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PET Six-Month Monitoring Report 2013-2

Evidence from Primary Studies and Systematic Reviews and Recommendations from Clinical Practice Guidelines July to December 2013

R. Poon and the Program in Evidence-Based Care Disease Site Group Reviewers

Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: September 22, 2014

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 Positron Emission Tomography (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 PET Steering Committee approved this proposal, and this is the sixth 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 2013 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 Ontario PET Steering 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-fluorothymideine) (various)
    - ^{18}F-MISO (hypoxia tracer)
    - ^{18}F-FAZA (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 (RCT) or ≥50 patients for a retrospective study with the disease of interest

Inclusion Criteria for Systematic Reviews

1. Reviewed the use of FDG PET/computerized 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 studies from July to December 2013 met the inclusion criteria. A summary of the evidence from the 40 studies can be found in **Appendix 1A: Summary of Studies from July to December 2013**.

Breast Cancer
Two studies met the inclusion criteria (1,2). For detection of axillary lymph node metastasis in breast cancer, FDG PET/CT (81.1%) was demonstrated to be more accurate than axillary ultrasound (US) (77.1%) and contrast-enhanced magnetic resonance imaging (MRI) (77.9%) (1). In one prospective study, FDG PET/CT had a lower sensitivity (56.2%) than sentinel lymph node biopsy (85.7%) in the evaluation of axillary lymph node involvement, but was shown to be useful in 8.1% of the patients in whom sentinel lymph node biopsy could not identify metastatic spread to the axilla (2).

Esophageal Cancer
Two studies met the inclusion criteria (3,4). In one retrospective study, FDG PET/CT was shown to have a limited role in the initial staging of esophageal squamous cell carcinoma due to low sensitivity for detecting lymph node metastases (3). A systematic review reported high specificity (pooled estimate: 88%) and variable sensitivity for FDG PET/CT in detecting lymph node metastases (4).

Gastrointestinal Cancer
Four studies met the inclusion criteria (5-8). The sensitivity of FDG PET/CT for detecting liver metastasis was comparable to that of conventional imaging studies (digital subtraction angiography, MRI, CT, US) (7,8). In the preoperative assessment of peritoneal carcinomatosis, FDG PET/CT provided better diagnostic accuracy than MRI (6). Additional information obtained from FDG PET/CT altered the initial staging in 21.9% and changed treatment strategies in 3.2% of patients with colorectal cancer (5).

Genitourinary Cancer
One study met the inclusion criteria (9). FDG PET/CT provided additional staging information not detected by contrast-enhanced CT and influenced the treatment of bladder cancer in 13.5% of patients.

Gynecologic Cancer
Two studies met the inclusion criteria (10,11). In patients with endometrial cancer, FDG PET/CT demonstrated high specificity (98.4%) and accuracy (94.7%), but moderate sensitivity (78.6%) for the detection of pelvic and aortic nodal metastases (10). In the diagnosis of clinically suspicious recurrent cervical cancer, FDG PET/CT findings led to a change in management in 58% of patients by uncovering distant metastases and secondary malignancy (11).

Head and Neck Cancer
Seven studies met the inclusion criteria (12-18). Three of the studies evaluated the use of FDG PET/CT in differentiated thyroid cancer. Overall, FDG PET/CT was demonstrated to be superior to other conventional imaging modalities (^{131}I whole body scintigraphy and US) and had an impact on the therapeutic management of 10% to 43% of patients (16,18). In head and neck malignancy, FDG PET/CT showed high diagnostic performance (>90% in sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], and accuracy) in detecting recurrent or metastatic disease (13). Similarly, results from a systematic review confirmed the good diagnostic performance of FDG PET or FDG PET/CT in the M staging of nasopharyngeal carcinoma (12). In patients with malignant salivary gland tumours, FDG PET/CT changed treatment plans in 14.7% of cases due to detection of distant metastasis. Furthermore, FDG PET/CT was found to be comparable to either CT or MRI for cervical lymph node staging, but offered no additional benefit for detecting locoregional recurrence (14).

Hematologic Cancer
Four studies met the inclusion criteria (20-23). FDG PET/CT outperformed bone marrow biopsy or CT in the detection of bone marrow involvement in patients with Hodgkin's or non-Hodgkin's lymphoma (20-22). In particular, FDG PET/CT upstaged 42.3% of patients with negative bone marrow biopsy results (20). Furthermore, FDG PET/CT was able to identify more nodal and extranodal lesions than conventional staging methods, leading to treatment changes in 44.2% of patients (23).

Melanoma
One study met the inclusion criteria (24). PET staging was shown to have added benefit over conventional staging in the initial management of Merkel cell carcinoma patients. FDG PET or FDG PET/CT changed the management plan of 37% of patients and altered the staging of 22%. Impact on management included a change in treatment modality or intent in 19 patients, a change in both treatment modality and radiation therapy technique in four patients, and alteration of radiation technique or dose in 15 patients.

Non-FDG Tracers
Six studies met the inclusion criteria (35-40). The diagnostic performance of ^{11}C and ^{18}F-choline PET or PET/CT in prostate cancer was evaluated in three studies (35-37). In one meta-analysis, ^{11}C and ^{18}F-choline PET or PET/CT was found to have high sensitivity (pooled estimate: 100%) and specificity (pooled estimate: 81.8%) for the detection of lymph node metastases. The pooled sensitivity and specificity for detecting prostatic fossa recurrence were 75.4% and 82.0%, respectively (35). In another study, ^{11}C-choline PET/CT was able to identify prostate cancer lesions that were unnoticed on conventional imaging (CT, MRI, bone scan), thereby changing clinical management in 32% of cases (36). For detecting metastases from postoperative differentiated thyroid cancer, ^{18}F-FLT PET/CT was not found to be superior to FDG PET/CT (38). In neuro-oncology, ^{18}F-FET PET or ^{18}F-FET PET/CT showed a high sensitivity (87%) but modest specificity (68%) for the detection of high-grade brain tumours (39). One prospective study compared 18F-fluoride PET/CT to FDG PET/CT and ^{99m}Tc-MDP bone scan in the detection of bone metastases in patients with breast, lung or prostate cancer. Overall, 18F-fluoride PET/CT was found to be comparable or more accurate than the other two imaging techniques and changed patient management in 3% to 12% of all cases (40).

