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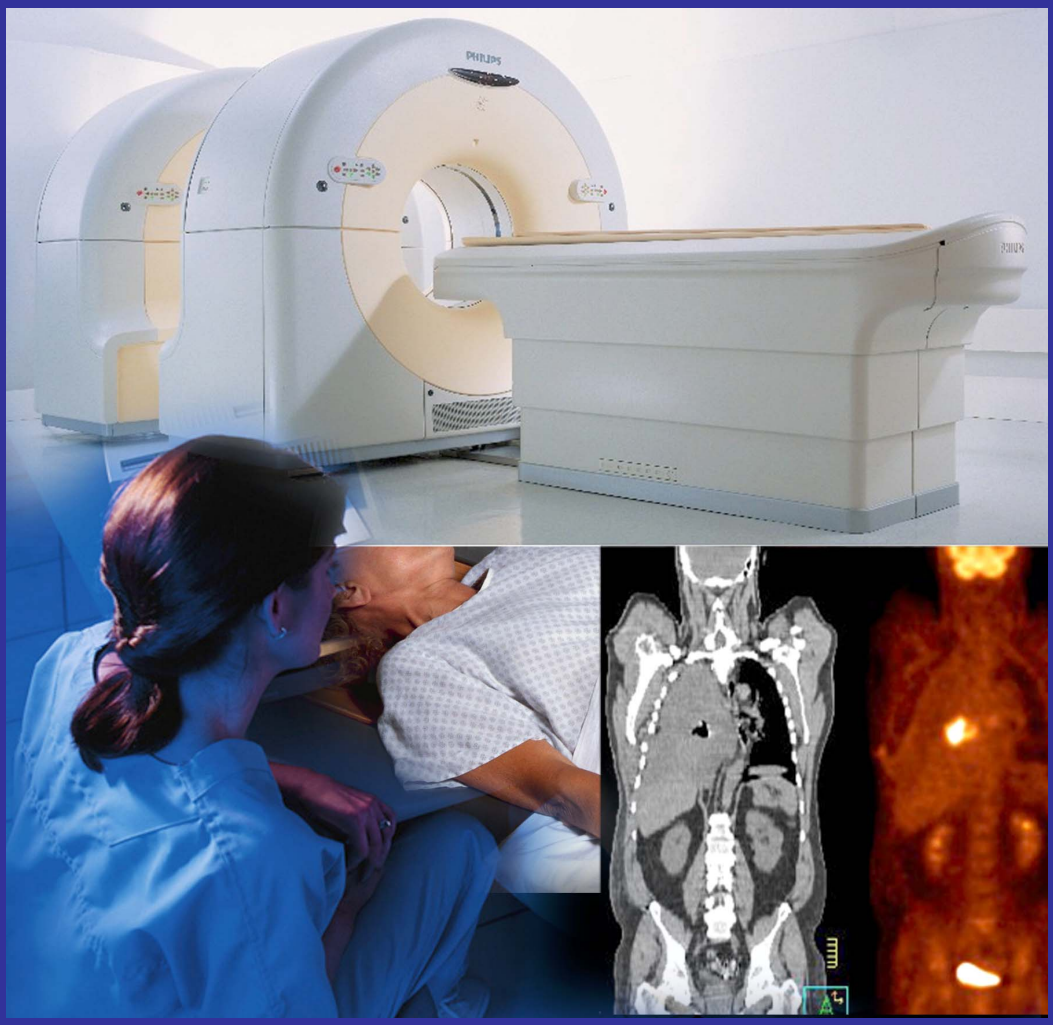
ICES Institute for Clinical Evaluative Sciences

Health Technology Assessment of Positron Emission Tomography (PET) in Oncology - A Systematic Review



ICES Investigative Report

Quarterly Update - January 2004

PET Literature review and assessment of articles:

Last updated January 2004

Our original report, "Health Technology Assessment of Positron Emission Tomography" was published on May 31, 2001. The report presented the results of a systematic review of the peer-reviewed, gray and web-based PET scanning literature up to December 2000 and is also available in the "investigative report" section of our website. Since that time, we have posted regular updates relative to PET scanning. The last update was posted on our website in September 2003.

This current report has been updated to include literature published up to and including January 1, 2004. As in previous reports, the current update focuses exclusively on clinical applications of PET among 6 commonly occurring categories of cancer: carcinoma of the lung, colorectal carcinoma, squamous carcinoma of the head and neck, carcinoma of the breast, malignant lymphoma, and malignant melanoma. The comprehensive results of our reviews are presented below.

