PET Six-Month Monitoring Report 2014-1

Evidence from Primary Studies and Systematic Reviews and Recommendations from Clinical Practice Guidelines January to June 2014

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Report Date: December 4, 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 Committee approved this proposal, and this is the seventh 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 2014 were systematically searched through MEDLINE and EMBASE for evidence from primary studies and systematic reviews. The search strategies used are available on request to the PEBC.

Inclusion Criteria for Clinical Practice Guidelines

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

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

Inclusion Criteria for Primary Studies

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

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

Inclusion Criteria for Systematic Reviews

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

Exclusion Criteria

1. Letters and editorials.

RESULTS

Literature Search Results

Primary Studies and Systematic Reviews

Twenty-eight studies from January to June 2014 met the inclusion criteria. A summary of the evidence from the 28 studies can be found in **Appendix 1A: Summary of Studies from January to June 2014**.

Bone Cancer

Two studies met the inclusion criteria (1,2). For the detection of bone metastases, the specificity and accuracy of FDG PET/CT were higher compared with conventional ^{99m}Tc-

methyl diphosphonate (^{99m}Tc-MDP) bone scan, while the sensitivity was lower (1). When compared to FDG PET or CT alone, FDG PET/CT demonstrated the highest diagnostic performance (i.e., sensitivity, specificity, positive predictive value, negative predictive value) (2).

Breast Cancer

One study met the inclusion criteria (3). FDG PET/CT was shown to be superior to conventional radiological imaging (ultrasound, x-ray, magnetic resonance imaging [MRI], bone scan, CT, sonomammography) by detecting additional lymph node lesions (40.1% more) and distant metastatic lesions (47.3% more). Due to the detection of metastatic lesions on FDG PET/CT, 33.3% of patients were upstaged and had their plan of management changed from surgery to chemotherapy.

Esophageal Cancer

One study met the inclusion criteria (4). In patients with primary esophageal cancer, FDG PET/CT demonstrated an overall sensitivity of 54.1% for diagnosing synchronous cancer in other organs.

Gastrointestinal Cancer

Three studies met the inclusion criteria (5,6,8). FDG PET/CT and multidetector CT showed comparable accuracy in detecting lymph node metastasis in patients with clinical stage III (42% vs. 36.2%, p=0.822) and stage IV (63.5% vs. 60.3%, p=0.509) colon cancer. The addition of FDG PET/CT led to a change in management plan for 6.8% of all cases (5). In a randomized clinical trial that evaluated the role of FDG PET/CT in the surgical management of colorectal liver metastases, 8% of patients had a revised plan based on FDG PET/CT results (6). The diagnostic accuracy of FDG PET/CT in the detection of gallbladder cancer was assessed in one prospective study. Diagnosis of the primary lesion (95.9%), lymph node involvement (85.7%), and metastatic disease (95.9%) were accurately made with FDG PET/CT. Furthermore, FDG PET/CT findings led to the modification of the therapy approach in 22.4% of patients (8).

Genitourinary Cancer

Two studies met the inclusion criteria (7,9). In patients with muscle-invasive bladder cancer who underwent initial conventional CT staging, FDG PET/CT revealed previously undetected metastases in 36.9% (59/160) of cases (7). When a lesion with high FDG uptake was considered to be metastatic, FDG PET/CT achieved higher accuracy (89.7%) at diagnosing adrenal metastasis than CT alone (85.3%) (9).

Gynecologic Cancer

Three studies met the inclusion criteria (10-12). Two systematic reviews examined the diagnostic accuracy of FDG PET/CT in the detection of recurrent cervical cancer. In both studies, the pooled sensitivity of FDG PET/CT was similar to that of FDG PET alone, CT or MRI (11,12). The pooled specificity of FDG PET/CT was found to be higher than that of CT (11) but lower than that of FDG PET alone (12). In another study of patients with cervical cancer, the addition of FDG PET/CT changed the stage of lymph node status and radiotherapy treatment volume in 25% of those who received definitive radiochemotherapy and 7.7% of those who received adjuvant radio/chemoradiation (10).

