

# 8 Appropriate investigations

## 8.1 Investigations following the diagnosis of primary melanoma

The body of evidence does not contain any randomised trials to support or exclude the routine use of investigations following the diagnosis of primary cutaneous melanoma. Specifically, there is no evidence about outcome (overall or relapse-free survival), with most studies assessing the accuracy of the investigations examined. The majority of studies are descriptive or observational, including one meta-analysis, two good-quality expert reviews and three good-quality clinical guidelines. There are no studies providing an economic evaluation.

### 8.1.1 Evidence statement

Investigations after the diagnosis of primary cutaneous melanoma are aimed at the detection of occult regional or systemic disease. The likely yield of such investigations for primary melanoma is directly proportional to the risk of metastatic disease. Hence the role of investigations following the diagnosis of primary melanoma might be stratified according to known prognostic factors, such as Breslow thickness. The first aim of detecting occult metastatic disease is to improve survival through an intervention or treatment that will change the natural history of the disease. However, there are no data to support the concept that the early detection of occult metastatic disease is associated with improved survival compared with later detection of symptomatic systemic disease. The second aim is to identify occult disease stage III or IV, not suggested by history and examination, which would result in a change in management.

The most accurate method for the identification of occult regional lymph node metastases is sentinel lymph node biopsy (SLNB) (see Chapter 12.1). In an attempt to avoid the morbidity of SLNB in patients with a negative SLNB, several radiological methods of regional lymph node assessment have been investigated. The meta-analysis by Bafounta et al<sup>1</sup> found that ultrasound examination of lymph nodes was consistently more accurate than palpation for the detection of lymph node metastases. Ultrasound can accurately detect lymph node metastases > 4.5mm in size.<sup>2,3</sup> However, prospective studies have shown that SLNB remains superior to ultrasound in the detection of occult regional lymph node metastases.<sup>2</sup> Similar prospective studies comparing the sensitivity and specificity of PET scan with SLNB as the reference standard found PET scan to be inferior to SLNB, with a sensitivity of 13% for PET scanning.<sup>4-6</sup> These studies also demonstrated significant false positive rates. No data regarding ultrasound or PET findings and survival were reported in these studies.

Elevated serum LDH has not been shown to be useful for the detection of occult metastatic disease in patients with stage I or II melanoma and the authors concluded that the routine use of serum LDH cannot be recommended.<sup>7</sup> Similarly, full blood count, serum electrolytes and liver function tests in combination with radiology, including CT scan, did not demonstrate any occult metastatic disease in a prospective study of 90 patients with primary melanoma.<sup>8</sup>

Four observational studies of low quality have investigated the yield of routine chest x-ray (CXR) for the detection of occult pulmonary metastases in patients with primary cutaneous melanoma and demonstrated true-positive rates of 0.0–0.1%.<sup>6–9</sup> Hence the routine use of CXR cannot be recommended. Similar findings have been demonstrated for CT scanning of the head, chest, abdomen and pelvis.<sup>8,10</sup> More recently, whole-body PET scanning has been investigated in two prospective non-randomised studies with comparable conclusions for patients with stage I or II cutaneous melanoma.<sup>6,11</sup> No sites of true-positive metastatic disease were demonstrated in any of the studies but both CT scanning and whole-body PET scanning yielded false positives.

In summary, the yield of any investigations for patients with stage I–II cutaneous melanoma is very low for the detection of occult stage IV disease. All of the investigational methods used are plagued by false positives and cannot be recommended. For the detection of occult stage III disease, the yields of ultrasound, CT scan or PET scan are inferior to SLNB and have been shown to be cost-inefficient.<sup>12</sup> There are no data regarding the utility of investigations with respect to outcome. Therefore, routine use of investigations for stage I–II cutaneous melanoma is not recommended. Radiological investigations may be routinely required for patients participating in clinical trials.

Evidence summary	Level	References
Regional lymph node ultrasonography is superior to palpation for the detection of regional lymph node metastasis	II	1
Both regional lymph node ultrasonography and PET scanning are inferior to sentinel lymph node biopsy for the detection of occult lymph node metastasis	III-2	2–6
The routine use of blood tests or radiological investigations, including chest x-ray, CT scanning, or whole-body PET scanning, rarely identifies occult stage IV disease in patients presenting with stage I or II cutaneous melanoma. The identification of false-positive metastatic disease is a consistently reported phenomenon for all reported investigations	III-2	3–9, 11–13

### Recommendation

	Grade
1. Following the diagnosis of primary cutaneous melanoma (stage I, II) routine investigations are not required for asymptomatic patients	<b>D</b>

## 8.2 Investigations following the diagnosis of locoregional disease

The body of evidence does not contain any randomised trials to support or exclude the routine use of investigations following the diagnosis of locoregional cutaneous melanoma. The majority of studies are descriptive or observational studies, with one meta-analysis, two good-quality expert reviews and three good-quality clinical guidelines. There are no studies providing an economic evaluation.

