Practical Manual for Dermatologic and Surgical Melanoma Management

Delphine J. Lee
Mark B. Faries
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Contents

Chapter 1
Can We End Melanoma As We Know It? The Role of Early Detection in Defeating Deadly Skin Cancer

Elizabeth G. Berry, Olivia M. Lucero, and Sancy A. Leachman

Learning Objectives

1. To understand the most potent risk factors for melanoma development
2. To recognize and appropriately screen those deemed at high risk for melanoma
3. To learn how to take a thorough clinical and family history and to apply the "rule of three" to those who may have a genetic predisposition to melanoma
4. To identify which patients can be managed by a generalist and those who may need the care of a dermatologist or melanoma specialist

Introduction

The American Cancer Society estimates that more than 96,000 people in the United States will be diagnosed with melanoma in 2019. Melanoma is now the fifth most common cancer diagnosed in the United States [1]. If the disease has not spread to the lymph nodes or other organs, the 5-year survival for melanoma is exceeds 98%. However, survival drops steeply for more advanced disease and decreases to 22.5% for those with distant metastasis [2]. Early detection remains critical. As the majority of melanomas arise on the skin, total body skin examination (TBSE) is arguably the least invasive and most cost effective screening modality for the disease [3]. However, the US Preventative Services Task Force (USPSTF) maintained in its 2016 Draft Recommendation that adult skin cancer screening has insufficient evidence of benefit [4]. In 2017, a group of experts responded to the USPSTF by developing and publishing their own recommendations for data-driven skin cancer screening guidelines. These recommendations are outlined below and provide a framework for identifying those at high risk for developing melanoma so that they can undergo appropriate screening [5].

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Case

Ms. Smith is a 45 year-old Caucasian woman who presents to your clinic for her annual physical exam. What factors determine whether she needs routine skin cancer screening?

Additional Clinical History

While looking for overt markers of melanoma risk (Box 1.1) one can ask additional history questions (Box 1.2).

Box 1.1 Immediately Recognizable Risk Factors for Melanoma

Doorway risk assessment

- Fair complexion
  - Blonde, red, or light brown hair
  - Blue, green, or hazel eyes
  - Light skin colors (Fitzpatrick I-III skin types) [21]
- Numerous freckles
- Many visible moles
- Evidence of sun-damaged skin (see Fig. 1.1)

Box 1.2 Important Questions to Ask When Taking a History During a Skin Cancer Screening

Key clinical history questions

Do you have a history of skin cancer?
- What type?
- What treatment did you receive?
  - Topical cream (5-fluorouracil, imiquimod)
  - Curettage and desiccation (C&D)
  - Excision
  - Lymph node biopsy
  - Lymph node dissection
  - Radiation
  - Systemic therapy

Have you ever had a mole biopsied?
- Was it normal or atypical?
- Did you need additional treatment?

Do you have a history of immunosuppression?
- Solid organ transplant
- Other immunosuppressive medications for inflammatory or autoimmune conditions
- Chronic lymphocytic leukemia (CLL)

Do you have a history of severe UV exposure?
- How many sunburns did you have as a child?
- How many blistering sunburns have you had in your lifetime?
- Have you ever used a tanning bed or solarium?
  - How old were you when you started?
  - How frequently do/did you tan?
  - How many years have you tanned?

Do you have a family history of skin cancer?
- See same sub-questions for personal history of skin cancer

Do any other cancers run in the family?
- If there is a strong family history of melanoma and other cancers, has genetic testing been performed?

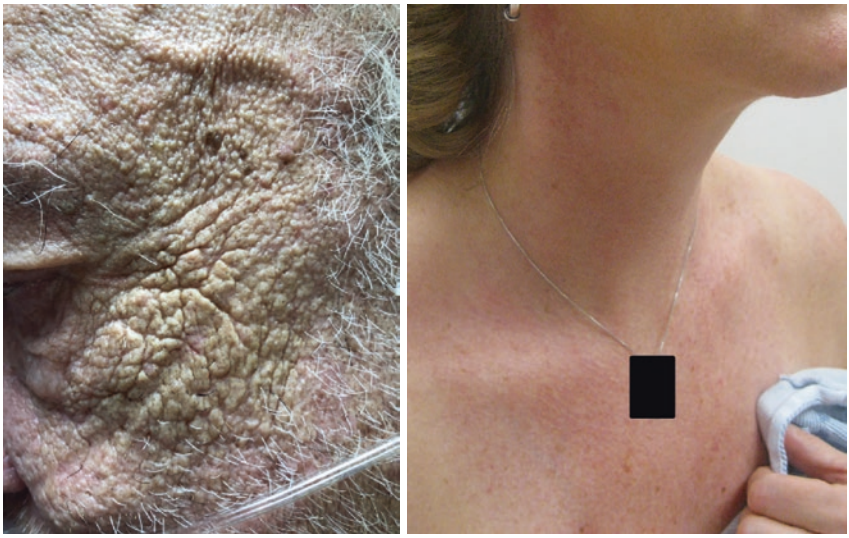

Fig. 1.1 In addition to the presence of numerous freckles, there are other recognizable features of chronic sun-damage. The deep, geometric furrows found on sun-exposed sites (called cutis rhomboidalis) are visible signs of prolonged ultraviolet (UV) radiation exposure. The combination of hyperpigmentation, hypopigmentation, and dilated blood vessels (termed poikiloderma) on the chest, anterior and lateral neck are also indicators of chronic solar damage. Poikiloderma classically spares the submental space which is relatively photoprotected. (Photos courtesy of Dr. Alex Ortega Loayza (right) and Dr. Sancy A. Leachman (left))

Ms. Smith has red hair, numerous freckles, and a few moles. She admits to using a tanning bed several times a month for about 5 years when she was in her 20s and having a few blistering sunburns as a child. Her maternal grandfather and mother were diagnosed with melanoma, but neither died from the disease. No other family members have cancer. She has never had a skin exam before. Ms. Smith is otherwise healthy.

Melanoma Risk Factors

With a comprehensive understanding of the risk factors and proposed screening guidelines listed below (Table 1.1 and Box 1.3), clinicians can identify patients who will benefit most from screening. Risk factors for melanoma development fall into several broad categories relating to phenotype, prior history of melanoma, immunosuppression, and hereditary risk. Important aspects of each category are outlined below.

While fair skin, lightly colored eyes, and poor tanning ability are all important phenotypic risk factors, red hair color, having >100 common moles, and 5 or more atypical moles are especially potent markers of risk for developing melanoma [6, 7]. Melanoma risk is elevated approximately four-fold in red heads [6, 8]. The genetic mutation primarily responsible for red hair color is *MC1R*, which encodes for the melanocortin-1 receptor. This receptor is critical for the synthesis of dark brown pigment, eumelanin, in response to UV exposure. Thus, those with an *MC1R* mutation have fair skin, red hair, increased tendency to freckle, and decreased tanning ability [8]. More recently, studies have shown that MC1R may participate in the body's ability to repair DNA damaged by UV radiation, which may further explain why mutations in the gene are so closely associated with melanoma development [9].

Moles, known clinically as nevi, are collections of melanocytes (pigment-producing cells) within the skin. In 1990, the International Agency for Research on Cancer sought to standardize the definition of the nevus. The organization defined common nevi as "brown to black pigmented macules or papules which are reasonably well defined and are darker in colour than the surrounding skin." Moreover, the IARC noted that it was important to differentiate nevi from other benign skin growths, especially "freckles, solar lentigines, seborrheic keratosis, café-au-lait spots, or non-melanocytic lesions" [7, 10]. Risk of melanoma development is directly proportional to the number of nevi. Having more than 100 nevi imparts a nearly seven-fold risk of melanoma [7].

Clinically atypical nevi are typically larger and more variegated in appearance than common nevi. To qualify as an atypical nevus, the IARC requires that one component of the nevus be macular or flat and meet at least three of the following criteria (a) poorly defined border, (b) size greater than 5 mm, (c) color variation, (d) uneven contours, (e) presence of erythema [7, 10]. Clinically atypical nevi are often biopsied due to features concerning for melanoma (see ABCDE criteria below in Fig. 1.3). Note that clinically atypical nevi are distinct from histologically dysplastic nevi, which are not discussed in this chapter. Patients with more than five clinically atypical nevi have 6.4 times the risk of developing melanoma than their peers without atypical nevi [7]. Mutations in the tumor suppressor gene *cyclin dependent kinase 2A* (*CDKN2A*), are thought to be responsible for familial atypical mole and malignant melanoma (FAMMM) syndrome and are reviewed below. Carriers of *CDKN2A* mutations have up to 28-fold risk of melanoma [11].

Table 1.1 Compilation of the most important melanoma risk factors ranked according to their associated relative risk (RR), odds ratio (OR), or standardized incidence rate (SIR) from the literature

Risk level	Melanoma risk factors	Melanoma RR/OR/SIR
Elevated risk	One atypical nevus vs 0 [7]	1.5
	Total common nevi 16–40 vs <15 [7]	1.5
	Blue eye color vs dark [6]	1.5
	Hazel eye color vs dark [6]	1.5
	Green eye color vs dark [6]	1.6
	Light brown hair vs dark [6]	1.6
	Indoor tanning ever use in any gender vs never use [12]	1.7
	Fitzpatrick II vs IV [6]	1.8
	Fitzpatrick III vs IV [6]	1.8
	History of sunburn vs no history [13]	2.0
	Blond hair vs dark [6]	2.0
	2 atypical nevi vs 0 [7]	2.1
	Fitzpatrick I vs IV [6]	2.1
	High density of freckles vs low [6]	2.1
	Total common nevi 41–60 vs <15 [7]	2.2
Moderately elevated risk	Family history of melanoma in ≥1 first degree relative [6, 14, 15]	1.7–3.0
	3 atypical nevi vs 0 [7]	3.0
	Total common nevi 61–80 vs <15 [7]	3.3
	Red hair vs dark [6]	3.6
	CLL [16]	3.9
	History of AK and/or KC vs no history [6]	4.3
	Indoor tanning ever use in women aged 30–39 years vs never use [12]	4.3
	4 atypical nevi vs 0 [7]	4.4
Marked risk	Transplant recipient vs general population [17–19]	2.2–4.6
	Indoor tanning ever use in women aged <30 years vs never use [12]	6.0
	5 atypical nevi vs 0 [7]	6.4
	Total common nevi 101–120 vs <15 [7]	6.9
	Personal history of melanoma [20]	8.2–13.4
	CDKN2A mutation carrier [11]	14–28

"Fitzpatrick" indicates Fitzpatrick skin types, ranging from type I skin that is very fair with propensity to burn to type VI skin that is very dark and never burns [21]. Atypical nevi are those that appear clinically (not histologically) atypical and have criteria based on the International Agency for Research on Cancer [7, 10]. *CLL* chronic lymphocytic leukemia, *AK* actinic keratosis, *KC* keratinocytic carcinoma. (Adapted from Johnson and Leachman (2017) [5])

Box 1.3 Proposed Skin Cancer Screening Guidelines. (Adapted from Johnson and Leachman (2017) [5])

Populations at risk for developing melanoma

Adults aged 35–75 years with one or more of the following risk factors should be screened at least annually with a total body skin examination:

- Personal history:
  - History of melanoma, actinic keratosis/es, basal cell carcinoma, or squamous cell carcinoma
  - *CDKN2A* (or other high-penetrance gene[a]) mutation carrier
- Family history:
  - Melanoma in one or more family members
  - Family history suggestive of a hereditary predisposition to melanoma
- Physical features:
  - Fair skin (Fitzpatrick I-III)[b]
  - Blonde or red hair
  - >40 total nevi
  - ≥2 atypical nevi [7, 10]
  - Many freckles
  - Severely sun-damaged skin
  - UV radiation overexposure
    History of blistering sunburns
    History of indoor tanning

[a]High penetrance genes [47–50] available in panel tests: *BAP1, CDK4, CDKN2A, MITF, POT1* – available on research panels: *ACD, BRCA1, BRCA1, MC1R, PTEN, RB1, TERF2IP, Tert* (promoter), *TP53*
[b]Fitzpatrick skin types [21]

Personal history of melanoma is also among the most potent risk factors for development of subsequent melanoma. Lifetime risk of a second primary melanoma is elevated nearly 13-fold. A study of patients within the Kaiser Permanente Healthcare System found that the risk of developing a second primary melanoma is approximately 2% per year for the first year after diagnosis of the first melanoma. The risk then remains at 1% a year for at least 15 years [22]. Patients with a history of melanoma should be managed carefully by a team of specialists in accordance with the National Comprehensive Cancer Network (NCCN) guidelines for the disease [23].

The immune system is the first line of defense against melanoma, and immunosuppression (whether exogenous or endogenous) can profoundly increase the risk of developing the disease. In solid organ transplant recipients (SOTR), melanoma has increased incidence and more aggressive behavior [17]. The risk of development of melanoma is 2.2–4.6 fold in SOTR [17–19]. This risk translates to patients on immunosuppressive medications for other inflammatory or autoimmune conditions, and this population should also be monitored closely. Chronic lymphocytic leukemia (CLL) also significantly increases the risk of skin cancer [19]. A recent study estimates that patients with CLL have 3.9 times the risk of developing melanoma [16].

Many researchers have questioned whether HIV impacts risk for development of melanoma. Although a meta-analysis in 2014 showed 50% increased risk of melanoma in patients with HIV (after adjusting for ethnicity) [24], more recent studies have been unable to demonstrate an association between HIV infection and development of melanoma [25–27]. In light of these findings, providers should use the other risk factors outlined in this paper to guide screening for patients with HIV.

The data are also mixed for risk of melanoma in the setting of exposure to TNF-alpha inhibitors (TNFi) and other biologic immunomodulating therapies. A 2016 meta-analysis showed an approximately 80% increased risk of melanoma in patients with rheumatoid arthritis (RA) treated with TNFi over the general population [28]. However, a large international collaboration involving more than 130,000 patients with RA and a more recent metanalysis of 53 studies failed to demonstrate increased risk of melanoma in the setting of TNFi exposure [29, 30]. More studies and long follow-up date are needed to better understand the risk of melanoma development in patients on TNFi and other biologic therapies for other inflammatory diseases (i.e. psoriasis and psoriatic arthritis).

Patients may be genetically predisposed to developing a melanoma. Approximately 5–12% of melanomas occur in patients with a strong family history of melanoma, with about 45% of these patients exhibiting a hereditary mutation in a melanoma predisposition gene with high penetrance.

The molecular techniques, collaboration and investment that bore the human genome project has greatly expanded our understanding of the genetic drivers underlying melanoma carcinogenesis in high-risk populations. The most well characterized and common predisposition gene is *CDKN2A*, a tumor suppressor that controls cellular proliferation and the loss of which is associated with melanoma, pancreatic cancer and astrocytoma [31–34]. Risk of melanoma in carriers of *CDKN2A* mutation has been estimated to be 28–67% by age 80 years [11, 33, 35–37]. This risk doubles in the presence of a *MC1R* pathogenic mutation [37]. Other highly penetrant melanoma predisposition genes include *cyclin-dependent kinase 4* (*CDK4*), *protection of telomeres* (*POT1*), *BRCA1-associated protein-1* (*BAP1*) and *microphthalmia-associated transcription factor* (*MITF*) (Table 1.2) [38–44].

Table 1.2 Highly penetrant melanoma predisposition genes

	Physiological role	Clinical manifestations
BAP1	Cell cycle, apoptosis and DNA damage response regulation	Uveal melanoma, paraganglioma, mesothelioma, cholangiocarcinoma, clear cell renal carcinoma, atypical Spitz tumors.
CDKN2A	Cell cycle regulation	Melanoma, pancreatic cancer, astrocytoma
CDK4	Cell cycle regulation	
MITF	Regulates genes involved in cell differentiation, proliferation and survival	Melanoma, renal cell carcinoma
POT1	Regulation of telomere length and protection	Melanoma, gliomas

Table 1.3 Hereditary cancer syndromes associated with melanoma

Syndrome	Gene
Xeroderma Pigmentosum	*XP A-G*
Li-Fraumeni	*TP53*
Cowden Syndrome	*PTEN*
Breast and Ovarian Cancer Syndrome	*BRCA1/2*

Additionally, it should not be surprising that other hereditary cancer syndromes that arise from mutations in genes that encode proteins critical in tissue homeostasis like cell cycle regulation or DNA repair have been associated with an increased risk of melanoma, including Xeroderma Pigmentosum, Li-Fraumeni, Cowden Syndrome, and Breast and Ovarian Cancer Syndrome (Table 1.3) [45].

The gold standard for diagnosis of a hereditary cancer syndrome is genetic sequencing of cancer predisposition genes. However, given the low incidence of hereditary cancer syndromes and risks of genetic testing (discussed below), it is not appropriate to test every patient diagnosed with melanoma. To alert providers to a potential *CDKN2A* mutation, an international consortium showed that the presence of three or more melanomas or *CDKN2A*-associated malignancies (pancreatic cancers or astrocytomas) in a patient with melanoma or a blood relative carries a 10% pre-test probability of finding a pathogenic mutation in *CDKN2A*. Accordingly, a "rule of three" has been used in the United States to identify these high-risk patients [46]. The pre-test probability of finding a highly penetrant *CDKN2A* mutation is impacted by the incidence of melanoma in the given geographic location. Thus, the higher incidence of melanoma in Australia raises the threshold to five instances to raise concern for a hereditary risk. Likewise, two instances are utilized in Italy where the relative incidence is lower. In the last decade, the recognition of other highly penetrant predisposition genes and hereditary cancer syndromes with a lower melanoma penetrance has led to an evolution in genetic testing guidelines (Fig. 1.2). In general, a provider should be suspicious of a genetic predisposition if a patient with melanoma and their blood relatives have three instances of melanoma or related cancers that raise concern for a melanoma dominant hereditary syndrome like *BAP1* or *CDKN2A*. Additionally, a high incidence of common cancers or high risk features that satisfy NCCN criteria for genetic testing should also prompt consideration given other cancer syndromes can manifest melanoma with lower penetrance. With advances in genetic sequencing, it is now most feasible to test a panel of predisposition genes rather than a single gene. This panel can be designed to include high risk predisposition genes in the cancers manifested in that patient's pedigree [47]. As an example, a patient who has a high incidence of colon cancer and melanoma in their familial pedigree would be tested for known colon cancer and melanoma predisposition genes.

Although genetic sequencing is incredibly powerful in uncovering an individual and family's risk of malignancy, it is also nuanced. For instance, not all variants in a predisposition gene are of equal importance and some variants have unknown significance with no clear management guidelines [47]. Furthermore, identification

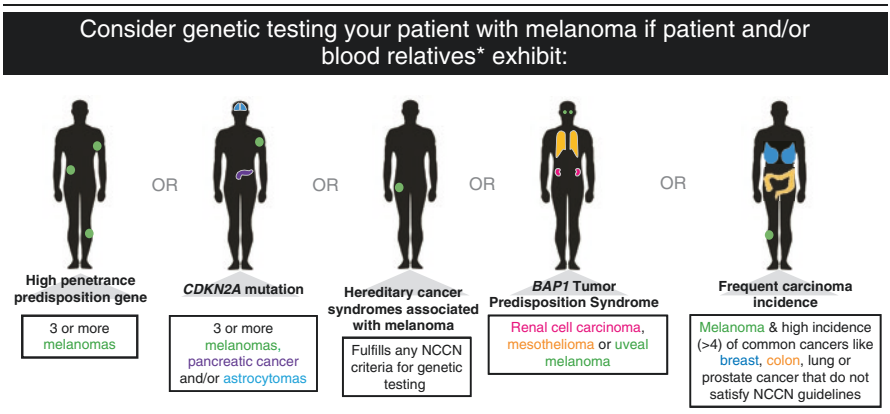

Fig. 1.2 Guideline for genetic testing. Criteria for genetic testing have been developed to identify those at highest risk for a hereditary cancer syndrome with melanoma as a feature. Of note, our identification of high risk predisposition genes continues to evolve with the increasing application of genetic sequencing to larger populations with cancer. [a]Blood Relatives include first and second degree family members related by blood. National Comprehensive Cancer Network (*NCCN*), cyclin-dependent kinase 2A (*CDKN2A*), BRCA1-associated protein 1 (*BAP1*)

of a pathogenic variant might impact the patient's ability to obtain life insurance. For this reason, a patient should always be referred to a genetic counselor to discuss the risks and benefits and to interpret the results to best guide patient management. If a genetic counselor is not available, then single gene testing for *CDKN2A* can be considered.

Patients that do not meet any established criteria for genetic testing should be managed according to their personal and family history. A positive family history (first degree relative with a diagnosis of melanoma) has been shown to have a relative risk of 1.74 (1.41–2.14) for developing melanoma when compared to those with a negative family history (see screening guidelines) [6].

Populations at highest risk for developing melanoma who should receive screening at least annually are outlined in Box 1.3. The personal history, family history, phenotypic and genotypic factors discussed above contribute significantly to melanoma risk.

Physical Exam Findings

Cutaneous melanoma can arise anywhere on the skin, even areas that have not been exposed to the sun. A TBSE comprises a systematic evaluation of all accessible skin and mucosal surfaces, including the scalp, hair, eyes, eyelids, oral mucosa, genitals, anus, and nails. The order of the examination does not matter as long as the clinician remains systematic to avoid missing any site. The clinician can easily

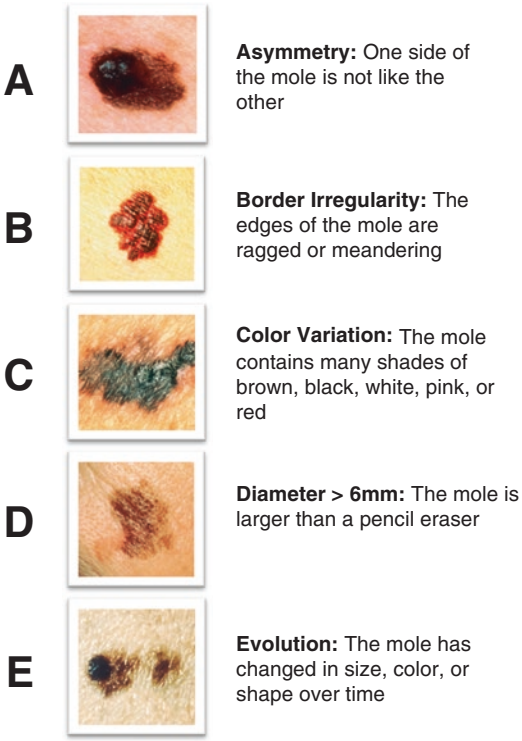

Fig. 1.3 The ABCDEs of melanoma. Figure adapted from the Oregon Health & Science University Knight Cancer Institute. Images courtesy of the National Cancer Institute

incorporate a TBSE into the workflow for a comprehensive physical exam as the patient is usually already undressed for examination of other organ systems [5, 51, 52].

The ABCDEs of melanoma (Fig. 1.3) are well-established criteria for identifying concerning lesions. Asymmetry, border irregularity, color variation (especially blue, black, and white), diameter greater than 6 mm, and evolution are all red flags for melanoma [53, 54]. The "ugly duckling sign" can be a tool in identifying outlier lesions concerning for melanoma in a patient who has many moles [55]. A clinician should always consider biopsying (or referring the patient for expedited evaluation of) any lesion that meets these criteria.

Of note, individuals who have fair complexions, especially those with red hair, may develop melanomas that have little or no pigment [56, 57]. Hypomelanotic or amelanotic melanoma often presents as a new, tender, pink macule (flat) or papule (raised). This type of melanoma is more likely to arise on sun-damaged skin. Diagnosis is often delayed for these lesions as their morphology can mimic other less aggressive types of skin cancer (i.e. basal cell carcinoma or squamous cell carcinoma) [58, 59].

For patients with a strong personal or family history of melanoma and those with numerous nevi, referral to a dermatologist or melanoma specialist is always appro-

priate. Remember importance of recording family cancer history and consider referral to a genetic counselor (Fig. 1.2).

Dermatologists are trained in the use of specialized hand-held magnifier and light source instruments called dermatoscopes to assess pigment network patterns, allowing for earlier identification of malignant lesions under the premise that microscopic architectural disorganization precedes gross observation of atypia. Furthermore, a reassuring pigment network in a lesion that appears clinically atypical can allow for avoidance of unnecessary procedures. Some dermatologists who specialize in pigmented lesions also harness the use of total body digital photography (colloquially known as mole mapping) and total body digital dermoscopy to follow patients with numerous clinically atypical nevi for mole changes or the appearance of new moles.

