 2022 [18]	Retrospective	61 patients who underwent initial staging (high-risk penile cancer)	FDG PET/CT	NA	Histopathology, cytology, clinical and imaging follow-up	**Pelvic lymph node metastases (patient-based)** Sens: 83% Spec: 60% PPV: 73% NPV: 75% Accu: 74% **(pelvic side-based)** Sens: 85% Spec: 75% PPV: 65% NPV: 90% Accu: 79% **Distant metastases** PPV: 93%	NA	NA
Lee et al, 2022 [19]	Meta-analysis	12 studies (479 patients with penile cancer who underwent staging)	FDG PET/CT	NA	Histopathology	**Pelvic and inguinal lymph node metastases** Pooled Sens: 87% Pooled Spec: 88% Pooled +LR: 7.2 Pooled -LR: 0.15 Pooled DOR: 47 AUC: 0.93	NA	NA
Yin et al, 2022 [20]	Meta-analysis	44 studies (2545 patients with suspected or known primary, recurrent or metastatic renal cell carcinoma)	FDG PET or PET/CT	MRI	Histopathology, clinical follow-up	**Diagnosis or restaging** ***PET*** Pooled Sens: 83% Pooled Spec: 86% AUC: 0.88 ***PET/CT*** Pooled Sens: 89% Pooled Spec: 88% AUC: 0.94	**Diagnosis or restaging** Pooled Sens: 80% Pooled Spec: 90% AUC: 0.93	NA
Petrovic et al, 2022 [21]	Retrospective	82 patients who underwent staging after orchiectomy, restaging after therapy, follow-up or for suspected	FDG PET/CT	CT, serum tumour marker	Histopathology, clinical follow-up	**Active disease** Sens: 92.3%* Spec: 86.0%* PPV: 85.7% NPV: 92.5% Accu: 89.0%*	**Active disease** ***CT*** Sens: 60.8%* Spec: 66.6%* PPV: 70.0% NPV: 57.1% Accu: 63.4%*	FDG PET/CT led to a change in management in 26.8% (22/82) of patients.

		recurrence (seminoma)						
Gynecologic Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Ruel-Laliberte et al, 2021 [22]	Retrospective	66 patients who underwent preoperative imaging (precancerous endometrial lesions)	FDG PET/CT	NA	Pathology	**Diagnosis** Sens: 78.3% Spec: 79.1% PPV: 66.7% NPV: 87.2%	NA	NA
Topuz et al, 2022 [23]	Retrospective	66 patients who underwent preoperative staging (endometrial cancer)	FDG PET/CT	NA	Pathology	**Lymph node metastases** Sens: 90.0% Spec: 96.4% PPV: 81.8% NPV: 98.2% Accu: 95.5%	NA	NA
Rockall et al, 2021 [24]	Prospective	118 patients who underwent preoperative staging (40 cervical and 78 endometrial cancer)	FDG PET/CT	DW-MRI	Histopathology	**Lymph node metastases** **Cervical cancer (patient-based)** Sens: 30.0% PPV: 100% NPV: 81.1% FPR: 0% **(region-based)** Sens: 25.0% PPV: 100% NPV: 88.5% FPR: 0% **Endometrial cancer (patient-based)** Sens: 80.0% PPV: 84.2% NPV: 93.2% FPR: 5.2% **(region-based)** Sens: 73.5% PPV: 75.8% NPV: 94.1% FPR: 5.3%	**Lymph node metastases** **Cervical cancer (patient-based)** Sens: 20.0% PPV: 66.7% NPV: 78.4% FPR: 3.3% **(region-based)** Sens: 16.7% PPV: 50.0% NPV: 87.0% FPR: 2.9% **Endometrial cancer (patient-based)** Sens: 70.0% PPV: 87.5% NPV: 90.3% FPR: 3.4% **(region-based)** Sens: 61.8% PPV: 80.8% NPV: 91.9% FPR: 3.3%	NA
Ferioli et al, 2022 [25]	Retrospective	58 patients who underwent postoperative	FDG PET/CT	NA	Pathology, consensus from	NA	NA	FDG PET/CT results modified the therapeutic strategy of 31.0% (18/58)

		imaging before any adjuvant treatment (high-risk endometrial cancer)			multidisciplinary group			of patients (3—referred to chemotherapy alone, 2—referred to nodal-directed treatment, 12—addition of radiotherapy boost, 1—change in radiotherapy target definition).
He et al, 2022 [26]	Meta-analysis	11 studies (2592 patients with cervical cancer who underwent lymph node staging)	FDG PET/CT	MRI	Pathology, biopsy	**Lymph node metastases** Pooled Sens: 65% Pooled Spec: 93% Pooled +LR: 4 Pooled -LR: 0.55 Pooled DOR: 8.57 AUC: 0.824*	**Lymph node metastases** Pooled Sens: 58% Pooled Spec: 91% Pooled +LR: 3.39 Pooled -LR: 0.65 Pooled DOR: 5.88 AUC: 0.702*	NA
Khebbeb et al, 2022 [27]	Retrospective	71 patients who underwent staging prior to para-aortic lymphadenectomy (locally advanced cervical cancer)	FDG PET/CT	NA	Pathology	**Para-aortic lymph node metastases** Sens: 55% Spec: 84% PPV: 33% NPV: 93% FNR: 7.1%	NA	NA
Akyel et al, 2022 [28]	Retrospective	93 patients who underwent primary staging or follow-up of recurrent disease (newly diagnosed or suspicion of recurrent ovarian cancer)	FDG PET/CT	CA-125	Histopathology, clinical and imaging follow-up	**Staging or recurrence** Sens: 93.0% Spec: 42.8% PPV: 95.2% NPV: 33.3% Accu: 89.2%	**Staging or recurrence** Sens: 79.1% Spec: 42.8% PPV: 94.4% NPV: 14.3% Accu: 76.3%	NA
Albano et al, 2022 [29]	Retrospective	63 patients who underwent restaging (suspected recurrent vulvar cancer)	FDG PET/CT	US, MRI, CT	Histopathology, clinical and imaging follow-up	**Recurrence** Sens: 100% Spec: 92% PPV: 98% NPV: 100% Accu: 98% +LR: 12.00 -LR: 0.00	NA	FDG PET/CT impacted treatment decision-making in 44.4% (28/63) of patients (12—local therapy to chemotherapy, 10—initiated specific therapy, 6—avoided unnecessary invasive treatments).
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**

