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PET Six-Month Monitoring Report 2014-2

Evidence from Primary Studies and Systematic Reviews and Recommendations from Clinical Practice Guidelines July to December 2014

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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 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 eighth 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 articles and abstracts published between July and December 2014 were systematically searched through MEDLINE and EMBASE for evidence from primary studies and systematic reviews. The search strategies used are available on 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 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, TOC, TATE)
    - ^{18}F, ^{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)
3. Published as a full 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 prospective study/randomized controlled trial or ≥50 patients for 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-nine studies from July to December 2014 met the inclusion criteria. A summary of the evidence from the 49 studies can be found in **Appendix 1A: Summary of Studies from July to December 2014**.

Breast Cancer

Three studies met the inclusion criteria (1-3). Compared with conventional explorations, FDG PET/CT upstaged 21.1% of patients and downstaged 16.2%. Stage migration

led to management and/or intent to treat changes in 12.7% of cases (1). In patients with invasive T1 breast cancer, FDG PET/CT demonstrated excellent specificity (100%) in the detection of axillary metastases, but sensitivity (73%) was suboptimal (2). Another study showed that FDG PET/CT has a high positive predictive value (87.1%) for internal mammary lymph node metastasis in clinical stage III breast cancer (3).

Epilepsy

One study met the inclusion criteria (4). With electrocorticography as the referential parameter, PET was more sensitive but less specific than magnetic resonance imaging (MRI) in the localization of the epileptogenic focus. The specificity of PET improved when its data were coregistered with MRI and electrocorticography.

Gastrointestinal Cancer

Six studies met the inclusion criteria (5-10). A comparison of diagnostic performance between FDG PET/CT and other radiological imaging techniques in resectable colorectal liver metastasis patients showed that FDG PET/CT had the lowest sensitivity and accuracy. The sensitivity and accuracy of FDG PET/CT decreased significantly in patients treated with preoperative chemotherapy (5). However, FDG PET/CT changed the management in 23% of patients who were initially deemed operable by CT. As a result, patients staged by FDG PET/CT showed significantly better survival than patients staged by CT alone (6). Following radiofrequency ablation of liver metastases, FDG PET/CT achieved the highest sensitivity for detecting residual tumour within two days of treatment (9). In another study, FDG PET/CT was superior to CT in the staging of colon cancer. For instance, FDG PET/CT correctly rejected lung metastases in 40% and liver metastases in 8% of patients falsely suspected on CT (7). FDG PET/CT also changed the staging and management of 14.1% of rectal cancer patients (8). The use of FDG PET/CT is limited in staging gastric cancer and appeared to be inferior to contrast-enhanced CT in the detection of region lymph node metastasis (10).

Genitourinary Cancer

Two studies met the inclusion criteria (11,12). For the assessment of patients with testicular tumour, FDG PET/CT showed good overall sensitivity (92%) and specificity (84%) for the detection of seminoma lesions. Although the specificity (95%) remained high, the sensitivity decreased to 77% for nonseminoma forms. In addition, FDG PET/CT provided valuable information that allowed clinical management to be changed in 87% of cases (11). In the staging of bladder cancer, FDG PET/CT (54%) was more sensitive than CT (41%) for detecting metastatic disease outside of the pelvis, whereas both FDG PET/CT and CT displayed equally low sensitivity (46%) for detecting pelvic lymph node disease (12).

Gynecologic Cancer

Three studies met the inclusion criteria (13-15). FDG PET/CT was shown to have high diagnostic value (accuracy: 96.8%) in the evaluation of patients with recurrent ovarian cancer and was particularly helpful in guiding therapeutic planning (13). In one prospective study of patients with suspected ovarian cancer, FDG PET/CT and whole-body diffusion-weighted MRI showed comparable accuracy for primary tumour characterization and for detecting retroperitoneal lymphadenopathies, both of which were superior to CT. However, FDG PET/CT (71%) showed lower accuracy for peritoneal staging compared with whole-body diffusion-weighted MRI (91%) and CT (75%) (14). Pooled estimates from a systematic review illustrated that FDG PET or FDG PET/CT had high diagnostic sensitivity and specificity for detecting distant metastasis (87% and 97%, respectively) and local regional recurrence (82% and 98%, respectively) in patients with cervical cancer (15).

Head and Neck Cancer

Five studies met the inclusion criteria (16-20). The diagnostic accuracy of FDG PET/CT was shown to be superior or comparable to standard conventional imaging for the detection of malignant lesions (17) and for the assessment of head and neck squamous cell carcinoma (18). Furthermore, a meta-analysis reported high sensitivity (pooled estimate: 92%) and specificity (pooled estimate: 95%) for FDG PET/CT in detecting distant metastases in patients with suspected recurrent disease after definitive treatment (16). In 41.6% of patients with differentiated thyroid carcinoma, FDG PET/CT revealed the precise anatomical localization of recurrent lesions not seen on I^{131} scan (19). The use of FDG PET/CT to assess treatment response at three months demonstrated poor sensitivity in patients with human papillomavirus-associated oropharyngeal cancer. FDG PET/CT surveillance after three months was more accurate in detecting locoregional recurrence (20).

Hematology Cancer

Eight studies met the inclusion criteria (21-28). Four of the studies evaluated the utility of FDG PET/CT in patients with diffuse large B-cell lymphoma (21-23,26). Using bone marrow biopsy as the reference standard, FDG PET/CT was found to be accurate and complementary for detecting bone marrow involvement. Overall, FDG PET/CT upstaged 6.9% to 28% of patients with negative bone marrow biopsy (21-23). The other study demonstrated FDG PET/CT to be an accurate predictor (93.5%) of relapse after completion of chemotherapy (26). One randomized controlled trial compared the use of FDG PET/CT with the use of ultrasound/chest radiography for follow up of patients with advanced-stage Hodgkin lymphoma. The sensitivity for detection of relapse was similar for the two imaging techniques. However, FDG PET/CT showed lower specificity (86.3% versus 96.3%, p=0.02) and positive predictive value (72.7% versus 90.7%, p=0.01) than ultrasound/chest radiography (25). In the surveillance of transformed indolent lymphoma, FDG PET/CT demonstrated limited clinical benefit in detecting relapse (27). With regard to radiation treatment planning, the addition of FDG PET/CT led to substantial changes in gross tumour volume and clinical target volume (24,28).