### 8.2.1 Evidence statement

As for patients with primary melanoma, the aim of routine investigations for patients with newly diagnosed locoregional melanoma is the detection of occult stage IV disease with a view to improving survival, changing management or providing more accurate prognostic information. There are no data that relate the use of investigations at the time of diagnosis of stage III cutaneous melanoma to outcome. Published studies to date have investigated the diagnostic yield of investigations in the detection of metastatic disease, with two studies examining the impact of investigations on management. Patients with stage III melanoma are essentially represented by three subgroups that will be considered separately: SLNB positive (microscopic stage III); clinically evident lymph node disease (macroscopic stage III); and in-transit metastases (stage IIIC).

For patients found to have positive sentinel lymph nodes, prospective cohort studies have investigated the role of routine CXR, CT scan of chest, abdomen and pelvis, and magnetic resonance imaging (MRI). The true-positive rate for these combined investigations was 0.5% and 1.9% for study groups of 185 and 270 patients respectively.<sup>14,15</sup> These results are similar to those for patients with stage I–II melanoma and do not include any outcome data.

The high probability of distant relapse for patients with macroscopic locoregional cutaneous melanoma has prompted the routine use of radiological investigations by many clinicians despite there being no evidence from randomised trials to support their use. Prospective cohort studies and non-randomised clinical trials assessing the role of CT scan in patients with stage III cutaneous melanoma without symptoms suggestive of metastatic disease have revealed true-positive rates of 0–26%, with most studies reporting rates < 10%.<sup>10,13,16–19</sup> False-positive diagnoses for metastatic disease remain problematic in these studies, with reported rates of 8–20%.<sup>10,16,18,19</sup> These studies do not include outcome data or whether the investigation altered management.

More recently, the role of PET scan has been investigated for patients with stage III disease at the time of diagnosis. These studies have generally shown PET scan to be superior to conventional imaging for the identification of unsuspected metastatic disease, except for the detection of small lung secondaries. However, false-positive diagnosis of metastatic disease remains in the order of 10%.<sup>20–23</sup> Three prospective studies have investigated the influence of PET scanning on management. These studies have reported that PET scan influenced clinical management by 22–49%.<sup>20,24,25</sup> However, all of these studies combined stage III patients with stage IV cutaneous melanoma patients and did not break down the results by stage, potentially limiting the applicability of the findings to patients with stage III disease.

In summary, the yield of routine CT or PET scanning for patients with stage III cutaneous melanoma is up to 20% for the detection of stage IV disease, although false positives remain a problem for all of the investigational methods used. For patients with newly diagnosed stage III disease where a potentially morbid treatment is planned that would be abandoned in the presence of metastatic disease, CT scan of the chest abdomen and pelvis or whole-body PET scan may be performed. No data exist for the role of investigations for patients with in-transit disease. Hence the recommendations for in-transit disease (as stage III disease) are the same as for macroscopic stage III disease. Routine radiological investigations may be required for patients with stage III disease considering entry into clinical trials.

Evidence summary	Level	References
The true-positive rate for routine radiological investigations for patients with positive sentinel lymph nodes is less than 2%	III-2	14, 5
The yield of routine CT or PET scanning for the detection of stage IV disease is up to 20% for patients with macroscopic stage III cutaneous melanoma. The false-positive rates for these investigations are in the order of 10%	III-2	10, 3, 5–23
For patients with stage III disease, the routine use of CT or PET scan may influence clinical management in up to 49% of patients	III-2	20, 24, 25

### Recommendations

	Grade
2. Routine investigations, including radiology, are not indicated for patients following the diagnosis of a positive sentinel lymph node in the absence of symptoms suggestive of metastatic disease	<b>D</b>
3. Following the diagnosis of locoregional melanoma, patients require a detailed history and physical examination. Investigations, including radiology, are indicated for symptoms suggestive of metastatic disease. CT scan of the chest, abdomen and pelvis or whole-body PET scan may be performed for the workup of otherwise asymptomatic patients prior to definitive therapy where the detection of occult metastatic disease would influence management	<b>D</b>
4. Patients suspected of having lymph node metastasis from cutaneous melanoma should undergo fine needle aspiration biopsy, with ultrasound or radiological guidance when required, to confirm the presence of stage III disease	<b>D</b>

### 8.3 Investigations following the diagnosis of metastatic melanoma

The body of evidence does not contain any randomised trials to support or exclude the routine use of investigations following the diagnosis of stage IV cutaneous melanoma. The majority of studies are descriptive or observational studies.

