IMAGING FOR MELANOMA AND NON-MELANOMA SKIN CANCERS

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Abstract
This review discusses the relevant imaging techniques for both melanoma and non-melanoma skin cancers, including basal cell carcinomas, cutaneous squamous cell carcinomas and Merkel cell carcinomas. The diagnostic value of sentinel lymph node mapping, CXR, CT, PET, PET/CT and MRI are discussed, and their role for each stage and type of cutaneous malignancies considered. There are currently no recommendations for the use of diagnostic CT or PET/CT for initial staging of low risk melanoma patients around the time of diagnosis. Both PET and PET/CT have been shown to change the management of many patients with advanced melanoma, and it is recommended that FDG-PET be performed prior to resection of regional or distant metastatic deposits. MRI plays an important adjunctive role in the assessment of brain metastases in melanoma, and for assessment of perineural invasion in non melanoma skin cancers. Cumulative doses of radiation to patients for staging and surveillance imaging, and the life expectancy of the individual patient, should be factored into any decisions regarding what scans are appropriate for them.

Recommendations for appropriate imaging in patients with melanoma rely heavily on the patient’s disease status. In patients with stage II melanoma, there is a documented role for sentinel lymph node mapping using lymphoscintigraphy, but no role for further imaging procedures in the absence of symptoms. However, the case is different in patients with higher risk tumours and those with recurrent disease, who may benefit from a range of imaging procedures.

Imaging of patients with early stage cutaneous melanoma (stages I and II)
Lymphatic mapping and sentinel lymph node biopsy are recommended for disease staging in patients with high risk stage I/II disease. Lymphoscintigraphy involves the injection of a small volume of radiolabelled colloid around the tumour site, and then imaging to determine which regional node field contains the sentinel node or nodes (a sentinel node being defined as any node receiving direct drainage from a tumour site). Imaging is important, as often more than one regional node field is involved, and for accurate staging all sentinel lymph nodes should be pathologically examined. Lymphoscintigraphy identifies 94.5% of sentinel nodes. The use of SPECT (Tomographic nuclear imaging)/CT, in addition to standard dynamic lymphoscintigraphy, further improves diagnostic accuracy. Two studies have undertaken direct comparisons between lymphoscintigraphy and PET imaging, as a staging procedure in early stage melanoma. These found that lymphoscintigraphy was vastly diagnostically superior to PET imaging, with a sensitivity of 14% for PET imaging in both studies and a sensitivity of 86-100% for lymphoscintigraphy.

In early stage melanoma, sensitivities of just 17% have been found in a number of meta-analyses and pooled study results assessing the diagnostic value of PET and PET/CT in early stage melanoma. This is not surprising, as sentinel lymph node involvement with metastatic melanoma is most commonly microscopic. The sensitivity of PET/CT is limited by the volume of disease present, with the sensitivity for metastatic and lymph node disease dropping off significantly with tumour deposits of < 78mm3 in size (4mm diameter). PET has a sensitivity of < 50% for lesions < 4mm in size (80mm3). Hence, there are currently no recommendations for the use of PET/CT or diagnostic CT for initial staging of low risk melanoma patients around the time of diagnosis.

Imaging of patients with metastatic melanoma (stages III and IV)
PET and PET/CT
Metastatic melanoma deposits characteristically have high metabolic activity, showing up distinctly in 18F-FDG-PET/CT imaging. While FDG-PET/CT has not been shown to be diagnostically useful in early stage (stage I and II) melanoma where lymph node disease, if present, is usually of low volume and below the resolution limits for PET or CT technology, it has an important diagnostic role in patients with stage III and IV melanoma. This change in sensitivity, based on the stage of disease, was demonstrated elegantly by Wagner et al, who found a PET sensitivity of 0% in stage I disease, 24% in stage II disease, 81% in stage III disease and 100% in stage IV disease in patients with cutaneous melanoma. Multi study reviews of PET have found similar high diagnostic accuracy values for identifying metastatic melanoma in stage III and IV disease. A pooled analysis of 753 patients with stage III and IV melanoma showed that F18- FDG-PET had a pooled sensitivity of 88%, a specificity of 82% and an accuracy of 86%.
The diagnostic accuracy of PET/CT is significantly higher, with fewer false positive and false negatives than FDG-PET alone. It is now routine to undertake combined PET/CT imaging that is simultaneously or concurrently acquired on the same camera. The CT component can be either multislice contrast-enhanced, or a low radiation dose CT. A study of 50 patients with metastatic melanoma compared the diagnostic accuracy of contrast-enhanced diagnostic CT, PET and PET/CT (both contrast-enhanced and non-contrast low dose). The authors reported a sensitivity and specificity for diagnostic contrast-enhanced CT of 85% and 63%, for PET of 90% and 88%, for PET/non diagnostic CT of 97% and 93% and for PET/diagnostic-contrast-enhanced CT of 100% and 93% respectively. It is interesting to note that while the addition of CT information to PET significantly improved sensitivity and specificity, there was little additional improvement in sensitivity and no improvement in specificity when comparing low-dose CT and contrast-enhanced CT.

