Chapter 15

# Surgery and the Staging of Melanoma

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## 1. Introduction

An estimated 166,900 patients were diagnosed with malignant melanoma in developed countries last year [1]. The reported incidence of malignant melanoma continues to rise despite increasing understanding of its aetiology. In the United States 76,250 new cases are expected in 2012 with melanoma far outstripping other skin cancers in terms of mortality [2]. Similarly, in the UK, 12,818 new cases of malignant melanoma were diagnosed in 2010 [3]. Approximately, 85% percent of patients with cutaneous melanoma are diagnosed at a localized stage, while 10% have associated regional lymph node involvement and 5% of patients will have distant metastatic disease at presentation. The corresponding 5-year overall survival rates are 98.2% for localized disease, 62.4% for regional lymph node involvement and 15.1% for distant melanomas [4, 5].

Advances in the understanding of the molecular mechanisms and immunology of melanoma have lead to the development of promising novel therapeutic agents. Surgery, however, remains the mainstay of treatment and changes in the surgical approach have been guided by the greater understanding of melanoma pathogenesis. The management of the primary tumour has become more conservative, with acceptance of narrower excision margins. In addition, there has been a move away from the routine performance of elective regional lymph node dissection towards sentinel lymph node biopsy which is associated with less morbidity [6].

The new American Joint Committee on Cancer (AJCC) guidelines for the staging of melanoma were introduced into clinical practice in 2010 [7]. The two most important distinctions with previous guidelines are the incorporation of the mitotic rate of the primary tumor and the key role of the sentinel lymph node, including methods of analysis, in accurately staging clinically occult nodal disease [8].

The purpose of this chapter is twofold. Firstly, this chapter describes the appropriate surgical management of the primary tumour, the associated regional lymph node basin and distant metastatic disease. Secondly, the updated and revised AJCC staging system will be discussed and current controversies addressed.

## 2. Risk factors

The worldwide incidence of melanoma doubles every ten to fifteen years [9]. Risk factors associated with the development of malignant melanoma are varied and include genetic susceptibility, exposure to ultraviolet radiation, and immunologic factors. The most important of these is ultraviolet exposure where intermittent, unaccustomed sun exposure and sunburn were found to have considerable roles as risk factors for melanoma. However, despite the increase in public awareness, the practice of ultraviolet radiation protection behaviour is low. Also worryingly a survey performed in the US in 2005 documented that up to 14% of adults, primarily women and young adults used an indoor tanning device on at least one occasion [10].

Epidemiological studies have found that blue, green or grey eyes, blonde or red hair, light complexion, freckles, sun sensitivity, and an inability to tan, are risk factors for the development of melanoma [11, 12]. Countries with close proximity to the equator with predominantly fair-skinned populations have shown a higher preponderance to developing melanoma. Risk factors for melanoma also include a positive family history or personal history of melanoma/non-melanoma cancer or in-situ skin carcinomas, large numbers of melanocitic naevi in childhood, and xeroderma pigmentosum [13].

It is suggested that minimising radiation, and the adoption of photo-protective measures, can significantly reduce the risk of developing melanoma [13-15].

## 3. Surgery

### 3.1. Initial surgical biopsy

Melanoma can develop either in a pre-existing pigmented lesion or de novo. Features raising suspicion of melanoma in a pre-existing pigmented lesion include a change in size, irregular shape, irregular colour, diameter 7 mm or more, inflammation, oozing or a change in sensation [5,16]. The ABCD system of diagnosis (Asymmetry, Border irregularity, Colour change, and a Diameter greater than 6 mm) has also been advocated to assist early clinical diagnosis, to which 'E' (Evolving or Elevation) has been added [5,17,18]. Table 1 illustrates the seven point checklist and ABCDE system for the assessment of pigmented lesions.

| Seven point checklist | The ABCDE lesion system |
|---|---|
| *Major features* | |
| Change in size | A Geometrical Asymmetry in 2 axes |
| Irregular shape | B Irregular Border |
| Irregular colour | C At least 2 different Colours in lesion |
| *Minor features* | D Maximum Diameter >6mm |
| Largest diameter 7mm or more | E Elevation |
| Inflammation | |
| Oozing | |
| Itch/ change in sensation | |

**Table 1.** Seven point checklist and ABCDE system for assessment of pigmented lesions [19]

An excision biopsy is indicated for lesions suspected of being a melanoma. An excision biopsy is the recommended method for suspected malignant melanoma as it enables diagnosis and staging of the tumour and may determine future treatment and prognosis [20, 21]. The whole lesion should be excised with a 1-3 mm margin of normal skin including sub-dermal fat. It is crucial to plan this excision carefully with a view towards definitive treatment. Knowledge of lymphatic drainage and subsequent need for sentinel node biopsy should lead to narrow margin excision potentially avoiding interference with subsequent lymphatic mapping. In addition, a longitudinal orientation is preferred in the extremities and incision orientation should be along Langer's lines on the trunk. This allows for subsequent closure of a wide local excision and reduces the need for skin grafting if primary closure is to be achieved.

In certain areas (such as the face, palm of hand, sole of foot, ears, digits and subungal lesions) an excision biopsy may not be appropriate. In these cases, an incisional or punch biopsy of the thickest portion of the lesion may be performed [21]. Shave biopsy is avoided as it makes characterising the lesion difficult by underestimating tumour thickness, which is important in determining further treatment [21]. It also risks leaving residual tumour at the radial and deep margins.

Obtaining an adequate biopsy specimen is crucial for histopathological diagnosis and tumour staging. The tumour thickness, which remains the most powerful prognostic parameter, provides a guide to the margin clearance required for delayed wide excision and need for adjuvant therapy [20, 22]. Pathological examination should evaluate macroscopic fea-

tures of the tumour such as width, symmetry, and circumscription, and microscopic features such as ulceration, microsatellitosis, angiolymphatic invasion and mitotic rate [22].

