PET Six-Month Monitoring Report 2019-1

Evidence from Primary Studies and Systematic Reviews and Recommendations from Clinical Practice Guidelines January to June 2019

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QUESTION

What is the role of positron emission tomography (PET) in the clinical management of patients with cancer, sarcoidosis, or epilepsy 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, or epilepsy. 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 17th 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 2019 were systematically searched through MEDLINE and EMBASE for evidence from primary studies and systematic reviews. The search strategies used are available upon request to the PEBC.

Inclusion Criteria for Clinical Practice Guidelines

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

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

Inclusion Criteria for Primary Studies

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

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

Inclusion Criteria for Systematic Reviews

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

Exclusion Criteria

1. Letters and editorials.

RESULTS

Literature Search Results

Primary Studies and Systematic Reviews

Seventy-one studies published between January and June 2019 met the inclusion criteria. A summary of the evidence from the 71 studies can be found in **Appendix 1: Summary of studies from January to June 2019**.

Breast Cancer

Six studies met the inclusion criteria [1-6]. One study compared the N- and M-staging performance of FDG PET/CT and FDG PET/magnetic resonance imaging (MRI). There were no remarkable differences between the two imaging modalities, with the exception of bone metastases where FDG PET/CT was found to be more specific (100% vs. 95%, p=0.0081) but less sensitive (69% vs. 92%, p=0.0034) than FDG PET/MRI [1]. For axillary lymph node staging, FDG PET/CT demonstrated moderate to high accuracy (74.1% to 88.0) [2,3]. As shown in a number of studies, FDG PET/CT was superior to conventional imaging methods in the assessment of recurrent or metastatic breast cancer [4-6].

Epilepsy

One study met the inclusion criteria [7]. Results from a retrospective review showed that of the 17 patients with concordant FDG PET/CT and video-electroencephalography who underwent surgical resection, 35.3% became seizure-free or had improvement in seizure frequency without the need for intracranial electroencephalography.

Esophageal Cancer

Four studies met the inclusion criteria [8-11]. In the restaging of patients with esophageal cancer after neodjuvant therapy, FDG PET/CT demonstrated low sensitivity (pooled estimate, 53%) but high specificity (pooled estimate, 96%) for assessing lymph node metastases [8]. FDG PET/CT also performed suboptimally for T staging (accuracy, 68.2%) [9]. However, FDG PET or PET/CT was able to detect distant interval metastases in 8-9.5% of patients [10,11].

Gastrointestinal Cancer

Seven studies met the inclusion criteria [12-18]. In gastric cancer, one study found FDG PET/MRI to be superior or comparable to FDG PET/CT in the T- and N-staging of patients [12], while another study showed high sensitivity (79%) and specificity (91%) for FDG PET/CT in predicting the curability of endoscopic submucosal dissection [13]. In patients with obstructive colorectal cancer, FDG PET/CT had high specificity but low sensitivity for detecting synchronous advanced lesions (sensitivity, 53.8%; specificity, 93.2%) and invasive cancers (sensitivity, 66.6%; specificity, 89.4%) [14]. For the detection of colorectal liver metastases in patients eligible for local treatment, MRI performed significantly better than both FDG PET/CT and contrast-enhanced CT [15]. In older Chinese patients with hilar cholangiocarcinoma, preoperative FDG PET/CT offered modest diagnostic accuracy in identifying lymph node metastases (77.4%), distant metastases (81.1%), and unresectable tumours (77.4%) [16]. In the preoperative assessment of patients with peritoneal disease who are being considered for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, FDG PET/CT affected management in 36.2% of patients by providing definitive answers for indeterminate lesions seen on CT and MRI [17]. In patients with hepatocellular carcinoma awaiting liver transplantation, FDG PET/CT (accuracy, 93.0%) performed better than contrast-enhanced CT (accuracy, 74.0%) in the detection of intrahepatic recurrence or

extrahepatic metastases following rising serum alpha-fetoprotein levels after locoregional therapy [18].

Genitourinary Cancer

Two studies met the inclusion criteria [19-20]. In patients with metastatic seminoma and residual masses after chemotherapy, FDG PET/CT has a low positive predictive value (PPV) (23%) for viable tumour [19]. In patients with suspected recurrent bladder cancer and/or upper urinary tract carcinoma, restaging with FDG PET/CT changed the management of 39.9% of cases [20].

Gynecologic Cancer

Three studies met the inclusion criteria [21-23]. In one RCT, patients with locally advanced cervical cancer who underwent FDG PET/CT plus CT of the abdomen and pelvis for staging received more extensive chemoradiotherapy or palliative treatment than those who underwent staging with CT alone (39.3% vs. 25.0%; odds ratio [OR], 2.05; 95% confidence interval [CI], 0.96 to 4.37; p=0.06). However, the difference was not significant because the trial was underpowered [21]. FDG PET/CT was particularly useful for assessing distant disease and evaluating nodal involvement in patients with stage IIIB cervical cancer by altering the stage and/or management of 39.8% cases [22]. In patients with ovarian cancer, pretreatment FDG PET/CT demonstrated moderate sensitivity (pooled estimate, 72%) but high specificity (pooled estimate, 93%) for identifying the presence of metastasis [23].

Head and Neck Cancer

Nine studies met the inclusion criteria [24-32]. Results from the ACRIN 6685 trial showed that FDG PET/CT has a high negative predictive value (NPV) (86.8%) for the evaluation of clinically N0 head and neck squamous cell carcinoma. Subsequently, surgeons changed treatment plans according to FDG PET/CT findings in 21.5% of patients [24]. A systematic review and meta-analysis also reported similar NPVs for FDG PET or PET/CT in this clinical setting based on a per-patient (pooled estimate, 83%), per-neck side (pooled estimate, 81%), and per-level (pooled estimate, 96%) analysis [25]. For patients with high-risk head and neck squamous cell carcinoma, FDG PET/CT provided high specificity (96.4%) but limited sensitivity (46.2%) in determining the presence of distant metastases [26]. For the detection of locoregional recurrence, FDG PET/CT was superior to CT [27] and comparable to MRI [27,28]. In differentiated thyroid cancer patients with progressively and/or persistently elevated thyroglobulin antibody levels and negative radioactive iodine whole body scan, FDG PET/CT demonstrated moderate sensitivity (pooled estimate, 84%) and specificity (pooled estimate, 78%) for identifying recurrent and/or metastatic disease [29]. In asymptomatic patients with sinonasal cancer, FDG PET/CT is a suitable post-treatment surveillance tool for discovering local recurrence (sensitivity, 84%; specificity, 95%), regional nodal metastases (sensitivity, 91%; specificity, 99%), and distant metastases (sensitivity, 81%; specificity, 99%) [30]. In patients with oropharyngeal cancer treated with radiotherapy with or without concurrent systemic therapy, FDG PET/CT is an improvement over MRI in detecting residual disease [31]. Likewise, FDG PET/CT is highly sensitive (92.3%) for the diagnosis and highly accurate (90.4%) for the preoperative staging of tongue squamous cell carcinoma [32].

Hematologic Cancer

Five studies met the inclusion criteria [33-37]. Two phase II trials examined the interim PET response-adapted strategy in patients with advanced stage Hodgkin lymphoma [33,34]. In the GOELAMS LH 2007 trial, patients with a positive interim FDG PET/CT scan after two cycles of front-line vindesine, doxorubicin, carmustine, etoposide, and

methylprednisolone (VABEM) and switched to salvage therapy followed by high-dose therapy and autologous stem cell transplantation achieved similar five-year overall survival (OS) (88.2% vs. 91.7%, respectively) as patients with a negative interim FDG PET/CT scan who received one additional course of VABEM [33]. In the GITIL/FIL HD 0607 trial, the addition of rituximab to escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone after two cycles of standard doxorubicin, vinblastine, vincristine, and dacarbazine (ABVD) did not improve the three-year progression-free survival (PFS) and OS of interim-PET positive patients. Furthermore, consolidation radiotherapy given at the end of six cycles of ABVD to PET-negative patients with a large nodal mass did not improve the three-year PFS and OS over no treatment [34]. In aggressive non-Hodgkin lymphoma, a multicentre, randomized phase III trial (PETAL) assessed whether interim-PET response can guide therapy in patients treated with two cycles of cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (R-CHOP). For interim-PET positive patients, switching from R-CHOP to the Burkitt protocol did not improve the two-year event-free survival (EFS) (hazard ratio [HR], 1.501; 95% CI, 0.896 to 2.514; p=0.1229) and OS (HR, 1.349; 95% CI, 0.756 to 2.406; p=0.3085) and was associated with higher toxicity. Likewise for interim-PET negative patients, exposure to two additional doses of rituximab did not improve the two-year EFS (HR, 1.048; 95% CI, 0.684 to 1.606; p=0.8305) and OS (HR, 0.876; 95% CI, 0.508 to 1.513; p=0.6351) [35]. Moreover, one study with T-cell lymphoma patients showed a higher sensitivity for FDG PET/CT (89.3%) than bone marrow biopsy (60.7%) for identifying bone marrow involvement while maintaining high specificity (100%) [36]. In contrast, another study reported poor sensitivity (58.3% to 65.2%) and moderate specificity (77.8% to 85.3%) for bone marrow involvement [37].

Neuro-oncology

One study met the inclusion criteria [38]. In a meta-analysis of patients with gliomas and metastatic brain tumours, gadolinium-enhanced MRI (pooled diagnostic OR [DOR], 2.2) and FDG PET or PET/CT (pooled DOR, 2.4) were the least accurate in differentiating between radiation necrosis and tumour progression.