Ahmad et al, 2022 [30]	Retrospective	99 treatment-naïve patients who underwent initial staging (head and neck cancer)	FDG PET/CT	CT, MRI	Biopsy, consensus from multidisciplinary clinic	**T-staging** Sens: 90.2% Spec: 100% PPV: 100% NPV: 43.8% Accu: 90.9%	**T-staging** ***CT*** Sens: 75.0% Spec: 100% PPV: 100% NPV: 23.3% Accu: 76.8% ***MRI*** Sens: 78.3% Spec: 100% PPV: 100% NPV: 25.9% Accu: 79.8%	PET/CT changed the T, N and M staging in 14.1% (14/99), 19.2% (19/99) and 3.0% (3/99) of patients, respectively. Overall, change in management due to PET/CT was seen in 36.4% (36/99) of patients (22—change in radiation dose, 11—change in radiation dose and volumes, 3—curative to palliative).
Subha et al, 2022 [31]	Prospective	30 patients who underwent pre-treatment staging (head and neck cancer)	FDG PET/CT	CeCT	Histopathology, pre- and post-PET information	**Malignancy** Sens: 96.0% Spec: 50.0% PPV: 96.0% NPV: 50.0% Accu: 93.0%	**Malignancy** Sens: 89.2% Spec: 50.0% PPV: 96.1% NPV: 25.0% Accu: 86.7%	FDG PET/CT changed the stage of 46.7% (14/30) of patients (13 upstaged, 1 downstaged). The treatment plans were altered in 43.3% (13/30) of cases.
Cao et al, 2021 [32]	Meta-analysis	53 studies (2946 patients with head and neck cancer)	FDG PET/CT	CT, MRI	Histopathology	**Mandibular invasion** Pooled Sens: 88% Pooled Spec: 81% Pooled +LR: 4.62 Pooled -LR: 0.15 Pooled DOR: 18.31 AUC: 0.92	**Mandibular invasion** ***CT*** Pooled Sens: 77% Pooled Spec: 87% Pooled +LR: 5.89 Pooled -LR: 0.26 Pooled DOR: 17.65 AUC: 0.90 ***MRI*** Pooled Sens: 88% Pooled Spec: 83% Pooled +LR: 5.1 Pooled -LR: 0.14 Pooled DOR: 23.11 AUC: 0.92	NA
Yang et al, 2022 [33]	Retrospective	174 patients who underwent pre-treatment staging (T3N1M0 nasopharyngeal carcinoma)	FDG PET/CT	MRI	Histopathology	**Cervical lymph node metastases** Sens: 97.7%* Spec: 80.4%* PPV: 87.8%* NPV: 96.1%*	**Cervical lymph node metastases** Sens: 87.1%* Spec: 64.1%* PPV: 77.7%* NPV: 77.6%*	NA
Yang et al, 2022 [34]	Retrospective	1377 treatment-naïve patients who underwent staging (nasopharyngeal carcinoma)	FDG PET/CT	MRI	Histopathology, clinical follow-up	**Cervical lymph node metastases** Pooled Sens: 96.7%* Pooled Spec: 75.9% Pooled PPV: 85.0% Pooled NPV: 94.2%*	**Cervical lymph node metastases** Pooled Sens: 88.5%* Pooled Spec: 70.7% Pooled PPV: 81.0% Pooled NPV: 81.3%*	Patients who were staged by PET/CT and MRI had significantly better 5-year OS (95.7% vs. 90.4%, p<0.001), 5-year FFS (85.7% vs. 71.7%, p<0.001), 5-year

						Pooled Accu: 88.0%* AUC: 0.863*	Pooled Accu: 81.1%* AUC: 0.796*	DMFS (93.9% vs. 87.9%, p<0.001), and 5-year LRRFS (93.0% vs. 81.4%, p<0.001) than those who were staged by MRI alone.
Kowalchuk et al, 2021 [35]	Prospective	261 patients who underwent staging (HPV-associated oropharyngeal cancer)	FDG PET/CT	CeCT	Pathology	**N2 staging** Sens: 61% Spec: 95% PPV: 67% NPV: 93% Accu: 90% **Extranodal extension** Sens: 49% Spec: 69% PPV: 71% NPV: 47% Accu: 57%	**N2 staging** Sens: 59% Spec: 92% PPV: 53% NPV: 94% Accu: 88% **Extranodal extension** Sens: 54% Spec: 71% PPV: 72% NPV: 53% Accu: 62%	NA
Muller et al, 2022 [36]	Retrospective	65 patients who underwent initial staging (HPV+ oropharyngeal squamous cell carcinoma)	FDG PET/CT	Triple endoscopy	Histopathology	**Synchronous primary tumour** Sens: 100% Spec: 95.3% PPV: 25.0% NPV: 100%	**Synchronous primary tumour** Sens: NA Spec: 90.2% PPV: NA NPV: 93.2%	NA
Kouketsu et al, 2021 [37]	Prospective	50 patients who were scheduled for mandibulectomy or maxillectomy (oral squamous cell carcinoma)	FDG PET/CT	CeMRI, CeCT, ^{99m}Tc bone scintigraphy, panoramic radiography	Histopathology	**Bone invasion** Sens: 83.3% Spec: 71.9% PPV: 62.5% NPV: 88.4% Accu: 76.0% +LR: 2.96 -LR: 0.23	**Bone invasion** ***CeMRI*** Sens: 88.9% Spec: 78.1% PPV: 69.6% NPV: 92.3% Accu: 82.0% +LR: 4.06 -LR: 0.14 ***CeCT*** Sens: 77.8% Spec: 87.5% PPV: 77.8% NPV: 87.5% Accu: 84.0% +LR: 6.22 -LR: 0.25 ***^{99m}Tc bone scintigraphy*** Sens: 88.9% Spec: 62.5% PPV: 57.1% NPV: 90.9% Accu: 72.0% +LR: 2.37	NA

