Does the addition of positron emission tomography/computed tomography (PET/CT) to the routine investigation and assessment of patients with melanoma yield clinical and economic benefits?

What is an evidence note
Evidence notes are rapid reviews of published secondary clinical and cost-effectiveness evidence on health technologies under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions and are produced in an approximately 3 month period. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify and retrieve within the time available. The reports are subject to peer review. Evidence notes do not make recommendations for NHSScotland.

Literature search
A literature search was conducted during September 2012 to identify evidence on the subject of melanoma and positron emission tomography/computed tomography (PET/CT). The searches sought to identify guidelines, health technology assessments (HTAs), systematic reviews and primary-level evidence, including economic studies. Database searches were limited to English language and publications from 2007 to September 2012.

Key points

Staging and recurrence
- The results of one systematic review suggest that when diagnostic imaging is indicated for staging or surveillance of melanoma, ultrasonography is better than CT, PET or PET/CT for the detection of lymph node metastases. However, PET/CT appears to be more suitable for the detection of distant metastases in patients at intermediate or high risk or when distant metastases are clinically indicated.
- Another systematic review reported that:
  - two prospective studies suggest that PET or PET/CT is useful for the staging of high-risk patients with potentially resectable disease.
  - the evidence does not support the use of PET or PET/CT for the diagnosis of sentinel lymph node micrometastatic disease or for staging of I, IIa, or IIb melanoma.
  - the identified evidence does not support the routine use of PET or PET/CT for the diagnosis of brain metastases or for the detection of primary uveal malignant melanoma.

- A third systematic review concluded that the use of either PET or PET/CT in addition to conventional staging in the assessment of patients with recurrent melanoma may:
  - be more accurate than CT alone for the detection of regional nodal metastases and distant metastases.
  - lead to changes in patient management, most commonly the avoidance of surgery.

Treatment response
- One systematic review noted that there were no prospective studies on the use of PET or PET/CT in the assessment of treatment response.

Cost effectiveness
- A cost-effectiveness analysis from Belgium found that PET/CT dominated whole body CT (ie PET/CT cost less and was more effective) in the diagnostic imaging work-up of patients with suspected pulmonary metastasised melanoma, the main benefit coming from avoidance of unnecessary surgery.
Introduction

Guidelines from the Royal College of Physicians and Royal College of Radiologists list the following indications for PET/CT in melanoma:

- staging of patients with known disseminated melanoma to assess extent of disease prior to treatment;
- to assess for distant disease in patients with melanoma when radical dissection is contemplated (nodal or metastatic disease);
- to assess response to isolated limb infusion for malignant melanoma;
- to exclude systemic involvement in skin lymphomas;
- to exclude primary malignancy where dermatomyositis suspected to represent a paraneoplastic manifestation; and
- not indicated for early-stage patients who should undergo sentinel node biopsy.

Some clinical experts in Scotland have expressed concern about the evidence supporting these recommendations, particularly the first. Therefore, this evidence note evaluates the role of PET/CT in the assessment of patients with melanoma.

Most of the evidence comes from secondary sources published since 2007. While the literature search was specifically for PET/CT, many of the reviews mixed studies on PET/CT and PET alone. These have been included, but reviews looking solely at PET have not. (NB reviews that included PET/CT in their search, but only identified evidence for PET, were still eligible for inclusion).

Health technology description

Medical imagery plays a role in the staging and management of people with melanoma. It can involve ultrasound, radiographic and nuclear techniques. It may be used to detect clinically occult disease (ie not detectable by clinical methods alone), evaluate the extent of known disease, and/or to determine therapeutic response.

PET is a non-invasive imaging technique that is widely accepted in oncological practice. It involves introducing a radiotracer to the body, such as fludeoxyglucose (FDG). FDG is similar to naturally occurring glucose, and the body treats it in a similar way. Metabolically active cells (eg malignant and inflammatory) utilise and import more glucose than other tissues, and thus take up FDG more rapidly.