#### 8.3.1 Evidence statement

The diagnosis of metastatic melanoma is made on the basis of investigations for symptoms or investigations as part of routine follow-up. Computerised tomography has been shown to be superior to chest x-ray alone in the diagnosis of pulmonary metastases, identifying 20% more metastatic lesions.<sup>26</sup> Recently, much attention has been focused on the utility of PET scanning in the diagnosis of metastatic melanoma. The sensitivity and specificity of PET scan for the detection of melanoma metastases are reported to be 85% and up to 97%, respectively.<sup>27,28</sup> However, the sensitivity of PET scan decreases to as low as 4% for lesions < 6mm in size.<sup>27</sup> Despite this limitation, PET scan is generally more sensitive than CT scan for the detection of metastatic melanoma at all sites, except for brain and possibly lung.<sup>29,30</sup> While the evidence suggests that PET is superior to CT with respect to the number of metastatic sites identified, once the diagnosis of metastatic melanoma has been established by conventional imaging techniques, the supplementary use of PET scan is of little value<sup>31</sup> unless the result would cause a change in management. Three studies have examined the influence of PET scan in addition to conventional imaging on the management of patients with stage IV melanoma who are planned to undergo metastasectomy.<sup>20,24,25</sup> In this setting, the additional use of PET scan influenced clinical management by 22–49%.<sup>20,24,25</sup> Pre-operative PET scan is associated with improved outcome after pulmonary metastasectomy by permitting the selection of patients without additional sites that are most likely to benefit from resection.<sup>32</sup>

Prospective and retrospective comparison studies of low quality have consistently shown contrast-enhanced MRI brain to be superior to computerised tomography for brain metastasis detection, anatomic localisation of lesions, and differentiation of solitary versus multiple lesions.<sup>33,34</sup> One retrospective study of patients with stage I–IV melanoma found that routine MRI only detected asymptomatic brain metastases in patients with known stage IV disease.<sup>35</sup> Overall, where the detection of asymptomatic brain metastases would impact on treatment strategy, more accurate and complete staging is achieved by MRI compared with CT brain.<sup>36</sup>

For patients in whom conventional imaging techniques yield equivocal results for metastatic melanoma, PET scan should be viewed as a complementary imaging technique.<sup>37</sup> Image-guided fine needle biopsy may be performed to establish the diagnosis of metastatic melanoma (see Chapter 12.2) where diagnostic doubt remains after imaging studies. Alternatively, clinical observation and serial imaging may be required to confirm the nature of lesions suspected to be metastatic melanoma. Serum LDH forms part of the current AJCC staging system for melanoma and may be measured, once the diagnosis of stage IV melanoma has been established by imaging and/or biopsy, to aid in the determination of prognosis (see Chapter 4 *Classification and staging of melanoma*).

Evidence summary	Level	References
Chest CT scan is superior to chest x-ray for the detection of pulmonary metastases	III-2	26
PET scan is generally more sensitive than CT scan for the detection of metastatic melanoma at all sites, except for brain, possibly lung, and lesions < 6mm in size	III-2	27–30
MRI brain is generally provides more accurate and complete staging compared with CT brain	IV	33–36
Once the diagnosis of metastatic melanoma has been established by conventional imaging techniques, the supplementary use of PET scan is of little value unless the result could cause a change in management	III-2	31
For patients with stage IV disease, the routine use of CT, MRI or PET scan may influence clinical management in up to 49% of patients	III-2	20, 24, 25

### Recommendations

	Grade
5. Investigations, including serum LDH, CT, MRI, and/or PET scan, are indicated for symptoms suggestive of metastatic melanoma	<b>D</b>
6. Following the diagnosis of metastatic melanoma, no further investigations are required unless surgery is planned and the detection of additional sites of distant disease would result in a change in management	<b>D</b>

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