### 3.2. Management of the primary tumour

The surgical management of the primary tumour has shifted from extensive surgical resection, which was not only debilitating but also disfiguring, to a more conservative approach. A multidisciplinary team in a tertiary referral centre should ideally manage patients with malignant melanoma. This team should include: a surgeon, dermatologist,,medical oncologist, pathologist, radiologist, counsellor, specialist nurse and palliative care specialist [23].

Pathological assessment of the surgically excised biopsy specimen allows for staging of the tumour while the thickness of the melanoma at initial biopsy serves as a guide to the subsequent resection. The Breslow thickness, which is the most important prognostic indicator of localised disease, is defined as the distance of invasion and is measured from the granular layer of the epidermis to the point of deepest invasion by tumour cells [5, 24, 25].

Large randomised controlled trials have been performed in an attempt to elucidate the optimal resection margin in melanoma of various thickness (thin, intermediate, and thick melanomas) [26-31]. The trials reported data with not only differing lengths of follow-up but also differing margin excision widths. Therefore interpretation of the results is largely restricted to survival outcomes as a result of this heterogeneity.

The management of lentigo maligna and in situ melanoma present unique problems because of the characteristic, yet unpredictable, subclinical extension of atypical junctional melanocytic hyperplasia, which may extend several centimeters beyond the visible margins [33]. There are no randomized trials looking at the optimal resection margin in these lesions. Guidelines from the American Academy of Dermatology in 2011 recommend a resection margin of 0.5 to 1.0 cm for melanoma in situ [34]. The NCCN recommends a margin of 0.5 cm around the visible lesion. For large in-situ lentigo maligna melanoma, it is felt that surgical margins greater than 0.5 cm may be necessary to achieve a histologically negative margin [33]. More recently, topical imiquimod has been used in lentigo melanoma treatment prior to definitive surgical resection. In a study that included 40 patients, 33 of these were found to have a complete clinical response after the use of imiquimod 5% cream. On histological review, 30 of the patients had no evidence of melanoma. While studies have shown a limited role for this treatment, it does not replace surgery [35].

Three main trials (The World Health Organisation Trial, Swedish Melanoma Study and the French Cooperative Group) looked at the optimal resection margin for T1 and T2 melanomas. The World Health Organisation (WHO) trial included 612 patients with melanomas less than 2.0mm with patients being randomly assigned to a wide local excision with a either a 3cm margin or 1cm margin. At 12 years of follow up, similar survival rates between the groups were noted (87% and 85% respectively) with no statistically significant difference in recurrence dependent upon margin width. As a consequence of this trial recommendations were made that a 1cm margin be used for melanomas ≤1mm. Similarly, the Swedish Melanoma Study Group studied 989 patients with melanomas 0.8 to 2mm thick who were ran-

domly assigned to either a 2cm or 5cm resection margin. At a median follow-up of 11 years the local recurrence rate for all groups was less than 1%. Again there was no significant difference noted in the overall or disease-free survival between the two groups. A third trial, the French Cooperative Group, included 362 patients with melanomas ≤2mm in thickness. Patients were randomly assigned to a wide local excision with either a 2cm or 5cm resection margin. No difference was noted between the groups in terms of local recurrence or overall survival. Therefore at present, a resection margin of 1cm is recommended for melanomas <1mm and 2cm for melanomas 1 - 2mm thick [26-28].

Melanomas between 2 - 4mm are considered intermediate thickness melanomas. Once again, there are a number of trials looking specifically at this cohort of patients which failed to show a benefit of greater than a 2cm excision margin. The Melanoma Intergroup Trial included 468 patients with melanomas of 1 to 4mm thickness. Patients were randomly assigned to an excision margin of either 2cm or 4cm. Forty two percent of patients in the group undergoing 2cm excision had a melanoma thickness >2.0mm, while 46% of patients in the 4cm resection group had melanomas >2.0mm. At mean follow up, a 2cm margin was shown to be as effective as a 4cm margin in both the local control and overall survival for patients with intermediate thickness melanomas. Local recurrence however, was primarily determined by the thickness of the primary lesion and the presence or absence of ulceration [29, 30]. A multi-centre European trial was also performed to tease out the need for wider margins in deeper, intermediate thickness melanomas. In total, 936 patients were included who were assigned randomly to have either a 2cm or 4cm resection margin. At a follow-up of almost 7 years there was no statistically significant difference noted for recurrence or survival between the two groups [31]. Finally a British trial was performed which recruited 900 patients with lesions greater than 2mm to a wide local excision with either a 1cm or 3 cm margin Interestingly, this study demonstrated a higher local recurrence rate when a 1cm margin was used. However, there was no statistically significant difference noted in overall survival. The authors therefore concluded that a margin of 1cm should be restricted to patients with a melanoma thickness of less than 2mm [32]. Therefore, at present a 2cm excision margin is recommended for intermediate (2 – 4mm) thickness melanomas.