Discussion

Returning to the case, Ms. Smith has a number of important risk factors. Although her red hair and freckling (an indicator of chronic sun damage) are identifiable from the doorway, only a careful clinical history elicits her history of blistering sunburns as a child, two family members with melanoma, and heavy tanning bed use before her fourth decade. She does not meet the "rule of three" as only two family members have melanoma and there is no other family history concerning for a hereditary cancer syndrome. However, should she or any other family members develop any of the cancers discussed above, referral to a genetic counselor would be reasonable at that time.

With her constellation of risk factors, Ms. Smith may require more frequent surveillance for skin cancer (i.e. every 6 months). Table 1.1 is meant to rank risk factors by their reported association with melanoma in the literature. Many of the characteristics or exposures that predispose a person to melanoma are not additive but synergistic. Thus, Table 1.1 is not intended for use as a risk calculator. The clinician must carefully weigh an individual's risk factors to determine if and at what frequency screening is indicated. We do not recommend screening individuals who do not have risk factors.

Critical Take Home Messages

- When deployed in the appropriate population, total body skin examination can be a powerful tool that has the potential to diagnose melanoma at its earliest, most treatable stage.
- If you do not look for melanoma, you will not find it. Melanoma can arise in any location (not just sun-damaged sites).
- The "rule of three" can be helpful in identifying those who may have strong melanoma predisposition genes.

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Chapter 2
Melanoma Risk Factors and Prevention

Alison S. Kang and Delphine J. Lee

Learning Objectives

1. To understand the risk factors for melanoma.
2. To learn the epidemiology of melanoma in different ethnic groups.
3. To identify patients at higher risk who may need more frequent skin cancer screening.

Introduction

Skin cancer is the most common malignancy in the United States. While the exact incidence of non-melanoma skin cancers including basal cell carcinomas and squamous cell carcinomas is unknown, as they are not consistently tracked by central cancer registries, over 3 million Americans are estimated to have non-melanoma skin cancer each year [1]. While melanoma only accounts for approximately 1% of skin cancers, it is responsible for a large majority of skin cancer deaths. In 2017, there were 87,110 new cases of cutaneous melanoma and 9730 deaths due to melanoma in the United States [2]. There are four major histologic subtypes of cutaneous melanoma: superficial spreading melanoma (most common), nodular melanoma,

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lentigo maligna melanoma and acral lentiginous melanoma. Acral lentiginous melanoma is a rare melanoma subtype, accounting for 2–3% of all melanomas, and it occurs most commonly in people of color. Acral lentiginous melanoma is a challenge to diagnose, which may be due to the high prevalence of benign pigmented lesions on the palms and soles. Studies have reported a prevalence of 28% and 36% of pigmented lesions on the palms and soles [3, 4]. Given the disparities of outcomes across various factors including race, socioeconomic status and education, it is critical for thorough skin examination, education, monitoring and screening for all patient populations.

Case

A 79-year-old woman presents to your office with a lesion on her right heel. She doesn't remember it being present but seems to have been growing for the past 6 months and it is now painful and bleeds occasionally. She has hypertension and hyperlipidemia and is of African descent. She sees her physicians regularly but does not remember ever having a complete skin exam nor anyone telling her to stay out of the sun or to use sunscreen. You immediately notice a 1.5 cm × 1.0 cm hyperkeratotic dark brown plaque with surrounding bluish-black 2 mm macules on the right heel (Fig. 2.1). You recommend a deep shave biopsy and she agreed. The histopathologic exam shows acral lentiginous melanoma, with a Breslow depth of at least 7.0 mm, with tumor invasion into at least the reticular dermis. Ulceration was focally present. She received a wide local excision of the melanoma and two of two sentinel lymph nodes were positive for melanoma. She received ipilimumab adjuvant therapy, but developed pneumonitis after 3 months

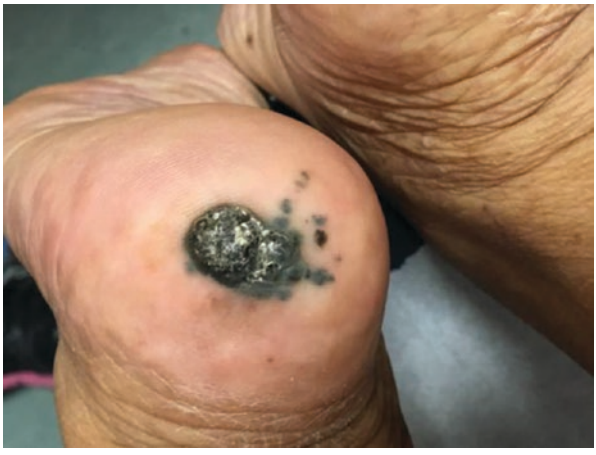

Fig. 2.1 Right heel with a 1.5 cm × 1 cm hyperkeratotic dark brown plaque with surrounding bluish-black 2 mm macules

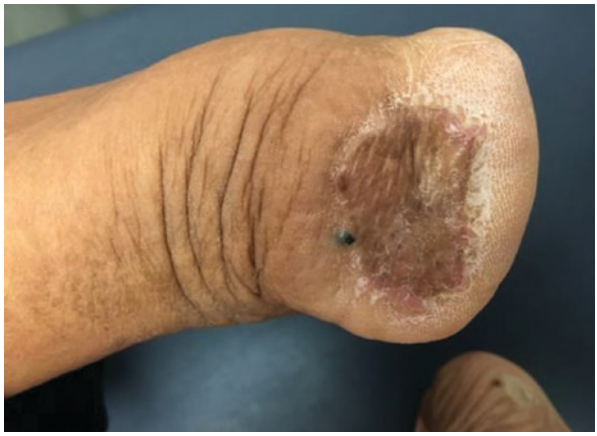

Fig. 2.2 A black macule adjacent to the wide local excision site on the right heel

of therapy and ipilimumab was discontinued. After 14 months she developed a recurrent lesion (Fig. 2.2).

Melanoma Disparities

There is disparity in melanoma diagnosis and outcome for white patients when compared to minority patients [5]. The incidence rate of melanoma varies by race, and invasive melanoma is most commonly diagnosed in non-Hispanic whites. The annual incidence rate of melanoma is 26 per 100,000 in non-Hispanic whites, 4 per 100,000 in Hispanics and 1 per 100,000 in blacks [6]. Incidence in Asians is similar to that of blacks (0.5–1.5 per 100,000) [7]. Although melanoma incidence is significantly lower in minority populations, studies have repeatedly shown that morbidity and mortality are higher in these populations when compared with whites [8–13]. Between years 2007–2014, the 5-year survival rate was 91% for white patients and 65% for black patients [2]. Even after adjustment for age, sex, histology, stage, anatomic site, treatment, and socioeconomic status, a statistically significant increased risk of death was observed for African Americans compared with non-Hispanic whites (HR, 1.60; 95% CI, 1.17–2.18) [14]. More recently, a US population-based study looking at survival trends among patients with metastatic melanoma in the pretargeted and the post-targeted era showed that while the overall survival in the post-targeted era was found to be significantly better compared with the pretargeted era in white patients, the post-targeted era showed worsening survival among African American patients [15].

Socioeconomic status has been shown to directly impact access to screening, diagnosis, treatment and overall survival in various cancers including lung and prostate cancers [16] as well as melanoma. The disparities seen in melanoma may be a consequence of socioeconomic and cultural barriers including low income, public

forms of health insurance, lower levels of education, lower levels of melanoma awareness, and lower rates of melanoma screening participation [17].

For example, a cohort of patients diagnosed with cutaneous melanoma showed that when stratified by income, patients who made less than $30,000 annually were more likely to present with advanced stages of disease at diagnosis and have thicker lesions (>2 mm Breslow depth) [18]. Medicare and Medicaid patients with cutaneous melanoma were less likely than privately insured patients to undergo sentinel lymph biopsies [19]. Furthermore, fewer Medicaid, Medicare, and uninsured patients received complete lymph node dissection [20]. The lower rate of sentinel lymph node biopsy and complete lymph node dissection may lead to understaging and subsequent undertreatment in publicly insured or uninsured patients.

When age-adjusted mortality rate trends by level of educational attainment was examined, it was found that melanoma mortality rates fell for highly educated individuals (≥13 years of education) while mortality for less-educated melanoma patients increased ($p = 0.17$) [21]. Furthermore, there is a relationship between race and levels of skin cancer awareness [22]. Minorities had lower levels of skin cancer awareness, physician-conducted skin exams, and self-conducted skin exams than whites [22]. Efforts to raise skin care awareness in the minority group is important as low levels of melanoma understanding and knowledge were associated with greater tumor thickness at the time of diagnosis [23].

Finally, health disparities also affect childhood melanoma diagnosis and outcome. A retrospective cohort study of all persons ≤18 years old diagnosed with melanoma enrolled in the Texas Cancer Registry between 1995 and 2009 showed that Hispanic children were three times more likely than non-Hispanic whites to present with advanced disease [24]. In addition, Hispanics and those in the lowest socioeconomic quartile had a significantly higher mortality risk (hazard ratios, 3.0 [95% CI, 1.2–7.8] and 4.3 [95% CI, 1.4–13.9], respectively) [24].

As providers, it is important to recognize the risk factors for the development of malignant melanoma and identify those who need screening skin exams, regardless of race or socioeconomic status.

Risk Factors

Risk factors for the development of melanoma can be divided into four broad categories: phenotypic features, personal medical history, genetic predisposition/family history, and environmental factors (Table 2.1).

Phenotypic Features

Studies have found that both the number and the type of nevi were associated with an increased risk of developing melanoma [25–28]. One clinically dysplastic nevus was associated with a 2.3-fold increased risk for melanoma (95% CI, 1.4–3.6) while

Table 2.1 Risk factors for the development of melanoma

Risk factors for the development of melanoma
Phenotypic features
• Fair skin color/Fitzpatrick skin type I • Multiple nevi (particularly large nevi) • Dysplastic nevi
Personal medical history
• History of melanoma • History of non-melanoma skin cancer • History of solid organ transplantation • History of hematopoietic cell transplantation • HIV infection
Genetic predisposition/family history
• Mutations predisposing to melanoma (e.g. CDKN2A, CDK4) • Family history of melanoma
Environmental factors
• History of sunburns • Intermittent sun exposure • Chronic sun exposure • Tanning bed use

10 or more dysplastic nevi was associated with a 12-fold increased risk for melanoma (95% CI, 4.4–31) [25]. A systematic meta-analysis showed that patients with five atypical nevi had a relative risk of 6.36 for developing melanoma compared to patients with no atypical nevus [26].

In the absence of any dysplastic nevus, the number of non-dysplastic nevi was also associated with the risk for melanoma in the case-control study mentioned above [25]. Small non-dysplastic nevi (<5 mm) were associated with increased risk for melanoma: 25–49 with 1.8-fold, 50–99 with 3-fold, and 100 or more with 3.4-fold increased risk for melanoma [25]. Ten or more large non-dysplastic nevi (>5 mm) were associated with a 2.3-fold increased risk for melanoma [25]. In addition, a systematic meta-analysis showed that the presence of 101–120 nevi compared to <15 nevi had a relative risk of 6.89 for developing melanoma [26]. Number of nevi was most strongly related to melanoma of the trunk (relative risk for having >10 nevi was 4.67 compared with having no nevi) [27]. Finally, a meta-analysis reported 42% of cutaneous malignant melanoma cases were associated with having over 25 nevi [28].

There is an inverse correlation between melanoma risk and skin color. Darker skinned individuals are at lower risk of developing melanoma on pigmented surfaces, and usually develop melanoma on less-pigmented surfaces, such as the palms and soles [29]. A systematic meta-analysis found that skin type I had a relative risk of 2.09 (1.67–2.58) when compared to skin type IV for melanoma [30].

While melanoma is more common in white patients, it is deadlier in non-white patients. Multiple studies have shown that lower survival among non-white patients with melanoma was mainly due to advanced stage and increased thickness at diagnosis [9, 12, 31, 32]. African American patients presented with tumors that were

deeper, more advanced stage, more ulcerated, and with higher rates of lymph node positivity than Caucasians [33]. Stage at presentation stratified by race showed that percentage of stage I diagnosis was 75.9% in white patients compared to 52.6% in black patients [5]. After adjustment for stage, black patients had an increased risk of death compared with non-Hispanic white patients [14, 34]. Black patients have higher cancer-specific mortality for nodular melanoma and lentigo maligna than Caucasian patients [33]. Overall survival in patients with primary cutaneous melanoma was poorest in blacks, followed by Asians, Hispanics, then whites [5]. Delay in melanoma diagnosis in non-white patients may be due to various factors including limited access to medical care, lack of melanoma awareness education, decreased providers' suspicion for melanoma in non-white, and occurrence in areas of skin that may be less examined [13]. Overall, improved education of both patients and physicians may help prevent delays in melanoma diagnosis in non-white patients.

Personal Medical History

Both personal history of melanoma as well as non-melanoma skin cancer (NMSC) are associated with increased risk of melanoma. A systemic review reported patients with history of a NMSC have a relative risk of 2.74 for developing melanoma when compared to those without a history of NMSC [35], with no large difference in relative risk between history of SCC or BCC and between male or female. Personal history of melanoma (odds ratio = 5.3) was associated with an increased risk of melanoma detection [36].

In addition personal skin cancer history, history of organ transplantation (solid organ and stem-cell) and human immunodeficiency virus infection are important risk factors. Transplant recipients' standardized incidence ratio was 2.20 for risk of invasive melanoma and these patients were reported to have higher melanoma-specific mortality compared to control non-transplant recipients (hazard ratio 2.98) [37]. Allogeneic hematopoietic stem-cell transplant recipients had an increased risk of melanoma (hazard ratio 5.5) compared with the background population [38]. Lastly, patients with human immunodeficiency virus infection/acquired immune deficiency syndrome, even after the highly active antiretroviral therapy era, have an increased risk of developing melanoma (relative risk 1.26) [39].

Genetic Predisposition/Family History

Patients may be genetically predisposed to developing a melanoma. Two high-penetrance melanoma susceptibility genes are cyclin-dependent kinase inhibitor (CDKN) 2A on chromosome 9p21 and cyclin-dependent kinase (CDK4) on 12q13 [40]. Risk of melanoma in carriers of CDKN2A mutation has been estimated to be 28–67% by age 80 years [41–44]. CDKN2A mutation carriers with one melanocortin 1 receptor (MC1R) variant showed a double melanoma risk as compared to CDKN2A mutation carriers without MC1R variants [45]. In addition, the median

age at melanoma diagnosis was 37 years in CDKN2A mutation carriers with MC1R variants versus 47 years in CDKN2A mutation carriers with no MC1R variants [45].

Patients with a positive family history (first degree relative with a diagnosis of melanoma) had a relative risk of 1.74 (1.41–2.14) for developing melanoma when compared to those with a negative family history [30].

Environmental Factors

Exposure to high levels of sunlight in childhood is a strong determinant of melanoma risk [46]. However, the definition of childhood is not consistent among studies. Individuals with a history of more than ten burns had a 6.86-fold higher risk of melanoma of upper extremity compared with those without a history of burns [27]. A meta-analysis showed that the relative risk for total sun exposure was 1.34 (1.02–1.77) and for intermittent sun exposure was 1.61 (1.31–1.99) for developing melanoma [47].

Ultraviolet light from tanning bed use can cause melanoma. Assessment of the association between risk factors and malignant melanoma using a multivariate logistic regression revealed that Fitzpatrick skin types I and II, frequent sunburns during childhood and adolescence, and use of tanning beds were strongly related to developing melanoma [48]. Individuals with first tanning bed use before the age of 35 years have a 75% increased risk of melanoma [49]. Comparing those who have ever used a tanning bed to those who never have, "ever"-users were at an increased risk of melanoma than "never"-users with an odds ratio of 1.41 (1.01–1.96) [50]. The effect of tanning bed ultraviolet light exposure may be dose responsive since patients who have used tanning beds ten or more times had an even higher odds ratio of 2.01 (1.22–3.31) [50].

Screening

There is no national consensus on skin cancer screening guidelines and the recommendations vary among professional organizations including the United States Preventive Services Task Force and the American Academy of Dermatology (Table 2.2) [51]. Although frequencies may vary, a thorough total body skin exam should be consistent. It is important to examine the toe webs, plantar surfaces and mucosal surfaces, areas which may be difficult to self-monitor.

United States Preventive Services Task Force (USPTF) published a statement in July 2016 for skin cancer screening in asymptomatic adults that reads "The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of visual skin examination by a clinician to screen for skin cancer in adults." [52].

The American Academy of Dermatology states "The AAD encourages everyone to serve as their own health advocate by regularly conducting skin self-exams.

Table 2.2 Comparison of US national skin cancer screening and counseling guidelines (Reprinted from Johnson MM, Leachman SA, Aspinwall LG, et al. [51])

US professional organization	Screening and counseling recommendations
US Preventive Services Task Force	Screening:
	– Published statement 2009: insufficient evidence to assess the balance of benefits and harms of screening for skin cancer by primary care providers or by patient skin self-examination [53]. Grade I[a]
	– Draft statement recommendation 2016: a clear statement cannot be made about the benefit of skin cancer screening for melanoma mortality and all-cause mortality or association with thinner lesions [54]
	Counseling:
	– Published statement 2012: it is recommended that children, adolescents and young adults aged 10–24 years who have fair skin be counseled about minimizing their exposure to UV radiation to reduce the risk for skin cancer [52]. Grade B[a]
	– Published statement 2012: there is insufficient evidence to assess the balance of benefits and harms of counseling adults older than age 24 years about minimizing risks to prevent skin cancer [52]. Grade I[a]
American Academy of Family Physicians	Screening:
	– Published statement 2009: current evidence is insufficient to assess the balance of benefits and harms of using a whole-body skin examination by a primary care provider or patient skin self-examination for the early detection of cutaneous melanoma, basal cell carcinoma or squamous cell carcinoma in the adult general population [55]. Grade I[a]
	Counseling:
	– Published statement 2012: it is recommended that children, adolescents and young adults ages 10–24 years who have fair skin be counseled about minimizing their exposure to UV radiation to reduce the risk for skin cancer [55]. Grade B[a]
	– Published statement 2012: there is insufficient evidence to assess the balance of benefits and harms of counseling adults older than age 24 years about minimizing risks to prevent skin cancer [55]. Grade I[a] Updated statement for 2016 pending.
American Cancer Society	Screening:
	– Published statement 2015: for people aged 20 or older who get periodic health examinations, a cancer-related check-up should include health counseling and, depending on a person's age and gender, examinations for cancers of the thyroid, oral cavity, skin, lymph nodes, testes and ovaries, as well as for other diseases besides cancer (i.e., tobacco, diet and nutrition, sexual practices, risk factors and environmental and occupational exposures [56]
	– Published statement 2016: the society recommends periodic cancer-related checkups to examine thyroid, oral cavity, skin, lymph nodes, testicles and ovaries [57]. Recommendations no longer include a specified age group

Table 2.2 (continued)

US professional organization	Screening and counseling recommendations
American Academy of Dermatologists	Screening: – Published statement 2015: the Academy encourages all members of the public to serve as their own health advocates by regularly conducting skin self-examinations. If an unusual lesion is detected, or if any lesions are changing, itching or bleeding, it is recommended that individuals seek evaluation by a board-certified dermatologist, It is also recommended that people with either a history of skin cancer or an increased risk of skin cancer discuss routine screening increments with a doctor [58]
Skin Cancer Foundation	Screening: – Recommend annual skin examinations with a physician [59]

Grade B and Grade I are based on US Preventive Services Task Force gracing definitions. Grade B: High certainty that the net benefit is moderate or moderate certainty that the net benefit is moderate to substantial. The service is recommended by the US Preventive Services Task Force and should be offered or provided to the patent. Grade I: The current evidence is insufficient to assess the balance of benefits and harms of the service

[a]Current skin cancer screening and counseling guidelines cased on several US medical organizations

Individuals who notice any unusual spots on their skin, including those that are changing, itching or bleeding, should make an appointment with a board-certified dermatologist. In addition, individuals with an increased risk of melanoma—including men older than 50; people with more than 50 moles, or large or unusual moles; individuals with fair skin; and those with a history of skin cancer—should talk to a dermatologist about how often they should receive a skin exam from a doctor." [58].

Finally, the Skin Cancer Foundation recommends that patients perform monthly self skin exams and see their physician every year for a professional skin exam [59].

Prevention

It is important to educate patients on safe sun practices and melanoma prevention. Patients should be reminded that sun's rays are the strongest between 10 a.m. and 2 p.m. Sun protection should include a broad-spectrum, water-resistant sunscreen with an SPF of 30 or higher, which should be reapplied every 2 h, as well as sun protective clothing including broad-brimmed hats and UV-blocking sunglasses. Patients should avoid tanning, both via natural sunlight as well as tanning beds. If patients desire darker "tanned" skin tones, they should consider self-tanning products in lieu of actual tanning. Finally, patients should be encouraged to perform regular self skin exams and to pay attention to any unusual spots on their skin.

While these recommendations are generally the same among patients of all skin types, providers should note that people of color may prefer sunscreens without inorganic filters such as titanium dioxide and zinc oxide due to better cosmesis on dark skin [52].

Skin exam practices and sun protective behavior vary between ethnic groups; whites and Hispanics are more likely to use sun screen than blacks and whites perform self skin examination more frequently than Hispanics [55]. A systematic review of studies that evaluated primary skin cancer prevention efforts among Hispanics in the US showed that 9.5–29.9% of the Hispanics reported wearing sunscreen either "most of the time" or "always" compared to 16.5–35.9% of the non-Hispanic whites [56].

Patients should be educated on the basic characteristics of melanoma, which may be summarized by the "ABCDEs of melanoma". ABCDE stands for asymmetry, borders, color, diameter (greater than 6 mm), and evolution. Keeping these characteristics in mind, patients should perform self-skin examinations regularly. Self-examination of skin requires a bright light, a full-length mirror, and a hand-held mirror. Blow dryers may be used to expose sections of the scalp during examination of the head and neck. In addition, a pencil and paper can be used to map out the nevi. Furthermore, family members or even smartphone apps may be helpful in detecting new or changing skin lesions. For example, the app MoleMapper™ uses the phone camera to track changes or growths of moles over time. It also helps gather data for melanoma research. Other skin monitoring apps include Miiskin™ and CompariSkin™.

Discussion of Case

1. **What is the next step in management?** The next step would be re-excision with appropriate margins of the recurrent melanoma. Then, there should be a multidisciplinary discussion involving the patient regarding the role of adjuvant therapy.
2. **How could this patient's primary melanoma have been diagnosed earlier?** As previously mentioned, the frequent delay in melanoma diagnosis in non-white patients may be due to various factors including limited access to medical care, lack of melanoma awareness education, decreased providers' suspicion for melanoma in non-white patients, and occurrence in areas of skin that may be less examined [13]. Overall, improved education of both the patient and her physicians may have led to an earlier diagnosis.
3. **How should this patient be followed in the future?** There are no standardized guidelines or recommendations for surveillance intervals. However, for this patient, it would be reasonable to perform a comprehensive history and physical every 3 months for 2 years, then every 6 months for 3 years, then annually thereafter in the absence of any disease recurrence or new skin cancer diagnosis.

Conclusions

What to remember before you walk into the room:

- Ask the patient about personal and family history that may increase his or her risk of melanoma.
- Explore patient's sun safety habits.
- Be thorough in performing a skin exam. Do not forget to examine the mucosal surfaces, hands and feet.
- Provide tips on skin cancer prevention, including how to perform self-skin examinations at home.
- Set the appropriate follow up for the patient.

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Chapter 3
The Laboratory Evaluation of Melanoma

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Learning Objectives

1. Identify key histopathological parameters for the pathologic staging of malignant melanoma
2. Identify immunohistochemical stains and molecular biological assays that may assist in confirming the diagnosis of a malignant melanoma
3. Identify immunohistochemical stains and molecular biological assays that may provide additional prognostic and therapeutic information

Introduction

The role of the histopathologist for melanoma diagnosis is two-fold. The first is to establish an accurate diagnosis documenting the necessary and appropriate histopathologic parameters that may accurately stage the primary tumor. The second is to perform adjuvant testing that may provide additional prognostic information and guide therapeutic options.