Non-Small Cell Lung Cancer and Other Lung Cancer
One study met the inclusion criteria (19). Results from a meta-analysis indicated similar diagnostic accuracy between dual time point and single-time point FDG PET/CT in the differential diagnosis of pulmonary nodules. However, dual time point FDG PET/CT appeared to be more specific.

Pancreatic Cancer
Five studies met the inclusion criteria (25-29). Several studies illustrated high sensitivity for FDG PET/CT in differentiating benign from malignant lesions of the pancreas (25,26,28). For detection of lymph node metastasis, FDG PET/CT showed superior diagnostic performance over multidetector CT (27). In another study, FDG PET/CT provided new information that assisted in the decision making about the strategy for therapy in 85% of renal cell carcinoma patients (29).

Pediatric Cancer
One study met the inclusion criteria (30). FDG PET/CT was demonstrated to be more accurate than contrast CT in the initial evaluation of pediatric Hodgkin's and non-Hodgkin's lymphoma.

FDG PET/CT led to significant upstaging in 23.3% of Hodgkin's patients and 33.3% of non-Hodgkin's patients by detecting additional lesions that were not observed on contrast CT.

Unknown Primary

Two studies met the inclusion criteria (31,32). Information provided by FDG PET/CT changed the medical management of 33.8% to 48% of patients due to the identification of primary tumours or additional metastases that were not detected by conventional diagnostic modalities (CT, MRI, single-photon emission computed tomography [SPECT], and mammography) (31,32).

CLINICAL EXPERT REVIEW

Breast Cancer

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

Reviewer's Comments (Dr. Muriel Brackstone)

There is currently not enough evidence to support making appropriate recommendations for the use of PET/CT in breast cancer. One retrospective trial compared PET/CT to axillary ultrasound for staging in early breast cancer and found PET/CT to be 4% more accurate (1). However, PET/CT was not compared with sentinel lymph node staging, which is considered the gold standard axillary staging procedure for early breast cancer. The second study (2) did prospectively compare PET/CT to sentinel lymph node biopsy and found that sentinel lymph node biopsy was superior (sensitivity: 85.7% vs. 56.2%). In spite of this, it appears that PET/CT was able to accurately stage the 8% of patients who had nonidentification by sentinel node biopsy (where dual tracer methodology fails to identify the axillary sentinel lymph node). Therefore, PET/CT may serve as a useful axillary tool in early breast cancer when the sentinel lymph node fails to identify an axillary lymph node instead of axillary dissection, the current standard procedure for this situation. It is worth noting that this represented a small cohort (3/37 patients) and, thus, more research is needed in this area.

Esophageal Cancer

Current Insured Indication

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

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

- For the staging workup of patients with esophageal cancer who are potential candidates for curative therapy, PET is recommended to improve the accuracy of M staging.
- A recommendation cannot be made for or against the use of PET (post 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 due to insufficient evidence.

Reviewer's Comments (Dr. Anand Swaminath)

The current recommendations for the utilization of PET/CT in esophageal cancer 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 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 [ASA] 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 (CEA) 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.

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.

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 radiologic 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 Cancer

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

Reviewer's Comments (Dr. Amit Singnurkar)

The current recommendations for the utilization of PET/CT in head and neck cancer remain valid and no changes are required. The study by Chang et al (12) supports the indication for

nasopharyngeal cancer staging and the Joo et al study (15) is informative, but does not provide a compelling reason to increase the coverage for head and neck patients.

Hematologic Cancer

Current Registry Indication (Lymphoma Staging)

- PET for the staging of Hodgkin's or non-Hodgkin's lymphoma being treated with curative intent:

    a. for the staging of limited disease as per conventional imaging or
    b. 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's 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's or non-Hodgkin's 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's lymphoma following two (2) or three (3) 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's 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 if 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's or non-Hodgkin's lymphoma.
- An FDG PET/CT scan is recommended for the evaluation of residual mass(es) following chemotherapy in a patient with Hodgkin's or non-Hodgkin's lymphoma when further potentially curative therapy (e.g., 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

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

Melanoma

Current Registry Indication

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

Current Recommendations for the Utilization of PET/CT in Melanoma

- PET is recommended for staging of high-risk patients with potentially resectable disease.
- PET is not recommended for the diagnosis of sentinel lymph node micrometastatic disease or for staging of I, IIA, or IIB melanoma.
- The routine use of PET or PET/CT is not recommended for the diagnosis of brain metastases.
- The routine use of PET is not recommended for the detection of primary uveal malignant melanoma.
- A recommendation cannot be made for or against the use of PET for the assessment of treatment response in malignant melanoma due to insufficient evidence.
- A recommendation cannot be made for or against the use of PET for routine surveillance due to insufficient evidence.
- PET is recommended for isolated metastases at time of recurrence or when contemplating metastasectomy.

Reviewer's Comments (Dr. Tara Baetz)

The current recommendations for the utilization of PET/CT in melanoma remain valid and no changes are required. The patient population for the Merkel cell carcinoma study is small and there is unlikely to be large trial data about the role of PET in this tumour site. However, this data would support adding it to the list of registry indications.

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. The study by Damle et al. (40) confirms the signal observed over the years with regards to ^{18}F-fluoride imaging for bone metastases. There is a Canadian multicentre study that will start shortly to look at this topic and it is likely prudent to wait for the results of this study. The study by Evangelista et al. (35) is interesting, but does not provide a sense of how ^{18}F/^{11}C-choline compares to standard imaging and whether there is a change in management.

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 SPN is inaccessible to needle biopsy; or the existence of a contra-indication to the use of needle biopsy.
- Non–small cell lung cancer:
    - Where curative surgical resection is being considered.
- Clinical stage III non–small cell lung cancer:

    - 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 SCLC 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 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 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 RT planning. Current evidence does not support the routine use of PET-CT imaging data in RT planning at this time outside of a research setting.

Reviewer's Comments (Dr. Yee Ung)

The current recommendations for the utilization of PET/CT in lung cancer remain valid and no changes are required. The dual- versus single-time point imaging does not change any of the approved indications.

