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PET Six-Month Monitoring Report 2011-1

Evidence from Primary Studies and Systematic Reviews and Recommendations from Clinical Practice Guidelines January to June 2011

S. Henderson and the Program in Evidence-based Care Disease Site Group Reviewers

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

Report Date: August 15, 2012

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 clinical management of patients' with cancer, with respect to the following:

- 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 PEBC provide regular updates to the Committee of recently published literature reporting on the use of PET in patients with cancer. 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 report is the third of what will be many 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 2011 were systematically searched through MEDLINE and EMBASE for evidence from primary studies and systematic reviews (see Appendix 1). The search strategies used are available on request to the PEBC. In addition, clinical practice guidelines published in 2010 were also searched for in the National Guidelines Clearinghouse (NGC) (http://www.guideline.gov/) and the SAGE

Inventory of Cancer Guidelines (http://www.cancerguidelines.ca/Guidelines/inventory/index.php) databases.

Inclusion Criteria for Clinical Practice Guidelines

Any clinical practice guidelines that contained recommendations with respect to PET were included.

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 (18F-FDG) PET in cancer in humans
2. Published as a full article in a peer reviewed journal
3. Reported evidence related to change in patient clinical management, or clinical outcomes OR reported diagnostic accuracy of PET compared to an alternative diagnostic modality
4. Used a suitable reference standard (pathological and clinical follow-up) when appropriate
5. Included ≥ 12 patients for prospective study or ≥ 50 patients for retrospective study with the cancer of interest

Inclusion Criteria for systematic reviews

1. Reviewed the use of PET in cancer
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.
2. Studies of non-FDG PET

Study design was not a criteria for inclusion or exclusion.

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

RESULTS

Literature Search Results

Primary Studies and Systematic Reviews

Twenty-five primary studies met the inclusion criteria. Out of the 25 primary studies, 12 were prospective cohort, 11 were retrospective studies, and two were randomized controlled trials. A summary of the evidence from the 25 primary studies is presented in the Appendix 1. No systematic reviews met the inclusion criteria.

Bone Cancer

One prospective study evaluated the diagnostic accuracy of full-dose, contrast-enhanced, fully diagnostic whole-body FDG-PET/computerized tomography (CT) and whole-body magnetic resonance imaging (MRI) for the detection of bone metastases in a defined patient population with FDG-PET positive tumours (non-small cell lung cancer patients and malignant melanoma) on initial whole-body staging (1). The sensitivity, specificity, positive

predictive value (PPV), negative predictive value (NPV), and accuracy of FDG-PET/CT and MRI for the detection of bone metastases were 45%, 99%, 83%, 94%, and 94%, as well as 64%, 94%, 54%, 96%, and 91%, respectively. Due to both modalities having a high false-negative rate, close patient follow-up is recommended.

Brain Cancer

One retrospective study evaluated the impact of dedicated brain FDG-PET on the intended management of patients with primary or metastatic brain tumours (2). For the primary brain tumor subgroup, a change in the pre-PET plan from treatment to non-treatment was more common (46.7%) than the converse (34.7%). Of the primary brain tumor patients with a pre-PET plan of treatment, the post-PET plan had a treatment goal change in 28.6%.

Breast cancer

Five studies compared 18F-FDG PET/CT to conventional imaging in breast cancer. Berg et al (3) evaluated the performance of positron emission mammography (PEM) as compared with MRI in ipsilateral breasts with cancer. The sensitivity of PEM was 91.2% compared to 86.3% for MRI. The PPV of biopsy prompted by PEM findings was 66% compared to MRI at 53%.

Champion et al (4) evaluated the utility of 18F-FDG PET/CT in suspected breast cancer recurrence. PET/CT scans were performed in 228 asymptomatic patients who presented with rising CA 15-3 and or CEA serum levels. PET/CT scans were positive in 181 patients (79.5%) and normal in 47 patients, whereas 187 true recurrences were diagnosed. The sensitivity, specificity, PPV, NPV, and accuracy of PET/CT imaging for detection of breast cancer recurrence were 93.6%, 85.4%, 96.7%, 74.5%, and 92.1%, respectively. Treatment alteration was a direct consequence of the detection of recurrence by PET/CT imaging in 123 patients.

Constantinidou et al (5) also evaluated the efficacy of FDG PET/CT in the recurrence and metastasis of breast cancer. The researchers retrospectively reviewed PET/CT scans carried out in breast cancer patients. For staging FDG PET/CT scans were useful in accurately defining the extent of disease and guided localized or systemic treatment. FDG PET/CT was also helpful for detecting early response assessment and, in some cases allowed for appropriate discontinuation of ineffective treatment.

Evangelista et al (6) carried out a study to assess the role of FDG PET/CT in the identification of disease relapse in patients with breast cancer who had already received treatment and to evaluate its impact on patient management. One hundred eleven patients were included in this retrospective study. All patients underwent both CT and whole-body FDG PET/CT within five months, and CA 15.3 values were available in all patients. PET/CT predicted the relapse of disease in 26 of 32 patients, with a true-positive rate of 81% and a true-negative rate of 52%. The 48% false-positive rate from FDG PET/CT was attributed to abnormal FDG uptake by the adrenal glands or bone and/or liver that was not subsequently confirmed by follow-up investigations. At the end of follow-up, PET/CT correctly predicted a relapse in 26 (81%) patients, whereas CT correctly identified it in 23 (72%). Therapeutic management was changed in 11 patients with increased CA 15.3, starting chemotherapy, whereas positive PET/CT modified the therapeutic regimen in 18 patients; in particular 17 patients who started chemotherapy for breast cancer and one patient for lymphoma.

Schilling et al (7) conducted a prospective study with the objective of comparing the sensitivity of PEM versus breast MRI in the depiction of known malignancies (index lesions) and to determine the performance characteristics of the two modalities for additional ipsilateral lesion detection in patients with newly diagnosed, biopsy-proven BC as part of their presurgical planning. A total of 182 patients were enrolled in this study. Both PEM and MRI had an index lesion detection sensitivity of 92.8%. Both were significantly superior to whole-

body PET, which had a sensitivity of 67.9%. There were 67 unsuspected lesions. For these lesions, PEM demonstrated a sensitivity of 85% and a specificity of 74% compared to the MRI sensitivity of 98% and specificity of 48%.

