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PET Six-Month Monitoring Report 2013-1

Evidence from Primary Studies and Systematic Reviews and Recommendations from Clinical Practice Guidelines July 2012 to July 2013

S. Kellett, 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: May 27, 2014

The complete PET Six-Month Monitoring Report consists of a Full Report

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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 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 fifth 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 2012 and July 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 paediatric 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-flurodeoxy-glucose (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 review journal.
4. Reported evidence related to change in patient clinical management or clinical outcomes *OR* reported diagnostic accuracy of PET compared to 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 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

July-December 2012

Fifty-seven studies from July to December 2012 met the inclusion criteria. A summary of the evidence from the 57 studies can be found in **Appendix 1A. Summary of studies from July to December 2012**.

January-July 2013

Forty-one studies from January to July 2013 met the inclusion criteria. A summary of the evidence from the 41 primary studies is presented in **Appendix 1B. Summary of studies from January to July 2013**.

Bone Cancer

Two studies (1,2) met the inclusion criteria. FDG PET/CT improved the staging of lymphoma in 23% of patients, myeloma in 10% of patients, breast cancer in 57% of patients, and lung cancer in 10% of patients. The diagnostic performance (i.e., sensitivity, specificity, diagnostic odds ratio, positive likelihood ratio, and negative likelihood ratio) for the detection of bone metastases was similar between FDG PET/CT and gadolinium-enhanced magnetic resonance imaging (MRI).

Breast Cancer

Fourteen studies met the inclusion criteria (3-16). Several studies evaluated the use of FDG PET/CT in inflammatory or late-stage breast cancer. Overall, PET/CT detected additional sites of metastasis in 0.9% to 44% of cases that were not demonstrated on conventional imaging techniques (7,11,16). Additional information provided by PET/CT changed the initial staging of patients in 18% to 52% of reported cases (4,8,12,14,16). In the majority of cases, patients were upstaged due to the discovery of unsuspected metastasis. Information provided by PET/CT modified the treatment plan of 8% to 41% of cases across studies (5,6,8,10,11).

Esophageal Cancer

Four studies met the inclusion criteria (17-20). When compared to conventional imaging techniques, FDG PET/CT had a superior or comparable performance and was shown to have value in M staging of esophageal cancer due to its ability to detect metastasis that were not evident on conventional imaging techniques. In T and N staging, PET/CT was found to be more accurate than conventional imaging in patients with or without prior chemoradiotherapy. Additional information provided by FDG PET/CT lead to changed management in 34% of the patients (17).

Gastrointestinal Cancer

Six studies met the inclusion criteria (21-26). Four of the studies looked at FDG PET/CT in the evaluation of colorectal cancer. The diagnostic accuracy of FDG PET/CT was found to be superior or comparable to contrast-enhanced CT in detecting colorectal metastases (23). FDG PET/CT had substantial impact on management in 34% to 67% of patients due to the identification of previously unsuspected metastasis and/or confirming indeterminate lesions (24-26).

Genitourinary Cancer

Two studies met the inclusion criteria (27-28). In the assessment of urinary bladder patients, the diagnostic accuracy of FDG PET/CT was comparable to that of contrast-enhanced CT (27).

Gynecologic Cancer

Twelve studies met the inclusion criteria (29-40). Six of the studies investigated the use of FDG PET/CT in cervical cancer. In most cases, the diagnostic accuracy of FDG PET/CT was comparable to that of either CT or MRI. One prospective study reported that the addition of FDG PET/CT to the initial workup of patients with cervical cancer led to the extension of the radiotherapy field in 34% of patients and major modifications to the treatment plan in 23% of patients (32). Four studies compared the diagnostic performance of FDG PET/CT to conventional modalities in the diagnosis and staging of patients with ovarian cancer. The ultimate diagnosis of complex ovarian masses rests on histopathology. Laparotomy, image guided biopsy, or cytology of ascites fluid cannot be safely omitted in patients with complex ovarian masses. PET imaging does not add significant value to the diagnostic evaluation of pelvic masses. In a prospective study by Zytoon et al, FDG PET/CT was proven to be valuable in detecting stage IV ovarian cancer with distant metastasis (35).

Head and Neck Cancer

Eleven studies met the inclusion criteria (41-49,90-91). In head and neck squamous cell carcinoma, the diagnostic accuracy of FDG PET/CT was demonstrated to be higher or comparable to other conventional imaging modalities in several studies (43,44,47). FDG-PET/CT had an impact on patient management, particularly through the initiation of previously unplanned treatment or through the correction of a previously planned therapeutic approach (41,42). The addition of FDG PET/CT was useful in the M staging or restaging of patients due to its whole-body approach. When FDG PET/CT was included in the staging regimen, some M0 patients were upstaged due to the discovery of distant sites of metastasis (41). In thyroid carcinoma, FDG PET/CT changed the management of 39% of cases by detecting recurrent or metastatic disease (90). However, adding FDG PET/CT findings to neck ultrasound provided no diagnostic benefit to the presurgical characterization of thyroid nodules (91).

Hematology Cancer

Four studies met the inclusion criteria (50-53). FDG PET/CT demonstrated a higher diagnostic accuracy in comparison to CT. In particular, FDG PET/CT correctly identified more extranodal lesions in patients with Hodgkin's and non-Hodgkin's lymphoma (50,51). Furthermore, FDG PET/CT identified sites of bone marrow involvement that were not previously detected with conventional imaging (52).

Melanoma

One study met the inclusion criteria (54). In the clinical management of stage III and IV melanoma, FDG PET/CT revealed previously undetected metastases in 12% of cases. As a result of the new findings, surgery was cancelled for two patients, and the planned approach was altered for two patients.

Neuro-Oncology

Three studies met the inclusion criteria (55-57). In glioma, FDG uptake on PET/CT scans provided prognostic information on survival (56,57). Patients with a higher uptake of FDG had a poorer survival compared to patients with a lower uptake. In the detection of

glioma recurrence, when compared to MRI, FDG PET/CT had good specificity and low sensitivity, which was opposite to that of MRI (56). For paragangliomas, FDG PET/CT and ^{123}I-MIBG/SPECT diagnostic accuracies were comparable.

Non-FDG Tracers

Twelve studies met the inclusion criteria (58-69). Two systematic reviews evaluated the diagnostic accuracy of ^{11}C and ^{18}F-Choline PET in intermediate- to high-risk prostate cancer and prostate cancer, respectively (58,59). In intermediate- to high-risk prostate cancer, PET showed a low sensitivity (49.2%) and demonstrated a higher specificity (95%) (58). Diagnostic accuracy statistics for comparison to conventional imaging were not reported. Conversely, when all prostate cancer patients were evaluated, PET/CT showed a higher sensitivity (84%) and marginally lower specificity (79%) (59). The utility of ^{68}Ga-DOTA NOC, TOC and TATE in neuroendocrine tumours (NETs) were evaluated in several studies. ^{68}Ga-DOTA-NOC was found to be superior to conventional imaging in the diagnosis of NETs (64) and ^{68}Ga-DOTA-TOC PET/CT contributed to a change in treatment decision in 59% of patients (61). In one study, ^{68}Ga-DOTA-NOC was found to have a higher sensitivity than ^{68}Ga-DOTA-TATE in the staging of NETs (62). ^{18}F DOPA PET/CT was shown to have a superior diagnostic accuracy when compared to conventional imaging modalities in neuroblastoma (66,67). Two studies evaluated ^{18}F-FLT PET/CT, one in pulmonary lesions (68) and the other in pancreatic masses suspicious for malignancy (69). In both cases the sensitivity and specificity of ^{18}F-FLT was not found to be superior to FDG PET/CT (68,69).

Non-Small Cell Lung Cancer and Lung Cancer

Eight studies met the inclusion criteria (70-77). The addition of FDG PET/CT in the diagnosis and staging of NSCLC improved the detection of metastases and led to treatment changes in 17%-79% of cases (71,72,74,76). In most cases, the addition of PET/CT demonstrated nodal and extranodal metastasis that were not clearly evident on conventional imaging leading to upstaging of patients. PET/CT led to high-impact changes in patient management such as a shift from one treatment modality to another or an adjustment in treatment intent (curative to palliative).

Pancreatic Cancer

Four studies met the inclusion criteria (78-81). The addition of FDG PET/CT led to the modification of treatment plans in several studies (79-81). Patients were found to have distant metastases by radiologic evaluation or cytological verification. With the combination of PET and CT, staging and surgical management were impacted in a large proportion of patients who are candidates for surgery.

