PET Six-Month Monitoring Report 2016-2

Evidence from Primary Studies and Systematic Reviews and Recommendations from Clinical Practice Guidelines July to December 2016

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: April 26, 2017

QUESTION

What is the role of positron emission tomography (PET) in the clinical management of patients with cancer, sarcoidosis, or epilepsy with respect to:

- Diagnosis and staging
- Assessment of treatment response
- Detection and restaging of recurrence
- Evaluation of metastasis

Outcomes of interest are survival, quality of life, prognostic indicators, time until recurrence, safety outcomes (e.g., avoidance of unnecessary surgery), and change in clinical management.

INTRODUCTION

In 2010, the Ontario PET Steering Committee (the Committee) requested that the Program in Evidence-Based Care (PEBC) provide regular updates to the Committee of recently published literature reporting on the use of PET in patients with cancer, sarcoidosis, or epilepsy. The PEBC recommended a regular monitoring program be implemented, with a systematic review of recent evidence conducted every six months. The Committee approved this proposal, and this is the 12th 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 published between July and December 2016 were systematically searched through MEDLINE and EMBASE for evidence from primary studies and systematic reviews. The search strategies used are available upon 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 to include them was made by the Committee based on the formation of a Pediatric PET Subcommittee that will explore and report on indications relating to PET in pediatric cancer.

Inclusion Criteria for Primary Studies

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

1. Studied the use of 18-fluorodeoxyglucose (FDG) PET in cancer, sarcoidosis, or epilepsy in humans.
2. Evaluated the use of the following radiopharmaceutical tracers:
    - ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTATOC, ^{68}Ga DOTATATE
    - ^{18}F-choline, ^{11}C-choline (prostate cancer)
    - ^{18}F-FET ([^{18}F]fluoroethyl-L-tyrosine) (brain)
    - ^{18}F-FLT ([^{18}F]3-deoxy-^{3}F-fluorothymidine) (various)
    - ^{18}F-MISO ([^{18}F]fluoromisonidazole) (hypoxia tracer)
    - ^{18}F-FAZA ([^{18}F]fluoroazomycin arabinoside) (hypoxia tracer)
    - ^{18}F-fluoride (more accurate than bone scanning)
    - ^{18}F-flurpiridaz (cardiac)
    - ^{18}F-florbetapir (Amyvid) (dementia imaging)
    - ^{18}F-FDOPA
    - ^{68}Ga-PSMA (prostate-specific membrane antigen)
    - ^{18}F-FACBC (fluciclovine)
3. Published as a full article in a peer-reviewed journal.
4. Reported evidence related to change in patient clinical management or clinical outcomes, or reported diagnostic accuracy of PET compared with an alternative diagnostic modality.
5. Used a suitable reference standard (pathological and clinical follow-up) when appropriate.
6. Included ≥12 patients for a prospective study/randomized controlled trial or ≥50 patients (≥25 patients for sarcoma) for a retrospective study with the disease of interest.

Inclusion Criteria for Systematic Reviews

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

Exclusion Criteria

7. Letters and editorials.

RESULTS

Literature Search Results

Primary Studies and Systematic Reviews

Eighty-two studies published between July and December 2016 met the inclusion criteria. A summary of the evidence from the 82 studies can be found in **Appendix 1: Summary of studies from July to December 2016**.

Breast Cancer

Four studies met the inclusion criteria [1-4]. In one meta-analysis [1], FDG PET/CT (pooled estimate, 88%) appeared to be more specific than magnetic resonance imaging (MRI) (pooled estimate, 63%) for detecting residual disease in patients who completed neoadjuvant chemotherapy. There was no significant difference in pooled sensitivity between the two modalities. Likewise, results from another meta-analysis [2] showed high sensitivity (pooled estimate, 90%) but moderate specificity (pooled estimate, 81%) for FDG PET or PET/CT in detecting suspected recurrence. In newly diagnosed stage I-IIIC breast cancers that are negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor, FDG PET/CT upstaged 12.9% and detected unsuspected synchronous malignancies in 2.6% of patients [3]. Garg et al. [4] also reported similar results with upstaging of newly diagnosed locally advanced breast cancer in 48.1% with FDG PET/CT and treatment changes in 17.7% of patients.

Esophageal Cancer

Five studies met the inclusion criteria [5-9]. The authors of a meta-analysis concluded that FDG PET or PET/CT should not be used routinely to guide treatment strategy in esophageal cancer patients due to suboptimal sensitivity (pooled estimate, 67%) and specificity (pooled estimate, 69%) in predicting treatment response after neoadjuvant chemoradiotherapy [5]. Yuan et al. [6] also reported modest sensitivity (71.0%) and specificity (66.7%) for FDG PET/CT, while Huang et al. [7] reported high specificity (96.7%) for FDG PET/CT. In the restaging of patients after neoadjuvant therapy, FDG PET/CT was found to be more sensitive than CT (39.5% versus 27.3%, $p=0.005$) in detecting incurable disease but its use is limited [8]. For preoperative lymph node staging of patients with adenocarcinoma of the esophagogastric junction or gastric cancer, FDG PET/CT had a higher specificity (91.3% versus 60.8%, $p<0.01$) and positive predictive value (89.8% versus 68.5%, $p<0.01$) but lower sensitivity (50.0% versus 73.3%, $p<0.01$) than endoscopic ultrasound. FDG PET/CT (accuracy, 88.5%) and multidetector spiral CT (accuracy, 83.3%) performed similarly when detecting extra-regional lymph nodes and systemic metastases [9].

Gastrointestinal Cancer

Eleven studies met the inclusion criteria [10-20]. Six of the studies evaluated the use of FDG PET/CT in patients with colorectal cancer. Centralized image interpretation of FDG PET/CT further improved the detection rate of metastatic disease in comparison to contrast-enhanced CT [10], and another study demonstrated a change in management plan in 25.9% of patients [11]. However, one prospective study found that FDG PET/CT (61%) was less sensitive than MRI (90%, $p<0.001$) or CT (68%, $p=0.031$) in detecting liver metastases [12]. In the setting of recurrent disease, FDG PET/CT was superior or comparable to CT or MRI in detecting liver, lung, peritoneum, lymph node, and bone recurrences [13]. FDG PET/CT was particularly valuable in detecting occult recurrence in asymptomatic patients with normal conventional imaging but an elevated carcinoembryonic antigen (CEA) level [14]. Overall, FDG PET/CT modified the treatment strategy in 15.0% to 22.5% of patients [13,15]. In the evaluation of patients with intrahepatic cholangiocarcinoma, FDG PET/CT impacted management in 15.4%

of cases due largely to disease upstaging [16]. On the other hand, FDG PET/CT has a limited role in assessing local resectability of hilar cholangiocarcinoma [17]. In anal cancer, post-treatment FDG PET/CT performed >13 weeks after treatment completion (negative predictive value [NPV], 92.9%) more accurately predicted disease progression than FDG PET/CT scans performed within 12 weeks of treatment completion (NPV, 71.4%) [18]. Furthermore, management was altered following 56.0% of FDG PET/CT scans in staging and post-treatment assessment of anal cancer [19]. In patients with gastric cancer, FDG PET/CT detected synchronous advanced colorectal neoplasia with high accuracy (94.5%) [20].

Genitourinary Cancer

Three studies met the inclusion criteria [21-23]. In patients with bladder cancer, results from a retrospective review and a meta-analysis both showed high specificity (greater than 95%) but poor sensitivity (approximately 56%) for FDG PET/CT in detecting lymph node metastasis [21]. FDG PET/CT was more useful in detecting metastatic or recurrent lesions in patients with renal cell carcinoma (pooled sensitivity, 88%; pooled specificity, 88%) [22]. One prospective study investigated the ability of FDG PET/CT to restage patients with urinary bladder transitional cell carcinoma. Initial staging with CT was altered by FDG PET/CT and subsequent management was changed in 14.8% of patients [23].

Gynecologic Cancer

Six studies met the inclusion criteria [24-29]. Three studies investigated the value of FDG PET or PET/CT in the preoperative diagnosis of cervical cancer. Results of the ACRIN6671/GOG0233 trial showed that the addition of FDG PET to CT offered borderline increase in sensitivity for the detection of abdominal lymph node metastasis [24]. A meta-analysis also reported slightly better diagnostic performance for FDG PET or PET/CT over CT or MRI in detecting metastatic lymph nodes [25]. Finally, FDG PET/CT was found to be more accurate than clinical examination in staging primary tumours (84.3% versus 45.1%, $p<0.01$) and lymph nodes (76.5% versus 19.6%, $p<0.0001$) [26]. In the diagnosis of patients with suspected ovarian tumour recurrence and normal tumour markers, FDG PET/CT with contrast enhancement was more accurate than contrast-enhanced CT on both patient-based (93% versus 65%, $p=0.0001$) and site-based (99% versus 92%, $p<0.0001$) analyses [27]. However, FDG PET/CT was inadequate in the preoperative evaluation of peritoneal disease [28]. In the preoperative staging of endometrial cancer, FDG PET/CT showed high specificity (pooled estimate, 96%) but limited sensitivity (pooled estimate, 67%) in detecting lymph node metastasis [29].

Head and Neck Cancer

Sixteen studies met the inclusion criteria [30-45]. Five of the studies assessed the role of FDG PET/CT in differentiated thyroid cancer management. In patients with elevated serum thyroglobulin level and negative ^{131}I whole-body scan after treatment, FDG PET/CT exhibited high sensitivity (87.0% to 95.9%) and specificity (87.3% to 98.5%) in detecting recurrent or metastatic disease [30-32], with one study showing a significantly better diagnostic performance for FDG PET/CT over CT alone [32]. These results seem to be higher than those reported in a meta-analysis (pooled sensitivity, 80.2%; pooled specificity, 75.5%); however, the meta-analysis included studies up to only 2014 [33]. In another study, FDG PET/CT identified recurrence or metastasis in 50.0% of scans without prior clinical suspicion and ruled out recurrence or metastasis in 36.8% of scans with prior clinical suspicion [34]. Treatment plan was altered in 47.8% of patients [32]. For differentiating benign from malignant follicular/Hurthle cell neoplasms, FDG PET/CT demonstrated good sensitivity (89.0%) but poor specificity (35.0%) [35]. Additionally, FDG PET/CT could reliably rule out cancer in patients

with cytologically defined indeterminate thyroid nodules (NPV, 90.0%) [36] and in patients with solitary neck cyst (NPV, 96.0%) [37]. In nasopharyngeal carcinoma, FDG PET or PET/CT was comparable to single-photon emission computed tomography (SPECT) but superior to MRI in the diagnosis of residual or recurrent disease [38]. FDG PET/CT also showed good accuracy in M staging, whereas MRI and CT were more accurate in T and N staging, respectively [39]. FDG PET or PET/CT was evaluated in head and neck squamous cell carcinoma in the other six studies. FDG PET/CT staging (87.1%) was significantly more accurate than conventional staging (82.0%, $p<0.001$), with 2.0% of the patients being upstaged and 8.5% of patients being downstaged. FDG PET/CT provided important staging information that led to management changes in 15.7% of patients [40]. FDG PET/CT diagnosed lung metastases or second primary lung cancers with great sensitivity (pooled estimate, 85.0%) and specificity (pooled estimate, 98.0%) [41]; however, FDG PET/CT was less specific (74.4% versus 92.1%, $p<0.001$) and less accurate (75.3% versus 88.6%, $p<0.001$) than contrast-enhanced CT in detecting extranodal extension [42]. After definitive chemoradiotherapy, ultrasound appeared to be highly sensitive (89.7%) while FDG PET or PET/CT appeared to be highly specific (97.9%) for evaluating lymph node metastasis in response to treatment [43]. For the assessment of residual or recurrent disease, FDG PET or PET/CT displayed good overall sensitivity and specificity, with the former being significantly higher than that of contrast-enhanced CT or MRI [44,45].

Hematologic Cancer

Five studies met the inclusion criteria [46-50]. In early-stage Hodgkin lymphoma (HL), patients with a negative interim (after 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine [ABVD]) or end-of-treatment (after 3 to 4 cycles of ABVD) FDG PET/CT scan had significantly better survival rates than those with positive scans [46]. In advanced-stage HL, patients with a positive interim FDG PET/CT scan after two cycles of ABVD appeared to benefit from early salvage treatment with ifosfamide, gemcitabine, and vinorelbine, followed by autologous bone marrow transplantation, as these patients achieved similar two-year progression-free survival as the patients with a negative interim FDG PET/CT scan (76% versus 81%, respectively) [47]. In diffuse large B-cell lymphoma (DLBCL), FDG PET/CT changed the Ann Arbor staging in 28.7% of patients. Furthermore, patients with a negative interim FDG PET/CT scan after two cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP-21) have good prognosis, particularly those of germinal centre origin [48]. For detecting bone marrow involvement in DLBCL patients, FDG PET/CT was highly accurate (96%) and could eliminate unnecessary bone marrow biopsy [49]. In the post-treatment follow-up of patients with non-Hodgkin lymphoma (NHL), management was changed after 37.8% of FDG PET/CT scans performed with prior clinical suspicion of recurrence, but in only 8.3% of FDG PET/CT scans done without clinical suspicion [50].

