

Melanoma Radiological Surveillance: A Review of Current Evidence and Clinical Challenges

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Melanoma is a common cancer in both young and older populations in many western countries. Rates of melanoma diagnosis worldwide are increasing. With the introduction of both targeted and immunotherapies there have been dramatic improvements in the care of patients with metastatic melanoma. With these new therapies being increasingly offered to patients with stage III metastatic melanoma and stage IV disease, radiological surveillance of melanoma has become a widely used method of monitoring melanoma patients for early locoregional and distant metastasis. However, concerns have been raised about risk of false positive results, which patients to consider radiological surveillance for, and at what intervals to do so. To date, there are no published review articles on the topic of radiological surveillance in melanoma patients identified in the MEDLINE database. A comprehensive literature review was performed by searching the MEDLINE database to review all published works on this topic. This article aims to present an extensive review of literature surrounding radiological surveillance in melanoma patients, a discussion of controversies, and recommendations for surveillance modalities.

INTRODUCTION

Worldwide, the incidence of melanoma has increased significantly in many countries at rates of 3-7% per year; a faster rate than any other cancer [1]. Whilst commonly diagnosed in individuals over the age of 60 years, a significant proportion of individuals diagnosed with melanoma are between the ages of 15-40 years [2]. Apart from the rising incidence, the mortality of melanoma and costs for treatment are rising in several countries worldwide in part due to increased diagnosis, the nature of surgical management required and expensive new systemic therapies for advanced disease [3-6].

Given the significant proportions of young people diagnosed with melanoma and the significant risk of

recurrence, metastatic progression, and death posed by their melanoma, radiological surveillance has been an increasingly sought-after tool by clinicians to direct management and follow-up. Patients are increasingly motivated in seeking imaging-based surveillance with the availability of effective targeted and immunotherapies [7-14]. Although primary melanoma tumors and locoregional metastases (*e.g.* lymph node metastasis and intransit cutaneous metastases) can often be detected on clinical examination [15,16], clinical monitoring for both deep lymph nodes and distant viscera pose a significant challenge for clinicians. Early distant visceral metastatic disease is often asymptomatic until advanced, whereby it may be difficult to surgically excise [17]. Patterns of distant disease spread for melanoma are also hard to predict

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Abbreviations: PET, Positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging; CXR, chest x-ray.

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and atypical compared to other solid tumors with atypical sites of metastasis such as small bowel, adrenal glands, and spleen [18,19].

There remains inconsistency between international guidelines for the use of surveillance imaging in melanoma patients. Current guidelines are mainly based upon expert consensus opinions rather than high strength evidence. The National Comprehensive Cancer Network (NCCN) recommends CT or PET scans every 3-12 months for patients with stage IIB-IV asymptomatic melanoma [20]. The European Society of Medical Oncology recommends only physical examination every three months [21].

This review therefore aims to focus on a critical discussion of evidence surrounding surveillance imaging to provide evidence-based recommendations for surveillance imaging in melanoma.

This was performed using the MEDLINE database. Keywords utilized in the search included “melanoma surveillance,” “Positron emission tomography (PET),” “ultrasound,” “melanoma imaging,” “computed tomography (CT),” “magnetic resonance imaging (MRI),” “chest x-ray (CXR),” and “melanoma follow-up.” Guidelines/publications from specialized collaborative teams were also sought.

BASIC INVESTIGATIONS

Traditionally, more basic radiological investigations such as chest x-ray (CXR) were utilized for detection of occult metastatic disease in melanoma patients. However, due to limited two-dimensional soft tissue views, the accuracy of CXR to accurately detect true pulmonary metastasis compared to false positives and false negatives is limited [22]. As such, there is seldom use of CXR in current clinical practice for melanoma surveillance.

Ultrasound imaging is frequently used to monitor regional lymph node basins for recurrence. Although the sensitivity of ultrasound is dependent upon the competency of the sonographer [23,24], ultrasound has been demonstrated to have the highest sensitivity and specificity, 96% and 99% respectively, for lymph node surveillance [23,25]. In particular, ultrasound surveillance of the regional lymph node basin is superior to clinical examination alone (palpation of lymph node basin) for patients with stage I and II melanoma [24]. Clinical examination appeared to have higher rates of false negative results than ultrasound in the clavicular and axillary lymph node groups [26]. Key findings from the Multicenter Selective Lymphadenectomy Trial II (MSLT-II) demonstrated there was equivalent survival between those randomized to complete lymph node dissection or 3-4 monthly clinical and ultrasound monitoring for at least 2 years then at least 6 monthly clinical and ultrasound assessment until

5 years [27]. Ultrasound surveillance therefore should be considered for surveillance of both patients who have a positive sentinel lymph node biopsy who do not undergo immediate completion lymph node dissection [27]. Ultrasound surveillance should also be advised in patients who are either not recommended or decline a sentinel lymph node biopsy but remain at high risk of progression to stage III disease due to unfavorable primary tumor characteristics.