Pediatric Cancer

Three studies met the inclusion criteria (82-84). In a retrospective study of children with primary bone tumours, FDG PET/CT was demonstrated to have a higher specificity but a lower sensitivity than conventional imaging in the detection of malignant lesions (83). In the staging of pediatric rhabdomyosarcoma, FDG PET/CT had a higher accuracy rate (95%) for the detection of nodal disease than did conventional imaging (49%) (82). In another study, FDG PET/CT modified the therapeutic strategy in 21% of children with non-Hodgkin lymphoma by uncovering new extranodal lesions (84).

Sarcoidosis

Three studies met the inclusion criteria (85-87). One prospective study evaluated the utility of FDG PET/CT in patients with biopsy-proven sarcoidosis, and additional information

provided by FDG PET/CT influenced the clinical management of 63% of scans (85). One retrospective evaluated FDG PET/CT for detecting bone and bone marrow involvement in sarcoidosis patients. More than one third of the patients with positive findings had osseous abnormalities on FDG PET/CT. The majority of these lesions (94%) could not be detected on low-dose CT (86). In the third study, the addition of FDG PET/CT led to clinical management changes in 81% of the patients over the course of follow-up, with either the previous treatment being modified or a new treatment introduced (87).

Sarcoma

Two studies met the inclusion criteria (88-89). In comparison to contrast-enhanced CT alone, FDG PET/CT had greater diagnostic accuracy in the detection of recurrent bone and soft tissue sarcoma (88).

Unknown Primary

Two studies met the inclusion criteria (92-93). In a prospective study that investigated the value of FDG PET/CT in the detection of unknown primaries in patients with cervical lymph node metastasis, treatment changes were made in 41% of cases due to FDG PET/CT findings (92). In another prospective study, FDG PET/CT did not show a clear diagnostic advantage over CT alone regarding the ability to identify the primary tumour site in patients with extracervical carcinoma of unknown primary site (93).

CLINICAL EXPERT REVIEW

Breast Cancer

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

Reviewer's Comments (Dr. Muriel Brackstone)

For the studies that evaluated the accuracy of PET in primary cancer staging (size of tumour) in comparison to final pathology, there is no compelling evidence that PET is significantly superior or that a change in tumour size is in any way clinically relevant (8). The acceptable standard of care for staging primary breast cancer (particularly in locally advanced breast cancer) is breast MRI, and none of these studies used MRI as the comparator. Therefore, there is not enough evidence to support making appropriate recommendations for the use of PET in the staging of primary breast cancer.

With respect to the staging of the axilla, the gold standard comparator should be axillary ultrasound. One prospective study (7) found that PET is not sufficiently sensitive to detect positive axillary lymph nodes, and sentinel lymph node biopsy remains the preferred technique for axillary staging. Therefore, the low sensitivity of PET in detecting lymph node positivity does not warrant incorporating PET as an axillary staging tool.

In one prospective cohort study (12) that compared PET to conventional imaging in staging patients with locally advanced or inflammatory breast cancer, the diagnostic accuracy of PET was found to be higher for detecting bone lesions. However, there is no indication as to whether this difference was statistically significant. Further studies should be conducted to validate this point estimate of accuracy for PET in identifying occult bone metastases when compared to bone scans. Therefore, there is insufficient evidence to warrant the disseminated use of PET in screening for bone metastases for all locally advanced breast cancer patients.

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 pre-operative/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. From the meta-analysis conducted by Shi et al (20), it is unclear whether FDG PET/CT improves the accuracy of N staging with the comparator being postsurgical histopathology as opposed to conventional imaging.

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 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. For endometrial cancer, the use of PET is not recommended for diagnosis, staging, or detecting recurrence.

Head and Neck Cancer

Current Insured Indication

- 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.

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 in patients with nasopharyngeal carcinoma if conventional imaging is equivocal.
- PET is recommended for restaging patients who are being considered for major salvage treatment, including neck dissection.

Reviewer's Comments (Dr. Amit Singnurkar)

The current recommendations for the utilization of PET/CT in head and neck cancer remain valid and no changes are required. The literature included in this review appears to demonstrate some positive results for the use of PET in salivary gland tumours and Merkel cell tumours.

Hematology 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 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 Hematology 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 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 HL or NHL.
- 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. Ur Metser)

The current recommendations for the utilization of PET/CT in hematology 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 the 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. Amit Singnurkar)

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

Neuro-Oncology

Current Recommendations for the Utilization 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)

In light of the prospective study by Santra et al (56), which demonstrated high specificity for FDG PET/CT in detecting recurrence in patients with gliomas that can lead to management changes, it may be worthwhile to look at recurrent glioma as an indication in a prospective registry. Since MRI is known to be sensitive but not very specific postradiation therapy/temozolomide, a registry where patients are suspected of having recurrence based on MRI may benefit from further evaluation with FDG PET/CT to exclude tumours that may otherwise lead to unnecessary biopsy and retreatment. The registry would allow confirmation of test characteristics and provide greater insight into the magnitude of change in clinical and radiologic management.

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 results for the ^{68}Ga-DOTA-(NOC, TOC, TATE) tracers appear to be promising, particularly in neuro-endocrine tumours. ^{18}F-Choline will be investigated in larger trials going forward but nothing compelling to date.

Non-Small Cell Lung Cancer and Lung Cancer

Current Insured Indications

- Solitary pulmonary nodule (SPN)
  - 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 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 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 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 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

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

Pancreatic Cancer

Current Registry Indication

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

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

- PET is not recommended for primary diagnosis of pancreatic cancer.
- PET is recommended for staging if a patient is a candidate for potentially curative surgical resection as determined by conventional staging.
- A recommendation cannot be made for or against the use of PET to guide clinical management based on assessment of treatment response due to insufficient evidence.
- PET is not recommended for clinical management of suspected recurrence, or 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.

Pediatric Cancer

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

Reviewer's Comments (Dr. Mark Greenberg)

There is currently not enough evidence to support making appropriate recommendations for the use of PET/CT in pediatric cancer. The retrospective study by London et al (83) was based largely on review of reports and the positive likelihood ratios demonstrated significant overlap between conventional imaging and PET/CT in detecting malignant lesions.

Sarcoidosis

Current Recommendations for the Utilization of PET/CT in Sarcoidosis

- No recommendation for or against the use of PET in the diagnosis, staging, or clinical management of sarcoidosis can be made at this time due to insufficient evidence.

Reviewer's Comments (Dr. Bob Hyland)

Although it is undoubtedly true that PET scanning is more sensitive than conventional CT in identifying sarcoidosis, particularly in extrapulmonary sites, there is not enough justification to change the current recommendations. In most of the cases identified in the

literature, there is no good outcome data suggesting that aggressive treatment significantly changes the natural progression of the disease. However, one should be open to occasional studies when the organ involvement could be life threatening; for example, the central nervous system and perhaps the heart.

Sarcoma

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

Reviewer's Comments (Dr. Gina Diprimio)

There is currently not enough evidence to support making appropriate recommendations for the use of PET/CT in sarcoma. The retrospective studies identified were of sound research methodology and compared PET/CT to CT and contrast enhanced-CT but not MRI or other imaging techniques. The sample sizes for these studies were relatively small. Nonetheless, the high sensitivities, specificities and accuracies reported for PET/CT (>90%) should not be overlooked and the potential use of PET/CT in sarcoma should be assessed on a greater scale.

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Appendix 1A. Summary of studies from July to December 2012.