Melanoma

Two studies met the inclusion criteria [51,52]. Both retrospective studies evaluated the impact of FDG PET/CT on the clinical management of patients with melanoma. FDG PET/CT displayed high diagnostic accuracy in stage I and III disease (91.3%), in resected stage III disease (92.5%), and in unresectable stage III and resected or unresectable stage IV disease (96.2%) [51]. Treatment was changed in 28.4% of patients upon restaging [51] and 16.7% of patients after fourth and subsequent follow-up scans [52].

Non-FDG Tracers

Twenty studies met the inclusion criteria [53-72]. ^{18}F-Choline PET/CT proved to be useful in detecting biochemical recurrence in patients with prostate-specific antigen (PSA)

levels <1 ng/ml following radical prostatectomy (accuracy, 78.7%) [53]. ^{18}F-Choline PET/CT performed after negative or equivocal conventional imaging also impacted treatment plan in 43.6% of patients [54]. On the other hand, ^{11}C-Choline PET/CT performed poorly in the setting of patients with biochemical relapse (accuracy, 32%) [55]. One retrospective study found that PET/CT with ^{68}Ga-DOTA-NOC is a highly sensitive and specific tracer for the diagnosis (90.0% and 96.2%, respectively), staging (84.4% and 100%, respectively), and follow-up (90.5% and 100%, respectively) of patients with neuroendocrine tumours [56]. Two prospective studies evaluated ^{18}F-FLT PET/CT, one in gastric cancer [57] and the other in pancreatic cancer [58]. In both cases, ^{18}F-FLT PET/CT was comparable to FDG PET/CT in the detection of nodal and distant metastases. For the diagnosis of brain tumour and glioma, ^{18}F-FET PET/CT performed much better than FDG PET or PET/CT [59]. PET/CT imaging with ^{18}F-FACBC was investigated in five studies, all in the diagnosis of recurrent prostate cancer. Results varied widely among the studies with sensitivity ranging from 37.0% to 90.7% and specificity ranging from 32.6% to 100% [55,60-62]. Despite the variation, one study did find that the diagnostic performance of ^{18}F-FACBC PET/CT was superior to that of CT [61], while a randomized controlled trial demonstrated the influence of ^{18}F-FACBC PET/CT in the radiotherapy management decisions of 40.5% of patients [63]. ^{68}Ga-PSMA PET/CT was also evaluated in prostate cancer. In the preoperative lymph node staging of patients with intermediate- to high-risk prostate cancer, ^{68}Ga-PSMA PET/CT performed significantly better than MRI or CT in both patient-based (area under the curve [AUC], 0.835 versus 0.691; p=0.002) and template-based (AUC, 0.877 versus 0.704; p<0.001) receiver operating characteristic curve analyses [64]. For primary tumour staging, a significant proportion of cancers were missed or underestimated by ^{68}Ga-PSMA PET/CT [65]. In terms of impact on decision-making, one retrospective study reported radiotherapy or hormone therapy changes in 53.7% of patients due to ^{68}Ga-PSMA PET/CT findings [66]. In the restaging of patients with increasing PSA levels (<5 ng/ml) and/or suspicion of recurrence after conventional imaging, ^{68}Ga-PSMA PET/CT displayed moderate sensitivity (76.5%) but high specificity (91.7%) [67]. Furthermore, ^{68}Ga-PSMA PET/CT changed the treatment strategy of 75.6% of patients [68]. In four studies, the ability to detect bone metastases in a number of malignancies was compared between ^{18}F-Fluoride or ^{18}F-NaF PET/CT and conventional imaging. ^{18}F-Fluoride PET/CT performed similarly to MRI in evaluating skull base invasion in nasopharyngeal carcinoma [69] but detected significantly more bone metastases than whole-body SPECT in breast cancer (lesion-based sensitivity, 95% versus 63%; p<0.001) [70]. As for ^{18}F-NaF PET/CT, it outperformed bone scintigraphy, SPECT, and SPECT/CT in detecting bone metastases in breast and prostate cancer [71], with another study also reporting the superiority of ^{18}F-NaF PET/CT over SPECT in lung cancer [72].

Non-Small Cell Lung Cancer

Three studies met the inclusion criteria [73-75]. Diffusion-weighted imaging showed a higher sensitivity than FDG PET/CT in diagnosing non-small cell lung cancer (NSCLC) (86% versus 71%; p=0.013). No significant difference in specificity was observed between the two modalities [73]. In terms of preoperative staging, FDG PET/CT could detect hilar and mediastinal lymph node metastases with good accuracy (82.5%), despite exhibiting poor sensitivity (47.4%) [74]. In stage III NSCLC patients treated with definitive radiotherapy and absence of early recurrence, post-treatment surveillance with FDG PET/CT did not offer significant survival benefits over CT-based surveillance [75].

Pancreatic Cancer

Two studies met the inclusion criteria [76,77]. A prospective study demonstrated that FDG PET/CT combined with CA19-9 levels was effective in differentiating pancreatic carcinoma from chronic mass-forming pancreatitis in elderly Chinese patients [76]. In

preoperative staging, FDG PET/CT using a maximum standardized uptake value (SUV_{max}) value of 2.5 (77.7%) achieved comparable sensitivity to multi-detector CT (75.5%); however, when tumour uptake rate with a cut-off point of 1.33 was used, the sensitivity for FDG PET/CT improved to 94.9% [77].

Sarcoma

Two studies met the inclusion criteria [78,79]. FDG PET/CT was shown to be highly accurate (95.4%), and comparable to MRI (96.7%), in evaluating locoregional recurrence after definitive surgery of soft tissue sarcoma [78]. Moreover, a meta-analysis reported good accuracy (pooled estimate, 89%) for FDG PET/CT in diagnosing musculoskeletal soft tissue tumours [79].

Unknown Primary Cancer

Two studies met the inclusion criteria [80,81]. FDG PET/CT was fairly accurate (78.0%) in locating the primary tumour site and upstaged 27% and downstaged 11% of patients [80]. In cases where the primary tumour site could not be confirmed using standard methods, FDG PET/CT guided treatment strategy modifications to some extent in 29.0% of patients [81].

CLINICAL EXPERT REVIEW

Breast Cancer

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

Reviewer's Comments (Dr. Muriel Brackstone)

In this time period, four publications were identified. One evaluated the role of PET in identifying residual disease after neoadjuvant chemotherapy, compared with the gold standard MRI. The PET in this meta-analysis study was found to be highly specific but showed no difference in sensitivity. This in isolation would not be sufficient to change practice to advocate for PET to identify residual disease after neoadjuvant chemotherapy. The second study evaluated the utility of PET in a meta-analysis in detecting recurrence. There was no gold standard comparator for imaging. The sensitivity was 90% but the specificity was 81%, which is lower and by itself not sufficient to warrant a change in practice in terms of adding PET as a surveillance tool for recurrence when image surveillance beyond mammography is not being used clinically.

The final two publications looked at the utility of PET in identifying recurrence compared with standard imaging: the first, Ulaner et al. [3] (232 patients), completed a retrospective study where PET was compared with a variety of standard imaging tools to predict recurrence, and it upstaged 12% of patients with occult metastases. Given the retrospective nature of this study and the fact that current guidelines do not support routine screening for occult distant metastases in patients with breast cancer, these data would not be sufficient to support a change in the current guidelines regarding use of PET in breast cancer.

The second, Garg et al. [4] (79 patients), completed a prospective study looking for distant metastases, comparing PET with chest x-ray, abdominal ultrasound, and bone scan. Although PET performed better than these (study was completed in India where these may be standard imaging modalities), the current standard for detecting distant metastases in North America would be CT chest/abdomen/pelvis. Therefore, these data are not sufficiently helpful in comparing the incremental benefit of PET over current standard imaging modalities.

During this time period, there were no publications evaluating the role of PET in breast cancer that were sufficient to warrant a change in current guidelines regarding PET in breast cancer.

Esophageal Cancer

Current Insured Indication

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

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

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

Reviewer's Comments (Dr. Rebecca Wong)

Multiple diagnostic objectives were pursued. These can be categorized into the following: 1. Prediction of pathological complete (or near complete) response (pCR); 2. Identification of malignant lymph nodes; and 3. Identification of disease beyond the local regional area (i.e., incurable). All series addressed the role of PET after neoadjuvant therapy except one (Lehmann et al. [9]), where approximately 40% of patients received neoadjuvant therapy and post-treatment PET diagnostic properties were available. None of the studies were designed to address or reported on how the PET findings changed the patients' management.

The ability to predict treatment response (i.e., pCRs) after neoadjuvant therapy has been studied by multiple authors. Cong et al. [5] conducted a meta-analysis involving 682 patients (15 studies) and observed suboptimal sensitivity (pooled estimate, 67%) and specificity (pooled estimate, 69%). Sensitivity was superior for studies with PET during therapy (pooled estimate, 85%) while the pooled specificity was 59%. The authors speculated that the superior diagnostic performance in some studies may be attributable to squamous cell histologies. Overall, the authors recommended against the routine use of PET (to predict pCR or near complete response) to guide treatment strategy in esophageal cancer patients. The retrospective review by Yuan et al. [6] reported supportive findings with a modest sensitivity (71.0%) and specificity (66.7%) for PET.

In terms of the value of PET in identifying malignant local regional nodes, two studies provided data. The study by Huang et al. [7] was designed to address the role of change in SUV (pre- and post-treatment) as a predictor of treatment outcomes and found a change of ≥60% to correlate with pCR and disease-free survival. The authors also provided data on the sensitivity (45.8%) and specificity (96.7%) for detecting malignant mediastinal nodes. Lehmann et al. [9] provided data on 221 gastroesophageal and gastric cancers, and reported similar sensitivity (50%) and specificity (91.3%) in regional node detection. This is similar to endoscopic ultrasound but superior to CT; they concluded that PET did not improve the overall accuracy of N staging.

As a tool to detect distant disease, Finlay et al. [8] found that restaging PET was more sensitive than CT (39.5% versus 27.3%; p=0.005) in detecting incurable disease but its use is

limited. Also, PET (accuracy, 88.5%) and multidetector spiral CT (accuracy, 83.3%) performed similarly when detecting extra-regional lymph nodes and systemic metastases. This was attributable to missed peritoneal carcinomatosis. The authors suggested that when limiting the use to intestinal/mixed-type tumours (i.e., excluding diffuse types), the sensitivity of detecting extra-regional lymph nodes increased to 95% for PET compared with 63% for CT (p=0.01).

In summary, if PET is to be used to predict pCR, its use during therapy is superior to that post-treatment, although the clinical impact of this strategy requires further clinical trial confirmation before it can be adopted for routine use. Restaging PET is more sensitive than CT alone in detecting incurable disease (i.e., extra-regional lymph nodes and systemic disease) post-neoadjuvant therapy, although the sensitivity is modest (and poor for diffuse subtypes) and its routine use is expected to have limited clinical impact.

Gastrointestinal Cancer

Current Insured Indication (Colorectal Cancer)

- Where recurrent disease is suspected on the basis of elevated and/or rising 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 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 to 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 who are at high risk for recurrence.
- PET is recommended to determine the site of recurrence in the setting of rising CEA levels, when a conventional work-up 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. There are some emerging papers on anal cancer that need to be closely monitored; all of them are retrospective at this point.

Genitourinary Cancer

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

- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET in the routine staging of patients with testicular cancer.
- 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.

- Due to insufficient evidence, a recommendation cannot be made for or against the routine use of PET for evaluation of recurrence.

Reviewer's Comments (Dr. Glenn 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.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET for staging advanced-stage cervical cancer. 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.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET for evaluation of suspected recurrence.
- 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.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET in the evaluation of asymptomatic ovarian mass.
- PET is not recommended for staging of ovarian cancer.
- PET is not recommended for detecting recurrence or restaging patients not being considered for surgery.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET for patients being considered for secondary cytoreduction.

Reviewer's Comments

A review was not completed by a clinical expert in gynecologic cancer.

Head and Neck Cancer

Current Insured Indications

- Head and neck cancer:
    - For the evaluation of metastatic squamous cell carcinoma in neck nodes when the primary disease site is unknown after standard radiological and clinical investigation, or for the staging of nasopharyngeal cancer.
- Thyroid cancer:
    - Where recurrent or persistent disease is suspected on the basis of an elevated and/or rising thyroglobulin level, but standard imaging studies, including I-131 scan and/or neck ultrasound, are negative or equivocal.

Current Recommendations for the Utilization of PET/CT in Head and Neck Cancer

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

Reviewer's Comments (Dr. Amit Singnurkar)

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

Hematologic Cancer

Current Registry Indication (Lymphoma Staging)

- PET for the staging of HL or NHL being treated with curative intent:
    - For the staging of limited disease as per conventional imaging, or
    - When imaging results are equivocal for differentiating between limited- and advanced-stage disease.
- PET for apparent limited-stage nodal follicular lymphoma or other indolent NHL 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 HL or NHL when further potentially curative therapy (such as radiation or stem cell transplantation) is being considered; or for the assessment of response in early-stage HL following two or three cycles of chemotherapy when chemotherapy is being considered as the definitive single modality therapy.