Non-FDG Tracers

Twenty studies met the inclusion criteria [39-58]. Two of the studies evaluated ^{18}F-fluorocholine PET/CT while three studies looked at ^{11}C/^{18}F-choline PET/CT in prostate cancer. In patients with intermediate- or high-risk features, ^{18}F-fluorocholine PET/CT performed suboptimally in the initial staging of lymph node metastases [39,40], but was superior to whole-body bone scintigraphy in detecting bone metastases (sensitivity, 100% vs. 37.5%, p=0.63; specificity, 96.3% vs. 85.2%, p=0.002) [39]. Nevertheless, clinical management was changed in 11.8% of patients [40]. Similarly, ^{11}C-choline PET/CT also performed suboptimally in detecting the sites of nodal relapse in patients with biochemical recurrence of prostate cancer [41]. Overall, ^{11}C/^{18}F-choline PET/CT showed excellent diagnostic performance for the detection of bone metastases (pooled sensitivity, 89% to 91%; pooled specificity, 97% to 98%) [42] and performed better than MRI in the evaluation of lymph node metastases (pooled sensitivity, 51% vs. 39%, p<0.05; pooled specificity, 92% vs. 87%, p<0.05) [43]. PET or PET/CT imaging with ^{68}Ga-DOTA-TATE/NOC/TOC was investigated in three studies, one in neuroendocrine tumours, one in pulmonary carcinoid, and the third in medullary thyroid cancer. The Society of Nuclear Medicine and Molecular Imaging advocated for 12 scenarios where the use of somatostatin receptor PET in patients with neuroendocrine tumours would be appropriate based on a multidisciplinary panel RAND/UCLA analysis (see Appendix 1A) [44]. A meta-analysis found that ^{68}Ga-DOTA-TATE/NOC/TOC (90.0%) was more sensitive than FDG PET/CT (71.0%) in the diagnosis of pulmonary carcinoid [45]. In regard to patients with

biochemical or metastatic medullary thyroid cancer, ^{68}Ga-DOTA-TATE PET/CT provided poor sensitivity for detecting cervical lymph node metastases (63%), lung metastases (63%), and liver metastases (9%). However, ^{68}Ga-DOTA-TATE PET/CT was superior to bone scan in identifying bone metastases, which primarily resulted in management changes in 20% of patients [46]. Results from the IDEAS trial demonstrated that amyloid PET was associated with a change in clinical management in 60.2% of patients with mild cognitive impairment and 63.5% of patients with dementia of uncertain etiology [47]. The utility of ^{68}Ga-PSMA PET/CT or PET/MRI in prostate cancer was examined in several studies. Prior to definitive treatment, ^{68}Ga-PSMA PET/CT detected lymph node metastases with high specificity (93.5% to 99.5%) but poor sensitivity (24.4% to 38.2%) [48]. ^{68}Ga-PSMA PET/CT or PET/MRI impacted management in 18.3% to 53.3% of patients [49,50]. In the setting of biochemical recurrence, ^{68}Ga-PSMA PET/CT or PET/MRI established high PPV (84% to 92%) for the localization of recurrent disease [51]. ^{68}Ga-PSMA PET/CT prompted a change in management in 19.3% to 56.8% of patients [52-54]. When ^{68}Ga-PSMA PET/CT was performed for a variety of indications, it detected bone metastases with significantly greater accuracy than whole-body MRI (100% vs. 82%, p=0.004) [55]. Overall, the pooled proportion of management changes due to ^{68}Ga-PSMA PET/CT was 54% [56]. The utility of ^{18}F-NaF PET/CT to detect bone metastases was also evaluated in prostate cancer in one study. The authors found no significant differences in diagnostic performances between ^{18}F-NaF PET/CT and whole-body MRI [55]. For detecting recurrent glioma, ^{18}F-DOPA PET/CT offered increased sensitivity as compared with contrast-enhanced MRI [57]. In patients with medullary thyroid carcinoma, ^{18}F-DOPA PET/CT uncovered mediastinal lymph node and distant metastases that were not evident on neck ultrasound in 12% of patients [58].

Non-Small Cell Lung Cancer and Other Lung Cancer

Five studies met the inclusion criteria [59-63]. In patients with solitary or indeterminate pulmonary nodules, FDG PET/CT was capable of ruling in malignancy (sensitivity, 79.0 to 98.4%), but was unreliable in ruling out malignancy (specificity, 39.8 to 81.8%) [59-61]. For primary and locoregional lymph node staging of non-small cell lung cancer (NSCLC), FDG PET/CT and FDG PET/MRI performed equally well [62]. For TNM stage assessment of small cell lung cancer (SCLC), FDG PET/CT performed superiorly to conventional staging (accuracy, 88.1% vs. 72.9%; p=0.004) [63].

Pancreatic Cancer

One study met the inclusion criteria [64]. The sensitivity (92.7% vs. 88.5%, p=0.01), specificity (75.8% vs. 70.6%, p=0.023) and NPV (92.0% vs. 87.1%, p=0.031) of FDG PET/CT in the diagnosis of pancreatic cancer were significantly higher than those of multidetector CT, respectively. FDG PET/CT correctly changed the staging in 14.2% of patients and was perceived to have changed 45.5% of the planned management.

Pediatric Cancer

One study met the inclusion criteria [65]. From the prospective AIEOP-LH2004 trial that investigated FDG PET or PET/CT in pediatric Hodgkin lymphoma with bulky masses, PET-negative patients experienced a significantly longer time-to-progression than PET-positive patients at response assessment after four cycles of cyclophosphamide, vincristine, procarbazine, prednisolone, adriamycin, bleomycin, and vinblastine (COPP/ABV) (32.7 months vs. 23.8 months; p<0.0001), after the end of chemotherapy (38.9 months vs. 34.2 months; p<0.0001), and after radiation treatment (43.4 months vs. 21.4 months; p<0.0001).

Sarcoma

One study met the inclusion criteria [66]. Performing FDG PET/CT for early evaluation of response to neoadjuvant imatinib led to a 25.7% change in management in gastrointestinal stromal tumour patients.

Unknown Primary

Two studies met the inclusion criteria [67-68]. FDG PET/CT is able to accurately (98.3%) diagnose malignant tumours in patients with unknown source of elevated serum carcinoembryonic antigen (CEA) level [67]. In patients with brain metastasis, FDG PET/CT did not provide significant advantage over contrast-enhanced CT in localizing the primary lesion but could detect additional extracranial metastases in 43.8% of patients [68].

CLINICAL EXPERT REVIEW

Breast Cancer

- No recommendations currently exist for the utilization of PET/CT in breast cancer.

Reviewer's Comments (Dr. Muriel Brackstone)

There is currently not enough evidence to support making appropriate recommendations for the use of PET/CT in breast cancer as we are awaiting the completion of the PET ABC trial.

Epilepsy

Current Registry Indication

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

Current Recommendations for the Utilization of PET in Epilepsy

- ^{18}F-FDG PET is recommended for the presurgical evaluation of adult and pediatric patients with medically intractable focal or partial epilepsy in the setting of a comprehensive epilepsy surgery program within a Regional Epilepsy Surgery Centre of Excellence.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of ^{18}F-FDG PET in the detection of cortical malformations in patients with intractable infantile spasms when MRI or CT fails to show structural abnormalities.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of ^{18}F-FDG PET/MRI coregistration in the presurgical evaluation of patients with medically intractable epilepsy.

Reviewer's Comments (Dr. Jorge Burneo)

The current recommendations for the utilization of PET/CT in epilepsy remain valid and no changes are required. The one reference identified was not a Class I study.

Esophageal Cancer

Current Insured Indications

- For baseline staging assessment of patients diagnosed with esophageal cancer who are being considered for curative therapy, and/or repeat PET/CT scan on completion of preoperative/neoadjuvant therapy, prior to surgery.

Current Recommendations for the Utilization of PET/CT in Esophageal Cancer

- For the staging work-up of patients with esophageal cancer who are potential candidates for curative therapy, PET is recommended to improve the accuracy of M staging.

- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET (post-therapy or neoadjuvant therapy) for the purpose of predicting response to neoadjuvant therapy.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET for the evaluation of suspected recurrence.

Reviewer's Comments

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

Gastrointestinal Cancer

Current Insured Indications (Colorectal Cancer)

- Where recurrent disease is suspected on the basis of elevated and/or rising CEA level(s) during follow-up after surgical resection but standard imaging tests are negative or equivocal; or prior to surgery for liver metastases from colorectal cancer when the procedure is high risk (e.g., multiple-staged liver resection or vascular reconstruction); or where the patient is at high risk for surgery (e.g., American Society of Anesthesiology score ≥4).

Current Registry Indication (Anal Canal Cancer)

- For the initial staging of patients with T2-T4 squamous cell carcinoma of the anal canal with or without evidence of nodal involvement on conventional anatomical imaging.

Current Recommendations for the Utilization of PET/CT in Colorectal Cancer

- The routine use of PET is not recommended for the diagnosis or staging of clinical stage I to III colorectal cancers.
- PET is recommended for determining management and prognosis if conventional imaging is equivocal for the presence of metastatic disease.
- The routine use of PET is not recommended for the measurement of treatment response in locally advanced rectal cancer before and after preoperative chemotherapy.
- PET is not recommended for routine surveillance in patients with colorectal cancer treated with curative surgery who are at high risk for recurrence.
- PET is recommended to determine the site of recurrence in the setting of rising CEA levels, when a conventional work-up fails to unequivocally identify metastatic disease.
- PET is recommended in the preoperative assessment of colorectal cancer liver metastasis prior to surgical resection.

Current Recommendations for the Utilization of PET/CT in Anal Canal Cancer

- PET or PET/CT may provide added benefit to the initial staging of patients with T2-4 squamous carcinoma of the anal canal with or without evidence of nodal involvement on anatomical imaging. However, no strong evidence is currently available to justify its use as part of routine investigation, and access should be restricted to the registry-type setting.
- There is insufficient evidence to recommend the use of PET or PET/CT in the assessment of treatment response.
- There is insufficient evidence to recommend the use of PET or PET/CT for evaluation of suspected or proven recurrence.

Reviewer's Comments

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

Genitourinary Cancer

Current Insured Indications (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 Recommendations for the Utilization of PET/CT in Testicular Cancer

- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET in the routine staging of patients with testicular cancer.
- PET is recommended for the assessment of treatment response in patients with seminoma and residual masses after chemotherapy.
- PET is not recommended for the assessment of treatment response in patients with nonseminoma.
- Due to insufficient evidence, a recommendation cannot be made for or against the routine use of PET for evaluation of recurrence.