Colorectal cancer

One study evaluated the clinical impact of 18F-FDG-PET in comparison with CT in the detection of colorectal cancer recurrence. Deleau et al (8) retrospectively evaluated the records of 92 patients with colorectal cancer between November 2002 and December 2006. A total of 213 lesions were detected in 78 patients, with 185 lesions detected by FDG-PET/CT and 117 lesions by CT. From those 213 lesions, 176 lesions (47 hepatic and 129 extrahepatic) detected in 71 patients were confirmed by either on histological (n=65) or on radiological follow-up. The global accuracy of F-FDG PET/CT in the detection of tumour lesions was 88%, with a sensitivity, specificity, PPV, and NPV of 95%, 54%, 91%, and 71%, respectively. The global accuracy of CT was of 53% with a sensitivity, specificity, PPV, and NPV of 55%, 43%, 82%, and 17%, respectively.

Esophageal cancer

Through a retrospective cohort study, Gillies et al (9) assessed the benefit of PET over CT and endoscopic ultrasound (EUS) in the staging of esophageal cancer. PET provided additional information in 37 patients (18.5%) and directly altered management in 34 (17%). Of these, 22 were upstaged, and 15 were downstaged.

Another retrospective study performed by Walker et al (10) also evaluated the role of PET versus endoscopic ultrasound in the staging of esophageal cancer. EUS by direct endoscopy and ultrasound imaging identified all 82 primary tumours, whereas PET/CT identified the primary tumour in 74 of 81 cases. Metastatic disease was detected in 17 of 81 patients undergoing PET/CT. The sites of metastasis were liver (3), lung (2) muscle (1), and non-regional lymph nodes (11). EUS did not identify any patients with distant metastasis but did identify one patient with T4 disease with tumour invasion into the pericardium.

Van Heijl et al (11) performed a phase III randomized controlled trial to determine what extent FDG-PET could distinguish between responding and non-responding esophageal tumours early in the course of neoadjuvant chemoradiotherapy. An FDG-PET scan was taken before, and two weeks after, the start of neoadjuvant therapy. Surgical specimens were assessed for objective tumour response and used as the gold standard. The identification of 76 as responders by PET was correct in 58 of these patients. Although the decrease in SUV before and 14 days after the start of chemotherapy was found to associated with histopathologic response, the accuracy and NPV was insufficient to apply FDG-PET for response assessment early in the course of neoadjuvant therapy.

Non-Small Cell Lung Cancer

Deandreis et al (12) evaluated PET versus chest CT in the effectiveness of lung radiofrequency ablation. The addition of PET revealed 15 previously unknown tumour sites in 11 patients. PET also contributed to a change in the clinical management of nine of the 34 patients.

Fischer et al (13) conducted a randomized clinical trial to compare PET with conventional work-up in multimodality mediastinal staging in non-small cell lung cancer. The study determined that preoperative lung cancer staging with PET improves discrimination between N0-1 and N2-3.

Hu et al (14) also evaluated single and dual time-point PET in the mediastinal staging of non-small cell lung cancer. The data indicated that dual time-point FDG PET/CT images

were more effective in differentiating between mediastinal lymph-node metastases and nonmetastases than were single-time-point scans.

Kolodziejczyk et al (15) conducted a prospective study in which treatment plans carried out without PET information were compared with treatment plans done with PET information. In 75 of the 100 patients, the decision to proceed with radical radiotherapy was maintained after PET staging. Among 25 cases not qualified after PET for curative radiotherapy, there were 19 (76%) cases with distant metastases, five (20%) with extensive locoregional disease precluding the use of curative radiotherapy, and one (4%) with no confirmation of malignancy of peripheral, slowly progressing tumours without histology confirmation. Thirty-two patients were upstaged after PET staging.

Thyroid Carcinoma

One primary study evaluated the role of PET in the evaluation of thyroid nodules with non-diagnostic cytology (16). A total of 88 patients with non-diagnostic ultrasound-guided fine-needle cytology (US-FNC) procedure were evaluated. The sensitivity, specificity, accuracy, PPV, and NPV were 100%, 69%, 79%, 62% and 100%, respectively.

Gynecologic Cancer

Two studies compared 18F-FDG-PET/CT with conventional modalities to evaluate gynecologic cancers. Pan et al (17) evaluated the efficacy of PET in the detection of recurrent ovarian cancer compared to conventional tumour markers (CD125, CEA, CA 15-3, CA 19-9, and AFP). The patient-based sensitivity, specificity, accuracy, PPV, and NPV of PET/CT were 100, 85, 94, 92, and 100%, respectively.

Sandvik et al (18) evaluated PET/CT in the staging of cervical cancer. Data collection was carried out retrospectively. Histology from stage I patients revealed a PPV of 25% and an NPV of 88%. Histology from stage 2 patients showed a PPV and NPV of 100%. Five patients (6%), all in stage ≥ IIb, all had a change in treatment owing to the additional information obtained from the PET-CT.

Unknown Primary

Two studies looked at PET/CT in the evaluation of unknown primary tumours. Hu et al (19) retrospectively evaluated the clinical applications of integrated FDG PET/CT information in patients with carcinoma of an unknown primary, including detecting the occult primary tumor and its effect on subsequent disease therapy. The sensitivity of FDG PET/CT for detecting the primary tumor was 86%, the specificity was 87.7%, and the accuracy was 87.2%. Forty-seven patients (31.5%) underwent a change in therapeutic management. In 31 of these patients, therapeutic treatment was specifically tailored as a result of the identification of the primary tumour by PET/CT.

Rudmik et al (20) conducted a prospective study to determine whether the addition of a preoperative PET/CT improves the detection rate of the primary site as compared to conventional approaches. Traditional work-up identified the primary site in five patients (25%), whereas PET/CT-directed biopsy identified the primary site in 11 patients (55%). The sensitivity and specificity of PET/CT were 92% and 63%, respectively. The PPV and NPV of PET/CT were 79% and 83%, respectively.