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

- When functional imaging is considered to be important in situations where anatomical imaging is equivocal, and/or in potentially curable cases, a FDG PET/CT scan is recommended.
- When functional imaging is considered to be important in situations where anatomical imaging is equivocal and treatment choices may be affected in limited-stage indolent lymphomas, a FDG PET/CT scan is recommended.
- An FDG PET/CT scan is recommended for the assessment of early response in early stage (I or II) HL following two or three cycles of chemotherapy when chemotherapy is being considered as the definitive single-modality therapy, to inform completion of therapy, or to determine 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 HL or NHL when further potentially curative therapy (such as radiation or stem cell transplantation) is being considered and when biopsy cannot be safely or readily performed.
- An FDG PET/CT scan is not recommended for the routine monitoring and surveillance of lymphoma.

Reviewer's Comments (Dr. Marc Freeman)

The study by Zinzani et al. [47] is a particularly powerful prospective study and warrants discussion as a future emerging add-on to the following indication (interim PET in advanced stage HL for consideration of risk-adaptive therapy) as the body of evidence develops.

Melanoma

Current Registry Indication

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

Current Recommendations for the Utilization of PET/CT in Melanoma

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

Reviewer's Comments (Dr. Tara Baetz)

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

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 evidence for ^{68}Ga-PSMA and ^{18}F-NaF is compelling and evidence development is ongoing in the province so there are no further recommendations. The meta-analysis describing the superiority of ^{18}F-FET over ^{18}F-FDG in the diagnosis is informative, but the true value of this agent will likely be in

differentiating radiation necrosis from residual/recurrent tumour in the brain. Therefore, there is no recommendation for this agent other than to continue to monitor the literature. No specific recommendation for the other non-FDG agents that have been tracked in this summary.

NSCLC and Other Lung Cancer

Current Insured Indications

- Solitary pulmonary nodule:
    - A lung nodule for which a diagnosis could not be established by a needle biopsy due to unsuccessful attempted needle biopsy; the solitary pulmonary nodule is inaccessible to needle biopsy; or the existence of a contraindication to the use of needle biopsy.
- NSCLC:
    - Where curative surgical resection is being considered based on negative standard imaging tests; or clinical stage III NSCLC where potentially curative combined modality therapy with radiotherapy and chemotherapy is being considered.
- Limited-disease small cell lung cancer (SCLC):
    - Where combined modality therapy with chemotherapy and radiotherapy is being considered.

Current Recommendations for the Utilization of PET/CT in SCLC

- PET is recommended for staging in patients with SCLC who are potential candidates for the addition of thoracic radiotherapy to chemotherapy.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET for the assessment of treatment response in SCLC.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET for evaluation of recurrence or restaging.
- Due to insufficient evidence, a recommendation cannot be made for or against the use of PET when metastasectomy or stereotactic body radiation therapy is being contemplated for solitary metastases.

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

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

Reviewer's Comments (Dr. Donna Maziak)

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

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.
- Due to insufficient evidence, 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 and lack of effective therapeutic options, PET is not recommended for clinical management of suspected recurrence, nor for restaging at the time of recurrence.
- A recommendation cannot be made for or against the use of PET for staging if a solitary metastasis is identified at recurrence because there are no trials that identify the utility of PET scanning in this setting.

Reviewer's Comments (Dr. Jim Biagi)

The current recommendations for the utilization of PET/CT in pancreatic cancer remain valid and no changes are required. Results from Gu and Liu [76] would support a role for PET/CT in diagnosis, but not change recommendation since the study was small and patient diagnosis was already known, so a validation component was not included. Sanchez-Bueno et al. [77] is a study of technique to increase sensitivity, which is quite interesting but does not alter current recommendations. Based on a previous study on surveillance after curative resection, PET/CT is not recommended for this setting. Furthermore, it may be worthwhile to assess the literature specifically for PET/CT in staging patients who are considered to have borderline resectable disease.

Sarcoma

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

Reviewer's Comments (Dr. Gina Diprimio)

There is enough evidence to support the use of PET/CT in sarcoma and a letter of request for review will be submitted.

Funding

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

Contact Information

For information about the PEBC and the most current version of all reports,
please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

REFERENCES

1. Sheikhbahaei S, Trahan TJ, Xiao J, Taghipour M, Mena E, Connolly RM, et al. FDG-PET/CT and MRI for evaluation of pathologic response to neoadjuvant chemotherapy in patients with breast cancer: a meta-analysis of diagnostic accuracy studies. Oncologist. 2016;21(8):931-9.
2. Xiao Y, Wang L, Jiang X, She W, He L, Hu G. Diagnostic efficacy of 18F-FDG-PET or PET/CT in breast cancer with suspected recurrence: a systematic review and meta-analysis. Nucl Med Commun. 2016;37(11):1180-8.
3. Ulaner GA, Castillo R, Goldman DA, Wills J, Riedl CC, Pinker-Domenig K, et al. (18)F-FDG-PET/CT for systemic staging of newly diagnosed triple-negative breast cancer. Eur J Nucl Med Mol Imaging. 2016;43(11):1937-44.
4. Garg PK, Deo SV, Kumar R, Shukla NK, Thulkar S, Gogia A, et al. Staging PET-CT scanning provides superior detection of lymph nodes and distant metastases than traditional imaging in locally advanced breast cancer. World J Surg. 2016;40(8):2036-42.
5. Cong L, Wang S, Gao T, Hu L. The predictive value of 18F-FDG PET for pathological response of primary tumor in patients with esophageal cancer during or after neoadjuvant chemoradiotherapy: a meta-analysis. Japan J Clin Oncol. 2016;4:4.
6. Yuan H, Tong DK, Vardhanabhuti V, Law SY, Chiu KW, Khong PL. PET/CT in the evaluation of treatment response to neoadjuvant chemoradiotherapy and prognostication in patients with locally advanced esophageal squamous cell carcinoma. Nucl Med Commun. 2016;37(9):947-55.
7. Huang JW, Yeh HL, Hsu CP, Lu YY, Chuang CY, Lin JC, et al. To evaluate the treatment response of locally advanced esophageal cancer after preoperative chemoradiotherapy by FDG-PET/CT scan. J Chin Med Assoc. 2015;78(4):229-34.
8. Findlay JM, Gillies RS, Franklin JM, Teoh EJ, Jones GE, di Carlo S, et al. Restaging oesophageal cancer after neoadjuvant therapy with (18)F-FDG PET-CT: identifying interval metastases and predicting incurable disease at surgery. Eur Radiol. 2016;26(10):3519-33.
9. Lehmann K, Eshmuminov D, Bauerfeind P, Gubler C, Veit-Haibach P, Weber A, et al. (18)FDG-PET-CT improves specificity of preoperative lymph-node staging in patients with intestinal but not diffuse-type esophagogastric adenocarcinoma. Eur J Surg Oncol. 2016;7:7.
10. Metser U, Halankar J, Langer D, Mohan R, Hussey D, Hadas M, et al. Effect of chemotherapy on the impact of FDG-PET/CT in selection of patients for surgical resection of colorectal liver metastases: single center analysis of PET-CAM randomized trial. Ann Nucl Med. 2016;15:15.
11. Kunawudhi A, Sereeborwornthanasak K, Promteangtrong C, Siripongpreeda B, Vanprom S, Chotipanich C. Value of FDG PET/contrast-enhanced CT in initial staging of colorectal cancer - comparison with contrast-enhanced CT. Asian Pac J Cancer Prev. 2016;17(8):4071-5.
12. Schulz A, Viktil E, Godt JC, Johansen CK, Dormagen JB, Holtedahl JE, et al. Diagnostic performance of CT, MRI and PET/CT in patients with suspected colorectal liver metastases: the superiority of MRI. Acta Radiol. 2016;57(9):1040-8.
13. Vigano L, Lopci E, Costa G, Rodari M, Poretti D, Pedicini V, et al. Positron emission tomography-computed tomography for patients with recurrent colorectal liver metastases: impact on restaging and treatment planning. Ann Surg Oncol. 2016;2:2.
14. Khan K, Athauda A, Aitken K, Cunningham D, Watkins D, Starling N, et al. Survival outcomes in asymptomatic patients with normal conventional imaging but raised

carcinoembryonic antigen levels in colorectal cancer following positron emission tomography-computed tomography imaging. Oncologist. 2016;14:14.
15. Falconer R, Connor S, Balasingam A, Eglinton T. Does positron emission tomography/computed tomography change management in colorectal cancer? ANZ J Surg. 2016;27:27.
16. Jiang L, Tan H, Panje CM, Yu H, Xiu Y, Shi H. Role of 18F-FDG PET/CT imaging in intrahepatic cholangiocarcinoma. Clin Nucl Med. 2016;41(1):1-7.
17. Zhang H, Zhu J, Ke F, Weng M, Wu X, Li M, et al. radiological imaging for assessing the respectability of hilar cholangiocarcinoma: a systematic review and meta-analysis. BioMed Res Int. 2015;2015:497942.
18. Goldman KE, White EC, Rao AR, Kaptein JS, Lien WW. Posttreatment FDG-PET-CT response is predictive of tumor progression and survival in anal carcinoma. Pract Radiat Oncol. 2016;6(5):e149-54.
19. Teagle AR, Gilbert DC, Jones JR, Burkill GJ, McKinna F, Dizdarevic S. Negative 18F-FDG-PET-CT may exclude residual or recurrent disease in anal cancer. Nucl Med Commun. 2016;37(10):1038-45.
20. Choi BW, Kim HW, Won KS, Song BI, Cho KB, Bae SU. Diagnostic accuracy of 18F-FDG PET/CT for detecting synchronous advanced colorectal neoplasia in patients with gastric cancer. Medicine. 2016;95(36):e4741.
21. Soubra A, Hayward D, Dahm P, Goldfarb R, Froehlich J, Jha G, et al. The diagnostic accuracy of 18F-fluorodeoxyglucose positron emission tomography and computed tomography in staging bladder cancer: a single-institution study and a systematic review with meta-analysis. World J Urol. 2016;34(9):1229-37.
22. Ma H, Shen G, Liu B, Yang Y, Ren P, Kuang A. Diagnostic performance of 18F-FDG PET or PET/CT in restaging renal cell carcinoma: a systematic review and meta-analysis. Nucl Med Commun. 2016;7:7.
23. Kassem TW. Up and down staging of TCC using ¹⁸F-FDG PET/CT scan. Egypt J Radiol Nucl Med. 2016 01 Sep;47(3):1095-102.
24. Atri M, Zhang Z, Dehdashti F, Lee SI, Ali S, Marques H, et al. Utility of PET-CT to evaluate retroperitoneal lymph node metastasis in advanced cervical cancer: results of ACRIN6671/GOG0233 trial. Gynecol Oncol. 2016;142(3):413-9.
25. Wu C, Lu L, Liu Y, Lu Y, Mi Y, Diao W. Evaluating MRI, CT, PET/CT in detection of lymph node status in cervical cancer: a meta-analysis. Int J Clin Exper Med. 2016;30 Jun;9(6):9917-31.
26. Xu X, Li Z, Qiu X, Wei Z. Diagnosis performance of positron emission tomography-computed tomography among cervical cancer patients. J Xray Sci Technol. 2016;24(4):531-6.
27. Abdelhafez Y, Tawakol A, Osama A, Hamada E, El-Refaei S. Role of ¹⁸F-FDG PET/CT in the detection of ovarian cancer recurrence in the setting of normal tumor markers. Egypt J Radiol Nucl Med. 2016 01 Dec;47(4):1787-94.
28. Lopez-Lopez V, Cascales-Campos PA, Gil J, Frutos L, Andrade RJ, Fuster-Quinonero M, et al. Use of (18)F-FDG PET/CT in the preoperative evaluation of patients diagnosed with peritoneal carcinomatosis of ovarian origin, candidates to cytoreduction and hipec. A pending issue. Eur J Radiol. 2016;85(10):1824-8.
29. Konuralp Atakul B, Taskin S, Soydal C, Sukur YE, Kahraman A, Koyuncu K, et al. Preoperative 18F-fluorodeoxyglucose positron emission tomography/CT in prediction of uterine risk factors and lymph node metastasis: an analysis of 111 endometrioid endometrial cancer patients. Gynecol Obstet Invest. 2016;22:22.
30. Doner RK, Sager S, Gortan FA, Topuz OV, Akyel R, Vatankulu B, et al. What is the role of florine-18 fluorodeoxyglucose/positron emission tomography/computed tomography