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 as 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. Despite the high sensitivity demonstrated by PET/CT in

differentiating between malignant and benign pancreatic lesions, the specificity was still quite low. Therefore, it cannot be recommended as a primary diagnostic modality.

Pediatric Cancer

Current Registry Indications (Patients Must Be <18 Years of Age)

- For the following cancer types (ICCC):
  - Bone/Cartilage - Osteosarcoma, Ewings sarcoma
  - Connective/Other soft tissue - Rhabdomyosarcoma, Other
  - Kidney - Renal Tumour
  - Liver - Hepatic Tumour
  - Lymphoma/PTLD – Hodgkin's Lymphoma, Non-Hodgkin's Lymphoma
  - Primary Brain - Astrocytoma, Medulloblastoma, Ependymoma, Other
  - Reproductive - Germ Cell Tumour
  - Sympathetic Nervous System - Neuroblastoma MIBG negative
  - Other – LCH, 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 (Dr. Mark Greenberg)

The current recommendations for the utilization of PET/CT in pediatric cancer remain valid and no changes are required. The Cheng et al. study (30) demonstrated superiority for PET/CT in detecting additional areas of disease and thus upstaging in both Hodgkin's and non-Hodgkin's lymphoma. However, significant limitations of the study include small size, retrospective analysis, and absence of pathologic confirmation of identified sites as true disease sites.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

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:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

REFERENCES

1. Hwang SO, Lee SW, Kim HJ, Kim WW, Park HY, Jung JH. The comparative study of ultrasonography, contrast-enhanced MRI, and 18F-FDG PET/CT for detecting axillary lymph node metastasis in T1 breast cancer. J Breast Canc. 2013 Sep;16(3):315-21.
2. Challa VR, Srivastava A, Dhar A, Parshad R, Bal C, Gona RMR, et al. Role of fluorine-18-labeled 2-fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography in the evaluation of axillary lymph node involvement in operable breast cancer in comparison with sentinel lymph node biopsy. Indian J Nucl Med. 2013 Jul-Sep;28(3):138-43.
3. Manabe O, Hattori N, Hirata K, Itoh K, Hosokawa M, Takahashi H, et al. Diagnostic accuracy of lymph node metastasis depends on metabolic activity of the primary lesion in thoracic squamous esophageal cancer. J Nucl Med. 2013;54(5):670-6.
4. Cheung GSM. Contribution of PET-CT in radiotherapy planning of oesophageal carcinoma: A review. Radiography. 2013 August;19(3):259-69.
5. Cipe G, Ergul N, Hasbahceci M, Firat D, Bozkurt S, Memmi N, et al. Routine use of positron-emission tomography/computed tomography for staging of primary colorectal cancer: does it affect clinical management? World J Surg Oncol. 2013;11:49.
6. Klumpp BD, Schwenzer N, Aschoff P, Miller S, Kramer U, Claussen CD, et al. Preoperative assessment of peritoneal carcinomatosis: intraindividual comparison of 18F-FDG PET/CT and MRI. Abdom Imaging. 2013;38(1):64-71.
7. Xu Y, Lu X, Mao Y, Sang X, Zhao H, Du S, et al. Clinical diagnosis and treatment of alpha-fetoprotein-negative small hepatic lesions. Chin J Cancer Res. 2013 August;25(4):382-8.
8. Park JM, Kim IY, Kim SW, Lee SM, Kim HG, Kim SY, et al. A comparative study of FDG PET/CT and enhanced multi-detector CT for detecting liver metastasis according to the size and location. Ann Nucl Med. 2013;27(3):217-24.
9. Mertens LS, Fioole-Bruining A, Vegt E, Vogel WV, van Rhijn BW, Horenblas S. Impact of (18) F-fluorodeoxyglucose (FDG)-positron-emission tomography/computed tomography (PET/CT) on management of patients with carcinoma invading bladder muscle. BJU Int. 2013;112(6):729-34.
10. Crivellaro C, Signorelli M, Guerra L, De Ponti E, Pirovano C, Fruscio R, et al. Tailoring systematic lymphadenectomy in high-risk clinical early stage endometrial cancer: the role of 18F-FDG PET/CT. Gynecol Oncol. 2013;130(2):306-11.
11. Bhoil A, Mittal BR, Bhattacharya A, Santhosh S, Patel F. Role of F-18 fluorodeoxyglucose positron emission tomography/computed tomography in the detection of recurrence in patients with cervical cancer. Indian J Nucl Med. 2013 October-December;28(4):216-20.
12. Chang MC, Chen JH, Liang JA, Yang KT, Cheng KY, Kao CH. Accuracy of whole-body FDG-PET and FDG-PET/CT in M staging of nasopharyngeal carcinoma: a systematic review and meta-analysis. Eur J Radiol. 2013;82(2):366-73.
13. Nakamura S, Toriihara A, Okochi K, Watanabe H, Shibuya H, Kurabayashi T. Optimal timing of post-treatment [18F]fluorodeoxyglucose-PET/CT for patients with head and neck malignancy. Nucl Med Commun. 2013;34(2):162-7.
14. Park HL, Yoo IR, Lee N, Yoon H, Choi EK, Choi HS, et al. The Value of F-18 FDG PET for Planning Treatment and Detecting Recurrence in Malignant Salivary Gland Tumors: Comparison with Conventional Imaging Studies. Nucl Med Mol Imaging. 2013;47(4):242-8.
15. Joo YH, Yoo IR, Cho KJ, Park JO, Nam IC, Kim MS. Extracapsular spread and FDG PET/CT correlations in oral squamous cell carcinoma. Int J Oral Max Surg. 2013;42(2):158-63.
16. Lee JW, Lee SM, Lee DH, Kim YJ. Clinical utility of 18F-FDG PET/CT concurrent with 131I therapy in intermediate-to-high-risk patients with differentiated thyroid cancer: dual-center experience with 286 patients. J Nucl Med. 2013;54(8):1230-6.

