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PET Six-Month Monitoring Report 2015-1

Evidence from Primary Studies and Systematic Reviews and Recommendations from Clinical Practice Guidelines January to June 2015

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

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

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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 ninth 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 January and June 2015 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)
    - ^{18}F-FDOPA
    - ^{68}Ga-PSMA (prostate-specific membrane antigen)
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

Twenty-six studies from January to June 2015 met the inclusion criteria. A summary of the evidence from the 26 studies can be found in **Appendix 1: Summary of Studies from January to June 2015**.

Breast Cancer

One study met the inclusion criteria (1). FDG PET/CT was less sensitive but more specific than magnetic resonance imaging (MRI) in the detection of additional ipsilateral lesions in patients with invasive lobular carcinoma (sensitivity: 0% versus 87.5%, p=0.001; specificity: 91.7% versus 58.3%, p=0.008) and invasive ductal carcinoma (sensitivity: 37.5% versus 100%, p<0.001; specificity: 94.7% versus 66.7%, p<0.001). The diagnostic performance for detecting additional contralateral lesions or axillary lymph node metastasis was similar between the two imaging modalities.

Gastrointestinal Cancer

Three studies met the inclusion criteria (2-4). In patients with rectal cancer who have undergone preoperative chemoradiation, the restaging accuracy of FDG PET/CT (65.7%) was superior to that of MRI (55.2%) for predicting pathologic complete response (2). In addition, results from a prospective study showed that FDG PET/CT was sensitive (96.6%) and accurate (93.3%) for detecting recurrent colorectal carcinoma. FDG PET/CT changed the stage of the disease in 42.7% of patients and influenced treatment decisions by 40% (3). For assessing the viability of hepatocellular carcinoma after transcatheter arterial chemoembolization, the accuracy of FDG PET/CT was shown to be higher than that of contrast-enhanced CT (80.2% versus 67.0%, p=0.04) (4).

Genitourinary Cancer

One study met the inclusion criteria (5). FDG PET/CT efficiently detected local recurrence and distant metastases with high sensitivity (92%), positive predictive value (PPV) (94%), and accuracy (90%) in the restaging of patients following radical cystectomy due to muscle-invasive bladder carcinoma.

Gynecologic Cancer

Two studies met the inclusion criteria (6,7). In patients with suspected recurrence of cervical squamous cell cancer, FDG PET/CT was demonstrated to have a higher sensitivity (100% versus 72.1%) but lower specificity (80.8% versus 92.3%) than squamous cell carcinoma antigen assay for the detection of tumour recurrence or malignancy. However, the overall accuracy favoured FDG PET/CT (95.5% versus 76.8%) (6). In another retrospective study of patients with cervical cancer, FDG PET/CT displayed very poor sensitivity (30.6% to 33.3%) but high specificity (92.7% to 98.9%) for detecting lymph node metastasis. Similar results were observed in the endometrial cancer population (7).

Head and Neck Cancer

Two studies met the inclusion criteria (8,9). Both were prospective studies that evaluated the clinical impact of FDG PET/CT on patient management. In advanced oral cavity squamous cell carcinoma, an additional FDG PET/CT scan before adjuvant radiotherapy or concurrent chemoradiotherapy modified the treatment plans of 14% of patients (8). In head and neck squamous cell cancer, FDG PET/CT upstaged 28.6% of patients and impacted radiation therapy planning in 42.9%. Compared with CT-alone contours, FDG PET/CT increased clinical target volumes by an average of 11.8% (9).

Hematologic Cancer

One study met the inclusion criteria (10). From a randomized controlled trial involving patients with negative PET findings after receiving three cycles of standard ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy, results did not show the noninferiority of the strategy of no further treatment as compared with consolidation

radiotherapy with respect to progression-free survival (rate ratio: 1.57, p=0.16). Thus, consolidation radiotherapy can be avoided for patients with negative PET findings.