Head and Neck Cancer

Three studies met the inclusion criteria (13-15). In the response assessment of patients with head and neck squamous cell carcinoma, FDG PET/CT and MRI showed similar diagnostic

performance at 12 weeks post-treatment, but by 24 weeks, FDG PET/CT was superior (13). With respect to staging, FDG PET/CT (95%) was more sensitive in identifying positive disease than CT (81%) or MRI (74%) (14). The sensitivity of FDG PET/CT (71%) in detecting occult neck metastasis was also observed to be higher than that of CT/MRI (50%) (15).

Hematology Cancer

Two studies met the inclusion criteria (16,17). In lymphoma patients, the diagnostic performance of FDG PET/CT proved to be better than conventional CT in the response assessment after first course of chemotherapy (16) and in the restaging for recurrence post-therapy (17). Additionally, FDG PET/CT showed higher sensitivity and specificity over conventional CT in the detection of extranodal disease sites and upstaged 10% of patients at initial staging (16).

Melanoma

One study met the inclusion criteria (18). Results from a phase III clinical trial revealed that FDG PET/CT had a statistically higher sensitivity, negative predictive value, and accuracy for diagnosis of melanoma metastases in comparison to ^{123}I-N-(2-diethylaminoethyl)-2-iodobenzamide (^{123}I-BZA2) scintigraphy. However, the specificity of FDG PET/CT (54% vs. 86%, $p<0.05$) was lower in the lesion-based analysis.

Non-FDG Tracers

Two studies met the inclusion criteria (19,20). A comparison of diagnostic performance between ^{11}C-choline PET/CT and MRI in patients with suspected recurrence of prostate cancer showed that ^{11}C-choline PET/CT was superior for the detection of pelvic lymph node metastasis, MRI was superior for local recurrence, and both modalities were equally accurate for pelvic bone metastasis (19). In neuroendocrine tumours (NETs), ^{68}Ga-DOTATATE helped correctly identify 90% (sensitivity) of patients with recurrent NETs and helped exclude recurrence of NETs in 82% (specificity) of patients (20).

Non-Small Cell Lung Cancer and Other Lung Cancer

Five studies met the inclusion criteria (21-25). One study demonstrated that FDG PET/CT (100%) was more sensitive than dedicated FDG PET (63.2%) at screening for lung lesions (21). Another study showed that FDG PET/CT improved the stratification of pulmonary malignancy in patients with indeterminate solid lung nodules on CT (22). For diagnosis of lung cancer recurrence, FDG PET/CT and FDG PET were shown to be superior modalities compared with conventional imaging techniques, and that FDG PET/CT was superior to FDG PET alone (24). However, for detection of malignant pulmonary tumours, FDG PET/CT was less sensitive and less accurate than diffusion-weighted MRI (23). In the clinical management of non-small cell lung cancer patients, FDG PET/CT findings led to treatment strategy changes in 19.4% of cases. More importantly, FDG PET/CT significantly reduced the sizes of target volumes in the planning of radiotherapy (25).

Pediatric Cancer

One study met the inclusion criteria (26). In a prospective study of children and young adults with lymphoma and sarcoma, FDG PET/CT and whole-body diffusion-weighted MRI displayed similar sensitivity, specificity, and accuracy for the detection of malignant lesions.

Sarcoma

Two studies met the inclusion criteria (27,28). FDG PET/CT was found to have a mean sensitivity of 93% and a mean specificity of 77% for the differentiation of soft tissue sarcomas

from benign fluid collections (27). In another retrospective study involving patients with newly diagnosed Ewing sarcoma, FDG PET/CT was able to show lung metastases in eight and lymph node metastases in three, none of which were evident on bone scan (28).