Case

A 29-year old man presented with a changing nevus on his right neck. A shave biopsy was performed revealing the histopathology of a compound proliferation of epithelioid and spindled melanocytes with no ulceration (Figs. 3.1 and 3.2). No Kamino

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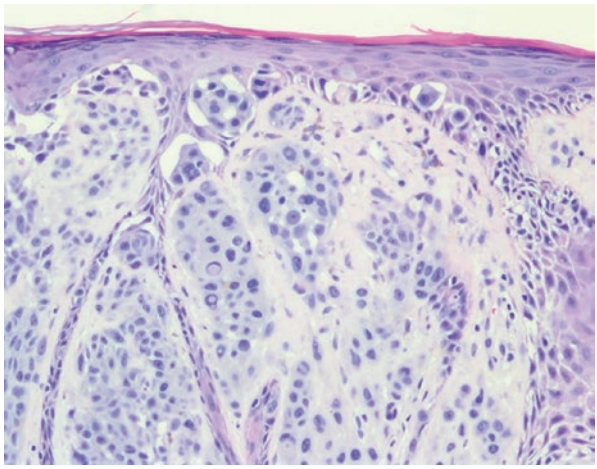

Fig. 3.1 Histopathology of epithelioid and spindled melanocytes showing junctional and dermal nests (H&E stain at 100× magnification)

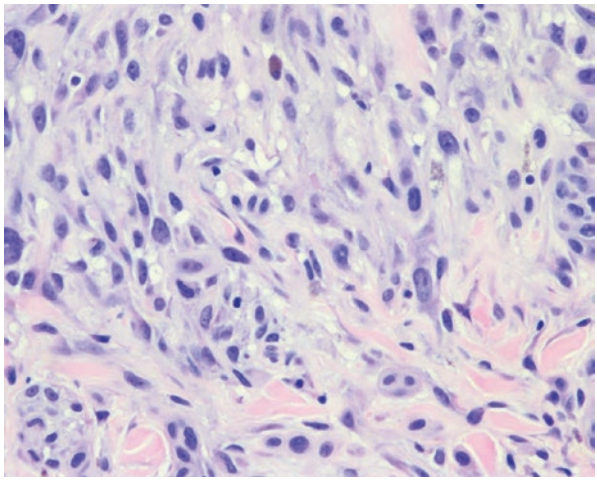

Fig. 3.2 Higher power magnification showing marked cytological atypia of the dermal melanocytes (H&E stain at 200× magnification)

bodies were present and no mitotic figures were noted within the dermal melanocytes. The lymphocytic host response was non-brisk with no lymphovascular invasion, perineural invasion, or regression.

Additional immunohistochemical studies were performed and the melanocytes were diffusely and strongly positive for S100, Melan-A, HMB-45, and SOX-10. The initial differential diagnosis was between an atypical Spitz tumor and a malignant melanoma with Spitzoid features. To assist in the diagnostic evaluation, an additional FISH assay (NeoSite™ Melanoma) was obtained which showed the following profile with the FISH results reproduced in Table 3.1 and Fig. 3.3.

These results were interpreted as positive, meeting the high stringency cut-off of >29% positive nuclei for any single probe, in this case, the CDKN2A gene on chromosome 9.

Table 3.1 Case FISH assay results

Chromosome	Results
Chrom 6: RREB1 (6p25)	13.3%
Chrom 8: cMYC (8q24)	8.9%
Chrom 9: CDKN2A (p16)/CEN 9	63.7%
Chrom 11: CCND1 (11p13)	14.2%

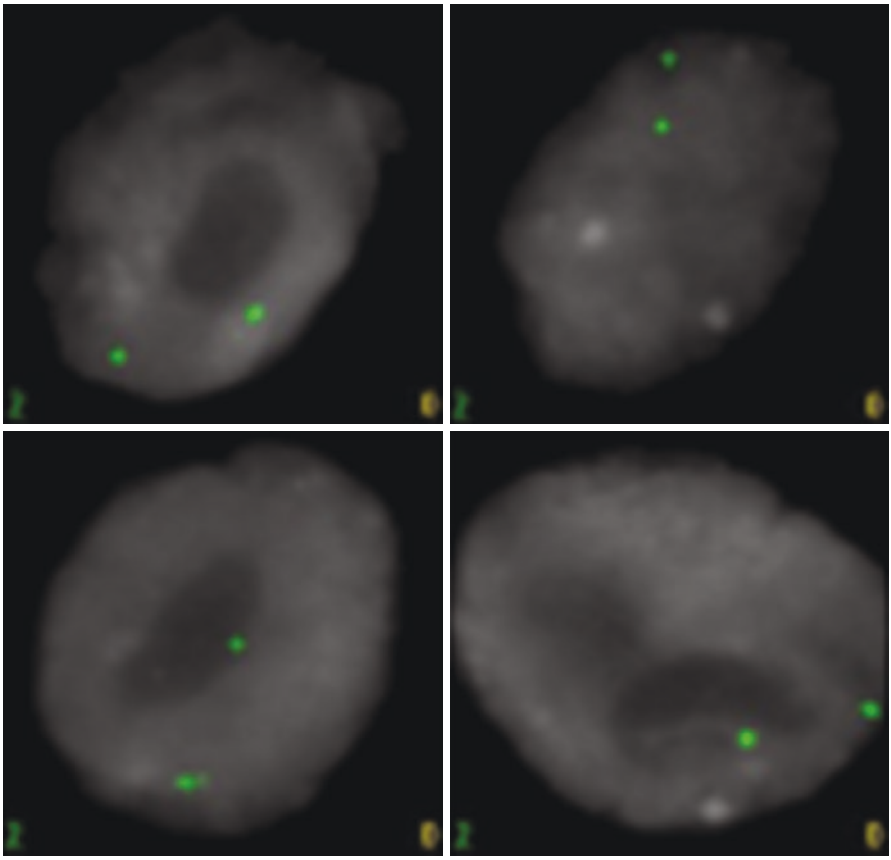

Fig. 3.3 FISH probes showing positive results for the CDKN2A gene. (Used with permission from NeoGenomics)

The final histopathologic diagnosis was:

- Malignant Melanoma with Spitzoid features
- Breslow thickness of 1.9 mm
- No ulceration
- No mitotic figures per mm^2
- Inflammatory host response non-brisk
- No lymphovascular invasion, perineural invasion, or satellite metastasis present
- Pathologic stage IB (pT2a Nx Mx)

At the request of the treating oncologist, additional adjuvant studies were performed. The melanoma was negative for BRAF-v600e mutations. After discussion with the patient and his family, the surgeon and medical oncologist elected to perform a sentinel lymph node biopsy (SLN). Three lymph nodes were obtained and were negative for metastatic disease.

Histopathology

The tissue biopsy remains the gold standard to establish a primary diagnosis of cutaneous malignant melanoma. Melanoma presents a broad diagnostic histopathologic spectrum of cytologic and architectural variants and must be distinguished from benign melanocytic lesions such as the dysplastic nevus, Spitz nevus, atypical Spitz tumors, blue nevus, and nevi harboring the BAP-1 mutation [1]. In addition, melanomas have several histopathologically subtle variants, such as nevoid melanomas, that may mimic benign nevi, and desmoplastic melanomas that mimic benign conditions such as a scar. Melanomas that metastasize to other skin sites may also histopathologically mimic a primary cutaneous melanoma, displaying an epidermotropic growth pattern [2]. There is still diagnostic discordance even amongst expert dermatopathologists when diagnosing early malignant melanomas or distinguishing melanomas from borderline atypical nevi [3, 4]. Thus, additional tests including immunohistochemistry and molecular assays may be helpful to assist in the diagnostic accuracy and interobserver concordance by providing an objective analysis of the melanoma.

The histopathologic diagnosis of melanoma is dependent upon both architectural pattern and cytomorphology. Melanoma typically displays poor circumscription and asymmetry, with a confluence of melanocytic nests composed of individual melanocytes of varied size and shape. Within the epidermis, both individual and nests of melanocytes may extend far above the dermal-epidermal junction, as far as the cornified cell layer. Within the dermis, an absence of melanocytic maturation is often noted [5]. The various histopathologic subtypes of melanoma exhibit unique findings. For example, lentigo maligna melanoma is characterized by the presence of associated solar elastosis with solitary atypical melanocytes predominating over nested melanocytes within the epidermis and extending down adnexal structures. Acral lentiginous melanomas also display a predominance of single atypical melanocytes along the basal layer, with significant pagetoid scatter of melanocytes and melanin granules. See Table 3.2 for a more comprehensive list of melanoma histopathologic subtypes.

The diagnostic report should include several important histopathological parameters. The American Joint Commission on Cancer (AJCC) 2018 update has identified Breslow thickness and ulceration as the primary histopathological parameters to stratify the pathologic stage [6]. Breslow thickness is the strongest prognostic feature for survival and is reported in millimeters measured from the top of the granular cell layer to the deepest point of tumor infiltration. Ulceration is defined as lack of an intact epidermis over a majority of the primary tumor. Additional parameters such as mitotic figure count per mm^2, tumor infiltrating lymphocytes, regression, lymphovascular

Table 3.2 Melanoma histopathologic subtypes [8–11]

Superficial spreading melanoma	The most common subtype of melanoma. This is typically a broad lesion composed of poorly-nested epithelioid melanocytes with pagetoid spread and lack of associated actinic elastosis. There is a lack of melanocytic maturation, with cytologic atypia and size of melanocytic nests in the dermis exceeding the size of nests along the dermoepidermal junction. A dense lymphoid infiltrate may be present with numerous plasma cells.
Lentigo maligna	A broad lesion of atypical, sometimes spindled, melanocytes confined to the epidermis with frequent extension along adnexal structures. The epidermis may appear atrophic with loss of rete ridges, and pagetoid spread is a less commonly observed feature. The differential diagnosis includes pigmented actinic keratosis, solar lentigo, and seborrheic keratosis. Of note, sun-damaged skin frequently exhibits solar melanocytic hyperplasia which may make the evaluation of histologic margins difficult in this entity, even with the use of MART-1 staining which may highlight keratinocytes and lead to overdiagnosis.
Lentigo maligna melanoma	The histologic features of lentigo maligna are seen (see above) but with the dermal invasion of malignant melanocytes, representing a vertical growth phase.
Lentiginous melanoma on the sun-damaged skin of the elderly (LME)	The distinctive diagnostic feature of this entity is a disproportionately broad, nested melanocytic proliferation at the dermoepidermal junction associated with significant solar elastosis. Cytologically, the melanocytes are bland and pagetoid spread is infrequently observed. Diagnosis may be impossible if partial biopsies are obtained. This entity belongs to the family of "nevoid melanomas" (see below).
Nodular melanoma	Characterized by a predominant vertical growth phase with lack of melanocytic maturation, a heavy pigment within deep dermal melanocytic nests, and foci of necrosis. A dermal lymphoid infiltrate may be present with numerous plasma cells.
Acral lentiginous melanoma	Per the name, this entity occurs on acral skin and features relatively bland-appearing and spindled melanocytes. Elongation of the rete ridges is a common feature. Of note, the pagetoid spread may also occur in benign melanocytic lesions of the acral skin.
Nested melanoma of the elderly	The junctional proliferation of atypical nests associated with significant solar elastosis. These lesions fall under the umbrella of nevoid melanomas.
Amelanotic melanoma	Melanin deposition is absent or minimally present with H&E staining. Staining for standard melanocytic markers such as S100, HMB45, and MART-1 will assist in diagnostic confirmation.

(continued)

Table 3.2 (continued)

Desmoplastic melanoma	Distinct type of spindle cell melanoma, characterized by wavy, elongated melanocytes within an abundant fibrous stroma accounting for >90% of the tumor. A lentigo maligna-like component is sometimes identified, and a dermal lymphoid infiltrate is a near constant feature. These lesions may be amelanotic. Staining is almost always positive for S100 and SOX10, but is negative for other melanocytic markers. If a conventional epithelioid or spindled melanocytic population accompanies the desmoplastic component, this is subcategorized as a mixed desmoplastic melanoma which may indicate a greater need for SLN biopsy. A diagnosis of dermatofibrosarcoma protuberans, fibrous histiocytoma, scar, and fibromatosis must be excluded. Of note, desmoplastic melanoma has a significantly higher mutational burden compared to other melanomas; frequently, loss of *NF1* and activation of MAPK and PI3K pathways are observed. P53 staining may help to differentiate desmoplastic melanoma from neurofibroma.
Spindle cell melanoma	Melanocytes with spindled, elongated nuclei predominate with less than 10% of the tumor content with a collagenous component in comparison to >90% seen in desmoplastic melanoma. Distinction of these two entities is important as spindle cell melanoma carries a less favorable prognosis and is more frequently associated with *BRAF* mutations. It is important to rule out a diagnosis of other nonmelanocytic spindle cell neoplasms with IHC staining. Of note, melanocytes with spindled features may be seen in many melanoma histologic subtypes.
Regressing melanoma (melanoma with complete regression)	Melanomas may be categorized as having either focal, partial, or complete regression, however, a unanimous definition of regression does not currently exist amongst pathologists. Even melanomas with complete regression (devoid of melanocytic complexes) can be identified by an irregular, asymmetric fibrosis of the papillary dermis, scattered distribution of melanophages, actinic elastosis, and patient age. Of note, "nodular melanosis" is a discrete entity of complete regression consisting of abundant melanophages with sparse fibrosis and inflammatory infiltrate. To date, the prognostic value of histologic regression remains unclear.
Epithelioid melanoma in situ ("Invisible" melanoma)	Intraepithelial proliferation of amelanotic epithelioid melanocytes aligning the dermoepidermal junction with areas of overlying focal parakeratosis, mimicking an actinic keratosis. Identification of this entity is heavily dependent upon IHC, however, focal areas of melanin deposition or nesting may rarely be seen to aid in accurate diagnosis.
Neurotropic melanoma and melanoma with neural differentiation	This entity exhibits overlapping features with desmoplastic melanoma, and is thought to be a variant of desmoplastic melanoma by some. Typically, peri-neural extension or infiltration of melanocytic fascicles is seen throughout the dermis, and neural differentiation promotes the development of neural-like structures. Lesions may be amelanotic, and S100 and SOX10 remain positive.

Table 3.2 (continued)

Nevoid melanoma (minimal deviation melanoma)	A term the represents a broad spectrum of melanomas that simulate benign melanocytic lesions. Diagnosis of nevoid melanoma can be exceptionally difficult, however, clues to diagnosis lie in architectural and cytologic atypia, and possible associated solar elastosis. Unfortunately, IHC typically cannot distinguish benign melanocytic lesions from melanoma, however, identification via FISH or CGH may be helpful. Traditionally, two main architectural patterns have been described: papillomatous, and non-papillomatous. A clear definition of nevoid melanoma is evasive, as nevoid melanomas may mimic any benign melanocytic variant.
Spitzoid melanoma	This entity represents a significant diagnostic challenge. Nests are vertically oriented along the dermoepidermal junction with peripheral clefting, and increased cell density, mitosis, poor zonation, and consumption of epidermis point toward malignancy. The melanocytes may appear large and cytologically atypical with amphophilic cytoplasm. Kamino bodies may be present in both Spitz nevi and Spitzoid melanoma. Of note, metastasis of benign Spitz nevi has also been demonstrated with SNL biopsy, further confounding the diagnostic picture.
Blue nevus-like melanoma and melanoma arising in blue nevus ("Malignant blue nevus")	Blue nevus-like melanoma and melanoma arising in a blue nevus are distinct entities, which histologically mimic or are associated with an existing benign blue nevus, respectively. An atypical melanocytic proliferation at the dermoepidermal junction may differentiate blue nevus-like melanoma, while a well-demarcated transition between benign and malignant portions of the melanocytic tumor suggests melanoma arising in blue nevus. Both entities have prominent melanophages, cytologic atypia, and mitoses.
Plexiform melanoma (deep penetrating nevus-like melanoma)	Histologic criteria differentiating plexiform melanoma and deep penetrating nevus (DPN) is still widely disputed amongst experts, sharing many clinical and histopathologic features. Presence of confluent melanocytic nests, lack of maturation, cytologic atypia, increased tumor thickness, and mitotic count favor malignancy, however, these features are also frequently found in DPN.
Polypoid melanoma	Defined as a melanocytic lesion with greater than half of its vertical diameter extending over the skin surface. Severe cytologic atypia and increased mitotic index lead to a straightforward diagnosis. This variant is believed to be more aggressive as increased tumor thickness and ulceration are commonly seen, however, disputes exist as to whether measurement of Breslow depth may be accurate in these lesions.
Dermal melanoma	A well-circumscribed melanocytic tumor of the dermis and subcutis without intraepithelial involvement or identifiable areas of regression, ulceration, or scar. It is important to rule out cutaneous metastasis as well as consider the diagnosis of melanoma with blue nevus-like features, clear cell sarcoma, or melanoma arising within a nevus prior to confirming this diagnosis.

(continued)

Table 3.2 (continued)

Balloon cell melanoma (melanoma with clear cells, granular cell melanoma, sebocyte-like melanoma, pseudolipoblastic melanoma)	A term reserved for melanomas composed of greater than 50% of melanocytes with very large, finely vacuolated cytoplasm. Distinction from balloon cell nevus depends on cytologic atypia, mitoses, necrosis, and pagetoid spread of melanocytes. It is also important to consider other clear cell tumors, this distinction may rely on IHC markers.
Monster melanoma	Melanocytes with hyperchromatic nuclei of markedly increased size. Multinucleated melanocytes and melanocytes exhibiting a syncytial pattern may also be observed. This morphology is commonly seen in polypoid melanomas.
Multinucleated cell melanoma	Defined as melanocytes with multiple, large, hyperchromic, and pleomorphic nuclei representing a majority of the melanocytic cell type within a lesion. Of note, multinucleated melanocytes may stain positively for CD68 and can also be observed in benign nevi.
Small cell melanoma	Characterized by uniform, small, "basaloid" cells with coarse chromatin and hyperchromasia. The differential diagnosis for these entities includes other small round blue cell tumors such as Merkel cell carcinoma, lymphoma, and Ewing sarcoma; the distinction is achieved with IHC. This lesion has been associated with a poor prognosis and increased risk of positive SLN, with a predominance in the pediatric population.
Micromelanoma	Defined as a melanoma less than 3 mm in diameter. Of note, "small diameter" melanomas are defined as melanomas less than 6 mm in diameter.
Basosquamous melanoma (basomelanocytic tumor, squamomelanocytic tumor)	Combination of epithelial carcinoma (basal cell more common than a squamous cell) with atypical nested and single-cell melanocytes growing in close proximity. The measurement of Breslow's depth is challenging in these lesions, however, current recommendations state only intradermal melanocytes outside of carcinomatous component should be considered invasive. It is important to differentiate this from benign melanocytic hyperplasia occasionally seen with these carcinomas.
Bullous acantholytic melanoma ("Dyscohesive malignant melanoma")	Numerous dyscohesive melanocytes with intratumoral epidermal, basilar, or suprabasilar blisters of varying extent. See Fig. 3.9. Measurement of Breslow's depth should be attained by subtracting the vertical diameter of the blister cavity to avoid overestimation of overall thickness. Dermal melanocytic acantholysis may also be seen in pseudoglandular melanoma (see below).
Signet ring cell melanoma	Melanocytes in this entity demonstrate a large intracytoplasmic vacuole containing intermediate vimentin filaments, thereby displacing the nuclei to the periphery with a flattened, crescent-like appearance. Abundant signet ring cells may mimic clear cell changes leading to a balloon cell melanoma appearance. Stains may be positive for PAS but negative for mucin, standard melanocytic markers are positive. This entity is not believed to carry prognostic significance.

Table 3.2 (continued)

Pseudoglandular melanoma	May appear histologically similar to bullous acantholytic melanoma (see above), but is characterized by architectural artifact generating the appearance of pseudolumina. When pseudoglandular structures involve the majority of the neoplastic proliferation, these may be confused for adenocarcinomas. Of note, melanomas with adenocarcinomatous transdifferentiation have been reported with loss of conventional ICH melanocytic markers.
Pigment-synthesizing melanoma ("Animal type, pigmented epithelioid melanocytoma")	A heterogeneous group of "pigment-synthesizing" melanomas, typically composed of nodular aggregates of spindled and epithelioid dermal melanocytes obscured by abundant melanin and melanophages. Pagetoid spread and ulceration are rare. These may be difficult to distinguish from deep penetrating nevus and blue nevus. Of note, some authors have argued that the term "pigmented epithelioid melanocytoma" be acknowledged as a separate entity, defined as a lesion with less pigmentation than other pigment-synthesizing melanomas, along with less cytologic atypia and wedge-shape infiltrative pattern.
Clear cell sarcoma or melanoma of soft parts	A deep tumor of uncertain lineage displaying a melanocytic phenotype and positive staining for melanocytic markers such as S100, HMB45, Sox-10, Melan-A, Mitf. Fibrous septa and hyalinized fascicles and nests of epithelioid and fusiform cells with low-grade nuclear atypia and low mitotic rate. Melanin deposition and multinucleated giant cells at the tumor periphery may be seen. Identification of a unique t(12;22) translocation aids in diagnosis. Of note, an intraepidermal growth pattern in conjunction with typical dermal involvement may closely mimic Spitz nevi.
Sarcomatoid melanoma	Rare subtype with near-complete loss of melanocytic differentiation with possible loss of typical markers such as SOX10 and S100. Identification of a biphasic tumor population consisting of pleomorphic sarcomatoid cells and scattered foci of typical melanoma features aids in diagnosis. Staining may be positive for SMA, desmin, and CD10. The differential diagnosis often includes other spindled neoplasms such as atypical fibroxanthoma/pleomorphic dermal sarcoma, malignant peripheral nerve sheath tumor, and sarcomatoid squamous cell carcinoma.
Rhabdoid melanoma	An exceedingly rare entity characterized by melanocytes resembling rhabdomyoblasts with eosinophilic inclusions and polygonal cytoplasm. See Fig. 3.10. Staining may be positive for desmin, MyoD1, and myogenin, as well as standard melanocytic markers. The differential diagnosis for this entity may include adnexal neoplasm, infundibular cyst, and basal cell carcinoma.
Osteocartilaginous melanoma	Chondro-osteoid differentiation composes only a small portion of the overall melanocytic tumor mass, therefore, diagnosis is fairly straightforward. This differentiation may be related to repeated trauma, as these lesions are frequently found on acral skin. Foci of chondro-osteoid differentiation will be positive for SOX9 and SATB2.

(continued)

Table 3.2 (continued)

Myxoid melanoma	Defined as melanomas with >15% of the stroma exhibiting myxoid changes. See Fig. 3.11. These changes are more frequently seen in desmoplastic melanoma, melanoma metastasis, and melanoma with neuroid differentiation. Of note, pseudo-myxoid changes may occur with significant intratumoral tissue edema. Confirmation with alcian blue and colloidal iron should be obtained. Staining for S100 and SOX10 is positive, however, HMB-45 and Mart-1 may be lost.
Angiomatoid melanoma	Irregular pseudovascular structures lined by melanocytes with hemorrhagic spaces separating melanocytic nests and single cells or small aggregates of melanocytes suspended within.
Plasmacytoid melanoma ("Melanoma with plasmacytic features")	These lesions mimic plasma cell neoplasms, consisting of melanocytes with perinuclear halos, eccentric nuclei, eosinophilic cytoplasm. Stains may be positive for CD138, MUM1, and immunoglobulin light chains, but are also invariably positive for standard melanocytic markers. Of note, inflammatory antitumor responses may be composed of plasmacytoid dendritic cells in other melanoma subtypes and are not neoplastic tumor cells in these entities.
Syringotropic melanoma	Determination of syringotropic melanoma is reserved for those melanomas with peri-eccrine and peri-glandular involvement in the reticular dermis and subcutaneous tissue that extends more deeply than any other area of invasion. Prognostic significance of Breslow depth may be challenging, and measurement of both traditional Breslow depth as well as the extent of horizontal melanocytic involvement from the center of the eccrine gland has been proposed.
Follicular melanoma	Prominent involvement of the pilosebaceous unit with the depth of follicular involvement greater than the lateral extent of intraepidermal growth, thus differentiating this subtype from melanoma with folliculotropism. Discrepancies in reporting Breslow depth exist even amongst experienced dermatopathologists. It is presently suggested that the final report include both the traditional Breslow depth as well as the horizontal thickness of the perifollicular invasion from the inner level of the outer root sheath to the center of the hair follicle.
Verrucous melanoma and melanoma with pseudoepitheliomatous hyperplasia	Melanomas with overlying epidermal hyperplasia exhibiting acanthosis, papillomatosis, orthokeratosis, and possible keratotic cyst formation mimicking seborrheic keratoses, keratoacanthomas, and squamous cell carcinomas. Melanocytic nesting and pagetoid spread may be absent. Presently, agreement on standardization of Breslow depth measurement in this entity is lacking, with typical Breslow measurement leading to overestimation of tumor extension.
Lichenoid keratosis-like melanoma	A prominent lichenoid tissue reaction with abundant dermal melanophages and scattered necrotic keratinocytes is observed, while malignant melanocytes are few in number. This lesion may be categorized conceptually with melanomas with regression and present a considerable diagnostic challenge, thus, a broad panel of melanocytic IHC markers should be performed for any lichenoid keratosis with focal pigmentation.