If you have any comments or questions please do not hesitate to contact Susan Garfinkel, Research Coordinator, 416-480-4055 ext. 2869. (mailto:susan.garfinkel@ices.on.ca)

New in this report

Response to treatment, following radical radiotherapy or chemoradiotherapy, was assessed using PET and CT in 73 patients with NSCLC. PET was concluded to be superior in treatment response-assessment, compared to CT, and thus a better predictor of survival in these patients.[1]

REVIEW PROCESS AND ABSTRACTION CRITERIA

Abstracts of all peer-reviewed articles were reviewed to determine which articles should be photocopied in their entirety. Those articles with original data were evaluated to determine whether they met the inclusion criteria:

- Studies of PET in the diseases of interest (lung cancer, solitary pulmonary nodules, head and neck cancer, breast cancer, lymphoma or Hodgkin's disease, melanoma, colorectal cancer)
- English language studies reporting primary data, published in a peer-reviewed journal; and
- Studies with > 12 human subjects.

Using a grading scheme used by the VA and NHS Health Technology Assessments (HTA) of PET scanning, diagnostic studies were given a rating from A-D (see Table 1) by two independent reviewers. Disagreements among reviewers were resolved by consensus. It was decided a priori that **grade A and B studies** would be given preferential consideration in this review process.

Table 1. Grading Scheme for Diagnostic Studies

GRADE	CRITERIA
A	Prospective studies with broad generalizability to a variety of patients and no significant flaws in research methods.
B	Prospective studies with a narrower spectrum of generalizability, and with only a few flaws that are well described (and impact on conclusions can be assessed).
C	Studies with several methods flaws (e.g., small sample size (<35) and retrospective)
D	Studies with multiple flaws in methods (e.g., no credible reference standard for diagnosis)

Adapted from National Health Service Health Technology Assessment, 1999. [2]

In addition, the major review articles were hand-searched and back-referenced for additional potentially relevant articles.

1. BREAST CANCER (See Table 1)

1.1 Populations Studied (9 "B" Grade Studies)

a) Pre-operative staging

Rieber et al. [3] compared PET with MR mammography (MRM) in the diagnosis and staging of suspected breast cancer, as confirmed by histological examination. In diagnosis of the primary tumour the sensitivity of PET/MRM was 93/100%. For diagnosis of contralateral tumours, both PET and MRM were 100% sensitive and the specificity of MRM vs. PET was 100 vs. 97.5%.

b) Detection of axillary lymph node metastases

Five studies have compared the results of PET imaging of axillary lymph nodes prior to axillary dissection, with the histological examination of the nodes as the gold standard. Sensitivity ranged from 50% to 94%, specificity from 86% to 100%, positive predictive value 82% to 100%, and negative predictive value from 69% to 95%. [3-7] . PET was 25% sensitive and 97% specific in a more recent study of 70 patients with primary operable breast cancer. The sensitivity of PET was positively related to the tumour load and FDG avidity for the primary tumour.[8]

c) Detection of bone metastases

A study of 34 patients with carcinoma of the breast compared the PET image of the bones to regular radionuclide bone scanning. The area under the receiver-operating characteristic (ROC) curve was 1.00 for PET and 0.82 for bone scanning ($p<0.05$). The PET scan changed the treatment recommendation for 4 of 44 patients, compared to what would have been recommended if only information from the bone scanning was available.[9]

d) Early assessment of response to chemotherapy

A study of 30 patients receiving neoadjuvant or primary chemotherapy for carcinoma of the breast underwent PET evaluation before the first course, and after the second and fifth courses of chemotherapy. Regression of PET uptake in the primary tumour or lymph nodes was related to histological evidence of response to therapy.[10]

1.2 Potential impact of PET on processes of care for breast cancer

These clinical applications appear to provide additional information that may be used in the selection of therapy for carcinoma of the breast. It is unclear if PET would replace the utilization of any currently used assessment procedures.

The practice regarding axillary assessment varies widely at present. Some practitioners perform axillary dissection routinely for most patients with newly diagnosed carcinoma of the breast, whereas others perform it only if a sentinel lymph node biopsy is positive. A sentinel node biopsy consists of injecting the patient's breast cancer with a blue dye and nuclear medicine marker 24 hours before surgery. By the time of surgery the injected material has been taken up by the lymph nodes in the axilla. The surgeon can then identify and biopsy the first lymph node in the axilla, which is examined histologically during the operation. Proponents of this technique

maintain that if this node does not contain metastases, then the axilla need not be dissected. There is no evidence to support the routine use of sentinel lymph node biopsy at present, however, a randomized trial of this approach is now underway. For surgeons routinely performing axillary dissection, PET might reduce the rate of axillary dissection in patients with PET-negative axillary imaging. There has been no comparison of PET imaging of the axilla to sentinel lymph node biopsy.

The diagnosis of bone metastases in newly diagnosed patients and patients being followed after treatment of breast cancer is a major clinical issue. In one study, PET appears to be more effective than radionuclide bone scanning in the detection of bone metastases due to carcinoma of the breast. If PET is used instead of bone scan, this would be a major shift in nuclear medicine practice in breast cancer. It is difficult however to draw definitive conclusions from these study results due to the relatively small number of patients included (34 patients).