17. Ozkan E, Aras G, Kucuk NO. Correlation of 18F-FDG PET/CT findings with histopathological results in differentiated thyroid cancer patients who have increased thyroglobulin or antithyroglobulin antibody levels and negative 131I whole-body scan results. Clin Nucl Med. 2013;38(5):326-31.
18. Riemann B, Uhrhan K, Dietlein M, Schmidt D, Kuwert T, Dorn R, et al. Diagnostic value and therapeutic impact of (18)F-FDG-PET/CT in differentiated thyroid cancer. Results of a German multicentre study. Nucl Med-Nukl. 2013;52(1):1-6.
19. Zhang L, Wang Y, Lei J, Tian J, Zhai Y. Dual time point 18FDG-PET/CT versus single time point 18FDG-PET/CT for the differential diagnosis of pulmonary nodules: a meta-analysis. Acta Radiol. 2013;54(7):770-7.
20. Berthet L, Cochet A, Kanoun S, Berriolo-Riedinger A, Humbert O, Toubeau M, et al. In newly diagnosed diffuse large B-cell lymphoma, determination of bone marrow involvement with 18F-FDG PET/CT provides better diagnostic performance and prognostic stratification than does biopsy. J Nucl Med. 2013;54(8):1244-50.
21. Cheng G, Alavi A. Value of 18F-FDG PET versus iliac biopsy in the initial evaluation of bone marrow infiltration in the case of Hodgkin's disease: a meta-analysis. Nucl Med Commun. 2013;34(1):25-31.
22. Khan AB, Barrington SF, Mikhaeel NG, Hunt AA, Cameron L, Morris T, et al. PET-CT staging of DLBCL accurately identifies and provides new insight into the clinical significance of bone marrow involvement. Blood. 2013;122(1):61-7.
23. Moon SH, Cho SK, Kim WS, Kim SJ, Chan Ahn Y, Choe YS, et al. The role of 18F-FDG PET/CT for initial staging of nasal type natural killer/T-cell lymphoma: a comparison with conventional staging methods. J Nucl Med. 2013;54(7):1039-44.
24. Siva S, Byrne K, Seel M, Bressel M, Jacobs D, Callahan J, et al. 18F-FDG PET provides high-impact and powerful prognostic stratification in the staging of Merkel cell carcinoma: a 15-year institutional experience. J Nucl Med. 2013;54(8):1223-9.
25. Bertagna F, Treglia G, Baiocchi GL, Giubbini R. F18-FDG-PET/CT for evaluation of intraductal papillary mucinous neoplasms (IPMN): a review of the literature. Jpn J Radiol. 2013;31(4):229-36.
26. Hu SL, Yang ZY, Zhou ZR, Yu XJ, Ping B, Zhang YJ. Role of SUV(max) obtained by 18F-FDG PET/CT in patients with a solitary pancreatic lesion: predicting malignant potential and proliferation. Nucl Med Commun. 2013;34(6):533-9.
27. Raj P, Kaman L, Singh R, Dahyia D, Bhattacharya A, Bal A. Sensitivity and specificity of FDG PET-CT scan in detecting lymph node metastasis in operable periampullary tumours in correlation with the final histopathology after curative surgery. Updates Surg. 2013;65(2):103-7.
28. Santhosh S, Mittal BR, Bhasin D, Srinivasan R, Rana S, Das A, et al. Role of (18)F-fluorodeoxyglucose positron emission tomography/computed tomography in the characterization of pancreatic masses: experience from tropics. J Gastroen Hepatol. 2013;28(2):255-61.
29. Ferda J, Ferdova E, Hora M, Hes O, Finek J, Topolcan O, et al. 18F-FDG-PET/CT in potentially advanced renal cell carcinoma: a role in treatment decisions and prognosis estimation. Anticancer Res. 2013;33(6):2665-72.
30. Cheng G, Servaes S, Zhuang H. Value of (18)F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography scan versus diagnostic contrast computed tomography in initial staging of pediatric patients with lymphoma. Leukemia Lymphoma. 2013;54(4):737-42.
31. Saidha NK, Ganguly M, Sidhu HS, Gupta S. The Role of 18 FDG PET-CT in Evaluation of Unknown Primary Tumours. Indian J Surg Oncol. 2013 Sep;4(3):236-41.

32. Wang G, Wu Y, Zhang W, Li J, Wu P, Xie C. Clinical value of whole-body F-18 fluorodeoxyglucose positron emission tomography/computed tomography in patients with carcinoma of unknown primary. J Med Imag Radiat On. 2013;57(1):65-71.
33. Alfonso A, Redondo M, Rubio T, Del Olmo B, Rodriguez-Wilhelmi P, Garcia-Velloso MJ, et al. Screening for occult malignancy with FDG-PET/CT in patients with unprovoked venous thromboembolism. Int J Cancer. 2013;133(9):2157-64.
34. Nguyen ML, Gervais DA, Blake MA, Mueller PR, Sahani DV, Hahn PF, et al. Imaging-guided biopsy of (18)F-FDG-avid extrapulmonary lesions: do lesion location and morphologic features on CT affect the positive predictive value for malignancy? Am J Roentgenol. 2013;201(2):433-8.
35. Evangelista L, Zattoni F, Guttilla A, Saladini G, Zattoni F, Colletti PM, et al. Choline PET or PET/CT and biochemical relapse of prostate cancer: a systematic review and meta-analysis. Clin Nucl Med. 2013;38(5):305-14.
36. Mitchell CR, Lowe VJ, Rangel LJ, Hung JC, Kwon ED, Karnes RJ. Operational characteristics of (11)c-choline positron emission tomography/computerized tomography for prostate cancer with biochemical recurrence after initial treatment. J Urology. 2013;189(4):1308-13.
37. Rybalov M, Breeuwsma AJ, Leliveld AM, Pruim J, Dierckx RA, de Jong IJ. Impact of total PSA, PSA doubling time and PSA velocity on detection rates of 11C-Choline positron emission tomography in recurrent prostate cancer. World J Urol. 2013;31(2):319-23.
38. Nakajo M, Nakajo M, Jinguji M, Tani A, Kajiya Y, Tanabe H, et al. Diagnosis of metastases from postoperative differentiated thyroid cancer: comparison between FDG and FLT PET/CT studies. Radiology. 2013;267(3):891-901.
39. Hutterer M, Nowosielski M, Putzer D, Jansen NL, Seiz M, Schocke M, et al. [18F]-fluoro-ethyl-L-tyrosine PET: a valuable diagnostic tool in neuro-oncology, but not all that glitters is glioma. Neuro-Oncology. 2013;15(3):341-51.
40. Damle NA, Bal C, Bandopadhyaya GP, Kumar L, Kumar P, Malhotra A, et al. The role of 18F-fluoride PET-CT in the detection of bone metastases in patients with breast, lung and prostate carcinoma: a comparison with FDG PET/CT and 99mTc-MDP bone scan. Jpn J Radiol. 2013;31(4):262-9.