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 continue to be no published data to support the incorporation of PET/CT in breast cancer staging or surveillance. Only one relevant publication was found (3). This study was a single-institution prospective case series of a heterogeneous group of patients with breast cancer. Fifty-two patients in total were evaluated; 24 received PET/CT for diagnostic staging, 10 patients had PET/CT to confirm recurrence when suspected clinically, and the remainder had the procedure during their adjuvant therapy for unknown rationale. Although the authors quote a 100% sensitivity with PET/CT, most patients did not have any conventional imaging tests (CT [n=6], bone scan [n=8], MRI [n=4]) because the patients could not afford them, making a comparison impossible. Likewise, for patients where PET/CT was evaluated to diagnose distant recurrence when suspected locally, these were in patients where fine needle aspiration was indeterminate (n=3), while in all of the other patients, the diagnosis of recurrence was already histologically confirmed. No statistical comparisons were performed between PET/CT and the fraction of patients who received conventional imaging; therefore, this study cannot be considered useful in determining the value of PET imaging in breast cancer.

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, prior to 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. However, based on the accumulation of evidence from a systematic review, there is not enough evidence to suggest PET/CT is useful in detecting lymph node metastases in esophageal cancer patients being worked up for curative treatment.

Gastrointestinal Cancer

Current Insured Indication (Colorectal Cancer)

- Where recurrent disease is suspected on the basis of an elevated and/or rising carcinoembryronic 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 and Dr. Ur Metser)

In light of the results from the PETCAM trial (6), the current recommendation for PET in the preoperative assessment of colorectal cancer liver metastasis prior to surgical resection should be changed to align with the Ontario Health Insurance Plan indication; that is, PET is recommended in patients undergoing resection of liver metastases prior to surgery in cases where there is high surgical risk or a complex surgical procedure is being considered. The small benefit of PET demonstrated in the PETCAM trial was viewed to be insufficient for recommending routine use. However, patients at high risk of surgery or with complex surgical procedures may still benefit from PET.

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. Based on the last few reviews, there seems to be an evolving body of evidence for bladder cancer. There is also an Ontario Clinical Oncology Group (OCOG) PET trial in the works for bladder cancer.

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. However, the Lazzari et al (10) study is interesting and supports PET/CT for changing radiotherapy.

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 Cancers

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

- PET is recommended for restaging patients who are being considered for major salvage treatment, including neck dissection.

Reviewer's Comments (Dr. Amit Singnurkar)

The current recommendations for the utilization of PET/CT in head and neck cancer remain valid and no changes are required. The study by Mukundan et al (13) did not report a median follow-up for the patient cohort and it is unclear as to what is the gold standard for a negative scan. Additionally, it may be worthwhile to keep track of studies for recurrent squamous cell carcinoma.

Hematologic Cancer

Current Registry Indication (Lymphoma Staging)

- PET for the staging of Hodgkin's or non-Hodgkin's 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'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 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'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 lymphoma 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 (such as radiation or stem cell transplantation) is being considered and when biopsy cannot be safely or readily performed.
- An FDG PET/CT scan is not recommended for the routine monitoring and surveillance of lymphoma.

Reviewer's Comments (Dr. Marc Freeman)

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

Melanoma

Current Registry Indication

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

Current Recommendations for the Utilization of PET/CT in Melanoma

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

Reviewer's Comments (Dr. Tara Baetz)

The current recommendations for the utilization of PET/CT in melanoma 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. A number of planned trials in Ontario will be covering these areas.

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

- 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 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 metastectomy or stereotactic body radiation therapy is being contemplated for solitary metastases due to insufficient evidence.