There is unfortunately limited evidence or published data on the optimal resection margin for melanomas with a thickness of 4mm or greater. The British Trial included 243 patients with melanomas of > 4mm thickness and the results showed a higher local recurrence rate associated with a margin of 1cm [32]. However, the local recurrence rates with a 3cm margin appeared similar to other trials with only a 2cm margin of excision. In a retrospective review from MD Anderson which assessed patients with melanomas of greater than 6mm thickness, excision margins greater than 2 cm were not found to effect overall survival when compared to margins of 2cm or less. The 5-year overall and disease free survival rates were 55% and 30% in node negative compared to node positive patients which were included in the study. Nodal status, thickness, and ulceration were significantly associated with overall survival by multivariate analysis. However, the neither the disease free nor overall survival was effected by the presence of a local recurrence or the original excision margin in this study [36]. The study authors therefore concluded that a 2 cm margin of excision is adequate

for patients with thick melanoma [36].However, overall there is insufficient data to support the preferred use of either a 2cm or 3cm margin, and consequently, it may be reasonable to allow the patient to decide, following an informed discussion of surgical options. The use of the larger 3cm margin may be recommended in patients with deep tumours (> 4mm depth), due to the higher risk of loco-regional recurrence [32]. In selected cases, however, margin size may be modified to accommodate individual anatomic or cosmetic considerations [23].

Although radial excision margins remain somewhat controversial, the depth of excision in clinical practice is defined as an excision down to but not including the deep fascia [37]. This definition has been internationally accepted and forms the basis of the current gold-standard management of melanoma. Unfortunately in facial areas where the 'deep fascia' is less clearly defined (for example, on the ear, nose, or eyelid), or other anatomic sites such as over the breast, existing studies provide no clear guidelines for optimal depth of excision [5].

| Margins | |
|---|---|
| Tis | Histologically clear margins are adequate |
| T1 | 1cm margin is recommended |
| T2 | 1-2cm margin recommended |
| T3 | 2-3cm margin recommended |

**Table 2.** Recommended excision margins based on tumor size [23]

Despite all the evidence discussed above, controversy still remains regarding the optimal width of the surgical excision margins in malignant melanoma and current evidence is not sufficient to address the optimal surgical management for all melanomas. Indeed a Cochrane review which has been recently published attempted to address this complex question [5]. Overall, there was no statistically significant difference in overall survival between either a narrow or wide excision, but this meta-analysis was confounded by the fact that excision margins were not standardized between studies within the overall analysis. Therefore the dilemma regarding surgical margin remains. However, guidelines regarding margin width have been published and should be adhered to where feasible. Further studies are required to determine the appropriate local treatment for thick melanoma which has not been comprehensively addressed in trials thus far.

### 3.3. In-transit metastasis

The treatment of advanced or recurrent melanoma remains controversial. Around 10% of patients develop in-transit or multiple cutaneous metastases but at least half will survive for two years without developing distant disease [38, 39]. Unfortunately, the 5-year survival has been reported as 12% with a median survival of 19 months [39].

In-transit metastases are defined as cutaneous or subcutaneous deposits of melanoma between the site of the primary disease and regional lymph nodes [40]. These deposits may be

found localized around the primary tumour or may be widespread throughout the affected limb or on the head and neck or trunk, depending on the primary site [40] (Figure 1). It is thought that these metastases arise from dissemination of melanoma cells via the lymphatics to tissues located between the primary tumor and the regional lymph node basin. Other theories include that of drift metastases within tissue fluid of the limb or the local implantation of circulating haematogenous melanoma cells [41, 42].

The presence of small in-transit metastatic melanoma presents specific surgical problems. Unlike nodal disease, which can be managed by regional lymph node dissection, in-transit disease is often widespread and may necessitate multiple surgeries as the disease progresses and new deposits become apparent. In its most severe form, in-transit metastasis may become severely disabling and may be refractory to treatment. Treatment is therefore, palliative, even if staging investigations fail to show evidence of distant metastatic disease [40]. Recent studies have recommended that treatment should be tailored to the extent of the disease, with treatments associated with significant morbidity being reserved for bulky advanced metastases [40].

Several therapies have been proposed for the management of in-transit metastasis including surgery, radiotherapy, and intra-lesional therapy. In-transit metastasis are sharply circumscribed with a clear line of demarcation from normal dermis and epidermis. This line does not contain any in-situ component. Therefore, wide excision margins are not recommended for these lesions and a complete macroscopic excision and primary closure is sufficient. If lesions are grouped closely together, an en bloc excision is acceptable [40].

