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PET Six-Month Monitoring Report 2010-2

Evidence from Primary Studies and Systematic Reviews and Recommendations from Clinical Practice Guidelines July to December 2010

Amidu Raifu and the PEBC Disease Site Group Reviewers

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

Report Date: April 15, 2011

The complete PET 6-Month Monitoring Report consists of a Summary and a Full Report

For further information about this report, please contact:

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SUMMARY

Question

What is the role of positron emission tomography (PET) in the clinical management of patients with cancer, 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, or safety recurrence, safety outcomes (e.g., avoidance of unnecessary surgery), and change in clinical management.

Target Population

The target population for this report is adult patients with suspected or diagnosed cancer(s) (The cancer is not limited to those cancers with approved or Ontario Health Insurance (OHIP) insured services).

Methods

MEDLINE and EMBASE were systematically searched for full articles and abstracts published between July 1 and December 31, 2010 for evidence from primary studies and systematic reviews. The search strategies used are available in Appendix 1 and 2, respectively. As all of 2010 had been searched for clinical practice guidelines in the previous six-month monitoring report, no search for these documents was conducted for this report.

Results

Twenty-three primary studies and seven systematic reviews were extracted from the search. Ten of the primary studies are prospective cohort studies, and 13 are retrospective studies.

Funding

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

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FULL REPORT

QUESTION

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- Diagnosis and staging?
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INTRODUCTION

In 2010, the Ontario Positron Emission Tomography (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 cancer patients. The PEBC recommended that a regular monitoring program be implemented, with a systematic review of recent evidence conducted every six months. The Committee approved this proposal, and this report is the second of what will be a series of six-month monitoring reports. This report is a high-level but brief summary of the identified evidence and not a detailed evaluation of its quality and relevance.

METHODS

Literature Search Strategy

MEDLINE and EMBASE were systematically searched for full articles and abstracts published between July 1 and December 31, 2010 for evidence from primary studies and systematic reviews. No search was conducted for clinical practice guidelines. The search strategies used are available in Appendix 1 and 2, respectively. All the clinical practice guidelines published in 2010 were included in the previous six-month report.

Inclusion Criteria for Clinical Practice Guidelines

Any clinical practice guideline that contained recommendations for PET were to be included.

Inclusion Criteria for Primary Studies

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

1. Studied the use of flurodeoxy-glucose (FDG) PET in cancer in humans
2. Published as a full article in a peer review journal
3. Reported evidence related to change in patient clinical management, or clinical outcomes
4. Used a suitable reference standard (pathological and clinical follow-up) when appropriate
5. Were one of the following (1):
    - Randomized controlled trial (RCT)
    - Quasi-randomized controlled trial (Q-RCT)
    - Non-randomized controlled trial (NRCT)
    - Historically controlled trial (HCT)
    - Controlled before and after study (CBA)

- Prospective cohort study (PCS)
- Nested case-control study (NCC)
- Case-control study (CC)
- Retrospective study (RCS)

6. Included 12 or more patients for prospective study or 50 or more patients for retrospective study with the cancer of interest

Inclusion Criteria for systematic reviews

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

Exclusion Criteria

1. Pediatric studies
2. Letters and editorials.
3. Studies of non-FDG PET

RESULTS

Literature Search Results

Primary Studies and Systematic Reviews

Of the 23 primary studies that met the inclusion criteria, 10 are prospective cohort studies, and 13 are retrospective. Their summarized evidence is presented in Appendix 3. Seven systematic reviews (1-7) met the inclusion criteria. Each of these seven reviews conducted a meta-analysis to pool the results from the selected studies.

Non-Small Cell Lung Cancer

The Paesmans et al (5) systematic review that was an update of a systematic review and meta-analysis published in 2008 analyzed 21 studies. The review aim was to examine the possible prognostic value of FDG PET for non-small cell lung cancer patient survival. The results of the updated systematic review showed a poor prognostic value for high standardized uptake value (SUV) compared to low SUV. The overall hazard ratio (HR) was 2.08 (95% CI, 1.69 to 2.56). The individual HR for each of the included studies ranges from 0.21 to 1.80.

Solid Extracerebral Tumours

The systematic review by Quarles van Ufford et al (7) was based on the treatment response of solid extracerebral tumours. Nineteen observational studies were included, with an average overall histopathologic response rate of 0.47, a median of 0.50 and ranging from 0.17 to 0.88. The relative change in FDG PET uptake was the strongest indicator for the tumour response ($p<0.0001$). A baseline FDG PET was not a significant factor, but the interaction with a relative change in FDG PET uptake was significant ($p< 0.001$).

Esophageal Cancer

The Ngamruengphong et al (4) systematic review based on esophageal cancer included 22 studies in total for analysis. Seven of the studies used endoscopic ultrasonography (EUS), and 15 used FDG PET. The accuracy of the two imaging modalities were compared with a summary receiver operating characteristic (SROC). The sensitivity of EUS and FDG PET ranged from 20% to 100% and 42% to 100%, respectively, and specificity ranged from 36% to 100% and 27% to 100%, respectively. The corresponding areas under the curve (AUC) were 0.86 (95% CI, 0.77 to 0.96) and 0.80 (95% CI, 0.72, 0.89) for EUS and FDG PET, respectively (p=0.37). The overall diagnostic accuracy for the assessment of the response to adjuvant therapy in esophageal cancer patients was similar.

Thyroid Carcinoma

The Ma et al (3) systematic review reported on the effects of thyroid-stimulating hormone (TSH) stimulation on FDG PET uptake in differentiated thyroid carcinoma (DTC) with thyroglobulin-positive and scan-negative metastases. Seven prospective RCTs were included in the review. The overall odds ratio was 2.45 (95% CI. 1.23 to 4.90) for the comparison of PET true-positive patients during TSH stimulation. The overall odds ratio for the comparison of PET sensitivity for the number of detected lesions observed during TSH stimulation was 4.92 (95% CI, 2.70 to 8.95). The overall mean difference for the comparison of the mean SUVmax in the PET detected lesions observed during TSH stimulation was 0.02 (95% CI, 0.45 to 0.41).

Cervical Cancer

Choi et al (1) reviewed the diagnostic performance of FDG PET in detecting metastatic lymph nodes in cervical cancer and included 41 studies in the systematic review. The summarized sensitivity and specificity of PET were 82% and 95%, respectively, compared to computerized tomography (CT) (50% and 92%, respectively) and magnetic resonance imaging (MRI) (56% and 91%, respectively). The PET AUC was significantly higher than that of MRI ((0.9641 versus [vs.] 0.8270, respectively; p<0.001). The sensitivity of PET and CT (in region- or node-based analysis were higher than that of MRI (54% and 52%; p<0.02 vs. 38%; p<0.001, respectively).

Colorectal Cancer

The systematic review by Floriani et al (2) reviewed the diagnostic performance of FDG PET in detecting liver metastases from colorectal cancer and included 25 primary studies. FDG PET sensitivity and specificity was higher than that of ultrasonography (US), CT, and MRI (PET; 93.8% and 98.7%, respectively; US, 63.0% and 97.6%, respectively; CT, 74.8% and 95.6%, respectively; and MRI, 81.1% and (97.2%, respectively). The sensitivity on a per-lesion basis was 86.0%, 86.3%, 82.6% and 86.3%, respectively.

Breast Cancer

Peare et al (6) reviewed the diagnostic performance of FDG PET in detecting axillary lymph node status in breast cancer. The range of the sensitivity for FDG PET was 20 to 100% and specificity was 65% to 100%. The estimated AUC from the ROC curve was 0.95 (95% CI, 0.91 to 0.97) based on the included 25 studies.

PEBC Disease Site Group Reviews

- **Esophageal Cancer**:
  PET Recommendation Report 4: PET Imaging in Esophageal Cancer (http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=43137)
  Reviewer: Dr. Rebecca Wong, Gastrointestinal Cancer Disease Site Group (GI DSG)
  Last updated: November 30, 2010
  Recommendations:
  - For the staging workup of patients with esophageal cancer who are potential candidates for curative therapy, PET is recommended to improve the accuracy of M staging.
  - A recommendation cannot be made for or against the use of PET (post or neoadjuvant therapy) for the purpose of predicting the response to neoadjuvant therapy, because of insufficient evidence.
  - A recommendation cannot be made for or against the use of PET for the evaluation of suspected recurrence, because of insufficient evidence.