Appendix 1A: Summary of Studies from July to December 2013

Citation	Study type	Population	PET type	CI	Reference standard	Diagnostic accuracy (PET)	Diagnostic accuracy (CI)	Change in patient management
Breast Cancer								
Hwang et al., 2013 (1)	Retrospective	349 patients (T1 breast cancer)	FDG PET/CT	AUS, CeMRI	Histopathology	**Axillary lymph node metastasis** Sens: 44.5% Spec: 94.2% PPV: 73.2% NPV: 82.6% Accuracy: 81.1%	**Axillary lymph node metastasis** ***AUS*** Sens: 44.6% Spec: 88.7% PPV: 58.6% NPV: 81.7% Accuracy: 77.1% ***CeMRI*** Sens: 47.8% Spec: 88.7% PPV: 60.2% NPV: 82.6% Accuracy: 77.9%	NA
Challa et al., 2013 (2)	Prospective	37 patients (biopsy proven breast carcinoma)	FDG PET/CT	SLNB	ALND	**Axillary metastases** Sens: 56.2% Spec: 90.4% PPV: 81.8% NPV: 73% Accuracy: 75.6%	**Axillary metastases** Sens: 85.7% NPV: 90% Accuracy: 93.7%	PET/CT was useful in 8.1% (3/37) of patients in whom SLNB could not detect metastatic spread to axilla
Esophageal Cancer								
Manabe et al., 2013 (3)	Retrospective	156 patients (esophageal cancer)	FDG PET/CT	NA	Histopathology	**Lymph node metastasis** ***SUVmax <5*** Sens: 15.2% Spec: 95.7% PPV: 45.5% NPV: 82.8% ***SUVmax ≥5*** Sens: 41.5% Spec: 92.3% PPV: 76.3% NPV: 71.3%	NA	NA
Cheung, 2013 (4)	Systematic review	37 studies (1921 patients with oesophageal cancer)	FDG PET/CT	CT, EUS	Pathology	**Primary lesions** Overall accuracy: 92.7% **Lymph node metastases** Pooled sens: 66% Pooled spec: 88%	NA	NA
Gastrointestinal Cancer								
Cipe et al.,	Prospective	64 patients	FDG PET/CT	Abdominal-	Histology,	**T staging**	NA	PET/CT results upstaged

Citation	Study type	Population	PET type	CI	Reference standard	Diagnostic accuracy (PET)	Diagnostic accuracy (CI)	Change in patient management
2013 (5)		(39 rectal, 25 colon)		pelvic MDCT and MRI	follow-up imaging	Sens: 95.7% Spec: 75% PPV: 91.8% NPV: 85.7% Accuracy: 90.5% **N staging** Sens: 52.4% Spec: 85% PPV: 88% NPV: 47.4% Accuracy: 63.5%		9.4% (6/64) of patients and downstaged 12.5% (8/64) of patients. Treatment strategies changed in 3.2% (2/64) of patients (1—a chemotherapy regimen for metastatic disease was administered, 1—changed surgical treatment strategy)
Klumpp et al., 2013 (6)	Prospective	15 patients (peritoneal carcinomatosis)	FDG PET/CT	MRI	Surgical exploration, histopathology	Sens: 93% Spec: 96% PPV: 98% NPV: 84% Accuracy: 94%	Sens: 87% Spec: 92% PPV: 97% NPV: 73% Accuracy: 88%	NA
Xu et al., 2013 (7)	Retrospective	103 patients (alpha-fetoprotein–negative small hepatic lesions)	PET/CT	DSA, DCe-MRI, CeUS	Pathology	**Hepatic malignancies** Sens: 88.9%	**Hepatic malignancies** ***DSA*** Sens: 88.2% ***DCe-MRI*** Sens: 93.9% ***CeUS*** Sens: 88.9%	NA
Park et al., 2013 (8)	Retrospective	56 patients (suspected liver metastasis)	FDG PET/CT	MDCT	Histopathology, follow-up imaging	**Liver metastases** Sens: 78%	**Liver metastases** Sens: 77%	NA
Genitourinary Cancer								
Mertens et al., 2013 (9)	Retrospective	96 patients (bladder cancer)	FDG PET/CT	CeCT	Histology, repeat imaging, clinical follow-up	PET/CT detected second primary tumours in 8 patients, which were not detected by CeCT	NA	Clinical management changed in 13.5% (13/96) of patients as a result of PET/CT upstaging (6—direct cystectomy to NIC, 7—curative to palliative)
Gynecologic Cancer								
Crivellaro et al., 2013 (10)	Prospective	76 patients (endometrial cancer)	FDG PET/CT	Chest x-ray, abdominal and pelvic MRI, trans-vaginal US	Histopathology	**Pelvic and aortic nodal metastases** ***Patient-based*** Sens: 78.6% Spec: 98.4% PPV: 91.7% NPV: 95.3% Accuracy: 94.7% ***Lesion-based*** Sens: 67.6%	NA	NA