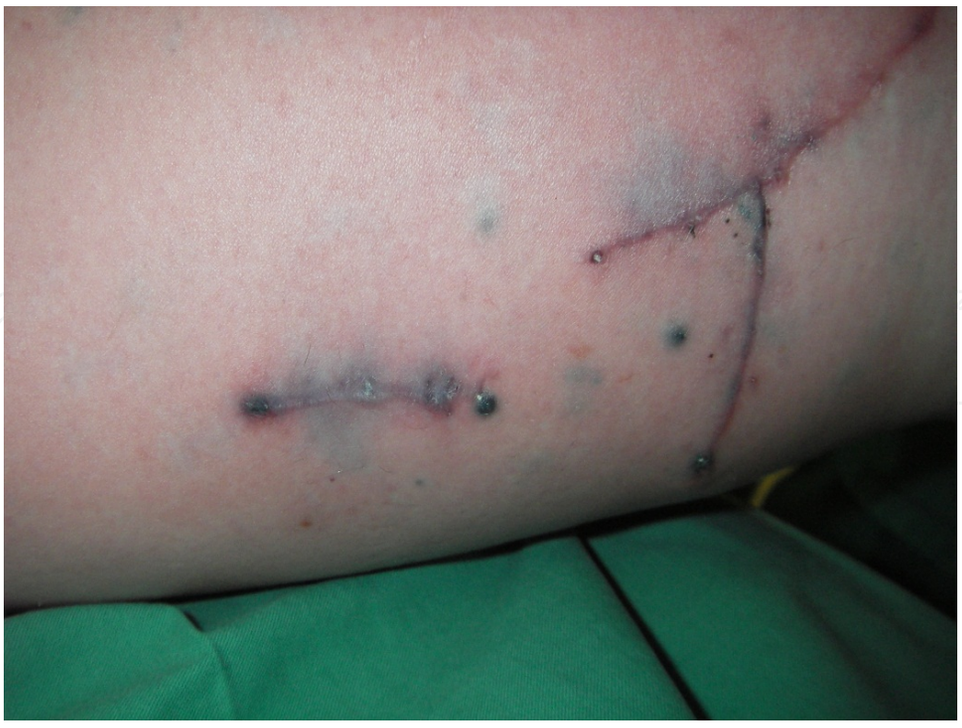

**Figure 1.** In-transit metastases on the left lower limb

There are numerous treatments available for the management of in-transit metastases that are not suitable for surgical treatment. Carbon dioxide laser therapy has been used in the management of small in-transit metastasis that are not amenable for surgical excision. This is performed as a day case under local anesthetic. Small lesions may be vaporized completely, while larger lesions are first circumscribed with the laser prior to excision of the central core. This well tolerated procedure is more suitable for smaller lesions.

In more advanced diseased, isolated limb perfusion has traditionally been the main method of treatment. This invasive procedure has been replaced by isolated limb infusion, which is simpler, minimally invasive, and a more economical alternative with comparable results [38, 39]. Isolated limb perfusion with chemotherapeutic agents was developed in New Orleans in the mid 1950s by Creech *et al* [38, 39, 43]. It is based on the principle of vascular isolation of the affected limb using a cardiopulmonary bypass circuit through open surgical cannulation of the major limb vessels. This procedure is technically difficult, expensive, and complications are common. Repeated limb perfusions are difficult to perform and morbidity rates increase from 28% to 51% [38]. A simpler alternative, isolated limb infusion was developed by Dr John Thompson in the Sydney Melanoma Unit [44]. It is a less invasive procedure, which involves percutaneous placement of venous and arterial catheters and the infusion of chemotherapeutic agents. This negates the need for a bypass circuit. As opposed to isolated limb perfusion, autologous blood or autologous transfusion of allogenic units is not required. The operating time is reduced from four hours to one hour, and the complication rates are documented to be lower, at only 1% [38, 43].

The presence of in-transit metastases indicates a poor prognosis. The development of in-transit disease may be rapidly followed by distant metastases [40]. The American Committee on Cancer Staging (AJCC) classify it as stage IIIB or IIIC disease, along with regional lymph node metastases. Five year survival rates in patients with stage III disease ranges from 18% to 60%. However, patients with in-transit metastasis have the worst prognosis, with 5 year survival of approximately 25%.

### 3.4. Reconstruction

The optimal treatment of patients undergoing melanoma excision is primary closure of the wound. Unfortunately, this is not always possible especially in patients with thick melanomas requiring wider excision margins. Therefore, in these cases reconstructive surgery must be considered and where feasible offered to the patient. This will usually depend on the site and extent of the excision to be performed. Skin grafting is the commonest technique employed to ensure skin cover of the anatomical defect. Traditionally, the graft is harvested from the contralateral limb, as melanoma was thought to metastasize primarily via lymphatic routes [15, 45, 46]. However, a recent study looking at the recurrence rates within skin graft donor sites, reported no difference in local recurrence rates when either the ipsilateral or contralateral limbs were used as graft sites. The authors of this study recommended that to improve patient recovery, harvesting the graft from the same limb as the primary tumor is both oncologically safe and technically superior to contralateral skin graft harvest [47]. In certain sites, such as the head and neck, the use of skin grafts may not always be ideal and

may result in significant deformity. Local rotation flaps, such as rhomboid flaps, have been found to be safe, versatile, and more aesthetically pleasing when used in these areas [15, 48].

## 4. Management of the regional lymph node basin

The presence of regional lymph node metastatic disease is a significant predictor of outcome in melanoma and is associated with a 50% reduction in overall survival compared to that of patients without nodal involvement [23]. Indeed the regional lymph node status is thought to be the most powerful prognostic indicator in clinically localised melanoma. The risk of patients developing lymph node metastases increases exponentially with the increasing thickness of the primary melanoma. Melanomas less than 1mm rarely metastasise (less than 10%), while at least 25% of melanomas 1.5- 4.0mm and over 60% of melanomas greater than 4.0mm thick will have lymph node metastasis at presentation[49]. These data form the basis for the current guidelines on which patients should be offered a sentinel lymph node biopsy.

Patients with melanoma can present with either a clinically normal regional lymph node basin or palpable regional lymphadenopathy. Patients with stage III disease commonly have clinically negative lymph nodes but are found to have micro-metastatic disease on their sentinel lymph node biopsy. Such patients have been found to have a more favourable outcome than patients with clinically involved nodes at presentation [8]. The outcome of patients with stage III disease is determined by the number of metastatic nodes and the presence of either microscopic or macroscopic disease. The 5-year survival rate for patients with stage IIIA disease is 67%, and the 10-year survival is 60%. Patients with stage IIIB disease have survival rates estimated at 53%, while stage IIIC disease patients have the worst prognosis with a 5-year survival of approximately 26% [49]. The surgical management of the associated lymph node basin depends on the initial presentation of the patient.

### 4.1. The sentinel lymph node biopsy

Metastasis to regional lymph nodes is an important prognostic factor in patients with melanoma, upstaging patients to stage III disease and has been shown to occur in about 20% of patients with intermediate thickness melanoma [50]. A sentinel lymph node biopsy (SLNB) is a minimally invasive procedure that aims to identify patients with microscopic lymph node metastasis who would benefit from further lymph node dissection and adjuvant treatment. The sentinel node is defined as any lymph node that receives lymphatic drainage directly from a primary tumour site [51] (Figure 2).