imaging in well-differentiated thyroid cancers with negative iodine-131 scan high thyroglobulin and normal anti-thyroglobulin levels. J Cancer Res Ther. 2016;12(2):1010-7.
31. Okuyucu K, Ince S, Alagoz E, Emer O, San H, Balkan E, et al. Risk factors and stratification for recurrence of patients with differentiated thyroid cancer, elevated thyroglobulin and negative I-131 whole-body scan, by restaging (18)F-FDG PET/CT. Hell J Nucl Med. 2016;8:8.
32. Son MH, Bieu BQ, Ha LN. Value of dedicated head and neck (18)F-FDG PET/CT protocol in detecting recurrent and metastatic lesions in post-surgical differentiated thyroid carcinoma patients with high serum thyroglobulin level and negative (131)I whole-body scan. Asia Ocean J Nucl Med Biol. 2016;4(1):12-8.
33. Haslerud T, Brauckhoff K, Reisaeter L, Kufner Lein R, Heinecke A, Varhaug JE, et al. F18-FDG-PET for recurrent differentiated thyroid cancer: a systematic meta-analysis. Acta Radiol. 2016;57(10):1193-200.
34. Marcus C, Antoniou A, Rahmim A, Ladenson P, Subramaniam RM. Fluorodeoxyglucose positron emission tomography/computerized tomography in differentiated thyroid cancer management: Importance of clinical justification and value in predicting survival. J Med Imaging Radiat Oncol. 2015;59(3):281-8.
35. Pathak KA, Goertzen AL, Nason RW, Klonisch T, Leslie WD. A prospective cohort study to assess the role of FDG-PET in differentiating benign and malignant follicular neoplasms. Ann Med Surg. 2016;12:27-31.
36. Merten MM, Castro MR, Zhang J, Durski JM, Ryder M. examining the role of preoperative positron emission tomography/computerized tomography (PET/CT) in combination with ultrasonography in discriminating benign from malignant cytologically indeterminate thyroid nodules. Thyroid. 2016;20:20.
37. Abadi P, Johansen A, Godballe C, Gerke O, Hoilund-Carlsen PF, Thomassen A. (18)F-FDG PET/CT to differentiate malignant necrotic lymph node from benign cystic lesions in the neck. Ann Nucl Med. 2016;05:05.
38. Wei J, Pei S, Zhu X. Comparison of 18F-FDG PET/CT, MRI and SPECT in the diagnosis of local residual/recurrent nasopharyngeal carcinoma: A meta-analysis. Oral Oncol. 2016;52:11-7.
39. Chen WS, Li JJ, Hong L, Xing ZB, Wang F, Li CQ. Comparison of MRI, CT and 18F-FDG PET/CT in the diagnosis of local and metastatic of nasopharyngeal carcinomas: an updated meta analysis of clinical studies. Am J Transl Res. 2016;8(11):4532-47.
40. Ryu IS, Roh JL, Kim JS, Lee JH, Cho KJ, Choi SH, et al. Impact of (18)F-FDG PET/CT staging on management and prognostic stratification in head and neck squamous cell carcinoma: A prospective observational study. Eur J Cancer. 2016;63:88-96.
41. Xi K, Xie X, Xi S. Meta-analysis of (18) fluorodeoxyglucose positron emission tomography-CT for diagnosis of lung malignancies in patients with head and neck squamous cell carcinomas. Head Neck. 2015;37(11):1680-4.
42. Lee JR, Choi YJ, Roh JL, Kim JS, Lee JH, Cho KJ, et al. Preoperative contrast-enhanced CT versus 18F-FDG PET/CT evaluation and the prognostic value of extranodal extension for surgical patients with head and neck squamous cell carcinoma. Ann Surg Oncol. 2015;22 Suppl 3:S1020-7.
43. Nishimura G, Yabuki K, Hata M, Komatsu M, Taguchi T, Takahashi M, et al. Imaging strategy for response evaluation to chemoradiotherapy of the nodal disease in patients with head and neck squamous cell carcinoma. Int J Clin Oncol. 2016;21(4):658-67.
44. Cheung PK, Chin RY, Eslick GD. detecting residual/recurrent head neck squamous cell carcinomas using PET or PET/CT: systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2016;154(3):421-32.

45. Kim SA, Roh JL, Kim JS, Lee JH, Lee SH, Choi SH, et al. 18F-FDG PET/CT surveillance for the detection of recurrence in patients with head and neck cancer. Eur J Cancer. 2016;72:62-70.
46. Ciammella P, Filippi AR, Simontacchi G, Buglione M, Botto B, Mangoni M, et al. Post-ABVD/pre-radiotherapy (18)F-FDG-PET provides additional prognostic information for early-stage Hodgkin lymphoma: a retrospective analysis on 165 patients. Br J Radiol. 2016;89(1061):20150983.
47. Zinzani PL, Broccoli A, Gioia DM, Castagnoli A, Ciccone G, Evangelista A, et al. Interim Positron Emission Tomography Response-Adapted Therapy in Advanced-Stage Hodgkin Lymphoma: Final Results of the Phase II Part of the HD0801 Study. J Clin Oncol. 2016;34(12):1376-85.
48. de Oliveira Costa R, Hallack Neto A, Siqueira S, Lage LA, de Paula HM, Coutinho AM, et al. Interim fluorine-18 fluorodeoxyglucose PET-computed tomography and cell of origin by immunohistochemistry predicts progression-free and overall survival in diffuse large B-cell lymphoma patients in the rituximab era. Nucl Med Commun. 2016;37(10):1095-101.
49. Soydal C, Koksoy EB, Yasar A, Turgal E, Erdogan BD, Akbulut H, et al. Prognostic importance of bone marrow uptake on baseline 18F-FDG positron emission tomography in diffuse large B cell lymphoma. Cancer Biother Radiopharm. 2016;31(10):361-5.
50. Taghipour M, Marcus C, Nunna P, Subramaniam RM. Follow-up FDG PET/CT in Patients With Non-Hodgkin Lymphoma: Value to Clinical Assessment and Patient Management. Clin Nucl Med. 2016;41(2):e93-7.
51. Gellen E, Santha O, Janka E, Juhasz I, Peter Z, Erdei I, et al. Diagnostic accuracy of (18)F-FDG-PET/CT in early and late stages of high-risk cutaneous malignant melanoma. J Eur Acad Dermatol Venereol. 2015;29(10):1938-44.
52. Mena E, Taghipour M, Sheikhbahaei S, Mirpour S, Xiao J, Subramaniam RM. 18F-FDG PET/CT and melanoma: value of fourth and subsequent posttherapy follow-up scans for patient management. Clin Nucl Med. 2016;41(9):e403-9.
53. Simone G, Di Pierro GB, Papalia R, Sciuto R, Rea S, Ferriero M, et al. Significant increase in detection of prostate cancer recurrence following radical prostatectomy with an early imaging acquisition protocol with 18F-fluorocholine positron emission tomography/computed tomography. World J Urol. 2015;33(10):1511-8.
54. Colombie M, Campion L, Bailly C, Rusu D, Rousseau T, Mathieu C, et al. Prognostic value of metabolic parameters and clinical impact of 18F-fluorocholine PET/CT in biochemical recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 2015;42(12):1784-93.
55. Nanni C, Zanoni L, Pultrone C, Schiavina R, Brunocilla E, Lodi F, et al. (18)F-FACBC (anti1-amino-3-(18)F-fluorocyclobutane-1-carboxylic acid) versus (11)C-choline PET/CT in prostate cancer relapse: results of a prospective trial. Eur J Nucl Med Mol Imaging. 2016;43(9):1601-10.
56. Haidar M, Shamseddine A, Panagiotidis E, Jreige M, Mukherji D, Assi R, et al. The role of 68Ga-DOTA-NOC PET/CT in evaluating neuroendocrine tumors: real-world experience from two large neuroendocrine tumor centers. Nucl Med Commun. 2016;02:02.
57. Nakajo M, Kajiya Y, Tani A, Jinguji M, Nakajo M, Yoshiura T. FLT-PET/CT diagnosis of primary and metastatic nodal lesions of gastric cancer: comparison with FDG-PET/CT. Abdom Radiol. 2016;41(10):1891-8.
58. Nakajo M, Kajiya Y, Tani A, Jinguji M, Nakajo M, Nihara T, et al. A pilot study of the diagnostic and prognostic values of FLT-PET/CT for pancreatic cancer: comparison with FDG-PET/CT. Abdom Radiol. 2016;28:28.
59. Dunet V, Pomoni A, Hottinger A, Nicod-Lalonde M, Prior JO. Performance of 18F-FET versus 18F-FDG-PET for the diagnosis and grading of brain tumors: systematic review and meta-analysis. Neuro-Oncology. 2016;18(3):426-34.

60. Ren J, Yuan L, Wen G, Yang J. The value of anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid PET/CT in the diagnosis of recurrent prostate carcinoma: a meta-analysis. Acta Radiol. 2016;57(4):487-93.
61. Odewole OA, Tade FI, Nieh PT, Savir-Baruch B, Jani AB, Master VA, et al. Recurrent prostate cancer detection with anti-3-[(18)F]FACBC PET/CT: comparison with CT. Eur J Nucl Med Mol Imaging. 2016;43(10):1773-83.
62. Bach-Gansmo T, Nanni C, Nieh PT, Zanoni L, Bogsrud TV, Sletten H, et al. Multi-site experience of the safety, detection rate and diagnostic performance of fluciclovine ((18)F) PET/CT imaging in the staging of biochemically recurrent prostate cancer. J Urol. 2016;13:13.
63. Akin-Akintayo OO, Jani AB, Odewole O, Tade FI, Nieh PT, Master VA, et al. Change in salvage radiotherapy management based on guidance with FACBC (Fluciclovine) PET/CT in postprostatectomy recurrent prostate cancer. Clin Nucl Med. 2016;5:5.
64. Maurer T, Gschwend JE, Rauscher I, Souvatzoglou M, Haller B, Weirich G, et al. Diagnostic efficacy of (68)Gallium-PSMA positron emission tomography compared to conventional imaging for lymph node staging of 130 consecutive patients with intermediate to high risk prostate cancer. J Urol. 2016;195(5):1436-43.
65. Rhee H, Thomas P, Shepherd B, Gustafson S, Vela I, Russell PJ, et al. Prostate specific membrane antigen positron emission tomography may improve the diagnostic accuracy of multiparametric magnetic resonance imaging in localized prostate cancer. J Urol. 2016;196(4):1261-7.
66. Shakespeare TP. Effect of prostate-specific membrane antigen positron emission tomography on the decision-making of radiation oncologists. Radiat Oncol. 2015;10:233.
67. Kabasakal L, Demirci E, Nematyazar J, Akyel R, Razavi B, Ocak M, et al. The role of PSMA PET/CT imaging in restaging of prostate cancer patients with low prostate-specific antigen levels. Nucl Med Commun. 2016;28:28.
68. Albisinni S, Artigas C, Aoun F, Biaou I, Grosman J, Gil T, et al. Clinical impact of 68 Ga-PSMA PET/CT in prostate cancer patients with rising PSA after treatment with curative intent: preliminary analysis of a multidisciplinary approach. BJU Int. 2016;15:15.
69. Le Y, Chen Y, Zhou F, Liu G, Huang Z, Chen Y. Comparative diagnostic value of 18F-fluoride PET-CT versus MRI for skull-base bone invasion in nasopharyngeal carcinoma. Nucl Med Commun. 2016;37(10):1062-8.
70. Abikhzer G, Srour S, Fried G, Drumea K, Kozlener E, Frenkel A, et al. Prospective comparison of whole-body bone SPECT and sodium 18F-fluoride PET in the detection of bone metastases from breast cancer. Nucl Med Commun. 2016;37(11):1160-8.
71. Jambor I, Kuisma A, Ramadan S, Huovinen R, Sandell M, Kajander S, et al. Prospective evaluation of planar bone scintigraphy, SPECT, SPECT/CT, 18F-NaF PET/CT and whole body 1.5T MRI, including DWI, for the detection of bone metastases in high risk breast and prostate cancer patients: SKELETA clinical trial. Acta Oncol. 2016;55(1):59-67.
72. Rao L, Zong Z, Chen Z, Wang X, Shi X, Yi C, et al. 18F-Labeled NaF PET-CT in detection of bone metastases in patients with preoperative lung cancer. Medicine. 2016;95(16):e3490.
73. Nomori H, Cong Y, Sugimura H, Kato Y. Comparing diffusion-weighted imaging and positron emission tomography for pulmonary nodules measuring from 1 to 3 cm in size. Surg Today. 2015;45(12):1535-41.
74. Kaseda K, Watanabe K, Asakura K, Kazama A, Ozawa Y. Identification of false-negative and false-positive diagnoses of lymph node metastases in non-small cell lung cancer patients staged by integrated (18F-)fluorodeoxyglucose-positron emission tomography/computed tomography: A retrospective cohort study. Thorac Cancer. 2016;7(4):473-80.

75. Reddy JP, Tang C, Shih T, Kim B, Kim C, Nguyen QN, et al. Influence of surveillance PET/CT on detection of early recurrence after definitive radiation in stage III non-small-cell lung cancer. Clin Lung Cancer. 2016;10:10.
76. Gu X, Liu R. Application of 18F-FDG PET/CT combined with carbohydrate antigen 19-9 for differentiating pancreatic carcinoma from chronic mass-forming pancreatitis in Chinese elderly. Clin Interv Aging. 2016;11:1365-70.
77. Sanchez-Bueno F, Garcia-Perez R, Claver Valderas MA, de la Pena Moral J, Frutos Esteban L, Ortiz Ruiz E, et al. Utility of 18 fludeoxyglucose in preoperative positon-emission tomography-computed tomography (PET-CT) in the early diagnosis of exocrine pancreatic cancer: A study of 139 resected cases. Cirugia Espanola. 2016;3:3.
78. Park SY, Chung HW, Chae SY, Lee JS. Comparison of MRI and PET-CT in detecting the loco-regional recurrence of soft tissue sarcomas during surveillance. Skeletal Radiol. 2016;45(10):1375-84.
79. Etchebehere EC, Hobbs BP, Milton DR, Malawi O, Patel S, Benjamin RS, et al. Assessing the role of 18F-FDG PET and 18F-FDG PET/CT in the diagnosis of soft tissue musculoskeletal malignancies: a systematic review and meta-analysis. Eur J Nucl Med Mol Imaging. 2016;43(5):860-70.
80. Riaz S, Nawaz MK, Faruqui ZS, Saeed Kazmi SA, Loya A, Bashir H. Diagnostic accuracy of 18F-Fluorodeoxyglucose positron emission tomography-computed tomography in the evaluation of carcinoma of unknown primary. Mol Imaging Radionucl Ther. 2016;25(1):11-8.
81. Yu X, Li X, Song X, Dai D, Zhu L, Zhu Y, et al. Advantages and disadvantages of F-18 fluorodeoxyglucose positron emission tomography/computed tomography in carcinoma of unknown primary. Oncol Lett. 2016 November;12(5):3785-92.
82. Taghipour M, Marcus C, Sheikhbahaei S, Mena E, Prasad S, Jha AK, et al. Clinical indications & impact on management: fourth and subsequent post-therapy follow-up FDG-PET/CT scans in oncology patients. J Nucl Med. 2016;3:3.

