PET Six-Month Monitoring Report 2018-1

Evidence from Primary Studies and Systematic Reviews and Recommendations from Clinical Practice Guidelines January to June 2018

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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 15th 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 2018 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

Forty-three studies published between January and June 2018 met the inclusion criteria. A summary of the evidence from the 43 studies can be found in **Appendix 1: Summary of studies from January to June 2018**.

Breast Cancer

One study met the inclusion criteria [1]. For the diagnosis of multiple invasive lobular carcinomas, digital breast tomosynthesis (73.3%) and FDG PET/CT (73.0%) provided the highest accuracy, while breast-specific gamma imaging (58.0%) and digital mammography (62.5%) had the lowest accuracy.

Esophageal Cancer

Two studies met the inclusion criteria [2,3]. In the follow-up of surgically treated patients, FDG PET/CT was highly accurate for the detection of regional (87%) and distant recurrences (96%) [2]. Conversely, FDG PET/CT performed after neoadjuvant chemoradiation often led to a high proportion of false positive findings for interval metastatic disease (positive predictive value, 15.6%) [3].

Gastrointestinal Cancer

Two studies met the inclusion criteria [4,5]. In the preoperative chemoradiotherapy assessment for locally advanced rectal cancer, dynamic contrast-enhanced magnetic resonance imaging (MRI) predicted pathological complete response with higher sensitivity (93.3% versus 80.0%, $p<0.05$) and specificity (68.9% versus 31.1%, $p<0.05$) than FDG PET/CT [4]. In newly diagnosed anal carcinoma, FDG PET/CT had an impact on the target definition of 12.5% to 43% of patients (summary estimate, 23%) and changed the treatment intent from curative to palliative in 0% to 5% of patients (summary estimate, 3%) [5].

Genitourinary Cancer

Five studies met the inclusion criteria [6-10]. In the preoperative staging of patients with bladder cancer, FDG PET/CT had a higher sensitivity (63.6% versus 27.3%, $p=0.046$) but lower specificity (88.1% versus 96.6%, $p=0.025$) than contrast-enhanced CT for detecting pelvic lymph node metastases at 10 mm cutoff [6]. In patients with urothelial cancer, FDG PET/CT outperformed conventional imaging (e.g., CT and/or MRI) both in the staging (pooled sensitivity, 53.1% versus 38.9%; pooled specificity, 91.7% versus 90.8%) and restaging (pooled sensitivity: 94.7% versus 83.8%; pooled specificity: 90.5% versus 86.8%) setting [7]. Similarly, FDG PET/CT (96.7%) detected recurrent renal cell carcinoma more accurately than CT (73.3%) in postoperative assessment [8]. Two of the studies looked at FDG PET or PET/CT in patients with adrenal masses. The authors of a meta-analysis reported a pooled sensitivity and specificity of 91% for the characterization of adrenal lesions [9], while the authors of a prospective study reported an accuracy of 95.8% for the diagnosis of metastatic adrenal masses [10].

Gynecologic Cancer

Three studies met the inclusion criteria [11-13]. In a prospective multicentre trial, FDG PET/CT demonstrated high specificity but low sensitivity for detecting distant metastatic disease in patients with local–regionally advanced cervical cancer (specificity, 93.9% to 97.7%; sensitivity, 47.6% to 54.8%) and high-risk endometrial cancer (specificity, 93.9% to 98.6%; sensitivity, 64.6% to 66.7%) [11]. In a smaller prospective study consisting of patients with

different gynecological malignancies, FDG PET/CT proved to be more accurate (82.1% versus 50.0%, $p<0.05$) than CT in detecting lymph node metastases [12]. Similarly, FDG PET/CT was more sensitive (48.6% versus 24.3%, $p=0.004$) but less specific (89.5% versus 96.3%, $p=0.002$) than MRI in predicting pelvic lymph node metastases of uterine cervical cancer [13].

Head and Neck Cancer

Five studies met the inclusion criteria [14-18]. In surgically resected oral squamous cell carcinoma, FDG PET/CT performed poorly in detecting locoregional recurrences (sensitivity, 55.6%; specificity, 75.0%) but improved markedly when detecting distant recurrences (sensitivity, 100%; specificity, 95.2%) [14]. For the staging and restaging of head and neck cancer, FDG PET/CT (91.4%) and FDG PET/MRI (93.1%) were equally accurate in defining local resectability [15]. In patients with differentiated thyroid carcinoma and suspicion of tumour recurrence, FDG PET/CT established a higher sensitivity (94.3% versus 65.4%) but a lower specificity (78.4% versus 87.9%) than conventional imaging [16]. In comparison to neck ultrasonography alone, FDG PET/CT also had a higher sensitivity (93.3% versus 66.7%) but equivalent specificity (70.6%) [17]. In another study, FDG PET/CT can reliably detect malignancy in sonographically suspicious and scintigraphically hypofunctional thyroid nodules (sensitivity, 100%; specificity, 87%) [18].