							-LR: 0.18 ***Panoramic radiography*** Sens: 61.1% Spec: 84.4% PPV: 68.8% NPV: 79.4% Accu: 76.0% +LR: 3.91 -LR: 0.46	
de Koster et al, 2022 [38]	RCT (EfFECTS trial)	132 patients randomized 2:1 to either FDG PET/CT-driven work-up or scheduled diagnostic surgery (indeterminate thyroid nodules)	FDG PET/CT (n=91)	No FDG PET/CT (n=41)	Histopathology, imaging follow-up	**Diagnosis** Sens: 94.1% Spec: 39.8% PPV: 35.2% NPV: 95.1% Accu: 53.8%	NA	The proportion of management considered unbeneficial was significantly lower in the FDG PET/CT-driven group than in the diagnostic surgery group (41.8% vs. 82.9%, p<0.001). FDG PET/CT-driven management avoided significantly more surgery than the diagnostic surgery group (39.7% vs. 2.9%, p=0.002). The rate of surgical complication (p=0.17) and perceived HRQoL (p=0.11) did not differ significantly between the two groups.
Younis et al, 2022 [39]	Prospective	20 patients with negative I-131 WBS and elevated serum thyroglobulin level after thyroidectomy (suspected recurrent differentiated thyroid cancer)	FDG PET/CT	CT	Histopathology, clinical follow-up	**Recurrence** Sens: 100% Spec: 100% PPV: 100% NPV: 100% Accu: 100%	**Recurrence** Sens: 84.2% Spec: 0% PPV: 94.1% NPV: 0% Accu: 80.0%	NA
Hematologic Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Gupta et al, 2021 [40]	Meta-analysis	25 studies (814 patients with suspected primary central	FDG PET/CT	MRI	Histopathology, follow-up	**Diagnosis** Pooled Sens: 87% Pooled Spec: 85% Pooled PPV: 84%	NA	NA

		nervous system lymphoma)				Pooled NPV: 87% Pooled DOR: 29.78 AUC: 0.919 Q index: 0.852		
Rama et al, 2022 [41]	Meta-analysis	12 studies (373 patients with multiple myeloma who underwent treatment response assessment)	FDG PET/CT	Whole-body MRI	Bone marrow biopsy, International Uniform Response Criteria, other clinical criteria	**Treatment response** Pooled Sens: 64% Pooled Spec: 82%* AUC: 0.83	**Treatment response** Pooled Sens: 87% Pooled Spec: 57%* AUC: 0.84	NA
Jitani et al, 2021 [42]	Prospective	80 treatment-naïve patients who underwent staging (37 HL, 43 NHL)	FDG PET/CT	BMB	BMB	**Bone marrow involvement** **HL** Sens: 100% Spec: 61.3% PPV: 33.3% NPV: 100% **NHL** Sens: 83.3% Spec: 67.7% PPV: 50.0% NPV: 91.3%	NA	NA
Dai et al, 2021 [43]	Retrospective	63 patients who underwent treatment evaluation after allogeneic stem cell transplantation (lymphoblastic lymphoma)	FDG PET/CT	CT	Pathology, clinical and imaging follow-up	**Residual disease** Sens: 100% Spec: 92.2% PPV: 75.0% NPV: 100% Accu: 93.7%	**Residual disease** Sens: 91.7% Spec: 76.5% PPV: 47.8% NPV: 97.5% Accu: 79.4%	The 3-year PFS for PET-positive and PET-negative patients were 18.8% and 70.2%, respectively (HR, 3.957, 95%CI: 1.839 to 8.514, p<0.001).
Jin et al, 2022 [44]	Prospective (Phase II)	129 patients who underwent interim response assessment after 4 cycles of R-CHOP (limited-stage DLBCL)	FDG PET/CT (Interim-PET negative patients received 2 additional cycles of rituximab monotherapy. Interim-PET positive patients received another 4	NA	Clinical follow-up	NA	NA	The 3-year PFS (78.6% vs. 91.9%, respectively, p=0.24) and OS (85.7% vs. 95.6%, respectively, p=0.16) were not significantly different between patients with positive and negative interim-PET.

			cycles of R-CHOP)					
Casasnovas et al, 2022 [45]	Phase III RCT (AHL2011)	823 patients randomized 1:1 to either standard treatment with 6 cycles of BEACOPP or PET-driven treatment (advanced HL)	FDG PET/CT (PET-negative patients after 2 cycles of BEACOPP received 4 cycles of ABVD while PET-positive patients after 2 cycles of BEACOPP received 4 additional cycles of BEACOPP)	NA	Clinical follow-up	NA	NA	The 5-year PFS in the PET-driven group was non-inferior to that of the standard group (86.7% vs. 87.5%, respectively; HR=1.07; 95% CI, 0.74 to 1.57; p=0.67). The 5-year OS was 97.7% in the PET-driven group and 97.7% in the standard group (97.7% vs. 97.7%; HR=1.01; 95% CI: 0.50 to 2.10; p=0.53). 3.1% (13/413) and 2.2% (9/410) of patients developed a second primary malignancy in the standard and PET-driven groups, respectively.
Melanoma								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Helvind et al, 2021 [46]	Retrospective	138 asymptomatic patients who underwent routine surveillance imaging; 243 scans (stage IIB-III cutaneous melanoma)	FDG PET/CT	NA	Histopathology, other imaging modality	**Recurrence (scan-based)** Sens: 100% Spec: 94.7% PPV: 74.4% NPV: 100%	NA	FDG PET/CT findings caused change in management in 14.5% (20/138) of patients. However, 12.3% (17/138) of patients received unnecessary additional investigations due to false positive findings.
Jaeger et al, 2022 [47]	Retrospective	63 asymptomatic patients who underwent routine surveillance imaging after primary surgical resection (stage IIB, IIC, or IIIA cutaneous melanoma)	FDG PET/CT	NA	Pathology, clinical and imaging follow-up	**Recurrence** PPV: 32.0% NPV: 88.0%	NA	NA