Pancreatic Cancer

One study (21) evaluated the use of FDG PET/CT versus contrast-enhanced FDG PET/CT in the detection of pancreatic cancer in 45. Of these, 36 had malignant tumours, and nine had benign lesions. The sensitivity of enhanced versus unenhanced PET/CT in the

detection of pancreatic cancer was 96% versus 72%, the specificity 66.6% versus 33.3%, the PPV 92.3% versus 80%, the NPV 80% versus 25%, and the accuracy 90.3% versus 64%.

Prostate Cancer

Miniamimoto et al (22) conducted a prospective study to evaluate the potential of FDG PET/CT for detecting prostate cancer in patients with an elevated PSA level. The region-based sensitivity, specificity, and PPV of FDG-PET/CT in the prostate were 51.9%, 75.7% and 42.9%, respectively. The sensitivity, specificity and PPV of peripheral zone patients were 73.3%, 64.3% and 46.8%, respectively; those in the central gland were 22.7%, 85.9% and 31.3%, respectively. Sensitivities and specificities were higher when Gleason scores were taken into account and more specifically in patients with Gleason scores of seven or greater.

Pediatric Cancers

Three studies evaluated PET in lymphoma and neuroblastoma. London et al (23) conducted a retrospective study that compared FDG PET/CT to conventional imaging (CI) in the detection of pediatric lymphoma to predict response to therapy. Diagnostic statistics calculations were done on lesion-based regional analysis. For the detection of malignant lesions the sensitivity, specificity, and accuracy of PET/CT and CI were 95.9%, 99.7% and 99.6% and 70.1%, 99.0% and 98.3%, respectively. For response to treatment, the specificity of PET/CT and CI was 99.2% and 96.9%, respectively (statistics were not available to calculate sensitivity).

Similarly, Robertson et al (24) evaluated the impact of FDG PET/CT on staging and disease control. The influence of PET on patient staging was profound. Of the 30 patients analyzed, 50% experienced a change in stage with the addition of PET information. Eight patients (27%) were upstaged, two from stage I to II, four from stage II to III because of splenic or para-aortic disease, and two from stage III to IV because of bone involvement. Seven (23%) patients were downstaged due to non-FDG avid pulmonary nodules, pericardial/pleural effusions, or bone abnormalities not confirmed on PET; two patients changed from stage IV to II and five from stage III to II.

Papathanasiou et al (25) evaluated the diagnostic performance and prognostic significance of 18F-FDG PET/CT in comparison with 123I-MIBG imaging in patients with high-risk neuroblastoma. All 28 patients were under the age of 18 except for four aged 45, 19, 21 and 24. Overall, meta-Iodobenzylguanidine (123I-MIBG) was superior to FDG PET/CT in mapping tumour load. 18F-FDG PET/CT missed six cases of skull involvement, five cases of bone–bone marrow disease, and four cases of soft-tissue disease that were positive on 123I-MIBG scans.

Six-month summaries were not completed for head and neck cancers or lymphoma as these recommendation reports were recently updated, and all relevant studies within this six-month time period have been reviewed. The reports can be found at https://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=75520.

Disease Site Group (DSG) Reviews

Colorectal Cancer: Review by Dr. Kelvin Chan and Stephen Welsh, GI DSG

In a recent study by Deleau et al (8) PET had more sensitivity for detecting recurrence than CT. This was a retrospective study evaluating patients who had PET for suspected recurrence (CEA, clinical suspicion). The results of this study do not change our current recommendation for PET in the recurrence of colorectal cancer.

CONCLUSION
The current PET recommendation remains valid and up-to-date in light of these publications

Gynecological Cancer: Review by Dr. Anthony Fyles, Gyne DSG

This study (17) is limited to assessment of patients after surgery and chemotherapy, comparing PET-CT with histological findings at laparotomy or laparoscopy. Interestingly a large proportion of patients were found to have disease limited to para-aortic or pelvic nodes, raising the possibility that they may be salvaged with further surgery. However the study is limited in that no assessment of impact on treatment or outcome was undertaken, and PET-CT was not compared to CT alone.

This study (18) is limited by its retrospective design, small size (particularly for stage greater than IB and lack of comparison with contemporary imaging (CT and MRI). However it suggests that a proportion of patients with more advanced disease may have their management changed following PET-CT

Melanoma: Review by Dr. Tara Baetz, Melanoma DSG

Upon close review of the evidence included in this monitoring report, the current recommendations for the utilization of PET in Melanoma remain valid and no changes are required.

Pancreatic Cancer: Review by Dr. Sindu Kanjeekal, GI DSG

One study was identified for the 6 month monitoring update (21). These results do not change the previous recommendations. This was a prospective study of 45 patients with suspected potentially operable pancreatic cancer. All participants underwent a standardized work-up protocol including FDG PET and high resolution contrast-enhanced CT scan and CT angiogram obtained simultaneously on a hybrid FDG PET/CT scanner, and endoscopic ultrasound for selected cases.
31 received contrast-enhanced PET/CT and 14 had non-contrast enhanced PET/CT because of renal insufficiency or allergy.

The overall sensitivity/PPV of FDG-PET/CT was high (88.9%) but the specificity/NPV was low (55.6%) for an overall accuracy of 82.2%. But in 3 of the 4 false negative cases, contrast-enhanced PET/CT was not used because of renal insufficiency.

When contrast-enhanced PET/CT was looked at separately (31 patients) the results were better with sensitivity=96%, specificity=66.6% and accuracy of 90.3%. Of note, high resolution CT alone was not compared with PET/CT.

These test characteristics are similar to the studies previously reviewed in the CCO guideline and provides further data to support the use of PET/CT for staging if a patient is a candidate for potentially curative surgical resection as determined by conventional staging. Additionally, it does make the case to use high resolution PET/CT rather than low-resolution PET/CT in order to obtain better accuracy.