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 number of patients in the study by Cathomas et al. [19] was small but it may be worthwhile to look at the other evidence base supporting the current guideline to see if the size of this series is enough to revisit the recommendation for evaluating residual masses in seminoma.

Gynecologic Cancer

Current Insured Indication

- 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 restaging of patients with recurrent gynecologic malignancies under consideration for radical salvage surgery (e.g., pelvic exenteration).

Current Recommendations for the Utilization of PET/CT in Cervical Cancer

- PET is not recommended for diagnosis of cervical cancer.
- PET is not recommended for staging early-stage cervical cancer.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET for staging advanced-stage cervical cancer. However, ongoing studies will clarify the role of PET in advanced disease.
- PET is not recommended (following or early during therapy) for the purpose of predicting response to chemoradiation therapy.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET for evaluation of suspected recurrence.
- PET is recommended for women with recurrence who are candidates for pelvic exenteration or chemoradiation with curative intent.

Current Recommendations for the Utilization of PET/CT in Ovarian Cancer

- PET is not recommended in the diagnosis of ovarian cancer.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET in the evaluation of asymptomatic ovarian mass.
- PET is not recommended for staging of ovarian cancer.
- PET is not recommended for detecting recurrence or restaging patients not being considered for surgery.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET for patients being considered for secondary cytoreduction.

Reviewer's Comments (Dr. Anthony Fyles)

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

Head and Neck Cancer

Current Insured Indication (Unknown Primary)

- For the evaluation of metastatic squamous cell carcinoma in neck nodes when the primary disease site is unknown after standard radiological and clinical investigation.

Current Insured Indication (Nasopharyngeal Cancer)

- For the baseline staging of nasopharyngeal cancer.

Current Insured Indication (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.

Current Recommendations for the Utilization of PET/CT in Head and Neck Cancer

- PET is recommended in the M and bilateral nodal staging of all patients with head and neck squamous cell carcinoma where conventional imaging is equivocal, or where treatment may be significantly modified.
- PET is recommended in all patients after conventional imaging and in addition to, or prior to, diagnostic panendoscopy where the primary site is unknown.
- PET is recommended for staging and assessment of recurrence of patients with nasopharyngeal carcinoma if conventional imaging is equivocal.
- PET is recommended for restaging patients who are being considered for major salvage treatment, including neck dissection.

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 Registry Indication (Lymphoma)

- For the staging of patients with Hodgkin or non-Hodgkin lymphoma.

Current Registry Indications (Multiple Myeloma/Plasmacytoma)

- For patients with presumed solitary plasmacytoma who are candidates for curative intent radiotherapy; or for work-up of patients with smoldering myeloma and negative

or equivocal skeletal survey; or for baseline staging and/or response assessment of nonsecretory or oligosecretory myeloma.

Current Insured Indications (Lymphoma)

- For the evaluation of residual mass(es) following chemotherapy in a patient with Hodgkin or non-Hodgkin lymphoma when further potentially curative therapy (such as radiation or stem cell transplantation) is being considered; or for the assessment of response in Hodgkin lymphoma following two or three cycles of chemotherapy when chemotherapy curative therapy is being considered.

Current Recommendations for the Utilization of PET/CT in Hematologic Cancer

- When functional imaging is considered to be important in situations where anatomical imaging is equivocal, and/or in potentially curable cases, a FDG PET/CT scan is recommended.
- When functional imaging is considered to be important in situations where anatomical imaging is equivocal and treatment choices may be affected in limited-stage indolent lymphomas, a FDG PET/CT scan is recommended.
- An FDG PET/CT scan is recommended for the assessment of early response in early stage (I or II) Hodgkin lymphoma following two or three cycles of chemotherapy when chemotherapy is being considered as the definitive single-modality therapy, to inform completion of therapy, or to determine whether more therapy is warranted.
- In potentially curable cases, when functional imaging is considered to be important and conventional imaging is equivocal, a FDG PET/CT scan is recommended to investigate recurrence of Hodgkin or non-Hodgkin lymphoma.
- An FDG PET/CT scan is recommended for the evaluation of residual mass(es) following chemotherapy in a patient with Hodgkin or non-Hodgkin lymphoma when further potentially curative therapy (such as radiation or stem cell transplantation) is being considered and when biopsy cannot be safely or readily performed.
- An FDG PET/CT scan is not recommended for the routine monitoring and surveillance of lymphoma.

Reviewer's Comments (Dr. Marc Freeman)

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

Melanoma

Current Registry Indication

- For the staging of melanoma patients with localized "high-risk" tumours with potentially resectable disease; or for the evaluation of patients with melanoma and isolated metastasis at the time of recurrence when metastasectomy is being contemplated.

Current Recommendations for the Utilization of PET/CT in Melanoma

- PET is recommended for staging of high-risk patients with potentially resectable disease.
- PET is not recommended for the diagnosis of sentinel lymph node micrometastatic disease or for staging of I, IIa, or IIb melanoma.
- The routine use of PET or PET/CT is not recommended for the diagnosis of brain metastases.

- The routine use of PET is not recommended for the detection of primary uveal malignant melanoma.
- A recommendation cannot be made for or against the use of PET for the assessment of treatment response in malignant melanoma due to insufficient evidence.
- A recommendation cannot be made for or against the use of PET for routine surveillance due to insufficient evidence.
- PET is recommended for isolated metastases at time of recurrence or when contemplating metastasectomy.

Reviewer's Comments (Dr. Tara Baetz)

The current recommendations for the utilization of PET/CT in melanoma remain valid and no changes are required. The data from Poulsen et al. [40] do support staging for high-risk patients with Merkel cell carcinoma with PET/CT but this is not a standard indication.

Neuro-oncology

Current Recommendations for the use of PET/CT in Neuro-oncology

- PET is not recommended for the determination of diagnosis or grading in gliomas.
- A recommendation cannot be made for or against the use of PET for the assessment of treatment response in gliomas due to insufficient evidence.
- A recommendation cannot be made for or against the use of PET or PET/CT in the assessment of patients with recurrent gliomas due to insufficient evidence.

Reviewer's Comments (Dr. Amit Singnurkar)

The current recommendations for the utilization of PET/CT in neuro-oncology remain valid and no changes are required. However, new tracers such as ^{18}F-FET, ^{11}C-MET, and ^{18}F-DOPA now have societal endorsement for clinical use in brain tumours.

Non-FDG Tracers

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

- ^{68}Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT is recommended for the initial diagnosis of adult patients with clinical (e.g., signs, symptoms) and biochemical (e.g., markers) suspicion of neuroendocrine tumours but for whom conventional imaging is negative or equivocal or for whom biopsy is not easily obtained.
- ^{68}Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT is recommended for the staging of adult patients with localized primary neuroendocrine tumours and/or limited metastasis where definitive surgery is planned.
- ^{68}Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT is recommended for determining somatostatin receptor status and suitability for peptide receptor radionuclide therapy.
- ^{68}Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT is recommended for the staging of adult patients with neuroendocrine tumours where detection of occult disease will alter the treatment options and decision making.
- There is no recommendation regarding the use of ^{68}Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT in the assessment of treatment response for neuroendocrine tumours.
- There is no recommendation regarding the use of ^{68}Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT in the routine surveillance of neuroendocrine tumours.

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. PSMA agents have gained widespread acceptance

and are currently being used in Ontario. IDEA trial data are being considered in the dementia Working Group.

NSCLC and Other Lung Cancer

Current Insured Indications

- 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.
- NSCLC:
    - For initial staging of patients with NSCLC (clinical stage I-III) who are being considered for potentially curative therapy; or for restaging of patients with locoregional recurrence, after primary treatment, who are being considered for definitive salvage therapy.

- SCLC:
    - For initial staging of patients with limited-disease SCLC where combined modality therapy with chemotherapy and radiotherapy is being considered.

Current Recommendations for the Utilization of PET/CT in SCLC

- PET is recommended for staging in patients with SCLC who are potential candidates for the addition of thoracic radiotherapy to chemotherapy.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET for the assessment of treatment response in SCLC.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET for evaluation of recurrence or restaging.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET when metastasectomy or stereotactic body radiation therapy is being contemplated for solitary metastases.

Current Recommendations for the Utilization of PET/CT in Radiation Treatment Planning for Lung Cancer

- Combination PET/CT imaging data may be used as part of research protocols in radiation treatment planning. Current evidence does not support the routine use of PET/CT imaging data in radiation treatment planning at this time outside of a research setting.

Reviewer's Comments (Dr. Donna Maziak)

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

Pancreatic Cancer

Current Recommendations for the Utilization of PET/CT in Pancreatic Cancer

- PET is not recommended for primary diagnosis of pancreatic cancer.
- PET is recommended for staging if a patient is a candidate for potentially curative surgical resection as determined by conventional staging.

- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET to guide clinical management based on assessment of treatment response.
- Due to insufficient evidence and lack of effective therapeutic options, PET is not recommended for clinical management of suspected recurrence, or for restaging at the time of recurrence.
- A recommendation cannot be made for or against the use of PET for staging if a solitary metastasis is identified at recurrence because there are no trials that identify the utility of PET scanning in this setting.

Reviewer's Comments (Dr. Jim Biagi)

The current recommendations for the utilization of PET/CT in pancreatic cancer remain valid and no changes are required. The study by Ghaneh et al. [64] strengthens the staging recommendation and also makes a cost-effectiveness argument which, considering the similarities between Britain and Canada, could be worth emphasizing.

Pediatric Cancer

Current Registry Indications (patients must be <18 years of age)

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

Reviewer's Comments

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

Sarcoma

Current Registry Indication

- Diagnosis (plexiform neurofibromas): for patients with suspicion of malignant transformation of plexiform neurofibromas.
- Initial Staging: 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.
- Re-staging: 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 DiPrimio)

The current recommendations for the utilization of PET/CT in sarcoma remain valid and no changes are required. Although the study by Farag et al. [66] showed that PET/CT may affect management, there is not enough cumulative evidence currently to suggest that this is the standard of care for follow-up of gastrointestinal stromal tumours or other tumours.

Unknown Primary Cancer

No recommendations currently exist for the utilization of PET/CT in unknown primary cancer.