Appendix 1: Summary of studies from July to December 2016.

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
Breast Cancer								
Sheikhbahaei et al, 2016 [1]	Meta-analysis	10 studies (595 patients who underwent neoadjuvant chemotherapy for breast cancer)	FDG PET/CT	MRI	Pathology	**Residual disease** Pooled Sens: 71% Pooled Spec: 88%	**Residual disease** Pooled Sens: 88% Pooled Spec: 63%	NA
Xiao et al, 2016 [2]	Meta-analysis	26 studies (1752 patients with suspected recurrence of breast cancer)	FDG PET or PET/CT	NA	Histopathology, clinical and imaging follow-up	**Relapse** Pooled Sens: 90% Pooled Spec: 81% Pooled +LR: 4.64 Pooled –LR: 0.12 Pooled DOR: 46.52 AUC: 0.936 Q test: 0.872	NA	NA
Ulaner et al, 2016 [3]	Retrospective	232 patients (newly diagnosed stage I-IIIC triple-negative breast cancer)	FDG PET/CT	Physical exam, mammography, breast US, if available, breast MRI and/or surgical findings	Histology, pathology, imaging follow-up	NA	NA	PET/CT upstaged 12.9% (30/232) of patients by revealing unsuspected distant metastases. PET/CT identified unsuspected synchronous malignancies in 2.6% (6/232) of patients.
Garg et al, 2016 [4]	Prospective	79 patients (newly diagnosed locally advanced breast cancer)	FDG PET/CT	Chest X-ray, abdominal sonography, bone scintigraphy	Histopathology	NA	NA	PET/CT upstaged the disease in 48.1% (38/79) of patients and led to a change in management plan in 17.7% (14/79) of patients. Treatment was changed from surgery with or without neoadjuvant chemotherapy to systemic chemotherapy.
Esophageal Cancer								
Cong et al, 2016 [5]	Meta-analysis	15 studies (682 patients with esophageal cancer eligible for surgery after neoadjuvant chemoradiother	FDG PET or PET/CT	NA	Pathology, clinical and imaging follow-up	**Predicting treatment response (during neoadjuvant chemoradiotherapy)** Pooled Sens: 85% Pooled Spec: 59% Pooled DOR: 6.82	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
		apy)				**(after neoadjuvant chemoradiotherapy)** Pooled Sens: 67% Pooled Spec: 69% Pooled DOR: 6.34		
Yuan et al, 2016 [6]	Retrospective	52 patients who completed neoadjuvant chemoradiotherapy followed by esophagectomy (newly diagnosed locally advanced esophageal squamous cell carcinoma)	FDG PET/CT	NA	Pathology	**Response assessment (SUV_{max} of 2.7)** Sens: 71.0% Spec: 66.7% PPV: 75.9% NPV: 60.9%	NA	NA
Huang et al, 2015 [7]	Prospective	49 patients who underwent preoperative chemoradiotherapy and subsequent surgical treatment (locally advanced esophageal carcinoma, clinical stage T2-4N0-3M0)	FDG PET/CT (3 weeks after preoperative chemoradiotherapy)	Physical examination, laboratory tests, US of the abdomen, barium esophagogram, bronchoscopy, spiral CT of the chest and abdomen, trans-esophageal EUS	Histopathology	**Predicting malignant lymph nodes** Sens: 45.8% Spec: 96.7% PPV: 44.0% NPV: 96.9%	NA	NA
Findlay et al, 2016 [8]	Retrospective	383 patients restaged after neoadjuvant chemotherapy (esophageal or gastroesophageal junctional cancer)	FDG PET/CT	CT	Histopathology	**Incurable disease** Sens: 39.5%* Spec: 100% NPV: 89.4%	**Incurable disease** Sens: 27.3%* Spec: 100% NPV: 91.0%	NA
Lehmann et al, 2016 [9]	Prospective	221 patients (adenocarcinoma of the stomach or esophagogastric junction Siewert types I-III)	FDG PET/CT	EUS, MDCT	Histopathology	**Preoperative lymph node staging** Sens: 50.0%* Spec: 91.3%* PPV: 89.8%* NPV: 54.3% Accuracy: 66.3% **Extra-regional lymph**	**Preoperative lymph node staging** ***EUS*** Sens: 73.3%* Spec: 60.8%* PPV: 68.5%* NPV: 66.2%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
						nodes and systemic metastases Sens: 56.9% Spec: 98.7% PPV: 93.5% NPV: 87.6% Accuracy: 88.5%	Accuracy: 67.5% ***MDCT*** Sens: 47.6% Spec: 82.2% PPV: 79.4% NPV: 52.2% Accuracy: 61.8% **Extra-regional lymph nodes and systemic metastases** ***MDCT*** Sens: 40.0% Spec: 98.1% PPV: 88.0% NPV: 82.7% Accuracy: 83.3%	
Gastrointestinal Cancer								
Metser et al, 2016 [10]	Retrospective	120 patients (CRC liver metastases)	FDG PET/CT	CeCT	Findings at time of surgery, surgical pathology	**Extrahepatic metastases** ***Local interpretation*** Sens: 73.3% Spec: 94.4% PPV: 81.5% NPV: 91.4% Accuracy: 89.2% ***Central interpretation*** Sens: 96.7% Spec: 96.7% PPV: 90.6% NPV: 98.9% Accuracy: 96.7%	**Extrahepatic metastases** Sens: 40.0% Spec: 96.7% PPV: 80.0% NPV: 82.7% Accuracy: 82.5%	NA
Kunawudhi et al, 2016 [11]	Prospective	58 patients who underwent PET/CT for preoperative staging (colorectal cancer)	FDG PET/CeCT	CeCT	Histopathology, consensus from multidisciplinary team	**N staging** Sens: 53% Spec: 76% PPV: 63% NPV: 68% Accuracy: 66%	**N staging** Sens: 79% Spec: 24% PPV: 44% NPV: 60% Accuracy: 48%	PET/CT altered the management plans in 25.9% (15/58) of patients (9—changing extent of surgery, 4—chemotherapy to surgery, 2—avoided futile surgery).
Schulz et al, 2016 [12]	Prospective	46 patients considered for liver resection (suspected colorectal liver metastases)	FDG PET/CT	MRI, CT	Histopathology, follow-up	**Colorectal liver metastases (patient-based)** Sens: 95% Spec: 100% PPV: 100% NPV: 67%	**Colorectal liver metastases *MRI* (patient-based)** Sens: 100% Spec: 25% PPV: 93%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
						(lesion-based) Sens: 61%* Spec: 99% PPV: 97% NPV: 78%	NPV: 100% **(lesion-based)** Sens: 90%* Spec: 87% PPV: 82% NPV: 93% ***CT*** **(patient-based)** Sens: 93% Spec: 50% PPV: 95% NPV: 40% **(lesion-based)** Sens: 68%* Spec: 94% PPV: 89% NPV: 81%	
Vigano et al, 2016 [13]	Retrospective	107 patients who had received PET/CT at diagnosis of recurrence before chemotherapy (colorectal liver metastases)	FDG PET/CT	CT/MRI	Histology, multidisciplinary consensus, clinical and imaging follow-up	**Recurrence** ***Liver*** Sens: 96.7% NPV: 83.3% Accuracy: 97.2% ***Lung*** Sens: 95.8% NPV: 98.8% Accuracy: 99.1% ***Lymph node*** Sens: 93.5%* NPV: 97.4%* Accuracy: 98.1%* ***Peritoneum*** Sens: 80.0%* NPV: 98.0% Accuracy: 98.1% ***Bone*** Sens: 87.5% NPV: 99.0% Accuracy: 99.1%	**Recurrence** ***Liver*** Sens: 100% NPV: 100% Accuracy: 100% ***Lung*** Sens: 95.8% NPV: 98.8% Accuracy: 99.1% ***Lymph node*** Sens: 64.5%* NPV: 87.4%* Accuracy: 89.7%* ***Peritoneum*** Sens: 20.0%* NPV: 92.4% Accuracy: 92.5% ***Bone*** Sens: 37.5% NPV: 95.2% Accuracy: 95.3%	PET/CT modified the treatment strategy in 15.0% (16/107) patients (15—avoided surgery, 1—scheduled for surgery).
Khan et al, 2016 [14]	Retrospective	88 patients who had an elevated CEA level but normal or equivocal conventional investigations after curative therapy	FDG PET/CT	CT, MRI, US, colonoscopy, CEA measurements	Histopathology, clinical and imaging follow-up	**Recurrence** Sens: 88% Spec: 88% PPV: 93% NPV: 80%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
		(colorectal cancer)						
Falconer et al, 2016 [15]	Retrospective	105 patients; 111 PET/CT scans (colorectal cancer)	FDG PET/CT	US, CT, MRI	Consensus, imaging follow-up	NA	NA	PET/CT changed surgical management following 22.5% (25/111) of scans.
Jiang et al, 2016 [16]	Retrospective	65 patients (intrahepatic cholangiocarcinoma)	FDG PET/CT	Abdominal MRI	Histopathology	**Regional lymph node metastasis** Sens: 70.0% Spec: 91.7% Accuracy: 81.8%	**Regional lymph node metastasis** Sens: 50.0% Spec: 83.3% Accuracy: 68.2%	PET/CT upstaged 12.3% (8/65) and downstaged 3.1% (2/65) of patients. Subsequently, management was changed in these patients.
Zhang et al, 2015 [17]	Meta-analysis	16 studies (651 patients with hilar cholangiocarcinoma)	FDG PET/CT	CT, MRI	Consensus	**Resectability** Pooled Sens: 91%* Pooled Spec: 81% Pooled DOR: 35.01 Q test: 0.855 AUC: 0.922	**Resectability** ***CT*** Pooled Sens: 95%* Pooled Spec: 69% Pooled DOR: 38.66 Q test: 0.862 AUC: 0.927 ***MRI*** Pooled Sens: 94%* Pooled Spec: 71% Pooled DOR: 33.50 Q test: 0.853 AUC: 0.919	NA
Goldman et al, 2016 [18]	Retrospective	141 patients treated with chemoradiation (biopsy-proven, non-metastatic anal squamous cell carcinoma)	FDG PET/CT	Clinical examination	Clinical and imaging follow-up	**Predicting tumour progression (≤12 weeks posttreatment response)** Sens: 50% Spec: 62.5% PPV: 40% NPV: 71.4% **(13-25 weeks posttreatment response)** Sens: 81.8% Spec: 76.5% PPV: 52.9% NPV: 92.9%	NA	NA
Teagle et al, 2016 [19]	Retrospective	52 patients; 75 PET/CT scans (histologically confirmed anal cancer)	FDG PET/CT	CT, MRI	Histology, clinical and imaging follow-up	**Recurrent or residual disease** Sens: 100% Spec: 74% PPV: 71% NPV: 100%	NA	Patient management was altered in 56.0% (42/75) of PET/CT scans (1—change in treatment type and dose/field, 2—change in treatment type and new

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
								investigations, 1—change intent and type and additional investigations, 6—change in treatment intent and type, 11—additional investigations, 12—change in treatment type, 5—change in radiation dose/field, 4—change in treatment intent).
Choi et al, 2016 [20]	Retrospective	256 patients who underwent PET/CT for preoperative staging (gastric cancer)	FDG PET/CT	NA	Histopathology	**Synchronous CRC** Sens: 83.3% Spec: 93.9% PPV: 40.0% NPV: 99.1% Accuracy: 93.4% **Synchronous advanced CRN** Sens: 76.2% Spec: 96.2% PPV: 64.0% NPV: 97.8% Accuracy: 94.5%	NA	NA
Genitourinary Cancer								
Soubra et al, 2016 [21]	Retrospective and meta-analysis	78 patients (histologically confirmed MIBC or non-muscle-invasive refractory to intravesical treatment); 8 studies (384 patients with bladder cancer)	FDG PET/CT	CT	Pathology	**Lymph node metastasis (retrospective study)** Sens: 56.3% Spec: 98.4% +LR: 34.88 -LR: 0.45 Accuracy: 89.7% **(meta-analysis)** Pooled Sens: 56.5% Pooled Spec: 95.4% Pooled +LR: 9.02 Pooled –LR: 0.50	**Lymph node metastasis (meta-analysis)** Pooled Sens: 35% Pooled Spec: 95% Pooled +LR: 4.91 Pooled –LR: 0.7	NA
Ma et al, 2016 [22]	Meta-analysis	7 studies (535 patients with renal cell carcinoma)	FDG PET/CT	NA	Histopathology, clinical and imaging follow-up	**Metastatic or recurrent disease** Pooled Sens: 88% Pooled Spec: 88% Pooled +LR: 6.82 Pooled –LR: 0.13 Pooled DOR: 67.04	NA	NA
Kassem, 2016 [23]	Prospective	27 patients referred for	FDG PET/CT	CT	Histopathology	NA	NA	The initial staging was altered by PET/CT in 14.8%