The technical details of sentinel lymph node biopsy can be broken down into a number of steps. First, the patient undergoes preoperative lymphoscintigraphy which identifies the regional nodal basin and estimates the location of the sentinel node. Four intra-dermal injections of 0.1–0.2 ml of 10 MBq radio-colloid are performed around the melanoma or melanoma scar: the injection should raise a small wheal on the skin. The most commonly used radiotracers are 99mTc-labeled albumin (Europe), 99mTc-labeled sulphur colloid and

99mTc-antimony trisulphide colloid. Scintillation cameras are used to obtain dynamic images. These images allow identification of sentinel nodes within the regional nodal basin. They also allow discrimination of second-tier nodes, which may be falsely interpreted as sentinel nodes on delayed imaging. The surface location of the sentinel node may be marked on the skin preoperatively or, alternatively, a gamma probe can be use to locate the node intra-operatively. Intra-operative lymphatic mapping involves injection of vital blue dye (Isosulfan blue (Lymphazurin), Methylene Blue or Patent Blue V are used). A combination of radiotracers and blue dye has been shown to allow sentinel node identification in 99% of cases. The blue dye is injected intra-dermally in 2-4 locations at the site of the primary lesion, 10-15 minutes before skin incision. The dye is used to visualize the sentinel node intra-operatively. A gamma probe (covered in a sterile plastic sheath), which detects radiation, may be used to locate the sentinel node (Figure 3). Counts should be obtained over the skin before incision, to confirm the location of the sentinel node. A short skin incision is made, bearing in mind the potential need for complete lymph node dissection. The sentinel nodes are then identified using the blue dye and gamma probe as a guide, and they are removed with minimal dissection. An ex-vivo count should be obtained, by measuring the radioactivity of the sentinel node(s) after removal. A bed count is then also obtained following removal of the sentinel node(s), to ensure that no sentinel nodes remain [15, 52].

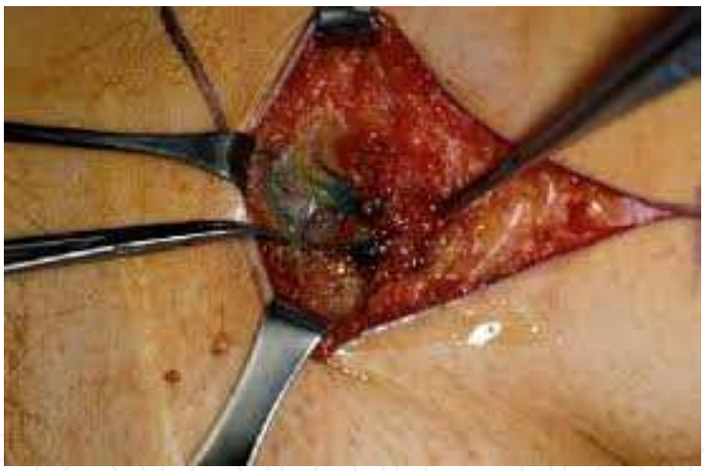

**Figure 2.** The Sentinel Lymph Node Biopsy

The Multicenter Selective Lymphadenectomy Trial-1 (MSLT-1) is the largest trial to address the role of lymphatic mapping with SLNB in determining prognosis and its impact on survival [53]. Patients with a primary cutaneous melanoma were randomly assigned to wide excision and postoperative observation of the regional lymph nodes with lymphadenectomy being performed only if nodal relapse was confirmed or to wide excision and sentinel-node biopsy with immediate lymphadenectomy if nodal micro-metastases were detected on biopsy [53]. The MSLT-1 trial confirmed the prognostic importance of SLN status, demonstrating that SLN status is the most statistically significant predictor of survival for clinically localized (stage I/II) intermediate thickness melanoma (1.2 to 3.5 mm). The 5-year disease-free

survival for patients with positive SLN status was 72.3%, compared to 90.2% in those with negative SLN status [53].

**Figure 3.** Gamma probe used to locate sentinel lymph node

The AJCC Melanoma Staging Committee recommends that a sentinel lymph node biopsy be performed as a staging procedure in patients for whom the information will be useful in planning subsequent treatments and follow-up regimens. Significant controversy surrounds the use of sentinel lymph node biopsy in thin, early melanomas. There are a number of reasons for this. Firstly, patients with a low-risk of nodal metastases are exposed to the morbidity of a potentially unnecessary procedure. Secondly, the routine use of sentinel lymph node biopsy is expensive: global application of sentinel lymph node biopsy in all patients is estimated to cost between $700,000 and $1,000,000 for every sentinel node metastasis detected [15, 54]. Therefore, for thin melanomas, the routine use of SLNB has not been advocated as the risk of positive nodes is around 5.1% [55]. Indeed, a rate of only 2.7% has been documented with melanomas thinner than 0.75mm [55]. SLNB may be considered, however, in patients with high risk features such as ulceration, a mitotic rate of greater than or equal to 1/mm$^2$ especially in patients with melanomas of ≥ 0.76 mm as they are associated with an approximately 10% risk of occult metastases in their sentinel lymph nodes [8]. SLNB is also recommended for patients with intermediate thickness melanoma (2 – 4mm). With regards to thick melanomas, it is expected that around 30% of patients will have evidence of lymph node involvement and the role for SLNB is less clear. It is, however, recommended that SLNB be performed in patients with no clinically evidence positive nodes as it allows for better chances at local disease control [50].

Recent editions of the AJCC melanoma guidelines have altered the criteria for the presence of regional lymph node disease. Originally, the 6$^{th}$ Edition of the AJCC melanoma guidelines

recommended histological confirmation of all immunohistochemically (IHC) detected metastasis by routine H&E staining and only after this confirmation could metastatic disease be documented [56]. However, the more recently published guidelines state that positive nodes may be confirmed by either H&E staining or IHC staining with melanoma associated markers [7]. The three most commonly used IHC markers for melanoma are S-100, HMB-45, and Melan A/MART 1. Currently, S-100 remains the most sensitive marker for detection of melanoma, while HMB-45 and Melan A/MART 1 are used for their specificity [57].