Reviewer's Comments (Dr. Amit Singnurkar)

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Appendix 1: Summary of studies from January to June 2019.

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Breast Cancer								
Botsikas et al, 2019 [1]	Prospective	80 patients (newly diagnosed or recurrent breast cancer)	FDG PET/CT, FDG PET/MRI	NA	Biopsy, pathology, clinical and imaging follow-up	**Bone metastases (lesion-based)** ***PET/CT*** Sens: 69%‡ Spec: 100%‡ PPV: 100% NPV: 95% ***PET/MRI*** Sens: 92%‡ Spec: 95%‡ PPV: 77% NPV: 99% **(patient-based)** ***PET/CT*** Sens: 67% Spec: 100% PPV: 100% NPV: 96% ***PET/MRI*** Sens: 89% Spec: 97% PPV: 80% NPV: 99% **Contralateral tumours (lesion-based)** ***PET/CT*** Sens: 25% Spec: 99% PPV: 50% NPV: 96% ***PET/MRI*** Sens: 100% Spec: 99% PPV: 80% NPV: 100% **(patient-based)** ***PET/CT*** Sens: 33% Spec: 99%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						PPV: 50% NPV: 97% ***PET/MRI*** Sens: 100% Spec: 99% PPV: 75% NPV: 100% **Axillary lymph nodes (lesion-based)** ***PET/CT*** Sens: 81% Spec: 92% PPV: 81% NPV: 92% ***PET/MRI*** Sens: 85% Spec: 89% PPV: 77% NPV: 93% **(patient-based)** ***PET/CT*** Sens: 83% Spec: 76% PPV: 83% NPV: 76% ***PET/MRI*** Sens: 87% Spec: 68% PPV: 78% NPV: 79% **Internal mammary lymph nodes (lesion-based)** ***PET/CT*** Sens: 90% Spec: 100% PPV: 100% NPV: 99% ***PET/MRI*** Sens: 90% Spec: 100% PPV: 100% NPV: 99% **(patient-based)** ***PET/CT***		

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Sens: 89% Spec: 100% PPV: 100% NPV: 99% ***PET/MRI*** Sens: 89% Spec: 100% PPV: 100% NPV: 99% **Mediastinal lymph nodes (lesion-based)** ***PET/CT*** Sens: 100% Spec: 100% PPV: 100% NPV: 100% ***PET/MRI*** Sens: 100% Spec: 100% PPV: 100% NPV: 100% **(patient-based)** ***PET/CT*** Sens: 100% Spec: 100% PPV: 100% NPV: 100% ***PET/MRI*** Sens: 100% Spec: 100% PPV: 100% NPV: 100%		
Orsaria et al, 2018 [2]	Prospective	50 patients undergoing preoperative staging (early primary unilateral, locally advanced, or recurrent invasive operable breast cancer)	FDG PET/CT	Mammography, US	Histopathology	**Axillary lymph node metastases** Sens: 86.7% Spec: 90.0% PPV: 92.9% NPV: 81.8% Accu: 88.0%	NA	NA
Kutluturk et	Retrospective	232 patients	FDG	SLNB and/or	Histopathology	**Axillary metastases**	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
al, 2019 [3]		who underwent staging prior to surgery (invasive breast cancer)	PET/CT	axillary dissection		Sens: 72.6% Spec: 77.9% PPV: 88.8% NPV: 54.0% Accu: 74.1%		
Sheng et al, 2019 [4]	Retrospective	87 patients who received treatment (breast cancer)	FDG PET/CT	CT, MRI, US	Pathology, imaging or clinical follow-up	**Lymphatic metastasis** Sens: 94.6%* Spec: 88.0% PPV: 85.4% NPV: 95.7%* Accu: 90.8%*	**Lymphatic metastasis** Sens: 73.0%* Spec: 84.0% PPV: 77.1% NPV: 80.8%* Accu: 79.3%*	NA
Rezk et al, 2019 [5]	Prospective	23 patients (suspected breast cancer recurrence)	FDG PET/CT	Whole body MRI-DWIBS	Pathology, clinical follow-up	**Local breast lesion** Sens: 77.8% Spec: 80.0% PPV: 87.5% NPV: 66.7% **Loco-regional lymph nodes** Sens: 89.5% Spec: 81.8% PPV: 89.5% NPV: 81.8% Accu: 85.4% **Distant lymph nodes** Sens: 86.2% Spec: 92.0% PPV: 92.6% NPV: 85.2% **Distant lesions** Sens: 83.6% Spec: 84.4% PPV: 90.2% NPV: 75.0%	**Local breast lesion** Sens: 88.9% Spec: 60.0% PPV: 80.0% NPV: 75.0% **Loco-regional lymph nodes** Sens: 84.2% Spec: 72.7% PPV: 84.2% NPV: 72.7% Accu: 80.5% **Distant lymph nodes** Sens: 82.8% Spec: 80.0% PPV: 82.8% NPV: 80.0% **Distant lesions** Sens: 80.0% Spec: 81.2% PPV: 88.0% NPV: 70.3%	NA
Guo et al, 2018 [6]	Retrospective	121 patients treated with primary surgery and received neoadjuvant therapy and/or adjuvant therapy (with or without clinically and/or	FDG PET/CT	Chest radiography, CT, bone scan, clinical examination, US, MRI, mammogram	Histology, clinical and/or imaging follow-up	**Locoregional recurrence** PPV: 91% NPV: 100%* +LR: 13.8 **Systemic recurrence** PPV: 92% NPV: 100%* +LR: 8.3	**Locoregional recurrence** PPV: 94% NPV: 78%* +LR: 21.8 **Systemic recurrence** PPV: 86% NPV: 68%* +LR: 4.6	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		radiologically suspicious findings for recurrent breast cancer)						
Epilepsy								
Chan et al, 2018 [7]	Retrospective	62 patients who underwent presurgical evaluation (refractory epilepsy)	FDG PET/CT	MRI, vEEG, iEEG	Follow-up, Engel's classification	NA	NA	Of the 36 patients with concordant PET and vEEG, 17 underwent surgical resection, of which 10 (5 with iEEG and 5 without) became seizure-free and 7 (6 with iEEG and 1 without) showed improvement in seizure frequency.
Esophageal Cancer								
Hu et al, 2018 [8]	Meta-analysis	14 studies (1142 patients with esophageal cancer)	FDG PET/CT	NA	Histopathology	**Lymph node metastases** ***Without neoadjuvant therapy*** Pooled Sens: 57% Pooled Spec: 91% Pooled +LR: 6.3 Pooled –LR: 0.47 Pooled DOR: 13 AUC: 0.83 ***With neoadjuvant therapy*** Pooled Sens: 53% Pooled Spec: 96% Pooled +LR: 13.0 Pooled –LR: 0.49 Pooled DOR: 26 AUC: 0.82	NA	NA
Tamandl et al, 2019 [9]	Retrospective	88 patients who underwent restaging after neoadjuvant chemotherapy or chemoradiotherapy before curative surgical	FDG PET/CT	CeCT	Histopathology	**T stage** Sens: 81.1% PPV: 81.1% Accu: 68.2% **N stage** Sens: 70.2% PPV: 93.7% Accu: 67.0%	**T stage** Sens: 78.8% PPV: 70.2% Accu: 59.0% **N stage** Sens: 59.5% PPV: 75.9% Accu: 50.0%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		resection (locally advanced esophageal cancer)						
Kroese et al, 2018 [10]	Meta-analysis	14 studies (1110 patients with esophageal cancer who received baseline staging and restaging after neoadjuvant therapy)	FDG PET or PET/CT	NA	Pathology, clinical follow-up	**Distant interval metastases** Pooled TP: 8% Pooled FP: 5%	NA	NA
Noordman et al, 2018 [11]	Prospective	207 patients who were eligible for potential curative therapy with neoadjuvant chemoradiotherapy followed by oesophagectomy (histologically proven, resectable, squamous cell carcinoma or adenocarcinoma of the oesophagus or oesophagogastric junction)	FDG PET/CT	Endoscopy with regular biopsies and FNA, endoscopy with bite-on-bite biopsies and FNA, endoscopic US with maximum tumour thickness	Pathology	**Residual disease after neoadjuvant chemoradiotherapy (second clinical response evaluation)** FN: 14%	**Residual disease after neoadjuvant chemoradiotherapy (first clinical response evaluation)** ***Endoscopy with regular biopsies and FNA*** FN: 31% ***Endoscopy with bite-on-bite biopsies and FNA*** FN: 11% **(second clinical response evaluation)** ***Endoscopic US with maximum tumour thickness*** FN: 29%	PET/CT detected interval distant metastases in 9.5% (18/190) of patients.
Gastrointestinal Cancer								
Liu et al, 2019 [12]	Prospective	30 patients who underwent pretreatment staging (gastric cancer)	FDG PET/CT, FDG PET/MRI	NA	Pathology, clinical and imaging follow-up	**T1 staging** ***PET/CT*** Sens: 60% Spec: 95% Accu: 88% AUC: 0.78 ***PET/MRI*** Sens: 100%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Spec: 100% Accu: 100% AUC: 1.00 **T2 staging** ***PET/CT*** Sens: 50% Spec: 82% Accu: 77% AUC: 0.66 ***PET/MRI*** Sens: 50% Spec: 95% Accu: 88% AUC: 0.73 **T3 staging** ***PET/CT*** Sens: 25% Spec: 89% Accu: 69% AUC: 0.57 ***PET/MRI*** Sens: 50% Spec: 94% Accu: 81% AUC: 0.72 **T4 staging** ***PET/CT*** Sens: 89% Spec: 75% Accu: 77% AUC: 0.83 ***PET/MRI*** Sens: 100% Spec: 75% Accu: 81% AUC: 0.88 **N0 staging** ***PET/CT*** Sens: 73% Spec: 73% Accu: 73% AUC: 0.73 ***PET/MRI*** Sens: 73% Spec: 93% Accu: 85%		