Table 3.2 (continued)

Melanoma with aberrant phenotype	Variable loss of conventional melanocytic markers with aberrant expression of non-melanocytic markers. The term "undifferentiated" melanoma should be reserved for a "vimentin-only" phenotype. SOX10 remains positive in a majority of these lesions, but other diagnoses such as atypical fibroxanthoma/undifferentiated pleomorphic sarcoma, adenosarcoma, myofibrosarcoma, leiomyosarcoma, and rhabdomyosarcoma should be considered.

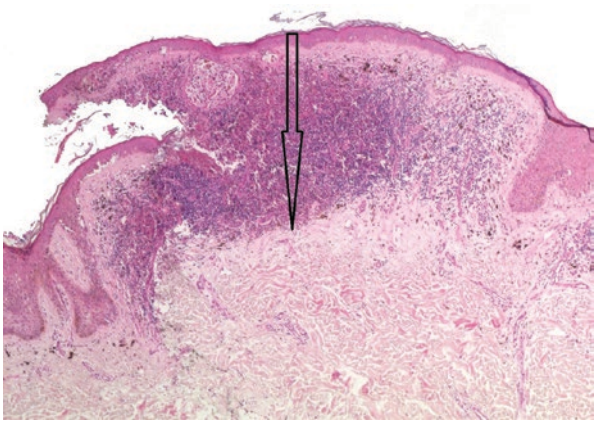

Fig. 3.4 Breslow thickness measured from top of granular layer to deepest part of tumor (H&E stain at 40× magnification)

invasion, perineural invasion, histopathologic subtype, associated nevus, and histologic margins may still be incorporated to help guide therapeutic decisions for consideration of additional treatments such as sentinel lymph node biopsy.

Fine needle aspiration may have an important role to confirm a metastatic lesion within the skin, soft tissue, or visceral organs. However, the technique sacrifices the assessment of histopathological parameters such as depth of dermal invasion and lymphovascular and perineural invasion. Thus it should not be utilized alone to establish a primary diagnosis, but it may provide additional tissue to perform IHC or molecular assays [7]. Both pathological and clinical nodal status, as well as satellite or in-transit disease affect current AJCC staging guidelines (Figs. 3.4, 3.5, 3.6, 3.7 and 3.8).

Immunohistochemistry

Diagnostic IHC

In the majority of cases, H&E histopathology is sufficient to establish the primary diagnosis of melanoma. However, in cases of amelanotic malignant melanoma, poorly differentiated malignancies, or characterization of metastatic tumors of unknown

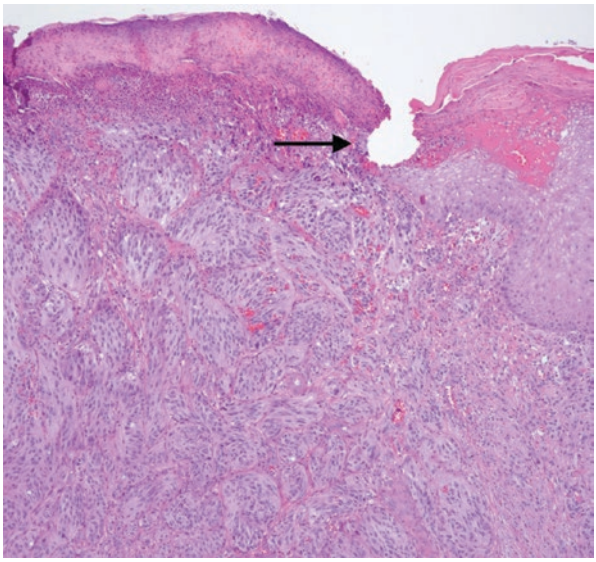

Fig. 3.5 Melanoma with overlying ulceration (H&E stain at 40× magnification)

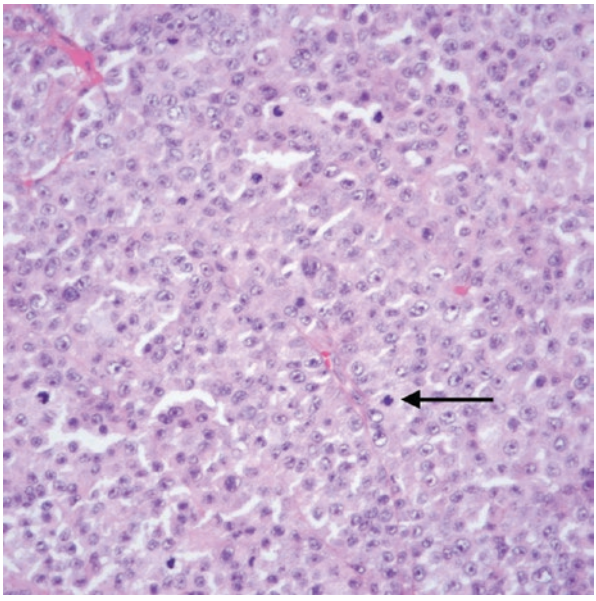

Fig. 3.6 Arrow highlighting a mitotic figure (H&E stain at 200× magnification)

origin, an IHC panel has great value to differentiate melanomas from other histopathologic mimics, such as dysplastic nevus, Spitz nevus, cellular blue nevus, deep penetrating nevus, and scar in the case of desmoplastic melanoma [1, 12]. However, it is important to note that there are no specific patterns of immunostaining which clearly and uniformly differentiate between benign and malignant melanocytic neoplasms.

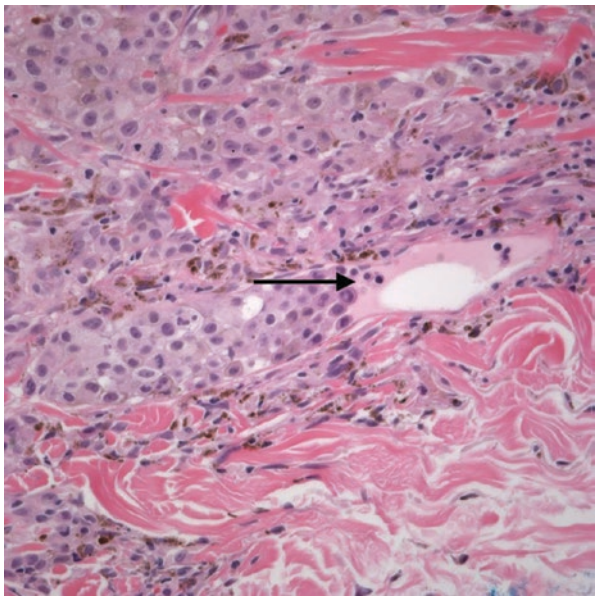

Fig. 3.7 Arrow highlighting lymphovascular invasion (H&E stain at 400× magnification)

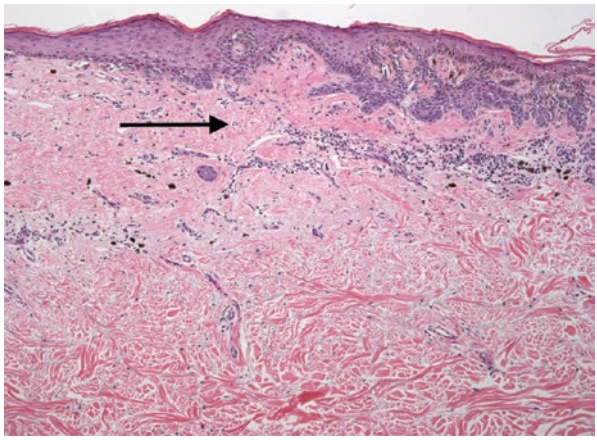

Fig. 3.8 Arrow highlighting scar-like changes with decreased density of melanocytes relative to adjacent melanoma demonstrating histologic regression (H&E stain at 40× magnification)

IHC stains may also be useful to determine the extent of the lesion, particularly with respect to the radial growth phase and depth of invasion in cases of partially or completely regressed melanomas. In addition, the use of a red instead of brown counterstain is particularly valuable in heavily pigmented melanocytes which may be difficult to distinguish from melanophages. While bleaching is used to reduce the degree of melanin pigmentation, the technique is challenging for some histotechnologists and the process may hinder the immunoreactivity of the target antigens. However, recent modifications to previous bleaching methodologies have improved upon this, leaving tissue suitable for immunohistochemical staining as well as PCR amplification-based molecular assays [13, 14].

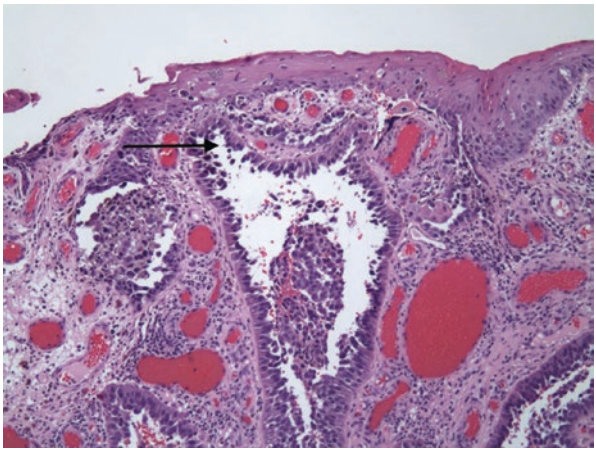

Fig. 3.9 Bullous acantholytic melanoma. Arrow highlights numerous dyscohesive melanocytes (H&E stain at 200× magnification)

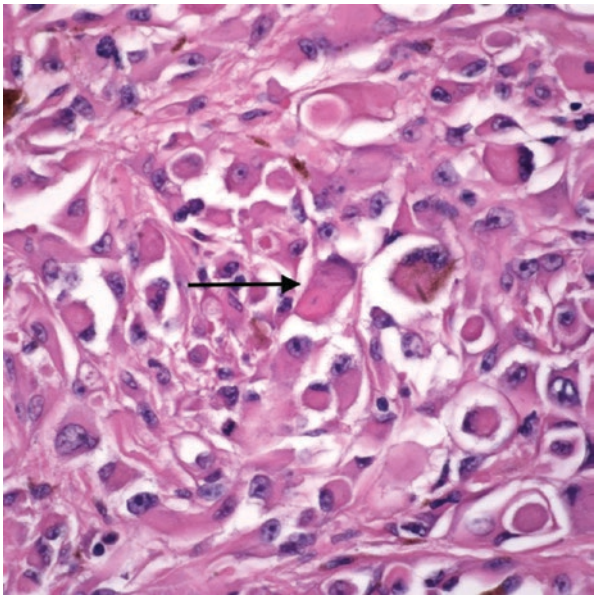

Fig. 3.10 Rhabdoid melanoma. Arrow highlighting melanocytes resembling rhabdomyoblasts with eosinophilic inclusions and polygonal cytoplasm (H&E stain at 400× magnification)

A standard screening stain is S100. While S100 is a sensitive marker for melanomas (97–100%), it is also non-specific (75–87%), present in all tumors of neural crest origin as well as many other carcinomas and sarcomas [15]. There are at least 21 S100 proteins and recent studies have focused upon S100A, S100A13, S100B, and S100P, as additional diagnostic aids [16]. Of note, S100 is the most sensitive marker for the detection of desmoplastic melanomas. To further assist in increasing the diagnostic specificity of IHC, there are several melanoma-specific markers including Melan-A (MART-1), HMB-45, and SOX10. Melan-A is a transmembrane protein found on the melanocyte surface and is encoded by the *MLANA* gene [17, 18]. HMB-45 is a mono-

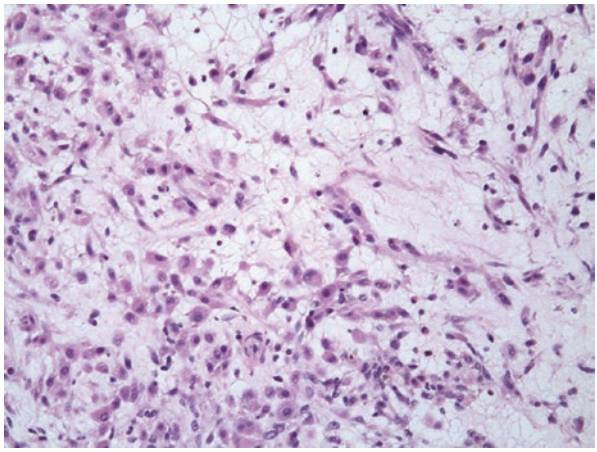

Fig. 3.11 Myxoid melanoma. Mucinous changes are observed in a majority of the tumor stroma (H&E stain at 200× magnification)

clonal antibody that recognizes the melanosomal glycoprotein gp100 (Pmel17) encoded by the *PMEL* gene [19, 20]. SRY-related HMG-Box gene 10 protein (SOX10) is a transcription factor and is encoded by the *SOX10* gene. SOX10 has an advantage over the other two markers with greater sensitivity and specificity with regard to melanocytic differentiation [21]. Antibodies label SOX10 in the nucleus while Melan-A and the other two are cytoplasmic stains, allowing for easier visualization of the melanoma cells, particularly in lesions with melanophages. SOX10 is superior to cytoplasmic stains which may under or over-report the density of melanocytes, particularly in cases attempting to distinguish atypical junctional melanocytic proliferations from melanoma in situ [22, 23]. In one study, MIS was detected with an 87% sensitivity using SOX10, while the highest specificity (78%) for MIS was achieved using both Mart-1 and SOX10 in combination [22]. SOX10 is also superior in identifying desmoplastic melanomas which are often negative for other melanoma-specific markers such as Melan-A and HMB-45 [24]. However, a recent retrospective analysis revealed 86% of re-excision specimens contained SOX10 positive histiocytes within dermal scars. Therefore, the sole use of SOX10 staining to evaluate melanocytic neoplasms following re-excision may lead to false positive staining [25]. A panel of IHC stains, such as S100, Tyrosinase, and Melan-A, shows greater sensitivity and specificity than a single stain and is desirable for confirming the diagnosis of melanoma [26].

Microphthalmia transcription factor (Mitf) is a transcription factor active during melanocyte embryogenesis. Like SOX10, it is a nuclear stain and was initially touted as a melanoma-specific stain. However, it suffers from lack of sensitivity and specificity for melanomas, including desmoplastic melanomas which are often Mitf negative. Recent studies suggest a specificity as low as 88% as it has been shown to also stain lymphocytes, histiocytes, Schwann cells, fibroblasts, and smooth muscle cells [27].

Tyrosinase mRNA expression can be assayed by an immunohistochemistry stain and reverse transcriptase PCR on tissue sections [28]. Like other melanoma stains, it lacks the specificity and sensitivity of S100 but may have merit in identifying melanomas that are S100 positive and negative for other melanoma-specific markers.

However, the overall sensitivity and specificity for melanoma for this single stain are low as melanosome transfer to keratinocytes can lead to false positive staining [15]. Additionally, the sensitivity is further decreased in both metastatic lesions and melanomas of advanced clinical stage, ranging from 79–93% [15, 27].

BAP1 (BRCA1 Associated Protein 1) is found in a cancer syndrome that includes benign melanocytic nevi and later development of cutaneous and uveal melanomas, and mesotheliomas [29]. There are many complex mutations and deletions that may result in BAP1 inactivation making it difficult to identify utilizing conventional molecular assays. Thus, IHC is the preferred method to assay for the detection of BAP1 mutations with inactivation [30].

p16 assays for the gene product of the cyclin-dependent kinase inhibitor 2a gene (CDKN2A) which is usually constitutively expressed in normal melanocytes and may show loss of 50–98% expression in melanomas [15]. However, this is not consistently reproducible and the p16 staining patterns may not represent the status of this gene [23]. One study showed no statistical difference in staining intensity between Spitz nevi and Spitzoid melanomas [31, 32]. Other studies have demonstrated strong and diffuse staining for acral Spitz nevi for a combined staining pattern of p16/p21 but not for acral nevi or acral melanomas [33]. There was preferential p16 staining for >5% of melanocytes within nevi arising during pregnancy versus <5% staining for nevoid melanomas [34]. Thus, p16 may have utility in special site nevi and within specific clinical conditions. Additionally, loss of p16 has been associated with decreased survival, especially with increased Ki-67 index [35, 36].

Ki-67 is part of a large group of proliferation markers targeting different steps in the cell cycle with notable absence during the quiescent phase (G_0). Some of these markers include p16, PCNA, cyclin A, cyclin B, cyclin D1, cyclin D3, and p53. Melanomas exhibit a generally higher growth index (13–30%) than benign nevi (<5%) [15]. However, Ki-67 and other proliferation markers have shown poor reproducibility to consistently differentiate benign nevi from melanoma as indexes may be increased in both atypical and Spitz nevi. Overall, studies are conflicting regarding independent prognostic value [35, 36]. There may be merit in utilizing Ki67 in combination with other diagnostic markers such as Melan-A and SOX-10 [15].

Prognostic and Therapeutic IHC

The list of molecular targets for malignant melanoma has exploded in the last decade leading to new therapeutic options which are discussed elsewhere in this book. A comprehensive list of potential targets, in varying stages of clinical trials, is also available through several recent reviews [37–39] (Fig. 3.12).

The following IHC antibodies are available in most reference laboratories and target gene expression products for current FDA-approved therapies. For the detection of mutations of these gene products, both PCR and IHC have been utilized. While PCR is the current gold standard for many of these assays, the faster turnaround time, lower cost, and greater ease of use of IHC is a reasonable first choice and has generally shown good correlation with PCR.

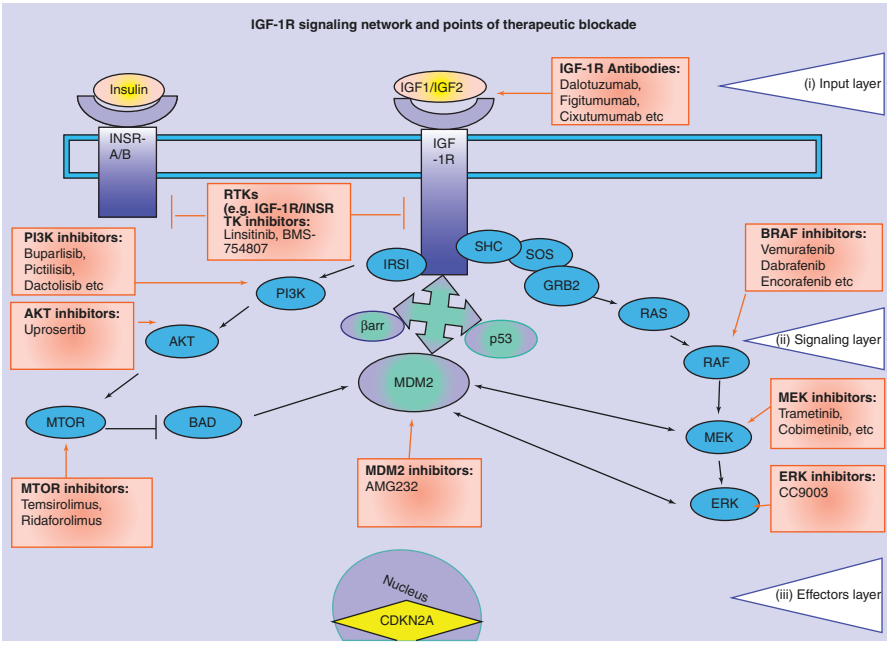

Fig. 3.12 The IGF-1R signaling network illustrating points of potential therapeutic blockade for melanoma with FDA approved drugs and some experimental drugs in current clinical trials. (© 2018 Helgadottir, Rocha Trocoli Drakensjö and Girnita) [40]

BRAF and MEK

BRAF is the gene that encodes the B-Raf protein and is part of the family of signal transduction protein kinases that help to regulate cell division and differentiation. BRAF mutations have been identified in 30–50% of cutaneous melanomas and a lesser percentage of nevi [41, 42]. The most common mutation is the V600E, accounting for nearly 50–70% of all mutations, but at least 30 other mutations have been identified [43]. BRAF mutations lead to constitutive activation of the mitogen-activated protein kinase pathway (MAPK), which includes the MEK enzymes, an important pathway for malignant transformation in melanoma and several other cancers. The MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinases) pathway includes the MEK1 and MEK2 enzymes [44]. This pathway consists of proteins that signal a cell surface receptor and activates this pathway within the cell which enters the cell nucleus and promotes DNA transcription. Defects in this pathway may lead to neoplastic transformation.

BRAF inhibitors are a group of therapeutic agents which block the primary mutated BRAF kinase [41]. Current FDA approved BRAF inhibitors are Vemurafenib, Dabrafenib, and Encorafenib [45]. MEK inhibitors inhibit steps in the MAPK/ERK pathway and may assist in overcoming resistance to BRAF inhibitors [41]. Current FDA approved MEK inhibitors, include Trametinib, Cobimetinib, and Binimetinib

[45]. Because of the shared common pathogenic pathway, BRAF inhibitors have been paired with MEK inhibitors and may act synergistically [43, 46].

The current gold standard for detection of BRAF mutations is PCR, however, IHC is a cost-effective methodology to identify the BRAF-V600E mutation with quicker turnaround time. A meta-analysis of studies that compared PCR to IHC found a 95% concordance rate between the two testing methods. If a test is negative or equivocal for IHC staining, PCR could still be performed [47, 48]. Since BRAF mutations are involved in the activation of the MAPK/ERK pathway, assays for BRAF mutations are part of the clinical decision tree to determine whether a MEK inhibitor is used. Thus assays for MEK enzymes are not included as part of the routine laboratory evaluation of melanoma. Next-generation sequencing (NGS) shows promise in identifying additional BRAF mutations, other than the BRAF-V600E mutation. In one study, two-thirds of cases that were negative for BRAF-V600E by IHC showed additional mutations by NGS [49].

Identifying BRAF mutations aids in the selection of patients eligible to receive BRAF inhibitors. There is also evidence that these mutations may have a prognostic role. Melanocytic nevi harboring the BRAF B600 mutation, identified by IHC, showed a predominately dermal location with congenital features as well as junctional intraepidermal nests of melanocytes that were larger in size with abrupt lateral circumscription and larger cytology when compared to BRAF negative nevi [50]. Melanocytic nevi that harbor mutations in non-V600E BRAF, as well as mutations in other genes such as NRAS, TERT, and hemizygous deletion of CDKN2A gene, may have a greater propensity to evolve to melanoma [51]. In melanomas harboring the BRAF V600E mutation, there was a significant correlation with nodular and superficial spreading histopathologic subtypes and ulceration [42].

c-Kit

c-Kit is a transmembrane tyrosine kinase involved in cell growth, development, and differentiation. Mutations in the c-Kit gene are found in several clinical subsets of melanomas including acral and mucosal melanomas as well as melanomas arising on sun-damaged skin. The mutations are not as common as BRAF mutations [52]. c-Kit inhibitors block the actions of the mutated protein product. Current FDA approved c-Kit inhibitors are Imatinib and Nilotinib [45].

PCR is the preferred laboratory assay for c-Kit mutations. IHC correlation with PCR has mixed results. In 82% of cells positive for kit mutation by PCR, kit expression was found in more than 50% of the cells by IHC. Conversely, melanoma cells showing less than 10% expression by IHC were negative for kit mutations [53].

Immune Checkpoints (CTLA4/PD-1/PD-L1)

Immune checkpoints are key regulators of the immune system and are critical for immunological tolerance, creating a state of immune unresponsiveness and preventing the immune system from attacking the host cells. There are several

Table 3.3 Current FDA approved checkpoint inhibitors with clinical relevance to melanoma

CTLA4 inhibitors	Ipilimumab Tremelimumab
PD-1 inhibitors	Pembrolizumab Nivolumab Cimiplimab
PD-L1 inhibitors	Atezolizumab Avelumab Durvalumab

important checkpoints that are relevant to melanoma pathogenesis and treatment. CTLA4 (Cytotoxic T-lymphocyte-associated protein 4, CD152) is a protein receptor that is expressed on activated T lymphocytes and suppresses its induction. PD-L1 (Programmed death ligand 1, CD274) is located on host cells and binds to its main receptor PD-1 (Programmed cell death 1, PDCD1) located on T-lymphocytes. These proteins also suppress the immune system. In melanomas, PD-L1 is upregulated by the cancer cells, interacting with PD-1 on the T-lymphocytes, reducing the T-cell signaling and preventing the immune system from attacking the tumor cells [54].