More recently, reverse transcriptase polymerase chain reaction (RT-PCR) has been shown to be a promising staging tool used to identify patients with histologically unidentified micrometastatic disease. This technique relies on detection of distinct mRNA expressed by melanoma cells, such as tyrosinase, MAGE-3, MART-1, gp100 and other markers [58, 59]. There has been evidence suggesting the correlation between RT-PCR positive results in blood with stage of melanoma, tumor thickness and known prognostic indicators. The value of RT-PCR in regional lymph nodes is less clear. The number of false positives due to the presence of melanocytic naevi and Schwann cells has limited its use. However, there are results that show that positive results correlate with melanoma thickness [60]. Initial results from 30-month follow-up of the Sunbelt Melanoma Trial did not show any difference in disease-free or overall survival in RT-PCR positive and negative patients [61]. The results were subsequently included in meta-analysis where it has been suggested that RT-PCR may have valuable prognostic use in the prediction of overall and disease free survival [62]. The clinical relevance of the ability to detect micro-metastases by RT-PCR is still under investigation.

### 4.2. Elective regional lymph node dissection

Completion lymph node dissection (CLND) is recommended for patients with a positive SLN biopsy. It is performed with the intention of halting metastatic spread of melanoma in the early stages of the disease [15, 62, 64]. The five-year survival rate in patients with negative complete lymph node dissection stands at 62.5%, compared with 20.3% in patients with positive non-sentinel nodes [65]. However, the exact role of this and its reflection on overall survival in the setting of positive sentinel nodes has yet to be fully elucidated.

Currently, a complete lymph node dissection is carried out for all patients with a positive sentinel lymph node, irrespective of the type of metastases (micro or macro-metastasis) identified. The value of a complete lymph node dissection in this group of patients has not been extensively investigated and it must constantly be borne in mind that completion lymph node dissection is associated with significant patient morbidity [66]. Indeed, in the MSLT-1, no improvement in OS was seen in the total group randomized to receive SLNB followed by completion lymph node dissection (CLND) if the SLN was positive compared to those randomized to WLE and observation, with nearly identical 5-year melanoma specific-survival of 87.1% versus 86.6% (P = 0.58) [53]. Studies that looked at this difference did not show any statistical significant between the two groups. In addition, it is felt that micro-metastases will become evident if left untreated. Patients with nodal metastases were shown to have a survival advantage with early intervention com-

pared with those who had a delayed lymphadenectomy only when they presented with clinically evident nodal metastasis [15, 53, 67].

However, a significant survival benefit has been noted in patients with a positive sentinel lymph node biopsy, who undergo a complete lymph node dissection, when compared with patients undergoing complete lymph node dissection after nodal metastases become apparent [68]. In a study conducted by Morton et al, a 5-year survival rate of 72% was seen in patients with positive sentinel lymph nodes, followed by immediate lymph node dissection, whereas patients undergoing a delayed lymph node dissection had a 5-year survival rate of only 52% [53]. Further positive non-sentinel lymph nodes are found in a relatively small proportion of patients: previously quoted figures ranged from 17%-24% [15, 69-71]. Interestingly a recent study has shown rates of further positive findings to be as low as 14.8% [15, 53].

Researchers have sought to identify factors which may increase a patient's likelihood of non-sentinel node metastases. Increasing Breslow depth has been associated with increased risk of non-sentinel node metastases, while a depth of less than 1mm has no association with any further positive nodes on completion lymph node dissection [15,65]. Studies have failed to show an association between specific tumour and patient characteristics with an increased rate of non-sentinel nodal metastasis [15, 71], However, a number of histopathological features have been shown to be associated with positive complete lymph node dissections. These include: nodular melanoma, ulceration, melanoma regression, and naevus association [15, 65]. Using a size/ulceration score, Reeves et al. showed ulceration to be an independent predictor of non-sentinel node deposits [72].

Recent studies have examined the association between the size of the sentinel lymph node deposits and the rate of positive complete lymph node dissection. Kunte et al. did not report any patients with micro-metastatic deposits on sentinel lymph node biopsy to have positive findings on complete lymph node dissection [15, 65, 73]. Another study showed a 3-year survival rate in patients with 1mm sentinel lymph node metastasis to be 100%, while 3-year survival in patients with deposits greater than 1mm was 80% [15, 74]. Ollila et al., however, found a significantly higher rate of recurrence in patients with submicrometastatic disease (ie. sentinel lymph node deposits less than 0.1mm), compared with node-negative patients [15, 75].

A significant number of these questions will be address by the publication of the results of The Multicenter Selective Lymphadenectomy Trial-II (MSTL-II) which are currently awaited [76, 77]. This trial aims to address the importance of SLN metastases, the relevance of molecular assessment of the SLN and to evaluate the therapeutic benefit of CLNB after SLNB. Within the trial, all patients with primary melanoma ≥1.2 mm or ≤1.2 mm with Clark level IV / V or ulceration undergo a SLNB. This will be analyzed by both H&E and IHC techniques. Patients with a negative SLNB by H&E and IHC will undergo RT-PCR. All SLN-positive patients identified by H&E/IHC or RT-PCR are randomized to one of two groups: observation of lymph node basin with clinical examination and repeated follow-up ultrasound scanning or to immediate CLND. Patients with negative SLN as determined by RT-PCR are assigned to routine follow-up. The primary endpoint of this study is to determine if

CLND will improve melanoma specific survival in patients with a positive SLNB. Secondary endpoints include assessing the predictive value of immune responses to melanoma- associated antigens, to analyze blood samples from patients for molecular markers of melanoma, both before and after surgery and to assess the quality of life of patients undergoing either CLND or observation after SLNB. Finally the study analyses the predictive value of certain DNA markers of the primary tumor in relation to disease outcome [76, 77].