Reviews Not Completed by DSG Reviewers

- Breast Cancer
- Esophageal Cancer
- All lung cancer

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Appendix 1: Summary of primary studies evidence for PET 6-month monitoring between January and July 2011.

Author, year	Objective	# of pts	PET study type	Reference test	Comparison test	Results	Conclusions of the author
Bone Cancer							
Heusner et al (1)	Diagnostic accuracy of full-dose, contrast-enhanced, fully diagnostic whole-body FDG-PET/CT and whole-body MRI for the detection of bone metastases in a defined patient population with FDG-PET positive tumours (non-small cell lung cancer patients and malignant melanoma) on initial whole-body staging.	109	Prospective	Histopathology	MRI	The sensitivity, specificity, the PPV, NPV, and accuracy of FDG-PET/CT and MRI for the detection of bone metastases were 45%, 99%, 83%, 94%, and 94%, as well as 64%, 94%, 54%, 96%, and 91%, respectively. According to Fisher's Exact test the difference between both modalities concerning the detection of bone metastases was not statistically significant (p = 0.6147). The mean size of bone metastases correctly detected by FDG-PET/CT was 20mm (±5 mm), the mean size of those metastases correctly detected by MRI was 15mm (±7 mm). The mean size of those metastases detected by MRI, but not by FDGPET/ CT was 10mm (±5 mm). In those 4 patients with false-negative MRI the FDG-PET/CT scan was also falsely negative concerning the detection of bone metastases. The 6 false-positive lesions on MRI were rib fractures (n = 2), activated osteochondral lesions (n = 3), and one indeterminate lesion (with equal size during entire follow-up, while metastases on other sites increased in size). The only false-positive lesion on FDG-PET/CT was a solitary rib fracture.	In conclusion whole-body FDG-PET/CT and whole-body MRI seem to be equally suitable for the detection of skeletal metastases in patients suffering from newly diagnosed non-small cell lung cancer and malignant melanoma. Due to a substantial rate of false-negative findings both modalities seem to be of limited value for the detection of bone metastases on initial staging of malignant melanoma and NSCLC patients with low tumour stages. As a consequence close patient follow-up must be recommended.
Brain Cancer							
Hillner et al (2)	Assess the impact of dedicated brain FDG-PET on intended management of patients with primary or metastatic brain tumours.	479	Retrospective	Histopathology	None	The pre-PET patient management plans in the primary brain tumour metastasis subgroup were similar. A pre-PET plan of tissue biopsy was slightly more frequent than on of the treatments (31.3% versus 28.6%) in the primary brain tumour subgroup and was more common than in the overall NOPR cohort (142.%) Changes from treatment to non-treatment were also more frequent than in the overall NOPR cohort (13.4% versus 7.7%).	Among National Oncologic PET Registry patients, dedicated brain PET was associated with similar net changes in intended management as the overall NOPR cohort. However, brain PET patients were younger, more likely to be symptomatic and less likely to have a change in management from non-treatment t treatment as a post-PET plan.
Breast cancer							
Berg et al (3)	To determine the performance of PEM as compared with MRI including the effect on surgical	388	Prospective	Histopathology	MRI	The sensitivity was 91.2% for PEM and 86.3% for MRI. The PPV of biopsy prompted by PEM findings was 66% as compared to MRI at 53%. Of 116 additional cancers, 61 (53%) were	PEM and MR imaging had comparable breast-level sensitivity, although MR imaging had greater lesion-level sensitivity and more accurately depicted the need for mastectomy. PEM had greater

Author, year	Objective	# of pts	PET study type	Reference test	Comparison test	Results	Conclusions of the author
	management in ipsilateral breasts with cancer.					depicted by MR imaging and 47 (41%) were depicted by PEM (p=.043). Fifty-six (14%) of 388 women required mastectomy: 40 (71%) of these women were identified with MR imaging, and 20 (36%) were identified with PEM (p=.001). Eleven (2.8%) women underwent unnecessary mastectomy, which was prompted by only MR findings in five women, by only PEM findings in one, and by PEM and MR findings in five. Thirty-three (8.5%) women required wider excision: 24 (73%) of these women were identified with MR imaging, and 22 (67%) were identified with PEM.	specificity at the breast and lesion levels. Eighty-nine (23%) participants required more extensive surgery: 61 (69%) of these women were identified with MR imaging, and 41 (46%) were identified with PEM (*P* = .003). Fourteen (3.6%) women had tumours seen only at PEM.
Champion et al (4)	Retrospective analysis of asymptomatic breast cancer patients in whom FDG-PET/CT scan was performed because of rising tumour markers, addressing the issue of its impact on patient management.	378	Retrospective	Histopathology	Various (chest x-ray, abdominal and pelvic ultrasound, bone scintigraphy, CT scan)	The standard CI workup available in 67 patients identified sites of recurrence with sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 33% (17 of 52), 100% (15 of 15), 100% (17 of 17), 30% (15 of 50), and 48% (32 of 67), respectively, versus 94.5% (53 of 56), 91% (10 of 11), 97.5% (53 of 54), 77% (10 of 13), and 94% (63 of 67) for PET/CT. Restaging performed by PET/CT imaging had an impact on the management of patients in more than 50% of cases.	In asymptomatic patients with rising tumour markers, FDG-PET/CT imaging is an accurate modality to screen for breast cancer recurrence. It is more sensitive than a conventional imaging workup. Demonstrating the extent of disease, it enables the adjustment of further treatment, providing a general picture in a high-performance procedure. Future directions should prospectively address the potential interference with endocrine treatment and the real impact on patient outcomes.
Constan-tinidou et al (5)	Reviewed PET/CT scans carried out in breast cancer patients, the indication, concordance/discordance with other imaging and whether their use had altered patient management.	122	Retrospective	Histopathology	CT, MRI, BS (Bone Scan)	*Staging Recurrent/Metastatic Disease:* While in the majority of cases (65%) the results of PET/CT were in agreement with those of CT, in five cases (29%), PET/ CT revealed more sites of disease than CT alone. In two cases, the PET/CT showed bone lesions that were not identified on CT. In the third case, PET/CT showed lymphadenopathy in multiple areas, while CT showed lymphadenopathy in one area only, and in the fourth case, while the CT showed axillary thickening only, the PET showed local recurrence and axillary lymphadenopathy. In the fifth case, the PET/CT showed small volume but widely spread FDG avid disease involving the lung, liver, mesentery, bone and lymphadenopathy, whereas the CT showed lung metastases only.	PET/CT may be useful in staging recurrent/ progressive metastatic disease. It is more accurate than BS in detecting metastatic lytic bone disease. It may be used in assessing response to treatment and can result in early termination of treatment in non-responders. By clarification of lesions on other imaging, PET/CT may contribute to management optimisation either by allowing administration of appropriate treatment or by preventing unnecessary treatment. Appropriate use of this modality can help tailor and optimise treatment of individual pt.