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy: (PET)	Diagnostic Accuracy: (CI)	Change in Patient Management
Bone Cancer								
Evangelista et al, 2012 (1)	Retrospective	198 pts. (bone marrow involvement)	FDG PET/CT	CT	Clinical follow-up and subsequent imaging	NA	NA	Upgraded the stage of lymphoma in 7 (23%) patients, of myeloma in 3 patients (10%), of breast cancer in 17 patients (57%), of lung cancer in 3 patients (10%).
Breast Cancer								
Evangelista et al, 2012 (3)	Retrospective	190 pts. (with previous breast cancer after surgery and other primary treatments)	FDG PET/CT	CT	Clinical evaluation and/or radiological findings	**Disease relapse:** Sens: 89% Spec: 73% PPV: 90% NPV: 72%	**Disease relapse:** Sens: 77% Spec: 53% PPV: 75% NPV: 55%	Not evaluated
Groheux et al, 2012 (4)	Prospective	254 pts. (breast cancer stages (II to III)	FDG PET/CT	BS, chest x-ray or CT, liver US, abdominal pelvic CT	Histopathology and additional imaging	NA	NA	18FDG-PET-CT changed the clinical stage in 77 of 254 patients (30.3%).
Manohar et al, 2012 (5)	Retrospective	111 pts. (recurrence breast cancer)	FDG PET/CT	CT, CeCT	Histopathology, correlative imaging and clinical or imaging follow-up	Sens: 98.7% Spec: 85.3% PPV: 92.5% NPV: 97.2%	NA	41% (42/103)
Riegger et al, 2012 (6)	Retrospective	106 pts. (primary breast cancer)	FDG PET/CT	US	Histopathology, clinical follow-up, cross-sectional imaging follow-up	**Distant Metastasis:** Sens: 75% Spec: 97% PPV: 80% NPV: 96% Accuracy: 93%	**Distant Metastasis:** Sens:50% Spec: 98%, PPV: 80% NPV: 92% Accuracy:90%	14% (15/106) In 13 cases change was correct. In 2 cases change was incorrect.
Pritchard et al, 2012 (7)	Prospective	325 pts. (early stage breast cancer)	FDG PET/CT	Axillary nodal assessment	Pathology (ALNA was used as the gold standard)	Sens: 23.7% Spec: 99.6% PPV: 95.8% NPV: 75.4%	Not Stated	3 confirmed as metastatic disease and 10 were false positive.
Garami et al, 2012 (8)	Prospective	115 pts.	FDG PET/CT	CI	Histopathology	(primary tumour) Sens: 93% (8 FN)	(primary tumour) Sens: 43.8%	15.6% (18/115) TMN classification changed in 47% (54/115).
Groves et al, 2012 (9)	Prospective	70 pts. (early stage breast cancer)	FDG PET/CT	Mammography, ultrasound	Histology	Primary tumour identified in 91.4% (64/70) pts.	NA	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy: (PET)	Diagnostic Accuracy: (CI)	Change in Patient Management
Koolen et al, 2012 (10)	Prospective	154 pts. (invasive breast cancer)	FDG PET/CT	BS, US of the liver, chest radiograph	Histology, imaging, clinical follow-up	Detection of distant lesions: Sens: 100% Spec: 96% PPV: 80% NPV: 100% Accuracy: 97%	NA	8% (13/154)
Walker et al, 2012 (11)	Retrospective	62 pts. (inflammatory breast cancer)	FDG PET/CT	Mammography, US of the breast and draining lymphatics, chest radiography or BS, liver imaging, abdominal CT, MRI, chest CT	Pathology	New areas detected in 43.5 (27/62).	NA	17.7% (11/62)
Ovarian and Cervical Cancer								
Akkas et al, 2012 (32)	Prospective	47 pts. (LACC)	FDG PET/CT	Pelvic and abdominal MRI	Clinical follow-up data	PET was superior to MRI in 62% (24/39) hypermetabolic LN's PET detected 54% (13/24) LNs that were not detected with MRI.	NA	34% (16/47): changes to radiotherapy field. 23% (11/47): major alterations to treatment plan.
Antunovic et al, 2012 (36)	Retrospective	121 pts. (epithelial ovarian carcinoma)	FDG PET/CT	Chest CT scan, abdominopelvic CeCT, US, pelvic MRI	Histology	**Low Grade** tumours: Sens: 86% Spec: 92% PPV: 97% NPV: 65% Accuracy: 87% **High Grade** Tumours: Sens: 80% Spec: 83% PPV: 96% NPV: 53% Accuracy: 80%	**Low Grade** tumours: Sens: 72% Spec: 57% PPV: 91% NPV: 25% Accuracy: 70% **High Grade** Tumours: Sens: 67% Spec: 40% PPV: 86% NPV: 19% Accuracy: 62%	NA
Chung et al, 2012 (33)	Retrospective	276 pts. (uterine cervical cancer)	FDG PET/CT	CI	Histopathology, serial imaging, clinical follow-up	Sens: 94.7% Spec: 87.8% PPV: 80.4% NPV: 97.0% Accuracy: 90.2%	NA	24.3% (67/276)