Non-FDG Tracers

Four studies met the inclusion criteria (11-14). One prospective study compared the diagnostic performance of ^{18}F-choline PET/CT and diffusion-weighted MRI in the staging of patients with high-risk prostate cancer. On a patient-based analysis, ^{18}F-choline PET/CT displayed higher sensitivity (78% versus 33%, p=0.015) and PPV (78% versus 50%, p=0.015) in the detection of lymph node involvement, whereas diffusion weight MRI showed greater specificity (69% versus 44%) for sextant analysis and sensitivity (73% versus 36%) for detecting seminal vesicle invasion (11). Two studies evaluated ^{68}Ga-DOTA-TATE PET/CT, one in primary or recurrent meningioma and the other in metastatic pheochromocytoma and paraganglioma. Regarding the differentiation of meningioma from tumour-free tissue, ^{68}Ga-DOTA-TATE PET/CT showed a higher sensitivity (90.1% versus 79.0%, p=0.049) than MRI while specificity (73.5% versus 64.7%) and PPV (89.0% versus 84.2%) were only marginally better (12) for ^{68}Ga-DOTA-TATE PET/CT. In the other study, the sensitivity (91.5% versus 51.3% and 15.7%, p<0.0001, respectively) and accuracy (92.6% versus 57.8% and 26.0%, p<0.0001, respectively) of ^{68}Ga-DOTA-TATE PET/CT were superior to both FDG PET/CT and ^{123}I-metadiodbenzylguandine (^{131}I-MIBG) scintigraphy in mapping metastatic pheochromocytoma and paraganglioma on a per-lesion basis (13). The utility of ^{18}F-FLT PET/CT in squamous cell head and neck carcinomas was demonstrated in one prospective study where 73.1% of patients were upstaged and 11.5% of patients were downstaged as a result of ^{18}F-FLT PET/CT findings. This led to a change in treatment strategy in 42.3% of cases (14).

Mesothelioma

One study met the inclusion criteria (15). Compared with contrast-enhanced CT, the diagnostic accuracy of FDG PET/CT was found to be higher for T staging (92% versus 84%) but lower for N staging (78% versus 87%) of malignant pleural mesothelioma.

Non-Small Cell Lung Cancer and Other Lung Cancer

Six studies met the inclusion criteria (9,16-20). In the diagnosis of solitary pulmonary lesions, FDG PET/CT using the corrected standardized uptake value (SUV) of 1.1 was shown to have great value for improving accuracy (15). However, FDG PET/CT with a SUV_{max} of 2.0 showed poor diagnostic accuracy (67% versus 84% and 76%, respectively) and specificity (31% versus 71% and 49%, respectively) in comparison to dynamic perfusion area-detector CT and dynamic MRI (17). In patients with non-small cell lung cancer (NSCLC), FDG PET/CT was more useful than CT in assessing mediastinal lymph nodes (18) but appeared to have limitations in detecting hilar lymph node involvement (19,20). In another study, FDG PET/CT upstaged 16.1% of patients and impacted the radiation therapy planning in 45.2% (9).

Neuro-oncology

One study met the inclusion criteria (21). The diagnostic capability of FDG PET/CT for grading meningioma was found to be comparable to that of thallium-201 single-photon emission CT.

Pancreatic Cancer

One study met the inclusion criteria (22). FDG PET with SUV_{max} of 2.5 achieved high sensitivity (100%) but low specificity (62.5%) and accuracy (66.7%) for differentiating G3 pancreatic neuroendocrine tumours (PNETs) from G1/G2 PNETs. Likewise, when the cut-off

tumour size of 25 mm was used, the sensitivity, specificity, and accuracy for the differential diagnosis were 100%, 50.0%, and 55.6%, respectively.

Pediatric Cancer

Three studies met the inclusion criteria (23-25). Overall, FDG PET/CT was superior or comparable to conventional imaging for staging and follow-up of pediatric osteosarcoma and Ewing sarcoma. Specifically, FDG PET/CT provided diagnostic benefit in 47.7% of patients with Ewing sarcoma and 45% of patients with osteosarcoma (23). In childhood rhabdomyosarcoma, a systematic review also reported the superiority of FDG PET or PET/CT over conventional imaging in the detection of nodal involvement and distant metastatic spread. FDG PET or PET/CT changed the management or treatment course of 17.5% of patients in this population (24). For detection of primary neuroblastoma, FDG PET/CT had a higher sensitivity than ^{123}I-MIBG scan (25).