Melanoma

One study met the inclusion criteria (29). A systematic review reported high overall sensitivity (pooled estimate: 89.4%) and specificity (pooled estimate: 88.8%) for FDG PET or FDG PET/CT in detecting systemic metastases. A change in stage and/or clinical management was noted in 22% of patients.

Non-Small Cell Lung Cancer and Other Lung Cancer

Eight studies met the inclusion criteria (30-37). The integration of FDG PET/CT as a first-line diagnostic tool to a rapid outpatient diagnostic program produced high sensitivity (97.7%) but poor specificity (60.2%) in the detection pulmonary malignancy (30). Results from two meta-analyses supported the use of FDG PET or FDG PET/CT in the differential diagnosis between malignant and benign pleural lesions and in the assessment of pleural abnormalities in cancer patients, with a superior diagnostic performance over CT alone in both clinical settings (32,33). In newly diagnosed non-small cell lung cancer (NSCLC) patients, FDG PET/CT detected distant unexpected metastases on thorax CT in 28.8% (35). In advanced NSCLC patients, FDG PET/CT was more sensitive than ^{99m}Tc-MDP bone scintigraphy in the detection of bone metastases (36). FDG PET/CT scan after treatment of NSCLC with stereotactic body radiation therapy was specific (94%) but insensitive (50%) for detecting recurrence or treatment failure (37).

Non-FDG Tracers

Seven studies met the inclusion criteria (38-44). Three of the studies evaluated ^{11}C-choline PET/CT only (38,40,41) while one meta-analysis included both ^{11}C- and ^{18}F-choline PET/CT (39). In patients with bladder cancer, ^{11}C-choline PET/CT displayed low sensitivity (42%) but was more accurate than contrast-enhanced CT in the detection of lymph node metastases (38). In patients with prostate cancer, ^{11}C-choline PET/CT also showed low sensitivity (57.1%) comparable to conventional imaging for lymph node metastases (40) and low positive predictive value (34.8%) for detecting single node recurrence (41). Despite the low sensitivity (pooled estimate: 59%) for detecting pelvic lymph node metastases, ^{11}C/^{18}F-choline PET/CT led to a treatment change in 41% of patients, of which 25% had complete prostate-specific antigen response (39). PET/CT imaging with ^{68}Ga-DOTA-NOC was evaluated in the other three studies (42-44). ^{68}Ga-DOTA-NOC PET/CT was shown to be highly accurate in diagnosing neuroendocrine tumours (43) and superior to FDG PET/CT for detecting gastroenteropancreatic neuroendocrine tumours (42). Similarly, ^{68}Ga-DOTA-NOC PET/CT (accuracy: 88.7%) was superior to ^{131}I-MIBG scintigraphy (accuracy: 66.6%) in the diagnosis of pheochromocytoma (44).

Pancreatic Cancer

Two studies met the inclusion criteria (45,46). The authors of a meta-analysis concluded that FDG PET/CT offered no benefit over current primary diagnostic tools (i.e., CT, MRI) in confirming suspected pancreatic cancer (45). In another study, FDG PET/CT detected unsuspected distant metastases in 33% of patients previously evaluated with conventional CT (46).

Pediatric Cancer

One study met the inclusion criteria (47). FDG PET/CT was found to have a low positive predictive value in the staging or post-treatment evaluation of pediatric patients with Hodgkin (65%) and non-Hodgkin (61%) lymphoma. The positive predictive value was higher for other high-grade solid tumours (81%). Negative FDG PET/CT results could reliably predict the absence of malignancy in all forms of cancer (negative predictive value: 100%).

Sarcoma

One study met the inclusion criteria (48). A prospective study reported good accuracy (89.6%) for FDG PET/CT in differentiating benign from malignant solid soft-tissue lesions.

CLINICAL EXPERT REVIEW

Breast Cancer

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

Reviewer's Comments (Dr. Muriel Brackstone)

The three studies identified in this six-month period are insufficient to change current guidelines. One prospective study (T2 or greater tumours) used liver ultrasound and chest x-ray as the conventional imaging, when most physicians would consider CT chest/abdomen/pelvis and bone scan to be the current appropriate staging investigation. Additionally, histological confirmation of upstaging was present in 25% of cases and clinical follow-up for confirmation in 35% of cases; therefore, there are insufficient data from this study alone to confirm the findings of the PET scan (given that a significant amount of downstaging was seen as well as upstaging). In another prospective study, the sensitivity for axillary staging in early tumours is much lower than the current sentinel lymph node biopsy procedure (false negative rate 4% to 8%); therefore, FDG PET/CT does not appear to be a

useful staging procedure for early breast cancers. With respect to the retrospective study that evaluated the utility of PET/CT in identifying internal mammary nodal disease in 249 stage III breast cancer patients, there was no comparator imaging study. Sixty-two of 249 patients had visible internal mammary nodes on PET/CT, which were deemed positive for metastases. Unfortunately, only one-half (n=31) of those patients had histological confirmation of disease.

Overall, in order to confirm the utility of an imaging test for the purposes of staging cancer patients, studies should demonstrate histological or clinical confirmation of disease, particularly in patients who have been upstaged or downstaged using FDG PET/CT. The high positive predictive value seen in PET/CT evaluating internal mammary lymph node metastasis is promising, because this may be an area not as well assessed clinically or with current imaging; however, further studies are required given a lack of confirmation of disease. With the high sensitivity of sentinel lymph node biopsy, it is not expected that PET/CT will be found useful in staging early breast cancer.

Epilepsy

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 in epilepsy remain valid and no changes are required.

Gastrointestinal Cancer

Current Insured Indication (Colorectal Cancer)

- Where recurrent disease is suspected on the basis of an elevated and/or rising carcinoembryronic antigen level(s) during follow-up after surgical resection but standard imaging tests are negative or equivocal; 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 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–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 at high risk for recurrence.
- PET is recommended to determine the site of recurrence in the setting of rising carcinoembryonic antigen when a conventional workup fails to unequivocally identify metastatic disease.
- PET is recommended in the preoperative assessment of colorectal cancer liver metastasis prior to surgical resection.