  Monitoring report findings

  The January 28, 2011 monitoring report identified one prospective cohort study, Jingu et al (8). In this study, 20 patients with squamous cell carcinoma (locoregional recurrence only after curative surgery) who were offered "curative" doses of chemoradiotherapy (CRT) and who had FDG PET performed less than two weeks before CRT were eligible. The authors used the median value as the cut-off point to divide patients into two groups (low and high) for the maximum SUV (SUVmax) before CRT, SUVmax post-CRT (<7 days following completion of CRT) and SUV percent change (pre- and post-CRT). The results were evaluated against cause-specific survival, local control, and overall survival at one and three years post-treatment. Univariant analysis was conducted for the three SUV parameters, age, (≤63 vs. ≥63), ECOG PS (0 vs. 1), and baseline sum longest diameter <4.5 cm vs. ≥4.5 cm). For cause-specific survival, an SUVmax less than or equal to 2.4 post-CRT (p=0.033) was statistically significant for predicting outcome. For local control, an SUVmax greater than or equal to 2.4 post-CRT (p = 0.01) and an SUV percentage change (>68.5%) were significant (p = 0.04).

  Reviewer's comments

  This study did not address any of the three indications for the use of FDG PET, and therefore does not alter our existing recommendations.

  This study is the first study to address the role of FDG PET in predicting for a response to CRT in local regional recurrence but the patient population is too small to serve as a basis for a recommendation in this area.

- **Colorectal Cancer:**
  Reviewer: Dr. Kelvin Chan, GI DSG

  New systematic review

  NCCN guidelines version 2, Engestom et al (38) does not recommend the routine use of PET for general surveillance, baseline imaging, or follow-up. The use of preoperative PET-and CT scan at baseline is recommended only if prior anatomic imaging indicates the presence of potentially surgically curable M1 disease.

A systematic review by Floriani et al (2) examined 25 studies and concluded that the sensitivity and specificity of PET scan are higher than those for US, CT, and MRI in the detection of liver metastasis from colorectal cancer.

New evidence

Glazer et al (9) suggested that PET within four weeks of chemotherapy is not useful for the evaluation of CRC liver metastasis because of the high rate of false-negative results due to metabolic inhibition caused by the chemotherapeutic agents.

Conclusion

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

- **Melanoma:**

Reviewer: Dr. Teresa Petrella and Dr. Frances Wright, Melanoma DSG

National Comprehensive Cancer Network (NCCN) guideline publications (Coit et al (39))

Work-up and use of PET scans (NCCN): The NCCN recommendations (39) were against the use of PET scanning or routine cross-sectional imaging (CT, MRI) in the work-up for patients with localized (node-negative) melanoma. The recommendation was that the cross-sectional imaging should only be utilized in a work-up setting to investigate specific signs and symptoms. Coit et al (39) also reported a low yield of screening CTs or PET scans for patients with stage III melanoma. Consequently, the NCCN left the use of such imaging to the discretion of the treating physician, apart from the setting of inguinofemoral lymphadenopathy. If inguinofemoral lymphadenopathy existed, a pelvic CT was suggested to rule out pelvic or retroperitoneal lymphadenopathy. In stage IV melanoma, a CT chest, abdominal/pelvic CT with or without PET, and/or head MRI should be considered.

Follow-up and use of PET scans (NCCN)

Coit et al (39) suggest that, for stage IIB-IV melanomas, a chest x-ray, CT, MRI, and/or PET/CT every six to 12 months could be considered to screen for recurrent or metastatic disease, at the discretion of the physician, for the first five years after treatment. However, this course was not strongly recommended as there are low-yield false positives and risks of cumulative radiation exposure.

Other evidence

Jimenez-Requena et al (10): The goal of the Jimenez-Requena et al meta-analysis (10) was to evaluate the accuracy of FDG PET in staging and restaging of cutaneous melanoma. The authors reviewed 431 potentially relevant articles published between 2000 and 2006, and 24 were selected for the meta-analysis. Eight studies were included in the regional staging analysis, 13 studies were included in the detection of distant metastases, and three studies were included in both analyses. FDG PET was found not to be useful in the evaluation of regional metastases as it cannot detect microscopic disease. The authors suggested, however, that FDG PET could be useful in the detection of distant metastases.

Conclusions

The NCCN guidelines and the meta-analysis do not support a change in the current recommendations. Given that the previous recommendations include studies up to June 2008, and the meta-analysis includes studies up to 2006, this review does not support a

change to the present recommendations of PET use for staging and isolated metastases. There is no new data that would suggest the use of PET for routine surveillance or for the detection of microscopic disease.

- **Pancreatic Cancer:**

New evidence

There was a retrospective study (level 3 evidence) conducted by Izuishi et al (11) at a single institution that was designed to compare the usefulness of PET scan in comparison to multi-detector CT scan (MD-CT) in diagnosing pancreatic cancer, determining operability, and detecting metastases.

One hundred three patients were diagnosed with pancreatic cancer, with similar detection rates of pancreatic cancer for MD-CT (89%) and FDG PET (91%). From the MD-CT findings, 38 patients were judged as operable and 65 inoperable. Among the inoperable patients, noncurative factors (metastasis to the liver, peritoneum, remote lymph nodes, bones, and other organs and major arterial invasion) were detected by MD-CT and/or FDG PET. Detection rates of liver metastasis and arterial invasion by FDG PET were significantly inferior to those of MD-CT (neither was detected by FDG PET alone). Remote lymph nodes and bone metastasis were detected more frequently by FDG PET alone compared to MD-CT; however, MD-CT indicated other noncurative factors in these patients. The 65 patients deemed inoperable could be diagnosed as inoperable without FDG PET. Therefore, there was no change in management based on the addition of FDG PET.

There was a possible correlation between the SUV and the maximum tumour diameter (Pearson's correlation coefficient $r=0.347$; $p<0.001$). However, the SUV in the main tumour did not indicate the ability to undergo resection ($p=0.064$).

Therefore, FDG PET did not add clinically useful information in terms of diagnosis or in determining operability beyond the information provided by the MD-CT. Although FDG PET did detect more remote lymph nodes and bone metastases, this information did not impact on the decision of operability since those patients already had other sites of metastatic disease detected by MD-CT, thereby rendering them inoperable. The authors' conclusion was that FDG PET is not a suitable imaging modality for either diagnosis or preoperative treatment in pancreatic cancer patients. Since it is expensive, FDG PET as a routine diagnostic tool in pancreatic cancer patients must be used with caution.

The second paper is a retrospective study (level 3) published from a single institution and designed to analyze the prognostic value of PET for locally advanced pancreatic cancer patients undergoing SBRT. Fifty-five patients with untreated, unresectable locally advanced pancreatic cancer were included. All received a single fraction of 25Gy SBRT sequentially with gemcitabine-based chemotherapy. The pretreatment PET scans were analyzed, and the SUVmax and metabolic tumour burden (MTB) were calculated. Various subgroups were created, including low and high SUVmax, low and high MTB, and clinically relevant subgroups based on low, intermediate, and high SUVmax. Multivariate analysis was performed on these and other subgroups. The results showed there was a statistically significant difference in median survival between low and high SUVmax subgroups (9.8 vs. 15.3m; $p<0.01$), low and high MTB subgroups (10.1 vs. 18.0; $p<0.01$). The clinical SUVmax was an independent predictor for overall survival and progression-free survival.

Assessment

CCO currently does recommend PET for staging if a patient is a candidate for potentially curative surgical resection as determined by conventional staging. The first study challenges the added value of PET to conventional staging and measurement of serum carbohydrate-associated antigen (Ca-) 19-9. However, as with the four studies cited in the original report, it is also a retrospective analysis and does not provide enough evidence to change the recommendation. A prospective trial is definitely warranted to determine the added value of PET scans in this population. The second study introduces the SUVmax as an independent prognostic factor for survival in locally advanced pancreatic cancer, which may be helpful when making clinical decisions regarding the benefit of aggressive treatment balanced with the toxicities, but this study would not change the current recommendations for PET scans.