Unknown Primary Cancer

One study met the inclusion criteria (26). FDG PET/CT was more sensitive (69% versus 16% and 41%, respectively) and more accurate (77% versus 42% and 48%, respectively) than either contrast-enhanced CT or CT/MRI when detecting primary tumours in patients with cervical metastases of unknown primary tumours. FDG PET/CT depicted primary tumours in 50% of patients previously undetected by CT/MRI, and revealed additional cases of synchronous cancers and distant metastases.

CLINICAL EXPERT REVIEW

Breast Cancer

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

Reviewer's Comments (Dr. Muriel Brackstone)

Based on the one study published within the current six-month period, there remains insufficient data to support the use of PET imaging (PET-MRI or PET-CT) for primary breast cancer diagnostic imaging. This study was designed to evaluate whether PET imaging would be beneficial over standard MRI in the diagnostic phase for patients with the invasive lobular cancer subtype. It retrospectively compared invasive lobular cancers with invasive ductal cancers in three ways: the ability of either imaging tool to identify other foci of disease within the same breast (ipsilateral lesions), in the other breast (contralateral lesions), or within the axillary lymph nodes (regional staging). The ability of the diagnostic imaging modality to determine extent of disease or presence of multifocal or multicentric disease determines what the surgical plan should be, and is therefore critical for breast cancer care. Flawed by a small sample size, retrospective nature and differences in tumour biology, the authors found that PET-CT failed to identify other primary lesions within the ipsilateral breast in invasive lobular cancer patients (sensitivity of 0%), but with higher specificity (91.7%) compared with MRI. In identifying cancers in the contralateral breast or disease in the axillary lymph nodes, PET-CT and MRI performed similarly. Therefore, PET-CT would not be clinically beneficial based on these data. No data have been found to date that have supported the role of PET imaging in screening, diagnosis, or surveillance among breast cancer patients.

Gastrointestinal Cancer

Current Insured Indication (Colorectal Cancer)

- Where recurrent disease is suspected on the basis of an elevated and/or rising carcinoembryonic antigen level(s) during follow-up after surgical resection but standard imaging tests are negative or equivocal; 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 change is required. The Huh et al (2) study looked at PET as a modality to evaluate response to treatment (i.e., complete response rate) and found that it was better than conventional imaging; however, it has a small number of non-randomized patients. Nevertheless, this study should be reassessed once more publications come out suggesting PET as being useful in this manner.

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. However, it does seem like there is an increasing number of studies on PET in bladder cancer and this may suggest a need for its own systematic review. The other area where PET is evolving quickly is in prostate cancer with non-FDG agents and it might be worth considering a similar retrospective review. In particular, fairly large ^{18}F-fluoromethylcholine and PSMA PET series have arisen in the last year or two.

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 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 Cancer

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

Reviewer's Comments (Dr. Amit Singnurkar)

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

Hematologic Cancer

Current Registry Indication (Lymphoma 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.

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 (Dr. Donna Maziak)

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

Neuro-oncology

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

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

Reviewer's Comments (Dr. Amit Singnurkar)

The current recommendations for the utilization of PET/CT in neuro-oncology remain valid and no changes are required.

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 change is required.

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.

Unknown Primary Cancer

Current Recommendation for the Utilization of PET/CT in Unknown Primary Cancer

- PET is recommended in all patients after conventional imaging and in addition to, or prior to, diagnostic panendoscopy where the primary site is unknown.

Reviewer's Comments (Dr. Amit Singnurkar)

The current recommendation for the utilization of PET/CT in unknown primary cancer remains valid and no change is required.

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

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Appendix 1: Summary of Studies from January to June 2015