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						The MRI results were identical with the PET/CT results in 78% of cases. With regard to the BS, in 70% of cases, the results were in agreement with the PET/CT. In all three cases (30%) of disagreement, PET/CT identified a lytic lesion that was missed on BS (false negative). *Response Assessment:* The commonest sites of metastatic disease identified on PET/ CT included lymphadenopathy (57/87, 65%), bone (50/87, 57%), liver (36/87, 41%) and lung (31/87, 36%) metastases. In some cases, changes in the PET FDG uptake (decrease) suggesting response to treatment preceded the anatomical changes documented on the CT component of the scan. This occurred in 14% of cases with nodal metastases, in 18% of cases with bone metastases, in 18% of cases with lung metastases and in 11% of cases with liver metastases. PET/CT showed a complete response in 2 cases (2%), partial response in 36 cases (41%), stable disease in 23 cases (26%), progressive disease in 18 cases (21%) and mixed response in 8 cases (9%).	
Evangelista et al (6)	To assess the role of tumour markers, CT and 18F-FDG PET/CT in identification of disease relapse in patients with breast cancer already treated and to assess the impact of PET/CT findings on patient management.	101 (100 women and 1 man)	Retrospective	Histopathology	CT and CA 15.3 (Tumour marker)	PET/CT findings showed a high sensitivity (81%), high NPV (87%), but low specificity (52%) and low PPV (41%). Therapeutic management was changed in 11 patients with increased CA 15.3, starting chemotherapy, whereas positive PET/CT modified the therapeutic regimen in 18 patients; in particular 17 patients started chemotherapy for BC and 1 patient for lymphoma. The change in management was significantly important after PET/CT evaluation (change in 56 vs. 34%, respectively, for PET/CT and CA 15.3).	FDG PET/CT appears to be more sensitive than CT and CA 15.3 in the evaluation of disease relapse. The metabolic information provided by hybrid imaging PET/CT might be considered as a complement to other common technique during long-term follow-up, increasing the sensitivity in the evaluation of potential disease sites. Nevertheless, both CA 15.3 and PET/CT are based on metabolic changes due to tumour activity. They provide information on disease progression in a different way than conventional imaging, but PET/CT seems to better predict the presence of disease relapse than tumour marker values in patients with BC.

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Schilling et al (7)	compare the performance characteristics of 18F-fluorodeoxyglucose (FDG) positron emission mammography (PEM) with breast magnetic resonance imaging (MRI) as a presurgical imaging and planning option for index and ipsilateral lesions in patients with newly diagnosed, biopsy-proven breast cancer	208	Prospective	Biopsy pathology	Positron Emission Mammography (PEM), MRI	Both PEM and MRI had a lesion depiction sensitivity of 92.8% and both were significantly better than whole-body FDG-PET (67.9%, p<0.0001).	The present trial demonstrates that PEM has comparable sensitivity to MRI in depiction of index and ipsilateral lesions. The sensitivity of PEM and MRI were both 92.8% for index lesion and for depiction of additional unsuspected ipsilateral lesions, the sensitivity of PEM was 85% and 97% for MRI and were not significantly different from each other. Although whole-body PET had proven to be highly useful in the diagnosis and staging of a variety of malignancies, for breast cancer, its sensitivity ranges between 64 and 96% with an average of 74% across multiple studies.
Esophageal cancer							
Gillies et al (8)	Assessed the benefit of FDG PET/CT over CT and endo-scopic ultrasound (EUS) and determined if tumour histo-logy has any significant impact on PET/CT findings	200	Retrospective cohort	Histology	CT, EUS	PET/CT provided additional information in 37 patients (18.5%) and directly altered management in 34 (17%). Of these, 22 were upstaged and 15 were downstaged (12 of whom received radical treatment).	Staging with PET/CT offers additional benefit over conventional imaging and should form part of the routine stating for esophageal cancer.
Walker et al (10)	Evaluate the role of integrated PET/CT imaging and endoscopic ultrasound (EUS) in the staging of esophageal cancer.	81	Retrospective	Histopathology	EUS	EUS by direct endoscopy & ultrasound imaging identified all 82 primary tumours, whereas PET/CT identified the primary tumour in 74 of 81 cases. EUS identified 49 or 81 pts as having regional or loco-regional lymphadenopathy compared to 29 of 81 for PET/CT (p<0.0001). Metastatic disease was detected in 17 of 81 pts undergoing PET/CT. Sites of metastasis were liver (3), lung (2) muscle (1), & nonregional lymph nodes (11). EUS did not identify any pts with distant metastasis but did identify one pt with T4 disease with tumour invasion into peri-cardium. PET/CT detected metastatic disease and directed care to either chemoradiation or palliative care in 17 of 69 cases. EUS redirected pt care to neoadjuvant therapy prior to surgical resection in 26 of 69 cases.	The results of this study have validated that multimodal screening with locoregional staging provided by EUS and metastatic staging by PET/CT is mandatory in esophageal cancer as both modalities heavily influence treatment decisions.