- **Breast Cancer:**
  Reviewer: Dr. Muriel Brackstone, Breast DSG

  Six-month monitoring report 2010-1 (January to June 2010)
  Current Guideline Recommendations for PET Usage in Breast Cancer: The NCCN guideline publications (Ettinger et al (40)) recommendation was against the use of PET scanning for stage 1, stage 2, or stage 3 (T3N1M0) breast cancer, given the high false-negative rates. No mention is made of its use in metastatic breast cancer, but it is not utilized in current clinical practice for this indication.

  Review: Over the period of review in question (January – June 2010), there were three publications identified by the literature search: one RCT, one PCS and one RCS.

  The RCT (Jung et al (12)) provides Level 1 evidence, based on a study evaluating 66 patients receiving neoadjuvant chemotherapy, not to stage patients but to evaluate their response to treatment. In this study, pathological complete response outcomes at surgery were correlated to survival, but this usage is not a usual one for PET. The response by serial PET as measured by SUVs demonstrated that those who responded by PET were significantly correlated to those whose response was evident upon clinical examination. Thus, this study does not support the incorporation of PET scanning into staging or serial treatment response evaluation beyond physical examinations.

  The prospective study (Martoni et al (13)) provides Level 2 evidence, based on a comparative cohort study in 34 patients receiving preoperative chemotherapy with patients divided into those receiving serial PET scanning, to evaluate response to treatment versus standard imaging. The study reports that patients who responded to preoperative chemotherapy were identified by PET if that treatment response was correlated with histopathological response at surgery. However, PET scans did not predict patients who would or would not respond to this treatment (with the exception of those with estrogen-positive tumours, which are known to be correlated inversely with optimal response to preoperative chemotherapy). Therefore, this study does not support the incorporation of PET scanning into staging or serial treatment response evaluation.

  The retrospective study (Aukema et al (14)) provides Level 3 evidence based on a study using 56 patients with locoregional breast cancer recurrence, to see whether addition of PET scanning to traditional imaging aided in the interpretation of resectability. In this study, 48% of these 56 patients had a change in locoregional treatment based on the PET findings. There is no mention about whether this impacted survival or not. The

limitation of this study is its retrospective nature, and that clinical treatment was based on findings prior to validation of the findings, without any mention of impact on overall outcomes such as survival in the PET versus non-PET cohorts.

Conclusions: All three studies identified in the review period (Jan-June 2010) do not support a change in current recommendations for PET usage in breast cancer, and there exists no published data to date to support its use in breast cancer staging, serially in response to treatment, or it its use to predict feasibility of locoregional treatment for disease recurrence.

Six-month monitoring report 2010-2 (July to December 2010)

Review: Over the period of review in question (July - Dec 2010), there were two publications identified by the literature search, one a systematic review/meta-analysis and one an RCS.

The systematic review/meta-analysis (Peare et al (6)) reviewed the diagnostic benefit of FDG PET for detecting axillary lymph nodes in breast cancer patients and reported a wide variability in sensitivity and specificity (20%-100% and 60%-100%, respectively) in a review of 20 studies. The variability in these findings does not support FDG PET use as a diagnostic tool for lymph node staging at present as current methods are more sensitive and specific than is FDG PET, based on this study.

The retrospective study (DeGiorgi et al (15)) (Level 3 evidence) compared the addition of FDG PET to clinical follow-up only as the control standard for diagnosing or predicting disease progression in metastatic patients with bony-only metastases (n=55). Bearing in mind the retrospective nature of the study and the lack of randomization or for controlling for inherent biases, as well as the small sample size, the study suggests that the addition of FDG PET results in significantly better diagnoses of disease progression in bony metastases than does clinical examination alone, with a significant difference in the HR for progression-free survival and overall survival in patients followed by FDG PET. Unfortunately, this study did not do a comparison to current standards for imaging used to assess bony disease progression (bone scan or CT scan) and, therefore, is not a clinically useful comparison. Its limitations in sample size and study design precludes any significant contribution at present.

Conclusions: Both publications above, including the only clinical study on FDG PET in breast cancer during this six-month review period (July – December 2010), do not support a change in current recommendations for PET usage in breast cancer. No data are published to date to support its use in breast cancer staging, serially in response to treatment, or its use to predict the feasibility of locoregional treatment for disease recurrence.

- **Renal Cell Carcinoma and Bladder Cancer**
  Reviewer: Dr. Glenn Bauman, Genitourinary Cancer (GU) DSG

Renal cancer

Rodriguez et al (16), reported on the RCS of 58 patients, stating that PET proved useful in 40% of them for making the decision to change treatment management involving chemotherapy versus immunotherapy. However, the study was published in an obscure journal, and the evidence was low quality. It is not clear whether the management

change is relevant to the current standard of care with tyrosine kinase inhibitors (TKIs). Clearly, renal cell cancer could benefit from a functional test such as PET but, based on this paper, no suggestion will be made to change anything.

Bladder cancer

In the Apolo et al (17) prospective case series of 57 patients, 21% of biopsies were eliminated and 21% of additional imaging was avoided due to PET. In 19% of patients, organ-confined treatment was changed to metastatic treatment, in 6% surveillance was changed to treatment, and in 2% local radiotherapy was changed to chemotherapy. Overall, 68% of patients had a change in management based on PET results. The overall sensitivity and specificity were 87% and 88%, respectively, using either biopsy or serial imaging as the gold standard.

This study seems to be a solid prospective case series suggesting a significant clinical benefit for PET in staging bladder cancer. Systemic relapse is a very real problem in bladder cancer, and morbidities of therapies (i.e., cystectomy and neo or adjuvant chemotherapy) are significant such that a better systemic staging could have a significant impact on quality of life if it allows for a more rational selection of therapy. This case series suggests that PET has sensitivity and specificity similar to other cancers, where used routinely, and with similar challenges (i.e., lung cancer). It should be feasible to mount an RCT of +/- PET prior to definitive therapy for localized bladder cancer (i.e., similar to the lung cancer trials prior to x-ray therapy and pre-surgery). Perhaps the Committee should be advocating for this site to be evaluated in this way (or added to the registry to allow the collection of more data).

Reviews not completed

- All Gynecology
- All Hematology
- All Head and Neck
- Gastric, Anal, and Hepatocellular Cancer and Carcinoma

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Appendix 1. MEDLINE search strategy.