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. However, the Ozis et al (8) study is interesting, given a considerable amount of patients were upstaged with PET in the primary staging of colorectal cancer. While it does not necessitate a change in the current recommendation at this time, it would be worthwhile to keep a close eye on future studies as they come through and consider discussing them if there is consistent evidence of a benefit of PET in a prospective fashion.

Genitourinary Cancer

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

- A recommendation cannot be made for or against the use of PET in the routine staging of patients with testicular cancer due to insufficient evidence.
- 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.
- A recommendation cannot be made for or against the routine use of PET for evaluation of recurrence due to insufficient evidence.

Reviewer's Comments (Dr. Glen Bauman)

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

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.
- A recommendation cannot be made for or against the use of PET for staging advanced-stage cervical cancer due to insufficient evidence. 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.
- A recommendation cannot be made for or against the use of PET for evaluation of suspected recurrence, due to insufficient evidence.
- 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.

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

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. The studies are either methodologically flawed or lack novelty. A previous study demonstrated that the addition of PET/CT led to a change in radiotherapy treatment in 25% of patients with cervical cancer; however, this warrants further assessment. The recently completed PETLACE trial in Ontario will be of interest.

Head and Neck Cancer

Current Insured Indications

- Head and neck cancer:
    - for the evaluation of metastatic squamous cell carcinoma in neck nodes when the primary disease site is unknown after standard radiological and clinical investigation; or for the staging of nasopharyngeal cancer
- Thyroid cancer:
    - where recurrent or persistent disease is suspected on the basis of an elevated and/or rising thyroglobulin but standard imaging studies are negative or equivocal

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

- 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 Staging)

- PET for the staging of Hodgkin or non-Hodgkin lymphoma being treated with curative intent:
    - for the staging of limited disease as per conventional imaging, or

    - when imaging is equivocal for differentiating between limited and advanced-stage disease
- PET for apparent limited-stage nodal follicular lymphoma or other indolent non-Hodgkin lymphomas where curative radiation therapy is being considered for treatment.

Current Insured Indication (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 early stage Hodgkin lymphoma following two or three cycles of chemotherapy when chemotherapy is being considered as the definitive single modality therapy.

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 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 metastectomy.

Reviewer's Comments (Dr. Tara Baetz)

The systematic review by Rodriguez Rivera et al (29) strongly supports the current recommendations for the utilization of PET/CT in melanoma. The strength of this article may suggest the use of PET be an insured service rather than on the PET registry in stage III patients.

Non-FDG Tracers

No recommendations currently exist for the utilization of PET/CT with non-FDG tracers.

Reviewer's Comments (Dr. Amit Singnurkar)

There is currently not enough evidence to support making appropriate recommendations for the use of PET/CT with non-FDG tracers.

Non-Small Cell Lung Cancer and Other Lung Cancer

Current Insured Indications

- Solitary pulmonary nodule:
    - a 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
    - where curative surgical resection is being considered
- Clinical stage III NSCLC
    - where potentially curative combined modality therapy with radical radiotherapy and chemotherapy is being considered
- Limited-disease small cell lung cancer
    - where combined modality therapy with chemotherapy and radiotherapy is being considered

Current Recommendations for the Utilization of PET/CT in Small Cell Lung Cancer

- PET is recommended for staging in patients with small cell lung cancer who are potential candidates for the addition of thoracic radiotherapy to chemotherapy.

- A recommendation cannot be made for or against the use of PET for the assessment of treatment response in small cell lung cancer 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 due to insufficient evidence.

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

A review was not completed by a member of the Lung Cancer Disease Site Group.

Pancreatic Cancer

Current Registry Indication

- For staging if the patient is a candidate for potentially curative surgical resection (pancreatectomy) as determined by conventional staging.

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.
- 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.
- PET is not recommended for clinical management of suspected recurrence, nor for restaging at the time of recurrence due to insufficient evidence and lack of effective therapeutic options.
- 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. Anand Swaminath)

The current recommendations for the utilization of PET/CT in pancreatic cancer remain valid and no changes are required. The study by Chang et al (46) confirms the need of PET to rule out distant disease when considering radical treatment. However, these patients receiving radiation would not be surgical candidates likely due to significant locally advanced disease; therefore, it doesn't really support the claim. The meta-analysis conducted by Rijkers et al (45) continues to support the recommendation that PET is not useful in diagnosing primary pancreatic cancer.

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, 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 oncology.

Sarcoma

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

Reviewer's Comments (Dr. Gina Diprimio)

The article supports PET as an excellent staging tool and is believed to be underutilized in this area.

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Contact Information

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
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Appendix 1A: Summary of Studies from July to December 2014