Hematologic Cancer

Four studies met the inclusion criteria [19-22]. FDG PET or PET/CT displayed good sensitivity (pooled estimate, 88%) and specificity (pooled estimate, 86%) in diagnosing primary central nervous system lymphoma in immunocompetent patients [19]. In patients with Hodgkin and non-Hodgkin lymphoma, FDG PET/CT can accurately (90.0%) differentiate post-treatment fibrosis from residual viable tumour; the accuracy for contrast-enhanced CT was 80.0% [20]. Results for the evaluation of therapeutic response did not differ significantly whether FDG PET/CT was visually (Deauville score) or semi-quantitatively (change in maximum standardized uptake value [ΔSUV_{max}]) analyzed [21]. In both early and advanced-stage Hodgkin lymphoma, FDG PET/CT scans carried out after the first cycle of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) can identify fast responders with a three-year PFS of 88%. The three-year PFS for slow responders and non-responders were 79% and 34%, respectively. Nonetheless, interim-PET after two cycles of ABVD still remains optimal for distinguishing responders from non-responders [22].

Melanoma

Four studies met the inclusion criteria [23-26]. For the staging of patients with a positive sentinel lymph node, FDG PET/CT was shown to have limited value [23]. In the follow-up of surgically treated patients, FDG PET/CT demonstrated high sensitivity (87.7% to 89%) and specificity (90.1% to 92%) for detecting recurrences [24,25]. In patients with cutaneous melanoma, FDG PET/CT using various parameters (e.g., maximum standardized uptake value, total lesion glycolysis, tumour-to-liver ratio) all showed a higher diagnostic accuracy than contrast-enhanced CT for assessing lymph node metastases [26].

Non-FDG Tracers

Six studies met the inclusion criteria [27-32]. Three of the studies evaluated ^{18}F-choline/^{18}F-fluorocholine PET/CT in prostate cancer. In patients with high prostate-specific antigen levels and previous negative or inconclusive biopsy, the use of ^{18}F-choline PET/CT for diagnosis is very limited due to a high rate of false positive results (specificity, 12%) [27]. In the clinical settings of staging and biochemical recurrence, one study found that ^{18}F-choline PET/CT changed the M staging of 23.3% of patients [28] while another study reported that ^{18}F-

fluorocholine PET/CT had a clinical impact in 55.9% of patients [29]. For the differentiation of radiation necrosis from brain tumour recurrence, both ^{18}F-FET (pooled sensitivity, 82%; pooled specificity, 80%) and ^{18}F-DOPA (pooled sensitivity, 85%; pooled specificity, 77%) PET/CT exhibited moderate overall diagnostic accuracy [30]. In patients with persistent or suspected recurrence of medullary thyroid carcinoma, ^{18}F-DOPA PET/CT had a higher sensitivity (66.7% versus 50.0%, $p<0.01$) than FDG PET/CT in detecting tumour-positive patients [31]. In morbidly obese cancer patients, ^{18}F-NaF PET/CT retained its high diagnostic accuracy (95.3%) in staging metastatic bone disease [32].

Non-Small Cell Lung Cancer and Other Lung Cancer

Five studies met the inclusion criteria [33-37]. In non-small cell lung cancer (NSCLC), the sensitivity of FDG PET/CT was greater than that of chest CT for evaluating regional nodal (94.4% versus 78.6%) and distant (91.9% versus 70.7%) metastases, while having comparable specificity (regional, 87.1% versus 88.9%; distant, 87.1% versus 88.4%) [33]. In patients with solitary pulmonary nodules, FDG PET/CT demonstrated satisfactory sensitivity (pooled estimate, 81.9%) and poor specificity (pooled estimate, 62.4%) for predicting malignancy [34] and appeared to be inferior to dynamic contrast-enhanced-MRI [35]. In bronchioalveolar carcinoma, FDG PET/CT proved to be highly accurate (95.4%) for detecting recurrence [36]. For mesothelioma, FDG PET/CT correctly staged the nodal status in significantly more patients than CT (63.3% versus 45.0%, $p=0.001$). FDG PET/CT was also more sensitive (91.7% versus 33.3%) in identifying distant metastases while maintaining high specificity [37].

Pancreatic Cancer

One study met the inclusion criteria [38]. Results from a meta-analysis showed that preoperative assessment using FDG PET or PET/CT improved the likelihood of detecting distant metastases compared with CT alone (odds ratio [OR], 1.52; 95% confidence interval [CI], 1.23 to 1.88), thereby saving patients from unnecessary radical resection. However, there was no significant difference between FDG PET or PET/CT and CT in detecting regional lymph nodes invasion (OR, 0.97; 95% CI, 0.63 to 1.47).

Sarcoma

Four studies met the inclusion criteria [39-42]. The use of FDG PET/CT was evaluated in a large retrospective cohort of patients with different histological subtypes of bone and soft tissue sarcoma. Overall, 20.8% of FDG PET/CT scans performed for staging, restaging, and treatment response were considered to have added value over CT and/or MRI [39]. To differentiate uterine sarcoma from leiomyoma, FDG PET/CT using SUV_{max} greater than 7.5 yielded a sensitivity of 73.3% and a specificity of 100% [40]. In patients with suspected recurrence of chondrosarcoma, FDG PET/CT demonstrated recurrent disease with moderate sensitivity (88.9%) and specificity (79.0%) [41]. In a meta-analysis of seven studies, FDG PET or PET/CT predicted the malignant potential of gastrointestinal stromal tumours with a pooled sensitivity of 88% and a pooled specificity of 88% [42].

Unknown Primary Cancer

One study met the inclusion criteria [43]. In a prospective study of patients with cancer of unknown primary, FDG PET/CT was able to detect the site of the primary tumour with sensitivity of 74.4% and specificity of 69.2%.