1. Tomography, Emission-Computed/ or (positron adj emission adj tomography).ti,ab. or PET.ti,ab. or PET-FDG.ti,ab. or Fluorodeoxyglucose F18/ or 18f fluorodeoxyglucose.ti,ab. or 18f fluorodeoxyglucose.ti,ab. or 18fdg.ti,ab. or 2-fluoro-2-deoxy-d-glucose.ti,ab. or 2-fluoro-2-deoxyglucose.ti,ab. or 18f-fdg.ti,ab. or fluorine-18-flourodeoxyglucose.ti,ab. or fluorine-18-fluorodeoxyglucose.ti,ab. or flourine-18-fluorodeoxyglucose.ti,ab. or flourine-18-flourodeoxyglucose.ti,ab. or fluorine-18-fluordeoxyglucose.ti,ab. or positron emission tomography/ or PET-CT.ti,ab. or PET$CT.ti,ab.
2. deoxyglucose/ or deoxyglucose.ti,ab. or desoxyglucose.ti,ab. or desoxy-glucose.ti,ab. or desoxy-d-glucose.ti,ab. or deoxy-d-glucose.ti,ab. or 2deoxyglucose.ti,ab. or 2deoxy-d-glucose.ti,ab. or fluorodeoxyglucose.ti,ab. or fluorodesoxyglucose.ti,ab. or fludeoxyglucose.ti,ab. or fluordeoxyglucose.ti,ab. or fluodeoxyglucose.ti,ab. or fluordesoxyglucose.ti,ab. or 18fluorodeoxyglucose.ti,ab. or 18fluorodesoxyglucose.ti,ab. or fdg$.ti,ab. or 18fdg$.ti,ab. or 18f-dg$.ti,ab.
3. (fluor or 2fluor$ or fluoro or flouro or fluorodeoxy or fludeoxy or flourodeoxy or fluorine or 18f or 18flu$ or 18fluo$).ti,ab.
4. glucose.ti,ab.
5. (pet or petscan$ or pet ct).ti,ab.
6. Tomography, Emission-Computed/
7. emission.ti,ab.
8. (tomograph or tomographs or tomographic$ or tomogrpahy or tomographies).ti,ab.
9. 7 and 8
10. 5 or 6 or 9
11. 3 and 4
12. 2 or 11
13. 10 and 12
14. exp neoplasm/ or neoplasm staging/ or cancer$.ti,ab. or tumor$.ti,ab. or tumour$.ti,ab. or carcinoma$.ti,ab. or neoplasm$.ti,ab. or staging.ti,ab. or metastas$.ti,ab. or metastatic.ti,ab. or exp neoplasm metastasis/ or exp neoplastic processes/ or neoplastic process$.ti,ab. or adenocarcinoma$.ti,ab.
15. 1 and 14
16. 13 and 14
17. 15 or 16
18. limit 17 to (human and english language and yr="2010")
19. (comment or editorial or letter or case reports).pt.
20. 18 not 19
21. (integrative research review$ or research integration or (methodologic$ adj10 review$) or (methodologic$ adj10 overview$) or (quantitativ$ adj10 review$) or (quantitativ$ adj10 overview$) or (quantitativ$ adj10 synthes$) or (systematic adj10 review$) or (systematic adj10 overview$) or (metaanal or meta anal$)).ti,ab. or meta-analysis/
22. (review-tutorial or review-academic or review).pt. or (pooling or pooled analys$ or mantel heanszel$).ti,ab.
23. (peto$ or der simonian or dersimonian or fixed effect$).ti,ab.
24. 21 or 22
25. 20 and 24
26. 20 not 24
27. (conference or conference proceeding or conference proceeding$ or conference paper or conference paper$ or discussion or discussion$ or in brief or invited comment or invited comment$).ti,ab.
28. 25 not 27
29. 26 not 27
30. (201007: or 201008: or 201009: or 201010: or 201011: or "201012").ed.
31. 28 and 30
32. 29 and 30

Appendix 2. EMBASE search strategy.

1. Tomography, Emission-Computed/ or (positron adj emission adj tomography).ti,ab. or PET.ti,ab. or PET-FDG.ti,ab. or Fluorodeoxyglucose F18/ or 18f fluorodeoxyglucose.ti,ab. or 18f fluorodeoxyglucose.ti,ab. or 18fdg.ti,ab. or 2-fluoro-2-deoxy-d-glucose.ti,ab. or 2-fluoro-2-deoxyglucose.ti,ab. or 18f-fdg.ti,ab. or fluorine-18-flourodeoxyglucose.ti,ab. or fluorine-18-fluorodeoxyglucose.ti,ab. or flourine-18-fluorodeoxyglucose.ti,ab. or flourine-18-flourodeoxyglucose.ti,ab. or fluorine-18-fluordeoxyglucose.ti,ab. or positron emission tomography/ or PET-CT.ti,ab. or PET$CT.ti,ab.
2. deoxyglucose/ or deoxyglucose.ti,ab. or desoxyglucose.ti,ab. or desoxy-glucose.ti,ab. or desoxy-d-glucose.ti,ab. or deoxy-d-glucose.ti,ab. or 2deoxyglucose.ti,ab. or 2deoxy-d-glucose.ti,ab. or fluorodeoxyglucose.ti,ab. or fluorodesoxyglucose.ti,ab. or fludeoxyglucose.ti,ab. or fluordeoxyglucose.ti,ab. or fluodeoxyglucose.ti,ab. or fluordesoxyglucose.ti,ab. or 18fluorodeoxyglucose.ti,ab. or 18fluorodesoxyglucose.ti,ab. or fdg$.ti,ab. or 18fdg$.ti,ab. or 18f-dg$.ti,ab.
3. (fluor or 2fluor$ or fluoro or flouro or fluorodeoxy or fludeoxy or flourodeoxy or fluorine or 18f or 18flu$ or 18fluo$).ti,ab.
4. glucose.ti,ab.
5. (pet or petscan$ or pet ct).ti,ab.
6. Tomography, Emission-Computed/
7. emission.ti,ab.
8. (tomograph or tomographs or tomographic$ or tomogrpahy or tomographies).ti,ab.
9. 7 and 8
10. 5 or 6 or 9
11. 3 and 4
12. 2 or 11
13. 10 and 12
14. exp neoplasm/ or neoplasm staging/ or cancer$.ti,ab. or tumor$.ti,ab. or tumour$.ti,ab. or carcinoma$.ti,ab. or neoplasm$.ti,ab. or staging.ti,ab. or metastas$.ti,ab. or metastatic.ti,ab. or exp neoplasm metastasis/ or exp neoplastic processes/ or neoplastic process$.ti,ab. or adenocarcinoma$.ti,ab.
15. 1 and 14
16. 13 and 14
17. 15 or 16
18. limit 17 to (human and english language and yr="2010" and em=201027-201052)
19. (comment or editorial or letter or case reports).pt.
20. 18 not 19
21. (integrative research review$ or research integration or (methodologic$ adj10 review$) or (methodologic$ adj10 overview$) or (quantitativ$ adj10 review$) or (quantitativ$ adj10 overview$) or (quantitativ$ adj10 synthes$) or (systematic adj10 review$) or (systematic adj10 overview$) or (metaanal or meta anal$)).ti,ab. or meta-analysis/
22. (review-tutorial or review-academic or review).pt. or (pooling or pooled analys$ or mantel heanszel$).ti,ab.
23. (peto$ or der simonian or dersimonian or fixed effect$).ti,ab.
24. 21 or 22
25. 20 and 24
26. 20 not 24
27. (conference or conference proceeding or conference proceeding$ or conference paper or conference paper$ or discussion or discussion$ or in brief or invited comment or invited comment$).ti,ab.
28. 25 not 27
29. 26 not 27

Appendix 3. Summary of primary studies evidence for PET 6-month monitoring between July to December 2010.

Author, year	Objective	# of pts	PET study type	Reference Test	Compari-son Test	Results	Conclusions of the authors
Bladder cancer							
Apolo et al, 2010 (17)	To investigate the value of FDG PET/CT imaging in the management of patients with advanced bladder cancer.	57	PCS	Histopath	CT, MRI	47 pts out of the 57 pts included in the study were evaluable. Organ-based analysis with 47 evaluable pts: PET/CT: Overall sensitivity=87% (95% CI, 76% to 94%), specificity=88% (95% CI, 78% to 95%). Pt-based analysis: PET/CT scans followed with biopsy (n=22; sensitivity=75%) or follow-up scan (n=25; specificity=84%). Clinical impact analysis: PET/CT results changes the treatment plan in 36 out of 53 pts but further biopsy negated 11 (21%) pts. Changes in clinical management finally occurred in 47% of pts.	FDG PET/CT has excellent sensitivity and specificity in the detection of metastatic bladder cancer and provides additional diagnostic information that enhances clinical management more than CT/MRI alone. FDG PET/CT scans may provide better accuracy in clinical information for directing therapy.
Breast cancer							
De Giorgi et al, 2010 (15)	To compare the predictive significance of 18FDG PET/CT and CTC count in pts with bone metastases from breast cancer treated with standard systemic therapy.	55	RCS	Clinical follow-up	CTC	The mean PFS and OS were 10.5 ± 7.2 month (range, 1.9 to 33.8 month) and 18.1 ± 6.7 month (range, 3.1 to 36.8 month) respectively. PET/CT follow-up assessment for the factor associated with PFS: HR between non-progression and progression group of pts was 7.14 (95% CI, 3.25 to 15.70) with p<0.0001 for both univariate and multivariate analysis. Baseline CTC count associated with PFS: The HR between <5 and ≥5 baseline CTC count is 1.09 (95% CI to 0.59, 2.02) Follow-up CTC count associated with PFS: The HR between <5 and ≥5 follow-up CTC count is 2.02 (95% CI, 1.11 to 3.65) PET/CT follow-up assessment for the factor associated with OS: HR between non-progression and progression group of pts was 3.29 (95% CI, 1.28 to 8.48) for only univariate analysis. Baseline CTC count associated with OS: The HR between <5 and ≥5 baseline CTC count is 1.19 (95% CI, 0.42 to 3.35) Follow-up CTC count associated with OS: The HR between <5 and ≥5 follow-up CTC count is 2.99 (95% CI, 1.16 to 7.75)	To our knowledge, this is the first study to assess the role of 18FDG PET/CT and CTC counts in the therapeutic monitoring of bone metastases in pts with breast cancer. The multivariate analysis indicated that 18FDG PET/CT was the only predictive sign; however, the combination of FDG PET/CT and CTC might be a useful tool to monitor response to therapy in pts without measurable extra-osseous disease, especially in pts with elevated CTC at baseline. The discordance of 18FDG PET/CT and CTC individually and in combination. A prospective study could validate the benefit of these 2 approaches used separately and in combination in determining prognosis, monitoring response, and establishing bone-dominant disease as a tumour response-measurable disease.
Cervical cancer							
Goyal et al, 2010 (18)	To assess the value of PET/CT in the	82	PCS	Histopath	CT	Sensitivity=92.8%, specificity=58.33%, PPV=77.7%, NPV=83.8%.	PET-CT in the primary evaluation of operable cervical cancer can help in the optimal selection of