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
Breast Cancer								
Cochet et al, 2014 (1)	Prospective	142 patients (biopsy-proven invasive breast cancer and at least T2 tumour)	FDG PET/CT	Physical examination, mammogram and/or US of the breast and liver, chest x-ray and bone scintigraphy (CT of the chest, abdomen, pelvis and/or brain, MRI of the breast and/or brain were also performed in some patients)	Pathology, serial imaging and clinical follow-up	NA	NA	PET/CT upstaged 21.1% (30/142) of patients, including 12 from stage II/III to stage IV and downstaged 16.2% (23/142) of patients, including 4 from stage IV to stage II/III. Of 32 patients with validation of imaging results, stage migration due to PET/CT was correct in 29 (90.6%). PET/CT changed management and/or intent to treat in 12.7% (18/142) of patients (11—from curative to palliative, 4—from palliative to curative, 1—treatment modality was changed but not the intent to treat, 2—change in radiation treatment volume).
Koolen et al, 2014 (2)	Prospective	62 patients from two distinct, prospective trials (invasive T1 breast cancer)	Whole-body FDG PET/CT	MRI, US, bone scintigraphy, chest radiography	Histopathology, additional imaging	**Axillary metastasis** Sens: 73% Spec: 100% PPV: 100% NPV: 72% Accuracy: 84% PET/CT depicted the primary tumour in 87% (54/62) of patients (7 of 7 triple negative and HER2+ patients and 40 of 48 ER+/HER2- patients). PET/CT detected 12 distant lesions in 16% (10/62) of	NA	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
						patients (1—lung metastasis, 3—FP, 8—new primary proliferative lesions)		
Seo et al, 2014 (3)	Retrospective	216 patients (clinical stage III breast cancer)	FDG PET/CT	Physical examination, mammography, US, MRI, chest CT	Histopathology	**Internal mammary lymph node metastasis** PPV: 87.1%	NA	PET/CT scan data changed 9 previously negative readings to positive (3.6%) and 2 previously positive readings to negative (0.8%) for internal mammary lymph node metastasis.
Epilepsy								
Chandra et al, 2014 (4)	Prospective	37 patients (refractory neocortical epilepsy)	FDG PET	MRI	Electrocorticography	**Localization** Sens: 72.6% Spec: 69.9% PPV: 51.7%	**Localization** Sens: 27.4% Spec: 83.2% PPV: 22.2%	NA
Gastrointestinal Cancer								
Rojas Llimpe et al, 2014 (5)	Prospective	51 patients; 175 resected lesions (colorectal liver metastasis)	FDG PET/CT	CT, MRI, CEUS, i-CEUS	Histological examination	**Liver metastasis (Per-lesion basis)** Sens: 60% Spec: 90% PPV: 98% NPV: 24% Accuracy: 64% **Note:** Sensitivity (p=0.000) and accuracy (p=0.001) were significantly lower in patients treated with preoperative chemotherapy than those without.	**Liver metastasis (Per-lesion basis)** ***CT*** Sens: 82% Spec: 60% PPV: 94% NPV: 31% Accuracy: 80% **Note:** Sensitivity (p=0.024) and accuracy (p=0.005) were significantly lower in patients treated with preoperative chemotherapy than those without. ***MRI*** Sens: 91% Spec: 59% PPV: 95% NPV: 45% Accuracy: 88% ***CEUS*** Sens: 81% Spec: 53%	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
							PPV: 92% NPV: 27% Accuracy: 77% ***i-CEUS*** Sens: 96% Spec: 45% PPV: 93% NPV: 60% Accuracy: 90%	
Abbadi et al, 2014 (6)	Retrospective	188 patients with colorectal liver metastases undergoing hepatectomy (57 CT, 131 PET/CT)	Whole-body FDG PET/CT	CT	Histological or cytological confirmation, clinical and radiological follow-up	**Patient outcome (PET/CT staged)** 3-year survival: 79% 5-year survival: 54% Median survival: 6.4 years	**Patient outcome (CT staged)** 3-year survival: 59% 5-year survival: 39% Median survival: 3.9 years	PET/CT resulted in management changes in 23% (30/188) of patients who were initially deemed operable by CT.
Engelmann et al, 2014 (7)	Prospective	65 patients (colon cancer)	FDG PET/CT	CT	Histology, cytology, repeated imaging	**T-staging** Sens: 50-58% Spec: 86-91% Accuracy: 80-82% **N-staging** Sens: 33% Spec: 81-90% Accuracy: 60-66% **M-staging** Sens: 95-100% Spec: 78-87% Accuracy: 85-89%	**T-staging** Sens: 17-25% Spec: 82-93% Accuracy: 70-77% **N-staging** Sens: 17-33% Spec: 81% Accuracy: 53-60% **M-staging** Sens: 84-100% Spec: 35-63% Accuracy: 54-69%	PET/CT correctly rejected lung metastases in 40% (26/65) of patients with falsely suspected lung metastases on CT. Likewise, PET/CT correctly rejected liver metastases in 8% (5/65) of patients with falsely suspected liver metastases on CT.
Ozis et al, 2014 (8)	Prospective	97 patients (primary rectal cancer)	Whole-body FDG PET/CT	CeCT, pelvic MRI and ERUS as deemed necessary	Intraoperative examination, imaging, or histology where possible	NA	NA	PET/CT changed the stage of the disease in 14.4% (14/97) of patients (11 upstaged, 3 downstaged). As a result, patient's treatment strategy was changed in 10 and type of operation was changed in 4.
Zheng et al, 2014 (9)	Systematic review	7 studies (155 patients underwent RFA of liver metastases)	FDG PET or FDG PET/CT	Not specified	Histopathology, clinical and imaging follow-up	**Residual tumour following RFA** ***Within 2 days*** Pooled Sens: 79% Pooled Spec: 84% ***At 1 week*** Pooled Sens: 48% Pooled Spec: 94% ***At 3 months***	NA	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
						Pooled Sens: 52% Pooled Spec: 94%		
Park et al, 2014 (10)	Retrospective	74 patients (gastric cancer)	FDG PET/CT	CeCT	Histopathology	**Primary tumour** Sens: 67% **Region lymph node metastasis** Sens: 34% Spec: 88% PPV: 78% NPV: 78% Accuracy: 58%	**Primary tumour** Sens: 55% **Region lymph node metastasis** Sens: 51% Spec: 79% PPV: 52% NPV: 57% Accuracy: 65%	NA
Genitourinary Cancer								
Ambrosini et al, 2014 (11)	Retrospective	56 patients; 121 scans (testicular tumour)	Whole-body FDG PET/CT	CeCT	Clinical and imaging follow-up	**Seminoma** Sens: 92% Spec: 84% **Nonseminoma** Sens: 77% Spec: 95%	NA	On a scan basis, PET/CT led to a change in clinical management in 87% (106/121) of cases (47 of 51 seminomas [6—chemotherapy started/continued, 3—radiotherapy started/continued, 2—surgery of secondary lesions, 36—clinical surveillance]; 59 of 70 nonseminomas [18—therapy/surgery started/continued, 41—clinical surveillance).
Goodfellow, et al, 2014 (12)	Retrospective	207 patients (MIBC or high-risk non-MIBC being considered for radical cystectomy)	FDG PET/CT	CT	Histopathology, biopsy, follow-up imaging	**Distant metastases** Sens: 54% Spec: 97% PPV: 88% NPV: 85% Accuracy: 86% **Pelvic lymph node involvement** Sens: 46% Spec: 97% PPV: 87% NPV: 81% Accuracy: 82%	**Distant metastases** Sens: 41% Spec: 98% PPV: 88% NPV: 82% Accuracy: 83% **Pelvic lymph node involvement** Sens: 46% Spec: 98% PPV: 93% NPV: 81% Accuracy: 83%	NA
Gynecologic Cancer								
Chen et al, 2014 (13)	Retrospective	152 patients (ovarian cancer)	Whole-body FDG PET/CT	Pelvic US, CT, MRI, bone scanning	Pathology, physical examination, clinical and	**Recurrent disease** Sens: 98.3% Spec: 91.2%	NA	Among 34 patients with increasing CA-125 levels and negative or indeterminate conventional