Neoadjuvant, or primary chemotherapy prior to surgery and/or radiation therapy, at present is applied chiefly in the setting of locally advanced breast cancer, a small subset of the population of newly diagnosed breast cancer patients. It is unclear if information from PET about a poor prognosis or response to chemotherapy would prompt a change in therapy that would improve clinical outcomes (because of the likelihood in this clinical setting that other therapies would also fail).

2. LUNG CANCER (See Table 2)

2.1 Populations Studied (2 "A" Grade, 19 "B" Grade Studies)

a) Diagnosis of the solitary pulmonary nodule

Four prospective, observational studies have demonstrated the effectiveness of PET in distinguishing malignant from benign solitary pulmonary nodules in the settings where CT guided biopsy has failed to make a definitive diagnosis, or where a CT guided biopsy has been contraindicated. The gold standard has been histological evaluation. Sensitivity ranged from 86% to 100%, specificity from 40% to 90%, positive predictive value from 88% to 95%, and negative predictive value from 55% to 100%.[11-14]

b) Staging of primary carcinoma of the lung / evaluation of mediastinal lymph nodes

Several recent studies have evaluated the effectiveness of PET in the evaluation of mediastinal lymph nodes in proven or suspected cases of carcinoma of the lung. Evaluation of mediastinal lymph nodes is an important component of estimating the extent of carcinoma of the lung, and the information is frequently used to guide decisions about treatment.

Two random control trials have been performed in which subjects were randomized to have preoperative PET or not. In one study by van Tinteren et al., there was a 51% relative reduction in thoracotomy rate as a result of PET(P=0.003).[15] When patients were randomly assigned to receive conventional work-up (CWU) (n=92) versus conventional work-up and PET (n=92), 41% of patients had a futile thoracotomy in the CWU only group whereas 21% had a futile thoracotomy in the CWU and PET group. On the other hand, in an abstract presented by Boyer

et al. there was no observed reduction in thoracotomy rate.[16] A sample of 179 patients were assigned to conventional staging (CS) (n=78) versus CS and PET (n=81) and it was reported that 97.5% of patients received thoracotomy in the CS group, compared with 96.4% in the CS and PET group. It appears that the former study stipulated adherence to entire processes of care based on PET results whereas the latter study did not. The former study is an efficacy study; the latter may be a study of the effectiveness of PET. We must await further report of the Boyer et al. study because it has been published in abstract only.

Eight prospective observational studies have indicated that preoperative or pretherapeutic PET imaging is superior to CT, using histological confirmation or refutation as the gold standard. Sensitivity of PET compared to histology ranged from 61% to 98% (for CT 20% to 72%); specificity of PET ranged from 81% to 100% (for CT 60% to 90%); positive predictive value of PET ranged from 64% to 97% (for CT 30% to 64%); negative predictive value of PET ranged from 89% to 98% (for CT 72% to 87%).[17-24]

In one prospective observational study, tumour-node-metastasis was estimated in fifty patients with proven or suspected non-small-cell lung cancer using PET, CT and integrated PET-CT.[25] Integrated PET-CT improved the diagnostic accuracy, over PET alone, of tumour staging ($p<0.001$), node staging ($p=0.013$) and metastasis staging. Integrated PET-CT provided additional information in 41% of patients.

Two prospective observational studies have failed to find evidence that PET may replace preoperative surgical staging in clinical scenarios where surgical staging is utilized.[26;27]

c) Detection of residual or recurrent carcinoma of the lung

A study of 58 patients who had undergone potentially curative treatment for carcinoma of the lung compared PET to CT as predictors of clinical signs or histologic samples of recurrent carcinoma. The sensitivity was 100% for PET vs. 69% for CT; specificity was 98% for each; positive predictive value 93% vs. 90% and negative predictive value 100% vs. 92%.[28] Reasonable evidence about the clinical importance of this improvement is lacking at present.

d) Detection of bone metastases from primary carcinoma of the lung

A study of 110 patients compared PET to conventional radionuclide bone scanning for the detection of bone metastases. Using clinical and radiological correlation or clinical evolution as the gold standard, the comparison of PET to bone scan demonstrated the following: sensitivity 90% for each; specificity 98% vs. 61%; positive predictive value 90% vs. 35%; and negative predictive value 98% vs. 96%.[29]

e) Detection of malignant pleural effusion

A study of 35 patients with proven lung cancer compared PET and CT scanning to cytology/histology in detecting pleural involvement and in detecting malignant involvement of the pleura and/or pleural effusion. Based on histology or clinical follow-up, 18 patients had evidence of malignant effusion , 16 of which were correctly detected by PET. PET correctly ruled out malignancy in 16 of 17 patients based also on histology or clinical follow-up. The sensitivity, specificity and accuracy of PET was thus reported to be 88.8%, 94.1% and 91.4% respectively.[30]

f) Prediction of survival

Response to treatment, following radical radiotherapy or chemoradiotherapy, was assessed using PET and CT in 73 patients with NSCLC. PET and CT were performed a median of 70 days after completion of radiotherapy, with a 1-day median interval between them. Both CT and PET findings predicted survival at one year. However, compared with CT, PET was concluded to be superior in treatment response-assessment, and thus a better predictor of survival in these patients ($p<0.0001$).[1]