Checkpoint inhibitor therapy targets these checkpoints, blocking the inhibitory checkpoints, restoring the normal immune system function to attack the tumor cells (see Table 3.3).

Currently, there are no biomarkers that can definitively include or exclude a patient from consideration of immune checkpoint inhibitor (ICI) therapy. PD-L1 expression has shown some predictive value for treatment response in melanoma, however, larger prospective clinical studies are needed to further elucidate predictive and prognostic significance [55, 56]. Given the complex and dynamic interplay of cytokines, proteins, and cell surface molecules such as immune checkpoint molecules within the tumor microenvironment, the predictive and prognostic utility of a single biomarker is unlikely [39]. Of note, melanomas with a higher mutational load have been shown to have increased immune response and improved survival with ICI therapy [55].

There are several competing IHC assays with different methodologies and different scoring systems by reviewing histopathologists. This has resulted in poor reproducibility between laboratories with concordance levels as low as 50% [57]. NGS has shown good correlation with IHC and may provide a more objective analysis. A combined positive result for PD-L1 with increased IHC score and high expression by the RNA sequencing correlated with a 2–5 fold overall response rate to the checkpoint inhibitor therapies [58].

Molecular Assays

There are currently several options that may assist in the diagnosis and determination of prognostic categories as well as to help to guide therapeutic options. Key drivers of the adoption of these assays will depend upon statistical validations as well as the cost. Like IHC, these assays can be broadly divided into diagnostic, prognostic and therapeutic. Some of these assays may also be used in conjunction with IHC, particularly when gene expression is present but no gene product is detected by IHC [59].

Comparative Genomic Hybridization (CGH) and Single Nucleotide Polymorphism (SNP) Arrays

These assays analyze chromosome copy number relative to ploidy level throughout the entire genome. SNP microarrays provide copy number and allelic frequency and can detect copy neutral loss of heterozygosity, identifying selective mutations. Used together, CGH/SNP arrays compare the genome of the melanocytic neoplasms to normal human DNA. Chromosomal aberrations are more common in melanomas and these may be identified by non-overlapping patterns. The arrays may not be as sensitive in detecting clonal aberrations if there is tumor heterogeneity, increased background inflammation, or the quantity of the tumor is less than 30% of the lesion. In addition, CGH/SNP may require several weeks for the arrays to be completed [60, 61]. Acknowledging these limitations, these arrays have shown great utility in identifying chromosomal aberrations that may distinguish metastasizing from non-metastasizing tumors [62]. CGH has yielded distinct ALK rearrangements that correlated with distinct histopathologic features in Spitz tumors [63]. CGH has also shown that melanomas that metastasize have more mutations than melanomas that do not [57]. Used in conjunction with FISH, CGH is a powerful tool for both diagnostic and prognostic work for melanomas. However, CGH is not readily available in most commercial reference laboratories and is not routinely used by all pathologists. It is largely limited to expert opinion consults at tertiary referral centers.

Fluorescence in Situ Hybridization (FISH)

FISH analyzes chromosomal copy number alterations at targeted genomic foci. A DNA fluorescent probe binds to complementary DNA sequences in tissue sections. The probes are either centromere or locus specific and are able to detect amplifications, deletions, and translocations. FISH is advantageous when a small amount of tumor is available for analysis and has a relatively rapid turn-around time of a few days. Since the probes are DNA sequence-specific, it may miss other chromosomal aberrations and false-positive results may result from tetraploidy. FISH probes can directly assay for aberrant foci of chromosomal aberrations identified by other methodologies, such as CGH. The standard FISH panel varies by laboratories and published studies but the most common probes target the following chromosomal loci [64]. See Table 3.4.

Table 3.4 Common FISH probes utilized in melanoma

Chromosomal loci	Gene
6p25	RREB1
6q23	MYB
8q24	MYC
9p21	CDKN2A
11q13	CCND1

Depending upon the probes used and the cutoff thresholds, the sensitivity and specificity to discriminate melanoma from benign nevi have been reported as 86.7% and 95.4% respectively. However, in histopathologically ambiguous lesions, particularly Spitzoid melanomas, the sensitivity drops to 70%. Incorporating additional probes, notably the 9p21 probe, improves the sensitivity to 94% and specificity to 98% [64, 65]. It is likely that the addition of other probes will further aid in discrimination. FISH has not been a good discriminator between desmoplastic melanomas and other sclerotic melanocytic lesions such as sclerosing melanocytic nevi, desmoplastic Spitz nevi, or sclerotic blue nevi [66].

FISH has also been used as a prognostic assay with melanomas containing a greater number of chromosomal aberrations at a greater risk for metastasis [67]. Spitzoid melanomas harboring a homozygous 9p21 deletion are at greater risk for aggressive disease [65].

Molecular Assays-Diagnostic/Prognostic

Current National Comprehensive Cancer Network (NCCN) guidelines published in July 2018 are stratified by risk assessment and recommend consideration of offering a SLN biopsy if the risk is 5–10% and offering the SLN if the risk is above 10% [68]. Currently, primary stage IA tumors which are defined as less than 0.8 mm without ulceration are not currently recommended for SLN biopsy since the overall risk of a positive SLN is less than 5%. The newest revision of the AJCC staging has resulted in refinement of the pathologic staging. Since 70% of newly diagnosed melanomas are less than 1.0 mm in thickness, but still account for 30% of deaths, molecular assays are being developed to assist in stratifying risk for patients with pathologic stage IA and IB tumors who may be at increased risk for lymph node metastasis. These assays aim to assist in determining whether to offer an SLN biopsy and identifying patients at risk for treatment failures [69–71].

RNA-Base Gene Expression Profiling (Quantitative Reverse Transcription Polymerase Chain Reaction-qRT-PCR)

These assays currently present the most comprehensive molecular profiles of melanomas and detect the level of expression of specific mRNA transcripts. Gene expression signatures have been collected to attempt to discriminate benign versus malignant melanocytic neoplasms [72]. By expanding the gene expression profiles, these assays have differentiated benign melanocytic nevi from melanomas with a sensitivity of 91.5% and specificity of 92.5% [73]. Given the diagnostic challenge of histopathologically ambiguous lesions and the severe consequences of misdiagnosis, these assays may be utilized to guide the clinician's recommendation of clinical surveillance frequency, additional diagnostic imaging, need for sentinel lymph node biopsy or adjunctive therapy, specialty referrals, or to reassure both clinician and patient of

lesions deemed lower risk [74]. There are several commercially available assays marketed under different names. DecisionDx-Melanoma Test™ (Castle BioScience) utilizes a 31 gene expression profile (GEP) that stratifies risk. A meta-analysis of over 1200 patients found that the result of the 31-GEP was an independent prognostic indicator of recurrence-free survival, distant metastasis-free survival, and melanoma-specific survival [75–77]. This test reports lesions as low-risk Class 1 or high-risk Class 2 based on gene expression patterns that were compared to a validated patient set with known clinical outcomes. A recent study revealed that lesions categorized as Class 1 were associated with only a 5% and 1% rate of recurrence or distant metastasis respectively, compared to 55% and 36% of Class 2 lesions [78]. Recurrence of Stage 2 lesions was anticipated with 79% sensitivity, and the negative predictive value of a Stage 1A classification for recurrence or distant metastasis was 85% [78, 79]. Additional assays include the Myriad MyPath Melanoma Gene™ expression test which utilizes a 23-gene expression profile. The Pigmented Lesion Assay™ (DermTech) has popularized a noninvasive adhesive patch skin test. The differentiation of melanoma from non-melanoma samples via adhesive patch achieved a sensitivity of 91% and specificity of 69% [80].

There are a few studies that examine a cohort of cases comparing the different molecular assays. One prospective study examined a set of 268 diagnostically challenging melanocytic lesions, divided into morphologically unequivocal and morphologically ambiguous [81]. FISH and the gene expression profiling were performed upon each group. The morphologically unequivocal group had a histopathological agreement of 84% for FISH and 74% for gene expression. In the ambiguous group, FISH and gene expression showed 69% inter-test agreement. Cases that were discordant with either FISH or gene expression (81/268 cases) were submitted for additional re-evaluation by two experienced dermatopathologists and also by SNP-array. SNP-array results correlated better than FISH, which correlated better than MyPath™, and the morphologic interpretation. Some of the reported discordances were attributed to interobserver variations amongst the refereeing dermatopathologists. Another study found a similar overall 73% concordance between FISH and gene expression assays [82].

GEP has great potential to reduce the diagnostic discordance amongst expert dermatopathologists, however, currently, none of these assays are recommended as part of the routine evaluation of melanocytic neoplasms. The most recent meeting of the NCCN (National Comprehensive Cancer Network) on 06.20.2018 unanimously agreed to not consider the inclusion of the DecisionDX-Melanoma Test in the current guidelines as a prognostic test to stratify metastatic risk for melanomas [83]. The final decision to utilize these assays must be decided on a case by case basis by the dermatopathologist.

Liquid (Serologic) Biomarkers

These assays are popularly known as liquid biopsies since the assays are performed upon a small blood sample extracted from the patient and assays for proteins, circulating tumor cells (ctDNA) and circulating RNA (miRNA and lncRNA) for their

respective cancers [84–86]. Serological biomarkers for melanoma have the advantage of a rapid and non-invasive test to assist in the initial staging of primary melanomas as well as monitor the effectiveness of therapeutic interventions. Although there is currently no standard serological screening test for melanoma, recent advances with molecular assays have brought this possibility a step closer. Reverse transcriptase-PCR (RT-PCR) and real-time quantitative-PCR (qPCR) are the most reliable and reproducible assays. Proteomic profiling assays include mass spectrometry proteome profiling and affinity-based multiplex proteomic assays, based upon enzyme-linked immunosorbent assays (ELISA), with the latter assay more common, have also been used. Illustrating the difficulties facing widespread adoption of either of these two latter methodologies, one study compared two different affinity-based multiplex proteomic assays and found a poor correlation for the protein quantification [87]. The relatively small size of these proteins, variations between protein levels in serum and plasma, pre-analytical methodological differences of sample preparation, the requirement for high-technical proficiency to perform the assays, and the dearth of FDA approved biomarkers, have all resulted in a waning of initial interest as an assay to monitor therapy [86].

Biomarkers have been an important part of routine serum chemistries within the clinical laboratory. One of the oldest, serum lactate dehydrogenase (LDH), is currently utilized as a part of the AJCC Melanoma staging system as a criterion of Stage IV disease [6]. Together with the anatomic site of melanoma metastasis, an elevated serum LDH portends a worse prognosis with shorter overall survival at 1 and 2 years.

S100 was previously discussed as a sensitive IHC for the histopathological tissue confirmation of a melanoma. Elevated serum levels of S100B have been associated with advanced stages of melanoma. Unlike serum LDH, S100B shows a positive correlation with both Stage III and IV disease [16].

Circulating tumor cells (ctDNA) are defined as single- or double-stranded DNA that is released by tumor cells into the circulating peripheral blood [29, 88]. In most cases, the mutations that are harbored by the primary tumor are also present in the ctDNA providing a potential source for early stage detection and to monitor tumor progression, prognosis, and efficacy of tumor treatment. Factors complicating detection include the low concentration in the peripheral blood (1 per million leukocytes), a short half-life (1–2.4 h), and even lower levels in early-stage tumors [89]. Studies with melanomas are in general agreement with other tumors with low detectable levels in early-stage melanomas and higher levels correlating with disease detection, staging, monitoring of treatment and progression, and predicting overall disease-free survival. The sensitivity of detection is low and suffers from a lack of a standardized protocol to identify these cells [90]. Current assays utilize qPCR of melanoma-specific genes, digital droplet PCR (ddPCR), and next-generation sequencing. However, all of these assays are susceptible to variations in pre-analytical factors such as time of collection, plasma versus serum analysis, and white blood cell lysis [91].

Presently, the utility of these ctDNA assays has focused upon the detection of BRAF and NRAS mutations in ctDNA to predict treatment response and outcome in patients. One study found that detection of mutant BRAF and NRAS predicted

relapse and decreased overall survival for high-risk resected stage II/III melanomas suggesting that assaying for ctDNA could aid in the selection of patients for adjuvant therapy [92, 93]. Another study found that pre-operative levels of ctDNA may be an independent predictor of melanoma-specific survival in Stage III melanomas in patients undergoing lymph node dissection, independent of Stage III subclass [94].

Circulating immune cells have been shown to predict the response of melanoma to different types of therapy, providing a real-time analysis that tissue sections utilizing IHC are unable to provide. Flow cytometry and mass cytometry have been utilized to identify subsets of these inflammatory cells within the peripheral blood. Initial studies utilizing these assays showed promise for a non-invasive methodology of monitoring melanoma treatment and identifying possible immunological profiles of patients who may fail treatment, particular with therapies utilizing checkpoint inhibitors such as anti-PDL and anti-PD-L1 drugs [56, 95, 96]. In one of the largest study of patients treated with pembrolizumab, a high relative eosinophil and lymphocyte count and low serum LDH were identified as favorable baseline characteristics for the patient's overall survival [97]. Another study of melanoma patients also treated with pembrolizumab identified a subset of T-cells dubbed reinvigorated exhausted CD8 T-cells with an increased proliferation rate. Clinical failures demonstrated an imbalance in the ratio of T-cell reinvigoration and tumor burden, with higher levels before and after treatment correlating with better objective response rates, progression-free survival, and overall survival [96]. These assays provide a surrogate test of the microenvironment of the tumor cell, simultaneously assaying multiple subsets of immune cells and potentially yielding prognostic information for the patient's likelihood of response to different therapeutic regimens. The clinical significance of ctDNA and miRNA/lncRNA of the tumor is uncertain and is still under investigation and is predominately utilized as a research assay.

MicroRNA (miRNA) and long noncoding RNA (lncRNA) are post-transcriptional regulators of gene expression. miRNAs typically range from 20–200 nucleotides while lncRNA are larger than 200 nucleotides. Individual miRNA bind to several mRNAs, functioning like another mRNA, and are involved in wide-ranging activities of normal cell function as well as tumorigenesis. Unlike DNA, these mRNA sequences are stable in the peripheral blood and are relatively resistant to mRNases [98]. miRNAs are not tumor-specific but certain clusters have been associated with melanomas and have statistical significance in positively correlating with tumor burden, stage, and recurrence. Networks of miRNAs that may regulate the resistance to BRAF and MEK inhibitors have been identified [99]. In addition, there is upregulation of lncRNA in higher stage melanomas as compared to a lower stage [100, 101]. Current assays are limited by methodologies that require sensitive amplification methods. In addition, the levels are normalized against housekeeping miRNAs which may also be deregulated and elevated in patients with other cancers [102].

Mutational Load

Mutational load, also known as tumor mutation burden (TMB), examines the total number of non-synonymous point mutations in a tumor and is defined as the number of mutations per megabase of DNA. Tumors with a higher somatic mutational burden may be more responsive to immunotherapy. However, there are no standardized approaches to measure or report TMB with both whole genome sequencing and next-generation sequencing the most common assays. Practical applications of this technique have examined a smaller set of genes, constructing statistical models to predict treatment response to various immunotherapies [55, 63]. Refinement of this type of study is rapidly developing and has the capability of personalizing therapy for melanoma in the future [103].

Sentinel Lymph Nodes (SLN)

The sentinel lymph node biopsy is currently recommended for cutaneous melanomas of at least pathological stage IB after the primary excision of the melanoma [68]. SLN status provides both prognostic and therapeutic data to properly manage melanoma patients. The identification of melanoma cells metastatic to the SLN has relied upon a combination of H&E histopathology aided by immunohistochemistry and molecular pathological assays. A standard panel of melanoma-specific IHC antibodies are currently recommended, usually staining several consecutive sections with HMB-45 and/or Melan-A [104]. Patients with larger tumor burden in the SLN and parenchymal location of the metastases have an overall poorer prognosis than those with smaller tumor burdens and subcapsular metastases [105].

Potentially confounding issues in the assessment of the SLN biopsy include the identification of benign melanocytic nevus cells, usually localized to the SLN capsule (Fig. 3.13). Examining SLNs containing metastatic melanoma and benign nodal nevi, analysis by FISH identified 83% of metastatic melanoma with FISH aberrations with four probes directed against aberrations in chromosome 6 and 11. In contrast, FISH identified aberrations in one case of a nodal nevus and upon further histopathological review of both the nodal nevus and the original primary tumor, it was concluded the original tumor and nodal nevus was misdiagnosed and were reclassified as a melanoma [106].

Molecular staging of SLN relies upon additional molecular assays and qRT-PCR is an important adjuvant test. A gene expression profile of 31 melanoma genes was more sensitive and specific than the histopathological examination of the SLN alone [74]. In the patients with a negative SLN, the nodes that exhibited a high-risk gene expression profile had a 30% increased risk of metastatic disease. Tyrosinase mRNA expression by qRT-PCR may also show superior rates of detection of metastatic melanomas cells with one study detecting evidence of metastatic disease in 73.2% versus 1.4% by H&E histology and 7% by IHC [107].

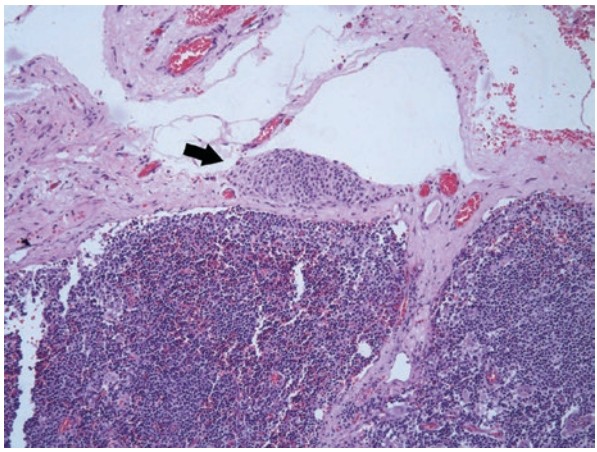

Fig. 3.13 Arrow showing circumscribed nests of benign nevus cells in the capsule of the SLN (H&E stain at 40× magnification)

Discussion of Case

1. **What are the histopathological parameters that should be included in every diagnostic report of malignant melanoma?**
   The AJCC 2018 guidelines identify Breslow thickness and ulceration as key parameters to determine primary pathologic staging. Additional parameters such as mitotic figure count per mm^2, lymphovascular invasion, perineural invasion, tumor infiltrating lymphocytes, regression, histopathologic subtype, associated nevus, and margins may still be incorporated to help guide therapeutic decisions for consideration of sentinel lymph node biopsy and adjuvant therapy.
2. Which additional laboratory tests should be considered to confirm the diagnosis of malignant melanoma?
   The answers depend upon the degree of diagnostic certainty of the histopathologist who is establishing the initial diagnosis. A panel of IHC stains utilizing melanoma-specific antibodies such as SOX10 and prognostic markers such as p16 may be useful. However, there is no single stain or combination of IHC that may reliably distinguish benign or borderline melanocytic lesions from melanoma. Molecular assays may provide a guide to statistical likelihoods that mutations in selected genes are more common in melanomas versus melanocytic nevi. The RNA gene expression profile offers a promising start and with additional testing, the current gene expression profiles will likely expand, improving the statistical certainty of a diagnosis of melanoma. By combining the CGH/SNP assay which identifies the key chromosomal aberrations, the statistical diagnostic certainty of a melanoma will likely improve. These assays should be utilized by a dermatopathologist or surgical pathologists with experience in diagnosing melanomas and should only be interpreted by individuals with expertise in performing these assays.

3. Which laboratory tests are most predictive of prognosis and response to different therapeutics for malignant melanoma?
   The answers depend upon the initial stage of the melanoma and is a multidisciplinary approach with the patient's oncologists and surgeons. First line therapeutics include BRAF inhibitors, CTL4A inhibitors, and PD-1/PD-L1 inhibitors. Thus, IHC or molecular assays for the anticipated targeted protein will be prioritized. For example, if the patient is considered for a BRAF or PD-1 inhibitor, determination of the BRAF or PD-1 status of the melanoma should be performed. The decision to utilize IHC or a molecular assay depends upon a number of factors, including the sensitivity, specificity, and cost of the assay. GEP is currently used to predict metastatic risk in uveal melanomas, and current studies suggest there may be utility in predicting metastatic risk for cutaneous melanomas as well. To monitor the efficacy of therapy utilizing these therapeutics, liquid biomarkers offer great promise. Assays for ctDNA and circulating immune cells have the advantage of non-invasive and real-time monitoring of the tumor cell microenvironment in the peripheral blood, identifying subsets of immune cells that may predict treatment response to specific therapeutic agents.

Conclusions

The foundation of all prognostic and treatment considerations for the management of melanoma is dependent upon the laboratory and histopathologist to establish an accurate diagnosis. The histopathological diagnosis of malignant melanoma continues to evolve with the identification of new histopathological parameters that show greater positive predictive values for risk stratification. Adjuvant testing utilizing a combination of immunohistochemistry and molecular testing will continue to expand the role of the histopathologist to provide additional data that will assist in risk stratification and bring the management of malignant melanoma closer to the ultimate goal of improving patient outcomes.

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Chapter 4
Melanoma Epidemiology, Staging and Prognostic Factors

Mohammed Almashali, Robert Ellis, and Gyorgy Paragh

Learning Objectives

- Melanoma epidemiology and changes in incidence and mortality
- Current melanoma staging system
- Prognostic factors incorporated into the staging system
- Other clinicopathologic prognostic factors
- Emerging prognostic factors

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Introduction

Melanoma is a potentially deadly disease, feared for its metastatic potential. Melanoma is one of few tumors that even when presenting smaller than a grain of rice, may lead to distant disease spread and death. However, most melanomas are treated by wide local excision with no subsequent recurrence; only a minority of patients diagnosed with melanoma will succumb to the disease [1]. As treatment and follow-up measures after definitive treatment aim to reduce disease morbidity and mortality, it is essential to know expected outcomes in patients diagnosed with melanoma based on their clinical features at the time of treatment. This is even more important now in the "golden age" of melanoma therapy when that promising agents to treat and cure melanoma exist. Several clinicopathological factors have been recognized as predictors of melanoma mortality risk. Some factors correlate very strongly with outcomes and can be used to cluster patients into groups based on their risk of expected disease outcomes. Staging provides excellent approximation for melanoma mortality, but does not provide accurate, personalized risk prediction. Recent studies also report many prognostic factors currently not included in recognized staging systems. Here, we review basic melanoma epidemiology, the main staging system and introduce other established and emerging clinical, histological and molecular prognostic markers [2].

Melanoma Epidemiology

Melanoma has shown the greatest rise in incidence of all major malignancies in the past decades. An overall three-fold rise in incidence has been documented since the mid 1970s. Fortunately, and for unknown reasons, mortality rates have remained consistently low during this period (Fig. 4.1) [1].