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
					imaging follow-up	PPV: 97.5% NPV: 93.9% Accuracy: 96.8%		imaging findings, PET/CT detected peritoneal metastasis in 5. Among 23 patients suspected of recurrence, 6 patients avoided unnecessary surgical exploration and further examination after PET/CT results. Among 36 patients who underwent PET/CT to assess the extent of disease, PET/CT detected additional metastatic lesions and changed the management from surgery or radiotherapy to comprehensive treatment with combined chemotherapy. Among 12 patients who underwent PET/CT for evaluation of therapeutic response, 8 had terminated their primary therapy or changed to other chemotherapeutic schemes because PET/CT indicated progressive disease.
Michielsen et al, 2014 (14)	Prospective	32 patients (suspected ovarian cancer)	FDG PET/CT	Clinical and CA-125 assessment, gynecological US, thoraco-abdominal CT, diagnostic open laparoscopy, WB-DWI/MRI	Histopathology, PET/CT	**Primary lesions** Sens: 100% Spec: 33% PPV: 94% NPV: 100% Accuracy: 94% **Peritoneal staging** Sens: 52% Spec: 85% PPV: 73% NPV: 70% Accuracy: 71% **Bowel serosal and mesenterial metastases** Sens: 24% Spec: 93% PPV: 67% NPV: 69%	**Primary lesions** ***WB-DWI/MRI*** Sens: 100% Spec: 50% PPV: 93% NPV: 100% Accuracy: 94% ***CT*** Sens: 96% Spec: 25% PPV: 90% NPV: 50% Accuracy: 88% **Peritoneal staging** ***WB-DWI/MRI*** Sens: 91% Spec: 91% PPV: 89% NPV: 93%	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
						Accuracy: 69% **Retroperitoneal lymphadenopathies** Sens: 77% Spec: 91% PPV: 77% NPV: 91% Accuracy: 87% **Hepatic-hilar lymphadenopathies** Sens: 13% Spec: 100% PPV: 100% NPV: 90% Accuracy: 91%	Accuracy: 91% ***CT*** Sens: 65% Spec: 82% PPV: 74% NPV: 75% Accuracy: 75% **Bowel serosal and mesenterial metastases** ***WB-DWI/MRI*** Sens: 83% Spec: 80% PPV: 69% NPV: 89% Accuracy: 81% ***CT*** Sens: 49% Spec: 91% PPV: 74% NPV: 76% Accuracy: 76% **Retroperitoneal lymphadenopathies** ***WB-DWI/MRI*** Sens: 77% Spec: 91% PPV: 77% NPV: 91% Accuracy: 87% ***CT*** Sens: 54% Spec: 78% PPV: 50% NPV: 81% Accuracy: 71% **Hepatic-hilar lymphadenopathies** ***WB-DWI/MRI*** Sens: 63% Spec: 97% PPV: 71% NPV: 96% Accuracy: 93% ***CT*** Sens: 13%	

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
						Spec: 97% PPV: 33% NPV: 90% Accuracy: 88%		
Chu et al, 2014 (15)	Systematic review	20 studies (patients with cervical cancer)	FDG PET or FDG PET/CT	Not specified	Histopathology, clinical and imaging follow-up	**Distant metastasis** Pooled Sens: 87% Pooled Spec: 97% **Local regional recurrence** Pooled Sens: 82% Pooled Spec: 98%	NA	NA
Head and Neck								
Gao et al, 2014 (16)	Meta-analysis	10 studies (756 patients with suspected recurrent head and neck cancer after definitive treatment)	FDG PET/CT	Not specified	Histopathology, clinical and imaging follow-up	**Distant metastases** Pooled Sens: 92% Pooled Spec: 95% Pooled +LR: 16.7 Pooled -LR: 0.09 Pooled DOR: 195	NA	NA
Kubiessa et al, 2014 (17)	Prospective	17 patients (suspected or known cancer of the head and neck region)	FDG PET/CT	CT, MRI	Consensus from multidisciplinary team, histopathology and imaging follow-up where available	**Malignant lesions** Sens: 78.3-87% Spec: 85.5-89.1% PPV: 71.4-75% NPV: 90.7-94%	**Malignant lesions** ***CT*** Sens: 82.6-91.3% Spec: 70.9-87.3% PPV: 56.8-73.1% NPV: 92.3-95.1% ***MRI*** Sens: 73.9% Spec: 85.5-96.4% PPV: 68-89.5% NPV: 88.7-89.8%	NA
Rohde et al, 2014 (18)	Systematic review and meta-analysis	9 studies (987 patients head and neck squamous cell carcinoma)	FDG PET/CT	MRI, CT	Biopsy	**Diagnosis** Pooled Sens: 89.3% Pooled Spec: 89.5%	**Diagnosis** Pooled Sens: 71.6% Pooled Spec: 78%	NA
Hamed et al, 2014 (19)	Prospective	12 patients (histologically proven differentiated thyroid	Whole-body FDG PET/CT	Whole-body I^{131} scan	Other radiological (US, CT, MRI) and/or cytological	NA	NA	PET/CT revealed the precise anatomical localization of recurrent lesions in 41.6% (5/12) of patients with negative