Both PET and PET/CT have been shown to change the management of many patients with advanced melanoma, and it is recommended that FDG-PET be performed prior to resection of regional or distant metastatic deposits. Etchebehere et al assessed the ability of PET/CT to change management in 78 patients with locoregional or distant recurrence of melanoma. PET/CT changed management in 27% of the group studied.

There are a number of limitations to FDG-PET imaging that should be taken into account in evaluating scan results. High background activity in normal brain tissue reduces the sensitivity of PET for the detection of melanoma brain metastases. This mandates that either diagnostic CT of the brain or MRI be undertaken in patients at high risk of melanoma brain metastases. For technical reasons, the intensity of FDG uptake in small lung metastases may often be reduced, particularly at the lung bases. The combined technique PET/CT is particularly useful in the detection of small lung metastases, often missed on PET alone. As FDG-PET measures glucose uptake, a low false positive rate due to scan findings related to inflammation, sarcoidosis and unrelated tumours, is inevitable.

**Diagnostic CT**

Although it is a widely used technique for staging and surveillance, there have been relatively few studies assessing the diagnostic value of contrast-enhanced CT in patients with melanoma. The technique suffers the same limitations as FDG-PET in early stage melanoma as it requires anatomical distortion for detection. A meta-analysis of diagnostic imaging modalities in later stage melanoma found a significantly higher diagnostic accuracy for PET/CT in disease surveillance (86% sensitivity, 91% specificity) than for CT alone (sensitivity 63%, specificity 71%). In fact, no study has found the diagnostic accuracy of contrast-enhanced CT to be higher than PET or PET/CT for cutaneous malignancies.

**Magnetic Resonance Imaging**

MRI plays an important adjunctive imaging role in the management of patients with cutaneous melanoma, particularly those with suspected or documented brain metastases. MRI is significantly more sensitive than CT for the detection of metastatic disease in the brain, and also provides more detailed information about possible involvement of the spinal cord and leptomeninges. Contrast enhanced CT scanning is widely used because of its ready accessibility and relatively low cost. However, brain MRI for patients with primary cancers that frequently

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**Figure 1:** Contrasted enhanced axial MRI image demonstrates enhancement and thickening of the left trigeminal nerve (thick arrow) in the preoptic cistern extending into the left cavernous sinus. Right trigeminal nerve is of normal appearance (thin arrow).

**Figure 2:** PET/CT of a patient presenting with a right axillary mass. The PET images show the intense FDG uptake that is characteristic for metastatic melanoma. The organs involved, including lymph node, lung, bone and subcutaneous nodularity, show a classic pattern of metastatic dissemination commonly seen in patients with metastatic melanoma.
metastasise to the brain (including melanoma) is probably cost effective. Numerous studies have shown that contrast-enhanced MRI detects two to three times as many lesions as contrast-enhanced CT, especially lesions less than 5mm in diameter. In addition, approximately 20% of patients with solitary metastatic lesions in the brain on CT show multiple lesions on MRI.21–25

**Plain chest X-ray**

Routine surveillance of patients at higher risk of melanoma recurrence with plain chest x-ray (CXR) has been recommended in treatment guidelines until recently. However, a review of 1235 patients with melanomas >1mm in Breslow thickness, followed for a median of 74 months, found that the sensitivity of surveillance CXR was 7.7% and the specificity 96.5%. Of those diagnosed with metastatic disease on CT (0.9%), only 0.2% had isolated pulmonary metastases amenable to resection. Hence, CXR is no longer recommended for standard surveillance in melanoma patients.26,27

**Imaging of non-melanoma skin cancers**

**Merkel cell carcinoma**

Merkel cell carcinoma is a rare, aggressive skin malignancy with a high recurrence rate in regional node fields. Unlike in melanoma, the role of lymphoscintigraphy and sentinel lymph node biopsy is controversial in the management of Merkel cell carcinoma. Lymphoscintigraphy sensitivity in Merkel cell carcinoma varies in the literature from just 27% to 32%.28–30 However, a positive sentinel node has a high predictive value for relapse in the regional node field, and is an indicator for adjuvant radiotherapy treatment.29,30 Unfortunately, a negative sentinel node biopsy in Merkel cell cancer does not preclude early recurrence in the same lymph node field. The use of F18-FDG-PET in the staging of Merkel cell cancer is also yet to be established, with no large prospective studies to date. A retrospective study evaluating the use of diagnostic CT, PET/CT and MRI in the initial lymph node staging of 99 patients with Merkel cell carcinoma found a sensitivity of 85% and specificity of 95% with PET, 47% and 97% for CT, and 0% and 86% for MRI (histopathology of lymph nodes was used for determining sensitivity and specificity).31 A further small study of 18 patients found that PET had a significant management impact in patients with Merkel cell cancer, altering staging in 33% and changing management in 43%.32 While Merkel cell cancer is a form of neuroendocrine tumour, it tends to have a high mitotic rate, but imaging with radiolabelled Somatostatin analogues has not been shown to be more sensitive than 18F FDG-PET imaging.33