A newer generation of PET scanners is now available, known as PET/CT scanners. These incorporate a CT scanner, to provide complementary anatomical images. There are currently five PET/CT scanners in Scotland (two in Glasgow, and one each in Edinburgh, Aberdeen and Dundee) (P McAuley, Scottish Government. Personal Communication, 8 May 2012). Although still in use, standalone PET scanners are no longer manufactured.

Epidemiology

Melanoma is the most serious type of skin cancer. Malignant melanoma is the fifth most common cancer in the United Kingdom (UK). In 2010, there were 12,818 new cases in the UK, and 1,141 in Scotland. Between 2008 and 2010, an average of 27% of new cases were diagnosed in people under the age of 50. In the same time period, 45% of cases were diagnosed in people aged over 65.

The incidence of malignant melanoma is rising. During the last 30 years, incidence rates in the UK have increased more rapidly than any of the current 10 most common cancers in males and females.

Melanoma is an aggressive cancer, and can spread in an unpredictable manner to any organ in the body. Disease dissemination may occur by direct extension from the primary site, lymphatic spread to regional or distant lymph nodes, or by the haematogenous route. The most common site of distant metastases are lungs and lymph nodes, followed by the liver, gastrointestinal tract, brain and bone.

Although early detection of melanoma results in high rates of cure, it is estimated that approximately one-quarter to one-third of all people with melanoma may develop recurrent or metastatic disease. The greatest annual risk of recurrence is in the first year after treatment of the primary melanoma.

Staging of the disease is essential to determine prognosis and to select appropriate treatment. The American Joint Committee on Cancer recommends staging using the International Union against Cancer’s TNM (tumour, node,
metastases) classification system, which groups according to the extent of the primary tumour (T0–T4), spread to regional lymph nodes (N0–N3) and presence of distant metastases (M0–M1). An alternative staging system, proposed by M.D. Anderson, classifies melanoma into stage I (primary cutaneous melanoma, any thickness), stage II (focal recurrence or satellites), stage IIIa (in-transit metastases), stage IIIb (regional lymph node metastases), or stage IV (distant spread).5

Clinical effectiveness

A UK HTA from 2007 provided an overview on the uses of PET in various cancers, including malignant melanoma. This is widely referred to in the more recent literature. The authors did not identify any studies on the use of PET/CT, but included two systematic reviews and 17 primary studies on PET. In summary, the review concluded that:

– for early-stage disease staging, FDG-PET is less sensitive than sentinel lymph node biopsy due to an inability to detect small lesions;

– for later-stage disease staging, FDG-PET has poor accuracy for small lesions and it is unclear whether it is superior to CT and/or magnetic resonance imaging (MRI); and

– in recurrent disease one diagnostic study and one patient management study report that FDG-PET influenced management in at least 30% of patients.

As the HTA did not identify any studies on the use of PET/CT in melanoma (only PET), the search for this evidence note concentrated on evidence post-2007. Seven systematic reviews were identified and eligible for inclusion.3,5,7-11

PET/CT can be used at various different stages in the disease pathway (e.g., staging, monitoring of treatment response, recurrence). While it is useful to consider the evidence under these headings, the mixed patient groups presented in the included reviews makes this difficult. Therefore, each review has been considered separately, with the patient group and use of PET/CT being described.

Xing et al. 201111

The most recent systematic review includes Bayesian meta-analyses, and is of good quality. The authors’ aim was to examine the utility of ultrasonography, CT, PET and PET/CT for the staging and surveillance (‘surveillance’ was interpreted as screening for recurrence after treatment of primary melanoma) of melanoma patients. The review included patient-level data from 74 studies, consisting of 10,528 patients. The included studies compared single or multiple imaging modalities with a gold standard.11

The quality of the included studies was assessed using the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) scale. The overall mean score for quality was 5.8 (standard deviation = 2.5), with the maximum possible score being 14. Approximately 90% of the studies had a total quality score of less than 9.0. The most commonly unmet quality criteria related to insufficient detail when reporting patient withdrawals, intermediate results, and the selection and training of raters. No studies were excluded because of the assigned quality score.