Author, year	Objective	# of pts	PET study type	Reference Test	Compari-son Test	Results	Conclusions of the authors
	preoperative assessment of pelvic nodes in operable cervical cancer by correlating PET/CT findings with histopathologic findings and to assess its role in avoiding multimodality therapy.					Avoidance of multimodality therapy without PET/CT: Eighty (100%) pts undergoing primary therapy, 24 (30%) requiring adjuvant chemoradiation, and 24 (30%) requiring multimodality therapy. Avoidance of multimodality therapy with PET/CT: Eighteen (22.5%) pts undergoing primary chemoradiation, 62 (77.5%) pts undergoing primary surgery, 10 (12.5%) pts requiring adjuvant chemoradiation, and 10 (12.5%) pts requiring multimodality therapy. There is statistically significant difference in the risk of multimodality therapy for pts with operable cervical cancer using Chi-square test with p<0.01.	pts for surgery such that multimodality treatment with its attendant increase in morbidity is avoided. Cost and availability of PET-CT are expected to limit a wide adoption of this decision-making strategy at present. Future studies that assess long-term treatment-related toxicity in the 2 treatment strategies for operable cervical cancer may further substantiate the conclusions of our study.
Esophageal cancer							
Hyun et al, 2010 (19)	To evaluate the prognostic value of MTV measured by 18 FDG PET in pts with esophageal carcinoma.	151	RCS	Histopath	CT	Median survival time for the 54 (35.8%) surviving pts as the time of analysis was 61 month (range, 34 to 80 months). Median OS time was 37 months (95% CI, 27 to 46 months). Three-year cumulative and 5-year survival rate were 52% and 34% respectively. The independent predictive factors associated with decreased OS were T stage, M stage, and MTV with HR=4.325; p=0.006, 2.009; p=0.007, 1.013; p=0.021. The SUVmax was not a significant factor with HR=0.97; p=0.061. MTV had good predictive performance for OS than SUVmax AUC of 0.798 for MTV and 0.687 for SUVmax through ROC curve.	The present study suggests that MTV as a volumetric parameter of 18F-FDG PET is an important independent prognostic factor for survival in addition to TNM stage, and that MTV is a better predictor of survival than is SUVmax for primary tumour in pts with esophageal carcinoma. A new prognostic stratification based on TNM stage and the volumetric parameter of 18FDG PET may help optimize patient care by providing better prognostic information. Additional prospective studies with a larger numbers of pts are needed to validate the prognostic utility of this promising functional biomarker derived from 18F-FDG PET.
Monjazeb et al, 2010 (20)	To determine 18FDG PET can delineate pts with esophageal cancer who may not benefit from esophagectomy after CRT.	163	RCS	Histopath	CT	The median survival time was 16.6 months and the 2-year survival rate was 39%. Median for FLL had not been reached and median for freedom from distant metastases was 29.7 months. Pts with trimodality had better OS than pts treated with CRT alone. Fourteen pts (25%) among those treated with trimodality achieved a FDG PET complete response after CRT (PET-CR) but not correlated with outcomes. LFF was significantly better in pts achieving PET-CR p<0.01. PET-CR was significant correlated with survival and LFF with HR 9.82 and 14.13 respectively through multivariate analysis.	Pts treated with trimodality therapy found no benefit with PET-CR, likely because FDG PET residual disease was resected. Definitive chemoradiotherapy pts achieving PET-CR had excellent outcomes equivalent to trimodality therapy despite poorer baseline characteristics. Pts who achieve a PET-CR may not benefit from added resection given their excellent outcomes without resection. These results should be validated in a prospective trial of FDG PET–directed therapy for esophageal cancer.
Patnana et al, 2010(21)	To assess whether the outcome of pts with postCRT HSUV is different in pts who underwent surgery	204	RCS	NR	CT, Esopha-goscopy	The median OS time for all pts is 2.85 years (95% CI, 2.43, 4.24 years). The 1-year, 3-year, and 5-year OS rates for all pts are 79.1% (95% CI, 73.5% to 85.1%), 48% (95% CI, 39.5% to 58.4%), 28.2% (95% CI, 17% to 46.6%) Pts with HSUV-NS: Median OS time: 1.22 years (95% CI,	Data from the current study indicate that, after chemoradiation, LGC pts can be divided into 3 subgroups and that the poor prognostic group of pts with HSUV after chemoradiation could be salvaged by surgery. Continued evaluation of PET during

Author, year	Objective	# of pts	PET study type	Reference Test	Compari-son Test	Results	Conclusions of the authors
	compared with those who did not undergo surgery.					1.02 to 2.16), 1-year OS rate: 63.8% (95% CI to 51.3% to 79.2%), 3-year OS rate: 12.3% (95% CI, 2.6% to 57.4%) Pts with HSUV-S: Median OS time= 2.70 years (95% CI, 2.43 to NA), 1-year OS rate: 84.5% (95% CI, 76.4% to 93.4%), 3-year OS rate: 48.2% (95% CI, 33.3% to 69.6%) Pts with LSUV-S: Median OS time= 4.24 years (95% CI, 3.60 to NA), 1-year OS rate: 83.5% (95% CI, 75.4% to 92.5%), 3-year OS rate: 63.2% (51.3% to 77.7%), 5-year OS rate: 38.3% (95% CI, 22.7% to 64.7%) The median EFS time for all pts is 1.69 years (95% CI, 1.32 to 2.55 years). The 1-year, 3-year, and 5-year EFS rates for all pts are 65.7% (95% CI, 59.3% to 72.7%), 37.6% (95% CI to 29.9% to 47.4%), 26.4% (95% CI, 16.4% to 42.4%) Pts with HSUV-NS: Median EFS time= 0.84 year (95% CI, 0.65 to 1.70), 1-year EFS rate: 41.9% (95% CI, 29.9% to 58.8%), 3-year EFS rate: 13.6% (95% CI, 3.1% to 59.8%) Pts with HSUV-S: Median EFS time= 1.69 years (95% CI, 1.51 to NA), 1-year EFS rate: 71.2% (95% CI, 61.5% to 82.5%), 3-year EFS rate: 34.8% (95% CI, 22.2% to 54.5%) Pts with LSUV-S: Median EFS time= 3.54 years (95% CI, 1.67 to NA), 1-year EFS rate: 75.5% (95% CI, 66.3% to 86.0%), 3-year EFS rate: 50.8% (95% CI, 39.2% to 65.9%), 5-year EFS rate: 36.0% (95% CI, 21.8% to 59.4%).	treatment of pts with LGC might provide some insights as to how to optimize complex and morbid treatments for these individuals.
Gastric cancer							
Chihara et al, 2010 (22)	To assess the value of pretreatment PET scan, and to identify potential prognostic factors.	75	RCS	Histopath	CT	The sensitivity of FDG PET in 52 pts in group A was 77% and 100% in 11 pts in group B. OS: The estimated 3-year OS rate was 78% with median follow-up of 32 months. Low haemoglobin (< 12.0g/dL): HR=4.32 (95% CI, 1.58 to 11.8) with p=0.004. Low albumin (< LLN): HR=3.07 (95% CI, 1.07 to 8.80) with p=0.037. Treatment without rituximab: HR=2.70 (95% CI, 1.00 to 7.25) with p=0.049. PFS: The estimated 3-year PFS rate was 70%. Low hemoglobin (<12.0g/dL): HR=3.52 (95% CI, 1.47 to 8.45) with p=0.005. Low albumin (<LLN): HR=2.52 (95% CI, 1.00 to 6.35) with p=0.049. Advanced stage III/IV: HR=2.85 (95% CI, 1.23 to 6.62) with p=0.015.	We showed potential prognostic value of hemoglobin and albumin level in pts with primary gastric DLBCL. Larger-scale studies are needed to validate our findings, and more data is needed to determine the value of pretreatment PET scan in this patient group.
Chung et al,	To evaluate the role	35	PCS	Histopath	CT	The SUVmax of distant metastatic sites was 8.7± 4.4	FDG PET/CT images of metastatic gastric