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						AUC: 0.83 **N1 staging** ***PET/CT*** Sens: 25% Spec: 82% Accu: 73% AUC: 0.53‡ ***PET/MRI*** Sens: 25% Spec: 100% Accu: 88% AUC: 0.63‡ **N2 staging** ***PET/CT*** Sens: 20% Spec: 67% Accu: 58% AUC: 0.57 ***PET/MRI*** Sens: 20% Spec: 76% Accu: 65% AUC: 0.52 **N3 staging** ***PET/CT*** Sens: 0% Spec: 95% Accu: 73% AUC: 0.53 ***PET/MRI*** Sens: 67% Spec: 70% Accu: 69% AUC: 0.68		
Chung et al, 2019 [13]	Retrospective	199 patients who underwent initial routine staging (newly diagnosed gastric cancer)	FDG PET/CT	Endoscopy	Pathology	**Predicting curability of endoscopic submucosal dissection** Sens: 79% Spec: 91% PPV: 81% NPV: 89% AUC: 0.85	NA	NA
Maeda et al, 2019 [14]	Retrospective	72 patients who underwent	FDG PET/CT	Total colonoscopy	Follow-up	**Synchronous colon lesions**	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		surgical resection (obstructive colorectal cancer)				Sens: 53.8% Spec: 93.2% PPV: 63.6% NPV: 90.2% Accu: 86.1% **Synchronous invasive cancers** Sens: 66.6% Spec: 89.4% PPV: 36.4% NPV: 96.7% Accu: 87.5%		
Sivesgaard et al, 2018 [15]	Prospective	80 patients who are eligible for hepatic resection and/or local ablation (colorectal cancer liver metastases)	FDG PET/CT	MRI, CeCT	Histopathology, intra-operative findings, application of ablative therapy, appearance on consecutive standard-of-care CeCT scans, imaging follow-up	**Colorectal liver metastases (lesion-based)** Sens: 72.0-72.1%* Spec: 92.1-93.6% AUC: 0.83-0.84 **(segment-based)** Sens: 78.6-79.6%* Spec: 97.2-98.1% AUC: 0.90-0.91*	**Colorectal liver metastases (lesion-based)** ***MRI*** Sens: 83.8-85.9%* Spec: 91.5-92.6% AUC: 0.88-0.92 ***CeCT*** Sens: 62.3-69.1% Spec: 91.8-95.5% AUC: 0.80-0.82 **(segment-based)** ***MRI*** Sens: 88.8-90.2%* Spec: 97.2-97.6% AUC: 0.96* ***CeCT*** Sens: 68.6-78.1% Spec: 97.2-98.3% AUC: 0.89-0.90	NA
Li et al, 2018 [16]	Prospective	53 older Chinese patients who underwent preoperative evaluation (hilar cholangiocarcinoma)	FDG PET/CT	NA	Pathology	**Lymph node metastases** Sens: 67.9% Spec: 88.0% Accu: 77.4% **Distant metastases** Sens: 47.1% Spec: 97.2% Accu: 81.1% **Unresectable tumours** Sens: 73.9% Spec: 80.0% Accu: 77.4%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Wang et al, 2018 [17]	Retrospective	128 patients who are being considered for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (peritoneal metastases)	FDG PET/CT	MRI, CT	Histopathology, imaging follow-up	NA	NA	PET/CT provided definitive conclusions for indeterminate lesions seen on CT and/or MRI in 36.2% (33/91) of patients (15—spared from unnecessary surgery and referred for palliative therapy, 10—underwent successful cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, 8—surgical resection of primary disease without hyperthermic intraperitoneal chemotherapy)
Refaat et al, 2018 [18]	Prospective	100 patients with rising serum alpha-fetoprotein levels after loco-regional therapy awaiting liver transplantation (hepatocellular carcinoma)	FDG PET/CT	CeCT	Histopathology, clinical and imaging follow-up	**Recurrence** Sens: 92.8% Spec: 94.1% PPV: 98.7% NPV: 72.7% +LR: 15.77 -LR: 0.08 Accu: 93.0% AUC: 0.93	**Recurrence** Sens: 74.7% Spec: 70.6% PPV: 92.5% NPV: 36.4% +LR: 2.54 -LR: 0.36 Accu: 74.0% AUC: 0.73	NA
Genitourinary Cancer								
Cathomas et al, 2018 [19]	Retrospective	90 patients with PET-positive residual lesions after chemotherapy (metastatic seminoma)	FDG PET/CT	NA	Histology, clinical or imaging follow-up	**Viable tumour** PPV: 23%	NA	NA
Zattoni et al, 2019 [20]	Retrospective	286 patients who underwent disease restaging after primary treatment (suspicion of recurrent	FDG PET/CT	CeCT, MRI, chest x-ray	Clinical and imaging follow-up	NA	NA	Patient management was changed in 39.9% (114/286) of patients (33—received local therapies, 43—received chemotherapy, 33—received a combination of local and systemic

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		bladder cancer and/or upper urinary tract carcinoma)						therapy, 5—observed without any therapy)
Gynecologic Cancer								
Elit et al, 2018 [21]	RCT	171 patients who were candidates for chemotherapy and radiotherapy (newly diagnosed histologically confirmed FIGO stage IB-IVA carcinoma of the cervix)	FDG PET/CT	CT alone	Clinical follow-up	NA	NA	Patients who underwent PET/CT plus CT for staging received more extensive chemotherapy and radiotherapy or palliative treatment than those who underwent CT alone for staging (39.3% vs. 25.0%; OR=2.05; 95% CI: 0.96 to 4.37; p=0.06). The rates of potentially curative extended field radiotherapy to para-aortic nodes (21.4% vs. 14.3%) and common iliac nodes (12.5% vs. 5.4%) were higher in the PET/CT group (OR=1.64; 95% CI: 0.68 to 3.92; p=0.27). There were no significant differences in the 2-year EFS (HR=1.13; 95% CI: 0.64 to 1.99; p=0.66) and OS (HR=0.97; 95% CI: 0.49 to 1.93; p=0.93) between the PET/CT and CT alone groups.
Morkel et al, 2018 [22]	Retrospective	88 patients undergoing pretreatment staging (stage IIIB cervical carcinoma)	FDG PET/CT	Abdominal US, chest x-ray, pelvic MRI, chest CT, cystoscopy	Biopsy	NA	NA	Additional findings from PET/CT affected the management of 39.8% (35/88) of patients (17—change in radiation field, 18—upstaged to stage IV).
Han et al, 2018 [23]	Meta-analysis	8 studies (594 patients with clinically suspected or newly diagnosed ovarian cancer)	FDG PET or PET/CT	NA	Histopathology	**Metastases** Pooled Sens: 72% Pooled Spec: 93% Pooled +LR: 10.5 Pooled –LR: 0.30 AUC: 0.89	NA	NA
Head and Neck Cancer								

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Lowe et al, 2019 [24]	Prospective (ACRIN 6685 trial)	248 patients being considered for surgical resection (newly diagnosed T2-T4N0 head and neck squamous cell carcinoma)	FDG PET/CT	Physical examination, MRI and/or CT	Pathology	**N0 staging** NPV: 86.8%	NA	PET/CT findings changed the surgical treatment plans of 21.5% (51/237) of patients (34—dissection of additional nodal levels, 6—dissection of fewer nodal levels, 6—surgery cancelled, 4—both additional and fewer planned dissection of nodal levels, 1—unknown).
Kim et al, 2019 [25]	Meta-analysis	18 studies (1044 patients with clinically node negative head and neck squamous cell carcinoma)	FDG PET or PET/CT	NA	Histopathology	**Cervical lymph node metastases (patient-based)** Pooled Sens: 58% Pooled Spec: 87% Pooled PPV: 62% Pooled NPV: 83% Pooled +LR: 4.5 Pooled –LR: 0.49 Pooled DOR: 9 AUC: 0.84 **(neck side-based)** Pooled Sens: 67% Pooled Spec: 85% Pooled PPV: 68% Pooled NPV: 81% Pooled +LR: 4.5 Pooled –LR: 0.38 Pooled DOR: 12 AUC: 0.78 **(level-based)** Pooled Sens: 53% Pooled Spec: 97% Pooled PPV: 61% Pooled NPV: 96% Pooled +LR: 15.8 Pooled –LR: 0.49 Pooled DOR: 32 AUC: 0.92	NA	NA
Deurvorst et al, 2018 [26]	Retrospective	190 patients with high-risk factors for distant metastases (head and neck	FDG PET/CT	Panendoscopy, CeCT and/or MRI	Imaging follow-up, endoscopic work-up, biopsy, consensus from multidisciplinar	**Distant metastases** Sens: 46.2% Spec: 96.4% PPV: 82.8% NPV: 82.6%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		squamous cell carcinoma)			y team			
Kim et al, 2019 [27]	Retrospective	93 patients who underwent curative surgical treatment for loco-regional recurrence (head and neck cancer)	FDG PET/CT	CT, MRI	Histopathology, clinical and imaging follow-up	**Primary site recurrence (patient-based)** Sens: 97.5% Spec: 92.9% PPV: 98.7% NPV: 86.7% Accu: 96.8% AUC: 0.952* **Regional nodal recurrence (level-based)** Sens: 85.5% Spec: 94.9% PPV: 81.6% NPV: 96.1% Accu: 93.0% AUC: 0.902*	**Primary site recurrence (patient-based)** ***CT*** Sens: 89.9% Spec: 85.7% PPV: 97.3% NPV: 60.0% Accu: 89.3% AUC: 0.878* ***MRI*** Sens: 94.9% Spec: 85.7% PPV: 97.4% NPV: 75.0% Accu: 93.6% AUC: 0.903 **Regional nodal recurrence (level-based)** ***CT*** Sens: 66.3% Spec: 99.4% PPV: 96.5% NPV: 91.8% Accu: 92.4% AUC: 0.828* ***MRI*** Sens: 74.7% Spec: 99.4% PPV: 96.9% NPV: 93.7% Accu: 94.2% AUC: 0.870	NA
Driessen et al, 2019 [28]	Prospective	75 patients (clinical suspicion of local recurrent head and neck squamous cancer)	FDG PET/CT	DW-MRI	Histopathology, clinical and imaging follow-up	**Local recurrence** Sens: 97%* Spec: 46%* PPV: 64% NPV: 94% Accu: 72%	**Local recurrence** Sens: 69%* Spec: 77%* PPV: 75% NPV: 71% Accu: 73%	NA
Kim et al, 2018 [29]	Meta-analysis	9 studies (515 differentiated thyroid cancer	FDG PET/CT	RI-WBS, TgAb levels	Not specified	**Recurrent and/or metastatic disease** Pooled Sens: 84%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		with progressively and/or persistently elevated TgAb levels and negative RI-WBS)				Pooled Spec: 78% Pooled PPV: 75% Pooled NPV: 89% Pooled +LR: 3.8 Pooled –LR: 0.21 Pooled DOR: 18 AUC: 0.88		
Ozturk et al, 2019 [30]	Retrospective	80 patients treated with definitive surgical resection and adjuvant radiotherapy with or without chemotherapy; 197 post-treatment surveillance scans (asymptomatic sinonasal cancer)	FDG PET/CT	Endoscopic examination, CT, MRI	Histopathology, clinical and imaging follow-up	**Local recurrence** Sens: 84% Spec: 95% PPV: 84% NPV: 95% **Regional nodal metastases** Sens: 91% Spec: 99% PPV: 91% NPV: 99% **Distant metastases** Sens: 81% Spec: 99% PPV: 97% NPV: 96%	NA	NA
de Ridder et al, 2019 [31]	Retrospective	352 patients who underwent radiotherapy with or without concurrent systemic therapy (oropharyngeal cancer)	FDG PET/CT	MRI	Biopsy, clinical follow-up	**Residual disease** Sens: 100% Spec: 85% PPV: 38% NPV: 100% Accu: 86%	**Residual disease** Sens: 63% Spec: 83% PPV: 18% NPV: 98% Accu: 82%	NA
Zheng et al, 2019 [32]	Retrospective	52 patients who underwent preoperative staging (tongue squamous cell carcinoma)	FDG PET/CT	CT	Pathology	**Diagnosis** Sens: 92.3% **Staging** Accu: 90.4%	**Diagnosis** Sens: 19.2%	NA
Hematologic Cancer								
Carras et al, 2018 [33]	Phase II (GOELAMS LH 2007)	51 patients who underwent interim response assessment after 2 cycles	FDG PET/CT (interim PET-positive patients	NA	Clinical follow-up	NA	NA	For patients with negative interim-PET, the 5-year EFS and OS were 77.8% (95% CI: 65.3% to 92.7%) and 88.2% (95% CI: 78% to 99.8%), respectively. For