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy: (PET)	Diagnostic Accuracy: (CI)	Change in Patient Management
Ferrandina et al, 2012 (34)	Prospective	96 pts. (cervical cancer)	FDG PET/CT	MRI	Histology	Sens: 28.6% Spec: 97.8% PPV: 66.7% NPV: 90.0% Accuracy: 88.7%	Sens: 35.7% Spec: 95.9% PPV: 57.1% NPV: 90.8% Accuracy: 88.0%	NA
Hynninen et al, 2012 (37)	Prospective	30 pts. (epithelial ovarian cancer	FDG PET/CT	US	Histology	PET showed LNM in 67% (20/30) pts.	CT showed LMN in 33% (10/30) pts.	NA
Sanli et al, 2012 (38)	Prospective	47 pts. (suspected ovarian cancer recurrence)	FDG PET/CT	MRI	Histopathology	Sens: 97.5% Spec: 100% PPV: 100% NPV: 87.5% Accuracy: 97.8%	Sens: 95% Spec: 85.7% PPV: 97.4% NPV: 75% Accuracy: 93.6%	NA
Sharma et al, 2012 (40)	Retrospective	101 pts. (suspected endo. recurrence)	FDG PET/CT	CeCT, MRI, USG, bone scan (segmental examination of chest, abdomen, and pelvis)	Clinical follow-up, imaging follow-up, histopathology	Sens: 89.5% Spec: 96.4% PPV: 97.7% NPV: 84.3% Accuracy: 92.1%	Sens: 85.1% Spec: 62% PPV: 78.4% NPV: 72% Accuracy: 76.3%	NA
Colorectal Cancer								
Engledow et al, 2012 (25)	Prospective	64 pts. (with CRC lover metastasis)	FDG PET/CT	CEMDCT scan of the thorax, abdomen and pelvis	Histology	NA	NA	Disease upstaging in 31% (20/64); downstaging in 3% (2/64).
McLeish et al, 2012 (26)	Retrospective	470 pts. (585 scans)	FDG PET/CT	CT	Histology	NA	NA	66.7% (36/54) 24 cases: hepatic surgery cancelled. 12 cases: hepatic surgery initiated.
Esophageal Cancer								
Barber et al, 2012 (17)	Prospective	139 pts. (patients for primary staging)	FDG PET/CT	EUS, CT of the chest, abdomen and pelvis	Pathology, intraoperative findings, clinical follow-up, serial anatomic imaging	NA	NA	34% (47/139). 36 (26%) were of high impact and 11 (8%) of medium impact.
Nakaminato et al, 2012 (18)	Prospective	33 pts. (newly diagnosed with hypopharyngeal cancer)	FDG PET/CT	EGD	Histopathology	FDG PET/CT detected 6/33 lesions. Sens: of FDG-PET/CT at each T classification: T1a, 0/21 (0%);	EGD detected 17/33 (51.5%) lesions.	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy: (PET)	Diagnostic Accuracy: (CI)	Change in Patient Management
						T1b, 1/3 33%); and T3, 5/5 100%).		
Yen et al, 2012 (19)	Retrospective	118tpns Group1: without neoadjuvant CRT (n=28) Group 2: with CRT (n=90)	FDG PET/CT	EUS	Surgical pathology	**Group 1** T staging Accuracy: 100% N staging Accuracy: 54.5% **Group 2** T staging Accuracy: 69.4% N staging Accuracy: 86.1%	**Group 1** T staging Accuracy: 85.2% N staging Accuracy: 55.6% **Group 2** T staging Accuracy: 34.9% N staging Accuracy: 39.8%	NA
Other Gastrointestinal Cancer								
Lee et al, 2012 (21)	Retrospective	138 pts. (hepatocelluar carcinoma)	FDG PET/CT	Chest x-ray, CeCT, BS, bone MRI	Histology	**Detection of Lung Mets (n=23):** Sens: 60.9% Spec: 99.1% Accuracy: 92.6% PPV: 93.3% NPV: 92.5% **Detection of LN mets (n=22)** Sens: 90.9% Spec: 96.5% Accuracy: 95.6% PPV: 83.3% NPV: 98.2% **Bone Metastasis (n=11):** Sens: 100% Spec: 100% Accuracy: 100% PPV: 100% NPV: 100%	**Detection of Lung Mets (n=23):** Sens: 100% Spec: 98.2% Accuracy: 98.5% PPV: 92% NPV: 100% **Detection of LN mets (n=22)** Sens: 100% Spec: 96.5% Accuracy: 97.1% PPV: 84.6% NPV: 100% **Bone Metastasis (n=11):** Sens: 63.6% Spec: 96.8% Accuracy: 94.1% PPV: 63.6% NPV: 96.8%	NA
Soussan et al, 2012 (22)	Retrospective	30 pts. (peritoneal carcinomatosis)	FDG PET/CT	MR-DWI	Pathology, clinical or imaging follow-	Sens: 84% Spec: 73% PPV: 84%	Sens: 84% Spec: 82% PPV: 89%	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard up	Diagnostic Accuracy: (PET) NPV: 73% Accuracy: 80%	Diagnostic Accuracy: (CI) NPV: 75% Accuracy: 83%	Change in Patient Management
Genitourinary Cancer								
Schlenker et al, 2012 (28)	Prospective	35 pts. (invasive penile carcinoma)	FDG PET/CT	CT, abdominopelvic MRI	Histopathology	Sens: 88.2% Spec: 98.1% PPV: 93.8% NPV: 96.3%	NA	NA
Head and Neck								
Fogh et al, 2012 (45)	Retrospective	182 pts. (newly diagnosed HNC scanned for possible metastatic disease)	FDG PET/CT	CeCT, MRI of the head and neck, chest x-ray	Histopathology, clinical follow-up, follow-up imaging	Sens: 90% Spec: 92% PPV: 39% NPV: 99.4%	NA	NA
Gilbert et al, 2012 (46)	Retrospective	55 pts. (laryngeal cancer recurrence)	FDG PET/CT	NA	Histopathology	TP: 7 FP: 0 TN: 5 FN: 3	NA	NA
Lee et al, 2012 (47)	Retrospective	114 pts. (HNSCC)	FDG PET/CT	CT, MRI, US	Histopathology	Sens: 69.18% Spec: 88.67% Accuracy: 84.62% PPV: 61.59% NPV: 91.64%	**CT** Sens: 63.01% Spec: 94.06% Accuracy: 87.61% PPV: 73.60% NPV: 90.64% **MRI** Sens: 66.44% Spec: 95.32% Accuracy: 89.32% PPV: 78.86% NPV: 91.54% **US** Sens: 65.07% Spec: 94.42% Accuracy: 88.32% PPV: 75.40% NPV: 91.15%	NA
Radhakrishnan et al, 2012 (48)	Prospective	25 pts. (IRSS stage III)	FDG PET/CT	MRI	Pathology	**PET/CT-1: at baseline for OS** Sens: 50% Spec: 66.67% **PET/CT-2: after 3 cycles of CRT for OS** Sens: 37.5% Spec: 92.3% PPV: 75% NPV: 70.6%	NA	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy: (PET)	Diagnostic Accuracy: (CI)	Change in Patient Management
Stoeckli et al, 2012 (49)	Prospective	76 pts. (untreated HNSCC)	FDG PET/CT	CT, US, US-guided FNAC	Histology	Correct: 63% Overstaging: 16% Understaging: 21%	**CT**: Correct: 62% Overstaging: 13% Understaging: 24% **US**: Correct 62% Overstaging: 13% Understaging: 25% **US-Guided FNAC** Correct: 69% Overstaging: 7% Understaging: 25%	NA
Hematology								
Richardson et al, 2012 (52)	Retrospective	50 pts. (HL)	FDG PET/CT	Chest radiography, CT of chest/abdomen/pelvis, BMB	Pathology	All patients with + bone marrow were identified on PET/CT	NA	NA
Melanoma								
Bronstein et al, 2012 (54)	Prospective	32 pts. (stage IIIC and IV melanoma pts.)	FDG PET/CT	CeCT (chest abdomen, pelvis, neck), MRI of the brain	Pathology or clinical follow-up, follow-up imaging	NA	NA	PET/CT revealed unsuspected mets in 12% (4/33). Surgery cancelled in 2 pts., planned approach altered in 2 pts.
Neuro-Oncology								
Santra et al, 2012 (56)	Prospective	90 glioma pts.	FDG PET/CT	MRI	Clinical follow-up repeat imaging and biopsy	Sens: 70% Spec: 97% PPV: 98% NPV: 63% Accuracy: 80%	Sens: 95% Spec: 23% PPV: 70% NPV: 70% Accuracy: 70%	NA
Timmers et al, 2012 (57)	Prospective	216 pts. (Pheochromocytomas and PPGLs)	FDG PET/CT	I-MIBG SPECT/CT, CT/MRI	Biopsy, clinical follow-up, clinical imaging	**Non metastatic** Sens: 76.8% **Metastatic:** Sens: 82.5% **Bone met:** Sens: 93.7%	**Non metastatic** I-MIBG SPECT Sens: 75% CT/MRI Sens: 95.7% **Metastatic:** I-MIBG SPECT Sens: 50%	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy: (PET)	Diagnostic Accuracy: (CI)	Change in Patient Management
							CT/MRI Sens: 74.4% **Bone met:** I-MIBG SPECT Sens: 61.5% CT/MRI Sens: 76.7%	
NSCLC								
Gregory et al, 2012 (72)	Prospective	168 pts. (NSCLC)	FDG PET/CT	CT (supplemented with BS)	Pathology, Clinical follow-up	NA	NA	Stage discordant with CI in 50.6% of pts. (41.1% upstaged, 9.5% downstaged). Management change in 42.3% of pts..
Jung et al, 2012 (73)	Retrospective	63 pts. (NSCLC)	FDG PET/CT	CeCT	Histology, cytology	PET/CT could differentiate plural mets with 70.8% of pts. when CeCT was indeterminate.	NA	NA
Lin et al, 2012 (74)	Retrospective	649 pts.	FDG PET/CT	Conventional imaging techniques (not specified)	Histopathology, endoscopy and progress PET/CT scans	NA	NA	3.1% (20/649) had a second primary (n=11) or pre-malignant (n=9) lesions discovered by PET/CT. 27.0% (3/20) patients had a high impact change in management (from curative to palliative).
Lee et al, 2012 (75)	Retrospective	160 pts. (T1 sub-solid NSCLC)	FDG PET/CT	Chest CT	Pathology	**Total LN staging (n=9):** Sens: 11.1% Spec: 86.1% Accuracy: 81.9%	**Total LN staging (n=9):** Sens: 11.1% Spec: 96.7% Accuracy: 91.9%	NA
Nawara et al, 2012 (76)	Prospective	91 pts. (NSCLC)	FDG PET/CT	CT	Clinical or imaging follow-up	NA	NA	PET provided additional diagnostic information in 20% (n=18) and lead to upstaging in 17% of them.
Pancreatic Cancer								
Zhang et al, 2012 (81)	Retrospective	116 pts. (pancreatic cystic tumours)	FDG PET/CT	CT, EUS	Pathology	Sens: 100% Spec: 93.7% Accuracy: 95%	**CT** Sens: 75% Spec: 87.5% Accuracy: 85% **EUS** Sens: 67.6% Spec: 93.7% Accuracy:	Treatment options were altered in 5/116 cases (n=2 follow-up instead of surgery, n=1 limited resection instead of Whipple's resection, n=2 surgery instead of follow-up).