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
		restaging (urinary bladder transitional cell carcinoma)						(4/27) of patients (2—upstaged, 2—downstaged). The plan of management was adjusted for these patients by adding or omitting systemic chemotherapy.
Gynecologic Cancer								
Atri et al, 2016 [24]	Prospective	80 patients who underwent lymphadenectomy (primary, histologically confirmed, untreated loco-regionally advanced invasive cervical cancer)	FDG PET/CeCT	CeCT	Pathology	**Abdominal lymph node metastasis** Sens: 50% Spec: 85% AUC: 70% **Pelvic lymph node metastasis** Sens: 83% Spec: 63% AUC: 80%	**Abdominal lymph node metastasis** Sens: 42% Spec: 89% AUC: 68% **Pelvic lymph node metastasis** Sens: 79% Spec: 62% AUC: 76%	NA
Wu et al, 2016 [25]	Meta-analysis	53 studies (15,479 patients with cervical cancer)	FDG PET or PET/CT	CT, MRI	Histopathology	**Lymph node metastasis (patient-based)** Pooled Sens: 60% Pooled Spec: 91% AUC: 0.88 **(node-based)** Pooled Sens: 55% Pooled Spec: 98% AUC: 0.94	**Lymph node metastasis** ***CT*** **(patient-based)** Pooled Sens: 54% Pooled Spec: 90% AUC: 0.87 **(node-based)** Pooled Sens: 45% Pooled Spec: 94% AUC: 0.93 ***MRI*** **(patient-based)** Pooled Sens: 56% Pooled Spec: 85% AUC: 0.75 **(node-based)** Pooled Sens: 43% Pooled Spec: 96% AUC: 0.83	NA
Xu et al, 2016 [26]	Retrospective	51 patients (newly diagnosed cervical cancer FIGO stage IB-IVA)	FDG PET/CT	Clinical examination	Pathology	**Staging** ***Primary tumour*** Sens: 88.0%* Spec: 80.8%* Accuracy: 84.3%* ***Lymph nodes*** Sens: 82.6%* Spec: 71.4%*	**Staging** ***Primary tumour*** Sens: 44.1%* Spec: 47.1%* Accuracy: 45.1%* ***Lymph nodes*** Sens: 28.6%* Spec: 8.7%*	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
						Accuracy: 76.5%*	Accuracy: 19.6%*	
Abdelhafez et al, 2016 [27]	Prospective	41 patients with normal tumour markers (suspected ovarian tumour recurrence)	FDG PET/CT	CeCT	Histopathology, tumour markers, clinical and imaging follow-up	**Recurrence (patient-based)** Sens: 92% Spec: 93%* Accuracy: 93%* **(site-based)** Sens: 94%* Spec: 100%* Accuracy: 99%	**Recurrence (patient-based)** Sens: 73% Spec: 57%* Accuracy: 65%* **(site-based)** Sens: 48%* Spec: 96%* Accuracy: 92%*	NA
Lopez-Lopez et al, 2016 [28]	Retrospective	59 patients who are candidates for cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy (primary FIGO stages IIIC/IV or recurrent ovarian cancer).	FDG PET/CT	CT	Intraoperative findings	**Peritoneal carcinomatosis** Sens: 24% Spec: 93% PPV: 66% NPV: 68% LR+: 3.47 LR-: 0.82	**Peritoneal carcinomatosis** Sens: 35% Spec: 98% PPV: 90% NPV: 72% LR+: 15.3 LR-: 0.67	NA
Konuralp Atakul et al, 2016 [29]	Prospective	111 patients who underwent preoperative PET/CT and were staged surgically (endometrioid endometrial cancer)	FDG PET/CT	NA	Histopathology	**Lymph node metastasis** Sens: 67% Spec: 96% PPV: 60% NPV: 97% Accuracy: 93%	NA	NA
Head and Neck Cancer								
Doner et al, 2016 [30]	Retrospective	104 patients with elevated serum Tg levels with normal anti-Tg and negative ^{131}I WBS after total thyroidectomy and radioiodine ablation (histopathologically proven well-differentiated thyroid cancer)	FDG PET/CT	^{131}I WBS	Histology, imaging and clinical follow-up	**Recurrence or metastasis** Sens: 95.9% Spec: 87.3% PPV: 87.0% NPV: 96.0% Accuracy: 91.4%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
Okuyucu et al, 2016 [31]	Retrospective	165 patients with negative post-treatment ^{131}I WBS and elevated serum Tg level (differentiated thyroid cancer)	FDG PET/CT	Thyroglobulin levels, ^{131}I WBS, US, CT, MRI, bone scintigraphy	Histopathology, imaging	**Recurrent or metastatic disease** Sens: 90.0% Spec: 98.5%	NA	NA
Son et al, 2016 [32]	Prospective	69 patients with negative post-treatment ^{131}I WBS and elevated serum Tg level (differentiated thyroid carcinoma)	FDG PET/CT	Thyroglobulin levels, ^{131}I WBS, US, CT	Histopathology, clinical and imaging follow-up	**Recurrent or metastatic disease** Sens: 87.0%* Spec: 90.5% PPV: 95.2% NPV: 76.0%* Accuracy: 88.0%*	**Recurrent or metastatic disease *CT*** Sens: 54.3%* Spec: 95.2% PPV: 96.2% NPV: 48.8%* Accuracy: 67.2%*	PET/CT findings altered the treatment plan in 47.8% (33/69) patients (31—further surgeries, 2—referred for EBRT).
Haslerud et al, 2016 [33]	Meta-analysis	17 studies (905 patients with suspected recurrent or metastatic differentiated thyroid cancer after previous ablative therapy including total thyroidectomy)	FDG PET/CT	NA	Histology, cytology, follow-up	**Recurrence** Pooled Sens: 80.2% Pooled Spec: 75.5% AUC: 0.844	NA	NA
Marcus et al, 2015 [34]	Retrospective	202 patients who completed primary treatment (differentiated thyroid cancer)	FDG PET/CT	Clinical assessment	Clinical and imaging follow-up	NA	NA	PET/CT identified recurrence or metastasis in 50.0% (25/50) of scans without prior clinical suspicion and ruled out recurrence or metastasis in 36.8% (102/277) of scans with prior clinical suspicion.
Pathak et al, 2016 [35]	Prospective	47 patients; 50 thyroid nodules (follicular/Hurthle cell neoplasm)	FDG PET/CT	US, FNAC	Histopathology	**Diagnosis** Sens: 89% Spec: 35% PPV: 46% NPV: 85% Accuracy: 56%	NA	NA
Merten et al, 2016 [36]	Retrospective	51 patients (cytologically defined indeterminate	FDG PET/CT	NA	Pathology	**Malignancy** Sens: 71% Spec: 41% PPV: 16%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
		thyroid nodules)				NPV: 90%		
Abadi et al, 2016 [37]	Retrospective	58 patients with a solitary neck cyst	FDG PET/CT	NA	Biopsy, histopathology, clinical follow-up	**Differentiate between benign and malignant cystic lesions** Sens: 95% Spec: 61% PPV: 56% NPV: 96% Accuracy: 72%	NA	NA
Wei et al, 2016 [38]	Meta-analysis	17 studies (957 patients with nasopharyngeal carcinoma)	FDG PET or PET/CT	SPECT, MRI	Histology, clinical and imaging follow-up	**Local residual or recurrent disease** Pooled Sens: 90% Pooled Spec: 93%* Pooled +LR: 8.90 Pooled –LR: 0.15 Pooled DOR: 73.27* AUC: 0.952 Q test: 0.894	**Local residual or recurrent disease** ***SPECT*** Pooled Sens: 85% Pooled Spec: 81% Pooled +LR: 7.21 Pooled –LR: 0.22 Pooled DOR: 78.69 AUC: 0.955 Q test: 0.898 ***MRI*** Pooled Sens: 77% Pooled Spec: 76%* Pooled DOR: 12.09* AUC: 0.848 Q test: 0.780	NA
Chen et al, 2016 [39]	Meta-analysis	23 studies (2413 patients with nasopharyngeal carcinoma)	FDG PET/CT	CT, MRI	Histopathology, clinical and imaging follow-up	**T-stage** Pooled Sens: 85% Pooled Spec: 91% Pooled DOR: 42.94 Q test: 0.8673 **N-stage** Pooled Sens: 88% Pooled Spec: 95% Pooled DOR: 93.88 Q test: 0.9153 **M-stage** Pooled Sens: 82% Pooled Spec: 98% Pooled DOR: 176.62 Q test: 0.9002	**T-stage** ***CT*** Pooled Sens: 84% Pooled Spec: 80% Pooled DOR: 6.32 Q test: 0.7215 ***MRI*** Pooled Sens: 95% Pooled Spec: 76% Pooled DOR: 86.85 Q test: 0.9213 **N-stage** ***CT*** Pooled Sens: 92% Pooled Spec: 93% Pooled DOR: 93.81 Q test: 0.8872 ***MRI*** Pooled Sens: 88% Pooled Spec: 95% Pooled DOR: 93.68	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
							Q test: 0.9153 **M-stage** ***CT*** Pooled Sens: 80% Pooled Spec: 93% Pooled DOR: 42.62 ***MRI*** Pooled Sens: 53% Pooled Spec: 99% Pooled DOR: 95.99	
Ryu et al, 2016 [40]	Prospective	248 patients (newly diagnosed head and neck squamous cell carcinoma)	FDG PET/CT	Physical and endoscopic examinations, CeCT and/or MRI of the head and neck, CT of the chest, flexible oesophagogastroduodenoscopy	Histopathology, serial imaging and clinical follow-up, multidisciplinary team	**Staging** Accuracy: 87.1%*	**Staging** Accuracy: 82.0%*	PET/CT downstaged 2.0% (5/248) and upstaged 8.5% (21/248) of patients. PET/CT staging led to management changes in 15.7% (39/248) of patients (12—change in planned treatment modality or purpose, 9—change in radiation field and/or dose, 18—change in surgical extent).
Xi et al, 2015 [41]	Meta-analysis	12 studies (1431 patients with head and neck squamous cell carcinoma)	FDG PET/CT	NA	Histology, follow-up	**Lung malignancy** Pooled Sens: 85% Pooled Spec: 98% Pooled +LR: 52.0 Pooled –LR: 0.15 Pooled DOR: 335 AUC: 0.99	NA	NA
Lee et al, 2015 [42]	Prospective	186 patients who underwent preoperative evaluation (head and neck squamous cell carcinoma)	FDG PET/CT	CeCT	Histopathology	**Extranodal extension** Sens: 79.2% Spec: 74.4%* PPV: 40.9% NPV: 94.1% Accuracy: 75.3%*	**Extranodal extension** Sens: 72.9% Spec: 92.1%* PPV: 67.3% NPV: 93.8% Accuracy: 88.6%*	NA
Nishimura et al, 2016 [43]	Retrospective	235 patients undergoing chemoradiotherapy (lymph node-positive squamous cell carcinoma of the head and neck region)	FDG PET or PET/CT	US, CT and/or MRI	Pathology, clinical and imaging follow-up	**Response assessment** Sens: 51.7% Spec: 97.9% PPV: 78.9% NPV: 93.0% Accuracy: 91.7%	**Response assessment** ***US*** Sens: 89.7% Spec: 72.5% PPV: 33.3% NPV: 97.9% Accuracy: 74.8% ***CT and/or MRI*** Sens: 66.7% Spec: 73.8%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
							PPV: 27.6% NPV: 93.7% Accuracy: 72.8%	
Cheung et al, 2016 [44]	Meta-analysis	27 studies (1195 patients with residual or recurrent head and neck squamous cell carcinoma after treatment with radiotherapy or chemoradiotherapy)	FDG PET or PET/CT	NA	Histopathology, clinical and imaging follow-up	**Residual and/or recurrent disease** ***Local*** Pooled Sens: 86.2% Pooled Spec: 82.3% Pooled PPV: 52.7% Pooled NPV: 96.3% Pooled DOR: 32.93 AUC: 0.91 Q test: 0.85 ***Nodal*** Pooled Sens: 72.3% Pooled Spec: 88.3% Pooled PPV: 72.3% Pooled NPV: 88.3% Pooled DOR: 22.84 AUC: 0.86 Q test: 0.80 ***Distant*** Pooled Sens: 84.6% Pooled Spec: 94.9% Pooled PPV: 84.6% Pooled NPV: 94.9% Pooled DOR: 81.47 AUC: 0.98 Q test: 0.93 ***All sites*** Pooled Sens: 81.6% Pooled Spec: 86.3% Pooled PPV: 81.6% Pooled NPV: 86.3% Pooled DOR: 33.60 AUC: 0.93 Q test: 0.86	NA	NA
Kim et al, 2016 [45]	Prospective	278 patients who underwent curative surgery or definitive radiotherapy/chemoradiotherapy (head and neck squamous cell carcinoma)	FDG PET/CT (post-treatment surveillance)	Physical examination, endoscopy, CeCT/MRI of the head and neck, chest CeCT	Histopathology, imaging and clinical follow-up	**Recurrence or persistent disease (patient-based)** AUC:0.975* **Local recurrence (examination-based)** Sens: 100%* Spec: 96.7% PPV: 60.4% NPV: 100%	**Recurrence or persistent disease (patient-based)** ***CeCT/MRI*** AUC:0.789* **Local recurrence (examination-based)** ***CeCT/MRI*** Sens: 72.4%*	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
						Accuracy: 96.9% **Regional recurrence (examination-based)** Sens: 97.3%* Spec: 97.7% PPV: 73.5% NPV: 99.8% Accuracy: 97.7% **Distant recurrence (examination-based)** Sens: 100%* Spec: 99.0% PPV: 81.8% NPV: 100% Accuracy: 99.0%* ***Second primary cancer* (examination-based)** Sens: 75.0% Spec: 99.7% PPV: 60.0% NPV: 99.8% Accuracy: 99.5%	Spec: 97.1% PPV: 55.3% NPV: 98.6% Accuracy: 95.9% **Regional recurrence (examination-based)** ***CeCT/MRI*** Sens: 81.1%* Spec: 97.4% PPV: 66.7% NPV: 98.8% Accuracy: 96.4% **Distant recurrence (examination-based)** ***Chest CeCT*** Sens: 74.1%* Spec: 98.3% PPV: 66.7% NPV: 98.8% Accuracy: 97.2%* ***Second primary cancer* (examination-based)** ***CeCT/MRI and chest CeCT*** Sens: 50.0% Spec: 100% PPV: 100% NPV: 99.7% Accuracy: 99.7%	
Hematologic Cancer								
Ciammella et al, 2016 [46]	Retrospective	165 patients treated with ABVD followed by involved field radiotherapy (early stage HL)	FDG PET/CT (interim PET performed after two cycles and end of chemotherapy PET after 3-4	NA	Follow-up	NA	NA	The 5-year PFS rate of interim-PET negative patients (98%) was significantly (p=0.0014) higher than that of interim-PET positive patients (84%). The 5-year PFS and OS rates were also significantly (p≤0.0001) higher for patients with negative end-of-treatment