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
		carcinoma)			(FNAC) investigation			whole body I^{131} scan.
Vainshtein et al, 2014 (20)	Retrospective	101 patients (stage III-V HPV-associated oropharyngeal cancer who completed definitive chemoradiotherapy)	FDG PET/CT	CT	Histology	**Post-treatment assessment at 3 months** ***Primary tumour response*** Sens: 33% Spec: 68-91% PPV: 3-10% NPV: 97-98% Accuracy: 67-89% ***Neck response*** Sens: 0-63% Spec: 70-92% PPV: 0-16% NPV: 91-95% Accuracy: 69-85% **Post-treatment assessment after 3 months** ***Local recurrence*** Sens: 50% Spec: 97% PPV: 33% NPV: 98% Accuracy: 96% ***Regional recurrence*** Sens: 83% Spec: 98% PPV: 83% NPV: 98% Accuracy: 97%	**Post-treatment assessment at 3 months** ***Neck response*** Sens: 62% Spec: 55% PPV: 12% NPV: 94% Accuracy: 52%	NA
Hematology								
Adams et al, 2014 (21)	Systematic review	7 studies (654 patients with newly diagnosed DLBCL)	FDG PET/CT	BMB	BMB, imaging follow-up	**Bone marrow involvement** Pooled Sens: 88.7% Pooled Spec: 99.8%	NA	In one study, PET/CT upstaged 6.9% (9/130) of patients when BMB was negative. In another study, 8.3% (11/133) of patients were upstaged to stage IV due to positive PET/CT while BMB was negative (4 of these patients benefited from a change in consolidation treatment)
Adams et al, 2014 (22)	Retrospective	78 patients (newly	Whole-body FDG PET/CT	BMB	BMB	**Bone marrow involvement**	BMB detected bone marrow	BMB status but not PET/CT bone marrow status was a