Andersen et al, 2022 [48]	Retrospective	124 patients who underwent follow-up after resection followed by adjuvant immunotherapy; 366 scans (stage III or IV melanoma)	FDG PET/CT	NA	Biopsy, imaging follow-up	**Recurrence** Sens: 97% Spec: 82% PPV: 39% NPV: 100%	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**
Jaiswal et al, 2021 [49]	Retrospective	87 patients who underwent pre-treatment imaging (suspected pheochromocytoma and paraganglioma)	^{68}Ga-DOTA-TATE PET/CT	CeCT, ^{131}I-MIBG scintigraphy	Histopathology, clinical and imaging follow-up, composite of all anatomical and functional imaging tests	**Primary tumour (lesion-based)** Sens: 94%* **Metastatic disease (lesion-based)** Sens: 82%*	**Primary tumour (lesion-based)** ***CeCT*** Sens: 94% ***^{131}I-MIBG scintigraphy*** Sens: 75%* **Metastatic disease (lesion-based)** ***CeCT*** Sens: 48%* ***^{131}I-MIBG scintigraphy*** Sens: 52%*	NA
Bashir et al, 2021 [50]	Prospective	31 patients with gross-total resection on 3-month postoperative MRI (meningioma)	^{68}Ga-DOTA-TOC PET	MRI	Histology, imaging follow-up	**Residual disease** Sens: 90.0% Spec: 92.0% PPV: 94.0% NPV: 85.0% Accu: 90.0% AUC: 0.906	NA	NA
^{11}C/^{18}F-Choline								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Ciappuccini et al, 2021 [51]	Prospective	107 patients with indeterminate cytology for whom thyroid surgery had been recommended	^{18}F-FCH PET/CT	Neck US	Pathology	**Diagnosis (acquisition at 20 minutes)** Sens: 90% Spec: 49% PPV: 29% NPV: 96%	NA	^{18}F-FCH PET/CT findings would have hypothetically prevented unnecessary surgeries in 39.3% (42/107) of patients.

		(thyroid nodule ≥15mm)				Accu: 55% **(acquisition at 60 minutes)** Sens: 85% Spec: 49% PPV: 28% NPV: 94% Accu: 67%		
^{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**
Nuo et al, 2022 [52]	Retrospective	105 patients with elevated PSA level or suspicious lesions detected by US (suspected prostate cancer)	^{68}Ga-PSMA-11 PET/CT	Biparametric MRI	Histopathology	**Diagnosis** ***^{68}Ga-PSMA-11 PET/CT*** Sens: 69% Spec: 95% AUC: 0.85 ***^{68}Ga-PSMA-11 PET/CT + biparametric MRI*** Sens: 94% Spec: 81% AUC: 0.90	**Diagnosis** Sens: 79% Spec: 81% AUC: 0.87	NA
Emmett et al, 2021 [53]	Prospective (Phase II PRIMARY trial)	291 patients with abnormal PSA (<20 ng/ml) or abnormal digital rectal examination and scheduled for prostate biopsy (clinical suspicion of prostate cancer)	^{68}Ga-PSMA PET/CT	mpMRI	Histopathology	**Diagnosis** ***^{68}Ga-PSMA PET/CT*** Sens: 90% Spec: 50% PPV: 69% NPV: 80% ***^{68}Ga-PSMA PET/CT + mpMRI*** Sens: 97%* Spec: 40%* PPV: 67% NPV: 91%*	**Diagnosis** Sens: 83%* Spec: 53%* PPV: 69% NPV: 72%*	NA
Dekalo et al, 2021 [54]	Retrospective	149 patients who underwent staging prior to radical prostatectomy and bilateral pelvic lymph node dissection (localized or locoregional high-risk prostate cancer)	^{68}Ga-PSMA PET/CT	NA	Pathology	**Lymph node metastases** Sens: 68.0% Spec: 95.0% Accu: 92.0%	NA	The rate of PSA persistence was significantly lower in patients with PET-negative nodes than those with PET-positive nodes (15.0% vs. 84.0%, p<0.001).