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy: (PET)	Diagnostic Accuracy: (CI) 89.47%	Change in Patient Management
Pediatric Cancer								
London et al, 2012 (83)	Retrospective	86 scans (primary bone tumours)	FDG PET/CT	CT, US, MRI and/or BS	Histopathology or clinical follow-up when biopsy could not be taken	**All lesions** Sens: 81.8% Spec: 97.5% Accuracy: 95.9% **Excluding lung lesions:** Sens: 83.3% Spec: 98.1% Accuracy: 96.9% **Lung lesions**: Sens: 80.0% Spec: 95.8% Accuracy: 93.0%	**All lesions:** Sens: 84.8% Spec: 94.3% Accuracy: 93.3% **Excluding lung lesions:** Sens: 77.8% Spec: 96.7% Accuracy: 95.2% **Lung lesions:** Sens: 93.3% Spec: 87.3% Accuracy: 88.4%	NA
Nakatani et al, 2012 (84)	Prospective	19 pts.; 80 scans (pediatric NHL)	FDG PET/CT	US, CT, MRI (not standardized)	Imaging, BMB, cerebral fluid cytology, biopsy and histology	**Staging:** 4/6 correctly staged **End chemo response assessment**: Sens: 50% Spec: 71% PPV: 50% NPV: 71% Accuracy: 64% * in 1 case CI showed FP but PET showed TN. In another case, CI showed TN but PET showed FP.* **Surveillance:** Sens: 100% Spec: 87% NPV: 33% PPV: 100% Accuracy: 88%	**Staging**: 4/6 correctly staged **End chemo response assessment**: Sens: 50% Spec: 71% PPV: 50% NPV: 71% Accuracy: 64% **Surveillance:** NA	Response to treatment: PET modified treatment in 4 cases (new extranodal lesions).
Sarcoidosis								
Mostard et al, 2012 (86)	Retrospective	122 pts.	FDG PET/CT	Low-dose CT	Follow-up imaging	34% (n=32) of 94 + PET scans had evidence of BM uptake. Of these, diffuse and focal uptake were seen in 34% (11/32) of	CT identified 6% (n=2) pts. with PET/CT detected bone abnormalities.	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy: (PET) patients, only focal lesions were seen in 25% (8/32).	Diagnostic Accuracy: (CI)	Change in Patient Management
Sobic-Saranovic et al, 2012 (87)	Retrospective	90 pts.	FDG PET/CT	Multidetector CT, ACE	Clinical follow-up	Sens: 82%	Sens: 89%	81% (therapy initiated or changed).
Sarcoma								
Fuglo et al, 2012 (89)	Retrospective	89 pts. (30 bone and 59 soft tissue sarcoma pts.)	FDG PET/CT	MRI, plain radiography of chest, CT of chest, US, BS	Histology, follow-up imaging	**Distant metastasis** Sens: 95% Spec: 96% PPV: 87% NPV: 98% **LN metastasis** Sens: 100% Spec: 90% PPV: 27%(high FP – uptake in inflammatory tissue?) NPV: 100%	NA	3 patents with LN and 18/20 patients with distant metastases detected on PET/CT had change of management to chemotherapy instead of planned surgery.
Thyroid Cancer								
Deandreis et al, 2012 (91)	Prospective	55 pts. (pts. planned for surgery)	FDG PET/CT	US	Histology	Sens: 77% Spec: 62% PPV: 57% NPV: 81%	Sens: 82% Spec: 47% PPV: 50% NPV: 80%	NA
Vural et al, 2012 (90)	Prospective	105 pts. (differentiated thyroid carcinoma)	FDG PET/CT	^{131}I WB S	Histopathology, clinical follow-up	Sens: 87% Spec: 77% PPV: 92% NPV: 67% Accuracy: 85% (diagnostic Accuracy: improved with Tg levels ≥38.2 g/ml)	NA	PET/CT resulted in a change in the treatment plans for these patients 41/105 (39% of study population).
Unknown Primary								
Chen et al, 2012 (92)	Prospective	27 pts. (primary unknown cervical lymph node mets)	FDG PET/CT	CT, US, MRI, chest x-ray	Clinical follow-up, pathology	Sens: 91.7% Spec: 86.7% Accuracy: 88.9% PPV: 84.6% Primaries were confirmed in 11/27 cases (nasopharynx most common)	NA	11/27 (40.7%)
Moller et al, 2012 (93)	Prospective	136 pts. (newly diagnosed CUP pts.)	FDG PET/CT	CT	Multidisciplinary team	Sens: 57.6% Spec: 71%	Sens: 65.2% Spec: 60.9%	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy: (PET)	Diagnostic Accuracy: (CI)	Change in Patient Management
					(pathologist, oncologists, clinical follow-up)	Accuracy: 64.4% 38/136 CUP tumour sites identified	Accuracy: 63% 43/136 CUP tumour sites identified	
Various Sites								
Hillner et al, 2012 (94)	Retrospective	Pts. of the National Oncologic PET Registry from 2006 and 2009 **Restaging/recurrence**: 85,658 **Chemo Monitoring:** 25,845	FDG PET/CT	Various (not Specified – based on cancer type)	Not Specified	NA	NA	**Restaging/Recurrence** All cancer types: 33% in those ≤65 y and about 35% in those ≥65 y (range by cancer type, 31%-41%) **Chemotherapy Monitoring (2006, 2009) - Total Cases:** Continue Therapy: 34.7%, 46.9% Switch Therapy: 26.7%, 25.9% Adjust Therapy: 14.6%, 6.3% Stop Therapy: 18.6%, 16.3%
Salem et al, 2012 (95)	Prospective	105 pts. (different pathologies, increasing tumour markers but neg. or equivocal on CI)	FDG PET/CT	CECT, US, MRI (all negative or equivocal), mammography, BS	Histology, follow-up imaging, clinical follow-up	Sens: 95.7% Spec: 100% PPV: 100% NPV: 73.3% Accuracy: 96.2%	All CI was negative or equivocal upon study inclusion	PET/CT detected recurrence and/or metastases in 90 patients (85.7%), including 17 recurrences, 50 metastases, and 23 recurrences and metastases.
Other PET tracers ^{68}Ga-DOTA(NOC, TOC, TATE)								
Afshar-Oromieh et al, 2012 (63)	Retrospective	134 pts. (cranial meningioma's)	^{68}Ga-DOTATOC PET/CT	CE-MRI	Pathological tracer uptake	PET detected 190 lesions	CE—MRI detected 171 lesions	NA
Ambrosini et al, 2012 (64)	Retrospective	131 pts. (suspected NETs)	^{68}Ga-DOTANOC PET/CT	CT, US, MRI	Clinical or imaging follow-up, pathology (where available)	Sens: 89.5% Spec: 100% Accuracy: 98%	NA	NA
Hofman et al, 2012 (65)	Prospective	59 pts. (suspected gastro-entero-pancreatic or bronchial NETs and 7 neural crest/mesenchymal tumours)	^{68}Ga-DOTATATE	CECT, MRI, US, X-ray, BS (not standardized)	Clinical follow-up (histopathological confirmation not possible in most patients)	NA	NA	^{68}Ga-DOTATATE provided additional info in 68% (40/59) of pts. compared to CI. In 33 of 59 (56%), this related to identification of disease in an additional organ or

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy: (PET)	Diagnostic Accuracy: (CI)	Change in Patient Management
								distant nodal disease. In 17 of 59 (29%), this related to detection of additional lesions within known sites of involvement. Inter-modality change in 28 (47%), intra-modality change in 6 (10%), low management impact in 24 (41%).
^{18}F-DOPA								
Lopci et al, 2012 (67)	Prospective	21 pts. (advances stage III-IV neuroblastoma	^{18}F-DOPA PET/CT	CT/MRI	Multidisciplinary assessment (^{123}I-MIBG, selective biopsy, and clinical-instrumental monitoring)	**Total Scans** Sens: 100% Spec: 92.3% NPV: 100% PPV: 96% Accuracy: 97.3% **Total Lesions** Sens: 90.6% Spec: 90% NPV: 73.5% PPV: 96.9% Accuracy: 90.5%	**Total Scans** Sens: 91.7% Spec: 61.5% NPV: 80% PPV: 81.5% Accuracy: 81.1% **Total Lesions** Sens: 47.5% Spec: 27.5% NPV: 13.1% PPV: 69.5% Accuracy: 43%	NA
^{11}C-Choline								
Fuccio et al, 2012 (60)	Retrospective	123 pts. (prostate cancer pts. with demonstrated biochemical relapse)	^{11}C-choline PET/CT	BS (negative scans)	Longitudinal follow-up of lesions	^{11}C-choline PET/CT detected 30 lesions in 18/123 (14.6%) patients that BS did not	NA	NA
^{18}F-FLT								
Herrmann et al, 2012 (69)	Prospective	46 pts. (pancreatic mass suspicious for malignancy)	FLT PET *no CT	FDG PET/CT	Histopathology, cytology	FLT PET Sens: 72%	FDG PET/CT Sens: 96% FDG PET Sens: 92% CeCT Sens: 88%	NA

Abbreviations: ACE: angiotensin-converting enzyme; BMB: bone marrow biopsy; CeCT: contrast enhanced computerized; CEMDCT: contrast-enhanced multi-detector computed tomography; CI: conventional imaging; CUP: carcinoma of unknown primary; DWI: diffusion weighted imaging; EGD: esophagogastroduodenoscopy; EUS: endoscopic ultrasound; FLT PET: fluorothymidine positron emission tomography; FN: false negative; HL: Hodgkin lymphoma; HNSCC: head and neck squamous cell carcinoma; IRSS: International Retinoblastoma Staging System; IWBS: I whole-body scans; LACC: locally advanced cervical cancer; NET: neuroendocrine tumours; NHL: non-Hodgkin lymphoma; NPV: negative predictive value; NSCLC: non-small cell lung cancer; PET: positron emission tomography; PPGL: paraganglioma; PPV: positive predictive value; pts.: patients; Sens: sensitivity; US: ultrasound; 1-MIBG SPECT: [1]-metaiodobenzylguandine single photon emission CT; NA: not available

Appendix 1B. Summary of studies from January to July 2013.