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

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

Reviewer's Comments

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

Pediatric Cancer

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

- For the following cancer types (International Classification for Childhood Cancer [ICCC]):
    - Bone/cartilage – osteosarcoma, Ewing's sarcoma
    - Connective/other soft tissue – rhabdomyosarcoma, other
    - Kidney – renal tumour
    - Liver – hepatic tumour
    - Lymphoma/post-transplant lymphoproliferative disorder – Hodgkin's lymphoma, non-Hodgkin's lymphoma
    - Primary brain – astrocytoma, medulloblastoma, ependymoma, other
    - Reproductive – germ cell tumour
    - Sympathetic nervous system - neuroblastoma MIBG negative
    - Other – Langerhans cell histiocytosis (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 Klenk et al (26) study demonstrated high sensitivity, specificity and accuracy of PET/CT in the diagnosis of anatomical distribution of Hodgkin's lymphoma and non-Hodgkin's lymphoma in a small sample of patients aged eight to 33 years. The diagnostic performance of PET/CT was matched in similar dimensions by whole-body diffusion-weighted MRI enhanced with ferumoxytol, a very small nanoparticulate iron derivative. The advantage of the latter is the absence of radiation exposure. However, the technique is not available in almost any centre and is a research endeavour and, therefore, has no relevance to the Pediatric Registry indications. Perhaps of more interest are the sensitivity, specificity, and accuracy of PET/CT, and that when a reasonable sample size has been accumulated in the lymphoma and Hodgkin lymphoma categories, a preliminary analysis of utility be performed.

Sarcoma

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

Reviewer's Comments (Dr. Gina Diprimio)

The studies identified in this six-month review continue to show support for PET/CT imaging in sarcoma. The retrospective study by Amini et al (27), which included 100 patients, showed that PET/CT is able to differentiate various types of sarcomas from benign fluid collections. This study again showed that sarcomas are FDG-avid and is supportive for using PET/CT in recurrence assessment. The second retrospective study (28), despite its small sample size, provided convincing evidence that PET/CT obviates the need for bone scan (especially in lytic lesions) in the initial staging of Ewing's sarcoma. There may be a potential use of PET/CT in this indication.

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.

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Appendix 1A: Summary of Studies from January to June 2014

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
Bone Cancer								
Sahin et al, 2014 (1)	Retrospective	121 patients (653 bone lesions)	FDG PET/CT	^{99m}Tc-MDP whole-body scintigraphy	Pathology, laboratory or clinical examination, clinical or imaging follow-up	**Bone metastases** Sens: 88.3% Spec: 83.6% PPV: 91.7% NPV: 77.8% Accuracy: 86.7%	**Bone metastases** Sens: 91.7% Spec: 71.0% PPV: 86.6% NPV: 80.8% Accuracy: 84.9%	NA
Wafaie et al, 2014 (2)	Retrospective	123 patients (1705 bone lesions)	FDG PET/CT	FDG PET, CT	Biopsy, imaging follow-up	**Bone metastases** Sens: 98.7% Spec: 97.1% PPV: 99.3% NPV: 95.2%	**Bone metastases** ***FDG PET*** Sens: 94.4% Spec: 83.4% PPV: 95.7% NPV: 79.3% ***CT*** Sens: 29.5% Spec: 38.9% PPV: 65.1% NPV: 12.5%	NA
Breast Cancer								
Shetty et al, 2014 (3)	Prospective	52 patients (breast carcinoma)	FDG PET or FDG PET/CT	US abdomen, sonomammography, x-ray, CT scan, MRI, bone scan)	Histopathology, imaging follow-up	PET/CT detected 55 additional lymph node lesions and 36 additional distant metastatic lesions not seen on conventional imaging. PET/CT was found to be 100% sensitive and specific for confirming recurrent breast cancer.	NA	PET/CT upstaged 33.3% (8/24) of patients at initial diagnosis due to detection of additional lesions. All 8 patients changed plan of management from surgery to chemotherapy.
Esophageal Cancer								
Miyazaki et al, 2014 (4)	Retrospective	200 patients (esophageal cancer)	FDG PET/CT	CT scans of neck, chest, and abdomen, bone scan, EUS, endoscopy, esophagography	Biopsy, surgical procedures	**Synchronous primary cancer** Sens: 54.1%	NA	NA
Gastrointestinal Cancer								