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
Breast Cancer								
Jung et al, 2015 (1)	Retrospective	105 patients (32 ILC, 73 IDC)	FDG PET/CT	Breast MRI	Pathology, follow-up studies	**Additional ipsilateral lesions** ***ILC*** Sens: 0% Spec: 91.7% Accuracy: 68.8% ***IDC*** Sens: 37.5% Spec: 94.7% Accuracy: 82.2% **Additional contralateral lesions** ***ILC*** Sens: 100% Spec: 100% Accuracy: 100% ***IDC*** Sens: 100% Spec: 95.8% Accuracy: 95.9% **Axillary lymph node metastasis** ***ILC*** Sens: 60.0% Spec: 72.7% Accuracy: 68.8% ***IDC*** Sens: 40.7% Spec: 80.4% Accuracy: 65.8%	**Additional ipsilateral lesions** ***ILC*** Sens: 87.5% Spec: 58.3% Accuracy: 65.6% ***IDC*** Sens: 100% Spec: 66.7% Accuracy: 74.0% **Additional contralateral lesions** ***ILC*** Sens: 100% Spec: 93.6% Accuracy: 93.8% ***IDC*** Sens: 100% Spec: 93.1% Accuracy: 93.2% **Axillary lymph node metastasis** ***ILC*** Sens: 50.0% Spec: 81.8% Accuracy: 71.9% ***IDC*** Sens: 48.2% Spec: 82.6% Accuracy: 69.9%	NA
Gastrointestinal Cancer								
Huh et al, 2015 (2)	Prospective	181 patients (locally advanced rectal cancer who received neoadjuvant chemoradia	FDG PET/CT	Pelvic MRI	Pathology	**Predicting pathologic CR** Sens: 73.1% Spec: 64.5% PPV: 25.7% NPV: 93.5% Accuracy: 65.7%	**Predicting pathologic CR** Sens: 38.5% Spec: 58.1% PPV: 13.3% NPV: 84.9% Accuracy: 55.2%	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
		tion treatment)						
Artiko et al, 2015 (3)	Prospective	75 patients (resected primary colorectal adenocarcinoma)	FDG PET/CT	Contrast-enhanced MDCT, MRI, CEA	Histopathology, clinical and imaging follow-up	**Recurrent disease** Sens: 96.6% Spec: 82.4% PPV: 94.9% NPV: 87.5% Accuracy: 93.3% **Local recurrence** Sens: 88.0% Spec: 96.6% PPV: 88.0% NPV: 96.6% Accuracy: 94.7% **Distant metastatic disease** Sens: 94.9% Spec: 87.5% PPV: 96.6% NPV: 82.4% Accuracy: 93.3%	NA	PET/CT changed the stage of the disease in 42.7% (32/75) of patients (20 upstaged, 12 downstaged). Treatment changes occurred in 40% (30/75) of patients.
Song et al, 2015 (4)	Retrospective	73 patients; 91 lesions (hepatocellular carcinoma after transcatheter arterial chemoembolization)	Whole-body FDG PET/CT	CECT	Histopathology, clinical follow-up, digital subtraction angiography, biochemical and serial imaging studies	**Tumour viability** Sens: 89.3% Spec: 65.7% PPV: 80.7% NPV: 79.3% Accuracy: 80.2 AUC: 0.78	**Tumour viability** Sens: 60.7% Spec: 77.1% PPV: 81.0% NPV: 55.1% Accuracy: 67.0% AUC: 0.69	NA
Genitourinary Cancer								
Ozurk & Karapolat, 2015 (5)	Retrospective	51 patients (underwent radical cystectomy due to MIBC and had a PET/CT scan for restaging)	FDG PET/CT	Multidetector CT urography, MRI	Histopathology, clinical follow-up	**Recurrent or metastatic lesions** Sens: 92% Spec: 83% PPV: 94% NPV: 77% Accuracy: 90%	NA	NA
Gynecologic Cancer								
Hu et al, 2015 (6)	Retrospective	112 patients (suspected recurrence of cervical	FDG PET/CT	SCCAg assay	Histopathology, clinical or imaging follow-up	**Recurrent disease** Sens: 100% Spec: 80.8%	**Recurrent disease** Sens: 72.1% Spec: 92.3%	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
		squamous cell cancer)				PPV: 94.5% NPV: 100% Accuracy: 95.5%	PPV: 96.9% NPV: 50% Accuracy: 76.8%	
Nogami et al, 2015 (7)	Retrospective	123 patients (70 cervical cancer, 53 endometrial cancer)	FDG PET/CT	Not specified	Pathology	**Lymph node metastasis** ***Cervical cancer (Per-patient basis)*** Sens: 33.3% Spec: 92.7% PPV: 55.6% NPV: 83.6% +LR: 4.58 -LR: 0.72 Accuracy: 80.0% ***(Per-region basis)*** Sens: 30.6% Spec: 98.9% PPV: 55.0% NPV: 97.0% +LR: 27.6% -LR: 0.70 Accuracy: 96.0% ***Endometrial cancer (Per-patient basis)*** Sens: 50.0% Spec: 93.9% PPV: 40.0% NPV: 95.8% +LR: 8.17 -LR: 0.53 Accuracy: 90.6% ***(Per-region basis)*** Sens: 45.0% Spec: 99.4% PPV: 64.3% NPV: 98.6% +LR: 69.3 -LR: 0.55 Accuracy: 98.0%	NA	NA
Head and Neck Cancer								
Kang et al, 2015 (8)	Prospective	658 patients with	FDG PET/CT	No FDG PET/CT	Histopathology, imaging	NA	NA	19 (14%) patients had their treatment modified by