Esen et al, 2021 [55]	Retrospective	96 patients who underwent primary staging prior to radical prostatectomy and extended pelvic lymph node dissection (prostate cancer)	^{68}Ga-PSMA-11 PET/CT	NA	Histopathology	**Lymph node metastases (patient-based)** Sens: 53.3% Spec: 98.8% PPV: 88.9% NPV: 92.0% Accu: 91.7% **(lesion-based)** Sens: 31.0% Spec: 99.8% PPV: 81.3% NPV: 98.4% Accu: 98.3%	NA	NA
Hope et al, 2021 [56]	Prospective (Phase 3 trial)	277 patients who underwent primary staging before radical prostatectomy with pelvic lymph node dissection (intermediate- to high-risk prostate cancer)	^{68}Ga-PSMA PET/CT or PET/MRI	NA	Histopathology	**Pelvic lymph node metastases** Sens: 40.0% Spec: 95.0% PPV: 75.0% NPV: 81.0%	NA	NA
Baas et al, 2022 [57]	Retrospective	213 patients who underwent staging prior to robotic-assisted radical prostatectomy with extended pelvic lymph node dissection (intermediate or high-risk prostate cancer)	^{68}Ga-PSMA PET/CT	NA	Histopathology	**Lymph node metastases** Sens: 29% Spec: 84% PPV: 35% NPV: 80%	NA	NA
Szigeti et al, 2022 [58]	Prospective	81 patients who underwent preoperative staging (intermediate- and high-risk prostate cancer)	^{68}Ga-PSMA-11 PET/CT	mpMRI	Histopathology, clinical and imaging follow-up	**Primary tumour** Sens: 88.9% **Pelvic lymph node metastases** Sens: 60.0% Spec: 91.0% Accu: 83.0%	**Primary tumour** Sens: 98.6% **Pelvic lymph node metastases** Sens: 50.0% Spec: 97.0% Accu: 87.0%	NA
Moreira et al, 2022 [59]	Retrospective	126 patients who underwent primary staging (prostate cancer)	^{68}Ga-PSMA-11 PET/CT	NA	Histopathology, confirmatory imaging, clinical follow-up	**Lymph node metastases** Sens: 75.0% Spec: 96.3% PPV: 87.5% NPV: 91.8% Accu: 90.8%	NA	NA

						Bone metastases Sens: 90.9% Spec: 50.0% PPV: 76.9% NPV: 75.0% Accu: 76.5%		
Barbosa et al, 2022 [60]	Retrospective	91 patients who underwent staging prior to radical prostatectomy with extended lymph node dissection (prostate cancer)	^{68}Ga-PSMA PET/CT or PET/MRI	NA	Histopathology	**Lymph node involvement** ***^{68}Ga-PSMA PET/CT*** Sens: 58.3% Spec: 95.0% Accu: 86.5% ***^{68}Ga-PSMA PET/MRI*** Sens: 40.0% Spec: 100% Accu: 84.6% **Extra-prostatic extension** ***^{68}Ga-PSMA PET/CT*** Sens: 10.0% Spec: 96.5% ***^{68}Ga-PSMA PET/MRI*** Sens: 58.0% Spec: 92.3% **Seminal vesicle involvement** ***^{68}Ga-PSMA PET/CT*** Sens: 40.0% Spec: 95.5% ***^{68}Ga-PSMA PET/MRI*** Sens: 71.4% Spec: 100%	NA	NA
Dekalo et al, 2022 [61]	Retrospective	88 patients who underwent staging prior to radical prostatectomy and bilateral pelvic lymph node dissection (favorable intermediate-risk prostate cancer)	^{68}Ga-PSMA PET/CT	NA	Pathology	**Seminal vesicle invasion** Sens: 53% Spec: 98% PPV: 70% NPV: 92% **Lymph node involvement** Sens: 50% Spec: 97% PPV: 25% NPV: 99% AUC: 0.73	NA	NA
Stabile et al, 2022 [62]	Meta-analysis	27 studies (2832 prostate cancer	^{68}Ga-PSMA PET/CT,	NA	Histopathology	**Lymph node metastases**	NA	NA

		patients who underwent primary staging before radical prostatectomy with extended pelvic lymph node dissection)	^{18}F-DCFPyL PET/CT, ^{18}F-PSMA-1007 PET/CT, ^{64}Cu-PSMA PET/CT, ^{18}F-rhPSMA-7 PET/CT			**(patient-based)** Pooled Sens: 58% Pooled Spec: 95% Pooled PPV: 79% Pooled NPV: 87% Pooled DOR: 15 AUC: 0.84 **(node-based)** Pooled NPV: 97%		
Sonni et al, 2022 [63]	Prospective	74 patients who underwent initial staging prior to radical prostatectomy (intermediate- to high-risk prostate cancer)	^{68}Ga-PSMA-11 PET/CT	mpMRI	Histopathology	**Tumour localization (segment-based)** Sens: 84% Spec: 55% AUC: 0.70 **Bilateral intraprostatic disease** AUC: 0.54 **Extraprostatic extension** AUC: 0.59* **Seminal vesicle invasion** AUC: 0.63*	**Tumour localization (segment-based)** Sens: 86% Spec: 59% AUC: 0.73 **Bilateral intraprostatic disease** AUC: 0.65 **Extraprostatic extension** AUC: 0.79* **Seminal vesicle Invasion** AUC: 0.84*	NA
Pepe and Pennisi, 2022 [64]	Prospective	30 patients who underwent preoperative staging (high-risk prostate cancer)	^{68}Ga-PSMA PET/CT	CT, ^{99m}Tc-MDP bone scan	Histology	**Lymph node metastases** Accu: 76.9%*	**Lymph node metastases** Accu: 46.1%*	^{68}Ga-PSMA PET/CT changed the strategy of therapy in 10.0% (3/30) of patients.
Ekmekcioglu et al, 2021 [65]	Retrospective	65 patients who underwent initial staging (prostate cancer)	^{68}Ga-PSMA PET/CT	Pelvic MRI, CT, bone scan	Pre- and post-PET information	NA	NA	The clinical choice of treatment changed in 43.1% (28/65) of patients after evaluation with ^{68}Ga-PSMA PET/CT.
Abghari-Gerst et al, 2022 [66]	Prospective	2005 patients who underwent radical prostatectomy with or without radiation therapy or definitive radiation therapy (biochemically recurrent prostate cancer)	^{68}Ga-PSMA-11 PET/CT or PET/MRI	NA	Histopathology	**Recurrence (region-based)** ***Prostate/prostate bed*** PPV: 83% ***Pelvic lymph nodes*** PPV: 72% ***Soft-tissue*** PPV: 88% ***Bone*** PPV: 83%	NA	NA
Cerci et al, 2022 [67]	Prospective (IAEA-PSMA study)	1004 patients who received radical	^{68}Ga-PSMA PET/CT	CT, bone scintigraphy, MRI	Histology, correlative imaging,	NA	NA	Disease management changed as a result of ^{68}Ga-PSMA PET/CT in