Author, year	Objective	# of pts	PET study type	Reference Test	Compari-son Test	Results	Conclusions of the authors
2010 (23)	of FDG PET/CT in pts with metastatic gastric adenocarcinoma before palliative chemotherapy to predict prognosis and chemotherapy response.					with range 1.6 to 17.8. The correlation between the SUVmax of distant metastatic sites and that of primary tumours was 0.52 with p=0.001. Chemotherapy response available in 29 out of 35. The overall response rate was 69%. The mean SUVmax of the primary tumour before palliative chemotherapy was 9.1 ± 5.4 in partial response group, 6.5 ± 0.9 in stable disease group, and 8.7 ± 2.1 in progressive disease group. The median survival for all pts was 9.7 months with range 1.6, 22.2 months. Univariate analysis: There is significant difference between the median survival time for the pts with SUVmax of the primary tumour ≤ 8.0 and > 8.0 with p=0.03. No significant difference between the survival time for the pts with SUVmax of distant metastatic sites ≤ 9.0 and > 9.0 with p=0.09. Multivariate analysis: SUVmax of primary tumour > 8.0: RR=2.240 (95% CI, 1.007 to 5.815) with p=0.048. Presence of solid organ metastasis: RR=3.307 (95% CI, 1.258 to 8.695) with p=0.015. ECOG performance status 2/3: RR=4.444 (95% CI, 1.731 to 11.410) with p=0.002.	adenocarcinoma can visualize primary tumours and can also identify distant metastasis of solid organs with a high detection rate. Furthermore, high FDG uptake of primary tumours is associated with poor OS as an independent prognostic factor. However, the role in prediction of chemotherapeutic response is limited. Thus, in newly diagnosed pts with metastatic gastric adenocarcinoma, assessment of tumour FDG uptake provides potentially useful information with regard to patient prognosis.
Head and Neck cancer							
Farrag et al, 2010 (24)	To determine if 18FDG PET uptake assessment during treatment can be used as predictive factor for outcome in head and neck cancer pts treated with radical RT by tomotherapy ± chemotherapy.	43	PCS	Histopath	NR	Median follow-up was 12.7 months (range, 3 to 34.5 months).with 31 out of 43 (72%) pts still living at last follow-up and 25 (58%) pts were free from disease. 2-year OS and DFS were 66% and 52% respectively. There was decrease in the median SUVmax 8.11 (range, 2.41 to 15.13) in PET1 study to 4.03 (range, 1.94 to 7.58) in PET2.	Although the number of pts included in this study was relatively small we conclude that 18F-FDG PET evaluation during treatment is promising and in the future it may help in defining response categories and modifying treatment for non-responders. Our study adds to the very few studies which examined the issue of PET scan during radiotherapy. SUVmax value is more reliable than visual assessment in predicting the treatment outcome.
Kubicek et al, 2010 (25)	To examine the role of FDG PET imaging in altering management and providing prognostic information for head and neck cancer (HNC)	212	RCS	NR	CT	Median follow-up for all pts was 469 days (range, 40 to 1596 days). 119 pts were still alive at last follow-up with median OS and median DFS of 886 days and 726 days respectively. SUV > 8 was statistically significant for a worse survival with p<0.045 based on OS of 669 days and OS of 984 days for pts with SUV < 8. Maximum lymph node SUV was predictive factor for distant failure with p<0.0001 but not for overall or local failure.	FDG PET scanning has good accuracy and predictive value in determining lymph node status. SUV of the tumour mass is prognostic for OS. SUV of the lymph node is prognostic for ECE and also for distant recurrence. Pts with higher lymph node SUVs treated with definitive radiation may warrant higher radiotherapy doses to overcome a greater likelihood of ECE. Nodal SUV may be used to predict pts who would be more likely to benefit from induction chemotherapy.

Author, year	Objective	# of pts	PET study type	Reference Test	Compari-son Test	Results	Conclusions of the authors
Moeller et al, 2010 (26)	To address the potential roles of CT and FDG PET/CT as imaging-based biomarkers for mortality risk in head-and-neck RT pts using survival outcome analysis.	98	PCS	Histopath	CT	Primary tumour: SUVmax for pre-RT for survivor and non-survivor groups of pts was 19.6 and 18.0 respectively, p=0.51. Thus, no significant difference between SUVmax for two pt groups. There was significant difference between SUVmax for post-RT for survivor and non-survivor groups of pts. SUVmax was 4.2 and 7.2 respectively, p<0.01 and the percentage change of 74% and 58% with significant p=0.01 between pre-RT and post-RT. Nodal tumour: SUVmax for the pre-RT for survivor and non-survivor groups of pts was 12.7 and 14.6 respectively, p=0.38. Thus, no significant difference between SUVmax for two groups of pts. There was also no significant difference between SUVmax for post-RT for the survivor and non-survivor groups of pts. SUVmax was 2.4 and 3.1 respectively, p=0.06 and percentage change of 72% and 74% with non-significant p=0.81 between pre-RT and post-RT.	Our findings support the selective use of CT- and FDG PET/CT imaging biomarkers for squamous cell carcinomas of the head and neck (HNSCC) mortality risk assessment, although these conclusions will require independent corroboration. The ability to discriminate high-risk pts into groups differing in disease-specific survival by threefold, if confirmed, could have a major impact on risk stratification for this diagnosis.
Lung cancer							
Grgic et al, 2010 (27)	To determine diagnostic test parameters resulting from different SUV thresholds for differentiation of indeterminable SPN and to assess individual probability of malignancy by considering lesional SUV and pt pre-test probability for malignant disease. Also to investigate prognostic value of SUV for FDG in SPN pts.	140	RCS	Histopath	CT	The median survival time for the pts with benign SPNs was significantly higher than the median survival time for the pts with malignant SPNs (>68 months versus 36 months with p=0.0116). Survival analysis: Pts with SUV < 9.5: 3-year survival rate=62% and median survival time > 75 months Pts with SUV ≥ 9.5: 3-year survival rate=43% and median survival time=20 months. The result showed significant difference between two groups of pts with p=0.0144.	FDG PET allows assessment of the individual risk for malignancy in SPNs by considering tumoral SUV and pre-test probability. Higher FDG uptake in lung cancer as measured by SUV analysis is a prognostic factor. In pts with low FDG uptake in an SPN and increased risk during surgery omission of diagnostic thoracotomy may be warranted.
Lymphoma							
Cerci et al, 2010 (28)	To assess the prognostic value of 18FDG PET after 2 cycles of chemotherapy using	115	PCS	Histopath	CT	The primary end-point is the 3-year EFS. The median follow-up was 36 months with 3-year OS rate was 94.2%. The 3-year EFS rate was 74.2%. Only PET2 was significantly associated with treatment failure. The 3-year EFS rate was 53.4% for pts with PET2 positive	PET2 is an accurate and independent predictor of EFS in HL. A negative interim 18FDG PET result is highly predictive of treatment success in overall HL pts, as well as in subgroups with early or advanced stage disease and with low or high IPS risk.