2.2 Potential impact of PET on processes of care for carcinoma of the lung

There is evidence for the efficacy of PET in distinguishing benign from malignant solitary pulmonary nodules (SPN). The use of PET in this context would reduce patient morbidity by reducing the number of unnecessary thoracotomies performed for SPN. There is conflicting evidence from random control trials about whether or not preoperative PET among patients with a diagnosis of lung cancer would reduce the number of unnecessary thoractomies in this setting.[15;16] Possibly, PET may achieve reductions in the rate of unnecessary thoracotomies only if there is strict adherence to guidelines about processes of care for various results of preoperative PET among patients with a diagnosis of lung cancer.

There is evidence for the efficacy of PET in predicting the histological status of mediastinal lymph nodes and in detecting pleural involvement and malignant pleural effusion in patients with carcinoma of the lung, and that PET is more efficacious than CT. Staging and preoperative procedures prior to attempted resection of carcinoma of the lung vary among practitioners. Among those who use mediastinoscopy as a staging procedure, this procedure would be avoidable if PET were available. Among those who do not use mediastinoscopy and take patients with CT negative mediastinal nodes to resection directly, some thoracotomies might be avoided. It is unclear if the utilization of CT would decrease at all if PET were available, because the anatomical information provided by CT (which is better than that provided by PET) might still be needed. No study has been published evaluating the effect of PET upon the frequency of thoracotomy in this setting.

Although recurrent carcinoma of the lung is usually incurable, residual or recurrent carcinoma may be detected most accurately by PET, and would coincidentally provide better assessment of the possibility of bone metastases which frequently accompany residual or recurrent carcinoma. The number of bone scans would likely decrease.

In addition, PET appears to provide important prognostic information about patients with carcinoma of the lung,[31] and might allow radiation therapy for carcinoma of the lung to be designed in a manner which would reduce the amount of normal lung tissue exposed to radiation.[32;33] The role of PET as a predictor of survival in patients with NSCLC has recently been demonstrated. [1]

3. HEAD & NECK CANCER (See Table 3)

3.1 Populations Studied (7 "B" Grade Studies)

a) Detection of metastases from newly diagnosed squamous carcinoma of the head and neck

Brink et al. compared preoperative PET to histology from neck dissections for newly diagnosed squamous carcinoma of the head and neck and reported sensitivity = 71% and specificity =92%.[34] Hannah et al. compared preoperative PET to preoperative CT and to histology in the same scenario and reported PET sensitivity 82% compared to CT 81% and PET specificity 100% compared to 80%.[35] A study of 71 patients compared preoperative PET, CT and MRI (magnetic resonance imaging) for the detection of neck node metastases, with histological ascertainment as the gold standard. PET was superior to CT in terms of sensitivity (87% vs. 65%), specificity (94% vs. 47%), PPV (90% vs. 40%) and NPV (93% vs. 72%), and also performed better than MRI.[36] In an older prospective study of 48 patients, PET had sensitivity (72%) and specificity (99%) similar to CT (67% and 97% respectively).[37] PET may be superior to CT in the pre-treatment evaluation of clinically uninvolved lymph nodes in the neck. No study has examined the likelihood that doctors would use this information to alter therapy or to improve outcomes.

A prospective study of 56 head and neck cancer patients reported that PET of the thorax produced additional information in only 1 patient compared to conventional imaging (evidence of otherwise undetected pulmonary metastasis).[38]

b) Detection of recurrent squamous carcinoma of the head and neck

A study of 44 patients with Stage III or Stage IV head and neck cancer compared follow-up assessment by PET to CT and to clinical examination. Thirty evaluable patients had a complete response to treatment and were followed for signs of recurrence. For the detection of recurrence within 1 year of treatment, PET had a sensitivity of 100% compared to 38% for CT and 44% for clinical examination. All three methods had good to excellent specificity: PET 93%, CT 85%, clinical examination 100%.[39] Another prospective study of 44 patients with suspected recurrence of head and neck cancer, found that PET had sensitivity of 96% and specificity of 61%, which was superior to the combination of CT plus MRI (sensitivity 73%, specificity 50%).[40]

3.2 Potential impact of PET on processes of care for squamous carcinoma of the head and neck

More accurate assessment of cervical lymph node metastases has the potential to reduce the frequency of unnecessary lymph node dissections for patients with cancer of the head and neck. For the evaluation of lymph node metastases, PET appears to have superior specificity and may have superior sensitivity compared to CT scanning. It is unclear if adoption of PET would reduce the utilization of CT or MRI. It is also unclear what changes in treatment and outcomes would be observed if implemented. While there are studies of adequate quality of PET test characteristics compared to CT, squamous carcinomas at various anatomic locations of the head and neck have varying probabilities of lymph node metastases, and there has not been sufficient

examination of which anatomic cancer sites in the head and neck would or would not be most appropriate for PET.