		prostatectomy or radiotherapy (biochemically recurrent prostate cancer)			clinical and laboratory data, pre- and post-PET questionnaire			56.8% (570/1004) of patients (77—active surveillance, 35—radiotherapy only, 55—radiotherapy and ADT, 152—ADT only, 48—salvage lymphadenectomy, 5—bilateral orchiectomy, 140—second-generation ADT, 10—radionuclide therapy, 48—started taxane chemotherapy).
Metser et al, 2022 [68]	Prospective	1289 patients who received radical prostatectomy with or without salvage radiation therapy or primary radiation therapy (suspected persistent or recurrent prostate cancer)	^{18}F-DCFPyL PET/CT	Ct, bone scintigraphy	Pre- and post-PET questionnaire	NA	NA	Following ^{18}F-DCFPyL PET/CT examination, a change in planned management occurred in 58.0% (748/1289) of patients.
Morris et al, 2021 [69]	Prospective (Phase III CONDOR)	208 patients with negative or equivocal conventional imaging after radical prostatectomy or radiotherapy (suspected or metastatic prostate cancer)	^{18}F-DCFPyL PET/CT	CT, MRI, bone scintigraphy, ^{11}C-choline and ^{18}F-fluciclovine PET	Histopathology, imaging or clinical follow-up, pre- and post-PET questionnaire	**Recurrence** PPV: 84.8%-87.0%	NA	^{18}F-DCFPyL PET/CT changed the intended disease management plan of 63.9% (131/205) of patients.
^{18}F-FACBC								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Wakabayashi et al, 2021 [70]	Prospective	45 patients who underwent surgical planning (suspected high- or low-grade glioma)	^{18}F-FACBC PET/CT	CeMRI	Histopathology	**Diagnosis** Sens: 58.0% Spec: 61.5% PPV: 88.0% NPV: 30.8%	NA	The addition of ^{18}F-FACBC PET/CT modified the extent of planned tumour resection in 47.2% (17/36) of patients (11—extended resection

								area, 6—reduced resection area).
^{18}F-FET								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Brendle et al, 2022 [71]	Retrospective	172 patients with untreated suspected lesions or true progression during adjuvant treatment; 189 examinations (brain tumour)	^{18}F-FET PET/MRI	MRI	Histology, clinical and imaging follow-up	**Diagnosis** Sens: 78% Spec: 89% PPV: 78% NPV: 89% Accu: 85% **True progression** Sens: 93% Spec: 95% PPV: 99% NPV: 77% Accu: 93%	NA	At diagnosis, ^{18}F-FET PET/MRI changed the clinical management of 32.8% (19/58) of patients (11—active treatment to monitoring, 4—monitoring to active treatment, 1—therapy stratification, 3—treatment adaptation). At detection of progression, ^{18}F-FET PET/MRI changed the clinical management of 52.7% (69/131) of patients (15—active treatment to monitoring, 7—monitoring to active treatment, 43—therapy stratification, 4—treatment adaptation).
Puranik et al, 2021 [72]	Retrospective	72 patients who underwent surgery followed by radiotherapy or radiotherapy alone (grade III or IV glioma)	^{18}F-FET PET/CT	MRI	Histopathology, clinical or imaging follow-up	**Differentiating between recurrence and post-treatment changes (T/Wm with cutoff of 2.5)** Sens: 89.7% Spec: 81.8% PPV: 85.4% NPV: 87.1% Accu: 86.1%	NA	NA
Pancreatic Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Huang et al, 2021 [73]	Retrospective	467 patients who underwent initial diagnosis (suspected	FDG PET/CT	Serum CA19-9, CeCT, CeMRI	Histology, clinical follow-up	**Diagnosis** Sens: 91.9% Spec: 96.3% PPV: 96.6%	**Diagnosis** ***Serum CA19-9*** Sens: 80.0% Spec: 69.0%	NA

		pancreatic lesions)				NPV: 91.3% Accu: 94.0%	PPV: 74.5% NPV: 75.3% Accu: 74.9% ***CeCT*** Sens: 83.6% Spec: 77.8% PPV: 83.6% NPV: 77.8% Accu: 81.2% ***CeMRI*** Sens: 91.2% Spec: 75.0% PPV: 72.1% NPV: 92.3% Accu: 81.7%	
Pediatric Cancer								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Shah et al, 2022 [74]	Prospective	85 treatment naïve patients who underwent staging (42 neuroblastoma; 43 rhabdomyosarcoma)	FDG PET/CT	BMB	Histopathology	**Bone marrow involvement** Sens: 100% Spec: 86.1% PPV: 68.9% NPV: 100% Accu: 89.4%	NA	NA
Liu et al, 2022 [75]	Retrospective	98 patients who underwent pre-treatment imaging (newly diagnosed neuroblastoma)	FDG PET/CT	BMB, PHOX2B of blood, PHOX2B of bone marrow	Biopsy, clinical and imaging follow-up	**Bone marrow involvement** Sens: 97.0% Spec: 83.9% PPV: 92.9% NPV: 92.9% AUC: 0.904*	**Bone marrow involvement** ***BMB*** Sens: 61.2% Spec: 100% PPV: 100% NPV: 54.4% AUC: 0.806* ***PHOX2B of blood*** Sens: 68.7% Spec: 93.5% PPV: 95.8% NPV: 58.0% AUC: 0.806 ***PHOX2B of bone marrow*** Sens: 89.6% Spec: 93.5% PPV: 96.7% NPV: 80.6% AUC: 0.916	NA