CLINICAL EXPERT REVIEW

Breast Cancer

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

Reviewer's Comments (Dr. Muriel Brackstone)

One study was published contrasting a number of diagnostic imaging modalities for invasive lobular breast cancer. Seventy-five patients were included in this retrospective cohort study, but it is important to note that not every patient received every modality; for example, digital breast tomosynthesis was reported to be (along with MRI) the most accurate modality for detection of foci of invasive lobular disease, and yet was only performed in 15 patients. As well, the retrospective nature of this study makes it impossible to determine which of the numerous modalities noted were the ones that identified the lesion, rather than confirming it, because it was previously identified by another modality ('hindsight diagnosis'). The most limiting factor of this study was that multicentric lesions were not each individually confirmed surgically, and therefore the authors considered a lesion to be a true positive if the lesion was Birads 4 or higher, where the likelihood of cancer might only be 20%, and the majority of these being actually benign. The true positive and false positive rates of these novel imaging modalities need to be confirmed before patients are subjected to extensive investigations, biopsies, or morbid surgery that is not required. Nevertheless, the PET-CT was less accurate than MRI and tomosynthesis at identifying these possible or actual foci of cancer. This study is insufficient to change guidelines and insufficient at present to support the role of PET imaging in breast cancer.

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 (Dr. Rebecca Wong)

The current recommendations for the utilization of PET/CT in esophageal cancer remain valid and no changes are required. In the study by Betancourt Cuellar et al. [2], the authors did not provide data on how many solitary metastases were detected by PET/CT only. There were also no data presented on how treatment was influenced based on the results of the PET/CT scan. Therefore, PET/CT is not useful for anastomotic recurrence or nodal recurrence given the diagnostic properties. For selected patients where early detection of solitary distant metastases would influence decision making, PET/CT could be considered. However, routine PET/CT in the follow-up period is not recommended.

Gastrointestinal Cancer

Current Insured Indications (Colorectal Cancer)

- Where recurrent disease is suspected on the basis of elevated and/or rising carcinoembryonic antigen (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-T4 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 (Dr. Anand Swaminath)

The current recommendations for the utilization of PET/CT in gastrointestinal cancer remain valid and no changes are required. The meta-analysis by Albertsson et al. [5] consisted of mainly retrospective studies and has a high bias. The anal canal cancer registry should continue as it is as no current evidence would suggest a change to insured indication.

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. However, the meta-analyses by Cervino et al. [7] on urothelial cancer and Kim et al. [9] on adrenal masses are showing some clinically important results among large numbers of patients.

Gynecologic Cancer

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 for 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 in 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 workup 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 lymphoma 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.

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 (NETs) 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 NETs 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 NETs 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 NETs.
- There is no recommendation regarding the use of ^{68}Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT in the routine surveillance of NETs.

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.

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.
- Small cell lung cancer (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 single piece of new evidence is a study-based (not individual patient–based) meta-analysis of retrospective, non-randomized data on staging for patients who are being considered for resection. Two of the four studies in the 2008 recommendations were included in the Wang et al. [38] study. The likelihood ratio reported by the authors supports PET or PET/CT to improve detection of distant metastases compared with standard imaging.

Sarcoma

No recommendations currently exist for the utilization of PET/CT in sarcoma.

Reviewer's Comments (Dr. Gina Diprimio)

The evidence is supportive of new recommendations for PET/CT in staging and recurrence.

Unknown Primary Cancer

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

Reviewer's Comments (Dr. Amit Singnurkar)

This scenario is currently supported through the PET access program.

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Contact Information

For information about the PEBC and the most current version of all reports,
please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
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Appendix 1: Summary of studies from January to June 2018.

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Breast Cancer								
Chae et al, 2018 [1]	Retrospective	76 patients (surgically proven ILCs)	FDG PET/CT	DM, DBT, US, MRI, BSGI	Pathology	**Index ILCs** DR: 93.2% **Multiple ILCs** Sens: 56.0% Spec: 81.6% PPV: 60.9% NPV: 78.4% Accu: 73.0%	**Index ILCs** ***DM*** DR: 87.5% ***DBT*** DR: 100% ***US*** DR: 100% ***MRI*** DR: 100% ***BSGI*** DR: 96.0% **Multiple ILCs** ***DM*** Sens: 24.0% Spec: 83.0% PPV: 42.9% NPV: 67.2% Accu: 62.5% ***DBT*** Sens: 100% Spec: 42.9% PPV: 66.7% NPV: 100% Accu: 73.3% ***US*** Sens: 80.8% Spec: 66.7% PPV: 55.3% NPV: 87.2% Accu: 71.4% ***MRI*** Sens: 100% Spec: 50.0% PPV: 51.0% NPV: 100% Accu: 67.1% ***BSGI*** Sens: 35.0% Spec: 73.3% PPV: 46.7%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Esophageal Cancer								
Betancourt Cuellar et al, 2018 [2]	Retrospective	162 patients who had undergone surgery with or without pre-operative chemoradiation (esophageal carcinoma)	FDG PET/CT	NA	Histopathology, imaging follow-up	**Local recurrence** Sens: 77% Spec: 76% PPV: 16% NPV: 98% Accu: 76% **Regional recurrence** Sens: 88% Spec: 86% PPV: 45% NPV: 97% Accu: 87% **Distant recurrence** Sens: 97% Spec: 96% PPV: 91% NPV: 99% Accu: 96%	NA	NA
Gabriel et al, 2017 [3]	Retrospective	258 patients who underwent nCRT followed by esophagectomy (clinical T2-T4 esophageal or gastroesophageal junction)	FDG PET/CT	NA	Biopsy, imaging follow-up	**Interval metastases** PPV: 15.6%	NA	NA
Gastrointestinal Cancer								
Petrillo et al, 2017 [4]	Prospective	75 patients who underwent nCRT followed by total mesorectal excision (locally advanced rectal cancer)	FDG PET/CT	DCE-MRI	Pathology	**nCRT pathological complete response** Sens: 80.0%* Spec: 31.1%* PPV: 43.6% NPV: 70.0% Accu: 50.7% AUC: 0.57	**nCRT pathological complete response** Sens: 93.3%* Spec: 68.9%* PPV: 66.7% NPV: 93.9% Accu: 78.7% AUC: 0.82	NA
Albertsson et al, 2018 [5]	Meta-analysis	10 studies (patients with	FDG PET/CT	CT	Not specified	NA	NA	The proportion of patients in which PET/CT had an