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
		advanced oral cavity squamous cell carcinoma (136 PET/CT, 522 no PET/CT)			follow-up			preradiotherapy/concurrent chemoradiotherapy PET/CT (15—curative intent due to presence of locoregional disease, 4—palliative care due to distant metastases).
Davis et al, 2015 (9)	Prospective	49 patients (head and neck squamous cell cancer)	FDG PET/CT	CT, MRI	Departmental treatment planning constraints and metrics	NA	NA	As a result of PET/CT, 26.5% (13/49) of patients had nodal status upstaged while 2% (1/49) of patients had an upstage of both tumour and nodal status. PET/CT findings impacted the radiation therapy planning of 42.9% (21/49) of patients (2—radiation therapy intent from radical to palliative, 1—increase in radiation therapy dose, 18—rejected CT-alone test treatment plan). On average, PET/CT increased CTVs by 11.8%.
Hematologic Cancer								
Radford et al, 2015 (10)	RCT	602 patients; 1:1 allocation (newly diagnosed stage IA or IIA Hodgkin lymphoma who received 3 cycles of ABVD chemotherapy)	FDG PET or PET/CT (patients with negative PET findings were randomly assigned to receive 30 Gy of involved-field radiotherapy; n=209 or no further treatment; n=211)	NA	Routine clinical evaluation and CT scans after completion of the assigned treatment	NA	NA	The 3-year PFS was 94.6% in the radiotherapy group and 90.8% in the no further treatment group with a non-significant rate ratio of 1.57 (95% CI: 0.84-2.97; p=0.16). The 3-year OS was 97.1% in the radiotherapy group and 99.0% in the no further treatment group with a non-significant rate ratio of 0.51 (95% CI: 0.15-1.68; p=0.27).
Non-FDG Tracers ^{18}F-Choline								
Pinaquy et al, 2015 (11)	Prospective	47 patients (high-risk prostate cancer)	^{18}F-Choline PET/CT	DWIMRI	Histopathology	**Lymph node involvement** ***Per-patient basis***	**Lymph node involvement** ***Per-patient basis***	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
						Sens: 78% Spec: 94% PPV: 78% NPV: 94% ***Per-lymph node basis*** Sens: 56% Spec: 98% PPV: 56% NPV: 98% **Sextant invasion** Sens: 91% Spec: 44% PPV: 86% NPV: 57% **Capsular invasion** Sens: 76% Spec: 77% PPV: 86% NPV: 63% **Seminal vesicle invasion** Sens: 36% Spec: 98% PPV: 80% NPV: 90%	Sens: 33% Spec: 91% PPV: 50% NPV: 84% ***Per-lymph node basis*** Sens: 17% Spec: 99% PPV: 33% NPV: 97% **Sextant invasion** Sens: 72% Spec: 69% PPV: 89% NPV: 41% **Capsular invasion** Sens: 72% Spec: 77% PPV: 86% NPV: 59% **Seminal vesicle invasion** Sens: 73% Spec: 95% PPV: 95% NPV: 73%	
^{68}Ga-DOTATATE								
Rachinger et al, 2015 (12)	Prospective	21 patients (primary or recurrent meningiomas)	^{68}Ga-DOTATATE PET/CT	MRI	Histopathology	**Differentiation of tumour from tumour-free tissue** Sens: 90.1% Spec: 73.5% PPV: 89.0% NPV: 75.8% Accuracy: 85.2%	**Differentiation of tumour from tumour-free tissue** Sens: 79.0% Spec: 64.7% PPV: 84.2% NPV: 56.4% Accuracy: 74.8%	NA
Tan et al, 2015 (13)	Prospective	17 patients (clinically proven or suspicious metastatic pheochromocytoma or paraganglioma)	^{68}Ga-DOTATATE PET/CT	FDG PET/CT, ^{131}I-MIBG scintigraphy	Histopathology, anatomical and functional imaging	**Metastatic disease** ***(Per-patient basis)*** Sens: 93.3% Spec: 100% Accuracy: 94.1% ***(Per-lesion basis)*** Sens: 91.5% Spec: 100%	**Metastatic disease** ***FDG PET/CT (Per-patient basis)*** Sens: 90.9% Spec: 100% Accuracy: 91.7% ***(Per-lesion basis)*** Sens: 51.3%	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
						Accuracy: 92.6%	Spec: 100% Accuracy: 57.8% ***^{131}I-MIBG scintigraphy (Per-patient basis)*** Sens: 46.7% Spec: 100% Accuracy: 52.9% ***(Per-lesion basis)*** Sens: 15.7% Spec: 100% Accuracy: 26.0%	
^{18}F-FLT								
Vojtisek et al, 2015 (14)	Prospective	26 patients (squamous cell carcinoma of the head and neck)	^{18}F-FLT PET/CT	Neck US, chest x-ray	Pathology, all accessible clinical information	NA	NA	^{18}F-FLT PET/CT led to upstaging of the disease in 73.1% (19/26) of patients and downstaging in 11.5% (3/26) of patients. Consequently, a change in treatment strategy occurred in 42.3% (11/26) patients (6—radiotherapy conducted for palliative purposes, 4—adjuvant to radical radiotherapy, 1—radiotherapy was abandoned).
Mesothelioma								
Frauenfelder et al, 2015 (15)	Retrospective	62 patients (malignant pleural mesothelioma undergoing induction chemotherapy)	FDG PET/CT	CECT	Pathology	**T staging** Sens: 80% Spec: 95% PPV: 80% NPV: 95% Accuracy: 92% **N staging** Sens: 80% Spec: 78% PPV: 57% NPV: 91% Accuracy: 78% **IMIG staging** Sens: 66% Spec: 95% PPV: 66% NPV: 95% Accuracy: 91%	**T staging** Sens: 40% Spec: 95% PPV: 66% NPV: 87% Accuracy: 84% **N staging** Sens: 70% Spec: 97% PPV: 85% NPV: 88% Accuracy: 87% **IMIG staging** Sens: 50% Spec: 89% PPV: 50% NPV: 89% Accuracy: 82%	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