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		of front-line VABEM (advanced stage HL)	switched to salvage therapy followed by HDT and ASCT; interim PET-negative patients received 1 additional course of VABEM)					patients with positive interim-PET, the 5-year EFS and OS were 81.5% (95% CI: 61.1% to 100%) and 91.7% (95% CI: 77.3% to 100%), respectively.
Gallamini et al, 2018 [34]	Phase II RCT (GITIL/FIL HD 0607)	782 patients who underwent interim response assessment after 2 cycles of ABVD (advanced-stage HL)	FDG PET/CT (interim PET-positive patients received escalated BEACOPP with or without rituximab ; interim PET-negative patients continued with 4 cycles of ABVD while those with a large nodal mass ≥ 5 cm and negative PET at the end of chemothe	NA	Clinical follow-up	NA	NA	The 3-year PFS (60% vs. 87%; p<0.001) and OS (89% vs. 99%; p<0.001) were significantly worst for patients with a positive interim-PET than those with a negative interim-PET. For interim PET-positive patients, there were no significant differences in 3-year PFS (63% vs. 57%, respectively; p=0.534) and OS (89% vs. 90%, respectively; p=0.895) between patients who received BEACOPP with or without rituximab. For negative end-of-treatment PET patients with a large nodal mass, the addition of consolidation radiotherapy did not significantly improve the 3-year PFS (97% vs. 93%, respectively; p=0.288) and OS (100% vs. 99%, respectively; p=0.079) over no further treatment.

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
			rapy received either radiotherapy or no further treatment)					
Duhrsen et al, 2018 [35]	Phase III RCT (PETAL)	862 patients who underwent interim response assessment after 2 cycles of R-CHOP (newly diagnosed aggressive B-cell or T-cell lymphomas)	FDG PET or PET/CT (interim PET-positive patients received either 6 additional cycles of R-CHOP or 6 blocks of the Burkitt protocol; Interim PET-negative patients received either 4 additional cycles of R-CHOP or same treatment with 2 additional doses of rituximab)	NA	Clinical follow-up	NA	NA	For interim PET-positive patients, the 2-year EFS was 42.0% for those who received 6 additional cycles of R-CHOP and 31.6% for those who received 6 blocks of the Burkitt protocol (HR=1.501; 95% CI: 0.896 to 2.514; p=0.1229). The 2-year OS rates were 63.6% and 55.4%, respectively (HR=1.349; 95% CI: 0.756 to 2.406; p=0.3085). For interim PET-negative patients, the 2-year EFS was 76.4% for those who received 4 additional cycles of R-CHOP and 73.5% for those who received same treatment with 2 additional doses of rituximab (HR=1.048; 95% CI: 0.684 to 1.606; p=0.8305). The 2-year OS rates were 88.2% and 87.2%, respectively (HR=0.876; 95% CI: 0.508 to 1.513; p=0.6351).
Abe et al, 2019 [36]	Retrospective	83 patients (newly diagnosed peripheral T-cell lymphoma)	FDG PET/CT	BMB	Histopathology	**Bone marrow involvement** Sens: 89.3% Spec: 100% PPV: 100% NPV: 94.8%	**Bone marrow involvement** Sens: 60.7% Spec: 100% PPV: 100% NPV: 83.3%	NA
Koh et al,	Retrospective	109 patients	FDG	BMB	BMB	**Bone marrow**	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
2019 [37]		who underwent initial staging (41 AITCL; 46 NKTCL; 12 other PTCL)	PET/CT			**involvement** ***AITCL*** Sens: 65.2% Spec: 77.8% Accu: 70.7% ***NKTCL*** Sens: 58.3% Spec: 85.3% Accu: 78.3%		
Neuro-Oncology								
Furuse et al, 2019 [38]	Meta-analysis	32 studies (brain tumour patients treated with radiotherapy who exhibited clinical or radiological disease progression)	FDG PET or PET/CT	Gd-enhanced MRI, MR spectroscopy, perfusion MRI, DWI-MRI, ^{201}Tl-SPECT, ^{99m}Tc-MIBI-SPECT	Histology, clinical and imaging follow-up	**Differentiating between brain radiation necrosis from tumour progression** Pooled Sens: 81% Pooled Spec: 72% Pooled DOR: 2.4	**Differentiating between brain radiation necrosis from tumour progression** ***Gd-enhanced MRI*** Pooled Sens: 63% Pooled Spec: 82% Pooled DOR: 2.2 ***MR spectroscopy*** Pooled Sens: 83% Pooled Spec: 77% Pooled DOR: 3.0 ***Perfusion MRI*** Pooled Sens: 85% Pooled Spec: 81% Pooled DOR: 3.5 ***DWI-MRI*** Pooled Sens: 88% Pooled Spec: 80% Pooled DOR: 3.4 ***^{201}Tl-SPECT*** Pooled Sens: 80% Pooled Spec: 84% Pooled DOR: 3.1 ***^{99m}Tc-MIBI-SPECT*** Pooled Sens: 92% Pooled Spec: 91% Pooled DOR: 4.8	NA
Non-FDG Tracers ^{11}C/^{18}F-Choline								
Mortensen et al, 2019 [39]	Prospective	80 patients who underwent extended pelvic lymph node dissection	^{18}F-FCH PET/CT	Whole-body bone scintigraphy	Histology	**Lymph node metastases** Sens: 62.5% Spec: 69.6% PPV: 46.9%	**Bone metastases** Sens: 37.5% Spec: 85.2%*	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		(newly diagnosed prostate cancer)				NPV: 81.3% Accu: 67.5% **Bone metastases** Sens: 100% Spec: 96.3%*		
Gauvin et al, 2019 [40]	Retrospective	76 patients who underwent initial staging (high-risk prostate cancer)	^{18}F-FCH PET/CT	MRI, CT, bone scan	Histology, clinical and imaging follow-up	**Nodal metastases** Sens: 64% Spec: 100% PPV: 100% NPV: 80% **Distant metastases** Sens: 86% Spec: 100% PPV: 100% NPV: 98%	NA	PET/CT changed the clinical management in 11.8% (9/76) of patients (5—pelvic EBRT added to ADT, 3—referred for surgery, 1—SBRT added to pelvic EBRT).
Oderda et al, 2018 [41]	Retrospective	106 patients who underwent salvage lymph node dissection (biochemical recurrence of prostate cancer)	^{11}C-Choline PET/CT	NA	Histopathology	**Nodal relapse (patient-based)** Sens: 94.4% Spec: 6.2% PPV: 85.0% NPV: 16.6% Accu: 81.1% **(nodal-based)** Sens: 61.6% Spec: 79.3% PPV: 75.7% NPV: 66.3% Accu: 70.2%	NA	NA
Guo et al, 2018 [42]	Meta-analysis	14 studies (840 patients with prostate cancer)	^{11}C/^{18}F-Choline PET/CT	NA	Histopathology, clinical follow-up	**Bone metastases (patient-based)** Pooled Sens: 89% Pooled Spec: 98% Pooled +LR: 40.4 Pooled –LR: 0.12 Pooled DOR: 344 AUC: 0.99 **(lesion-based)** Pooled Sens: 91% Pooled Spec: 97% Pooled +LR: 34.1 Pooled –LR: 0.10 Pooled DOR: 358 AUC: 0.99	NA	NA
Huang et al, 2018 [43]	Meta-analysis	8 studies (362 patients with prostate	^{11}C/^{18}F-Choline PET/CT	MRI	Histopathology, clinical follow-up	**Lymph node metastases (patient-based)**	**Lymph node metastases (patient-based)**	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		cancer)				Pooled Sens: 59% Pooled Spec: 92%* Pooled +LR: 5.45* Pooled -LR: 0.38* Pooled DOR: 17.37* AUC: 0.953* Q Index: 0.894* **(node-based)** Pooled Sens: 51%* Pooled Spec: 99% Pooled +LR: 23.73* Pooled -LR: 0.42* Pooled DOR: 65.55* AUC: 0.986* Q Index: 0.949*	Pooled Sens: 52% Pooled Spec: 87%* Pooled +LR: 3.29* Pooled -LR: 0.62* Pooled DOR: 6.05* AUC: 0.778* Q Index: 0.717* **(node-based)** Pooled Sens: 39%* Pooled Spec: 97% Pooled +LR: 8.31* Pooled -LR: 0.61* Pooled DOR: 15.86* AUC: 0.933* Q Index: 0.869*	
^{68}Ga-DOTA-(TATE, NOC, TOC)								
Hope et al, 2018 [44]	Systematic review and appropriate use criteria recommendations	Patients with neuroendocrine tumours	^{68}Ga-DOTA-TATE/TOC PET or PET/CT	Octreoscan, CT/MRI	Consensus from a multidisciplinary panel (modified Delphi process)	• Initial staging after histologic diagnosis of NETs. (Score 9—Appropriate) • Localization of primary tumour in patients with known metastatic disease but unknown primary. (Score 9—Appropriate) • Selection of patients for SSTR-targeted PRRT. (Score 9—Appropriate) • Staging NETs before planned surgery. (Score 8—Appropriate) • Evaluation of mass suggestive of NET not amenable to endoscopic or percutaneous biopsy (e.g., ileal lesion, hypervascular pancreatic mass, mesenteric mass). (Score 8—Appropriate) • Monitoring of NETs seen predominantly on SSTR PET. (Score 8—Appropriate) • Evaluation of patients with biochemical evidence and symptoms of NET without evidence on conventional imaging and without prior histologic diagnosis of NET. (Score 7—Appropriate) • Restaging at time of clinical or laboratory progression without progression on conventional imaging. (Score 7—Appropriate) • New indeterminate lesion on conventional imaging, with unclear progression. (Score 7—Appropriate) • Restaging of patients with NETs at initial follow-up after resection with curative intent. (Score 6—Maybe appropriate) • Selection of patients with non-functional NETs for SSA treatment. (Score 6—Maybe appropriate) • Monitoring in patients with NETs seen on both conventional imaging and SSTR PET with active disease and no clinical evidence of progression. (Score 5—Maybe appropriate)		
Jiang et al, 2019 [45]	Meta-analysis	14 studies (352 patients with pulmonary carcinoid)	^{68}Ga-DOTA-TATE/NOC/TOC	FDG PET/CT	Histopathology	**Diagnosis** Pooled Sens: 90.0%	**Diagnosis** Pooled Sens: 71.0%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
			PET/CT					
Castroneves et al, 2018 [46]	Prospective	30 patients with biochemical disease or known metastatic disease (medullary thyroid cancer)	^{68}Ga-DOTA-TATE PET/CT	Bone scan, US, CeCT, MRI	Cytology, pathology, imaging follow-up	**Cervical lymph node metastases** Sens: 63% Spec: 93% **Mediastinal lymph node metastases** Sens: 100% Spec: 100% **Liver metastases** Sens: 9% Spec: 100% **Lung metastases** Sens: 63% Spec: 100% **Bone metastases** Sens: 100% Spec: 95%	NA	^{68}Ga-DOTA-TATE PET/CT results led to a change in management in 20% (6/30) of patients.
Amyloid								
Rabinovici et al, 2019 [47] (IDEAS)	Prospective	11409 patients (mild cognitive impairment or dementia of uncertain etiology)	Amyloid PET	CT, MRI, laboratory testing, Mini-Mental State Examination, Montreal Cognitive Assessment	Pre- and post-questionnaire	NA	NA	Amyloid PET changed the etiologic diagnosis from Alzheimer disease to non-Alzheimer disease in 25.1% (2860/11409) of patients and from non-Alzheimer disease to Alzheimer disease in 10.5% (1201/11409) of patients. Clinical management was changed in 60.2% (4159/6905) of patients with mild cognitive impairment (43.6%—change in Alzheimer disease drug therapy, 22.9%—change in other drug therapy, 24.3%—change in counselling) and 63.5% (2859/4504) of patients with dementia (44.9%—change in Alzheimer disease drug therapy, 25.4%—change in other drug therapy, 20.7%—change in counselling).
^{68}Ga-PSMA								