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		newly diagnosed anal carcinoma intended for curative treatment including radiation therapy)						impact on the target definition varied from 12.5% to 43% with a summary estimate of 23%. A change in the treatment intent from curative to palliative due to PET/CT occurred in 0% to 5% of cases with a summary estimate of 3%.
Genitourinary Cancer								
Pichler et al, 2017 [6]	Retrospective	70 patients undergoing preoperative staging (localized muscle-invasive bladder cancer or recurrent, high-risk non-muscle-invasive bladder cancer)	FDG PET/CT	CeCT	Histopathology	**Pelvic lymph node metastasis** **> 8 mm** Sens: 63.6% Spec: 86.4% PPV: 46.7% NPV: 92.7% Accu: 82.9% +LR: 4.69 -LR: 0.42 OR: 11.2 **>10 mm** Sens: 63.6%* Spec: 88.1%* PPV: 50.0% NPV: 92.9% Accu: 84.3% +LR: 5.36 -LR: 0.41 OR: 13.0	**Pelvic lymph node metastasis** **> 8 mm** Sens: 45.5% Spec: 91.5% PPV: 50.0% NPV: 90.0% Accu: 84.3% +LR: 5.36 -LR: 0.60 OR: 9.0 **>10 mm** Sens: 27.3%* Spec: 96.6%* PPV: 60.0% NPV: 87.7% Accu: 85.7% +LR: 8.05 -LR: 0.75 OR: 10.7	NA
Cervino et al, 2018 [7]	Meta-analysis	8 studies (patients with urothelial cancer)	FDG PET/CT	CT and/or MRI	Not specified	**N-staging** Pooled Sens: 53.1% Pooled Spec: 91.7% Pooled +LR: 5.19 Pooled –LR: 0.56 Pooled DOR: 13.43 **Restaging** Pooled Sens: 94.7% Pooled Spec: 90.5% Pooled +LR: 9.86 Pooled –LR: 0.06 Pooled DOR: 161.8	**N-staging** Pooled Sens: 38.9% Pooled Spec: 90.8% Pooled +LR: 3.01 Pooled –LR: 73.4 Pooled DOR: 5.36 **Restaging** Pooled Sens: 83.8% Pooled Spec: 86.8% Pooled +LR: 4.46 Pooled –LR: 0.22 Pooled DOR: 20.67	NA
Kassem et al, 2018 [8]	Prospective	30 patients who underwent	FDG PET/CT	CT	Histopathology, follow-up	**Local tumour residue or recurrence**	**Local tumour residue or recurrence**	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		radical nephrectomy (renal cell carcinoma)				Sens: 94.4% Spec: 100% PPV: 100% NPV: 92.3% Accu: 96.7%	Sens: 61.1% Spec: 91.7% PPV: 91.7% NPV: 61.1% Accu: 73.3%	
Adrenal Cancer								
Kim et al, 2018 [9]	Meta-analysis	29 studies (2421 patients with adrenal masses)	FDG PET or PET/CT	NA	Histopathology, clinical and imaging follow-up	**Characterization of adrenal lesions** Pooled Sens: 91% Pooled Spec: 91% Pooled +LR: 9.9 Pooled -LR: 0.09 Pooled DOR: 105 AUC: 0.96	NA	NA
Refaat and Elghazaly, 2017 [10]	Prospective	21 patients (proven extra-adrenal primary malignancy)	FDG PET/CT	NA	Histopathology, serial imaging follow-up	**Adrenal metastases** Sens: 93.3% Spec: 100% PPV: 100% NPV: 90.0% Accu: 95.8%	NA	NA
Gynecologic Cancer								
Gee et al, 2018 [11]	Prospective	356 untreated patients (153 local-regionally advanced cervical cancer, 203 high-risk endometrial cancer)	FDG PET/CT	NA	Surgical report, pathology, imaging follow-up	**Distant metastatic disease** ***Cervical cancer*** **(local review)** Sens: 47.6% Spec: 93.9% PPV: 55.6% NPV: 91.9% AUC: 0.75 **(central review)** Sens: 54.8% Spec: 97.7% PPV: 79.3% NPV: 93.1% AUC: 0.78 ***Endometrial cancer*** **(local review)** Sens: 66.7% Spec: 93.9% PPV: 59.3% NPV: 95.5% AUC: 0.84 **(central review)**	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Sens: 64.6% Spec: 98.6% PPV: 86.1% NPV: 95.4% AUC: 0.89		
Jiafu et al, 2017 [12]	Prospective	28 chemo-naïve patients (17 cervical cancer, 4 endometrial cancer, 7 ovarian cancer)	FDG PET/CT	CT	Pathology	**Distant Lymph node metastasis** Sens: 61.5%* Spec: 100%* Accu: 82.1%*	**Distant Lymph node metastasis** Sens: 23.1%* Spec: 73.3%* Accu: 50.0%*	NA
Jung et al, 2017 [13]	Retrospective	114 patients who underwent hysterectomy and bilateral pelvic lymphadenectomy (FIGO stage IA1-IIB uterine cervical carcinoma)	FDG PET/CT	CT, MRI	Histopathology	**Lymph node metastases (hemi-pelvis-based)** Sens: 48.6%* Spec: 89.5%* PPV: 47.4% NPV: 90.0% Accu: 82.9%	**Lymph node metastases (hemi-pelvis-based)** ***CT*** Sens: 51.4% Spec: 85.9% PPV: 41.3% NPV: 90.1% Accu: 80.3% ***MRI*** Sens: 24.3%* Spec: 96.3%* PPV: 56.3% NPV: 86.8% Accu: 84.6%	NA
Head and Neck Cancer								
Marquardt et al, 2018 [14]	Retrospective	54 patients treated with definitive surgical resection and adjuvant radiotherapy ± chemotherapy (oral squamous cell carcinoma)	FDG PET/CT	NA	Pathology, imaging follow-up	**Locoregional recurrence** Sens: 55.6% Spec: 75.0% PPV: 33.3% NPV: 88.2% **Distant recurrence** Sens: 100% Spec: 95.2% PPV: 77.8% NPV: 100%	NA	NA
Sekine et al, 2017 [15]	Prospective	58 patients referred for staging or restaging	FDG PET/CT or PET/MRI	NA	Intraoperative results, histopathology, clinical and	**Local resectability assessment** ***PET/CT*** **(patient-based)**	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		(head and neck cancer)			imaging follow-up	Sens: 96.4% Spec: 86.7% PPV: 87.1% NPV: 96.3% Accu: 91.4% **(factor-based)** Sens: 91.9% Spec: 99.0% PPV: 90.5% NPV: 99.1% Accu: 98.3% ***PET/MRI*** **(patient-based)** Sens: 96.4% Spec: 90.0% PPV: 90.0% NPV: 96.4% Accu: 93.1% **(factor-based)** Sens: 98.4% Spec: 99.3% PPV: 93.8% NPV: 99.8% Accu: 99.2%		