Lung Cancer (other than NSCLC)								
Ming et al, 2015 (16)	Retrospective	69 patients (peripheral solitary pulmonary lesions)	FDG PET/CT	Not specified	Pathology	**Diagnosis** ***$SUV_{corrected}$* of 1.1** Sens: 100% Spec: 91.7% PPV: 98.3% NPV: 100% Accuracy: 98.5% ***SUV_{max} of 2.5*** Sens: 94.7% Spec: 58.3% PPV: 90.2% NPV: 70.0% Accuracy: 88.7%	NA	NA
Ohno et al, 2015 (17)	Prospective	198 patients; 218 nodules (solitary pulmonary nodules)	FDG PET/CT	Dynamic CE perfusion area-detector CT, dynamic CEMRI	Microbiologic examination, cytology or histology, follow-up CT	**Differentiation of malignant from benign nodules** ***(SUV_{max} of 2.0)*** Sens: 89% Spec: 31% PPV: 67% NPV: 65% Accuracy: 67%	**Differentiation of malignant from benign nodules** ***Dynamic CE perfusion area-detector CT (Total perfusion)*** Sens: 92% Spec: 71% PPV: 83% NPV: 86% Accuracy: 84% ***Dynamic CEMRI (Maximum relative enhancement ratio)*** Sens: 92% Spec: 49% PPV: 74% NPV: 81% Accuracy: 76% ***(Slope of enhancement ratio)*** Sens: 93% Spec: 49% PPV: 74% NPV: 82% Accuracy: 76%	NA
NSCLC								
d'Amico et al,	Prospective	80 patients	FDG PET/CT	CT	Histopathology	**Mediastinal**	**Mediastinal**	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
2015 (18)		(NSCLC)				**lymph node involvement** Sens: 68% Spec: 79% PPV: 55% NPV: 87% Accuracy: 76%	**lymph node involvement** Sens: 39% Spec: 70% PPV: 35% NPV: 74% Accuracy: 61%	
Pepek et al, 2015 (19)	Retrospective	484 patients (resected NSCLC)	FDG PET or PET/CT	Not specified	Pathology	**Hilar (N1) lymph node involvement** Sens: 44% Spec: 83% PPV: 37% NPV: 86% Accuracy: 76%	NA	NA
Pattenden et al, 2015 (20)	Retrospective	247 patients (pulmonary carcinoid tumours)	FDG PET/CT	Not specified	Pathology	**Mediastinal lymph node disease** Sens: 33% Spec: 94% **Hilar lymph node disease** Sens: 16% Spec: 91%	NA	NA
Davis et al, 2015 (9)	Prospective	31 patients (NSCLC)	FDG PET/CT	CT, MRI	Departmental treatment planning constraints and metrics	NA	NA	As a result of PET/CT, 12.9% (4/31) of patients had nodal status upstaged while 3.2% (1/31) of patients had tumour status upstaged. PET/CT findings impacted the radiation therapy planning in 45.2% (14/31) of patients (2—radiation therapy intent from radical to palliative, 2—radiation therapy cancelled, 10—rejected CT-alone test treatment plan). On average, PET/CT increased CTV volumes by 3.1%.
Neuro-oncology								
Okuchi et al, 2015 (21)	Retrospective	67 patients (meningioma)	FDG PET/CT	Thallium-201 SPECT	Histopathology	**Differentiate between low- and high-grade meningiomas** SUV_{max} Sens: 72.7%	**Differentiate between low- and high-grade meningiomas** TUR_{mean} Sens: 72.7%	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
						Spec: 87.5% AUC: 0.817 ***$SUVR_{max}$*** Sens: 72.7% Spec: 83.9% AUC: 0.781	Spec: 82.1% AUC: 0.810 ***TUR_{max}*** Sens: 90.9% Spec: 71.4% AUC: 0.831	
Pancreatic Cancer								
Tomimaru et al, 2015 (22)	Prospective	36 patients (pancreatic neuroendocrine tumours)	FDG PET	Tumour size	Histology	**Differentiate between G1/G2 and G3 tumours *(SUV_{max} of 2.5)*** Sens: 100% Spec: 62.5% Accuracy: 66.7%	**Differentiate between G1/G2 and G3 tumours *(25 mm cutoff)*** Sens: 100% Spec: 50.0% Accuracy: 55.6%	NA
Pediatric Cancer								
Quartuccio et al, 2015 (23)	Retrospective	64 patients; 412 lesions (20 osteosarcoma, 44 Ewing sarcoma)	FDG PET/CT	CT, MRI, bone scanning	Histopathology, clinical and imaging follow-up	**Staging or follow-up** ***Ewing sarcoma*** Sens: 90.3% Spec: 77.8% PPV: 69.9% NPV: 93.3% Accuracy: 82.0%	**Staging or follow-up** ***Ewing sarcoma*** ***CT*** Sens: 71.1% Spec: 84.5% PPV: 69.2% NPV: 85.6% Accuracy: 80.1% ***MRI*** Sens: 92.1% Spec: 77.2% PPV: 72.9% NPV: 93.6% Accuracy: 83.2% ***Bone scanning*** Sens: 42.3% Spec: 66.7% PPV: 62.9% NPV: 46.4% Accuracy: 52.8% ***Osteosarcoma*** ***CT*** Sens: 89.3% Spec: 72.2% PPV: 83.1% NPV: 81.3% Accuracy: 82.4% ***MRI*** Sens: 80.0% Spec: 100% PPV: 100% NPV: 80.0%	PET/CT provided diagnostic benefit in 47.7% (21/44) of patients with Ewing sarcoma and 45% (9/20) of patients with osteosarcoma. Management changes occurred in at least 9 of 64 patients as a result of PET/CT findings, which included the initiation, direction, or avoidance of biopsies and initiation of radiotherapy or chemotherapy.