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
Lee & Lee, 2014 (5)	Retrospective	266 patients (colon cancer)	FDG PET/CT	MDCT	Intraoperative findings or examinations, pathology, imaging follow-up	**Lymph node metastasis** ***Stage III*** Sens: 88% Spec: 15.9% PPV: 37.3% NPV: 70% Accuracy: 42% ***Stage IV*** Sens: 97.4% Spec: 12% PPV: 62.7% NPV: 75% Accuracy: 63.5%	**Lymph node metastasis** ***Stage III*** Sens: 100% Spec: 0% PPV: 36.2% NPV: NA Accuracy: 36.2% ***Stage IV*** Sens: 97.4% Spec: 4% PPV: 60.7% NPV: 50% Accuracy: 60.3%	PET/CT findings led to changes in management plan in 6.8% (18/266) of patients (4—upstaged, 9—downstaged, 5—additional pathologic lesions).
Moulton et al, 2014 (6)	RCT	404 colorectal cancer patients (270 PET/CT, 134 no PET/CT)	FDG PET/CT	No FDG PET/CT (CT alone)	Pathology, clinical confirmation	NA	NA	Surgical management was changed in 8% (21/263) of patients who underwent PET/CT (7—avoided surgery, 4—more extensive hepatic surgery, 9—additional organ surgery, 1—open-close surgery).
Ramos-Font et al, 2014 (8)	Prospective	49 patients (gallbladder carcinoma)	FDG PET/CT	Abdominal US and/or abdominal-pelvic CT with and without contrast	Pathology, clinical and/or radiological follow-up	**Primary lesion** Sens: 100% Spec: 91.7% PPV: 92.6% NPV: 100% Accuracy: 95.9% **Lymph node involvement** Sens: 71.4% Spec: 96.4% PPV: 93.7% NPV: 81.8% Accuracy: 85.7% **Metastatic disease** Sens: 100% Spec: 92.6% PPV: 91.7% NPV: 100% Accuracy: 95.9%	NA	PET/CT changed the management of 22.4% (11/49) of patients (from planned curative radical resection to palliative surgery—4, to chemotherapy—2, to palliative care—5).
Genitourinary Cancer								
Mertens et al, 2014 (7)	Retrospective	211 patients (muscle-invasive bladder cancer)	FDG PET/CT	CeCT of the abdomen and chest	Histopathology, biopsy	PET/CT revealed one or more extravesical lesions in 46.4% (98/211) of	Conventional staging revealed extravesical lesions in 24.2% (51/211) of	PET/CT revealed metastases undetected by CeCT in 36.9% (59/160) of patients.