Although the greater accuracy of ultrasound has been demonstrated, the long-term survival benefit of ultrasound surveillance is unknown. Only a relatively low amount of patients (27 patients, 7% of study patients) had either earlier detection of lymph node metastasis or avoidance of unnecessary surgery due to ultrasound surveillance compared to clinical examination [24]. Six percent (22 patients) underwent unnecessary surgery or repeat scans for suspicious findings that were negative for recurrence [24]. These data highlights the need for careful selection of patients with higher risk, thicker primary melanoma for ultrasound surveillance in order to maximize benefit, and counteract risk of false positives. In another study of 90 individuals with stage I or II melanoma who declined sentinel lymph node biopsy, half of lymph node recurrence was detected by ultrasound examination, particularly axillary metastases [28]. An Australian study of 160 comorbid or elderly patients deemed unsuitable for sentinel lymph node biopsy demonstrated that ultrasound examination detected 33% of the nodal recurrences before they became clinically apparent over a 9-year period [29]. Further large prospective trials are needed in order to evaluate the long-term survival benefit of ultrasound surveillance.

ADVANCED MODALITIES

More modern imaging techniques such as computed tomography (CT) and positron emission tomography-CT (PET-CT) provide detailed three-dimensional tissue views and are commonly used in current practice. PET-CT has become the favored modality for surveillance of distant metastasis due to the fluorodeoxyglucose (FDG) tracer being preferentially absorbed in higher metabolic sites, leading to greater PET-CT accuracy for most body sites over CT (except liver and lung where specialized CT may be superior) [30].

A meta-analysis of over 10,000 patients has evaluated the overall accuracy of PET/CT for melanoma surveillance. Sensitivity and specificity of PET-CT was found to be 65% and 99% for regional disease and 86 and 91% for distant metastasis surveillance, respectively [31]. Another study found sensitivity and specificity to be 96 and 92% respectively for PET for distant metastatic disease in majority stage IIB and III patients [32]. Similar results

have been reported in another study [33].

Apart from being accurate in detecting metastasis, PET-CT surveillance results can change management of patients. In Australian data from twenty patients, PET-CT detected 24 metastases up to 6 months earlier than other imaging/physical examinations [34]. Two prospective trials and a systematic review demonstrated a change in a patient's treatment occurred in 19-35% of stage III patients following PET/CT scans [35-37]. Eighteen percent of 73 stage III patients were restaged to stage IV disease using image surveillance results over a 4-year follow-up period [38]. Overall, the role of PET/CT in sentinel lymph node positive patients has been investigated in four retrospective studies. In these four studies, the yield of PET/CT imaging in detecting occult metastases ranged from 0.5 to 3.7% [39-42].

Three larger cohort studies examining outcomes have provided the strongest data to support PET-CT use in melanoma surveillance to date for clinicians. One hundred and ten asymptomatic patients from Finland with stage IIB to IIIB melanoma underwent PET-CT surveillance after a mean interval of 7 months following initial surgery (more than 6, but less than 12 months) [32]. Within this cohort, a single PET/CT detected 24% of all recurrences in asymptomatic melanoma patients between this 6- and 12-month period. However, in 15 patients (14% of the cohort), a false positive result was obtained from the PET-CT scan, leading to invasive procedure or repetitive imaging [32].

In a larger cohort from Denmark, where PET/CT scans have been routinely included in the Danish guidelines for AJCC stage >IIB melanoma since 2015, the diagnostic performance of PET/CT imaging was compared in patients with and without a clinical suspicion of relapse [43]. A total of 238 patients (who underwent 526 PET-CT scans), of varying AJCC stages were included. Amongst the 526 PET-CT scans, 130 scans (25%) were positive for recurrence, 365 (69%) were negative for recurrence, and 28 (5%) had non-specific findings [43]. When patients were stratified by their reason of referral for PET/CT, there was no significant difference in the accuracy of PET/CT between patients with and without clinical suspicion of relapse [43]. Similar to the series from Finland, the frequency of false-positive findings was relatively high (9%), especially among patients undergoing a "routine" PET/CT with no clinical suspicion of relapse [43].