The results of the included studies were assessed according to the clinical intent of the tests (primary staging or follow-up surveillance) and the anatomical site of evaluation (lymph node or distant metastases).11

For the staging of regional lymph nodes, ultrasonography had the highest sensitivity (60%; 95% credible interval (CrI) 33% to 83%), specificity (97%; 95% CrI 88% to 99%), and diagnostic odds ratio (42; 95% CrI 8.08 to 249.80). For staging of distant metastases, PET/CT had the highest sensitivity (80%; 95% CrI 53% to 93%), specificity (87%; 95% CrI 54% to 97%), and diagnostic odds ratio (25; 95% CrI 3.58 to 198.70). Similar trends were observed for melanoma surveillance of lymph node involvement, with ultrasonography having the highest sensitivity (96%; 95% CrI 85% to 99%), specificity (99%; 95% CrI 95% to 100%), and diagnostic odds ratio (1,675; 95% CrI 226.6 to 15,920). For surveillance for distant metastases, PET/CT had the highest sensitivity (86%; 95% CrI 76% to 93%), specificity (91%; 95% CrI 79% to 97%), and diagnostic odds ratio (67; 95% CrI 20.42 to 229.70).

The positive predictive values (PPV) for the surveillance of lymph nodes were consistently higher for ultrasonography among low-risk patients (83%; 95% confidence interval (CI) 36% to 100%), intermediate-risk patients (94%; 95% CI 68% to 100%) and high-risk patients (98%;
95% CI 83% to 100%)\(^1\). However, the PPVs for the surveillance of distant metastases were consistently higher for PET/CT among patients at low risk (33%; 95% CI 9% to 61%), intermediate risk (63%; 95% CI 38% to 82%) and high risk (80%; 95% CI 64% to 93%). The authors note that for patients at low risk of metastases, the PPV indicated that the use of PET/CT is not warranted without additional clinical indications.

Based on these results, the authors concluded that when diagnostic imaging is indicated for staging or surveillance “ultrasonography was the best diagnostic imaging test to detect lymph node metastases and that PET/CT was more suitable for the detection of distant metastases in patients at intermediate or high risk or when distant metastases are clinically indicated”\(^1\).

These results suggest that when selecting a test from among the four diagnostic imaging modalities (ultrasonography, CT, PET, PET/CT), the anatomical site to be evaluated was more important than the clinical scenario (ie staging or surveillance). However, while this systematic review appears to be of good quality, it should be noted that the mean quality score of the included studies was quite low. Many of the 95% CIs and 95% CIIs are wide, indicating uncertainty surrounding the estimates. Further, the authors reported that the majority of the studies of patients undergoing the index test were retrospective in design, and so were prone to selection bias.

**Petrella and Walker-Dilks 2009\(^10\)**

A good quality systematic review (with recommendations) from 2009 was also indentified\(^10\). The results of this were based largely on the UK HTA\(^6\) and a further nine prospective primary studies (published between 2005 and 2008). Five of these studies related to PET/CT, and the remaining four to PET alone. The evidence is presented under the following headings:

- **Diagnosis or staging**
  - The authors identified two prospective studies, which suggested that PET was useful for the staging of high-risk patients with potentially resectable disease. The first study (Brady et al., 2006) included 103 patients, and evaluated the additive benefit of PET to CT as a preoperative imaging technique. The included patients were at high risk of occult metastatic disease (stage IIc, III and IV melanoma). The authors concluded that the combination of PET and CT had a higher sensitivity (77%) than either technique alone. Further, information from the preoperative imaging results of PET plus CT led to treatment change in 35% of patients. The second study (Strobel et al., 2007) included 124 patients with high risk melanoma (Breslow tumour thickness >4 mm; Clark level III or IV; or known metastases) referred for PET/CT imaging. The authors reported a sensitivity, specificity, and accuracy of 85%, 96% and 91%, respectively, for the detection of metastases in high-risk melanoma.
  - The authors did not recommend PET for the diagnosis of sentinel lymph node micrometastatic disease or for staging of I, IIa or IIb melanoma. The evidence behind this recommendation came from three prospective primary studies, which evaluated PET or PET/CT as an adjunct to lymphatic staging in patients with primary melanoma (Kell et al., 2007; Maubec et al., 2007; Cordova et al, 2006). Supporting the results of the UK HTA, these showed that the sensitivity of PET was too low to detect sentinel node metastases in early-stage melanoma (range 0% to 22%).
  - The authors of the review state that there are several small studies demonstrating the low sensitivity of PET for the detection of brain metastases, however do not provide references. They report on one prospective study (Pfannenbery et al., 2007) of 64 patients, which showed that MRI was superior to PET in detecting brain metastases.
  - The authors state that the routine use of PET is not recommended for the detection of primary uveal malignant melanoma. This is supported by one small (n=19) prospective study (Kato et al., 2006) which showed that single photon emission tomography was superior to PET for the detection of uveal metastases.
Assessment of treatment response