Schutz et al, 2018 [16]	Meta-analysis	29 studies (1012 patients with differentiated thyroid carcinoma, 185 patients with medullary thyroid carcinoma)	FDG PET/CT	US, CT, SPECT, chest X-ray, MRI, bone scintigraphy, octreotide scintigraphy, MIBI scintigraphy, whole-body scintigraphy	Histopathology, clinical follow-up	**Recurrence** ***Differentiated thyroid carcinoma*** Pooled Sens: 94.3% Pooled Spec: 78.4% ***Medullary thyroid carcinoma*** Pooled Sens: 62.8% Pooled Spec: 34.2%	**Recurrence** ***Differentiated thyroid carcinoma*** Pooled Sens: 65.4% Pooled Spec: 87.9% ***Medullary thyroid carcinoma*** Pooled Sens: 67.4% Pooled Spec: 67.1%	NA
Liu et al, 2018 [17]	Prospective	49 patients with elevated serum levels of TgAb, undetectable Tg and negative ^{131}I-WBS (differentiated thyroid cancer)	FDG PET/CT	Neck US	Pathology	**Recurrence** Sens: 93.3% Spec: 70.6% PPV: 58.3% NPV: 96.0%	**Recurrence** Sens: 66.7% Spec: 70.6% PPV: 50.0% NPV: 82.8%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Ruhlmann et al, 2017 [18]	Retrospective	65 patients (sonographically suspicious and scintigraphically hypofunctional thyroid nodules)	FDG PET/CT	^{99m}Tc-pertechnetate scintigraphy	Histopathology, imaging follow-up	**Malignancy** Sens: 100% Spec: 87% PPV: 61% NPV: 100%	NA	NA
Hematologic Cancer								
Zou et al, 2017 [19]	Meta-analysis	8 studies (129 immunocompetent patients with PCNSL)	FDG PET or PET/CT	NA	Histopathology, imaging and clinical follow-up	**Diagnosis** Pooled Sens: 88% Pooled Spec: 86% Pooled +LR: 3.99 Pooled –LR: 0.11 Pooled DOR: 33.40 Q index: 0.853 AUC: 0.919	NA	NA
Hassanien et al, 2018 [20]	Prospective	50 patients who have undergone assessment of treatment response after completion of therapy (28 NHL, 22 HL)	FDG PET/CT	CT	Pathology, clinical and imaging follow-up	**Differentiate post-treatment fibrosis from residual viable tumor** Sens: 100% Spec: 68.8% PPV: 87.2% NPV: 100% Accu: 90.0%	**Differentiate post-treatment fibrosis from residual viable tumor** Sens: 94.1% Spec: 50.0% PPV: 80.0% NPV: 80.0% Accu: 80.0%	NA
del Puig Cozar-Santiago et al, 2017 [21]	Retrospective	138 patients (46 DLBCL, 46 HL, 46 FL)	FDG PET/CT	NA	Follow-up	**Response to treatment** ***After 2-4 cycles (Deauville score)*** Sens: 71.9% Spec: 82.1% PPV: 54.8% NPV: 90.6% ***(ΔSUV_{max})*** Sens: 62.5% Spec: 84.9% PPV: 55.6% NPV: 88.2% ***End of therapy (Deauville score)*** Sens: 68.8% Spec: 87.7% PPV: 62.9% NPV: 90.3%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						(ΔSUV$_{max}$) Sens: 71.9% Spec: 87.7% PPV: 63.9% NPV: 91.2%		
Zaucha et al, 2017 [22]	Prospective	310 newly diagnosed patients who underwent response assessment after the end of the first or second ABVD course (106 early cHL, 204 advanced cHL)	FDG PET/CT	NA	Biopsy, clinical and imaging follow-up	**Response to treatment** **Early cHL** ***After first cycle*** PPV: 33% NPV: 95% 3-year PFS: 0.94, 95%CI: 0.86-0.99 (iPET-neg), 0.59, 95%CI: 0.27-0.89 (iPET-pos) ***After second cycle*** PPV: 100% NPV: 96% 3-year PFS: 0.96, 95%CI: 0.91-1 (iPET-neg), 0 (iPET-pos) **Advanced cHL** ***After first cycle*** PPV: 42% NPV: 84% 3-year PFS: 0.84, 95%CI: 0.78-0.91 (iPET-neg), 0.57, 95%CI: 0.43-0.71 (iPET-pos) ***After second cycle*** PPV: 57% NPV: 82% 3-year PFS: 0.82, 95%CI: 0.74-0.89 (iPET-neg), 0.4, 95%CI: 0.18-0.63 (iPET-pos)	NA	The 3-year PFS was 0.88, 95%CI: 0.82-0.94, for fast responders (iPET1-neg and iPET2-neg), 0.79, 95%CI: 0.64-0.93, for slow responders (iPET1-pos and iPET2-neg) and 0.34, 95%CI: 0.14-0.54, for non-responders (iPET1-pos and iPET2-pos).
Melanoma								
Holtkamp et al, 2017 [23]	Retrospective	143 patients with a positive sentinel lymph node	FDG PET/CT	CT	Pathology, clinical and imaging follow-up	**Staging** Sens: 17% Spec: 57% PPV: 6%	**Staging** Sens: 11% Spec: 73% PPV: 4%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		(melanoma)						
Vensby et al, 2017 [24]	Retrospective	238 treated patients; 526 scans (melanoma)	FDG PET/CT	US, MRI	Pathology, imaging and clinical follow-up	**Relapse** Sens: 89% Spec: 92% PPV: 78% NPV: 97% Accu: 92%	NA	NA
Leon-Ferre et al, 2017 [25]	Retrospective	299 patients who underwent surveillance PET/CT (resected stage III-IV melanoma)	FDG PET/CT	Physical examination	Biopsy, imaging follow	**Recurrence** Sens: 87.7% Spec: 90.1% PPV: 37.4% NPV: 99.1%	NA	NA
Cha et al, 2018 [26]	Retrospective	103 patients undergoing initial staging or recurrence evaluation (cutaneous melanoma)	FDG PET/CT	CeCT	Pathology, imaging follow-up	**Lymph node metastasis** ***SUV_{max}>2.51*** Sens: 73.1% Spec: 88.9% PPV: 89.5% NPV: 71.9% Accu: 80.0% ***TLR>0.91*** Sens: 77.4% Spec: 83.3% PPV: 85.7% NPV: 74.1% Accu: 80.0% ***TLG>3.5*** Sens: 65.6% Spec: 91.7% PPV: 91.0% NPV: 67.4% Accu: 77.0%	**Lymph node metastasis** Sens: 76.3% Spec: 66.7% PPV: 74.7% NPV: 68.6% Accu: 72.1%	NA
Non-FDG Tracers **$^{11}C/^{18}F$-Choline**								