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy: (PET)	Diagnostic Accuracy: (CI)	Change in Patient Management
Bone Cancer								
Duo et al, 2013 (2)	Systematic Review	9 ***studies*** (1116 pts. total with bone mets)	FDG PET/CT	Gadolinium-enhanced MRI	Not specifically stated but part of inclusion criteria and QUADAS score	Sens: 80.3% Spec: 98.9% Diagnostic Odds Ratio: 309.0 +LR: 61.7 -LR: 0.2	Sens: 83.7% Spec: 97.7% Diagnostic Odds Ratio: 221.9 +LR: 37.0 -LR: 0.167	NA
Breast Cancer								
Groheux et al, 2013 (12)	Prospective	117 pts. (with LABC)	FDG PET/CT	Bone scanning, chest examination by radiography or dedicated CT, and abdominopelvic examination by sonography or contrast-enhanced CT	Biopsy results, further work-up, or patient follow-up	***Bone Lesions*:** Sens: 100% Spec: 97.7% PPV: 93.7% NPV: 100% Accuracy: 98.3% ***Lung Metastasis:*** Sens: 85.7% Spec: 98.2% PPV: 75% NPV: 99.1% Accuracy: 97.4% ***Pleural Metastasis:*** Sens: 100% Spec: 99.1% PPV: 66.7% NPV: 100% Accuracy: 99.1%	***Bone Lesions (scanned with planar bone scanning)*** Sens: 76.7% Spec: 94.2% PPV: 82.1% NPV: 92.1% Accuracy: 89.7% ***Lung Metastasis (high res CT):*** Sens: 100% Spec: 98.2% PPV: 77.8% NPV: 100% Accuracy: 98.3% ***Pleural Metastasis (CT):*** Sens: 50% Spec: 100% PPV: 100% NPV: 99.1% Accuracy: 99.1%	PET/CT changed the clinical stage in 61 pts. (52%).
Hong et al, 2013 (13)	Systematic Review	8 ***studies*** (748 total pts. with breast cancer)	FDG PET/CT	Various	Not specifically stated but part of inclusion criteria and QUADAS score	Pooled Sens: 96% Pooled Spec: 95% Diagnostic Odds Ratio: 464 +LR: 18.9 -LR: 0.04	***CI type not Specifically stated*** Pooled Sens: 56% Pooled Spec: 91% Diagnostic Odds Ratio: 13.7 +LR: 6.5 -LR: 0.48	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy: (PET)	Diagnostic Accuracy: (CI)	Change in Patient Management
Manohar et al, 2013 (14)	Prospective	43 pts. (LABC, - for distant mets on CI)	FDG PET/CT	Chest radiography, abdominal ultrasound, CT of the chest and abdomen, and 99mTc-MDP skeletal scintigraphy – *type of CI was not Specified/ standardized*	8-month (mean) patient follow-up	Sens: 100% Spec: 97% PPV: 91% NPV: 100%	NA	32 pts. had no distant mets evident on FDG PET/CT (confirmed with follow-up) In the remaining 11 pts., 10 were TP for distant mets and 1 FP. PET/CT also suggested LN mets in 16/43 pts. Change in stage was noticed in 17/43 pts.
Rong et al, 2013 (15)	Systematic Review	7 ***studies*** evaluating bone mets in breast cancer (668 breast cancer pts.)	FDG PET/CT	Bone scintigraphy	Not specifically stated but part of inclusion criteria and QUADAS score	Sens: 93% Spec: 99% DOR: 2182 +LR: 149.8 -LR: 0.07	Sens: 81% Spec: 96% DOR: 109 +LR: 22 -LR: 0.2	NA
Sen et al, 2013 (16)	Retrospective	77 pts. (breast cancer)	FDG PET/CT	(CI was performed in 47/77 patients) abdominal ultrasound, CT of the chest and abdomen, and bone scan	Histopathology and clinical follow-up data	NA	NA	Upstaged by FDG PET/CT in 14 (18.2%) pts.. 12 of these patients upstaged to stage IV for distant mets.
Esophageal Cancer								
Shi et al, 2013 (20)	Systematic Review	12 ***studies*** evaluating PET in the detection of regional nodal metastasis in esophageal cancer	FDG PET/CT	NA	Not specifically stated but part of inclusion criteria and QUADAS score	***Per-patient (pooled):*** Sens: 0.55% Spec: 0.76% DOR: 3.7% +LR: 2.2% -LR: 0.59% ***Per-station:*** Sens: 0.62% Spec: 0.96% DOR: 37.8% +LR: 15.1% -LR: 0.4%	NA	NA
Gastrointestinal Cancer								
Garcia Vicente et al, 2013 (23)	Prospective	19 CRC pts. with liver mets (120 liver lesions total – 115 malignant, 5 benign)	FDG PET/CT	CeCT	Histopathology	Sens: 94.78% Spec: 100% PPV: 100% NPV: 45.45%	Sens: 91.3% Spec: 100% PPV: 100% NPV: 33.33%	Na
Georgakopoulos et al, 2013	Prospective	35 pts. (CRC with liver mets)	FDG PET/CT	Chest and abdomen CT or	Histopathology and/or clinical	NA	NA	FDG PET/CT scan revealed the same number of liver

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy: (PET)	Diagnostic Accuracy: (CI)	Change in Patient Management
(24)				MRI	follow-up			metastases with conventional imaging in 25 pts. (71.5%), in 5 pts. (14.2%) revealed additional lesions in the liver, while in 5 pts. (14.2%) detected fewer lesions. FDG PET/CT detected extrahepatic disease, missed by CI, in 9/19 pts. (47.3%). Findings altered management in 7 pts. (36.8%).
Genitourinary Cancer								
Nayak et al, 2013 (27)	Prospective	25 pts. (urinary bladder cancer)	FDG PET/CT	CECT	Histopathology	***Primary tumour*** Sens: 96% LN Mets Sens: 78%	***Primary Tumour*** Sens: 92% LN Mets Sens: 44%	NA
Gynecologic Cancer								
Antonsen et al, 2013 (39)	Prospective	318 pts. (endometrial cancer)	FDG PET/CT	MRI, 2DUS	Pathology	***Myometrial Invasion:*** Sens: 93% Spec: 49% PPV: 41% NPV: 95% Accuracy: 61% ***Cervical Invasion:*** Sens: 43% Spec: 94% PPV: 69% NPV: 85% Accuracy: 83% ***Lymph Node Mets*** Sens: 74% Spec: 93% PPV: 59% NPV: 96% Accuracy: 91%	***Myometrial Invasion:*** ***MRI:*** Sens: 87% Spec: 57% PPV: 44% NPV: 92% Accuracy: 66% ***2DUS:*** Sens: 71% Spec: 72% PPV: 51% NPV: 86% Accuracy: 72% ***Cervical Invasion:*** ***MRI:*** Sens: 33% Spec: 95% PPV: 60% NPV: 82% Accuracy: 82% ***2DUS:*** Sens: 29% Spec: 92% PPV: 48% NPV: 82%	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy: (PET)	Diagnostic Accuracy: (CI)	Change in Patient Management
							Accuracy: 78% ***Lymph Node Mets*** ***MRI:*** Sens: 59% Spec: 93% PPV: 40% NPV: 97% Accuracy: 90%	
Lee et al, 2013 (29)	Prospective	52 pts. (biopsy proven cervical cancer)	FDG PET/CT (scanned before, during and after CCRT)	MRI (scanned before, during and after CCRT)	Pathology	***During Treatment:*** CR in 18 patients (34.6%), PR in 26 patients (50.0%), and SD in 8 patients (15.4%) ***After Treatment:*** 41 patients (78.8%) achieved CR and 11 patients (21.2%) achieved PR	***During Treatment:*** CR in 4 patients (7.7%), PR in 33 patients (63.5%), and SD in 15 patients (28.8%) ***After Treatment:*** 33 patients (63.4%) achieved CR, 16 patients (30.8%) achieved PR, and 3 patients (5.8%) achieved SD	NA
Meads et al, 2013 (30)	Systematic Review	6 ***studies*** evaluating PET/CT in recurrent cervical cancer. 2 evaluated MRI, 3 evaluated CT, 1 evaluated both CT and MRI	FDG PET/CT	MRI, CT	Histopathology, clinical follow-up	Sens: 92.2% Spec: 88.1%	***MRI:*** Sens: 82%-100% Spec: 78%-100% ***CT:*** Sens: 78-93% Spec: 0-95%	One of the study reported PET/CT having an impact on management in 12 (23%) patients (4-initiate previously unplanned treatment; 5-changing previously planned therapeutic approach; 5-eliminating previously diagnostic procedure)
Perez-Medina et al, 2013 (31)	Prospective	52 pts. (diagnosed LACC)	FDG PET/CT	US, chest radiograph, MRI	Histopathology	Sens: 77.7% Spec: 94.1% PPV: 87.5% NPV: 88.9% +LR: 13.2	***MRI:*** Sens: 66.7% Spec: 94.1%	NA
Zytoon et al, 2013 (35)	Prospective	98 pts. (suspected ovarian cancer)	FDG PET/CT	US, CT, MRI	Histopathology	Sens: 92.6% Spec: 100% PPV: 100% NPV: 36.4% Accuracy: 92.9%	NA	57 pts. were found to have stage IV distant mets on PET/CT.
Head and Neck								