The authors of the review reported that no prospective studies were identified that examined the use of PET or PET/CT in the assessment of treatment response for melanoma, and so no recommendation was made.

Recurrence/restaging

The authors reported that no prospective studies were identified that examined PET or PET/CT in the assessment of recurrence, and so no recommendation was made.

Solitary metastasis identified at time of recurrence

The authors state that for solitary metastasis at the time of recurrence, there is some evidence showing a change in patient management with the use of PET or PET/CT prior to metastectomy (Facey et al., 2007; Koskivuo et al., 2007). The authors also stated that prospective studies assessing isolated metastases alone have not been conducted.

El-Maraghi and Kielar 2008

A systematic review evaluated the use of PET or PET/CT compared with sentinel lymph node biopsy in the staging of patients with intermediate-thickness primary cutaneous melanoma with clinically negative lymph nodes. This review was of reasonable quality, but the literature search was limited. The authors noted a lack of high quality evidence on this topic, but reported that all the included studies concluded that sentinel lymph node biopsy outperformed PET or PET/CT in the staging of local lymph nodes in this patient group.

Medical Services Advisory Committee – Australia 2008 (MSAC)

The review considered the value of the addition of PET (the authors used this to refer to both PET and PET/CT) to the assessment of patients with biopsy-proven recurrence of malignant melanoma considered on conventional staging to be potentially resectable with curative intent. It included the relevant studies from the UK HTA, as well as a further diagnostic accuracy study and a patient outcome study.

The diagnostic accuracy study investigated the value of PET and PET/CT, compared with CT alone, as a replacement test in the assessment of recurrent melanoma. The study was retrospective and enrolled 250 people referred for staging of cutaneous melanoma, including 65 referred for staging of clinically suspected recurrent disease. The MSAC review reported the sensitivity and specificity for the latter group of 65 patients. For N-staging the sensitivity of PET/CT was 100% (95% CI 98 to 100) and for CT alone 83.7% (95% CI 74.7 to 92.7). For N-staging the specificity of PET/CT was 100% (95% CI 98 to 100) and for CT alone 86.4% (95% CI 78.1 to 92.7). For M-staging the sensitivity of PET/CT was 100% (95% CI 98 to 100) and for CT alone 85.4% (95% CI 76.8 to 94.0). For M-staging the specificity of PET/CT was 95.8% (95% CI 90.9 to 100) and for CT alone 79.2% (95% CI 69.3 to 89.1). The authors concluded that “PET/CT appears to be more sensitive and specific for the detection of regional nodal metastases and distant metastases than CT alone in patients with clinically suspected recurrence of melanoma.”

The patient outcome study collected data prospectively from 134 participants at three PET facilities in Australia between 2003 and 2006. The patients had recurrent metastatic melanoma and were being considered for surgery. PET/CT scans were used in 85% of cases. The authors reported that PET (meaning PET or PET/CT) changed management plans in 61.9% of patients with potentially resectable recurrence of melanoma (95% CI 61.8 to 62). Surgery was planned in 95% of patients pre-PET, and was avoided in 34% of patients (95% CI 26 to 42) post-PET. Further, the authors reported a change in surgical procedure in 10% of patients and a change from surgery to chemotherapy in 13% of patients. Three additional systematic reviews were identified. The findings of these systematic reviews are in line with those presented.