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
		diagnosed DLBCL)				Sens: 68.8% (PET/CT detected bone marrow involvement in 43.6% [34/78] patients, of whom 11 of 16 BMB-positive patients were also PET/CT positive)	involvement in 20.5% (16/78) of patients.	significant predictor of PFS (p=0.016) and OS (p=0.004).
Cortes-Romera et al, 2014 (23)	Prospective	147 patients (84 DLBCL, 63 HL)	Whole-body FDG PET/CT	BMB	BMB	**Bone marrow involvement** Sens: 95% Spec: 86% PPV: 54% NPV: 99% Accuracy: 87%	NA	PET/CT upstaged 28% (5/18) of patients with a negative BMB result (2—therapeutic modification).
Girinsky et al, 2014 (24)	Prospective (patients enrolled in the randomized EORTC/LYSA/ FIL Intergroup H10 trial)	135 patients (clinical stages I/II supradiaphragmatic HL)	FDG PET/CT	CT	Multidisciplinary team (radiation oncologist, nuclear medicine physician, radiologist)	NA	NA	In comparison to INRT delineation with CT alone, PET/CT led to an increase in pre-chemotherapy GTV in 64.9% (87/134) of patients (mean volume increase of 8.8%) and a decrease in GTV in 20.9% (28/134) of patients. Likewise, PET/CT increased the post-chemotherapy CTV in 60% (69/115) of patients (mean volume increase of 7.1%) and a decrease in CTV in 6.1% (7/115) of patients.
Picardi et al, 2014 (25)	RCT	300 patients; 1:1 allocation (advanced-stage HL who had responded completely to first-line treatment)	Whole-body FDG PET/CT	US/chest radiography	Histology	**Relapse** Sens: 100% Spec: 86.3% PPV: 72.7% NPV: 100% +LR: 7.3 -LR: 0	**Relapse** Sens: 97.5% Spec: 96.3% PPV: 90.7% NPV: 99.1% +LR: 26.8 -LR: 0.02	Compared with US/chest radiography, PET/CT led to significantly more unnecessary major surgical biopsies, higher ionizing radiation exposure, and higher estimated cost per relapse.
Abo-Sheisha & Fattah, 2014 (26)	Retrospective	62 patients (DLBCL who had CT	FDG PET/CT	CT	Clinical and imaging follow-up	**Prediction of relapse** Sens: 100%	NA	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
		document residual masses)				Spec: 91.7% PPV: 77.8% NPV: 100% Accuracy: 93.5%		
Cheah et al, 2014 (27)	Retrospective	55 patients (transformed indolent lymphoma who achieved complete metabolic remission after primary therapy)	FDG PET/CT	Not specified	Biopsy, clinical follow-up	**Relapse** Sens: 83% Spec: 94% PPV: 63% NPV: 98%	NA	NA
Terezakis et al, 2014 (28)	Prospective	95 patients (70 NHL, 10 HL, 12 plasma cell neoplasm, 3 other)	FDG PET/CT	CT	Multidisciplinary review of imaging	NA	NA	Relative to CT-based treatment planning, PET/CT increased GTV in 38 patients (median volume increase=27%) and decreased GTV in 41 patients (median volume decrease=39.5%) as defined by radiation oncologists. When defined by nuclear medicine physicians, PET/CT increased GTV in 27 patients (median volume increase=26.5%) and decreased GTV in 52 patients (median volume decrease=70%).
Melanoma								
Rodriguez Rivera et al, 2014 (29)	Systematic review	9 studies (623 patients with stage III cutaneous melanoma)	FDG PET or FDG PET/CT	Not specified	Biopsy, clinical follow-up, further imaging	**Systemic metastases** Pooled Sens: 89.4% Pooled Spec: 88.8% Pooled +LR: 7.97 Pooled –LR: 0.12 Pooled DOR: 66.8	NA	PET/CT led to a change in stage and/or management in 22% (126/573) of patients.
Lung Cancer (other than NSCLC)								
Brocken et al, 2014 (30)	Retrospective	386 patients (radiological suspicion	Whole-body FDG PET/CT	Chest x-ray, CT angiography, high-resolution	Pathology, follow-up	**Malignancy** Sens: 97.7% Spec: 60.2%	NA	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
		of lung cancer		CT, FDG PET, bronchoscopy		PPV: 84.0% NPV: 92.5% Accuracy: 85.8%		
Li et al, 2014 (31)	Retrospective	298 patients (clinically suspected pulmonary malignancy)	FDG PET/CT	Not specified	Histopathology	**Malignant lesions** Sens: 80.2% Spec: 38% PPV: 86.5% NPV: 27.9% Accuracy: 73.1%	NA	NA
Treglia et al, 2014 (32)	Meta-analysis	11 studies (212 patients with suspicious malignant pleural mesothelioma or undergoing evaluation for pleural lesions)	FDG PET or FDG PET/CT	CT	Histopathology, biopsy, cytology, clinical and radiological follow-up	**Differential diagnosis between malignant and benign pleural lesions** Pooled Sens: 95% Pooled Spec: 82% Pooled PPV: 90% Pooled NPV: 91% Pooled Accuracy: 90% Pooled +LR: 5.3 Pooled –LR: 0.09 Pooled DOR: 74	NA	NA
Treglia et al, 2014 (33)	Meta-analysis	5 studies (208 patients, lung cancer and pleural effusion)	FDG PET/CT	CT	Histopathology, cytology, biopsy, thoracentesis, follow-up	**Differential diagnosis between malignant and benign pleural abnormalities** Pooled Sens: 81% Pooled Spec: 83% Pooled PPV: 86% Pooled NPV: 77% Pooled Accuracy: 82% Pooled +LR: 3.95 Pooled –LR: 0.24 Pooled DOR: 19.84	NA	NA
NSCLC								
Bugge et al, 2014 (34)	Retrospective	533 patients (potentially operable NSCLC)	FDG PET/CT	Bronchoscopy, diagnostic CT of the thorax and upper abdomen	Histology, cytology, biopsy, MRI	**Malignant lymph nodes in the mediastinum** Sens: 78% Spec: 88% PPV: 64% NPV: 94%	NA	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
						Accuracy: 86%		
Halac et al, 2014 (35)	Retrospective	567 patients (newly diagnosed NSCLC)	FDG PET/CT	Thorax CT	Histopathology, clinical and radiological follow-up	PET/CT detected distant unexpected metastases on thorax CT in 28.8% (163/567) of patients (34 TP; 5 FP—with solitary pulmonary lesions, 129 TP; 17 FP—initial staging).	NA	NA
Inal et al, 2014 (36)	Retrospective	53 patients (advanced NSCLC)	FDG PET/CT	^{99m}Tc-MDP bone scintigraphy	X-ray, MRI, follow-up screening	**Bone metastases** Sens: 90.4% Spec: 99.4% PPV: 98.1% NPV: 96.6% Accuracy: 97.0%	**Bone metastases** Sens: 84.6% Spec: 93.1% PPV: 82.5% NPV: 93.2% Accuracy: 90.8%	NA
Pastis Jr et al, 2014 (37)	Retrospective	88 patients (stage I or II NSCLC who underwent SBRT)	Whole-body FDG PET/CT	CT	Biopsy, radiographic follow-up	**Recurrence or treatment failure** ***3-month post-treatment assessment*** Sens: 50% Spec: 94% PPV: 67% NPV: 89%	NA	NA
Non-FDG tracers ^{11}C/^{18}F-choline								
Brunocilla et al, 2014 (38)	Prospective	26 patients (histologically proven transitional cell carcinoma of the bladder)	^{11}C-choline PET/CT	CeCT	Histopathology	**Lymph node metastases** ***Per-patient basis*** Sens: 42.0% Spec: 84.0% PPV: 50.0% NPV: 85.0% Accuracy: 73.0% ***Per-region basis*** Sens: 11.8% Spec: 82.6% PPV: 33.3% NPV: 55.9% Accuracy: 52.5% ***Per-lymph node***	**Lymph node metastases** ***Per-patient basis*** Sens: 14.3% Spec: 89.5% PPV: 30.0% NPV: 78.0% Accuracy: 6.09% ***Per-region basis*** Sens: 5.9% Spec: 80.0% PPV: 16.7% NPV: 55.6% Accuracy: 50.0% ***Per-lymph node***	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
						basis Sens: 10.5% Spec: 64.0% PPV: 30.7% NPV: 32.0% Accuracy: 31.7%	***basis*** Sens: 2.0% Spec: 63.0% PPV: 9.1% NPV: — Accuracy: 27.7%	
von Eyben & Kairemo, 2014 (39)	Meta-analysis	47 articles (3167 patients with prostate cancer who were examined for staging or restaging of biochemical recurrence)	$^{11}C/^{18}F$-choline PET/CT	Bone scanning, FDG PET/CT	Histology, CI, follow-up	**Pelvic lymph node metastases** Pooled Sens: 59% Pooled Spec: 92% Pooled PPV: 70% Pooled NPV: 85% Pooled +LR: 6.86 Pooled –LR: 0.45 Pooled DOR: 19.17	NA	PET/CT led to a treatment change (palliative to curative or curative to palliative) in 41% (381/938) of patients. The changes yielded complete PSA response in 25% (101/404) of patients.
Heck et al, 2014 (40)	Prospective	33 patients (intermediate- and high-risk prostate cancer undergoing radical prostatectomy and extended pelvic lymph node dissection)	^{11}C-choline PET/CT	CT, DWI/MRI	Histopathology	**Lymph node metastases** ***Per-patient basis*** Sens: 57.1% Spec: 89.5% PPV: 80.0% NPV: 73.9% Accuracy: 75.8% ***Per-field basis*** Sens: 61.8% Spec: 96.0% PPV: 70.0% NPV: 94.4% Accuracy: 91.6%	**Lymph node metastases** ***CT*** ***Per-patient basis*** Sens: 57.1% Spec: 68.4% PPV: 57.1% NPV: 68.4% Accuracy: 63.6% ***Per-field basis*** Sens: 47.1% Spec: 94.3% PPV: 55.2% NPV: 92.2% Accuracy: 88.1% ***DWI/MRI*** ***Per-patient basis*** Sens: 57.1% Spec: 78.9% PPV: 66.7% NPV: 71.4% Accuracy: 69.7% ***Per-field basis*** Sens: 55.9% Spec: 96.5% PPV: 70.4% NPV: 93.6%	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
							Accuracy: 91.9%	
Passoni et al, 2014 (41)	Prospective	46 patients (biochemical recurrence after radical prostatectomy who underwent pelvic or pelvic and retroperitoneal lymph node dissection)	^{11}C-choline PET/CT	Digital rectal examination, abdominopelvic CT, bone scan, prostatic fossa biopsies	Pathology	**Single node recurrence** ***Per-site basis*** PPV: 34.8% ***Per-lymph node basis*** PPV: 23.9%	NA	NA
^{68}Ga-DOTA-NOC								
Naswa et al, 2014 (42)	Retrospective	51 patients (histologically proven GEP-NETs	^{68}Ga-DOTA-NOC PET/CT	FDG PET/CT	Histopathology, morphologic imaging, follow-up imaging with biochemical markers	**Primary and metastatic lesions** ***Per-patient basis*** Sens: 91.4% Spec: 50% PPV: 95.5% NPV: 33.3% Accuracy: 88.2% ***Per-lesion basis*** ***Primary tumour*** Sens: 94.2% Spec: 87.5% Accuracy: 92.1% ***Lymph node*** Sens: 92.8% Spec: 100% Accuracy: 98% ***Liver*** Sens: 80.6% Spec: 100% Accuracy: 88.2% ***Bone*** Sens: 75% Spec: 100% Accuracy: 98%	**Primary and metastatic lesions** ***Per-patient basis*** Sens: 42.5% Spec: 100% PPV: 100% NPV: 12.9% Accuracy: 47% ***Per-lesion basis*** ***Primary tumour*** Sens: 25.7% Spec: 100% Accuracy: 49% ***Lymph node*** Sens: 28.5% Spec: 100% Accuracy: 80% ***Liver*** Sens: 54.8% Spec: 100% Accuracy: 88.2% ***Bone*** Sens: 75% Spec: 100% Accuracy: 98%	NA
Sharma et al, 2014 (43)	Retrospective	164 patients (suspected NET based on clinical features,	^{68}Ga-DOTA-NOC PET/CT	CT, MRI, US, endoscopic US, ^{131}I-MIBG scintigraphy, FDG PET/CT	Histopathology, clinical, biochemical and imaging follow-up	**Diagnosis** Sens: 94.8% Spec: 86.5% PPV: 91% NPV: 92%	NA	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
		raised biochemical markers, and/or imaging findings)				Accuracy: 91.4%		
Sharma et al, 2014 (44)	Retrospective	62 patients (clinical and/or biochemical suspicion of pheochromocytoma and suspicious adrenal lesion on CT)	^{68}Ga-DOTA-NOC PET/CT	^{131}I-MIBG scintigraphy	Histopathology, clinical, biochemical and imaging follow-up	**Diagnosis** ***Per-patient basis*** Sens: 90.4% Spec: 85% PPV: 92.7% NPV: 81% Accuracy: 88.7% ***Per-lesion basis*** Sens: 93.5% Spec: 85.7% PPV: 93.5% NPV: 85.7% Accuracy: 91.1%	**Diagnosis** ***Per-lesion basis*** Sens: 61.2% Spec: 78.5% PPV: 86.3% NPV: 47.8% Accuracy: 66.6%	NA
Pancreatic Cancer								
Rijkers et al, 2014 (45)	Meta-analysis	10 studies (suspected pancreatic cancer)	FDG PET/CT	Not specified	Histopathology, follow-up	**Diagnosis** Pooled Sens: 90% Pooled Spec: 76% Pooled PPV: 89% Pooled NPV: 78% Pooled Accuracy: 86% **Differentiate between pancreatic cancer and chronic pancreatitis** Pooled Sens: 96% Pooled Spec: 17% Pooled PPV: 83% Pooled NPV: 50% Pooled Accuracy: 81%	NA	NA
Chang et al, 2014 (46)	Retrospective	388 patients (locally advanced pancreatic cancer)	FDG PET/CT	CT	Biopsy where available	NA	NA	PET/CT imaging led to the detection of unsuspected distant metastasis in 33% (128/388) of patients with M_0 on conventional CT; these patients received systemic therapy immediately. The remaining