**Basal and squamous cell carcinoma**

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) constitute approximately 95% of non-melanoma skin cancers.34,35 The majority of these cancers do not require diagnostic evaluation. However, high risk patients, particularly with recurrent or invasive tumours, tumours at risk for regional or distant metastasis or accompanied by clinical signs of perineural involvement, warrant imaging to assess morphology of the primary tumour site, as well as to identify distant metastatic disease.36

Given its superior soft tissue resolution, MRI is considered to be the imaging modality of choice for evaluation of the primary tumour site, with excellent depiction of the extent of locoregional disease. In certain locations it is particularly important in presurgical planning.37 Given the tendency of some non-melanoma skin cancers to spread by perineural invasion, MRI is the modality of choice.38,39 Nemzek and colleagues reported a 95% sensitivity for MRI detection of perineural invasion.39 MRI is also superior in identifying intracranial metastases and intracranial extension, including meningeal involvement, as well as subtle marrow infiltration. Diffusion-weighted MRI has become a promising biomarker for assessing tumour response to therapy.39

For evaluation of nodal involvement and distant metastatic disease, molecular imaging with fusion PET-CT and diagnostic CT are the imaging modalities of choice.34 The sensitivity and specificity of PET/CT in staging and follow up for aggressive non-melanoma skin cancers remain to be elucidated. Over the last decade, fusion PET/CT has become an established, powerful imaging modality in the field of oncology, providing functional and anatomical correlation. However, in non-melanoma skin cancers, few data are available regarding staging and follow-up evaluation. Boswell and colleagues reported cases with metastatic BCC to the lung that was detected on PET/CT.40 In tumour of unknown origin, combined PET/CT has gained wide acceptance.41 A recent meta-analysis with encouraging data showed that, overall, FDG-PET/CT is able to detect 37% of primary tumours in patients with cancers from an unknown primary, with both sensitivity and specificity of 84%.42 Gourin and colleagues reported detection of distant metastatic disease in 15 of 64 patients, 13 of which were unsuspected prior to PET/CT.43 In patients with head and neck cancers receiving radiotherapy, a negative PET/CT result within six months after radiotherapy correlated with statistically significantly improved two-year overall survival rates in a study by Kao and colleagues, who followed 80 patients over a median of 21 months.44

Given its ready availability and rapid acquisition times, diagnostic CT has been used widely for routine surveillance. One advantage of CT over MRI is the increased sensitivity in the detection of subtle cortical bony erosion,34 but for small lesions or pathological changes in normal-sized tissues can be missed by CT.41

**Radiation doses**

Cumulative doses of radiation to patients for staging and surveillance imaging must be factored into any decisions regarding which scans are appropriate. Given that the diagnostic yield of either CT or PET/CT is low in melanoma patients with AJCC stage I or II disease, it is not recommended that diagnostic CT, PET/CT or CXR be used in the absence of symptoms requiring investigation. By contrast, lymphoscintigraphy has a high diagnostic accuracy and delivers a very low radiation dose to this group of patients with a better prognostic outcome. In patients with AJCC stage III or IV melanoma, life expectancy is considerably reduced, and the diagnostic value of regular imaging must be weighed up carefully against the relatively low lifetime risk of secondary cancers induced by frequent imaging procedures.

PET imaging now almost always incorporates a low dose CT for the purposes of attenuation correction and anatomical detailing. This low dose CT is weight dependent
in terms of radiation delivered and gives an average dose of 4mSv per patient in our institution (range 2.9-9.6 mSv). The 18F- FDG delivers 5-7 mSv per patient, giving an average radiation dose of 9 mSv per patient for a PET/low dose CT scan. A comparative study of radiation doses across institutions found similar results for low dose PET/CT images. They also found that, on average, a diagnostic CT scan added an extra 14-19 mSv to the procedure.\(^\text{40}\) Putting this in perspective, the expected background radiation dose for a person living in Australia is 2mSv/year.

### Conclusion

Rapidly evolving technology in imaging sometimes makes choosing the most appropriate imaging procedure for an individual patient difficult. MRI and lymphoscintigraphy have proven valuable in local disease characterisation and regional lymph node involvement, while PET/CT is proving the most diagnostic accurately for assessment of distant metastatic disease. The clinician must take into account both the stage and type of cutaneous malignancy in deciding which imaging technique to employ, or indeed whether imaging is required at all.

### References