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET) patients.	Diagnostic Accuracy (CI) patients.	Change in Patient Management
Park et al, 2014 (9)	Retrospective	69 patients (with adrenal masses)	FDG PET/CT	CT	Histology, clinical follow-up	**Adrenal metastasis** ***High FDG uptake*** Sens: 82.4% Spec: 92.2% PPV: 77.8% NPV: 94.0% Accuracy: 89.7%	**Adrenal metastasis** Sens: 88.2% Spec: 84.3% PPV: 65.2% NPV: 95.6% Accuracy: 85.3%	NA
Gynecological Cancer								
Lazzari et al, 2014 (10)	Prospective	66 cervical cancer patients (40—exclusive treatment, 26—adjuvant treatment)	FDG PET/CT	Thorax-abdominal-pelvic CT scan, abdominal-pelvic MRI	Pathology	NA	NA	PET/CT changed the stage of lymph- node status (N or M stage) and radiotherapy treatment planning in 25% (10/40) of exclusive patients and 7.7% (2/26) of adjuvant patients.
Meads et al, 2014 (11)	Systematic review	15 studies (patients with suspected persistent/ recurrent cervical cancer)	FDG PET/CT	CT, MRI	Histopathology, clinical follow-up	**Recurrent disease** Pooled Sens: 94.8% Pooled Spec: 86.9%	**Recurrent disease** ***CT*** Pooled Sens: 89.6% Pooled Spec: 76% ***MRI*** Sens: 82%-100% Spec: 78%-100%	NA
Xiao et al, 2014 (12)	Systematic review	23 studies (patients with recurrent cervical cancer)	FDG PET/CT	FDG PET, CT	Histopathology, clinical follow-up	**Recurrent disease** Pooled Sens: 94% Pooled Spec: 84%	**Recurrent disease** ***FDG PET*** Pooled Sens: 91% Pooled Spec: 92% ***CT*** Pooled Sens: 89% Pooled Spec: 87%	NA
Head and Neck								
Mukundan et al, 2014 (13)	Prospective	50 patients (head and neck squamous cell carcinoma)	Whole-body FDG PET/CT	MRI	Pathology, clinical follow-up	**Response assessment** ***12 weeks post-treatment*** Sens: 73.9% Spec: 74.2% PPV: 84.9% NPV: 81.8% ***24 weeks post-treatment*** Sens: 95.8% Spec: 92.0% PPV: 85.5%	**Response assessment** ***12 weeks post-treatment*** Sens: 69.6% Spec: 74.2% PPV: 67.3% NPV: 79.4% ***24 weeks post-treatment*** Sens: 95.8% Spec: 82.4% PPV: 78.9%	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET) NPV: 96.3%	Diagnostic Accuracy (CI) NPV: 96.3%	Change in Patient Management
Nguyen et al, 2014 (14)	Retrospective	71 patients; 142 neck dissections (head and neck squamous cell carcinoma)	FDG PET/CT	CT, MRI	Pathology	**Staging** Sens: 95% Spec: 90% PPV: 91% NPV: 94% FP: 10% FN: 5%	**Staging** ***CT*** Sens: 81% Spec: 88% PPV: 86% NPV: 83% FP: 13% FN: 19% ***MRI*** Sens: 74% Spec: 100% PPV: 100% NPV: 72% FP: 0% FN: 26%	PET/CT upgraded 21.1% (16/76) of lateral necks to radiologically positive disease not previously identified by conventional imaging.
Roh et al, 2014 (15)	Prospective	91 patients (head and neck squamous cell carcinoma and no palpable lymph nodes in the neck)	FDG PET/CT	CT/MRI	Histopathology	**Lymph node metastasis** ***Per-patient basis*** Sens: 71% Spec: 81% PPV: 73% NPV: 80% Accuracy: 77% ***Per-side basis (neck)*** Sens: 72% Spec: 85% PPV: 72% NPV: 85% Accuracy: 80% ***Per-level basis (cervical)*** Sens: 69% Spec: 92% PPV: 62% NPV: 94% Accuracy: 89%	**Lymph node metastasis** ***Per-patient basis*** Sens: 50% Spec: 87% PPV: 73% NPV: 71% Accuracy: 71% ***Per-side basis (neck)*** Sens: 51% Spec: 88% PPV: 71% NPV: 77% Accuracy: 75% ***Per-level basis (cervical)*** Sens: 39% Spec: 97% PPV: 68% NPV: 90% Accuracy: 88%	NA
Hematology								
Behairy et al, 2014 (16)	Prospective	50 patients (37 HL, 12 B-cell NHL, 1 T-cell lymphoma)	FDG PET/CT	CeCT	Pathology	**Response assessment** ***After first course of chemotherapy (4-6 weeks)*** Sens: 100% Spec: 96.7%	**Response assessment** ***After first course of chemotherapy (4-6 weeks)*** Sens: 94.7% Spec: 19.4%	PET/CT upstaged 10% (5/50) of cases at initial staging.