The ability of PET to identify recurrent disease [39;40] seems strong. The routine use of PET to identify recurrent cancer of the head and neck may be appropriate in the following conditions: if conventional methods of diagnosing recurrence are inconclusive and if a recurrence could be cured by subsequent definitive therapy.

4. MALIGNANT LYMPHOMA & HODGKIN'S DISEASE (See Table 4)

4.1 Populations Studied (1 "A" Grade, 4 "B" Grade Studies)

a) Staging of newly diagnosed malignant lymphoma and Hodgkin's disease

The extent of disease, or stage, of Non-Hodgkin's Lymphoma (NHL) or Hodgkin's disease (HD) is a key factor in the choice of therapy. A change in staging assignment can lead to the omission or addition of radiation therapy and can influence decisions regarding the number of chemotherapy cycles needed.

In a prospective study of 44 patients with Hodgkin's disease, changes in stage and treatment recommendation were made for 14% of patients.[41]. Similarly, a study of 42 patients with low grade lymphoma found that if conventional staging (CT and bone marrow biopsy) were replaced by PET scan plus marrow biopsy, 2 patients (5%) would be upstaged, and 3 (7%) would be down-staged. The sensitivity of PET scanning was poor for small lymphocytic lymphoma and for the detection of bone marrow involvement.[42] In contrast, in a series of 50 patients (38 with non-Hodgkin's malignant lymphoma and 12 with Hodgkin's disease) for whom PET was compared to bone marrow biopsy to detect bone marrow involvement, the results for PET were: sensitivity 79%, specificity 76%, positive predictive value 58% and negative predictive value 90%.[43] A study of 56 patients found that PET scans had better positive predictive value than bone scans for the identification of bony involvement of HD and NHL.[44]

The currently available information regarding the utility of PET for staging has significant limitations. Many published studies examining PET for staging of HD and NHL are retrospective, or do not adequately describe how the information provided by PET scan results is incorporated with conventional imaging to determine patients' final stage of disease. Interpretation of published studies examining the impact of PET on assigned stage is difficult because of the technical difficulty in obtaining a credible gold standard (i.e. biopsy proof) to verify that disease exisits in areas of abnormal uptake on PET studies. Moreover, most studies define "conventional imaging" as CT alone, whereas many patients in Ontario will also undergo a gallium scan.

b) Evaluation of response to treatment

After completion of therapy, patients treated for NHL and HD may have residual masses detected on CT at anatomic locations that were involved by lymphoma prior to treatment. It is frequently unclear if the residual masses contain potentially active tumour.

Numerous retrospective studies have examined the ability of PET scanning to predict relapse among lymphoma patients following initial therapy. Although many studies have methodological limitations (most often small numbers of patients), there is virtual unanimity in study results, indicating that patients with persistent abnormal uptake on FDG-PET following initial therapy have significantly worse progression-free survival than those with normal post-treatment PET scans.

Naumann et al. examined the value of PET for the assessment of post-treatment residual masses in 58 lymphoma patients (HD = 43, NHL = 15; 51 patients enrolled prospectively). Among HD patients, PET had a PPV of 25% and NPV of 100% for prediction of recurrence. This PPV is lower than that reported in most retrospective series. Among the small number of NHL patients, progression-free survival was significantly worse in those with abnormal PET scans.[45]

Spaepen et al. reported a prospective study of 70 patients who underwent PET as an early assessment of aggressive non-Hodgkin's lymphoma midway through a course of anthracyline-based chemotherapy. None of 33 cases with persistent abnormality on PET achieved a complete remission whereas 31/37 with a negative PET midway through chemotherapy maintained a continuous complete remission. The difference in overall survival was highly significant $p<0.0001$.[46]

A small (N=24) prospective study found that FDG-PET results also predicted outcome among patients undergoing salvage chemotherapy and autologous stem cell transplant for aggressive NHL.[47]

4.2 Potential impact of PET on processes of care for malignant lymphoma and Hodgkin's disease

We lack evidence about whether the addition of PET to conventional staging investigations would lead to appropriate modifications in treatment for HD or NHL.