Jimenez Londono et al, 2017 [27]	Prospective	36 patients with persistently elevated level of PSA in serum (>4 ng/mL) and a previous negative or	^{18}F-Choline PET/CT	TRUS-guided biopsy	Histology	**Diagnosis** Sens: 100% Spec: 12% PPV: 33% NPV: 100% Accu: 38%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		inconclusive biopsy (prostate cancer)						
Cardona Arbonies et al, 2017 [28]	Retrospective	55 patients who underwent initial staging or radiotherapy planning (prostate cancer)	^{18}F-Choline PET/CT	CT, bone scintigraphy	Clinical and imaging follow-up	NA	NA	M staging was changed following 23.2% (13/56) of ^{18}F-choline PET/CT scans (ruled out distant disease in 4 and detected unknown distant disease in 9).
Gillebert et al, 2018 [29]	Prospective	179 patients who received treatment with curative intent (biochemical recurrence of prostate cancer)	^{18}F-Fluorocholine PET/CT	Pelvic MRI, bone scintigraphy	Follow-up, independent assessor	NA	NA	^{18}F-FCH PET/CT had a clinical impact in 55.9% (100/179) of patients (11 cases were considered inadequate).
^{18}F-FET								
Yu et al, 2018 [30]	Meta-analysis	10 studies with patients glioma or brain metastasis	^{18}F-FET PET/CT	NA	Histopathology, clinical follow-up	**Differentiating radiation necrosis from brain tumour recurrence** Pooled Sens: 82% Pooled Spec: 80% Pooled +LR: 3.95 Pooled –LR: 0.21 Pooled DOR: 23.03 AUC: 0.897	NA	NA
^{18}F-DOPA								
Romero-Lluch et al, 2017 [31]	Prospective	18 patients with suspected recurrent or persistent disease after initial surgery by elevated calcitonin levels (medullary thyroid	^{18}F-DOPA PET/CT	FDG PET/CT	Cytohistology, imaging follow-up	**Recurrent or persistent disease** Sens: 66.7%*	**Recurrent or persistent disease** Sens: 50.0%*	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		carcinoma)						
Yu et al, 2018 [30]	Meta-analysis	5 studies(patients with glioma or brain metastasis)	^{18}F-DOPA PET/CT	NA	Histopathology, clinical follow-up	**Differentiating radiation necrosis from brain tumour recurrence** Pooled Sens: 85% Pooled Spec: 77% Pooled +LR: 3.43 Pooled –LR: 0.21 Pooled DOR: 21.7 AUC: 0.877	NA	NA
^{18}F-NaF								
Usmani et al, 2017 [32]	Retrospective	212 morbidly obese patients referred for osseous staging of malignancy (186 breast cancer, 9 colorectal cancer, 6 prostate cancer, 11 other)	^{18}F-NaF PET/CT	NA	Clinical and imaging follow-up	**Bone metastases** Sens: 93.1% Spec: 96.1% PPV: 90.0% NPV: 97.3% Accu: 95.3%	NA	NA
Non-Small Cell Lung Cancer and Other Lung Cancer								
Sheikhbahaei et al, 2017 [33]	Retrospective	275 patients who underwent post-treatment follow-up (251 NSCLC, 24 SCLC)	FDG PET/CT	Chest CT	Histopathology, clinical and imaging follow-up	**Local disease** Sens: 96.0% Spec: 82.1% PPV: 81.2% NPV: 96.2% Accu: 88.3% **Regional nodal metastasis** Sens: 94.4% Spec: 87.1% PPV: 77.8% NPV: 97.0% Accu: 89.5% **Distant metastasis** Sens: 91.9% Spec: 87.1% PPV: 75.8% NPV: 96.0% Accu: 88.5%	**Local disease** Sens: 95.4% Spec: 83.0% PPV: 81.9% NPV: 95.8% Accu: 88.6% **Regional nodal metastasis** Sens: 78.6% Spec: 88.9% PPV: 77.3% NPV: 89.7% Accu: 85.6% **Distant metastasis** Sens: 70.7% Spec: 88.4% PPV: 73.1% NPV: 87.2% Accu: 83.0%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Divisi et al, 2018 [34]	Meta-analysis	12 studies (1463 patients with 994 malignant SPNs)	FDG PET/CT	NA	Histology, clinical and imaging follow-up	**Diagnosis** Pooled Sens: 81.9% Pooled Spec: 62.4% Pooled +LR: 2.19 Pooled –LR: 0.29 Pooled PPV: 80.2% Pooled NPV: 65.2% Pooled AI: 64.9% Pooled DOR: 7.049 AUC: 0.725	NA	NA
Feng et al, 2018 [35]	Prospective	49 patients (SPNs)	FDG PET/CT	DCE-MRI	Surgical report, biopsy, imaging follow-up	**Differentiating malignant from benign SPNs** ***SUV_{max} of 3.807*** Sens: 75.0% Spec: 70.6% Accu: 73.5% AUC: 0.759	**Differentiating malignant from benign SPNs** ***K^{trans}*** Sens: 90.6% Spec: 82.4% Accu: 87.8% AUC: 0.909 ***K_{ep}*** Sens: 87.5% Spec: 76.5% Accu: 83.4% AUC: 0.838	NA
Sherif et al, 2018 [36]	Prospective	22 patients; 24 PET/CT scans (bronchioalveolar carcinoma)	FDG PET/CT	CT	Clinical and imaging follow-up	**Recurrence** Sens: 100% Spec: 83.3% PPV: 94.1% NPV: 100% Accu: 95.4%	NA	PET/CT scans led to upstaging in 10 cases and downstaging in 1 case in comparison to CT.
Mesothelioma								
Elliott et al, 2018 [37]	Retrospective	101 patients being considered for multimodality therapy (malignant pleural mesothelioma)	FDG PET/CT	CT	Histopathology, clinical and imaging follow-up	**Distant metastases** Sens: 91.7% Spec: 100% PPV: 100% NPV: 98.9%	**Distant metastases** Sens: 33.3% Spec: 98.9% PPV: 80.0% NPV: 91.7%	PET/CT and CT correctly staged the nodal status of 63.3% (38/60) and 45.0% (27/60) of patients, respectively (p=0.001).
Pancreatic Cancer								
Wang et al, 2017 [38]	Meta-analysis	17 studies (1343 patients with potentially operable pancreatic	FDG PET or PET/CT	CT	Pathology	NA	NA	PET or PET/CT showed significantly greater utility than CT in detecting distant metastases (OR=1.52, 95%CI: 1.23-1.88), which prevented