Citation	Study type	Population	PET type	CI	Reference standard	Diagnostic accuracy (PET)	Diagnostic accuracy (CI)	Change in patient management
						Spec: 98.2% PPV: 76.7% NPV: 97.3% Accuracy: 95.8%		
Bhoil et al., 2013 (11)	Retrospective	53 patients (histologically proven cervical cancer)	FDG PET/CT	Physical examination, laboratory findings, radiological imaging, morphological imaging (CT/MRI)	Histopathology, clinical follow-up	**Recurrent disease** Sens: 97.5% Spec: 63.6% PPV: 90.9% NPV: 87.5%	NA	PET/CT findings influenced management in 58% (30/52) of patients (27—distant metastases, 3—secondary malignancy)
Head and Neck Cancer								
Chang et al., 2013 (12)	Systematic Review	8 studies (1069 patients with nasopharyngeal carcinoma)	FDG PET or FDG PET/CT	Various	Histopathology, clinical or imaging follow-up	**M staging** Pooled sens: 83% Pooled spec: 97% Pooled +LR: 23.38 Pooled –LR: 0.19	NA	NA
Nakamura et al., 2013 (13)	Prospective	319 patients (post-treatment for head and neck malignancy)	FDG PET/CT	NA	Histopathology	**Recurrent or metastatic disease** Sens: 94% Spec: 91% PPV: 91% NPV: 94% Accuracy: 92%	NA	NA
Park et al., 2013 (14)	Retrospective	66 patients (malignant salivary gland tumour)	FDG PET/CT	CT or MRI of the neck with intravenous contrast enhancement	Histology, imaging and clinical follow-up	**Primary tumour** Sens: 91.2% **Locoregional tumour recurrence** Sens: 70.0% Spec: 97.1% PPV: 63.6% NPV: 97.8% Accuracy: 95.3% **Cervical lymph node staging** ***Visual analysis*** Sens: 60.9% Spec: 89.2% PPV: 56.0% NPV: 91.0% Accuracy: 84.0% ***Semiquantitativ***	**Primary tumour** Sens: 94.1% **Locoregional tumour recurrence** Sens: 80.0% Spec: 96.4% PPV: 66.7% NPV: 98.5% Accuracy: 95.3% **Cervical lymph node staging** Sens: 43.5% Spec: 94.1% PPV: 62.5% NPV: 88.1% Accuracy: 84.8%	PET/CT modified the treatment plan from curative surgery to palliative therapy in 14.7% (5/34) of initial staging patients due to detection of distant metastasis

Citation	Study type	Population	PET type	CI	Reference standard	Diagnostic accuracy (PET)	Diagnostic accuracy (CI)	Change in patient management
						e analysis Sens: 39.1% Spec: 95.0% PPV: 64.3% NPV: 87.4% Accuracy: 84.8%		
Joo et al., 2013 (15)	Retrospective	80 patients (oral squamous cell carcinoma)	FDG PET/CT	Physical examination, panendoscopy, CT and/or MRI of the head and neck, chest radiography, laboratory tests	Histology	**Cervical metastases** Sens: 74% Spec: 95%	NA	NA
Lee et al., 2013 (16)	Retrospective	286 patients (differentiated thyroid cancer)	FDG PET/CT	^{131}I whole-body scan	Histopathology, imaging follow-up	PET/CT detected additional recurrent or metastatic lesions that were not observed on the post therapy ^{131}I scan in 14% (39/286) of patients	NA	PET/CT findings led to treatment change from further ^{131}I treatment to surgical resection, EBRT, or multikinase inhibitor therapy in 10% (30/286) of patients
Ozkan et al., 2013 (17)	Prospective	59 patients (differentiated thyroid cancer)	FDG PET/CT	Neck US, thorax CT	Histopathology	**Recurrent disease** Sens: 80% Spec: 27% PPV: 72% NPV: 36% Accuracy: 64%	NA	NA
Riemann et al., 2013 (18)	Retrospective	327 patients (differentiated thyroid cancer)	FDG PET/CT	^{131}I-whole body scintigraphy, US	Histology, clinical and imaging follow-up	Sens: 92% Spec: 95% PPV: 94% NPV: 94% Accuracy: 94%	**^{131}I-whole body scintigraphy** Sens: 65% Spec: 94% **US** Sens: 37% Spec: 94%	PET/CT resulted in management change in 43% (57/133) of patients with proven tumour lesions (27—change surgical approach, 8—additional radioiodine therapy, 15—additional radiotherapy, 3—additional systemic therapy, 6—prevented radioiodine therapy)
Lung Cancer (other than NSCLC)								
Zhang et al., 2013 (19)	Meta-analysis	8 studies (415 patients	FDG PET/CT	NA	Pathology, clinical follow-up	**Differential diagnosis of pulmonary**	NA	NA

Citation	Study type	Population	PET type	CI	Reference standard	Diagnostic accuracy (PET)	Diagnostic accuracy (CI)	Change in patient management
		and 430 pulmonary nodules)				**nodules** ***Dual time point*** Pooled sens: 79% Pooled spec: 73% Pooled +LR: 2.61 Pooled –LR: 0.29 ***Single-time point*** Pooled sens: 77% Pooled spec: 59% Pooled +LR: 1.97 Pooled –LR: 0.37		
Hematologic Cancer								
Berthet et al., 2013 (20)	Retrospective	133 patients (diffuse large B-cell lymphoma)	FDG PET/CT	CT scan of neck, chest, abdomen, and pelvis, BMB	Pathology, follow-up imaging	**Bone marrow involvement** Sens: 93.9% Spec: 99% PPV: 96.9% NPV: 98% Accuracy: 97.7%	**Bone marrow involvement** ***BMB*** Sens: 24.2% Spec: 100% PPV: 100% NPV: 80% Accuracy: 81.2%	42.3% (11/26) of patients with negative BMB results were upstaged to stage IV by PET/CT (4 of these patients benefited from a change in consolidation treatment)
Cheng & Alavi, 2013 (21)	Meta-analysis	6 studies (687 patients with Hodgkin's disease)	FDG PET or FDG PET/CT	BMB	Imaging or clinical follow-up	**Bone marrow infiltration** Pooled sens: 94.5% Pooled spec: 99.5% Pooled PPV: 97.6% Pooled NPV: 98.8% Pooled +LR: 79.65 Pooled –LR: 0.06	**Bone marrow infiltration** Pooled sens: 39.4% Pooled spec: 100% Pooled PPV: 100% Pooled NPV: 87.9% Pooled +LR: 68.37 Pooled –LR: 0.54	NA
Khan et al., 2013 (22)	Retrospective	130 patients (diffuse large B-cell lymphoma)	FDG PET/CT	BMB	Histology	**Bone marrow involvement** Sens: 94% Spec: 100% Accuracy: 98.5%	**Bone marrow involvement** Sens: 40% Spec: 100% Accuracy: 84%	NA
Moon et al., 2013 (23)	Retrospective	52 patients (nasal-type natural killer/T-cell lymphoma)	FDG PET/CT	CeCT scans of neck, chest, and abdomen, physical and bone marrow examinations, biopsy	Biopsy, clinical and imaging follow-up	**Nodal and extranodal lesions** Sens: 97.7% Spec: 99.7% Accuracy: 99.5%	**Nodal and extranodal lesions** Sens: 80.7% Spec: 99.8% Accuracy: 97.9%	PET/CT altered initial staging in 23.1% (12/52) of patients and affected treatment planning in 44.2% (23/52) of patients (2—chemoradiation to chemotherapy, 21—modified radiotherapy field)