In the past 5 years a slow decline in mortally rate has become evident, most likely due to the wider use of molecular targeted and immunotherapy. In 2019 we expect 96,480 people to be diagnosed with invasive melanoma in the US, with 7230 patients dying as a result of melanoma [1]. Invasive melanoma is currently the fifth leading cause of cancer diagnosis when in-situ carcinomas and non-melanoma skin cancers are excluded from the statistics. Men are 1.46 times more likely to be diagnosed with invasive melanoma than women, but men have a 1.9 times greater chance of dying from melanoma. In addition to invasive melanoma, in 2019 we expect to diagnose 95,830 in-situ melanomas in the US, thus the combined number of newly diagnosed melanomas in 2019 will surpass 192,000 [3]. The median age at melanoma diagnosis is 65 years but melanoma affects many younger patients. Melanoma is the most common invasive cancer in men and is the third most common invasive cancer in women below 50 years of age [3]. Most melanomas are diagnosed in people with lighter skin types, with a 31 and 24-fold higher incidence in white compared to African American males and females respectively. Other darker skin types

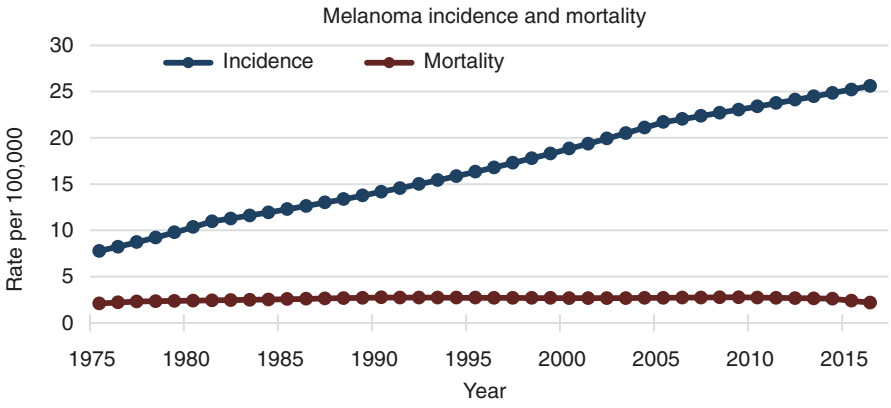

Fig. 4.1 Melanoma incidence and mortality rate from 1975 to 2016. Standardized melanoma incidence and mortality per 100,000 in the US population is depicted (data from Surveillance, Epidemiology, and End Results (SEER) Program 9, data accessed 4/29/2019) [1]

also show markedly lower melanoma risk. The overall burden of melanoma in the US population is high, with 1.2 million people in the US with prior history of invasive melanoma [1].

Melanoma Staging

Melanoma comes in many different sizes and forms at the time of diagnosis. It presents in varying anatomical locations in patients over a range of ages. Luckily, despite high malignant potential, less than 8% of all patients diagnosed with invasive melanoma will succumb to the disease within 5 years of diagnosis. To design optimal treatment, follow-up, and clinical trials, it is important to create well-defined disease categories and group patients based on expected outcomes. The American Joint Committee on Cancer (AJCC) Cancer Staging Manual has been the standard staging system to categorize melanoma patients for decades, and is used by melanoma-treating clinicians world-wide. AJCC staging builds on the traditional anatomical tumor, node, and metastasis (TNM) staging system, but also utilizes other features to create better-aligned disease categories.

Therefore, it is critical to understand both the TNM system and the AJCC clinical staging system to establish the correct melanoma stage and to understand our patients' morbidity and mortality risk. Currently the AJCC eighth manual is in effect and has been routinely used in the US healthcare system since January 2018 [2, 4, 5].

List of tumor categories in the TNM system (for table please see references [2, 5]):

- **Tx:** there is a known primary tumor, but it cannot be assessed
- **T0:** there is no evidence of a primary tumor

- **Tis:** the primary tumor is only intraepidermal and there is no primary tumor extension into the dermis
- **T1:** the primary tumor is ≤1.0 mm in Breslow depth and status of ulceration is unknown or unspecified
- **T1a:** the primary tumor is <0.8 mm in Breslow depth and there is no ulceration
- **T1b:** the primary tumor is <0.8 mm in Breslow depth and is ulcerated or Breslow depth is 0.8–1.0 mm and in the latter case the ulceration status does not matter.
- **T2:** the primary tumor is >1.0–2.0 mm in Breslow depth and ulceration status is unknown or unspecified
- **T2a:** the primary tumor is >1.0–2.0 mm in Breslow depth without ulceration
- **T2b:** the primary tumor is >1.0–2.0 mm in Breslow depth and ulcerated
- **T3:** the primary tumor is >2.0–4.0 mm in Breslow depth and ulceration status is unknown or unspecified
- **T3a:** the primary tumor is >2.0–4.0 mm in Breslow depth without ulceration
- **T3b:** the primary tumor is >2.0–4.0 mm in Breslow depth and ulcerated
- **T4:** the primary tumor is >4.0 mm in Breslow depth and ulceration status is unknown or unspecified
- **T4a:** the primary tumor is >4.0 mm in Breslow depth without ulceration
- **T4b:** the primary tumor is >4.0 mm in Breslow depth and ulcerated

The classic TNM system in melanoma, like other malignancies, assesses tumor (T), nodal (N) and metastasis (M) characteristics. Although similar to other malignancy staging, there are notable differences in the melanoma TNM classification. The primary tumor feature most closely associated with survival is an absence of invasion (Tis), or the vertical thickness of the tumor (Breslow depth) in cases of invasive melanoma [4, 5]. Thicker tumors have increased risk of distant disease spread and melanoma specific mortality. Breslow depth is measured on histology cross sections by assessing the distance between the area of maximal invasion and the overlying granular layer of the epidermis (Fig. 4.2).

If the epidermis is absent, then thickness is determined histologically from the most superficial aspect of the tumor specimen to the maximal depth of invasion. A melanoma with a Breslow depth of 1 mm or less has a 5-year melanoma specific mortality (MSM) of 1% while 5-year MSM in a melanoma with 1–2, 2–4 and ≥4 mm thickness is 5%, 9%, 14%, respectively, showing the prognostic significance of tumor thickness [2].

Besides Breslow depth the other most important primary melanoma feature that correlates with outcome is ulceration (loss of epidermis overlying the tumor) [2, 5]. The presence of ulceration substantially increases MSM in all primary melanomas. For instance, a non-ulcerated 2–4 mm thick melanoma has a 5-year MSM of 6%, while melanomas of the same thickness with ulceration have over two-fold higher MSM of 14% over 5-years. A similar increased risk of MSM between ulcerated and non-ulcerated melanomas is found within each Breslow depth category [2].

Although the mitotic rate (the proportion of cells within a tumor that are undergoing mitosis as a surrogate marker of tumor proliferation) was prominent in the AJCC seventh edition, this is no longer incorporated in the eighth edition. The melanoma dataset analyzed for the eighth edition revealed dichotomous mitotic rate (whether

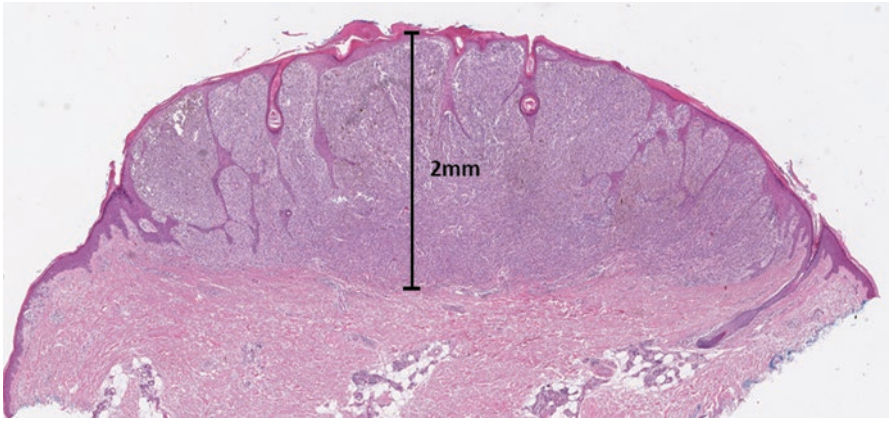

Fig. 4.2 Breslow depth is the most important prognostic marker of invasive melanoma. Breslow depth, primary tumor thickness, is measured on histology cross sections by assessing the distance between the area of maximal invasion and the overlying granular layer of the epidermis (Image courtesy of Robert Ellis)

mitotic figures were, or were not identified histologically) was not found to be an independent predictor of MSM in thin (T1) melanomas, thus mitotic rate could not be easily incorporated in the predictive model [2, 5]. However, mitotic rate still bares prognostic significance when assessed non-dichotomously in melanoma, with higher numbers of mitotic figures associated with worse prognosis; as such, mitotic rate is still routinely reported by pathologists [2]. There are many other histological features of tumors and nodal metastasis that carry prognostic value but could not be easily incorporated into a predictive model for staging [2, 5]. Many of these features will be reviewed amongst prognostic factors discussed later in this chapter.

Unfortunately, some melanomas are not confined to the primary tumor site and show locoregional spread. The majority of these melanomas will initially show features of lymph node or local skin and or subcutaneous metastasis before clinical signs of distant disease [2, 5]. Thus, features of locoregional spread are also important predictors of MSM and are utilized for establishing the N category of the TNM staging system. In the AJCC eighth data set the importance of microsatellite, satellite and in transit metastasis was comparable at all levels of nodal disease [2, 5]. More importantly the presence of any or all of these non-nodal locoregional disease features carried similar significance. The presence of nodal metastasis and the burden of nodal disease (occult, clinically detected, number of nodes involved and presence of matted nodes) all retained prognostic value. The combination of these features defines the N categories of the TNM system of melanoma (for table please see references [2, 5]).

List of N category terms:

- Microsatellite metastasis: microscopic cutaneous or subcutaneous metastasis
- Satellite metastasis: clinically evident cutaneous or subcutaneous metastasis within 2 cm of the primary tumor but discontinuous from it.

- In-transit metastasis: clinically evident cutaneous or subcutaneous metastasis over 2 cm from the primary tumor in the area between the primary tumor and the regional lymph nodes. These are mostly proximal to the primary site but in some cases may also present distally.
- Clinically detected lymph nodes: lymph nodes identified on clinical or radiological examination.
- Occult lymph nodes: lymph nodes in which the presence of metastasis is established via histological assessment of the lymph node.
- Matted nodes: two or more nodes that adhere to each other because of metastatic cancer involvement.

List of N categories:

- **Nx:** if regional disease cannot be assessed
- **N1:** One tumor-involved LN or in-transit, satellite, and/or microsatellite metastases with no tumor-involved LN
- **N1a:** One clinically occult LN and no in-transit, satellite, or microsatellite metastases
- **N1b:** One clinically detected LN and no in-transit, satellite, or microsatellite metastases
- **N1c:** No regional lymph node disease and in-transit, satellite, and/or microsatellite metastases found
- **N2:** Two or three tumor-involved LNs or in-transit, satellite, and/or microsatellite metastases with one tumor-involved LN
- **N2a:** Two or three clinically occult LNs and no in-transit, satellite, or microsatellite metastases
- **N2b:** Two or three involved nodes with at least one clinically detected and no in-transit, satellite, or microsatellite metastases
- **N2c:** One clinically occult or clinically detected LN and in-transit, satellite, and/or microsatellite metastases found
- **N3:** ≥4 tumor-involved LNs or in-transit, satellite, and/or microsatellite metastases with ≥2 tumor-involved LNs or any number of matted nodes
- **N3a:** ≥4 clinically occult LNs and no in-transit, satellite, or microsatellite metastases
- **N3b:** ≥4 LNs, at least one of which was clinically detected, or presence of any matted nodes and no in-transit, satellite, or microsatellite metastases
- **N3c:** ≥2 LNs clinically occult or clinically detected and/or presence of any matted nodes, with presence of in-transit, satellite, and/or microsatellite metastases

Once melanoma spreads to distant sites the location of distant metastases becomes the most important factor that defines survival. Skin and soft tissue metastases show more favorable outcome than lung and other visceral metastases, while CNS involvement carries a distinctly poor prognosis [2, 5]. Elevated blood lactate dehydrogenase (LDH) is also an important factor as patients who have elevated LDH in conjunction with any site of metastases tend to have a poorer prognosis than patients with normal LDH levels [2, 5]. Following detection of metastatic disease these above factors

carry the most important prognostic significance, and define the M categories of the AJCC eighth staging system (for table please see references [2, 5]).

List of M categories in the TNM staging system of melanoma [2, 5]:

- **M0:** No detectable evidence of distant metastases
- **M1:** Evidence of unspecified distant metastasis
- **M1a:** Metastases to skin, soft tissue (including muscle), and/or nonregional lymph nodes; if LDH is not elevated M1a(0) if LDH is elevated M1a(1)
- **M1b:** Lung metastasis, with or without M1a involvement; if LDH is not elevated M1b(0) if LDH is elevated M1b(1)
- **M1c:** Distant metastasis to non–central nervous system (CNS) visceral sites with or without M1a or M1b involvement; if LDH is not elevated M1c(0) if LDH is elevated M1c(1)
- **M1d:** Distant metastasis to CNS, with or without M1a, M1b or M1c involvement; if LDH is not elevated M1d(0) if LDH is elevated M1d(1)

The prognostic stage groups of the AJCC system are created by assembling different TNM subgroups of melanoma with similar clinical features and associated MSM. Clinical staging (indicated with a lowercase c: cTNM) takes place after biopsy assessment of the primary melanoma and clinical assessment for metastases. Pathological (indicated with a lowercase p: pTNM) staging combines all pathological information from the primary melanoma after wide local excision and about the regional lymph nodes after sentinel lymph node biopsy (SLNB) or after lymph node dissection.

Clinical staging is simpler at Stage III and includes all melanomas with any clinical evidence of locoregional disease, while clinical Stage IV includes all cases with clinical evidence of distant metastasis. In terms of the primary tumor, clinical staging only differs from pathological staging in case of Stage IA and IB. In clinical stage IA only cT1aN0M0 tumors are included, and cT1bN0M0 are classified as cStage IB, while in pStage IA both pT1aN0M0 and pT1bN0M0 are included [5]. The reason for this classification difference is the possibility of subclinical nodal metastasis in some cT1bN0M0 which increases MSM of cT1bN0M0 to that of the level of cT2aN0M0 tumors.

List of clinical prognostic stage groups in melanoma (for table please see references [2, 5]):

- **cStage 0: Tis**N0M0
- **cStage IA: T1a**N0M0
- **cStage IB: T1b**N0M0 & **T2a**N0M0
- **cStage IIA: T2b**N0M0 & **T3a**N0M0
- **cStage IIB: T3b**N0M0 & **T4a**N0M0
- **cStage IIC: T4b**N0M0
- **cStage III: AnyT N1-3 M0**
- **cStage IV: AnyT AnyN M1**

List of pathological prognostic stage groups in melanoma (for table please see references [2, 5]):

- **pStage 0: Tis**N0M0
- **pStage IA: T1a**N0M0 & **T1b**N0M0
- **pStage IB: T2a**N0M0
- **pStage IIA: T2b**N0M0 & **T3a**N0M0
- **pStage IIB: T3b**N0M0 & **T4a**N0M0
- **pStage IIC: T4b**N0M0
- **pStage IIIA: T1a/b N1a/N2a** M0
- **pStage IIIB: T0 N1b/N1c** M0 & **T1a-T2a N1b-2b** M0 & **T2b / T3a N1a-2b** M0
- **pStage IIIC: T0 N2b/c N3b/c** M0 & **T1a-3a N2c-3c** M0 & **T3b/T4a AnyN** M0 & **T4b N1a-2c** M0
- **pStage IIID: T4b N3a-c** M0
- **pStage IV: AnyT AnyN M1**

The pathological staging of melanoma in AJCC eighth manual compared to prior staging systems has been most altered in the stage III groups (Fig. 4.3) [2, 5]. The prognostic stage groups define disease categories with distinct differences in MSM (Fig. 4.4a, b). However, it is important to note that stage group numbering does not increase parallel to mortality. Stage IIIA patients in the AJCC eighth dataset showed similar 5- and 10-year MSM to Stage IIA patients and even Stage IIIB patients showed better MSM than Stage IIC [2]. Moreover, it is important to recognize that MSM in the stage groups is highly dependent on the assessed cohort of patients and the quality of the diagnostic workup for accurate staging. Despite marginal changes in how melanoma patients are categorized into prognostic groups in the seventh and eighth AJCC editions, the more contemporary eighth dataset showed markedly reduced MSM in all AJCC eighth Stage I and II groups compared to the AJCC seventh dataset (Table 4.1) [2, 6]. Although staging uses the best available prognostic markers, it is still imperfect. Staging only aims to create broad prognostic groups and many factors with proven prognostic significance are excluded from the current staging system. The rest of the chapter will review the most important established prognostic factors and will provide an overview of some emerging prognostic tools.

Prognostic Factors in Melanoma

Depth of Invasion

Originally, Clark described five levels of melanoma invasion which correlated with outcomes. These levels are: I—intraepidermal; II—melanoma in the papillary dermis; III—melanoma fills the papillary dermis and extends to the interface between the papillary and reticular dermis; IV—melanoma in the reticular dermis; and V—melanoma extending into the subcutis [7]. Several subsequent studies confirmed a strong positive correlation of Clark's levels with risk of metastasis and MSM [8]. Later, Clark's levels were found to be an inferior overall prognostic marker

AJCC Eighth Edition
Melanoma Stage III Subgroups

N Category	T Category								
	T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
N1a	N/A	A	A	A	B	B	C	C	C
N1b	B	B	B	B	B	B	C	C	C
N1c	B	B	B	B	B	B	C	C	C
N2a	N/A	A	A	A	B	B	C	C	C
N2b	C	B	B	B	B	B	C	C	C
N2c	C	C	C	C	C	C	C	C	C
N3a	N/A	C	C	C	C	C	C	C	D
N3b	C	C	C	C	C	C	C	C	D
N3c	C	C	C	C	C	C	C	C	D

Instructions
(1) Select patient's N category at left of chart.
(2) Select patient's T category at top of chart.
(3) Note letter at the intersection of T&N on grid.
(4) Determine patient's AJCC stage using legend.

N/A=Not assigned, please see manual for details.[4]

Legend

A	Stage IIIA
B	Stage IIIB
C	Stage IIIC
D	Stage IIID

Fig. 4.3 American Join Committee on Cancer (AJCC) eighth edition Stage III melanoma subgroups (Originally published in [2])

compared to another measure of invasion, Breslow tumor thickness [9]. Breslow thickness, the maximum thickness of the invasive component of the melanoma measured from the level of the epidermal granular layer in millimeters, is the best independent prognostic factor of metastasis and MSM [10]. As the thickness of melanoma increases, the risk of early metastasis compared to late metastasis also increases along with the risk of locoregional spread [11]. Tumor thickness even predicts occult sentinel lymph node metastasis in thin melanomas (<1 mm) [12]. The 10-year melanoma specific survival (MSS) in invasive melanomas with <0.8 mm vs >0.8–1.0 mm thickness was 93.4% and 81.1%, respectively [5]. Given its prognostic value, tumor thickness is the most important component of the current AJCC staging system. Although Clark's levels are no longer used for staging, the anatomic level of invasion is still an independent prognostic factor for thin (≤1.0 mm) melanomas in several cohorts [2, 6]. Patients with ≤1.0 mm thick melanomas with Clark's level of III–V have a 3.5-fold higher relative risk of MSM compared to patients with a Clark's level II [13]. Based on its prognostic significance pathologists continue to report Clark's level for melanomas during histological assessment of the tumor.

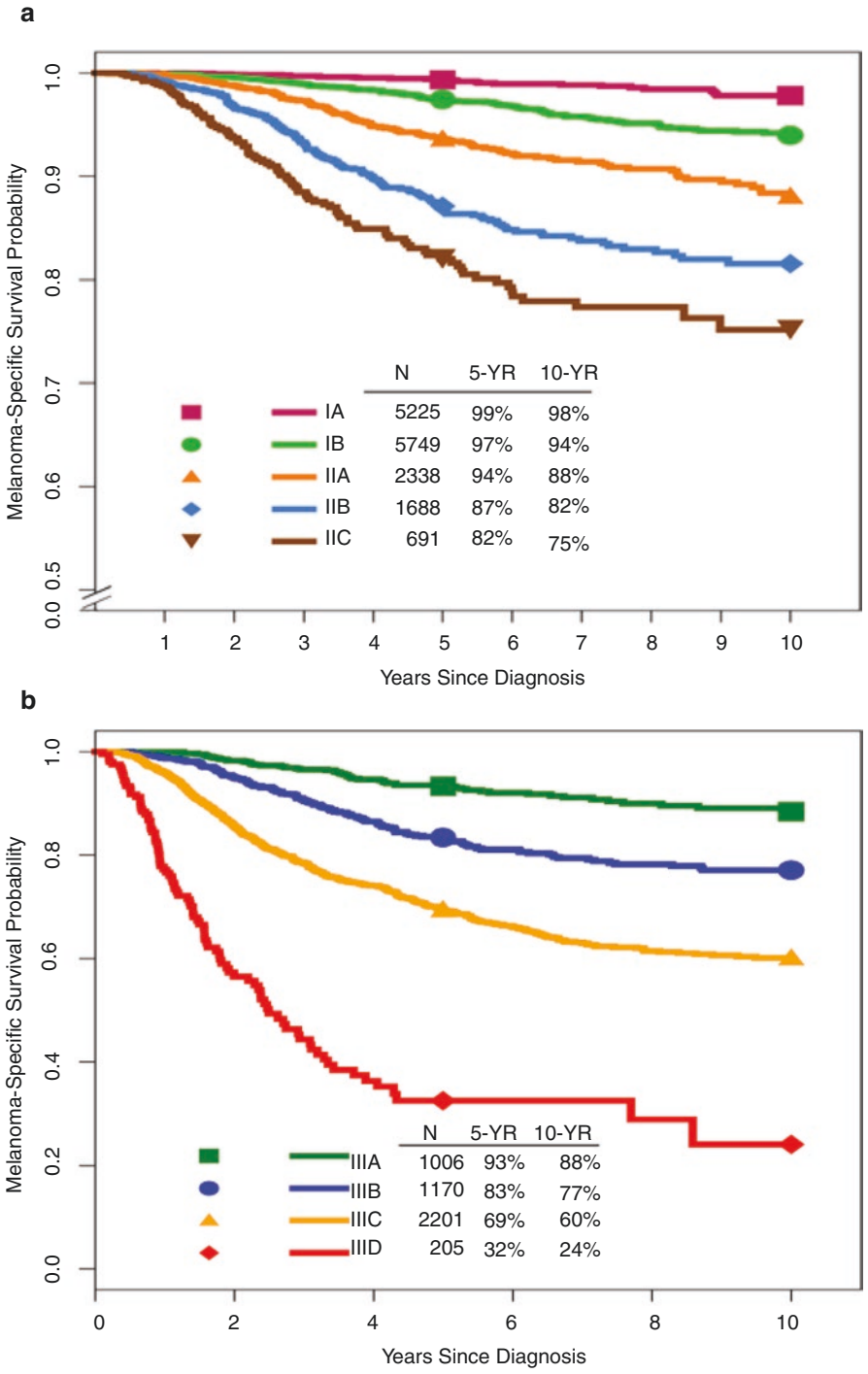

Fig. 4.4 Melanoma-specific survival, Kaplan-Meier Curves in AJCC eighth edition Stage I and II (**a**) and Stage III (**b**) melanoma patients (Originally published in [2])

Table 4.1 American Join Committee on Cancer (AJCC) eighth edition and seventh edition Stage I and II groups 10-year melanoma-specific survival

Stage	AJCC 7th	AJCC 8th
IA	0.95	0.98
IB	0.88	0.94
IIA	0.67	0.88
IIB	0.57	0.82
IIC	0.4	0.75

The survival in the more contemporary AJCC eighth dataset is markedly better in the same stage groups [2, 6]

Ulceration

The full thickness loss of epidermal cover over the melanoma, ulceration, has long been known to be associated with unfavorable outcome. Primary tumor ulceration even retains it prognostic significance in locally advanced melanoma and thus is an important independent poor prognostic factor [14]. Therefore, ulceration is a component of the current staging system and helps categorize patients in prognostic stage groups I–III [5]. The impact of ulceration on survival is reviewed in detail earlier in this chapter. Ulceration has long been considered a passive tumor feature caused by fast tumor growth and lack of sufficient nutrition and mechanical trauma to protruding tumors. New data, however, questions this simple mechanistic view and suggests that ulceration could be secondary to the effect of paracrine tumor derived mediators on the epidermis. These observations led to the identification of an immunohistochemical signature, where loss of two epidermal differentiation proteins (AMBRA1 and loricrin) in the epidermis overlying the invasive component of melanoma signals poor prognosis and increased melanoma-specific mortality [15].

Mitotic Rate

Mitotic rate describes the abundance of melanoma cells in active cell division in the tumor and provides information on the proliferative activity of the melanoma. In prior cohorts mitotic rate was the most significant prognostic factor for survival after tumor thickness according to multivariant analysis. The presence of 1 mitosis/mm^2 or more mitoses were associated with a significant decrease in 10-year survival, and increasing mitotic rate was associated with increasing MSM [16]. In the AJCC seventh Manual mitotic rate was used as a criterion for classifying thin invasive melanomas. Although the prognostic significance of mitotic rate in univariate analysis was also clear in the AJCC eighth dataset (Fig. 4.5) mitotic rate did not retain independent prognostic significance as a dichotomous variable in multivariant analysis of thin melanomas, therefore, it was excluded from the current staging system [2]. Nevertheless, mitotic rate is still reported and may become an important tool to determine individual risk in melanoma prediction models. Mitotic rate in sentinel lymph nodes is also a prognostic indicator. High sentinel lymph node mitotic rate predicts rapidly progressing disease and worse MSS [17].