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Van Heijl et al (11)	The aim of the study was to determine to what extent FDG-PET could distinguish between responding and non-responding esophageal tumours early in the course of neoadjuvant chemoradiotherapy.	100	Multicenter randomized phase III trial	Histopathology	None explicitly stated	76 patients were identified by PET as responders, and this was correct in 58 patients. The corresponding sensitivity specificity, PPV and NPV of PET to identify histopathologic responders using a 0% cut-off value were 91%, 50%, 76% and 75%, respectively.	A decrease in SUV as measured by FDG-PET before 14 days after the start of chemoradiotherapy was found to be significantly associated with histopathologic response in the surgical resection specimen. According to the data, a quarter of the patients would then erroneously discontinue potentially effective chemotherapy. Therefore, in its present for FDG-PET should not be applied for early response assessment in patients with potentially curable esophageal cancer who undergo neoadjuvant chemotherapy.
Pancreatic cancer							
Buchs et al(21)	Investigate the performance of contrast-enhanced PET/CT detection and presurgical assessment of pancreatic cancer	45	Prospective	Pathology	Contrast enhanced versus non-contrast enhanced CT	The sensitivity of enhanced versus unenhanced PET/CT in the detection of pancreatic cancer was 96% vs. 72% (p=0.076), the specificity 66.6% vs. 33.3% (p= 0.52), the positive predictive value 92.3% vs. 80% (p=0.3), the negative predictive value 80% vs. 25% (p= 0.2), and the accuracy 90.3% vs.64% (p= 0.085)	FDG PET/CT is an attractive hybrid imaging procedure applicable for detection and assessment of pancreatic cancer. FDG PET/CT is especially useful for preoperative diagnosis in patients with suspected pancreatic cancer in whom CT alone failed to identify a small tumour or in whom FNA was not diagnostic
Colorectal Cancer							
Deleau et al (8)	To compare the diagnostic performances of FDG-PET/CT and CT in the detection of CRC recurrence with special reference to the site of recurrence, and to evaluate a therapeutic impact of FDG-PET/CT on the clinical management of the patients.	78	Retrospective	Histopathology	CT	Global accuracy of FDG-PET/CT in detecting tumour lesions was 88%, with sensitivity 95%, specificity 54%, PPV 91%, & NPV 71%. Global accuracy of CT was 53% with sensitivity 55%, specificity 43%, PPV 82%, & NPV 17%. FDG-PET/CT results modified clinical management in 31/78 patients (40% of patients). In 28 patients, FDGPET/CT allowed detection of unknown metastases & led to modification of treatment strategy by replacing simple surveillance by active treatment (n=13) or by abandoning inappropriate surgery (n=15). In three patients, FDG-PET/CT allowed to exclude suspicion of recurrence & led to abandoning surgery (n=1) or stopping chemotherapy (n=2).	The study confirms higher diagnostic performances of FDG-PET/CT in comparison with CT in the detection of CRC recurrence, particularly, in the case of locoregional recurrence and lymph nodes metastases. It also shows that FDG-PET/CT may change clinical management in one-third of patients and should be thus recommended in routine use in patients with suspicion of CRC recurrence.

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Non small cell lung cancer							
Deandreis et al (12)	To compare FDG PET/CT and chest CT in the evaluation of the effectiveness of lung radiofrequency (RF) ablation	34	Prospective	Pathology	Chest CT	Pre ablation PET/CT depicted 15 previously unknown tumoral sites in 11 patients located in the lung (5), mediastinal lymph nodes (3), liver (4) abdominal lymph nodes (1) and adrenal gland (1). These findings lead to treatment changes in nine of the 34 patients (26%). Cancellation in four patients, additional treatment of lung lesions in four patients and a combination with thyroid surgery in one patient.	Results suggest that PET/CT can be a useful tool for early diagnosis of incomplete treatment after RF ablation of lung lesions. Its superiority to chest CT must be confirmed in larger scale studies.
Fischer et al (13)	The objective of the study was to compare PET/CT with conventional work-up in multimodality mediastinal staging in non-small cell lung cancer	189	Prospective randomized trail	Histopathology	Conventional work-up	By intention-to-treat analysis the accuracy of the staging strategy with PET-CT appears only slightly superior to the CWU staging strategy (90% (95% CI 82% to 95%) vs. 85% (95% CI 77% to 91%), p¼0.322), mainly based on an improved sensitivity (75% (95% CI 59% to 86%) vs. 59% (95% CI 41% to 74%), p=0.162). Excluding the 14 patients in the PETCT group on whom a PET-CT scan was not performed, the diagnostic accuracy of the consensus N stage was significantly higher in the PET-CT group compared with the CWU group (difference of 10% (95% CI 0.2% to 20%), p=0.034) again primarily based on the improved sensitivity as both groups had equally high specificity, based on the results of the invasive staging methods.	In accordance with current recommendations the authors strongly recommend preoperative staging by PET/CT of patients with lung cancer. In patients without enlarged lymph nodes and PET-negative mediastinum the data suggest that the patient may proceed directly to surgery; however, enlarged lymph nodes on CT needs confirmation independently of PE T findings and positive finding on PET/CT needs confirmation before a decision is made.
Hu et al (14)	assess the diagnostic capacity of dual-time-point FDG PET/CT for mediastinal nodal staging in NSCLC patients with coexisting inflammatory lung diseases.	102	Retrospective	Pathology	Single versus dual time-point scans	On a per-patient basis, overall sensitivity, specificity, accuracy, and positive and negative predictive values of single-time point PET/CT were 83.3% (15/18 patients with positive nodes), 67.7% (21/31 with negative nodes), 73.5% (36/49), 60% (15/25), and 87.5% (21/24), respectively. Those values of dual-time-point scan were 83.3% (15/18 patients with positive nodes), 71% (22/31 with negative nodes), 75.5% (37/49), 62.5% (15/24), and 88% (22/25), respectively. On per-nodal station basis, sensitivity, specificity, accuracy, and positive and negative predictive values of single-time-point PET/CT were 81.3% (39/48), 89% (154/173), 87.3% (193/ 221), 67.2% (39/58), and 94.5% (154/163), respectively. Those	Provide further evidence that dual-time-point FDG PET/CT images are more effective to differentiate mediastinal LN metastases from nonmetastases than single-time-point scan. It was useful to limit the false positive results in all patients, but it was sufficiently benefits in the patients with pulmonary comorbidity. However, there was no significant improvement when false-negatives were found in single-time- point scan. Dual-time point scan improved specificity, accuracy, and PPV and it is more effective for mediastinal nodal staging than single-time-point in pts with pulmonary comorbidity.