Most of the retrospective evidence indicates that an abnormal PET scan following initial therapy is associated with a poor outcome. This conclusion is supported by a recent prospective study indicating that PET midway through anthracycline-based chemotherapy for aggressive NHL clearly distinguishes patients with favourable and unfavourable prognosis. However, it is currently known that gallium scintigraphy, widely available in Ontario, also provides prognostic information in the assessment of response to treatment. Currently there are no data to indicate whether replacing gallium scintigraphy with PET scanning would provide marginally better prognostic information. Also, there are limited data to indicate whether using PET scan results to intensify treatment for poor responders will produce a clinically significant improvement in outcome.

5. MALIGNANT MELANOMA (See Table 5)

5.1 Populations Studied (4 "B" Grade Studies)

a) Staging of newly diagnosed malignant melanoma

A prospective study of newly diagnosed patients with high-risk malignant melanoma (i.e., thickness >1.5 mm or suspected recurrence) compared PET to 'conventional imaging' consisting of radiography, ultrasonography, CT, and MRI. The results for PET compared to 'conventional imaging' were sensitivity, 100% vs. 85%, and specificity 96% vs. 68%. [48] In a prospective study of 38 newly diagnosed melanoma patients, staging PET results were compared with pathology results following dissection of 56 lymph node basins. PET sensitivity was 95%; specificity, 84%; accuracy, 91%; positive predictive value, 92%; and negative predicative value, 89%. PET detected 83% of metastases 6-10mm in size, but only 23% of those <6mm.[49] Reinhardt et al reported a study of 67 cases, among whom the sensitivity of PET for metastases was 91.7%, specificity 97.7%, positive predictive value 95.6% and negative predictive value 95.5%.[50]

b) Follow-up of malignant melanoma

The detection of silent metastases among malignant melanoma patients compared PET to 'routine methods' including clinical examination, radiography, CT, ultrasound and serum profiles of liver enzymes. The results for PET compared to 'routine methods' were sensitivity 97% vs. 62%, and specificity 56% vs. 22%.[51]

5.2 Potential impact of PET on processes of care for malignant melanoma

It appears that PET may have be superior to conventional imaging in the detection of metastatic disease. However, PET is limited in its ability to detect small (5mm) nodal metastases. While the test characteristics of PET in various scenarios of malignant melanoma are favourable, we lack evidence about the nature and magnitude of benefit among these patients.

6. COLORECTAL CANCER (See Table 6)

6.1 Populations Studied (3 "B" Grade Studies)

a) Detection of recurrent/metastatic colorectal carcinoma

Three prospective observational studies of PET imaging of patients with a rising carcino-embryonic antigen serum level after therapy for primary colorectal carcinoma, or with other suspicion for recurrent disease, have compared PET and CT to surgical findings and/or ultimate clinical evaluation of disease. In the detection of hepatic metastases: sensitivity for PET imaging was 93% to 100% (for CT, 87%); specificity for PET imaging was 57% to 98% (for CT, 91%); positive predictive value for PET was 89% to 96% (for CT, 83%); and negative predictive value for PET was 67% to 100% (for CT, 93%). [52-54].

6.2 Potential impact of PET on processes of care for colorectal carcinoma

It is not clear that PET in this context would replace any currently applied investigations; the slightly higher values for PET might slightly reduce the number of unnecessary laparotomies performed in this clinical setting. Ruers et al. 2002 compared PET to conventional imaging and reported that patient care was changed by PET results for 29% of patients.[54]

7. TABLES

Table 1: BREAST CANCER (Updated October 15, 2002)											
Setting	**Grade**	**Author**	**Country**	**Yr**	**Pts**	**Compare**	**Blinded**	**Se / Se (%)**	**Sp / Sp (%)**	**PPV/PPV (%)**	**NPV/NPV (%)**
Axillary lymph node staging	B	Greco[4]	Italy	2001	167	Surgery	Yes	94	86	84	95
Axillary lymph node staging	B	Schirrmeister[5]	Germany	2001	117	Conventional imaging/ Surgery	Yes	79	92	82	79
Axillary lymph node staging	B	Smith [6]	Scotland	1998	50	Histol	Yes	88	97	95	92
Axillary lymph node staging	B	Yutani[7]	Japan	2000	38	Histol	Yes	50	100	100	69
Pre-operative staging	B	Rieber[3]	Germany	2002	42	PET/Histology MRR/Histology	Yes	PT 93/100 Cont 100/100 Nodes 80	Cont 97.5/100 Nodes 95	-	-
Primary operative breast cancer pre-axillary	B	Van der Hoeven[8]	Netherlands	2002	70	SNB or ALND	Yes	25	97	-	-
Bone Metastases	B	Schirrmeister[9]	Germany	1999	34	Bone Scan	Yes	-	-	-	-
Response to Chemotherapy	B	Smith[10]	UK	2000	30	-	Yes	-	-	-	-