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		cancer)						futile radical resection. There was no significant difference in detecting regional lymph nodes invasion between PET or PET/CT and CT (OR=0.97, 95%CI: 0.63-1.47).
Sarcoma								
Macpherson et al, 2018 [39]	Retrospective	493 patients; 957 PET/CT scans (high-grade bone and soft tissue sarcoma)	FDG PET/CT	CT, MRI	Histology, imaging follow-up	NA	NA	PET/CT upstaged 12.2% (42/344) of patients from M0 to M1. Overall, 20.8% (193/930) of PET/CT scans were considered to have added value over CT and/or MRI at staging, restaging and treatment response.
Kusunoki et al, 2017 [40]	Retrospective	34 patients with suspicious lesions on CE-MRI (uterine sarcoma)	FDG PET/CT	CE-MRI, serum LDH, CA125	Pathology	**Differentiate uterine sarcoma from leiomyoma** ***SUV_{max}>7.5*** Sens: 73.3% Spec: 100% PPV: 100% NPV: 82.6%	**Differentiate uterine sarcoma from leiomyoma** ***Serum LDH*** Sens: 53.3% Spec: 86.3% PPV: 72.7% NPV: 73.0% ***CA125*** Sens: 64.2% Spec: 70.5% PPV: 64.2% NPV: 70.5%	NA
Vadi et al, 2018 [41]	Retrospective	31 patients who underwent surgical resection of primary tumour; 46 PET/CT scans (suspected recurrence of chondrosarcoma)	FDG PET/CT	NA	Histology, clinical or imaging follow-up	**Recurrence (study-based)** Sens: 88.9% Spec: 79.0% PPV: 85.7% NPV: 83.3%	NA	NA
Kim et al, 2018 [42]	Meta-analysis	7 studies (188 patients with GISTs)	FDG PET or PET/CT	NA	Not specified	**Predicting malignant potential** Pooled Sens: 88%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Pooled Spec: 88% Pooled +LR: 7.2 Pooled –LR: 0.13 Pooled DOR: 54 AUC: 0.93		
Unknown Primary Cancer								
Wafaie et al, 2018 [43]	Prospective	52 patients with metastatic lesions that were proven pathologically (cancer of unknown primary)	FDG PET/CT	Physical examination, laboratory tests, endoscopy, chest, abdomen and pelvis CT and/or MRI, mammogram	Pathology, clinical and imaging follow-up	**Primary tumour origin** Sens: 74.4% Spec: 69.2% PPV: 87.9% NPV: 47.4% Accu: 73.1%	NA	NA