Finally, in Australian data, melanoma recurrence was identified in 38% of 170 Stage III metastatic melanoma patients who underwent PET/CT imaging, of which 69% were asymptomatic [17]. Positive predictive values of individual scans varied from 56-83%, while negative scans had predictive values of 89-96% for true non-recurrence [17]. A negative PET/CT at 18 months had negative predictive values between 80-84% for true non-recurrence

at any time in the 47-month (median) follow-up period [17]. Of PET/CT detected recurrent patients, 33 (52%) underwent potentially curative resection, although few patients (16%) remained disease-free after 24 months [17]. While the negative predictive value of a negative PET may be reassuring to patients and clinicians, this did not conclusively demonstrate that survival was improved by routine PET/CT surveillance [17].

The reliability of PET and CT brain in detecting brain metastasis is poor as demonstrated by multiple studies [44,45]. Despite this, the rate of brain metastasis among almost 700 varying stage melanoma patients was significant at 12% [46]. Surveillance of the brain for melanoma metastasis is crucial given the dramatic decrease in prognosis with development of intracerebral metastasis and the consequences of their unchecked growth such as seizures and hemorrhage [47]. Because of the limited accuracy of CT brain imaging, MRI is usually preferred for higher resolution imaging of the brain to evaluate for metastatic disease depending on availability. MRI may be also used to correlate suspicious findings from PET-CT prior to surgery/biopsy [48].

CONTROVERSIES AND DISCUSSION

There are potential benefits of surveillance. Early oligometastatic disease detected by surveillance can be cured by resection, radiotherapy, or systemic therapies [49-51]. Studies examining those treated with modern therapies have suggested superior survival in those with low volume metastatic melanoma compared to high volume metastatic disease [52,53]. However, this has not been definitively proven to date.

Apart from the benefit of assessing progression of melanoma patients through surveillance, radiographic investigations can detect incidental additional primary malignancies during a patient's follow-up [54,55]. Multiple studies of non-melanoma malignancy cohorts have shown that the chance of additional malignancy is low at 1-3% [56-60]

There are also many unknowns with regards to potential benefits of surveillance in melanoma patients. There are multiple observational studies examining follow-up imaging in melanoma but a lack of randomized studies or high-quality research evaluating PET-CT surveillance. Thus, without a randomized experimental design it is difficult to prove that melanoma survival is superior in those who were allocated imaging. Surveillance imaging has also not yet been associated with cost-effectiveness [15,61].

Expert consensus has largely informed American and European guidelines due to limited high quality data to support the use of imaging surveillance in melanoma patients for monitoring of relapse after curative

Table 1. Summarized Considerations for Melanoma Imaging Surveillance.

Patient group	Consideration/Recommendation
Sentinel lymph node positive, prior intransit metastasis or microsatellite	Regular PET-CT and MRI brain/CT brain surveillance (<i>i.e.</i> every 6 months) in addition to clinical examination and full skin examination
Sentinel lymph node positive patients without completion lymph node dissection	Additional consideration regular ultrasound surveillance of regional lymph node basin
Patients not recommended (<i>i.e.</i> Elderly or comorbid) or decline a sentinel lymph node biopsy	Regular ultrasound surveillance of regional lymph node basin in addition to clinical examination and full skin examination
Thick, ulcerated primary melanoma (Stage IIC)	Consideration of regular PET-CT and MRI brain/CT brain surveillance given poorer survival than Stage IIIA patients in AJCC 8 th edition staging

intent resection. The potential benefit of early detection of asymptomatic disease has only been realized with the recent availability of effective systemic treatment options for melanoma patients. Prior to modern therapies, the benefit of surveillance was difficult to ascertain due to largely ineffective chemotherapies and poorly tolerated interferon therapies. To further complicate available data, many studies have enrolled differing proportions of melanoma stages and varying AJCC staging editions, leading to difficulty in comparing results between studies. Initial imaging surveillance studies were traditionally limited by availability of less sensitive imaging modalities (*e.g.* CXR and CT only) compared to current modern approaches through the more accurate PET-CT. Small sample sizes and limited duration of follow-up to measure long term outcomes add to constraints of available evidence surrounding PET-CT use in melanoma patients.