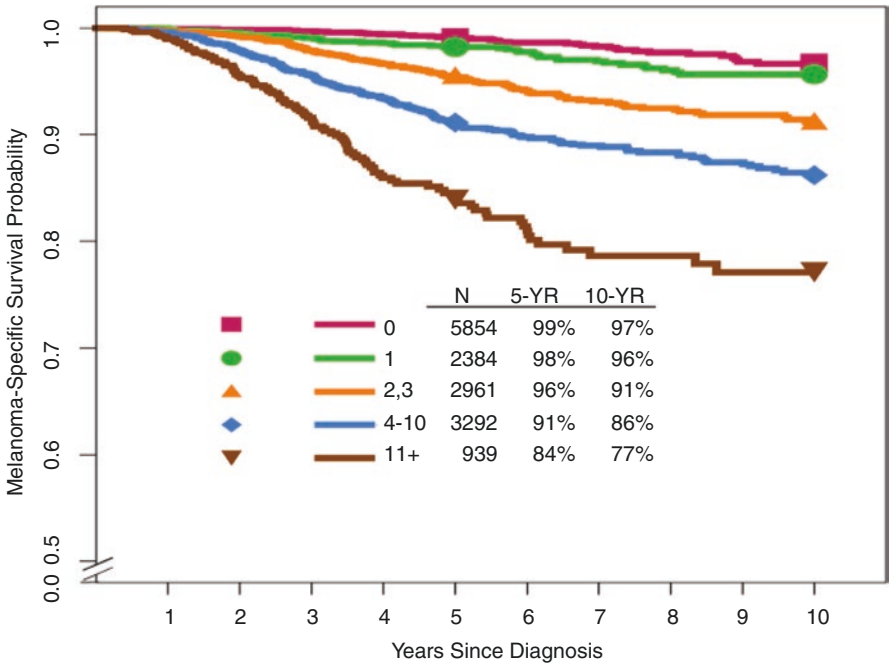

Fig. 4.5 The effect of primary melanoma mitotic rate (1/mm^2) in patients with Stage I–II melanoma. Kaplan-Meier melanoma-specific survival curves. AJCC eighth edition database (Originally published in [2])

Growth Phase and Melanoma Subtypes

The extension of melanomas primarily within the epidermis and along the dermoepidermal junction defines radial growth phase. Radial growth phase is diagnosed when the solitary aggregates of melanoma cells in the papillary dermis are smaller than the intraepidermal nests and dermal aggregates show no mitoses. Vertical growth phase describes clusters of melanoma cells in the dermis, and at least one nest in the dermis is larger than the largest intraepidermal nest, or mitoses are identified in any of the dermal melanoma cells indicating proliferative activity. The distinction between these phases of melanoma progression is important as vertical growth phase melanomas demonstrate a worse prognosis. In one study, a 42-fold increased risk of metastasis in tumors with vertical growth phase as compared with radial growth phase lesions [16], while in another study the radial growth phase melanomas had a 5-year survival rate of 98.2% compared with 84% for vertical growth phase melanomas [18]. The markedly increased mortality risk associated with vertical growth phase is also likely the reason why nodular melanomas, which present with early vertical growth phase tend to do worse than most other melanoma subtypes [19].

Melanoma is a group of clinically distinct diseases of melanocytes. Superficial spreading, nodular, lentigo maligna and acral lentiginous melanoma are the most common subtypes, but based on clinical and histological features desmoplastic, amelanotic and primary dermal cutaneous melanomas are also distinguished. Nodular growth pattern is an independent poor prognostic factor even when controlling for thickness, ulceration and stage [20]. Desmoplastic melanoma represents a rare locally aggressive subtype. Although desmoplastic melanomas are often diagnosed later their prognosis is better than those of other similar thickness primary lesions [21]. Melanomas without histological evidence of pigmentation are termed amelanotic melanomas. This rare subtype of melanoma is often diagnosed with a delay and thus bares more concerning primary tumor features, and poorer survival comparted to melanotic melanomas [22]. Melanomas that arise without evidence of epidermal involvement are called primary dermal melanomas. This variant of melanoma is usually thick at the time of diagnosis but overall shows favorable outcome compared to melanomas with epidermal involvement and similar thickness [23].

Despite some evidence for differences in patient outcomes with different melanoma subtypes, currently there is insufficient evidence to use growth pattern or melanoma subtype as a separate staging criterion. Therefore, all cutaneous melanoma subtypes and growth phases (radial and vertical) are staged similarly and categorized based on AJCC eighth criteria [5].

Regression

Regression is the elimination of tumor cells from a previously tumor cell laden area. Regression is mostly the result of lymphocytic inflammation. The tumor tissue is replaced with fibrosis and a variable component of degenerative melanoma cells, melanophages, lymphocytic proliferation and telangiectasia [24]. Due to regression the tumor may be measured thinner that it previously was, therefore, it may be under staged. However, regression may also suggest an active antitumor immune response, which is generally considered to be a potentially favorable feature. The influence of regression on prognosis for patients with melanoma remains controversial [25].

Tumor Infiltrating Lymphocytes

Tumor-infiltrating lymphocytes (TILs) are thought to be a key indicator of the host immune response to melanoma. TILs are categorized based on prominence of infiltrate as brisk, non-brisk and absent [26]. A better prognosis of melanoma is associated with the presence of a host inflammatory response [26] but TILs show variable prognostic significance in smaller studies and do not maintain prognostic significance in multivariate analysis on larger cohorts. The assessment of the intensity and distribution of the host lymphocytic infiltrate is highly subjective [27]. Recent

studies assess TIL compositions with immunohistochemical stains and molecular biology methods. A significant survival advantage was documented in tumors showing higher peritumoral infiltration by T-cell markers [28]. TILs may be important as a component of tumor immune profile in predicting response to immunotherapy [29].

Lymphatic Invasion and Angiotropism

Melanoma cells mostly spread to nearby or distant sites via lymphatic vessels. Thus, lymphatic vessel invasion by melanoma cells is an ominous sign of metastatic potential and was found to be an independent negative prognostic factor in multivariate analysis [30]. Angiotropism is defined as malignant cells wrapping the external surface of vessels. Angiotropism is a poor prognostic factor and indicates increased metastatic potential [31].

Neurotropism

Neurotropism is defined as infiltration of nerve fibers by neoplastic cells with extension of the tumor along the surrounding nerves. Neurotropic melanomas are those melanomas that have strictly perineural and or endoneural involvement without desmoplasia [32]. Neurotropism is rare and is present in less than 1% of all melanomas. Although only few studies assessed the prognostic significance of neurotropism, neurotropism tends to worsen prognosis [32]. Neurotropic melanomas demonstrate high local recurrence rates likely secondary to poorly defined borders, tendency to be amelanotic, infiltration and extension along nerve sheaths, and presence of skip areas [32].

Nevus Association

Most melanomas arise de novo. However, approximately 40% of melanomas are formed in a preexisting nevus. The presence of associated nevus on histology carries favorable prognosis and de novo melanomas were found to be associated with poor prognostic features [33].

Age

Age is an independent prognostic factor in patients with cutaneous melanoma [34]. Patients older than 65 years show poorer prognosis than younger patients. Increasing age is associated with higher risk primary tumor features in all age-groups except

patients younger than 20 years of age. Below 20 years melanomas tend to have more high-risk features than above 20 years but MSS is still better in the youngest patients. A not fully understood conundrum is the association of nodal metastasis with age. Younger patients have higher probability of SLN metastasis, but they have better prognosis than older patients. Older patients are less frequently SLN-positive but have higher risk of developing in-transit metastases and local recurrence [35].

Gender

Gender has also been established as an independent prognostic factor for melanoma specific survival. Men show less favorable outcomes. Women have an up to 30% lower chance of experiencing distant or locoregional metastasis. Women also show a different pattern of metastasis. Satellite and in-transit metastasis are significantly more common in women as opposed to the more proximal regional lymph node and distant metastasis which are more likely to occur in man after the diagnosis of primary tumor [36]. Men also have a higher incidence of thicker tumors and ulceration and more often present with axial melanomas. Therefore, male gender is an independent risk factor for worse overall survival (relative risk: 1.45; 95% CI: 1.21–1.77) [37].

Marital Status

Marital status also predicts outcomes. Unmarried patients and patients who live alone are more likely to present with thicker melanomas and late-stage, metastatic melanoma and are also more likely to succumb to melanoma [38]. Marriage likely plays are role because the presence of the partner aids earlier recognition of problem lesions and helps remove barriers for clinic visits and follow-up [39].

Anatomical Location

Anatomical location has also been recognized as significant prognostic factor. Several studies confirmed the overall poorer prognosis of patients with primary melanomas of the head, which also show significantly higher rates of satellite metastasis, increased mitotic rate as well as greater proportion of nodular melanoma. Posterior scalp melanomas carry particularly poor prognosis [40]. Besides the head, melanomas of the trunk showed increased MSM. Generally, patients with upper extremity melanomas tend to present with the thinnest melanomas and have better survival, however, the posterior upper arm shows unfavorable prognostic features, like the upper back [40, 41].

When a metastatic melanoma is discovered in a visceral, or a deep dermal or deep submucosal site and the anatomical location of the primary melanoma is unknown, it is diagnosed as a "melanoma with unknown primary." These metastatic melanomas tend to have slightly favorable prognosis compared to similar stage III or IV melanomas with identified primary tumors [42].

Tumor Derived Markers

Numerous proteins have been investigated as potential prognostic serum markers in melanoma. Currently there is ample evidence for the utility of lactate dehydrogenase (LDH), S100B and melanoma inhibitory activity protein (MIA) as prognostic factors.

In the AJCC eighth edition staging system, serum LDH is the only serum biomarker that is used for staging [5]. LDH is a ubiquitously expressed enzyme that can be released after cell damage or death from tumor cells. LDH is not specific for melanomas and can be elevated in numerous other malignancies. Higher serum LDH concentration is associated with lower overall survival in melanoma patients [43]. Furthermore, high serum LDH may also indicate lower likelihood of response to immunotherapy and further LDH increase during immunotherapy correlates with significantly reduced overall survival [44].

S100B is a calcium binding protein with a role in cell cycle progression and differentiation. S100B level increases with disease progression and tumor burden and can both serve as a prognostic factor in Stage III and IV disease. S100B elevations predicts non-sentinel node positivity and S100B level correlates with clinical response [43, 45]. In the US guidelines S100B measurement is currently not recommended but some European guidelines recommend every 3–6-month S100B measurement in patients with >1 mm primary melanomas.

MIA is a secreted protein involved in cell-cell contact, invasion and metastasis. Elevated MIA levels are associated with advanced disease and decreased disease free survival and may also help evaluate treatment response, however, its baseline levels are elevated in pregnancy and in children decreasing its utility in some patients [45].

Other tumor derived factors that are potential emerging prognostic markers include circulating tumor cells, circulating cell free tumor DNA and exosomes [46, 47]. These may help evaluate burden of disease and identify relapses and thus may provide prognostic information. Furthermore, capturing circulating melanoma cells or melanoma derived cell free DNA may enable detection of mutations and establish other tumor characteristics that may drive therapeutic interventions and thus enable a so-called liquid biopsy of melanomas. These techniques are currently not yet in mainstream clinical use [46, 47].

Molecular Markers of Melanoma Prognosis

Numerous studies have tried to identify protein, messenger-RNA (mRNA), micro-RNA or DNA analysis-based methods to create prognostic tools for melanoma. Several individual studies on low patient numbers have found promising prognostic profiles but have either not been validated by other studies or where validation exists there is limited information on their potential clinical utility. There has also been considerable interest in identifying mRNA signature-based tests after the prognostic significance of a similar test in uveal melanoma had be shown. Initial studies using non-hypothesis driven approaches to establish mRNA profiles associated with prognosis showed little overlap in signatures [48]. However, in 2015 a new melanoma gene expression profile test was created and commercialized. The test was created by assessing the expression of genes in FFPE specimens and creating a weighted measure of the change in the expression of this gene profile. This 31-gene expression profile (GEP) was established in small number of cases (total n = 375) in retrospective development, training and a validation datasets [49]. Since the publication of the gene profile, the test has been evaluated on numerous datasets of Stage I–III melanoma patients. Unfortunately, data establishing the clinical utility of this molecular signature test is still lacking, and while molecular profiles offer promise, these types of prognostic tests are not endorsed for use in the general clinical management of melanoma patients outside of research. Similar 9-GEP, 4-GEP and 53-GEP immune panels are also published as potential prognostic tools, but these have even lower levels of evidence supporting their potential role in establishing melanoma prognosis.

Conditional Survival

Melanoma prognosis is determined by many factors. One often forgotten factor is the time elapsed since melanoma diagnosis. Although melanoma may result in deadly metastatic disease even over a decade after diagnosis, most of the MSM is within the first few years of melanoma diagnosis and the slope of the Kaplan-Meier survival curves become similar in the different melanoma prognostic stage groups. In a registry-based analysis (n = 40,520) of invasive melanoma patients, the MSS was only 19% for patients originally diagnosed with Stage IV disease. However, stage IV melanoma patients who do not succumb to the disease in the first 5 years are expected to do statistically very similarly in future to Stage II and III patients who also survived 5-years after diagnosis. The 5-year Stage II, III and IV conditional MSS is 86%, 87% and 84% respectively [50]. This highlights the importance of time since diagnosis in assessing mortality risk and need for adjuvant therapy and imaging studies.

Summary

Accurate melanoma staging is a key requirement for all stages of clinical decision making and patient counselling. At present, commonly used staging systems such as the AJCC model only incorporate a limited number of relevant prognostic biomarkers, and as such, do not aim to accurately determine individual locoregional or distant metastatic spread, or overall survival. However, in future, the addition of newer, or previously underutilized prognostic factors will lead to more personalized and specific disease risk stratification. Online calculators do exist at present that incorporate further prognostic factors [51], but these rely on older disease datasets that encompass melanoma outcomes that are more bleak than can be expected by patients diagnosed with melanoma today. As such, these calculators often provide a misleading overestimate of actual disease risk. Better contemporary outcome prediction tools to assess individual risk based on several prognostic factors are being developed [4] which long term will also incorporate factors that predict response to treatment. The goal of these models will be to accurately quantify a patient's individual risk of disease progression allowing the most appropriate clinical care. Improved prediction of risk by also including likely treatment response will help usher in a new era of melanoma care.

Review Questions

Q1: A patient is in your clinic to discuss her melanoma results. She has a 0.6 mm thick, non-ulcerated melanoma on the left forearm with no palpable lymph nodes. How will you stage her disease? What is her approximate chance of dying from melanoma in the next 10 years?

A1: Clinical AJCC Stage IA. Approximately 2% of the people diagnosed with Stage IA disease will ultimately succumb to their melanoma.

Q2: The same patient from the above scenario reviews the pathology report and notices that her melanoma's mitotic rate is 5/mm^2 and would like to know whether this has any prognostic implications.

A2: Mitotic rate is not used for staging purposes since implementation of the AJCC eighth manual for melanoma staging. However, higher mitotic rate carries increased melanoma specific mortality risk.

Q3: A patient was referred to you for a skin check because of recent left axillary enlarged lymph node with biopsy results revealing melanoma cells. The patient has no prior history of melanoma and no concerning pigmented lesions on their skin. On imaging there is no evidence of systemic disease or other lymph node involvement. He is diagnosed with metastatic melanoma of unknown primary. He is concerned about the lack of primary melanoma. He worries that as his primary melanoma could not be removed he might be more likely to die of the disease. How would you respond to his concerns?

A3: Although the presence of metastatic melanoma has a generally poor prognosis overall, melanomas with unknown primaries tend to do slightly better than tumors in the same stage group with known primary site.

Q4: A 45-year-old man was diagnosed with a 5.5 mm thick, non-ulcerated primary melanoma on his right upper arm 5 years ago. On physical examination one palpable lymph node was felt which subsequently was positive for melanoma on core needle biopsy. During right axillary lymphadenectomy two other lymph nodes positive for melanoma were identified. Since the lymphadenectomy he has not had any evidence of disease progression. He needs to make an important financial investment decision and would like to better understand his mortality risk. What is his risk of succumbing to melanoma in the next 5 years and what other factors are important to consider when evaluating this risk?

A4: The patient has stage IIIC disease. According to the most contemporary AJCC eighth manual dataset his 5-year MSS is 69% while his 10-year MSS is 60%. As he is 5-years out from diagnosis his current conditional MSS is 87% (60/69% × 100). Moreover, with currently available treatments his likely true MSS is expected to be even higher than the calculated number.

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Chapter 5
Imaging in Melanoma

Roger F. Uren, David Chung, and Kevin London

Lymphoscintigraphy for Sentinel Node Biopsy

Sentinel lymph node (SLN) biopsy requires three procedures to come together with careful technique in each case. These are:

1. Accurate lymphatic mapping to locate and label all sentinel nodes
2. Surgical removal of all sentinel nodes while leaving non-sentinel nodes in-situ
3. Targeted histological examination of the sentinel nodes

When achieved, clinical practice has shown this leads to unprecedented accuracy in the staging of regional lymph nodes.

Since Donald Morton and colleagues [1] described the technique of SLN biopsy in 1992 using blue dye, it has developed to become the standard of care to stage the regional lymph nodes in melanoma patients.

Definition: Sentinel Lymph node = any lymph node receiving direct lymphatic drainage from a tumor site.

The role of high resolution pre-operative lymphoscintigraphy (LS) in melanoma patients is to map lymphatic drainage from the melanoma site, by following the lymphatic collectors to identify any lymph node directly receiving this drainage—by definition a SLN [2, 3] (see Fig. 5.1).

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LS using Technetium-99m labelled radiocolloids enables the above to be achieved in almost every patient with cutaneous melanoma. Not only does this technique identify the draining node fields and the exact number of SLNs in each field, but with SPECT/CT hybrid imaging [4] will also reveal the exact anatomical location of each SLN in the field. It also identifies any SLN lying outside a standard node field. These "interval nodes" if receiving direct drainage are SLNs and can also contain metastasis [5]. With this information and the surface mark placed on the skin over the SLNs the surgeon can plan the surgical approach with precision (Fig. 5.2).

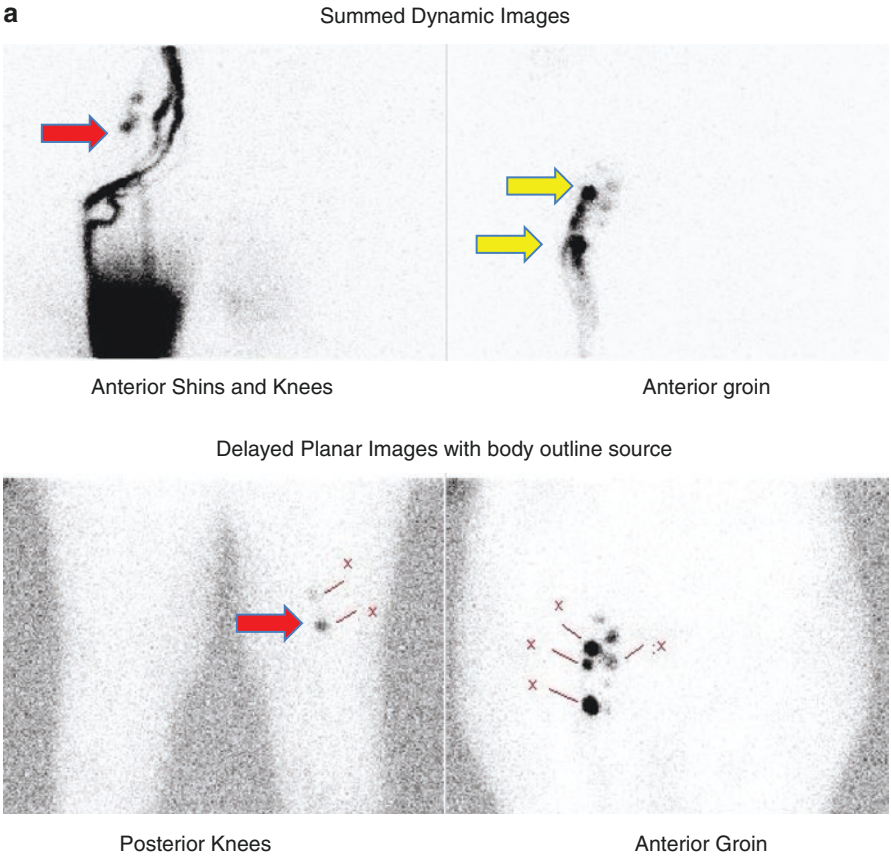

Fig. 5.1 (**a**) Patient with melanoma on the posterior right calf. The early summed dynamic image top row left shows four collecting vessels passing up the leg from the injection site, one reaching a SLN in the right popliteal fossa (horizontal red arrow) and three bypassing this node field reaching SLNs in the right groin. Two bright SLNs (horizontal yellow arrow) are seen with faint activity seen in other nodes. Delayed planar images show the right popliteal SLN and a probable second tier node above this and in the groin the two bright SLNs are marked with two other fainter nodes also probable SLNs marked. (**b**) A volume rendered SPECT/CT image anterior aspect of the groin shows the two bright SLNs (horizontal arrows) in blue and the two fainter SLNs also in blue

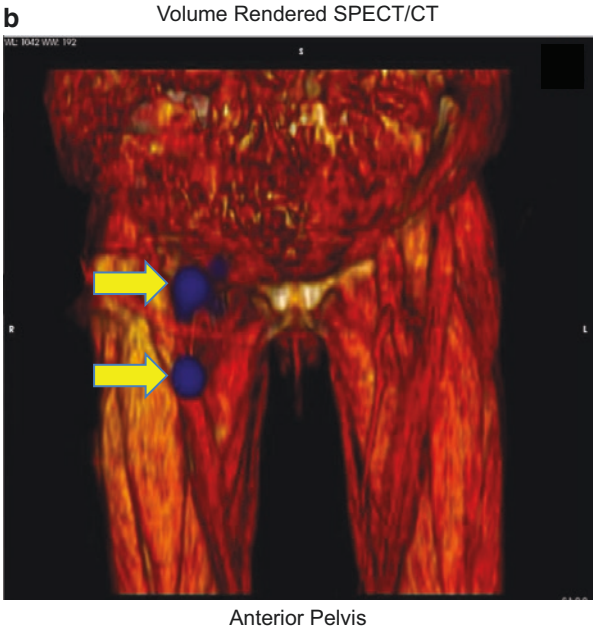

Fig. 5.1 (continued)

Teaching Point: When mapping lymph drainage in cutaneous melanoma with LS, mark only SLNs for surgical removal. Second tier nodes, if any, should be left in place.

Lymphoscintigraphy Technique

1. Intradermal injection of ^{99m}Tc labelled radiocolloid at the melanoma site
2. Dynamic phase images at 1 frame/min using a high-resolution collimator
3. Delayed planar images in Anterior, Posterior and Lateral projections as required
4. SPECT/CT hybrid images of the SLN sites
5. Skin marking of the SLNs location

Small particle radiocolloids are preferred as these enter the initial lymphatic capillaries in large numbers when injected intradermally and as these converge to eventually become a lymphatic collecting vessel this can then be seen and followed on the dynamic phase until a SLN is reached. Technetium-99m labelled antimony sulfide colloid, nanocolloid, filtered sulfur colloid and Tilmanocept all seem adequate.