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
			cycles)					PET (97% and 98%, respectively) than for patients with positive end-of-treatment PET (78% and 83%, respectively).
Zinzani et al, 2016 [47]	Prospective	512 patients treated with ABVD and underwent interim-PET evaluation after 2 cycles (newly diagnosed advanced-stage HL)	FDG PET/CT (PET-negative patients proceeded to four more cycles of ABVD, PET-positive patients received an early IGEV followed by ABMT)	NA	Follow-up	NA	NA	The 2-year PFS for interim-PET negative patients was 81% (95% CI: 76% to 84%) while the 2-year PFS for interim-PET positive patients was 76% (95% CI: 66% to 84%).
de Oliveira Costa et al, 2016 [48]	Prospective	147 patients treated with R-CHOP-21 (de-novo DLBCL)	FDG PET/CT (interim-PET performed after 2 cycles)	Neck, chest, abdomen, and pelvis CT	Follow-up	NA	NA	PET/CT changed the Ann Arbor staging in 28.7% (40/139) of patients (23 upstaged, 17 downstaged). The OS rates at 48 months were significantly better for interim-PET negative patients (89.3%) than for interim-PET positive patients (77.5%) (p=0.04). The PFS were 87.7% and 81.2%, respectively (p=0.44).
Soydal et al, 2016 [49]	Retrospective	54 patients who underwent pretreatment PET/CT for staging (histopathological confirmation of DLBCL)	FDG PET/CT	BMB	Histopathology	**Bone marrow involvement** Sens: 100% Spec: 96% PPV: 75% NPV: 100% Accuracy: 96%	NA	NA
Taghipour et al, 2016 [50]	Retrospective	204 patients; 560 follow-up PET/CT scans	FDG PET/CT	NA	Histopathology	NA	NA	PET/CT suggested recurrence in 12.4% (48/388) of scans obtained

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
		after primary treatment completion (biopsy-proven NHL)						without prior clinical suspicion and changed the management after 8.3% (32/388) of scans (29—no treatment to new treatment, 2—change in treatment, 1—treatment stopped). PET/CT ruled out malignancy in 16.3% (28/172) of scans obtained with clinical suspicion and changed the management after 37.8% (65/172) of scans (59—no treatment to new treatment, 5—change in treatment, 1—treatment stopped).
Melanoma								
Gellen et al, 2015 [51]	Retrospective	97 patients; 148 PET/CT scans (cutaneous malignant melanoma)	FDG PET/CT	NA	Histopathology, clinical and imaging follow-up	**Restaging** ***Stage I/II*** Sens: 90.9% Spec: 91.4% Accuracy: 91.3% ***Resected stage III*** Sens: 100% Spec: 88.2% Accuracy: 92.5% ***Unresectable stage III/IV*** Sens: 100% Spec: 80% Accuracy: 96.2%	NA	PET/CT result influenced the clinical management of 28.4% of patients.
Mena et al, 2016 [52]	Retrospective	71 patients; 246 fourth or subsequent follow-up PET/CT scans (biopsy-proven melanoma)	FDG PET/CT	Clinical assessment	Clinical follow-up	NA	NA	PET/CT identified recurrence or metastasis in 6.5% (8/123) of scans obtained without prior clinical suspicion and changed the treatment management in 4.1% (5/123) of scans (4—new treatment started, 1—change in treatment regimen). PET/CT ruled out malignancy in 28.5% (35/123) of scans obtained with prior clinical suspicion or for secondary