Other reports have suggested that patients or their partners can detect the vast majority of recurrences in melanoma due to a relative high frequency of cutaneous and nodal spread that is visible or palpable [16,62]. In multiple studies a significant proportion of cases were found by clinical suspicion rather than true asymptomatic surveillance. The detection rates for cross sectional imaging of asymptomatic distant metastases vary between 15 and 72% depending on stage of patients screened [62-64], given that risk of distant metastatic disease varies by stage [65].

There can be disadvantages to surveillance imaging. One key risk to the patient is through detection of non-specific findings or false positive findings for metastasis [17,31,66]. In addition to this, patients can experience significant anxiety whilst awaiting their scan results affecting their quality of life. Additional invasive investigations are often required to further investigate both non-specific findings and false positives which can lead to further adverse effects and waiting [66,67]. False positive rates have attempted to be quantified. One study found PET surveillance in stage IIIA metastatic melanoma patients to be associated with an 8% false

positive rate [31]. An Australian study found that 7% of all patients had false positive PET findings with near all (86%) of these false positive findings undergoing biopsy to investigate these findings [17]. Amongst 154 patients with resected stage III melanoma over a 7-year period, the frequency of false positives was 5-14% per year, and an additional 181 tests, procedures, and referrals were initiated to investigate these findings [68]. The diagnosis was benign in 109 findings of 124 findings (88%). Fifteen patients with a benign finding underwent an unnecessary invasive procedure [68]. As part of the desirable characteristics of surveillance it has been argued that higher sensitivity tests are more favorable at the expense of specificity and thus false positives. It is also understood that PET/CT is unable to detect avid disease less than 5mm in size [69-71].

The first question for clinicians is who to consider for surveillance to best balance benefits and risks of surveillance. Patients with stage III metastatic melanoma, (where there has been histologically confirmed spread of melanoma to lymph nodes, intransit metastases or satellite metastases) are associated with a high risk of recurrence or progression of disease to stage IV metastatic melanoma despite curative intent resection [65,72,73]. This risk has been shown to be different for each sub-stage of Stage III metastatic melanoma (A, B, C) as per the latest 8th edition American Joint Committee on Cancer (AJCC) data [65] (Table 1). The relative poor mortality of stage IIC melanoma lesions in the AJCC data (thick, ulcerated primary melanoma lesions without evidence of lymph node metastasis) also merit consideration of surveillance [65]. Some patients groups pose additional challenges with respect to surveillance. Solid organ transplant patients who are BRAF negative have limited treatment options due to contraindication of immunotherapy due to risk of rejection [74]. Surveillance imaging in this group is therefore useful for directing surgical and radiotherapies and prognostication only. Similar issues arise in patients with pre-existing autoimmune conditions where immunotherapy is contraindicated [75].

The other conundrum for clinicians is at what frequency should surveillance scans be performed and for what duration of time, as some patients can experience late recurrence. Given some studies have performed PET scans every 6 months, it can be argued that PET/CT should be considered for high risk (e.g. Stage IIc and above patients) every 6 months [17,34,68]. Whilst there is lack of long term follow-up data to assist with answering the duration of surveillance PET-CT, two studies have demonstrated that the highest risk of recurrence occurs within the first 2 to 3 years [17].

CONCLUSIONS AND OUTLOOK

Informed consent remains a vital component of the discussion with patients with melanoma when clinicians consider surveillance radiographic investigations. Although many patients and clinicians have become more attracted to surveillance investigations with the goal of both early detection of progressive disease and reassurance, clinicians are recommended to always provide a risk versus benefits discussion to patients prior to requesting imaging. This discussion on the benefits and disadvantages of imaging surveillance in melanoma should include the risk of false positives compared to their risk of recurrence.

Overall, there are multiple imaging modalities available to patients for surveillance of their melanoma. Staging with PET-CT or CT of the neck, chest, abdomen, and pelvis in conjunction with brain imaging with either CT brain or MRI of the brain may be indicated in patients with Stage IIC melanoma and above. Surveillance imaging every 6 months is supported by limited data, with some patients with very high risk or high tempo aggressive disease potentially requiring more frequent imaging (e.g. every 3 months). Future research is needed to more precisely define benefits of melanoma imaging surveillance, especially cost-effectiveness.

Follow-up of any patient with melanoma, regardless of whether radiological surveillance is indicated or not, should be supported by regular routine clinical examination in patients with melanoma, again stratified to their risk for recurrence or new primary melanoma. This should include a full skin examination as well as palpation of nodal basins. Such clinical examination is important to facilitate detection of additional primary melanomas, which unless thick or metastasized, will not be generally detected on PET-CT due to their small size.

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