NB Just before this evidence note was due to be published, a further systematic review was identified. It does not alter the conclusions of this evidence note.

Safety

The most recent evidence on safety comes from the MSAC review. They report that FDG-PET is ‘considered to be a safe procedure’. They highlight that patients undergoing PET/CT will have additional radiation exposure from the CT component, but doses are typically lower than with diagnostic CT.
Cost effectiveness

The literature search identified one Belgian cost-effectiveness study, and two cost-consequence studies. The cost-consequence studies were excluded as they were not full economic evaluations, and were not generalisable to the Scottish context.

The cost-effectiveness study compared two different surveillance programs, either PET/CT or whole body CT, in patients with resected high-risk malignant melanoma (stage IIc and III) with suspected pulmonary metastases. The analysis used a Markov model over a 10-year period. The perspective of the health care payer was adopted.

The authors reported that the clinical data came from published studies and were confirmed by expert opinion. It was not clear how these studies were sourced. The probability of developing pulmonary metastases was derived from data from the Duke Comprehensive Cancer Centre. Mortality data were from Belgian life tables.

A micro-costing approach was used to calculate the true costs of a PET/CT investigation. Direct medical costs were considered, including: costs of screening (visit, blood sampling and chest X-ray), surgery and potential complications, chemotherapy and complications, palliative treatment, PET/CT and conventional CT. Surgery was considered to be stapled wedge resection, lobectomy, segmentectomy or pneumectomy and a weighted cost was calculated based on the proportion of surgery used in a published study. Chemotherapy was assumed to be 850–1,000 mg/m dacarbazine administered once every 4 weeks in an outpatient setting. The unit costs came from the Health Insurance Institution, Belgium. The patterns of resource consumption came from a cohort of patients whose data were stored in standard administrative databases of 19 hospitals between 2005 and 2006.

All costs and benefits were discounted yearly at 3% and 1.5% respectively. Her Majesty’s Treasury recommends that costs and benefits be discounted at an annual rate of 3.5%. Outcomes included life-months gained (LMG), the number of accurate diagnoses and the number of futile surgeries avoided. Quality of life was not considered within the model.

The results showed that the PET/CT approach provided 90.61 LMG at a cost of £3,438 (£2,788). The whole body CT approach provided 90.42 LMG at a discounted cost of £4,384 (£3,555). The PET/CT strategy was associated with a net saving of £946 (£767) per LMG and a life expectancy gain of 0.1929 LMG or 6 days. Therefore, PET/CT was dominant as it was cheaper and more effective than CT alone. Further, based on the PET/CT findings, the authors reported that 20% of futile surgeries could be avoided, and PET/CT had 5% more accurate diagnoses.

Univariate and probabilistic sensitivity analyses were conducted to evaluate uncertainty in all model parameters and the results suggested that the base-case conclusions appeared robust. In the probabilistic sensitivity analyses, the PET/CT strategy remained dominant with a net saving of £1,048 (£850) and a gain of 0.2 LMG. The dominance of PET/CT was found in 71% of simulations.

The authors discuss some limitations with their study. These relate to several assumptions within the model and the model structure; focusing only on pulmonary recurrences and resectability; heterogeneity between the patients within the studies and mixed referral; and also deriving the annual probabilities of developing pulmonary metastases from a study that included patients that were evaluated with chest x-ray. The authors also state the exclusion of second-line chemotherapy from the model may have influenced the results, however this contradicts the statement within the key assumptions of the model that dacarbazine was included as the second-line chemotherapy. A further limitation included the use of a micro-costing approach that based costs and model assumptions on a Belgian-specific care pathway, therefore potentially limiting the generalisability of the findings.

Based on these findings, the authors concluded that ‘PET/CT is cost-effective in the diagnostic imaging work-up of patients with suspected pulmonary metastasized melanoma’. The main benefit comes from saving patients from undergoing unnecessary surgical treatments and its associated complications.

All reported costs were converted to pounds sterling using the exchange rate as at 3 December 2012. In Scotland, the average cost per PET/CT scan is £1,164.
Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The evidence note process has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org

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References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network http://www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

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