Citation	Study type	Population	PET type	CI	Reference standard	Diagnostic accuracy (PET)	Diagnostic accuracy (CI)	Change in patient management
Melanoma								
Siva et al., 2013 (24)	Prospective	102 patients (Merkel cell carcinoma)	FDG PET or FDG PET/CT	Physical examination, chest imaging with radiography or CT, CT of the locoregional nodal stations	Histology, clinical follow-up	NA	NA	PET/CT staging differed from conventional staging in 22% (22/102) of patients (17—upstaged, 5—downstaged). PET/CT resulted in a change in management plan for 37% (38/102) of patients (14—change in treatment modality, 5—change in treatment intent, 4—change in both treatment modality and radiation therapy technique, 15—alteration of radiation therapy technique or dose)
Pancreatic Cancer								
Bertagna et al., 2013 (25)	Meta-analysis	5 studies (308 patients with intraductal papillary mucinous neoplasms)	FDG PET or FDG PET/CT	Various	Histology, long-term follow-up	**Differential diagnosis between benign and malignant** Pooled sens: 88% Pooled spec: 98%	NA	NA
Hu et al., 2013 (26)	Retrospective	80 patients (solitary pancreatic lesions)	FDG PET/CT	MRI, enhanced CT	Histopathology	**Pancreatic malignancies** Sens: 96.3% Spec: 61.5% PPV: 88.9% NPV: 83.9% Accuracy: 85.0%	NA	NA
Raj et al., 2013 (27)	Prospective	24 patients (periampullary carcinoma)	FDG PET/CT	MDCT	Histopathology	**Lymph node metastasis** ***≥2.0 SUV$_{max}$*** Sens: 71.4% Spec: 77.8% PPV: 71.4% NPV: 77.8% Accuracy: 75% ***≥2.5 SUV$_{max}$*** Sens: 57.1% Spec: 77.8% PPV: 66.7% NPV: 70% Accuracy: 68.8% ***≥2.8 SUV$_{max}$***	**Lymph node metastasis** Sens: 28.6% Spec: 55.6% PPV: 33.3%	NA

Citation	Study type	Population	PET type	CI	Reference standard	Diagnostic accuracy (PET)	Diagnostic accuracy (CI)	Change in patient management
						Sens: 42.9% Spec: 77.8% PPV: 60% NPV: 63.6% Accuracy: 62.5%		
Santhosh et al., 2013 (28)	Prospective	87 patients (diagnosed to have periampullary or pancreatic mass)	FDG PET/CT	CT, MRI, EUS	Histopathology	**Characterizing benign and malignant lesions** Sens: 93% Spec: 90% PPV: 95% NPV: 87% Accuracy: 92%	NA	NA
Ferda et al., 2013 (29)	Retrospective	60 patients (locally advanced or generalized renal cell carcinoma)	FDG PET/CT	Two-phase CT-angiography	Histology, clinical follow-up	NA	NA	PET/CT provided new information in 85% (51/60) of the patients (26—demonstrated metastases, 18—led to radical surgery, 7—demonstrated tumorous invasion into the inferior vena cava)
Pediatric Cancer								
Cheng et al., 2013 (30)	Retrospective	51 patients (30 HD, 21 NHL)	FDG PET/CT	Contrast CT	Pathology, clinical and imaging follow-up	Detected 94.8% (HD) and 88.3% (NHL) of all lesions. Detected additional lesions in 50% (HD) and 42.9% (NHL) of patients	Detected 82.6% (HD) and 69.1% (NHL) of all lesions. Detected additional lesions in 16.7% (HD) and 23.8% (NHL) of patients	PET/CT led to upstaging in 23.3% (7/30) of HD patients and 33.3% (7/21) of NHL patients
Unknown Primary								
Saidha et al., 2013 (31)	Retrospective	50 patients (metastases of unknown primary tumour)	FDG PET/CT	CT/MRI scans, mammography, endoscopies, tumour marker assays	Histology	**Primary lesion** ***Patients with extracervical metastases*** Sens: 39.3% PPV: 92% ***Patients with cervical metastases*** Sens: 61.5% PPV: 72.2%	In all cases, the primary tumour could not be detected by conventional diagnostic modalities	PET/CT results influenced the oncological treatment of 48% (24/50) of patients (21—specific oncological treatment started due to identification of primary site, 3—disease stage modified due to detection of additional metastases)
Wang et al., 2013 (32)	Retrospective	142 patients (carcinoma of unknown primary)	FDG PET/CT	SPECT, CT	Histopathology, imaging and clinical follow-up	**Primary site** Sens: 95.7% Spec: 91.7% Accuracy: 93.7%	NA	PET/CT scan changed the medical management of 33.8% (48/142) of patients (34—initiated a specific