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	ABVD in Hodgkin lymphoma (HL) pts overall and subgroups of pts with early and advanced stages and with low and high risks according to the IPS.					scans and 90.5% for pts with PET2 negative scans (p<0.001). Pts subgroups: Overall: Sensitivity=72.2% (95% CI, 49% to 88%), Specificity=82.9% (95% CI, 72% to 90%), PPV=53.3% (95% CI, 34% to 71%), NPV=91.8% (95% CI, 82% to 96%). Early stage (I-II): Sensitivity=66.7% (95%CI, 24% to 34%), specificity=86.5% (95% CI, 70% to 94%), PPV=44.4% (95% CI, 15% to 77%), NPV=94.1% (95% CI, 78% to 98%) Advanced stage (III- IV): Sensitivity=75.0% (95% CI, 47% to 91%), specificity=80.0% (95% CI, 64% to 89%), PPV=57.1% (95% CI, 34% to 77%), NPV=90.0% (95% CI, 75% to 96%). Low-risk IPS (0-2): Sensitivity=76.9% (95% CI, 45% to 93%), specificity=83.7% (95% CI, 69% to 92%), PPV=55.6% (95% CI, 31% to 77%), NPV=93.2% (95% CI, 80% to 98%) High-risk IPS (3-7): Sensitivity=66.7% (95% CI, 30% to 90%), specificity=81.8% (95% CI, 63% to 92%), PPV=50.0% (95% CI, 22% to 77%), NPV=90.0% (95% CI, 72% to 97%).	
Petrausch et al, 2010 (29)	To evaluate the impact of 2-[fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography/compute d tomography (FDG–PET/CT) during follow-up of pts with diffuse large B-cell lymphoma (DLBCL) being in complete remission or unconfirmed complete remission after first-line therapy.	75	RCS	Histopath	CT	The median follow-up was 16.5 months (range, 6 to 93 months). Twenty-one (91%) of 23 pts with relapsed were sufficiently follow-up. Median RFS until second relapse was 16 months (range, 1.4 to 99 months). No significant difference in RFS until second relapse for pts with age > 60 years compared with younger pts (HR=0.88 (95% CI, 0.20 to 3.61); p=0.83). Also, no significant difference between clinical signs at time of first relapse and no clinical signs (HR=1.39 (95% CI, 0.13 to 17.51); p=0.74). Risk factor assessment: Stage at diagnosis: HR=1.72 (95% CI, 0.72 to 4.15); p=0.22, residual disease: HR=0.60 (95% CI, 0.22 to 3.85); p=0.31, extranodal disease: HR=1.64 (95% CI, 0.70 to 3.85); p=0.25 were not statistically significant predictors for relapse. Pts with age > 60 years old: HR=2.82 (95% CI, 1.02 to 7.77); p=0.036, pts with symptoms indicative of relapse: HR=4.1 (95% CI, 1.20 to 14.03); p=0.015.	FDG–PET/CT reliably detects recurrent DLBCL after first-line therapy. FDG–PET/CT can be considered during follow-up in high-risk pts for relapse with age <60 years when clinical signs of relapse are present and in pts with age >60 years regardless of clinical symptoms of relapse. However, the routine use of PET/CT during follow-up cannot be recommended until prospective trials have demonstrated a survival benefit for pts followed by PET/CT.
Petrausch et al, 2010(30)	To evaluate the impact of 2-[fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography (FDG-	134	RCS	Histopath	CT	The mean RFS among the pts with recurrence was 26.9 months (range, 4.6 to 191.5 months). The mean follow-up time of pts without recurrence until last negative FDG PET/CT scan was 38.72 months (range, 4.8 to 203 months). Risk factor assessment:	FDG–PET/CT reliably detects recurrent HL after first-line therapy. However, it should only be considered in pts with clinical signs of recurrence at any time point, in pts with morphological residual mass within the first 24 months and in pts with advanced initial stage (greater than IIB) after

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	PET)/computed tomography (CT) during follow-up of pts with Hodgkin's lymphoma (HL).					Single risk factors: Symptoms before follow-up FDG PET/CT (HR=4.886 (95% CI to 2.403 to 9.938); p<0.0001), morphological residual masses seen on CT after the end of treatment (HR=3.362 (95% CI, 1.710 to 6.609); p=0.0005) were the predictors of recurrence. Morphological residual mass after first-line treatment was the only risk factor for relapse Asymptomatic: HR=9.033 (95% CI to 2.418 to 336.700; p=0.0011). Symptomatic: HR=2.4068 (95% CI to 1.1667, 4.9647; p=0.01802.) Multiple risk factors: The significant risk factors were morphological residual mass: HR=3.8387 (95% CI, 1.9158 to 7.6915; p=0.00016), advanced stage: HR=1.9900 (95% CI, 1.0478 to 3.7794; p=0.03644) and symptoms before referral: HR 5.1161 (95% CI, 2.5002 to 10.4688; p<0.0001).	24 months after end of first-line treatment.
Qiao et al, 2010 (31)	To assess the value of 18F-FDG hybrid PET/CT prior to and after ASCT for prediction of PFS in non-Hodgkin lymphoma (NHL).	31	PCS	Histopath	ASCT	Kaplan-Meier results for PFS showed a better clinical outcome for pts with FDG PET negative than those with FDG PET positive both prior and after ASCT. There was significant correlation of FDG PET negative and positive both prior and after ASCT with PFS. Prior to ASCT: FDG PET negative: 1-year PFS rate=88.2% FDG PET positive: 1-year PFS rate=28.6% HR=10.688 (95% CI, 2.181 to 22.531; p=0.001). After ASCT: FDG PET negative: 1-year PFS rate=88.9% FDG PET positive: 1-year PFS rate=23.1% HR=14.030 (95% CI, 2.932 to 31.111; p=0.000)	18F-FDG Hybrid PET/CT imaging has an important prognostic role in the pre- and post-transplantation evaluation of pts with NHL. No obviously additional prognostic value appears to be derived from 18F-FDG imaging performed after ASCT. 18FFDG imaging should be the imaging modality of choice for predicting the outcome of NHL lymphoma scheduled for ASCT.
Thomas et al, 2010 (32)	To assess the role of FDG PET in predicting EFS and OS in pts with DLBCL following primary treatment given with curative intent, with particular attention to the frequency and outcomes of pts with 'indeterminate' FDG PET reports.	125	PCS	Histopath	NR	The median follow-up time for the eligible 125 pts was 35.2 months (range, 3.9 to 66.7 months). There was no significant difference between EFS and OS HR of the eligible pts and those that were excluded were (HR=0.84; p=0.38) and (HR=1.09; p=0.74). Indeterminate group of pts: 2-year and 3-year EFS rate were 80% and 71% respectively. Negative group of pts: 2-year and 3-year EFS rate were 88% and 85% respectively. Indeterminate and negative group: The 3-year OS rates were 88% and 89% respectively Positive group: 3-year OS rate was 48%. 3-year EFS rate across low, low-intermediate, high-intermediate and high risk prognostic categories 84%, 77%, 55%, and 50%, respectively, trend test p=0.002. 3-year OS rate across pre-therapy IPI categories, low, low-intermediate, high-intermediate and high risk	This study confirms the negative predictive value of the FDG PET scan following primary treatment of DLBCL for 3-year EFS. This is the first analysis of indeterminate FDG PET studies in DLBCL, and suggests that these pts have outcomes more similar to those with negative reports than those with positive reports. This study adds to the growing body of evidence that FDG PET cannot replace biopsy in the management of pts with DLBCL. Finally, interpreting the post-therapy FDG PET in the context of the pre-therapy IPI adds further predictive information in pts with de novo DLBCL.