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
							Accuracy: 88.9% ***Bone scanning*** Sens: 66.7% Spec: 25.0% PPV: 57.1% NPV: 33.3% Accuracy: 50.0%	
Norman et al, 2015 (24)	Systematic review	8 studies (272 patients with rhabdomyosarcoma)	FDG PET or PET/CT	MRI, US, CECT, CT, BMB, chest radiography, bone scintigraphy	Histopathology, clinical examination, follow-up	**Nodal involvement** Sens: 80% or 100% Spec: 89%-100% **Distant metastatic involvement** Sens: 95% or 100% Spec: 80%-100%	**Nodal involvement** Sens: 67%-86% Spec: 90% or 100% **Distant metastatic involvement** Sens: 17%-83% Spec: 43%-100%	PET/CT changed the management or treatment course of 17.5% (7/40) of patients in 3 studies that reported this outcome.
Fawzy et al, 2015 (25)	Prospective	30 patients (neuroblastoma)	FDG PET/CT	^{123}I-MIBG	CT/MRI, bone scan, BMA/BMB	**Primary tumour** Sens: 81.8% Spec: 100% PPV: 100% NPV: 66.6% Accuracy: 86.6% **Bone metastasis** Sens: 60.0% Spec: 95.0% PPV: 85.0% NPV: 82.6% Accuracy: 83.3% **Bone marrow involvement** Sens: 28.5% Spec: 100% PPV: 100% NPV: 61.5% Accuracy: 66.6%	**Primary tumour** Sens: 50.0% Spec: 100% PPV: 100% NPV: 42.1% Accuracy: 86.6% **Bone metastasis** Sens: 30.0% Spec: 100% PPV: 100% NPV: 74.0% Accuracy: 76.6% **Bone marrow involvement** Sens: 21.4% Spec: 100% PPV: 100% NPV: 59.2% Accuracy: 66.3%	NA
Unknown Primary Cancer								
Lee et al, 2015 (26)	Prospective	56 patients (cervical metastasis of an unknown primary tumour)	FDG PET/CT	CECT, CECT/MRI	Histopathology	**Primary tumours** Sens: 69% Spec: 88% PPV: 88% NPV: 69% Accuracy: 77%	**Primary tumours** ***CECT*** Sens: 16% Spec: 76% PPV: 45% NPV: 41% Accuracy: 42% ***CECT/MRI*** Sens: 41% Spec: 59%	PET/CT depicted primary tumours in 50% (8/16) of false-negative CECT/MRI cases, 1 distant metastatic case, and 2 cases of synchronous cancers. These findings guided adequate surgical resection or radiation therapy targeting the primary tumour and