Citation	Study type	Population	PET type	CI	Reference standard	Diagnostic accuracy (PET)	Diagnostic accuracy (CI)	Change in patient management
								oncological treatment, 14—disease stage and therapeutic plan changed due to detection of unexpected metastases)
Various Sites								
Alfonso et al., 2013 (33)	Prospective	99 patients (unprovoked venous thromboembolism)	FDG PET/CT	MDCT, MRI, ventilation/ perfusion scintigraphy, angiography, Doppler US, venography, CT	Diagnostic and clinical follow-up	**Occult malignancy** Sens: 77.8% Spec: 73.3% PPV: 22.6% NPV: 97.1%	NA	NA
Nguyen et al., 2013 (34)	Retrospective	227 patients (231 PET-positive lesions)	FDG PET/CT	CT	Pathology	**Malignancy** PPV: 71.9%	NA	NA
Other PET Tracers 11C/18F-choline								
Evangelista et al., 2013 (35)	Meta-analysis	19 articles (1555 prostate cancer patients)	11C/18F-choline PET or 11C/18F-choline PET/CT	Various	Histology, biopsy, imaging and clinical follow-up	**All sites** Pooled sens: 85.6% Pooled spec: 92.6% Pooled +LR: 8.53 Pooled –LR: 0.17 **Lymph node mets** Pooled sens: 100% Pooled spec: 81.8% Pooled +LR: 3.72 Pooled –LR: 0.03 **Prostatic fossa recurrence** Pooled sens: 75.4% Pooled spec: 82.0% Pooled +LR: 2.35 Pooled –LR: 0.44	NA	NA
Mitchell et al., 2013 (36)	Retrospective	176 patients (biochemically recurrent prostate	11C-choline PET/CT	CT, MRI, bone scan	Histology, follow-up imaging	**Recurrent disease** Sens: 93% Spec: 76% PPV: 91%	NA	PET/CT findings not identified on conventional imaging led to changes in management in 32% (56/176) of scans

Citation	Study type	Population	PET type	CI	Reference standard	Diagnostic accuracy (PET)	Diagnostic accuracy (CI)	Change in patient management
		cancer)				NPV: 81%		(2—observation, 12—targeted biopsy, 18—surgical resection, 7—anatomically targeted therapy, 17—systemic therapy)
Rybalov et al., 2013 (37)	Retrospective	185 patients (biochemically recurrent prostate cancer)	11C-choline PET/CT	CT, bone scan	Histology, confirmatory imaging, clinical follow-up	**Local recurrences** Sens: 80% Spec: 65% **Metastases** Sens: 95%	NA	NA
18F-FLT								
Nakajo et al., 2013 (38)	Prospective	20 patients (postoperative differentiated thyroid cancer)	18F-FLT PET/CT	FDG PET/CT	Histology, clinical and imaging follow-up	**Metastasis (patient-based)** Sens: 69.2% Spec: 28.6% PPV: 64.3% NPV: 33.3% Accuracy: 55.0% **Lymph node metastasis (lesion-based)** Sens: 50.0% Spec: 90.7% PPV: 42.5% NPV: 92.9% Accuracy: 85.7% **Distant metastasis (lesion-based)** Sens: 6.8% Spec: 100% PPV: 100% NPV: 75.3% Accuracy: 75.7%	**Metastasis (patient-based)** Sens: 92.3% Spec: 85.7% PPV: 92.3% NPV: 85.7% Accuracy: 90.0% **Lymph node metastasis (lesion-based)** Sens: 85.3% Spec: 99.6% PPV: 96.7% NPV: 98.0% Accuracy: 97.9% **Distant metastasis (lesion-based)** Sens: 45.2% Spec: 100% PPV: 100% NPV: 83.8% Accuracy: 85.7%	NA
18F-FET								
Hutterer et al., 2013 (39)	Retrospective	393 patients (236 glial tumours, 69 nonglial tumours, 13 inflammatory brain lesions, 74 other brain lesions)	18F-FET PET or 18F-FET PET/CT	MRI	Histology	**Brain tumours** Sens: 87% Spec: 68% PPV: 91% NPV: 58%	NA	NA
18F-Fluoride								

Citation	Study type	Population	PET type	CI	Reference standard	Diagnostic accuracy (PET)	Diagnostic accuracy (CI)	Change in patient management
Damle et al., 2013 (40)	Prospective	151 patients (30 NSCLC, 72 breast, 49 prostate)	18F-fluoride PET/CT	FDG PET/CT, 99mTc-MDP bone scan	Histology when feasible	**Bone metastases** ***NSCLC:*** Sens: 100% Spec: 63.6% PPV 83.6% NPV: 100% Accuracy: 86.7% ***Breast:*** Sens: 100% Spec: 71.1% PPV: 75.6% NPV: 100% Accuracy: 84.7% ***Prostate:*** Sens: 100% Spec: 70.6% PPV: 86.5% NPV: 100% Accuracy: 89.8%	**Bone metastases** ***NSCLC:*** **FDG PET/CT** Sens: 78.9% Spec: 100% PPV: 100% NPV: 73.3% Accuracy: 86.7% **99mTc-MDP** Sens: 100% Spec: 54% PPV: 79.2% NPV: 100% Accuracy: 83.3% ***Breast:*** **FDG PET/CT** Sens: 73.5% Spec: 97.4% PPV: 96.2% NPV: 80.4% Accuracy: 86.1% **99mTc-MDP** Sens: 91.2% Spec: 63.2% PPV: 68.9% NPV: 88.9% Accuracy: 76.4% ***Prostate:*** **FDG PET/CT** Sens: 71.9% Spec: 100% PPV: 100% NPV: 65.4% Accuracy: 81.6% **99mTc-MDP** Sens: 96.9% Spec: 41.2% PPV: 75.6% NPV: 87.5% Accuracy: 77.5%	18F-fluoride PET/CT changed management in 3% of NSCLC patients, 11% of patients with breast cancer and 12% of prostate cancer patients

Abbreviations: 99mTc-MDP: ^{99m}Tc-Methyl diphosphonate; ALND: axillary lymph node dissection; AUS: axillary ultrasonography; BMB: bone marrow biopsy; CeCT: contrast-enhanced computed tomography; CeMRI: contrast-enhanced magnetic resonance imaging; CeUS: contrast-enhanced ultrasonography; CI: conventional imaging; DCe-MRI: dynamic contrast-enhanced magnetic resonance imaging; DSA: digital subtraction angiography; EBRT: external-beam radiation therapy; EUS: endoscopic ultrasonography; FDG: 18-flurodeoxyglucose; HD: Hodgkin's disease; NHL: non Hodgkin lymphoma; MDCT: multidetector computed tomography; NA: not available; NIC: neoadjuvant/induction chemotherapy; -LR: negative likelihood ratio; NPV: negative predictive value; NSCLC: non-small cell lung cancer; PET: positron emission tomography; +LR: positive likelihood ratio;

PPV: positive predictive value; Sens: sensitivity; SLNB: sentinel lymph node biopsy; Spec: specificity; SPECT: single-photon emission computed tomography; SUV_{max}: maximum standardized uptake value