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy: (PET)	Diagnostic Accuracy: (CI)	Change in Patient Management
Abramyuk et al, 2013 (41)	Retrospective	102 pts. (untreated primary NHC)	FDG PET/CT	CeCT, US, pts. with nasopharyngeal cancer had MRI	Pathology	NA	NA	***N staging modifications*:** 8 of these patients were upstaged, while 27 patients were downstaged. ***M staging*:** 13 of 102 patients were shifted from M0 to M1. 1 of 102 pts with initial distant metastasis (M1) was found with no metastasis (M0). ***Clinical staging modifications:*** Nine patients were upstaged, 18 patients of 102 were downstaged and 75 patients were unchanged. ***Radiotherapy modifications:*** RT intention shifted from curative to palliative in 12 of 102 patients. Two patients changed from palliative to curative intention. For 88 patients the therapeutic intention remained unchanged.
Hawryluk et al, 2013 (42)	Retrospective	97 pts. (with Merkle cell carcinoma)	FDG PET/CT	Not standardized	Histology	NA	NA	FDG-PET/CT upstaged 16% of patients who underwent baseline scans.
Kim et al, 2013 (43)	Retrospective	62 pts. (underwent surgery for resectable SCC in the larynx, hypopharynx or esophagus and underwent compartment lymph node dissection)	FDG PET/CT	CT/MRI (co-registered)	Histopathology	Sens: 58% Spec: 88% Accuracy: 82% PPV: 53% NPV: 90%	Sens: 42% Spec: 90% Accuracy: 81% PPV: 50% NPV: 87%	NA
Kim et al, 2013 (44)	Prospective	54 pts. (confirmed salivary gland cancer)	FDG PET/CT	CT/MRI (co-registered)	Histopathology	***Patient-based:*** Sens: 92% Spec: 93% Accuracy: 93% PPV: 92% NPV: 93% ***Lesion-based:*** Sens: 81% Spec: 97% Accuracy: 92%	***Patient-based:*** Sens: 83% Spec: 97% Accuracy: 90% PPV: 95% NPV: 88% ***Lesion-based:*** Sens: 54% Spec: 96% Accuracy: 83%	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy: (PET)	Diagnostic Accuracy: (CI)	Change in Patient Management
						PPV: 93% NPV: 92%	PPV: 85% NPV: 82%	
Lung Cancer (other than NSCLC)								
Suzawa et al, 2013 (77)	Retrospective	143 pts. (malignant lung tumours receiving RF ablation)	FDG PET/CT	CT	Clinical follow-up	Area under the ROC Curve (AUC) was of PET was higher than CT in all 4 time points 3 months: 0.71 6 months: 0.82 9 months: 0.84 12 months: 0.92	***AUC:*** 3 months: 0.55 6 months: 0.6 9 months: 0.66 12 months: 0.68	NA
Hematology								
Awan et al, 2013 (50)	Prospective	53 pts. (35 HL, 18 NHL)	FDG PET/CT	CT	Clinical follow-up and histopathology when feasible	NA	NA	Upstaged 4/53 pts. (7.5%) from stage III to stage IV.
Kamel et al, 2013 (51)	Prospective	37 pts. (22 NHL, 15 HL)	FDG PET/CT	CT	Histology, clinical and imaging follow-up	Accuracy: 96.3% Sens: 88.3% Spec: 98.2%	Accuracy: 89.1% Sens: 60.1% Spec: 96.1%	PET/CT correctly identified more extranodal lesions (24 pts.) than CT (16 pts.) and PET (15 pts.). Correct staging was more accurate at PET/CT (31 pts.) in comparison to PET alone (23 pts.) and CT alone (21 pts.).
Malignant Myeloma								
Derlin et al, 2013 (53)	Prospective	31 pts. (multiple myeloma for determination of remission status)	FDG PET/CT	Whole-body MRI	European Group for Blood and Marrow Transplantation criteria modified by the International Uniform Response Criteria for multiple myeloma	Sens: 50% Spec: 85.7% PPV: 62.5% NPV: 78.3% Accuracy: 74.2%	Sens: 80.0% Spec: 38.1% PPV: 38.1% NPV: 80.0% Accuracy: 51.6%	NA
Neuro-Oncology								
Manohar et al, 2013 (55)	Retrospective	5110 pts. (various cancers)	FDG PET/CT (inclusion of brain in WB PET scans)	Various staging modalities (not standardized)	Various (not standardized)	NA	NA	Out of 63 patients with untreated cerebral metastases detected on the 18F-FDG PET/CT study, cerebral metastases were unknown before 18F-FDG