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
								260 patients underwent chemoradiation therapy and PET/CT detected additional lymph node diseases in 17.
Pediatric Cancer								
Bardi et al, 2014 (47)	Retrospective	86 patients (31 HL, 30 NHL, 25 other high-grade solid tumours)	FDG PET/CT	Not specified	Histopathology, repeated imaging and serial clinical follow-up	**Staging or post-treatment evaluation** ***HL*** PPV: 65% NPV: 100% ***NHL*** PPV: 61% NPV: 100% ***Other high-grade solid tumours*** PPV: 81% NPV: 100%	NA	NA
Sarcoma								
Leal et al, 2014 (48)	Prospective	44 patients (suspected soft-tissue lesions)	FDG PET/CT	MRI	Histopathology	**Differentiating benign from malignant lesions (SUV_{max} of 3.0)** Sens: 100% Spec: 83.3% PPV: 78.3% NPV: 100% Accuracy: 89.6%	NA	NA
Various Sites								
Li et al, 2014 (49)	Meta-analysis	13 studies (1067 patients with various primary lesion)	Whole-body FDG PET/CT	WB-DWI/MRI	Histopathology, clinical and imaging follow-up	**Primary and metastatic malignancies** Pooled Sens: 89.5% Pooled Spec: 97.5% Pooled +LR: 26.9 Pooled -LR: 0.07 Pooled DOR: 448.2	**Primary and metastatic malignancies** Pooled Sens: 89.7% Pooled Spec: 95.4% Pooled +LR: 11.9 Pooled -LR: 0.12 Pooled DOR: 120.8	NA

Abbreviations: ^{99m}Tc-MDP: 99mTc-methylene diphosphonate; BMB: bone marrow biopsy; CA-125: cancer antigen 125; CeCT: contrast-enhanced computed tomography; CTV: clinical target volume; CEUS: contrast-enhanced ultrasound; CI: conventional intervention; CT: computed tomography; DOR: diagnostic odds ratio; DLBCL: diffuse large B-cell lymphoma; ERUS: endorectal ultrasound; ER: estrogen receptor; FDG PET/CT: fluorodeoxyglucose positron emission tomography/computed tomography; FP: false positive; FNAC: fine needle aspiration cytology; GEP: gastroenteropancreatic; GTV: gross tumour volume; HL: Hodgkin lymphoma; HER2: human epidermal growth factor receptor 2; HPV: human papillomavirus; i-CEUS: intraoperative CEUS; INRT: involved-field radiation therapy; I^{131}: iodine-131; MIBC: muscle-invasive bladder cancer; MRI: magnetic resonance imaging; NA:

not available; NET: neuroendocrine tumor; NHL: non-Hodgkin lymphoma; NPV: negative predictive value; NSCLC: non-small cell lung carcinoma; -LR: negative likelihood ratio; +LR: positive likelihood ratio; PPV: positive predictive value; RCT: randomized controlled trial; RFA: radiofrequency ablation; Sens: sensitivity; Spec: specificity; SBRT: stereotactic body radiation therapy; SUV_{max}: maximum standardized uptake value;TP: true positive; US: ultrasound; WB-DWI: whole-body diffusion-weighted imaging