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Yaxley et al, 2019 [48]	Retrospective	208 patients who underwent primary staging prior to radical prostatectomy with pelvic lymph node dissection (intermediate and high risk prostate cancer)	^{68}Ga-PSMA PET/CT	NA	Histology	**Lymph node metastases (patient-based)** Sens: 38.2% Spec: 93.5% PPV: 67.7% NPV: 80.8% +LR: 5.84 -LR: 0.66 OR: 8.83 AUC: 0.66 **(node-based)** Sens: 24.4% Spec: 99.5% PPV: 75.0% NPV: 95.5% +LR: 48.63 -LR: 0.76 OR: 64.02 AUC: 0.62	NA	NA
Wong et al, 2018 [49]	Retrospective	131 patients who underwent initial staging prior to definitive treatment (newly diagnosed prostate cancer)	^{68}Ga-PSMA PET/CT	MRI, whole body bone scan, CT of the abdomen and pelvis	Follow-up	NA	NA	^{68}Ga-PSMA PET/CT resulted in a change of stage in 28.2% (37/131) of patients (17—upstaged, 20—downstaged). Management was impacted in 18.3% (24/131) of patients.
Wu et al, 2019 [50]	Prospective	45 treatment naïve patients (prostate cancer)	^{68}Ga-PSMA-11 PET/CT or PET/MRI	CT, MRI, bone scan	RTOG consensus guidelines	NA	NA	^{68}Ga-PSMA-11 PET/CT or PET/MRI resulted in major and/or minor changes to radiotherapy plans in 53.3% (24/45) of patients.
Fendler et al, 2019 [51]	Prospective	635 patients (biochemically recurrent prostate cancer)	^{68}Ga-PSMA-11 PET/CT or PET/MRI	NA	Histopathology, clinical and imaging follow-up	**Recurrence (patient-based)** Sens: 92% PPV: 84-92% **(region-based)** Sens: 90% PPV: 84-92%	NA	NA
Calais et al, 2018 [52]	Retrospective	270 patients who underwent radical prostatectomy	^{68}Ga-PSMA-11 PET/CT	CT	Biopsy, surgery, clinical or imaging follow-	NA	NA	^{68}Ga-PSMA-11 PET/CT implied a major impact on salvage radiotherapy planning in 19.3% (52/270)