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy: (PET)	Diagnostic Accuracy: (CI)	Change in Patient Management
NSCLC								PET/CT in 40 patients.
Bille et al, 2013 (70)	Retrospective	353 pts. (suspected or proven adenocarcinoma or squamous cell carcinoma)	FDG PET/CT	Conventional work-up (history and physical examination, laboratory tests, spirometry, chest x-ray, contrast-enhanced brain, chest and upper abdomen CT, and bronchoscopy)	Histopathology	Adenocarcinoma: Sens: 53.8% Spec: 91.5% Accuracy: 79.1% Squamous cell carcinoma: Sens: 87.5% Spec: 81.8% Accuracy: 83.5%	Not evaluated	Under-staging occurred in 37 (15.2%) and four (3.7%) patients, and over-staging in 14 (5.7%) and 14 (12.8%), in adenocarcinoma and squamous cell, respectively.
Jimenez-Bonilla et al, 2013 (71)	Prospective	55 pts. (NSCLC)	FDG PET/CT	CT	Histopathology	NA	NA	15 changed to chemotherapy and in 2, the radiotherapy field was changed. Treatment was started in 14 due to the FDG PET/CT findings, and in 11 was withdrawn.
Pancreatic Cancer								
Asagi et al, 2013 (78)	Retrospective	108 pts. (pancreatic lesion)	FDG PET/CeCT	CeCT	Clinical follow-up and histopathology where available	**Diagnostic Accuracy Rate:** 80% for most factors concerning local invasion 94% for distant metastasis 42% for lymph node metastasis	**Diagnostic Accuracy Rate:** 35% for lymph node metastasis	NA
Javery et al, 2013 (79)	Retrospective	49 pts. (pancreatic cancer)	FDG PET/CT	CT, MRI	Clinical follow-up, histopathology	NA	NA	69 (87.3%) of 79 PET/CT-MRI, CT pairs, PET/CT did not favorably impact management over findings on CT or MRI alone. Among all cases in which management was altered by PET/CT, 66.7% were favourable.
Matsumoto et al, 2013 (80)	Retrospective	232 pts. (pancreatic cancer)	FDG PET/CT	Multidetector CT, MRI	Histopathology	***Detection rates of liver mets:*** 38% ***Para-aortic LN Mets:*** 56% ***Lung Mets:*** 64% ***Bone Mets:***	***Detection rates of liver mets:*** MDCT: 60% SPIO-MRI: 60% ***Para-aortic LN Mets:*** MDCT: 65%	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy: (PET) 100% *all pts. with bone mets had other distant mets*	Diagnostic Accuracy: (CI) MRI: 44% ***Lung Mets:*** CT: 100% ***Bone Mets:*** MDCT: 20% MRI: 40% *all pts. with bone mets had other distant mets*	Change in Patient Management
Pediatric Cancer								
Frederico et al, 2013 (82)	Retrospective	30 pts. (Rhabdomyosarcoma)	FDG PET/CT	CT of the chest, CT or MRI of the primary site and local-regional nodal basin and 99mTc MDP bone scan (not standardized)	Pathology	**Accuracy rate for nodal disease:** 95% Sens: 94% Spec: 100% **Pulmonary nodules detected:** 4/7	**Accuracy rate for nodal disease:** 49% **Pulmonary nodules detected:** 7/7	NA
Sarcoidosis								
Ambrosini et al, 2013 (85)	Prospective	28 pts. (biopsy proven sarcoidosis)	FDG PET/CT	Chest x-ray or high-res CT (not standardized)	Clinical and imaging follow-up	NA	NA	PET/CT contributed to a change in clinical management after 18/19 discordant scans. In all scans PET/CT information influenced the clinical management of 22 (63%) of 35 scans.
Sarcoma								
Al-Ibraheem et al, 2013 (88)	Retrospective	43 pts. (sarcoma in remission (various histologies: 22 pts. with soft tissue sarcoma, 21 pts. with osseous sarcoma))	FDG PET/CT	CeCT	Clinical follow-up or histopathology	Sens: 94% Spec: 92% PPV: 94% NPV: 92% Accuracy: 93%	Sens: 78% Spec: 67% PPV: 78% Accuracy: 73%	In 6 patients, treatment was modified due to additional information gained by PET/CT
Various Sites								
Abdelmalik, 2013 (96)	Retrospective	1000 pts. (known or suspected malignancy. 102 pts. with potentially significant findings above base-of-skull were included)	FDG PET/CT	CT, MRI (not standardized)	Pathology or clinical follow-up	NA	NA	In 13 pts. with unsuspected mets, the finding of brain metastasis changed the management in 11/13 (85%) patients and upstaged 4/13 (31%) patients. PET/CT was FP in 4/25 pts..
Sebro, 2013 (97)	Retrospective	556 pts. (undergoing staging of a known or suspected	FDG PET/CT	Conventional Staging (various, not standardized)	Clinical and imaging follow-up, pathology	NA	NA	Forty-three (7.7%) patients had lesions that were suspicious for a newly

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy: (PET)	Diagnostic Accuracy: (CI)	Change in Patient Management
		malignancy or for restaging)						discovered primary malignancy that was different from the known/suspected malignancy (indication for study). Eight (1.4% of 556) of these patients had biopsy confirmation of an additional synchronous or metachronous primary malignancy. However, these suspicious lesions changed the clinical management for 18 (3.2% of 556) patients.
Xu, 2013 (98)	Systematic Review	13 ***studies*** (1239 pts.)	FDG PET/CT	WB MRI	Not specifically stated but part of inclusion criteria and QUADAS score	***Per patient (n-1070):*** Sens: 85% Spec: 96% ***Per lesion (n=210):*** Sens: 85% Spec: 90%	***Per-patient (n-1070):*** Sens: 86% Spec: 97% ***Per lesion (n=210):*** Sens: 89% Spec: 89%	NA
Other PET tracers **^{11}C-Choline**								
Evangelista et al, 2013 (58)	Systematic Review	18 ***studies*** (qualitative synthesis) 10 studies (quantitative synthesis)	^{11}C-Choline PET ^{18}F-Choline PET **Stats are for ^{11}C-Cl and ^{18}F-Cl combined**	Various (not standardized)	Pathology or other common imaging modalities	**Pooled:** Sens: 49.2% Spec: 95% +LR: 8.346 -LR: 0.549 DOR: 18.999 ** Comparison across the different radioisotope (^{18}F vs ^{11}C) demonstrated that ^{11}C-choline is more Sensitive than ^{18}F-choline (pooled sensitivity: 58% vs 40%, respectively), but ^{18}F-choline shows a high specificity*	NA	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy: (PET) *(pooled specificity: 96%; 95% CI, 0.91-0.98)* ^{11}C-Choline has a pooled specificity of 0.94; 95% CI, 0.90-0.97).*	Diagnostic Accuracy: (CI)	Change in Patient Management
Umbehr et al, 2013 (59)	Systematic Review	44 ***studies*** (2293 pts. with prostate cancer)	^{11}C-Choline PET ^{18}F-Choline PET **Stats are for ^{11}C-Cl and ^{18}F-Cl combined**	Various (not standardized)	Histology, additional imaging, clinical follow-up	***Per patient pooled (10 studies, n = 637):*** Sens: 84% Spec: 79% DOR: 20.4 +LR: 4.02 -LR: 0.20 ***Per lesion pooled (11 studies, n = 5117):*** Sens: 66% Spec: 92% DOR: 22.7 +LR: 8.29 -LR: 0.36	NA	NA
^{68}Ga-DOTA(NOC, TOC, TATE)								
Schraml et al, 2013 (61)	Retrospective	51 pts. (histologically proven NET and suspicion of metastatic spread)	^{68}G-DOTATOC PET/CT	WB MRI	Histopathology, correlation of all imaging data, clinical follow-up	***Lesion based:*** **Metastatic LN:** Sens: 100% **Pulmonary Mets:** Sens: 100% **Liver:** Sens: 92% **Bone lesion:** Sens: 82%	***Lesion-based:*** **Metastatic LN:** Sens: 73% **Pulmonary Mets:** Sens: 87% **Liver:** Sens: 99% **Bone lesion:** Sens: 96%	The imaging results influenced the treatment decision in 30 patients (59%) with comparable information from PET/CT and MRI in 30 patients, additional relevant information from PET/CT in 16 patients and from MRI in 7 patients.
Wild et al, 2013 (62)	Prospective	18 pts. (neuroendocrine tumours)	^{68}Ga-DOTATATE PET/CT, ^{68}Ga-DOTANOC PET/CT	CT, MRI, FDG PET/CT	Histopathology	***Lesion-based:*** ***DOTANOC PET:*** Sens: 93.5% ***DOTATATE PET:*** Sens: 85.5%	NA	3 of 18 pts. had management altered after DOTANOC PET/CT.
^{18}F-DOPA								
Lu et al, 2013 (66)	Retrospective	55 pediatric pts. (neuroblastic tumours)	F-DOPA PET/CT	^{123}I-MIBG scan	Histology and clinical follow-up	Sens: 100% Spec: 50% Accuracy: 94.4%	Sens: 75% Spec: 100% Accuracy: 77.8%	NA

Citation	Study Type	Population	PET Type	CI	Reference Standard	Diagnostic Accuracy: (PET)	Diagnostic Accuracy: (CI)	Change in Patient Management
18F-FLT								
Xu et al, 2013 (68)	Prospective	87 pts. (pulmonary lesions)	^{18}F-FLT PET/CT	^{18}F FDG PET/CT	Pathology and clinical follow-up	Sens: 80.0% Spec: 60.0% Accuracy: 65.0% PPV: 40.0% NPV: 90.0%	Sens: 90.9% Spec: 58.3% Accuracy: 68.3% PPV: 50.0% NPV: 93.3%	NA

Abbreviations: CCRT: concurrent chemoradiotherapy; CI: conventional imaging; CR: complete response; CRC: colorectal cancer; HNC: head and neck cancer; LABC: locally advanced breast cancer; LACC: locally advanced cervical cancer; NET: neuroendocrine tumour; PR: partial response; SD: stable disease; QUADAS: Quality Assessment of Diagnostic Accuracy Studies; SPECT: single-photon emission computed tomography; SPIO-MRI: superparamagnetic iron oxide magnetic resonance imaging; 1-MIBG: [1]-metaiodobenzylguanidine scintigraphy; NA: not available; +LR: positive likelihood ratio; -LR: negative likelihood ratio