Marner et al, 2021 [76]	Prospective	97 patients; 169 scans performed at initial diagnosis, before and after treatment, or at relapse (known or suspected primary CNS tumour)	^{18}F-FET PET/MRI	MRI	Pathology, clinical and imaging follow-up, multidisciplinary consensus	**Discriminating between tumour and non-tumour lesions (untreated lesions)** Sens: 98% Spec: 71% Accu: 96%* **(treated lesions)** Sens: 88% Spec: 100%* Accu: 91%*	**Discriminating between tumour and non-tumour lesions (untreated lesions)** Sens: 98% Spec: 14% Accu: 90%* **(treated lesions)** Sens: 93% Spec: 48%* Accu: 81%*	The addition of ^{18}F-FET PET to MRI impacted clinical management in 7.9% (12/151) of scans (2—avoided biopsy, 1—reoperated, 2—change of biopsy site, 2—continued chemotherapy, 2—change to chemotherapy, 2—initiated biopsy, 1—resection of an extra tumour site).
Sarcoma								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Bang and Kang, 2022 [77]	Meta-analysis	7 studies (196 patients with clinically suspected or detected uterine mass)	FDG PET or PET/CT	NA	Pathology, clinical or imaging follow-up	**Differentiating between uterine leiomyomas and uterine sarcomas** Pooled Sens: 88% Pooled Spec: 83% Pooled +LR: 4.24 Pooled -LR: 0.22 Pooled DOR: 29.59 AUC: 0.87	NA	NA
Pesque et al, 2022 [78]	Retrospective	75 patients who underwent staging (Kaposi sarcoma)	FDG PET/CT	NA	Clinical examination, standard imaging, endoscopy and/or pathology, follow-up	**Staging (patient-based)** Sens: 85% Spec: 57% PPV: 95% NPV: 29% Accu: 83% **(lesion-based)** Sens: 71% Spec: 98% PPV: 90% NPV: 92% Accu: 92%	NA	NA
Lee et al, 2022 [79]	Retrospective	183 patients who underwent staging or surveillance (bone and soft tissue sarcoma)	FDG PET/CT	NA	Consensus from multidisciplinary sarcoma conference	NA	NA	The clinical course of 14.8% (27/183) was altered as a result of FDG PET/CT findings.
Thoracic Cancer								

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Tezcan et al, 2022 [80]	Prospective	100 patients who underwent chest CT-guided transthoracic biopsy with or without PET/CT (suspected lung cancer)	FDG PET/CT (n=50)	Chest CT (n=50)	Histopathology	**Diagnosis** Sens: 96.0% PPV: 98.0%	**Diagnosis** Sens: 74.5% PPV: 82.0%	NA
Al-Ibraheem et al, 2021 [81]	Retrospective	101 patients who underwent preoperative staging (NSCLC)	FDG PET/CT	CeCT, EBUS/TBNA, mediastinoscopy	Histopathology, clinical and imaging follow-up	**Mediastinal lymph node metastases** Sens: 90.5%* Spec: 60.5%* PPV: 79.2% NPV: 79.3% Accu: 79.2%	**Mediastinal lymph node metastases** ***CeCT*** Sens: 75.0%* Spec: 43.6%* PPV: 67.2% NPV: 53.1% Accu: 62.6% ***EBUS/TBNA*** Sens: 84.6% Spec: 92.9% PPV: 95.7% NPV: 76.5% Accu: 87.5% ***Mediastinoscopy*** Sens: 66.7% Spec: 100% PPV: 100% NPV: 87.9% Accu: 90.2%	FDG PET/CT findings changed the staging and management of 17.5% (10/57) of patients (5 upstaged, 5 downstaged). However, 29.8% (17/57) of patients would have been incorrectly staged by FDG PET/CT.
Pencharz et al, 2022 [82]	Retrospective	58 patients who underwent staging (T1 part-solid lung adenocarcinoma)	FDG PET/CT	CT	Histopathology, follow-up	NA	NA	FDG PET/CT initiated further investigations in 3.4% (2/58) of patients but did not change final management plan in any cases.
Lim et al, 2022 [83]	Retrospective	2864 patients who underwent routine surveillance after curative therapy (clinically unsuspected recurrent NSCLC)	FDG PET/CT	NA	Pathology, imaging follow-up	**Recurrence** Sens: 98.9% Spec: 98.1% PPV: 77.6% NPV: 99.9% Accu: 98.2% **Second primary cancer** PPV: 42.7%	NA	NA
Ohno et al, 2022 [84]	Prospective	98 patients who underwent initial	FDG PET/CT,	Whole-body MRI, MRI, CT,	Pathology, clinical and	**T staging** ***FDG PET/CT*** Accu: 85.7%*‡	**T staging** ***Whole-body MRI*** Accu: 94.9%*	NA