Author, year	Objective	# of pts	PET study type	Reference test	Comparison test	Results	Conclusions of the author
						values on dual-time-point FDG PET/CT were 87.5% (42/48), 94.2% (163/173), 92.8% (205/221), 80.8% (42/52), and 96.4% (163/169), respectively.	
Kolodziejczyk et al (15)	Prospective study in which treatment plans carried out without PET information were compared with treatment plans done with PET information. The objective of the study was to evaluate the utility of PET if elective nodal irradiation (ERI) is being used.	100	Prospective	Pathologically confirmed NSCLC	Conventional work-up	In 75 of 100 patients, the decision to proceed with radical radiotherapy was maintained after PET staging. Among 25 cases not qualified after PET for curative radiotherapy, there were 19 (76%) cases with distant metastases; 5 (20%) cases with extensive locoregional disease, precluding use of curative radiotherapy; and 1 (4%) case with no confirmation of malignancy of peripheral, slowly progressing tumour without histology confirmation. Thirty-two patients were upstaged after PET staging. In 40 of 75 patients, the radiotherapy schedule was changed after PET. In a majority (30 of 40) of patients, the alterations consisted of omitting ENI.	Confirmed the value of PET/CT staging for radical radiotherapy candidates in terms of avoidance of unnecessary treatment and radiation volumes modifications leading to the choice of appropriate techniques.
Ovarian/Cervical cancer							
Pan et al (17)	To evaluate the accuracy of integrated FDGPET/ CT and tumour markers for the depiction of recurrent ovarian carcinoma	37	Prospective	Histopathology	Tumour Markers	A total of 37 patients underwent FDG-PET/CT scans. Among them, 22 patients underwent exploratory laparotomy and 15 had diagnostic laparoscopy. Overall, 24 patients were documented to have ovarian cancer recurrence after second operation. FDG-PET/CT had sensitivity, specificity, accuracy, and positive and negative predictive values of 100, 85, 94, 92, and 100%, respectively.	study has shown that PET/CT is a sensitive tool to assist in the early identification and recurrent ovarian cancer, amenable to secondary cytoreduction.
Sandvik et al (18)	Investigate the PPV and NPV of PET/CT in stage 1 disease and the clinical impact of scan results in all disease stages.	83	Retrospective	Histopathology	Conventional staging	Results of 36 patients who had undergone pelvic lymphadectomy. This yielded at PPV of 25% and a NPV of 88%. Five patients (6%) had their treatment changed as a result of PET/CT scans. One patient had their radiation field extended to include the para-aortic lymph nodes. In four cases the treatment strategy was changed from intended curative chemoradiation to palliative care.	Study supports the usefulness of PET/CT for the detection of lymph-node metastasis and distant metastasis in patients with cervical cancer, although the study had a relatively low PPV in patients with early stage disease. Histological verification of PET-positive findings is necessary, particularly in stage ≤ Ib. No positive scans were detected in patients with stage Ia1 and due to the low sensitivity, the researchers have ceased to offer PETCT scans to those patients.

Author, year	Objective	# of pts	PET study type	Reference test	Comparison test	Results	Conclusions of the author
Thyroid cancer							
Giovanella et al (16)	To assess the role of PET/CT scans with 18FDG in the evaluation of thyroid nodules with nondiagnostic cytology.	88	Prospective	Histology	Ultrasound-guided fine-needle cytology	Twenty-nine patients with thyroid malignancies had a positive 18FDG-PET/CT scan as indicated by focal 18FDG uptake within the nodule, while none had a diffuse or diffuse plus focal uptake pattern. The sensitivity, specificity, accuracy, positive predictive value and negative predictive value (NPV) were 100%, 69%, 79%, 62% and 100%, respectively	negative 18FDG PET/CT scan rules out malignancies among thyroid nodules with nondiagnostic cytology avoiding invasive procedures (i.e. surgery). Histology is still necessary to distinguish benign from malignant diseases in 18FDG-positive nodules, but unnecessary surgery could have been reduced from 88 to 41 (46%) cases.
Carcinoma of an unknown primary (CUP)							
Hu et al (19)	Evaluate the clinical applications of integrated FDG PET/CT information in patients with carcinoma of unknown primary, including detecting the occult primary tumor and effecting on disease therapy.	149	Retrospective	Clinical follow-up	conventional diagnostic imaging procedure (CT, MRI, Mammography and endoscopic procedures)	The sensitivity of FDG PET/CT for detecting the primary tumor was 86.0% (37 of 43), the specificity was 87.7% (93 of 106), and the accuracy was 87.2% (130 of 149). Forty-seven patients (31.5%, 47 of 149) underwent a change in therapeutic management. Thirty-one of these patients were treated with specifically-tailored chemotherapy as a result of their primary tumor diagnosis. In 16 of these patients, treatment was changed secondary to detection of previously unrecognized distant metastases.	FDG PET/CT is an efficient method for detecting the occult primary tumor in patients with CUP, as well as detecting previously unrecognized metastases. Upon FDG PET/CT imaging, cancer treatment was changed in parts of patients. Although the role of FDG PET/CT in the initial work-up of patients with CUP remains unknown, it may be particularly valuable in the diagnosis and management of CUP, which is known to be a multisystem disease with potential metastatic spread to the entire body
Rudmik et al (20)	Determine whether addition of preoperative PET/CT improves detection rate of primary site compared with traditional approach of expert clinical examination with endoscopy, preoperative CT/MRI, and panendoscopy with biopsies of high risk regions.	20	Prospective	Pathology	chest radiograph and contrast-enhanced, high-resolution CT scan of head and neck region	Traditional work-up identified the primary site in 5 patients (25%), whereas PET/CT directed biopsy identified the primary site in 11 patients (55%).The sensitivity and specificity of PET/CT were 92% and 63%, respectively. The positive predictive value (PPV) and negative predictive value (NPV) of PET/CT were 79% and 83%, respectively.	Researchers conclude that patients with cervical metastases and an unknown primary site after undergoing expert clinical and CT examination benefit from PET/CT prior to panendoscopy.
Prostate Cancer							
Minamimoto et al (22)	Evaluate the potential and limitation of FDG-PET for detecting prostate cancer in patients with an elevated PSA level in terms of several clinical and pathological factors.	50	Prospective	Pathology		The sensitivity, specificity, and positive predictive value (PPV) of FDG-PET/CT based on patients with Peripheral Zone cancer were 72.7% (16/22), 21.4% (6/28), and 42.1% (16/38), respectively, and with Central Gland cancer were 25.0% (4/16), 79.4% (27/34), and 36.4% (4/11), respectively.	