In conclusion, in the setting of a negative sentinel lymph node biopsy, a completion lymph node dissection is clearly not indicated. The presence of positive nodes warrants consideration of complete lymph node dissection of the involved lymph node basin. Results of the MSLT-II trial are awaited and will give answers to the option of nodal observation.

## 5. Management of distant metastatic disease

The management of patients with metastatic melanoma remains challenging. Despite improved therapeutic options the prognosis remains poor. A complete surgical resection of metastatic disease in distant sites offers the best chance to improve survival. Patients with in-transit metastasis may be offered further surgical resection of the lesions. Favourable prognostic factors in patients with metastatic disease include a longer disease free survival, single site disease, complete resection and non-visceral metastases [78]. Patients that undergo resection of their non-visceral metastasis have been shown to have a medium survival of between 17 - 50 months, and a 5 - year survival of 9 - 35%. Patients with pulmonary metastasis, who have a complete resection, have a median survival of 8 - 20 months and a 5 year survival of 10 -25%. Brain and gastrointestinal tract metastasis confers a median survival of only 7-10 months [78]. Surgical resection in cases of advanced melanoma has been shown to give good palliation, if all the disease is completely removed. More recently, new systemic biological therapies have been developed, and when combined with surgery may be shown to aid in improved survival. These combinations, however, are still under review [79].

Chemotherapeutic agents have little role to play in the management of metastatic melanoma. Regimens that have previously been utilised include dacarbazine, temozolomide, high dose interleukin-2, paclitaxel and cisplatin or carboplatin. These show a response rate of less than 20% [33]. There is little evidence of its value in metastatic melanoma, however with combination treatments their role is yet to be fully examined.

In 2011, the FDA approved two newer therapies for metastasis melanoma. These include the highly selective BRAF inhibitor, vemurafenib, and ipilimumab, a fully human IgG1 monoclonal antibody. Around 40% to 60% of melanomas are shown to harbor a mutation in the gene encoding for the serine / threonine kinase protein kinase B-raf (BRAF) with 90% of the mutations resulting in a substitution of valine for glutamate at amino acid 600 (V600E) [80]. Mutated BRAF leads to constitutive activation of the mitogen-activated protein kinase pathway (MAPK) that in turn increases cellular proliferation and drives oncogenic activity. Sorafenib, the initial BRAF inhibitor failed to demonstrate significant response rates in melanoma and its use has been largely discontinued. Vemurafenib is a

newer highly selective inhibitor with promising results. The main limitation of this novel agent is its limited response with an approximately 40% to 50% response rate in patients with a V600-mutated BRAF gene. Unfortunately, the median duration of response is only 5 to 6 months [33]. GSK2118436 is a newer highly selective inhibitor of BRAF that is still in pre-clinical trials [80].

Melanoma is an immunogenic tumor. Ipilimumab is a monoclonal antibody directed to the cytotoxic T lymphocyte antigen-4 (CTLA-4). Results of two randomized phase III trial of patients with unresectable metastatic disease that progressed during systemic therapy showed an overall improvement in survival in patients randomized to the ipilimumab arm [33,81,82]). In another phase III study looking at the role of ipilumumab and dacarbazine in patients with previously untreated metastatic melanoma, ipilumumab and dacarbazine was shown to have improved patient survival in comparison to the group receiving dacarbazine alone [83[. The limitation of ipilimumab is its association with autoimmune toxicity. In addition, clinical responses may take months to become apparent, and the overall response rate is less than 20% [33]. Research is ongoing in this area. The EORTC18071 trial is ongoing and compares adjuvant treatment with ipilimumab with observation in patients with high risk lymph node positive disease [84].

The role of biochemotherapy has also been studied. This involves using a combination of chemotherapy and biologic agents [33]. The results, however, show no additional survival benefit with this treatment. Finally, palliative radiotherapy may have a role in the setting of metastatic melanoma and has been shown to have good palliation of symptomatic disease [85-87].

## 6. Staging

An updated Cancer Staging Manual was recently published by the AJCC [7]. Modifications of the melanoma staging guidelines, which have been used since 2002, were based on a multivariate analysis on 38,918 patients [8]. In the revised guidelines melanoma patients have been categorised into 3 groups; those with localised disease with no evidence of metastases (stage I - II), patients with regional disease (stage III), and those with distant metastatic disease (stage IV). Primary tumour thickness remains the factor most associated with prognosis. Tumour thickness is defined in even integers (1.0, 2.0 and 4.0mm) with increasing thickness corresponding with worsening survival. Within each tumour thickness category, the presence of ulceration further upgrades the classification (Table 3).