		staging before treatment (SCLC)	FDG PET/MRI	bone scintigraphy	imaging follow-up	***FDG PET/MRI*** Accu: 94.9%‡ **N staging** ***FDG PET/CT*** Accu: 81.6%* ***FDG PET/MRI*** Accu: 83.7%* **M staging** ***FDG PET/CT*** Accu: 94.9%* ***FDG PET/MRI*** Accu: 94.9%* **TNM staging** ***FDG PET/CT*** Accu: 77.6%*‡ ***FDG PET/MRI*** Accu: 86.7%*‡ **VALSG staging** ***FDG PET/CT*** Accu: 98.0%* ***FDG PET/MRI*** Accu: 95.9%*	***MRI, CT, bone scintigraphy*** Accu: 89.8% **N staging** ***Whole-body MRI*** Accu: 84.7% ***MRI, CT, bone scintigraphy*** Accu: 75.5%* **M staging** ***Whole-body MRI*** Accu: 94.9% ***MRI, CT, bone scintigraphy*** Accu: 84.7%* **TNM staging** ***Whole-body MRI*** Accu: 88.8%* ***MRI, CT, bone scintigraphy*** Accu: 72.4%* **VALSG staging** ***Whole-body MRI*** Accu: 95.9% ***MRI, CT, bone scintigraphy*** Accu: 82.7%*	
Ohno et al, 2022 [85]	Prospective	64 patients who underwent staging (thymic epithelial tumour)	FDG PET/CT, FDG PET/MRI	Whole-body MRI, conventional examination (brain CeMRI, whole-body CeCT, bone scintigraphy)	Pathology, imaging follow-up	**Staging** ***FDG PET/CT*** Accu: 78.1% ***FDG PET/MRI*** Accu: 84.4%*	**Staging** ***Whole-body MRI*** Accu: 84.4% ***Conventional examination*** Accu: 71.9%*	NA
Hou et al, 2021 [86]	Retrospective	83 patients who underwent restaging after surgery with or without adjuvant therapy (suspected recurrent thymoma or thymic carcinoma)	FDG PET/CT	NA	Histopathology, clinical and/or imaging follow-up	**Recurrence** Sens: 100% Spec: 76.7% PPV: 80.0% NPV: 100% Accu: 87.9%	NA	NA
Gilbert et al, 2022 [87]	Prospective (SPUtNIk trial)	312 patients with nodules of ≥8mm and of ≤30mm in size (solitary	FDG PET/CT	Dynamic CeCT	Histology, clinical and imaging follow-up	**Diagnosis** Sens: 72.8% Spec: 81.8% PPV: 86.3%	**Diagnosis** Sens: 95.3% Spec: 29.8% PPV: 68.2%	NA

		pulmonary nodules)				NPV: 65.6% Accu: 76.3% AUC: 0.77*	NPV: 80.0% Accu: 69.9% AUC: 0.62*	
Various Sites								
Citation	**Study Type**	**Population**	**PET Type**	**Conventional Intervention**	**Reference Standard**	**Diagnostic Performance (PET)**	**Diagnostic Performance (Conventional Intervention)**	**Change in Patient Management**
Atilgan and Yalcin, 2022 [88]	Retrospective	68 patients who had biopsy or surgery after PET/CT (carcinoma of unknown primary)	FDG PET/CT	NA	Histopathology	**Primary site** Sens: 80.0% Spec: 66.7% Accu: 79.4%	NA	NA
Elshalakani et al, 2022 [89]	Prospective	40 patients with uncertain diagnosis (fever of unknown origin)	FDG PET/CT	Not specified	Histopathology, microbiological and other laboratory investigations, response to therapy	**Diagnosis of underlying cause** Sens: 93.5% Spec: 66.7% PPV: 90.6% NPV: 75.0% Accu: 87.5%	NA	NA

*p<0.05

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

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; Accu, accuracy; ADT, antiandrogenic therapy; AUC, area under the curve; AUS, axillary ultrasound; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; BMB, bone marrow biopsy; CA-125, cancer antigen-125; CA19-9, carbohydrate antigen 19-9; CeCT, contrast-enhanced computed tomography; CeMRI, contrast-enhanced magnetic resonance imaging; CI, confidence interval; CNS, central nervous system; CT, computed tomography; ^{64}Cu-PSMA, ^{64}Cu-labelled prostate-specific membrane antigen; DCE, dynamic contrast enhanced; DLBCL, diffuse large B-cell lymphoma; DMFS, distant metastasis-free survival; DOR, diagnostic odds ratio; DW-MRI, diffusion-weighted magnetic resonance imaging; EBUS, endobronchial ultrasound; EEG, electroencephalography; EfFECTS, Efficacy of [^{18}F]FDG-PET in Evaluation of Cytological indeterminate Thyroid nodules prior to Surgery; ^{18}F-DCFPyL, (2s)-2-[[(1S)-1-carboxy-5-[(6-(^{18}F)fluoranylpyridine-3-carbonyl)amino]pentyl]carbamoylamino]pentanedioic acid; FDG, fluorodeoxyglucose; ^{18}F-FACBC, anti-1-amino-3-[18F]fluorocyclobutane carboxylic acid, ^{18}F-FCH, ^{18}F-fluorocholine; ^{18}F-FET, O-(2[^{18}F]-fluoroethyl)-L-tyrosine; FFS, failure-free survival; FNR, false negative rate; FPR, false positive rate; ^{18}F-PSMA, ^{18}F-labelled prostate-specific membrane antigen; ^{18}F-rhPSMA-7, ^{18}F-labelled radiohybrid prostate-specific membrane antigen; G1, grade 1; ^{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; GEP, gastroenteropancreatic; HL, Hodgkin lymphoma; HPV, human papillomavirus; HR, hazard ratio; HRQoL, health-related quality of life; ILAE, International League Against Epilepsy; ^{131}I-MIBG, ^{131}I-meta-iodobenzylguanidine; -LR, negative likelihood ratio; +LR, positive likelihood ratio; LRRFS, locoregional relapse-free survival; MEG, magnetoencephalography; mpMRI, multiparametric magnetic resonance imaging; MRI, magnetic resonance imaging; NA, not applicable; NET, neuroendocrine tumour; NHL, non-Hodgkin lymphoma; NPV, negative predictive value; NSCLC, non-small-cell lung carcinoma; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PHOX2B, paired-like homeobox 2b; PPV, positive predictive value; PSA, prostate-specific antigen; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RCT, randomized controlled trial; SCLC, small cell lung cancer; Sens, sensitivity; Spec, specificity; SPUtNIk, Single Pulmonary Nodule Investigation; TBNA, transbronchial needle aspirate; ^{99m}Tc-MDP, Technetium 99m-methyl diphosphonate; TNM, tumour, node, metastasis; US, ultrasonography; VALSG, Veterans Administration Lung Cancer Study Group