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
						PPV: 95% NPV: 100% **Extranodal disease sites** Sens: 100% Spec: 100%	PPV: 41.8% NPV: 85.7% **Extranodal disease sites** Sens: 62.5% Spec: 97.6%	
Chiewvit et al, 2014 (17)	Retrospective	61 patients; 77 scans (HL and NHL)	FDG PET/CT	CT	Clinical follow-up	**Restaging for recurrence post-therapy** Sens: 86.7% Spec: 69.2% PPV: 61.9% NPV: 90.0% Accuracy: 75.6% **Residual disease within 2 months after chemotherapy** Sens: 88.9% Spec: 77.8% PPV: 80.0% NPV: 87.5% Accuracy: 83.3%	**Restaging for recurrence post-therapy** Sens: 86.7% Spec: 53.8% PPV: 52.0% NPV: 87.5% Accuracy: 65.8% **Residual disease within 2 months after chemotherapy** Sens: 100% Spec: 44.4% PPV: 64.3% NPV: 100% Accuracy: 72.2%	NA
Melanoma								
Cachin et al, 2014 (18)	Prospective clinical trial	87 patients (cutaneous or ocular melanoma)	FDG PET/CT	^{123}I-BZA2 scintigraphy	Other diagnostic tests, clinical follow-up, biopsy	**Melanoma metastases** ***Per-patient basis*** Sens: 87% Spec: 78% PPV: 91% NPV: 85% Accuracy: 83% ***Per-lesion basis*** Sens: 80% Spec: 54% PPV: 66% NPV: 74% Accuracy: 67%	**Melanoma metastases** ***Per-patient basis*** Sens: 39% Spec: 94% PPV: 88% NPV: 58% Accuracy: 65% ***Per-lesion basis*** Sens: 23% Spec: 86% PPV: 60% NPV: 57% Accuracy: 57%	NA
Other PET tracers **^{11}C-choline**								
Kitajima et al, 2014 (19)	Retrospective	115 patients (suspected recurrence of prostate cancer)	^{11}C-choline PET/CT	MRI	Histopathology, imaging follow-up	**Local recurrence** Sens: 54.1% Spec: 92.3% Accuracy: 65.5% **Pelvic lymph node metastasis** Sens: 90%	**Local recurrence** Sens: 88.5% Spec: 84.6% Accuracy: 87.4% **Pelvic lymph node metastasis** Sens: 64%	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
						Spec: 100% Accuracy: 92.9% **Pelvic bone metastasis** Sens: 81.3% Spec: 98.7% Accuracy: 95.8% **Body lymph node metastasis** Sens: 91.4% Spec: 100% Accuracy: 93.6% **Body bone metastasis** Sens: 90.6% Spec: 98.5% Accuracy: 96%	Spec: 85% Accuracy: 70% **Pelvic bone metastasis** Sens: 87.5% Spec: 96.2% Accuracy: 94.7%	
68Ga-DOTATATE								
Haug et al, 2014 (20)	Retrospective	63 patients (NET)	^{68}Ga-DOTATATE PET/CT	Standard imaging modalities (not specified)	Histopathology, clinical follow-up	**Recurrent disease** Sens: 90% Spec: 82% PPV: 81% NPV: 90% Accuracy: 86%	NA	PET/CT contributed to the treatment decision for 26 patients with recurrent NET (11—surgical resection, 6—chemotherapy, 5—treatment with radioactively labelled somatostatin analogues, 3—treatment with somatostatin analogues, 1—local treatment of liver metastases)
Lung Cancer (other than NSCLC)								
Minamimoto et al, 2014 (21)	Retrospective	854 patients (suspected lung cancer)	FDG PET/CT	FDG PET, chest CT	Surgical procedures, biopsy or cytology, other clinical information	**Lung lesions** Sens: 100% PPV: 37.6%	**Lung lesions** ***FDG PET*** Sens: 63.2% PPV: 43% ***Chest CT*** Sens: 97.4% PPV: 41.5%	NA
Evangelista et al, 2014 (22)	Retrospective	59 patients (indeterminate solid lung nodules on CT images)	FDG PET/CT	CT of the chest, abdomen, and pelvis	Histopathology, imaging follow-up	**Lung lesions** Sens: 77% Spec: 89% PPV: 89% NPV: 78% Accuracy: 83%	NA	NA