*p<0.05

Abbreviations: +LR: positive likelihood ratio; -LR: negative likelihood ratio; ^{11}C-choline: carbon-11 choline; ^{18}F-Choline: fluorine-18 choline; ^{18}F-FCH: ^{18}F-fluoromethyl-dimethyl-2-hydroxyethylammonium; ^{18}F-DOPA: 18-fluorodihydroxyphenylalanine; ^{18}F-FET: O-(2-18F-fluoroethyl)-L-tyrosine; ^{18}F-NaF: ^{18}F-sodiumfluoride; ^{99m}Tc: technetium-99m; ^{131}I: iodine-131; ^{131}I-WBS: radioiodine whole body scan; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine combination chemotherapy; Accu: accuracy/staging accuracy; AI: accuracy index; AUC: area under the curve; BSGI: breast specific gamma imaging; CA125: cancer antigen 125; CeCT: contrast-enhanced computed tomography; cHL: classical Hodgkin lymphoma; CI: confidence interval; CT: computed tomography; DBT: digital breast tomosynthesis; DCE-MRI: dynamic contrast-enhanced magnetic resonance imaging; DLBCL: diffuse large B-cell lymphoma; DM: digital mammography; DOR: diagnostic odds ratio; DR: detection rate; FDG: 2-fluoro-2-deoxy-D-glucose or fluorodeoxyglucose; FIGO: International Federation of Gynecology and Obstetrics; FL: follicular lymphoma; GIST: gastrointestinal stromal tumour; HL: Hodgkin's lymphoma; ILC: invasive lobular carcinoma; iPET-neg: interim positron-emission tomography negative; iPET-pos: interim positron-emission tomography positive; iPET1: interim positron-emission tomography after one doxorubicin, bleomycin, vinblastine, and dacarbazine cycle; iPET2: interim positron-emission tomography after two doxorubicin, bleomycin, vinblastine, and dacarbazine cycles; K^{trans}: trans-endothelial transfer constant; K_{ep}: redistribution rate constant; LDH: lactate dehydrogenase; MIBI: ^{99m}Tc-sestamibi; mL: millilitre; mm: millimetre; MRI: magnetic resonance imaging; NA: not applicable/not available; nCRT: neoadjuvant chemoradiation; ng: nanogram; NHL: non-Hodgkin lymphoma; NPV: negative predictive value; NSCLC: non-small cell lung cancer; OR: odds ratio; PCNSL: primary central nervous system lymphoma; PET: positron emission tomography; PFS: progression-free survival; PPV: positive predictive value; PSA: prostate-specific antigen; SCLC: small cell lung cancer; Sens: sensitivity; Spec: specificity; SPECT: single photon emission computed tomography; SPNs: solitary pulmonary nodules; SUV_{max}: maximum standardized uptake value; Tg: serum thyroglobulin; TgAb: antithyroglobulin antibody; TLG: total lesion glycolysis; TLR: tumour-to-liver ratio; TRUS: transrectal ultrasound; US: ultrasound