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		and had biochemical recurrence without prior radiotherapy at a PSA level of <1 ng/ml (prostate cancer)			up			of patients (19—extension of pelvic consensus clinical target volumes, 5—superior extension to cover paraaortic lymph nodes, 22—oligometastasis-directed stereotactic body radiation therapy, 6—radiotherapy futile due to polymetastatic or visceral disease).
Calais et al, 2018 [53]	Prospective	101 patients with PSA level >0.2 ng/mL after prostatectomy or a rise of ≥2 ng/mL above the PSA nadir value after definitive radiotherapy (biochemical recurrence of prostate cancer)	^{68}Ga-PSMA-11 PET/CT	NA	Histopathology, follow-up	NA	NA	^{68}Ga-PSMA-11 PET/CT brings about management changes in 53.5% (54/101) of patients (29—conversion to focal treatment/new focal treatment, 13—conversion to systemic treatment, 5—change of systemic treatment approach, 7—conversion to active surveillance).
Tan et al, 2019 [54]	Retrospective	55 Asian patients with two consecutive increases of PSA > 0.2 ng/mL within 36 months following radical prostatectomy (biochemical recurrence of prostate cancer)	^{68}Ga-PSMA PET/CT	Bone scintigraphy, CeCT of the thorax, abdomen, and pelvis	Pre-specified criteria	NA	NA	^{68}Ga-PSMA PET/CT prompted a change in management in 56.8% (25/44) of patients (10—received whole pelvic radiotherapy and combination hormonal therapy, 15—referred for palliative hormonal therapy).
Dyrberg et al, 2019 [55]	Prospective	55 patients (prostate cancer)	^{68}Ga-PSMA PET/CT	Whole-body MRI	Histology, panel diagnosis based on clinical data and available	**Bone metastases** Sens: 100% Spec: 100% PPV: 100% NPV: 100%	**Bone metastases** Sens: 80% Spec: 83% PPV: 73% NPV: 88%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
					clinical follow-up images	Accu: 100%*	Accu: 82%*	
Han et al, 2018 [56]	Meta-analysis	15 studies (1163 patients with prostate cancer)	^{68}Ga-PSMA PET/CT	CT, MRI, bone scintigraphy	Multidisciplinary oncology committee, referring physician	NA	NA	^{68}Ga-PSMA PET/CT altered the management in 54% of patients across the studies.
^{18}F-NaF								
Dyrberg et al, 2019 [55]	Prospective	55 patients (prostate cancer)	^{18}F-NaF PET/CT	Whole-body MRI	Histology, panel diagnosis based on clinical data and available clinical follow-up images	**Bone metastases** Sens: 95% Spec: 97% PPV: 95% NPV: 97% Accu: 96%	**Bone metastases** Sens: 80% Spec: 83% PPV: 73% NPV: 88% Accu: 82%	NA
^{18}F-DOPA								
Youland et al, 2018 [57]	Prospective	13 patients who underwent neurosurgical planning (suspected recurrence of glioma)	^{18}F-DOPA PET/CT	CeMRI	Histopathology	**Recurrence** Sens: 82% Spec: 50%	**Recurrence** Sens: 52% Spec: 50%	NA
Brammen et al, 2018 [58]	Prospective	50 patients who underwent initial surgery (histologically proven medullary thyroid carcinoma)	^{18}F-DOPA PET/CT	Neck US	Histopathology	**Primary tumour** Sens: 86% **Lymph node metastasis** Sens: 57% Spec: 100% PPV: 100% NPV: 76% Accu: 82%	**Primary tumour** Sens: 90% **Lymph node metastasis** Sens: 43% Spec: 97% PPV: 90% NPV: 70% Accu: 74%	^{18}F-DOPA PET/CT detected 6% (3/50) of patients with mediastinal lymph node metastasis and 6% (3/50) of patients with distant metastasis that were not evident on US.
Non-Small Cell Lung Cancer and Other Lung Cancer								
Tang et al, 2019 [59]	Retrospective	182 patients (SPN)	FDG PET/CT	CT	Histopathology, clinical follow-up	**Diagnosis** Sens: 98.4% Spec: 77.1% PPV: 89.5% NPV: 95.9% Accu: 91.2% AUC: 0.873*	**Diagnosis** Sens: 95.9% Spec: 55.7% PPV: 81.1% NPV: 87.2% Accu: 82.4% AUC: 0.758*	NA
Taralli et al, 2019 [60]	Retrospective	148 patients; 182 nodules (solitary and multiple pulmonary nodules)	FDG PET/CT	CT	Histopathology, imaging follow-up	**Malignancy (nodule-based)** Sens: 79.0% Spec: 81.8% PPV: 93.1% NPV: 55.4%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Accu: 79.7% **(patient-based)** Sens: 88.9% Spec: 55.6% PPV: 80.0% NPV: 71.5% Accu: 77.8%		
Maiga et al, 2018 [61]	Retrospective	1188 patients (known or suspected lung cancer)	FDG PET/CT	NA	Pathology, imaging follow-up	**Diagnosis** Sens: 90.1% Spec: 39.8% PPV: 86.4% NPV: 48.7%	NA	NA
Kirchner et al, 2019 [62]	Prospective	84 patients (NSCLC)	FDG PET/CT, FDG PET/MRI	NA	Histopathology	**T staging** ***PET/CT*** Accu: 92.3% ***PET/MRI*** Accu: 89.7% **N staging** ***PET/CT*** Accu: 92.9% ***PET/MRI*** Accu: 91.7%	NA	NA
Kishida et al, 2018 [63]	Prospective	59 patients who underwent staging before treatment (SCLC)	FDG PET/CT	Brain MRI, CeCT, bone scintigraphy	Pathology, clinical and imaging follow-up, consensus from multidisciplinary team	**T staging** Accu: 84.7% **N staging** Accu: 89.8%* **M staging** Accu: 96.6% **TNM staging** Accu: 88.1%* **VALSG staging** Accu: 96.6% **Differentiating stage I from other stages** Sens: 100% Spec: 98.0% PPV: 88.9% NPV: 100% Accu: 98.3%*	**T staging** Accu: 78.0% **N staging** Accu: 67.8%* **M staging** Accu: 91.5% **TNM staging** Accu: 72.9%* **VALSG staging** Accu: 91.5% **Differentiating stage I from other stages** Sens: 62.5% Spec: 92.2% PPV: 55.6% NPV: 94.0% Accu: 88.1%*	NA
Pancreatic Cancer								
Ghaneh et al, 2018 [64] (PET-PANC)	Prospective	550 patients (suspected pancreatic cancer)	FDG PET/CT	MDCT	Histology, clinical follow-up	**Diagnosis** Sens: 92.7%* Spec: 75.8%* PPV: 77.6% NPV: 92.0%*	**Diagnosis** Sens: 88.5%* Spec: 70.6%* PPV: 73.1% NPV: 87.1%*	PET/CT correctly changed the staging in 14.2% (56/393) of patients. PET/CT was perceived to have changed the planned

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
								management in 45.5% (250/550) of patients.
Pediatric Cancer								
Lopci et al, 2019 [65] (AIEOP-LH2004 trial)	Prospective	263 patients who underwent interim response assessment after 4 cycles of COPP/ABV, after the end of chemotherapy and after radiation treatment (HL with a bulky mass)	FDG PET or PET/CT (interim PET-positive patients received 2 additional cycles of IEP with or without 2 cycles of COPP/ABV + radiation therapy; interim PET-negative patients continued with 2 cycles of COPP/ABV + radiation therapy)	CT	Clinical follow-up	NA	NA	TTP was significantly longer for patients with a negative interim PET than those with a positive interim PET (32.7 months vs. 23.8 months; p<0.0001). At the end of chemotherapy, PET-negative patients had a significantly longer TTP than PET-positive patients (38.9 months vs. 34.2 months; p<0.0001). At the end of radiation therapy, TTP was significantly longer in PET-negative patients than in PET-positive patients (43.4 months vs. 21.4 months; p<0.0001).
Sarcoma								
Farag et al, 2018 [66]	Retrospective	63 patients; 70 scans to evaluate for an early response to neoadjuvant imatinib (gastrointestinal stromal tumour)	FDG PET/CT	NA	Follow-up	NA	NA	FDG PET/CT led to a change in management in 25.7% (18/70) of scans (1—change in surgical management, 8—change in systemic treatment, 7—change in dose and early planned surgery, 2—treatment adaptation due to discovery of second tumour).
Unknown Primary								
Fu et al, 2018	Prospective	120 patients	FDG	US, chest	Histopathology,	**Malignant tumours**	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
[67]		with elevated serum CEA level (unknown primary lesion)	PET/CT	radiography, MRI	clinical and imaging follow-up	Sens: 96.7% Spec: 98.9% PPV: 96.7% NPV: 98.9% Accu: 98.3%		
Wolpert et al, 2018 [68]	Retrospective	64 patients with brain metastasis (cancer of unknown primary site)	FDG PET/CT	CeCT	Histology	**Primary lesion localization** Sens: 92.2%	**Primary lesion localization** Sens: 87.5%	PET/CT identified additional lesions suspicious of extracranial metastases in 43.8% (28/64) of patients.
Various Sites								
Han et al, 2019 [69]	Prospective	54 patients (bone tumours)	FDG PET/CT	CT	Pathology	**Diagnosis** Sens: 95.0%* Spec: 85.7% PPV: 95.0%* NPV: 85.7%*	**Diagnosis** Sens: 75.0%* Spec: 64.3% PPV: 85.7%* NPV: 47.4%*	NA
Pfannenberg et al, 2019 [70]	Prospective	3724 patients; 4754 scans (22 tumour types)	FDG PET/CT, ^{68}Ga-PSMA-11 PET/CT, ^{68}Ga-DOTA-TATE PET/CT, ^{11}C-Choline, ^{18}F-FET PET/CT, ^{11}C-Methionine PET/CT	Not specified	Pre- and post-questionnaire	NA	NA	PET/CT resulted in a change in management in 37.1% (1763/4754) of examinations (1456—non-treatment to treatment, 307—treatment to non-treatment).
Caspersen et al, 2019 [71]	Retrospective	93 patients (suspected serious disease or occult cancer)	FDG PET/CT	NA	Biopsy, follow-up	**Malignancy** Sens: 77.3% Spec: 76.1% PPV: 50.0% NPV: 91.5%	NA	NA

*p<0.05

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

Abbreviations: 11C-choline: carbon-11 choline; 18F-Choline: fluorine-18 choline; 18F-DOPA: 3,4-dihydroxy-6-[18F]-fluoro-l-phenylalanine; 18-F-FCH: 18-F-fluorocholine; 68Ga-DOTA-(TATE, TOC): gallium-68-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-1-Nal3-octreotide; 18F-NAF: 18F-sodium fluoride; 68Ga-DOTATATE: 68Ga-labelled-1,4,7,10-tetraazacyclododecane-NI,NII,NIII,NIIII-tetraacetic acid (D)-Phe1-thy3-octreotate; 68Ga-PSMA: 68Gallium-labeled prostate-specific membrane antigen; 99mTc-MDP: Technetium 99m-methyl diphosphonate; ABVD: doxorubin, vinblastine, vincristine, and dacarbazine; Accu: accuracy; AITCL: angio-immunoblastic T-cell lymphoma; ASCT: autologous stem cell transplant; AUC: area under curve; BEACOPP: bleomycin, etoposide, doxorubin, cyclophosphamide, vincristine, procarbazine, and prednisone; BMB: bone

marrow biopsy; CEA: carcinoembryonic antigen; CeCT: contrast-enhanced computed tomography; COPP/ABV: cyclo-phosphamide, vincristine, procarbazine, prednisolone, Adriamycin, bleomycin, vinblastine; CT: computed tomography; DOR: diagnostic odds ratio; DW-MRI: Diffusion-weighted MRI; DWI: diffusion-weighted images; DWIBS: Diffusion–weighted whole-body imaging with background body signal suppression; EBRT: external beam radiation therapy; FDG: fluorodeoxyglucose; FIGO: International Federation of Gynecology and Obstetrics; FN: false negative; FNA: fine-needle aspiration; FP: false positive; HDT: high-dose therapy; HL: Hodgkin's lymphoma; iEEG: intracranial electroencephalography; IEP: ifosfamide, etoposide, prednisolone; LR: likelihood ratio; MDCT: multidetector CT; MIBI: methoxyisobutylisonitrile; MRI: magnetic resonance imaging; NA: not applicable/not available; NET: neuroendocrine tumour; ng: nanogram; NKTCL: NK/T-cell lymphoma; NPV: negative predictive value; PET: positron emission tomography; PPV: positive predictive value; PRRT: peptide receptor radionuclide therapy; PSA: Prostate-specific antigen; PSMA: prostate specific membrane antigen; PTCL: peripheral T-cell lymphoma; R-CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab; RI-WBS: radioactive iodine whole body scan; SBRT: stereotactic body radiation therapy; SCLC: small cell lung carcinoma; Sens: sensitivity; SLNB: sentinel lymph node biopsy; Spec: specificity; SPECT: single photon emission CT; SPN: solitary pulmonary nodule; SSA: somatostatin analogs; SSTR: somatostatin receptor; TgAB: thyroglobulin antibodies; TP: true positive; TTP: time to progression; US: ultrasonography; VABEM: vindesine, doxorubicin, carmustine, etoposide, and methylprednisolone; vEEG: video-electroencephalography.