Legend: Yr=year published; Pts=number of patients; Compare=Comparison modality; Histol=Histology; Se =Sensitivity; Sp=Specificity; PPV=Positive Predictive Value; NPV=Negative Predictive Value; - =data unavailable;MRM=MR mammography;PT=Primary tumour;Cont=Contralateral ;SNB=sentinal node biopsy;ALND=Axillary Lymph Node Dissection
(For Se/Se, Sp/Sp, PPV/PPV and NPV/NPV: single value refers to PET, subsequent values, if any, refer to comparator)

Table 2: LUNG CANCER (Updated October 15, 2002)											
Setting	**Grade**	**Author**	**Year**	**Country**	**Pts**	**Comparison**	**Blinded**	**Se / Se (%)**	**Sp / Sp (%)**	**PPV/PPV (%)**	**NPV/NPV (%)**
SPN	B	Bury[11]	1996	Belgium	50	Histol	Yes	100	88	94	100
SPN	B	Lowe[12]	1998	USA	89	CT/Histol	Yes	92/-	90/-	95/-	84/-
SPN	B	Imdahl[13]	2001	Belgium	109	CT/Histol	Yes	86			
SPN	B	Croft[14]	2002	USA	90	CT/Histol	Yes	93	40	88	55
Preop Assess	A	Van Tinteren[15]	2002	Netherlands	188	Thoracotomy Rate	-	-	-	-	-
Preop Assess	A	Boyer (Abstract) [16]	2001	Australia	179	Thoracotomy Rate	-	-	-	-	-
Staging	B	Bury[17]	1996	Belgium	50	CT/Histol	Yes	90/72	86/81	-	-
Staging	B	Chin[18]	1995	USA	30	CT/Histol	Yes	78/56	81/86	64/63	89/87
Staging	B	Stokkel[19]	1999	Neth	33	CT/Histol	Yes	90/-	97/-	85/-	98/
Staging	B	Gupta[20]	2000	USA	54	CT/Histol	Yes	96/68	93/65	86/47	98/82
Staging	B	Gupta[21]	1999	USA	103	CT/Histol	Yes	93/63	94/60	92/50	94/72
Staging	B	Saunders[22]	1999	UK	97	CT/Histol	Yes	71/20	97/90	86/30	93/84
Staging	B	Pieterman[23]	2000	Netherlands	110	CT	Yes	91	86	-	-
Staging	B	Vesselle[24]	2002	USA	142	Histol	Yes	80.9	96	91.9	90.1
Staging	B	Albes[26]	2002	Belgium	40	CT/bronch/ Med	Yes	67	100	-	-
Staging	B	Poncelet[27]	2001	Belgium	64	Mediastin-oscopy	Yes	67/33	85/90.6	43/37	93.6/89
Staging	B	Lardinois[25]	2003	Switzerland	50	Integrated PET-CT	Yes	-	-	-	-
Residual Recurrence	B	Bury[28]	1999	Belgium	58	CT/Relapse	Yes	100/69	98/98	93/90	100/92
Bone Metastases	B	Bury[29]	1998	Belgium	110	Bone Scan	Yes	90/90	98/61	90/35	98/96
Pleural Effusion	B	Gupta[30]	2002	USA	35	Histol/Cytol	Yes	88.8	94.1	-	-
Survival Prediction	B	Mac Manus[1]	2003	Australia	73	PET vs. CT (Death/Remission on posttreatment)	Yes	Survival Analysis (p<0.0001)			

Legend: SPN=solitary pulmonary nodule; preop assess=preoperative assessment; Yr=year published; Pts-number of patients; Histol=Histology; CT=Computed Tomography; Se =Sensitivity; Sp=Specificity; PPV=Positive Predictive Value; NPV=Negative Predictive Value; - =data unavailable; (For Se/Se, Sp/Sp, PPV/PPV and NPV/NPV: single value refers to PET, subsequent values, if any, refer to comparator)

Table 3: HEAD & NECK CANCER (Updated October 15, 2002)												
Setting	**Grade**	**Author**	**Country**	**Yr**	**Pts**	**Compare**	**Outcome**	**Blinded**	**Se / Se (%)**	**Sp / Sp (%)**	**PPV/PPV (%)**	**NPV/NPV (%)**
Lymph node metastases	B	Brink[34]	Netherlands	2002	78	Histology	Lymph nodes metastases	Yes	86.1	92	-	-
Lymph node metastases	B	Hannah[35]	Australia	2002	48	CT	Lymph Node metastases	Yes	81/81	100/81	-	-
Lymph node metastases	B	Kau[36]	Germany	2000	70	CT/MRI	-	Yes	87/65 /88	94/47/ 41	90/40/51	93/72/83
Lymph node metastases	B	Benchaou[37]	Switzerland	1996	48	CT/Palp	-	Yes	72/67 /61	99/97/ 97	89/74/72	99/95/95
Pulmonary Metastases	B	Keyes[38]	USA	2000	56	-	-	Yes	-	-	-	-
Recurrence	B	Lowe[39]	USA	2000	30	Imag/Ex	Recur	Yes	100/3 8/44	93/85/ 100	-	-
Recurrence	B	Lonneux [40]	Belgium	2000	44	CT + MRI	-	Yes	96/73	61/50	-	92/56