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						prognostic categories 90%, 81%, 72%, and 61% respectively, trend test p=0.004. Positive group of pts: 3-year OS rate across pre-therapy IPI categories, low, low-intermediate, high-intermediate and high-risk prognostic categories were 82%, 44%, 28%, and 0% respectively with trend test p=0.002.	
Non small cell lung cancer							
Burdick et al, 2010 (33)	To determine whether the pre-treatment SUVmax from the staging FDG PET/CT could predict mediastinal failure (MF), distant metastases (DM), and OS in medically inoperable pts treated with SBRT for early-stage non-small cell lung cancer NSCLC.	72	RCS	Histopath	CT	Out of 30 deaths, 13 (43%) died of lung cancer, another 13 (43%) died of known causes of death without evidence of disease, one (3%) died of non-cancer causes of death with evidence of disease and 3 (10%) died of unknown causes. 2-year MF, DM, and OS rates were 10.4%, 30.1%, and 61.3% respectively. PET/CT SUVmax did not predict MF, DM, and OS in the univariate analysis. T1 stage and smoking pack-year are the only predictors of OS in the multivariate analysis with HR=0.331 (95% CI, 0.156 to 0.701; p=0.0039) and 1.015 (95% CI, 1.004 to 1.026; p=0.0084.	Pretreatment PET SUVmax did not predict for MF, DM, or OS in pts treated with SBRT for early-stage NSCLC.
Lee, et al, 2010 (34)	To assess value of tumour response evaluation using combined inter-pretation of 18FDG PET and CT for prediction of clinical outcome & pathologic response in stage III NSCLC pts who underwent neoadju-vant chemotherapy followed by surgery.	44	PCS	Histopath	CT	The overall median postoperative follow-up time was 24.8 months (range, 3.1 to 66.2 months). The median TTR was 12 months (range, 4 to 31 months). The median change in the SUVmax before and after neoadjuvant chemotherapy was a decrease of 45% (range, 100% decrease to 19%). There was no significant difference in the TTR between responder and nonresponder (mean TTR of 42.1 months versus 23.9 months; p=0.19). Group of pts with metabolic responses ≥ 50% reduction in SUVmax had longer TTR then the pts without response (mean TTR=51.7 vs. 22.7 months; p=0.005)	Tumour response evaluation using combined interpretation of FDG PET and CT was more effective than the single interpretation of CT response or PET response alone for the prediction of tumour recurrence and pathologic response in pts with stage III NSCLC who underwent neoadjuvant chemotherapy followed by surgery.
Ovarian cancers							
Bilici et al, 2010 (35)	To evaluate the clinical value of FDG PET/CT in pts with suspected ovarian cancer recurrence as compared with diagnostic CT, and to assess the impact of the results of FDG PET/CT on treatment	60	RCS	Histopath	CT	PET/CT: The overall sensitivity, specificity, PPV, NPV, and accuracy are 95.5%, 93.3%, 97.7%, 87.5, and 95% respectively. CT alone: The overall sensitivity, specificity, PPV, NPV, and accuracy are 55.5%, 66.6%, 83.3%, 33.3%, and 58.3%. There is statistically significant difference in the detection rate between PET/CT and CT alone with p=0.02. The results of the PET/CT changed the management of	Our results confirm that FDG PET/CT is a better modality for post-therapy surveillance for the detection of recurrent ovarian cancer than diagnostic CT imaging in all settings including in pts with an elevated CA-125 level and a normal or abnormal diagnostic CT scan. FDG PET/CT might also be useful for the assessment of treatment response following chemotherapy. Furthermore, our results, together with those in the literature, indicate that integrated FDG PET/CT allows

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	planning.					in 31 (51.6%) pts with 19 (61.2%) pts treated with previous procedure and cancellation of the previously planned procedure in 12 (38.8%) pts.	optimization of the treatment plan and might play an important role in treatment stratification. Future studies will need to address the impact of FDG PET/CT on the survival of pts and clinical patient management in relation to its cost effectiveness.
Pancreatic cancer							
Izuishi et al, 2010 (11)	To compare the usefulness of PET with the glucose analogue 18FDG PET and MD-CT in diagnosing pancreatic cancer and in determining the pts' suitability for surgery.	103	RCS	Histopath	CT	Contribution of FDG PET to the decision of operative indication: There was significant correlation between the SUV and maximum tumour diameter with Pearson correlation coefficient ($r=0.347$, $p<0.001$). By comparing the tumour size in operable pts diagnosed by MD-CT and/or FDG PET, the tumour size was significantly smaller in operable group of pts than inoperable pts. The SUV in the main tumour did not indicate the ability to undergo resection with $p=0.064$.	FDG PET is not a suitable imaging modality for either diagnosis or preoperative treatment in pancreatic cancer pts. Since it is expensive, FDG PET as a routine diagnostic tool in pancreatic cancer pts must be used with caution.
Schellenberg et al, 2010 (36)	To analyzed the prognostic value of PET for locally advanced pancreas cancer pts undergoing SBRT.	55	RCS	Histopath	SBRT	The median follow-up for all pts and the survived pts were 12.7 months (range, 2.8 to 37.7 months) and 24.3 months (range, 15.6 to 27.3 months) respectively. There was significant difference between median survival time for the low and high SUVmax groups (15.3 versus 9.8 months) with $p<0.01$. The median survival time between MTB were 18.0 and 10.1 months with $p<0.01$. Median PFS for low and high MBT were 12.3 and 6.4 respectively with $p=0.06$ Multivariate analysis of all pre-treatment factors showed that clinical SUVmax was the only prognostic factor for OS and PFS with $p=0.01$ and 0.03 respectively.	In locally advanced non-resectable pancreatic cancer, pre-radiation PET scan parameters were prognostic of OS and PFS. PET parameters remained prognostic when controlling for age, presenting CA19-9, and single vs. combination chemotherapy. Both prospective studies evaluating the prognostic value of pre- and post-chemotherapy PET parameters as well as prospective SBRT trials of pancreatic cancer are warranted.
Carcinoma of an unknown primary							
Yapar et al, 2010 (37)	To investigate the value of FDG PET/CT in clarifying the primary site in our pts with HPM or with a high clinical suspicion of malignancy, and the clinical impact of this technique on the management of these pts.	94	PCS	Histopath /Clinical follow-up	CT	There was no statistically significant difference between the mean survival times of the pts PR and those RPU ($p=0.232$). The mean survival time for the PR group was 17.75 ± 2.21 (mean ± SD) and that of RPU group was 16.31 ± 1.95. The mean survival time for the group of pts with disseminated disease was significantly shorter than those with single or no lesion (13.44 ± 1.61 versus 26.67 ± 2.73; $p=0.014$). Within the RPU pt group, the mean survival time of the pts with multiple system involvement on PET/CT was also significantly shorter than those with single and	According to our findings, whole-body FDG PET/CT has to be considered as a useful method in CUP syndrome. In the management of these pts, the method offers several advantages such as (i) identification of the primary tumour in nearly half of the pts, (ii) optimal staging and thereby an opportunity to give a prognosis even when the primary could not be found, and (iii) identification of chemotherapy response. The role of the test seems important, especially in monitoring the chemotherapy response considering the metastatic state in most of these pts. Our preliminary results showed that FDG PET/CT could potentially detect

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						those with no lesion (13.95 ± 1.69), (20.69 ± 2.33), and 26.67 ± 2.73 respectively.	therapeutic efficacy. Pretherapeutic scanning could also be useful in evaluating the response after therapy, in addition to helping in the decision of the therapeutic approach according to the findings with regard to the primary site and metastatic state. These results suggest that FDG PET/CT can be used reliably in an early phase of the diagnostic workup of the pts with CUP syndrome to optimize their management.

Notes: ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; ASCT = autologous stem cell transplantation; AUC = area under curve; CI = confidence interval; CTC = circulating cell tumour; CTR = chemoradiotherapy; CT = computerized tomography; CUP = ; DFS = disease-free survival; EFS = event-free survival; FDG PET = fludeoxy-glucose positron emission tomography; FFL = freedom from local failure; Histopath =- Histopathology; HPM = histologically proven tumour metastasis; HR = hazard ratio; HSUV-NS = high standardized uptake value–no surgery; HSUV-S = high standardized uptake value–surgery; IPI = International Prognostic Index; IPS = International Prognostic Scores; MD = multi-detector; MTB = metabolic tumour burden; MTV = metabolic tumour volume; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; OS = overall survival ; PCS = prospective case studies; PFS = progression-free survival; PPV = positive predictive value; PR = primary/ies reached; pts = patients; HSUV-NS = high standardized uptake value-no surgery; HSUV-S = high standardized uptake value-surgery; LSUV-NS = low standardized uptake value-no surgery; LSUV-S = low standardized uptake value-surgery; RCS = retrospective case studies; RFS = relapse-free survival; RPU = remained primary/ies unknown; RR = relative risk; RT = radiotherapy; SBRT = stereotactic body radiation therapy; SPN(s) = solitary pulmonary nodule(s); SUVmax = maximum standardized uptake value; TTR = time to recurrence; vs. = versus.