Mitotic rate is an indicator of tumour proliferation and is measured as the number of mitoses per $mm^2$. Several studies have shown the mitotic rate to be an independent prognostic factor in patients with melanoma [88-91]. The AJCC guidelines now recommend the "hot spot" technique for calculating the mitotic rate, where the pathologist begins the mitotic count with the most active tumour focus. This is calculated as mitosis/$mm^2$ [8]. Multiple thresholds of mitotic rate were examined statistically, and the most significant correlation with survival was identified at a threshold of at least 1/$mm^2$, where a mitotic rate greater

than or equal to 1/mm$^2$ was found to be independently associated with a poorer disease-specific survival in patients with T1 disease. For non-ulcerated, thin melanomas the 10-year survival was 95% if there were fewer than 1 mitosis per mm$^2$, compared with 88% 10-year survival if at least one mitosis per mm$^2$ was present. In addition, the level of invasion, as defined by Wallace Clark, was found to have no statistical significance in staging with the mitotic rate replacing it as an upstaging criterion from stages 1a to 1b [92].

| T Classification | Thickness | Ulceration status/mitosis |
|---|---|---|
| Tx | Primary tumour cannot be assessed (for example, curettaged or severely regressed melanoma) | |
| T0 | No evidence of primary tumor | |
| Tis | Melanoma in situ | |
| T1 | Melanoma is 1.0mm or less in thickness | a: without ulceration and mitosis <1/mm2<br>b: with ulceration or mitoses ≥1/mm2 |
| T2 | Melanoma 1.01-2.0mm | a: without ulceration<br>b: with ulceration |
| T3 | Melanoma 2.01- 4.0mm | a: without ulceration<br>b: with ulceration |
| T4 | Melanoma more than 4.0mm | a: without ulceration<br>b: with ulceration |

**Table 3.** T Classification as recommended by the AJCC [7]

Stage III patients have documented lymph node metastasis (microscopic of macroscopic) (Table 4). S-100 is the most sensitive marker for melanocytic lesions while others such as HMB-45, MART-1/Melan-A, tyrosinase, and MITF are very specific but less sensitive [93]. In terms of documenting micro-metastasis, the AJCC accepts immunohistochemical staining of at least one melanoma specific marker to make the diagnosis. Around 5% to 40% of patients will be upstaged to stage III based on the presence of micro-metastatic disease. These patients have a better prognosis than those presenting with macro-metastatic disease as shown in several studies [8, 95]. The new AJCC guidelines reviewed the results of 3307 patients and make a clear distinction between each group. Staging of this group includes defining the number of nodes involved, the presence of microscopic versus macroscopic disease, as well as intra-lymphatic (in-transit or satellite) metastasis, the presence or absence of primary tumour ulceration, and the thickness of the primary melanoma. These factors were found to be predictive of survival on multivariate analysis. In the absence of nodal metastases, patients with intra-lymphatic metastases (N2c) have 5-year and 10-year survival rates of 69% and 52%, respectively while those with combined intra-lymphatic metastases and nodal metastases (N3) have survival rates of 46% and 33%, respectively [8].

| N Classification | Nodes involved | Nodal metastatic mass |
|---|---|---|
| Nx | Regional nodes cannot be assessed (for example, previously removed for another reason) | |
| N0 | No regional metastasis noted | |
| N1 | 1 node | a: micro-metastasis<br>b: macro-metastasis |
| N2 | 2-3 nodes | a: micro-metastasis<br>b: macro-metastasis<br>c: in transit mets(s)/ satellite(s) without metastatic nodes |
| N3 | 4 or more metastatic nodes, or matted nodes, or in transit met(s)/ satellite(s) with metastatic node(s) | |

**Table 4.** N Classification as recommended by the AJCC [7]

Finally, the database for stage IV patients was expanded to include 7972 patients and the new guidelines now incorporate the serum lactate dehydrogenase as a prognostic marker included in staging (Table 5). An elevated serum LDH was found to be an independent and a highly significant predictor of survival outcome. In a study that looked at the correlation between survival in advanced melanoma from two large trials (Oblimersen GM301 and EORTC 189510), the authors reported an elevated LDH in melanoma patients compared to the normal population. A relationship was found between LD and survival [95]. Patients with elevated serum LDH at diagnosis of melanoma are staged as M1c according to the AJCC guidelines.

| M Classification | Site | Serum LDH |
|---|---|---|
| M0 | No detectable evidence of distant metastases | |
| M1a | Metastases to skin, subcutaneous, or distant lymph nodes | Normal |
| M1b | Metastases to lung | Normal |
| M1c | Metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH | Normal- visceral met(s)<br>Elevated- Distant met(s) |

**Table 5.** M Classification as recommended by the AJCC [7]

## 7. Follow-up

All patients with invasive melanoma should be followed up post-operatively, except for patients with melanoma in-situ. The aim of follow-up is to detect evidence of recurrent disease or a new primary melanoma early [97,98]. The primary site and adjacent skin should be examined for recurrence of new suspicious lesions, as well as the draining lymph node basins [23]. It is estimated that the lifetime risk of developing a second melanoma is around 4 - 6%. Furthermore, around 60 - 80% of recurrences are found at local and/or regional nodal sites. Around two thirds of these will occur within the first three years, 16% after the first five years. Recurrence after more than ten years is also recognised [23].

There is little evidence for the optimum protocol for follow-up. It appears reasonable that all patients with invasive melanoma should be followed up 6-monthly for 2 years. Thereafter, those with melanomas less than 1.0 mm in depth may be discharged from routine follow-up; other patients should be followed up for a further 3 years at 6-monthly intervals. Patients with stage III or IV disease require lifelong follow up [23].

## 8. Conclusion

The incidence of melanoma continues to rise steadily in the Western World. Despite increased awareness of the disease this does not appear to have a significant impact on its overall poor prognosis. Surgery remains the mainstay of treatment as there is little in the way of adjuvant systemic treatment. Adequate surgical margins with or without local reconstruction can improve local recurrence rates. The utilisation of the sentinel lymph node biopsy has allowed for accurate staging of the disease. The finding of positive sentinel lymph nodes requires patients to undergo further regional lymph node dissection to reduce the risk of loco-regional disease. The impact of this on overall survival has not yet been clearly elucidated. Increased understanding of the melanoma pathogenesis and molecular biology may lead to the development of novel promising therapeutic agents and individualised treatment plans for these patients..

## Author details

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