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
							PPV: 61% NPV: 38% Accuracy: 48%	neck, initiated proper surgical management, and changed treatment strategy to palliative chemotherapy.

Abbreviations: ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; AUC: area under the curve; BMB: bone marrow biopsy; CEA: carcinoembryogenic antigen; CeCT: contrast-enhanced computed tomography; CI: conventional intervention; CR: complete response; CTV: clinical target volume; CT: computed tomography; FDG PET/CT: fluorodeoxyglucose positron emission tomography/computed tomography; ^{18}F-FLT: [^{18}F]3-deoxy-^{3}F-fluorothymidine; Gy: gray; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; ^{131}I-MIBG: Iodine-131 metaiodobenzylguanidine; MDCT: multidetector computed tomography; MIBC: muscle-invasive bladder cancer; MRI: magnetic resonance imaging; NA: not available; NPV: negative predictive value; NSCLC: non-small cell lung carcinoma; -LR: negative likelihood ratio; OS: overall survival; PFS: progression-free survival; +LR: positive likelihood ratio; PPV: positive predictive value; RCT: randomized controlled trial; SCCAg: squamous cell carcinoma antigen; Sens: sensitivity; Spec: specificity; $SUV_{corrected}$: corrected standardized uptake value; $SUVR_{max}$: maximum standardized uptake value ratio; SUV_{max}: maximum standardized uptake value; TUR_{max}: maximum T1 uptake ratio; TUR_{mean}: mean T1 uptake ratio; US: ultrasound; WB-DWI: whole-body diffusion-weighted imaging