Author, year	Objective	# of pts	PET study type	Reference test	Comparison test	Results	Conclusions of the author
Pediatric Cancer							
Papathanasiou et al (25)	The purpose of the study was to evaluate the diagnostic performance of FDG PET/CT in comparison with ^{123}I-MIBG imaging in patients with high-risk neuroblastoma.	28	Prospective	Qualitative comparison only (obtaining tissue histology from all sites was not feasible or ethical and there is no imaging gold standard in the evaluation of neuroblastoma patients)	123I-metaiodobenzylguanidine (123 I-MIBG)	18F-FDG PET/CT results were positive in 24 of 28 (86%) patients, whereas 123I-MIBG imaging results were positive in all patients. 18F-FDG was superior in mapping tumor load in 4 of 28 (14%) patients, whereas 123I-MIBG was better in 12 of 28 (43%) patients. In the remaining 12 (43%) patients, no major differences were noted between the 2 modalities. 18F-FDG PET/CT missed 5 cases of bone–bone marrow disease, 4 cases of soft-tissue disease, and 6 cases of skull involvement that were positive on 123I-MIBG scans. Cox regression and Kaplan–Meier survival curves showed that the group of patients (4/28) in whom 18F-FDG was superior to 123I-MIBG had a significantly lower survival rate than the others. Tumoral avidity for 18F-FDG (maximum standardized uptake value) and extent of 18F-FDG–avid bone–bone marrow disease were identified as adverse prognostic factors.	18F-FDG PET/CT cannot replace 123I-MIBG in high-risk neuro-blastoma, mainly because of its limitation in identifying bone–bone marrow infiltration. 18F-FDG PET/CT could be useful in evaluation of small proportion (less than 10%) of neuroblastoma patients who do not accumulate 123I-MIBG or in cases in which it is suspected that extent of disease exceeds that depicted with 123I-MIBG. Tumoral 18F-FDG avidity was associated with earlier adverse outcome within this cohort of patients with poor prognosis undergoing 131I-MIBG therapy. Practical incorporation of 18F-FDG PET/CT in treatment decision making would, however, require development of novel effective treatments. In such a setting, 18FFDG PET/CT could aid in identifying patients requiring more aggressive treatment strategy.
London et al (23)	In children with Hodgkin's disease and non- Hodgkin's lymphoma, the ability of 18F-fluoro-2-deoxy- D-glucose PET/CT and conventional imaging (CI) to detect malignant lesions and predict poor lesion response to therapy was assessed and compared.	209	Retrospective	Histopathologic findings or follow-up	Conventional Imaging (CT scan, Ultrasound, MRI scan or bone scintigraphy)	A total of 5,014 regions (3,342 lymph node, 1,672 extra-nodal) were analysed. PET/CT performed significantly better than CI in the detection of malignant lesions with sensitivity and specificity of 95.9 and 99.7% compared to 70.1 and 99.0%, respectively. For predicting poor lesion response to therapy, PET/CT had fewer false-positive lesions than CI. The specificity for predicting poor lesion response to treatment for PET/ CT was 99.2% compared to 96.9% for CI. PET/CT was the correct modality in 86% of lesions with discordant findings.	PET/CT is more accurate than CI in detecting malignant lesions in childhood lymphoma and in predicting poor lesion response to treatment. In lesions with discordant findings, PET/CT results are more likely to be correct.

Author, year	Objective	# of pts	PET study type	Reference test	Comparison test	Results	Conclusions of the author
Robertson et al (24)	Analyse how PET /CT imaging influences the initial staging and disease management of our patients with pediatric HL. Specifically, the correlation of PET and CT findings in detection and exclusion of disease in both nodal and extranodal sites was evaluated. We then analyzed the impact of PET findings on radiotherapy field design and subsequent disease control	30	Prospective	Disease outcome was based on clinical, laboratory, histologic, and radiographic evaluation s, which continued regularly at each patient's home institution	CT	The influence of PET on patient staging was profound. Of the 30 patients analyzed, 50% experienced a change in stage with the addition of PET information, with 8 patients (27%) upstaged and 7 (23%) downstaged. All 7 downstaged patients were due to non-FDG avid pulmonary nodules, pericardial/pleural effusions, or bone abnormalities not confirmed on PET. Two patients' staging changed from IV to II and five from Stage III to II. For the patients who were upstaged, two went from Stage I to II, four from Stage II to III because of splenic or para-aortic disease, and two from Stage III to IV because of bone involvement.	PET-CT represents an important tool in the management of pediatric patients with HL and has a substantial influence on both initial staging and radiation treatment target definition and field design

Abbreviations: 18FDG: 2-[fluorine-18]-fluoro-2-deoxy-glucose; PET/CT: positron-emission tomography/computed tomography; PPV: positive predictive value; NPV: negative predictive value; CT: computed tomography; MRI: magnetic resonance imaging; 123 I-MIBG: 123I-metaiodobenzylguanidine; NSCLC: non-small cell lung cancer; PEM: positron emission mammography; CI: conventional imaging; BS: bone scan; CA 15.3: Carcinoma Antigen 15-3; EUS: endoscopic ultrasound; pt(s): patient(s); RF: radiofrequency; LN: lymph node; ERI: elective nodal eradiation; CEA: carcinoembryotic antigen.