Zhang et al, 2014 (23)	Prospective	113 patients (pulmonary nodules)	FDG PET/CT	Diffusion-weighted MRI	Histopathology, biopsy, pathology	**Malignant pulmonary tumours** Sens: 88.3%	**Malignant pulmonary tumours** Sens: 96.1%	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
						Spec: 83.3% PPV: 94.4% NPV: 73.2% Accuracy: 86.7%	Spec: 83.3% PPV: 94.9% NPV: 75.0% Accuracy: 92.0%	
He et al, 2014 (24)	Meta-analysis	13 articles (1035 patients with lung cancer)	FDG PET/CT	FDG PET, CT	Histology, long-term follow-up	**Recurrent disease** Pooled Sens: 90% Pooled Spec: 90%	**Recurrent disease** ***FDG PET*** Pooled Sens: 94% Pooled Spec: 84% ***CT*** Pooled Sens: 78% Pooled Spec: 80%	NA
NSCLC								
Vojtisek et al, 2014 (25)	Prospective	31 patients (histologically proven, inoperable, locally advanced NSCLC)	FDG PET/CT	CT	Pathology, all accessible clinical information	NA	NA	PET/CT findings led to upstaging of the disease in 29% (9/31) of patients and downstaging in 32.3% (10/31) of patients. Changes in treatment strategy occurred in 19.4% (6/31) of patients (2—to palliative radiotherapy, 1—to palliative chemotherapy, 3—radical treatment was started). PET/CT scan information led to a significant decrease in target volume sizes in radiotherapy planning.
Pediatric Cancer								
Klenk et al, 2014 (26)	Prospective	22 patients (malignant lymphoma and sarcoma)	FDG PET/CT	Whole-body diffusion-weighted MRI	Histopathology, clinical and imaging follow-up	**Malignant lesions** Sens: 93.7% Spec: 97.7% Accuracy: 97.2%	**Malignant lesions** Sens: 90.8% Spec: 99.5% Accuracy: 98.3%	NA
Sarcoma								
Amini et al, 2014 (27)	Retrospective	100 patients (soft-tissue sarcoma and benign fluid collections)	FDG PET/CT	Not specified	Biopsy, imaging follow-up	**Differentiating soft tissue sarcomas from benign fluid collections** Mean Sens: 93% Mean Spec: 77%	NA	NA
Ulaner et al, 2014 (28)	Retrospective	60 patients (Ewing sarcoma)	FDG PET/CT	MDP bone scan	Pathology, imaging follow-up	**Osseous metastases** TP: 11/12	**Osseous metastases** TP: 9/12	PET/CT visualized 8 lung metastases and 3 lymph node metastases (PET/CT changed staging in 2 of these 3 patients), none of

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (CI)	Change in Patient Management
								which were evident on bone scan.

Abbreviations: CeCT: contrast-enhanced computed tomography; CI: conventional intervention; CT: computed tomography; EUS: endoscopic ultrasound; FDG PET/CT: fludeoxyglucose positron emission tomography/ computed tomography; FN: false negative; FP: false positive; HL: Hodgkin's lymphoma; MDCT: multidetector computed tomography; MDP: methylene-diphosphonate; MRI: magnetic resonance imaging; NA: not applicable; NET: neuroendocrine tumour; NHL: Non-Hodgkin's lymphoma; NPV: negative predictive value; NSCLC: non-small cell lung carcinoma; PPV: positive predictive value; RCT: randomized controlled trial; Sens: sensitivity; Spec: specificity; TP: true positive; US: ultrasound