Legend: Yr=year published; Pts=number of patients; Compare=Comparison modality; CT=Computed Tomography; Recur=Local Recurrence; Se =Sensitivity; Sp=Specificity; PPV=Positive Predictive Value; NPV=Negative Predictive Value; - =data unavailable
(For Se/Se, Sp/Sp, PPV/PPV and NPV/NPV: single value refers to PET, subsequent values, if any, refer to comparator)

Table 4: MALIGNANT LYMPHOMA (Updated October 15, 2002)												
Setting	**Grade**	**Author**	**Country**	**Yr**	**Pts**	**Compare**	**Outcome**	**Blinded**	**Se / Se (%)**	**Sp / Sp (%)**	**PPV/PPV (%)**	**NPV/NPV (%)**
Staging	B	Bangerter[41]	Germany	1998	44	CT	-	Yes	-	-	-	-
Staging	B	Jerusalem[42]	Belgium	2001	42	CT and clinical exam	-	Yes	-	-	-	-
Staging NHL	B	Carr[43]	UK	1998	50	Marrow Biopsy	-	Yes	79	76	58	90
Bone involvement	B	Moog[44]	Germany	1999	56	Bone Scan	-	Yes	71	87	71	87
Assessing Response to Treatment	A	Spaepen[46]	Belgium	2002	70	Standard evaluation	Remission /relapse	Yes	-	-	-	-

Legend: Yr=year published; Pts=Patients; Compare=Comparison modality; Se =Sensitivity; Sp=Specificity; PPV=Positive Predictive Value; NPV=Negative Predictive Value; CT=Computed Tomography; - =data unavailable;
(For Se/Se, Sp/Sp, PPV/PPV and NPV/NPV: single value refers to PET, subsequent values, if any, refer to comparator)

Table 5: MALIGNANT MELANOMA (Updated October 15, 2002)												
Setting	**Grade**	**Author**	**Country**	**Yr**	**Pts**	**Compare**	**Outcome**	**Blinded**	**Se / Se (%)**	**Sp / Sp (%)**	**PPV/PPV (%)**	**NPV/NPV (%)**
Staging	B	Rinne[48]	Germany	1998	52	'Routine'	-	Yes	100/85	96/58	-	-
Staging	B	Crippa[49]	Italy	2000	38	Histol	-	Yes	95	84	92	89
Staging	B	Reinhardt[50]	Germany	2002	67	Histol	Lymph Node Mets	Yes	91.7	97.7	95.6	95.5
Staging	B	Eigtved[51]	Denmark	2000	38	'Routine'	-	Yes	97/62	56/22	86	83

Legend: Yr=year published; Pts=number of patients; Compare=Comparison modality; Se =Sensitivity; Sp=Specificity; Signif=Significant difference; PPV=Positive Predictive Value; NPV=Negative Predictive Value; Histol=Histology; mets=metastases; -=data unavailable
(For Se/Se, Sp/Sp, PPV/PPV and NPV/NPV: single value refers to PET, subsequent values, if any, refer to comparator)

Table 6: COLORECTAL CANCER (Updated October 15, 2002)												
Setting	**Grade**	**Author**	**Country**	**Yr**	**Pts**	**Compare**	**Outcome**	**Blinded**	**Se / Se (%)**	**Sp / Sp (%)**	**PPV/PPV (%)**	**NPV/NPV (%)**
Recurrence	B	Imdahl[52]	Germany	2000	71	CT	Loc Rec	Yes	92/88	87/89	76/81	96/93
Recurrence	B	Imdahl[52]	Germany	2000	71	CT	Liver	-	100/87	98/91	96/83	100/93
Recurrence	B	Imdahl[52]	Germany	2000	71	CT	Lung	-	94/100	100/100	100/100	98/100
Liver Metastases	B	Lai[53]	Australia	1996	34	CT	-	Yes	93	57	89	67
Liver Metastases	B	Ruers[54]	Netherlands	2002	51	Conven-tional	-	Yes	-	-	-	-

Legend: Yr=year published; Pts=number of patients; Compare=Comparison modality; CT=Computed Tomography; Loc Rec=Local Recurrence; Se =Sensitivity; Sp=Specificity; PPV=Positive Predictive Value; NPV=Negative Predictive Value; - =data unavailable
(For Se/Se, Sp/Sp, PPV/PPV and NPV/NPV: single value refers to PET, subsequent values, if any, refer to comparator)

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