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
								therapy assessment and changed the treatment management in 29.3% (36/123) of scans (2—new treatment started, 33—change in treatment modality, 1—treatment discontinued).
Non-FDG Tracers								
^{11}C/^{18}F-Choline								
Simone et al, 2015 [53]	Prospective	146 patients with PSA levels between 0.2 and 1 ng/ml and negative conventional imaging following radical prostatectomy (prostate cancer)	^{18}F-choline PET/CT	DRE, TRUS	Histology, clinical and imaging follow-up	**Biochemical recurrence** Sens: 78.9% Spec: 76.9% PPV: 97.2% NPV: 26.3% Accuracy: 78.7%	NA	NA
Colombie et al, 2015 [54]	Retrospective	172 patients (biochemical recurrent prostate cancer after negative or equivocal conventional imaging)	^{18}F-choline PET/CT	Bone scan, CT, MRI	Clinical follow-up	NA	NA	^{18}F-choline PET/CT led to a change in the treatment plan in 43.6% (75/172) of patients (7—androgen deprivation therapy to active surveillance or EBRT, 4—curative to palliative, 28—palliative to a different treatment, 1—curative to a different treatment, 35—palliative to curative).
Nanni et al, 2016 [55]	Prospective	89 patients treated with radical prostatectomy (suspected recurrent prostate cancer)	^{11}C-choline PET/CT	NA	Pathology, imaging and clinical follow-up	**Relapse** Sens: 32% Spec: 40% PPV: 90% NPV: 3% Accuracy: 32%	NA	NA
^{68}Ga-DOTA-NOC								
Haidar et al, 2016 [56]	Retrospective	445 patients (neuroendocrine tumours)	^{68}Ga-DOTA-NOC PET/CT	NA	Histopathology, clinical and imaging follow-up	**Diagnosis** Sens: 90.0% Spec: 96.2% PPV: 90.0% NPV: 96.2% AUC: 0.931	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
						Follow-up Sens: 90.5% Spec: 100% PPV: 100% NPV: 77.8% AUC: 0.952 **Search for primary** Sens: 88.9% Spec: NA PPV: 100% NPV: NA AUC: NA **Staging** Sens: 84.4% Spec: 100% PPV: 100% NPV: 61.1% AUC: 0.922		
^{18}F-FLT								
Nakajo et al, 2016 [57]	Prospective	17 patients who underwent surgery of the primary lesion and regional nodes (newly diagnosed gastric cancer)	^{18}F-FLT PET/CT	FDG PET/CT	Pathology	**Lymph node metastasis (node-based)** Sens: 31.0% Spec: 100% PPV: 100% NPV: 89.2% Accuracy: 89.7%	**Lymph node metastasis (node-based)** Sens: 44.8% Spec: 98.7% PPV: 86.7% NPV: 91.1% Accuracy: 90.8%	NA
Nakajo et al, 2016 [58]	Prospective	15 patients (newly diagnosed pancreatic cancer)	^{18}F-FLT PET/CT	FDG PET/CT	Pathology, clinical and imaging follow-up	**Nodal metastases** Sens: 63.6% Spec: 100% PPV: 100% NPV: 50.0% Accuracy: 73.3% **Distant metastases** Sens: 50.0% Spec: 100% PPV: 100% NPV: 75.0% Accuracy: 80.0%	**Nodal metastases** Sens: 63.6% Spec: 100% PPV: 100% NPV: 50.0% Accuracy: 73.3% **Distant metastases** Sens: 100% Spec: 88.9% PPV: 85.7% NPV: 100% Accuracy: 93.3%	NA
^{18}F-FET								
Dunet et al, 2016 [59]	Meta-analysis	5 studies (119 patients with isolated brain lesion)	^{18}F-FET PET or PET/CT	FDG PET or PET/CT	Histology	**Diagnosis of brain tumour** Pooled Sens: 94% Pooled Spec: 88% Pooled +LR: 8.1 Pooled –LR: 0.07	**Diagnosis of brain tumour** Pooled Sens: 38% Pooled Spec: 86% Pooled +LR: 2.7 Pooled –LR: 0.72	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
						Pooled DOR: 113 AUC: 0.96 **Diagnosis of glioma** Pooled Sens: 92% Pooled Spec: 62% Pooled +LR: 2.4 Pooled –LR: 0.13 Pooled DOR: 18 AUC: 0.89	Pooled DOR: 4 AUC: 0.40 **Diagnosis of glioma** Pooled Sens: 35% Pooled Spec: 65% Pooled +LR: 1.0 Pooled –LR: 1.0 Pooled DOR: 1.0 AUC: 0.60	
^{18}F-FACBC								
Ren et al, 2016 [60]	Meta-analysis	6 studies (251 patients with prostate carcinoma)	^{18}F-FACBC PET/CT	NA	Histology, follow-up	**Recurrence** Pooled Sens: 87% Pooled Spec: 66% AUC: 0.93	NA	NA
Odewole et al, 2016 [61]	Retrospective	53 patients with a negative bone scan (suspected recurrent prostate carcinoma)	^{18}F-FACBC PET/CT	CT, bone scan	Histology, imaging and clinical follow-up, consensus	**Prostatic/bed recurrence** Sens: 77.8%* Spec: 54.6% PPV: 73.7%* NPV: 60.0%* Accuracy: 65.5%* **Extraprostatic recurrence** Sens: 56.3%* Spec: 100% PPV: 100% NPV: 58.8% Accuracy: 73.1%	**Prostatic/bed recurrence** Sens: 16.7%* Spec: 81.8% PPV: 60.0%* NPV: 37.5%* Accuracy: 17.2%* **Extraprostatic recurrence** Sens: 18.8%* Spec: 100% PPV: 100% NPV: 43.5% Accuracy: 50.0%	NA
Nanni et al, 2016 [55]	Prospective	89 patients treated with radical prostatectomy (suspected recurrent prostate cancer)	^{18}F-FACBC PET/CT	NA	Pathology, imaging and clinical follow-up	**Relapse** Sens: 37% Spec: 67% PPV: 97% NPV: 4% Accuracy: 38%	NA	NA
Bach-Gansmo et al, 2016 [62]	Retrospective	136 patients; 143 scans (suspected biochemical recurrence after primary surgery or radiotherapy for prostate cancer)	^{18}F-FACBC PET/CT	NA	Histology	**Recurrence (region-based)** ***Prostate/Bed*** Sens: 88.1% Spec: 32.6% PPV: 71.8% NPV: 58.3% ***Extra-prostatic*** PPV: 92.3% **(lesion-based)** Sens: 62.7%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
						Spec: 69.9% PPV: 62.2% NPV: 70.4% **(patient-based)** Sens: 90.7% Spec: 40.0% PPV: 82.4% NPV: 58.3%		
Akin-Akintayo et al, 2016 [63]	RCT	42 patients with no evidence of extrapelvic metastasis on bone scan, CT, or MRI (PSA failure after radical prostatectomy for prostate cancer)	^{18}F-FACBC PET/CT	Clinical history, pathology findings, PSA trajectory, CT, MRI, bone scan	Consensus	NA	NA	As a result of ^{18}F-FACBC PET/CT findings, radiotherapy management decisions were changed in 40.5% (17/42) patients (15—change in radiotherapy field, 2—radiotherapy decisions withdrawn).
^{68}Ga-PSMA								
Maurer et al, 2016 [64]	Retrospective	130 patients underwent staging before radical prostatectomy and template pelvic lymph node dissection (intermediate to high risk prostate cancer)	^{68}Ga-PSMA PET/CT	MRI or CT	Histopathology	**Lymph node metastasis (patient-based)** Sens: 65.9% Spec: 98.9% PPV: 96.4% NPV: 86.3% Accuracy: 88.5% AUC: 0.835* **(template-based)** Sens: 43.9% Spec: 85.4% PPV: 58.1% NPV: 76.8% Accuracy: 72.3% AUC: 0.877*	**Lymph node metastasis (patient-based)** Sens: 73.5% Spec: 99.2% PPV: 94.5% NPV: 95.2% Accuracy: 95.1% AUC: 0.691* **(template-based)** Sens: 28.2% Spec: 97.1% PPV: 64.7% NPV: 87.7% Accuracy: 86.1% AUC: 0.704*	NA
Rhee et al, 2016 [65]	Prospective	20 patients who were deemed suitable for retropubic radical prostatectomy (localized prostate cancer)	^{68}Ga-PSMA-HBED-CC PET/CT	Multiparametric MRI	Histopathology	**Primary tumour foci (region-based)** Sens: 49% Spec: 95% PPV: 85% NPV: 78% +LR: 10.52 -LR: 0.54 **(lesion-based)** Sens: 28% PPV: 91%	**Primary tumour foci (region-based)** Sens: 44% Spec: 94% PPV: 81% NPV: 76% +LR: 7.77 -LR: 0.6 **(lesion-based)** Sens: 30%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
							PPV: 81%	
Shakespeare, 2015 [66]	Retrospective	54 patients with either inconclusive conventional staging, high clinical suspicion despite negative or equivocal imaging, or being considered for radiotherapy to oligometastatic disease (prostate cancer)	^{68}Ga-PSMA PET/CT	CT, bone scan, MRI	Consensus	NA	NA	Radiotherapy or hormone therapy management was changed in 53.7% (29/54) of patients due to ^{68}Ga-PSMA PET/CT findings.
Kabasakal et al, 2016 [67]	Retrospective	50 patients with increasing PSA levels (<5 ng/ml) and/or a suspicion of recurrence after conventional imaging (prostate cancer)	^{68}Ga-PSMA-HBED-CC PET/CT	CT, MRI, bone scan	Histopathology, consensus reading of all imaging modalities, clinical and imaging follow-up	**Recurrence** Sens: 76.5% Spec: 91.7% PPV: 96.3% NPV: 57.9%	NA	NA
Albisinni et al, 2016 [68]	Retrospective	131 patients (biochemical recurrence or persistent PSA after treatment with curative intent)	^{68}Ga-PSMA PET/CT	NA	Multidisciplinary oncology committee	NA	NA	^{68}Ga-PSMA PET/CT results modified the treatment strategy of 75.6% (99/131) of patients (63—avoided androgen deprivation therapy, 22—avoided salvage radiotherapy, 14—other change in therapy).
^{18}F-Fluoride/^{18}F-NaF								
Le et al, 2016 [69]	Prospective	93 patients (biopsy-confirmed nasopharyngeal carcinoma)	^{18}F-fluoride PET/CT	MRI	Imaging follow-up	**Skull-base invasion** Sens: 94.2% Spec: 90.2% Accuracy: 92.5%	**Skull-base invasion** Sens: 88.5% Spec: 87.8% Accuracy: 88.2%	NA
Abikhzer et al, 2016 [70]	Prospective	41 patients (newly diagnosed stage III or IV breast cancer or	^{18}F-fluoride PET/CT	WB SPECT	Biopsy, clinical and imaging follow-up	**Bone metastases (patient-based)** Sens: 100% Spec: 85% PPV: 88%	**Bone metastases (patient-based)** Sens: 90% Spec: 95% PPV: 95%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
		suspected recurrent disease)				NPV: 100% **(lesion-based)** Sens: 95%* Spec: 96% PPV: 89% NPV: 98%	NPV: 90% **(lesion-based)** Sens: 63%* Spec: 97% PPV: 89% NPV: 87%	
Jambor et al, 2016 [71]	Prospective	53 patients with high risk of bone metastases after mastectomy/prostatectomy and/or external radiotherapy (26 breast cancer, 27 prostate cancer)	^{18}F-NaF PET/CT	Bone scintigraphy, SPECT, SPECT/CT, WB DW-MRI	Consensus reading of all imaging modalities, clinical and imaging follow-up, laboratory results	**Bone metastases (patient-based)** Sens: 95% Spec: 97% Accuracy: 96% AUC: 0.96 **(region-based)** Sens: 93%* Spec: 99%* Accuracy: 98% AUC: 0.96* **(lesion-based)** Sens: 94%* Spec: 96%* Accuracy: 95% AUC:0.95*	**Bone metastases (patient-based)** ***DW-MRI*** Sens: 100% Spec: 97% Accuracy: 98% AUC: 99% **(region-based)** ***Bone scintigraphy*** Sens: 62%* Spec: 98% Accuracy: 90% AUC: 0.80* ***SPECT*** Sens: 74%* Spec: 94%* Accuracy: 89% AUC: 0.83* ***SPECT/CT*** Sens: 85% Spec: 99% Accuracy: 96% AUC: 0.92 ***DW-MRI*** Sens: 91% Spec: 99% Accuracy: 97% AUC: 0.95 **(lesion-based)** ***Bone scintigraphy*** Sens: 54%* Spec: 88%* Accuracy: 65% AUC: 0.71* ***SPECT*** Sens: 71%* Spec: 79%* Accuracy: 74% AUC: 0.75* ***SPECT/CT*** Sens: 81%*	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
							Spec: 96% Accuracy: 85% AUC: 0.88* ***DW-MRI*** Sens: 95% Spec: 95% Accuracy: 95% AUC: 0.95	
Rao et al, 2016 [72]	Retrospective	181 patients (169 NSCLC, 12 SCLC)	^{18}F-NaF PET/CT	^{99m}Tc-MDP SPECT	Biopsy, imaging follow-up	**Bone metastases (patient-based)** Sens: 100%* Spec: 99.2%* PPV: 98.0% NPV: 100% Accuracy: 99.4% **(lesion-based)** Sens: 100%* Spec: 98.9%* PPV: 99.9% NPV: 100% Accuracy: 99.9%	**Bone metastases (patient-based)** Sens: 89.3%* Spec: 91.0%* PPV: 83.3% NPV: 94.4% Accuracy: 90.4 **(lesion-based)** Sens: 95.8%* Spec: 80.8%* PPV: 94.7% NPV: 84.3% Accuracy: 92.5%	NA
NSCLC								
Nomori et al, 2015 [73]	Prospective	77 patients; 87 nodules (NSCLC)	FDG PET/CT	DW-MRI	Histology	**Pulmonary malignancy** Sens: 71%* Spec: 81%	**Pulmonary malignancies** Sens: 86%* Spec: 90%	NA
Kaseda et al, 2016 [74]	Retrospective	388 patients staged by preoperative PET/CT (surgically resected NSCLC)	FDG PET/CT	CT	Histopathology	**Hilar and mediastinal lymph node metastases** Sens: 47.4% Spec: 91.0% PPV: 56.3% NPV: 87.7% Accuracy: 82.5%	NA	NA
Reddy et al, 2016 [75]	Retrospective	200 patients treated with definitive radiotherapy and absence of recurrence within the initial 6 months (stage III NSCLC)	FDG PET/CT-surveillance	CT-based surveillance	Follow-up	NA	NA	There were no significant differences in OS (HR=1.2; p=0.34), EFS (HR=0.90; p=0.60), LRFS (HR=1.10; p=0.71), or DMFS (HR=0.76; p=0.32) between the PET/CT-based and CT-based surveillance strategies.
Pancreatic Cancer								
Gu and Liu, 2016 [76]	Prospective	60 patients (focal pancreatic	FDG PET/CT	CA 19-9	Biopsy, pathology, clinical follow-	**Differentiating pancreatic carcinoma from**	**Differentiating pancreatic carcinoma from**	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
		lesions)			up	**chronic mass-forming pancreatitis** Sens: 95% Spec: 60% Accuracy: 83.3%	**chronic mass-forming pancreatitis** Sens: 87.5% Spec: 60% Accuracy: 78.3%	
Sanchez-Bueno et al, 2016 [77]	Prospective	139 patients who underwent pancreatic resection with curative intent (pancreatic cancer)	FDG PET/CT	MDCT	Intraoperative findings, pathology	**Preoperative staging** ***SUV_{max} of 2.5*** Sen: 77.7% ***TUR with cut-off point of 1.33*** Sens: 94.9%	**Preoperative staging** Sens: 75.5%	NA
Sarcoma								
Park et al, 2016 [78]	Retrospective	152 patients who were treated with definitive surgery on primary tumour (soft tissue sarcoma)	FDG PET/CT	MRI	Histology, clinical and imaging follow-up	**Locoregional recurrence** Sens: 95.0% Spec: 95.5% PPV: 76.0% NPV: 99.2% Accuracy: 95.4% AUC: 0.952	**Locoregional recurrence** Sens: 90.0% Spec: 97.7% PPV: 85.7% NPV: 98.5% Accuracy: 96.7% AUC: 0.939	NA
Etchebehere et al, 2016 [79]	Meta-analysis	4 studies (348 patients with suspicion of soft tissue and bone lesions)	FDG PET/CT	NA	Histopathology, follow-up	**Diagnosis of musculoskeletal soft tissue tumours** Pooled Sens: 91% Pooled Spec: 85% Pooled PPV: 91% Pooled NPV: 83% Pooled Accuracy: 89% AUC: 0.95	NA	NA
Unknown Primary								
Riaz et al, 2016 [80]	Retrospective	82 patients (carcinoma of unknown primary syndrome)	FDG PET/CT	NA	Histopathology	**Primary site** Sens: 80% Spec: 74% PPV: 88.7% NPV: 59% Accuracy: 78%	NA	PET/CT upstaged 27% and downstaged 11% of patients.
Yu et al, 2016 [81]	Retrospective	449 patients (biopsy-proven malignant metastases where the primary could not be confirmed using standard	FDG PET/CT	Physical examination, routine serum tumour marker test, chest X-ray, CT, MRI, mammography, cervical, abdominal and	Biopsy, imaging follow-up	NA	NA	PET/CT located the primary sites of 25.6% (115/449) of patients. The treatment plans of 29.0% (130/449) of patients required modification as a result of PET/CT.

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Accuracy (PET)	Diagnostic Accuracy (Conventional)	Change in Patient Management
		methods)		breast US, endoscopy				
Various Sites								
Taghipour et al, 2016 [82]	Retrospective	433 patients; 1659 fourth or subsequent follow-up PET/CT scans after completion of primary treatment (92 breast cancer, 77 NHL, 41 HL, 70 CRC, 69 melanoma, 84 lung cancer)	FDG PET/CT	NA	Consensus	NA	NA	Fourth or subsequent follow-up PET/CT resulted in a change in management in 23.3% (386/1659) of the scans.

Abbreviations: +LR: positive likelihood ratio; -LR: negative likelihood ratio; ^{11}C-choline: carbon-11 choline; ^{18}F-choline: fluorine-18 choline; ^{18}F-FLT: fluorine-18 2',3'-dideoxy-3'-fluoro-2-thiothymidine; ^{68}Ga-DOTA-NOC: gallium-68-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-1-Nal3-octreotide; ^{68}Ga-PSMA: gallium-68-labeled prostate-specific membrane antigen ligand with chelator HBED-CC; ^{99m}Tc: technetium-99m; ^{131}I: iodine-131; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine combination chemotherapy; AUC: area under the curve; CA19-9: cancer antigen 19-9; CEA: carcinoembryonic antigen; CeCT: contrast-enhanced computed tomography; CI: confidence interval; CRC: colorectal cancer; CRN: colorectal neoplasia; CT: computed tomography; DLBCL: diffuse large B-cell lymphoma; DMFS: distant metastasis-free survival; DOR: diagnostic odds ratio; DW-MRI: diffusion-weighted magnetic resonance imaging; EBRT: external beam radiotherapy; EFS: event-free survival; EUS: endoscopic ultrasonography; FDG: fluorodeoxyglucose; FIGO: Federation of Gynecology and Obstetrics; FNAC: fine-needle aspiration cytology; GI: gastrointestinal; HL: Hodgkin lymphoma; HR: hazard ratio; LRFS: locoregional recurrence free; MDCT: multiple detector computed tomography; MDP: methylene diphosphonate; MRI: magnetic resonance imaging; NA: not applicable/not available; NHL: non-Hodgkin lymphoma; NPV: negative predictive value; NSCLC: non-small cell lung cancer; OR: odds ratio; OS: overall survival; PET: positron emission tomography; PFS: progression-free survival; PPV: positive predictive value; PSA: prostate specific antigen; Q test: Cochran Q statistic; R-CHOP: rituximab-cyclophosphamide-hydroxydoxorubicin-oncovin-prednisone; RCT: randomized controlled trial; SCLC: small cell lung cancer; Sens: sensitivity; Spec: specificity; SPECT: single photon emission computed tomography; SUV: standardized uptake value; Tg: thyroglobulin; US: ultrasound

*$p<0.05$