As a guide, if multiple collectors are seen draining a melanoma site there are usually multiple SLNs. All such SLNs should be marked on the skin but any node that receives tracer via an efferent lymph vessel from a SLN is almost always a second tier node and should not be marked for removal. For melanomas on the

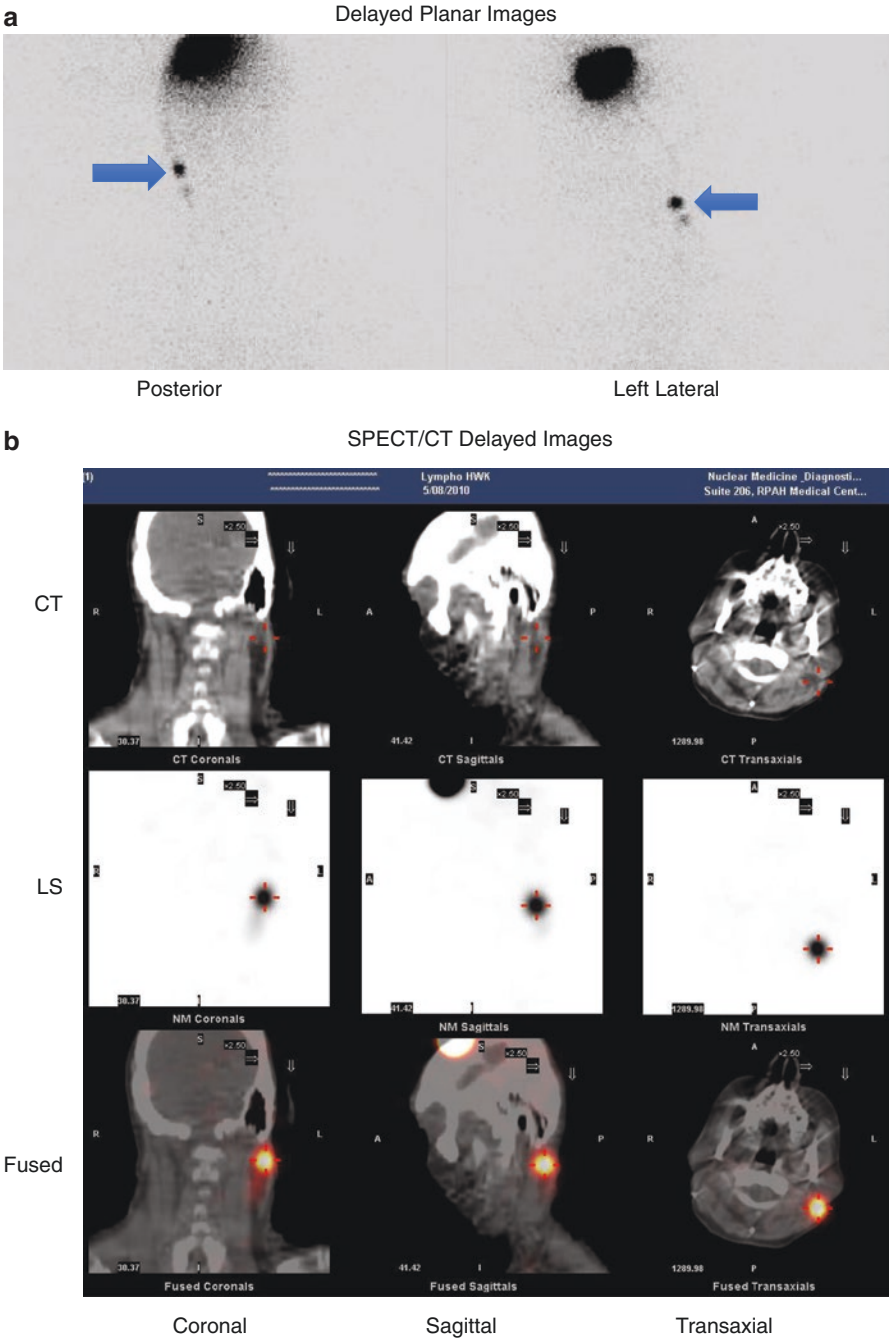

Fig. 5.2 (**a**) Patient with a left posterior scalp melanoma. Delayed planar images in the posterior and left lateral projections show a single collector passing to a SLN on the left side. (**b**) SPECT/CT images in three planes clearly show the left SLN lying deep to the upper fibres of the left sternomastoid muscle. (**c**) The SPECT/CT volume rendered images of the left side of the head and neck show the SLN lying in the left occipital node field just inferior to the left mastoid

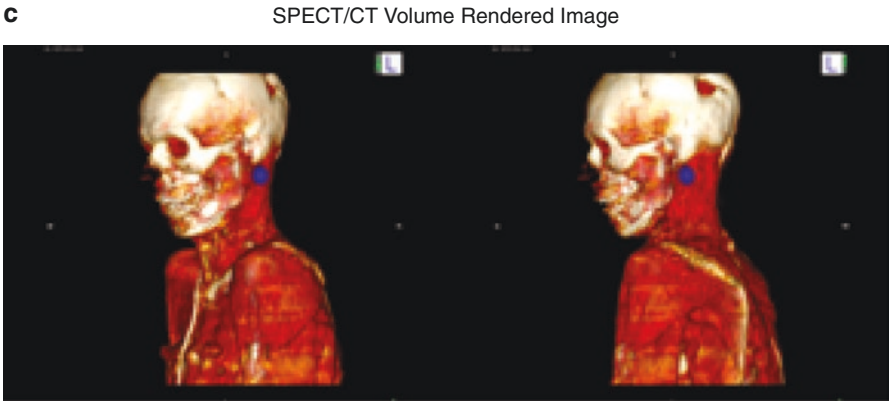

Fig. 5.2 (continued)

trunk, the median number of SLNs in the axilla is 1.3 and the same for SLNs in the groin. However, for lower limb melanomas the median number of groin SLNs is 3.3 (Fig. 5.1). In the head and neck region multiple draining node fields are seen in 73% of patients with 2.7 the median number of SLNs here. Multiple draining node fields are also common on the posterior trunk (49%) and anterior trunk (35%) [6].

Occasionally the lymphatic collectors are not visualised on the dynamic study adequately. In this situation using the "10% rule" has proved to be a practical method that can be used in surgery using a gamma probe [7]. This technique involves removal of the most radioactive node in the draining node field (that will certainly be a SLN) and any other node in the field with more than 10% of its activity. It should be remembered, however, that this approach will result in second tier nodes being removed in some patients.

The potential nodal locations draining the skin include:

- Axilla (Levels I, II and III)
- Epitrochlear
- Groin (Femoral, Inguinal, External Iliac, Internal Iliac and Obturator)
- Popliteal
- Triangular Intermuscular Space
- Cervical (Levels I–VI with Supraclavicular part of Level V)
- Parotid/Preauricular
- Postauricular
- Occipital
- Paravertebral
- Retroperitoneal
- Costal Margin
- Internal Mammary
- Interpectoral

Unexpected drainage patterns are common and all possible sites of drainage should be checked during the LS procedure so that SLNs are not overlooked. Some of these patterns include:

- Contralateral drainage
- Drainage to the triangular intramuscular space from the skin of the back
- Drainage to the retroperitoneal and paravertebral nodes from the posterior loin
- Drainage upward in the neck
- Drainage from the scalp directly to supraclavicular SLNs
- Drainage from the back over the shoulders to neck SLNs

The final group of SLNs that might be missed without careful technique are interval nodes mentioned previously. These lie between a melanoma site and a standard node field. We find interval nodes in 9.5% of our patients.

Teaching Point: SLNs should be removed surgically regardless of their location.

Possible Radiation Risk of LS

LS uses a small dose of the radioisotope Technetium-99m labelled to a small particle colloid. The dose used would typically be 1–2 mCi of ^{99m}Tc (37–74 MBq) injected intradermally. Migration from the injection site will depend on the radiocolloid used but with small particle colloids such as antimony sulfide colloid around 80–90% will remain at the injection site and this will be removed when the wide local excision is performed at the same time as SLN biopsy (we do not recommend LS for SLN biopsy after WLE—see below). Most of the remainder of the radiocolloid which is in the SLNs is removed when the nodes are excised for histological examination. The worst-case scenario we have tested would be a melanoma over the lower abdomen in a pregnant patient. In this case if surgery is done the same day as LS the fetus would receive the equivalent of about 6 days background radiation.

Teaching Point: It is safe to perform LS for SLN biopsy in pregnant women.

Potential Problems with LS

Wide Local Excision (WLE)

The LS pre-operative mapping study must be done before WLE to ensure point 1 described above—an accurate map of the lymph drainage of the melanoma. Once WLE has been performed the original lymphatic drainage of the melanoma may be completely changed. Over 26 years, we have had patients who after mapping for SLN biopsy at the time of WLE have then refused SLN biopsy. Some have returned within a couple of weeks and then wanted SLN biopsy. We have repeated the LS and most have shown a change in the lymphatic mapping. There are papers published reporting that SLN biopsy works post WLE, however, what these papers are saying

is that radiocolloid was injected, a "hot" node was removed and that equates to a successful LS. These studies do not know what the lymph drainage was prior to the WLE.

Teaching Point: It is important to perform LS and SLN biopsy before WLE if possible.

Reproducibility

We have repeated LS in about 70 patients who were unable to proceed to SLN biopsy following the LS procedure (operation time cancelled, medical issue intervened before surgery, etc.). In this circumstance when no surgery had been done in the 2–4 week interval from the first to second LS study we found exact reproducibility of every SLN original marked in 94% of patients [8]. There was only a minor difference in the other 6%. So, it is clear that in this circumstance it is fine to repeat the LS prior to SLN biopsy.

The Melanoma Site Immediately Overlies a Node Field

This is most common in the head and neck but can occur in the axilla and over the epitrochlear and popliteal node fields. In this circumstance we mark any lymph drainage we can see away from the injection site and then use high resolution ultrasound immediately deep to the melanoma site to exclude macroscopic metastasis. We also suggest that the area under the injection site be checked by the surgeon using the gamma probe when the injected activity has been excised as part of the wide local excision.

Conclusion

Pre-operative LS as part of SLN biopsy in melanoma patients was introduced in the early 1990s and has proved to be an excellent method to facilitate accurate staging of regional lymph nodes with minimal morbidity. The accuracy of SLN biopsy is crucial since current surgical practice is recommending US and clinical follow up of clinical node negative patients, if the SLN is positive for metastasis and completion dissection of the node field is no longer routinely recommended.

Furthermore, recent developments in the adjuvant treatment of metastatic melanoma emphasise the importance of this precise nodal staging to enable selection of those patients who might benefit from such systemic therapy. Finally, there appears to be a small subset of patients with microscopic metastasis in whom the SLN biopsy procedure itself may be therapeutic.

Ultrasound in Melanoma Patients

High resolution ultrasound (US) can be useful at several points in the diagnostic, staging, therapeutic and follow up pathway that patients with cutaneous malignant melanoma follow.

Diagnosis

Patient Case

A 35 year-old patient comes to your clinic concerned about recent change in a nevus on his right forearm: it is suspicious of a melanoma.

Does US Have a Role in Primary Assessment of Melanoma?

Very high frequency US utilizing frequencies >20 MHz produces high resolution images of the skin. The epidermis, subdermis and subcutis can be clearly defined [9] and there are a series of well documented changes that can help define the internal structure and thickness of a melanoma. However, in routine clinical practice this is not standard of care since the definitive diagnosis is made with excision biopsy. There were attempts to use the thickness measurement of the melanoma on US to guide surgical excision towards an initial diagnostic WLE but this will severely compromise the accuracy of lymphatic mapping to locate the sentinel nodes and is definitely not recommended.

Teaching Point: US is not recommended as a routine procedure in the diagnosis of melanoma and simple excision biopsy is preferred.

Staging

Case Continued

You perform an excision biopsy of the skin lesion. Histopathology reports a melanoma of Breslow thickness 1.4 mm. On examination you palpate two right axillary lymph nodes that are normal in size and consistency, but also one contralateral left axillary lymph node that is enlarged and firm.

What Are the US Criteria for Defining Normal and Abnormal Lymph Nodes?

When there is clinical lymph node disease or a subcutaneous mass for evaluation, an US is the best next test in most cases to examine the subcutaneous tissues or node fields. An US will confirm whether a pathological mass is present and guide biopsy

if indicated. The flexibility to position the US probe in any axis for optimal visualization, the ability to image in real time and the absence of radiation exposure make US the modality of choice. In this patient case, an US can assess the palpable lymph nodes in the bilateral axillae—both the right axilla which is the regional node basin, and the left axilla which is more likely due to other pathology.

As the regional lymph nodes of cutaneous lesions are mostly superficial, their location is ideal for assessment by high frequency US. In fact small parts US (10–15 MHz) is capable of producing images of higher resolution than CT and MRI.

A normal lymph node is seen by US as a solid ovoid structure. It has an echogenic or bright central hilum, produced by the reflective surfaces of innumerable sinuses. Around this the cortex is seen as a rim of lower echogenicity, produced by immune and stromal cells which are apposed closely and have fewer reflective surfaces. An arteriole and a venule enter through the hilum and branch into smaller vessels which branch outwards towards the cortex; in larger lymph nodes, these vessels may be seen by grey scale US as echo free tubes, but movement of blood even in smaller vessels can be detected and displayed by Doppler US (Fig. 5.3a). Afferent lymphatic capillaries penetrate the cortex and enter the subcapsular sinus. From there, the lymph flows through the cortex towards the hilum in sinuses that merge into larger intra-nodal vessels, eventually forming the efferent lymphatic capillary [6, 10].

Lymph node infiltration by melanoma metastasis occurs progressively resulting in a spectrum of abnormal US features (Fig. 5.3) [11–13]. New insights into how cancers such as melanoma prepare and invade lymph nodes inform what we see on US [14, 15]. The primary melanoma cells secrete chemokines and other intercellular messengers into the surrounding soft tissues that are transported by lymph fluid to the regional sentinel lymph node. These cytokines induce changes in the lymph node that are conducive to the later survival and proliferation of metastatic colonies. Two of these changes are hypervascularity and expansion of some intra-nodal cell lines: these are presumably the basis for early non-specific US features of hypervascularity and cortical hypertrophy in the lymph node. The earliest structural US feature of a metastatic lesion is a deposit of tumor cells in the subcapsular sinus, seen as a small hypoechoic focus in the peripheral cortex. This subcapsular lesion enlarges into a mixed colony of proliferating tumour cells and activated stromal and immune cells, seen as a segment of cortical thickening and eventually a solid hypoechoic (echo poor) mass. The smallest such lesion that can be identified on US ranges between 1–2 mm [16]. As the growth occurs radially in any direction, the lymph node eventually loses its ovoid shape and becomes rounded, recognised on US size measurements as a reduced length-to-side ratio or Solbiati index. Tumoral neovascularisation may be visualised by Doppler US as a cluster of peripheral vessels around the mass. The hilum of the lymph node is displaced by the cortical mass and as the mass continues to grow, the hilum is obliterated resulting in a diffusely hypoechoic mass. When the mass outgrows its blood supply, parts of it become necrotic and solid or cystic areas are seen on US with no Doppler flow signal.

Teaching Point: US is excellent in determining the nature of clinically palpable subcutaneous masses in node fields or elsewhere.

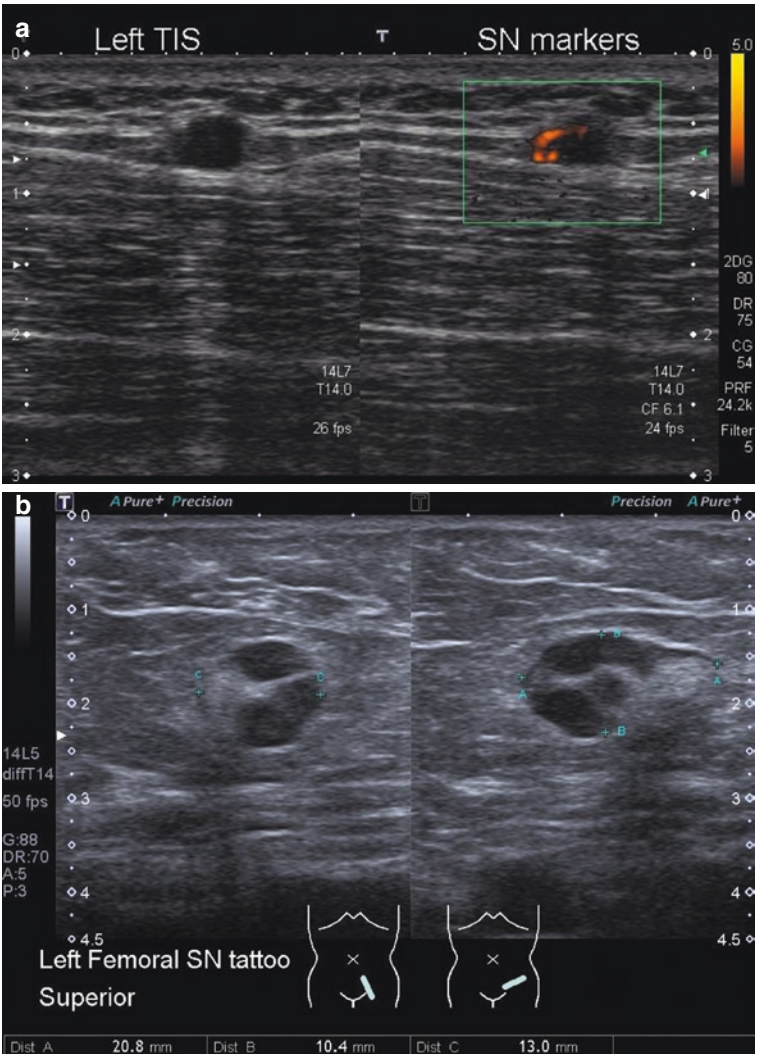

Fig. 5.3 (**a**) Small subcapsular metastasis in a left TIS SLN. This power Doppler display shows abnormal vascular flow signal around the metastasis caused by tumoral neovascularization. This is called the "peripheral perfusion" sign by Voit et al. (**b**) Larger subcapsular metastases in a left femoral SLN enlarge into solid hypoechoic lesions in the cortex. Two focal cortical lesions are seen in this lymph node. Longitudinal section on the left panel and transverse section on the right. (**c**) Larger metastatic colonies form solid hypoechoic masses in this left femoral SLN, recognized as "echo poor zones". As the cortical mass enlarges, the hilar echo is displaced into an eccentric location. Eventually the lymph node loses its ovoid shape and becomes rounded with lobulated margins. Longitudinal section on the left panel and transverse section on the right. (**d**) This SLN with metastasis is an interval node lying in the right mid axillary line inferior to the right axilla. The lymph node loses its normal central branching vascular flow pattern. This color Doppler display shows increased and irregular flow signal in the central vessel (Right panel). Neovascularization is also seen as peripheral vascular flow signal. (**e**) Metastases are typically hard or stiff. The gray scale image in the right panel shows a 5 × 3 mm focal cortical metastasis in a left axilla SLN (orange arrow). The strain elastogram on the left shows the lesion is blue (white arrow) indicating it is stiffer than the remainder of the lymph node

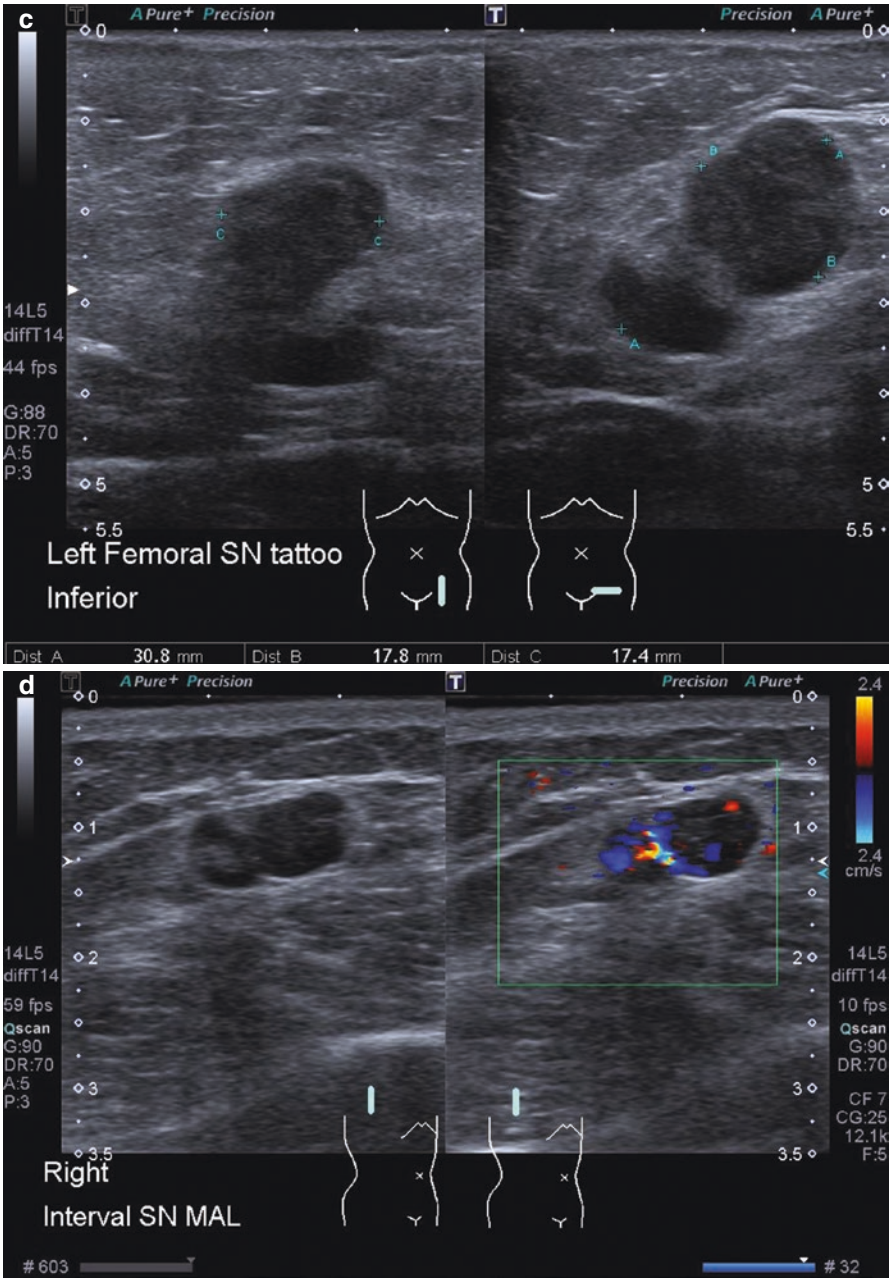

Fig. 5.3 (continued)

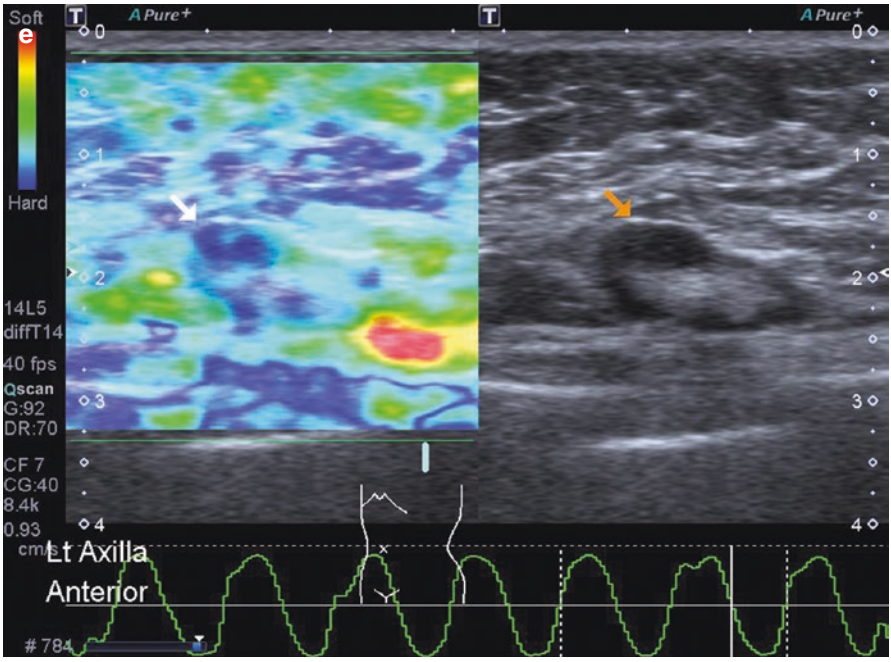

Fig. 5.3 (continued)

What Is the Role of US Assessment of the Regional Lymph Node Basins Before Sentinel Node Mapping and/or Biopsy?

Some of the above abnormal US features can be seen before an enlarged lymph node can be palpated. Multiple comparisons of palpation vs US for the detection of nodal melanoma have been performed, with a meta-analysis showing that US has higher sensitivity, specificity and discriminatory power [17]. In general however, it is not recommended routinely for thin melanomas with low risk of metastatic disease. In patients with melanomas over 1 mm in Breslow thickness we also do not recommend US screening of node fields based on clinical predictions of lymph drainage. Firstly, the pattern of lymphatic drainage in individual patients is not predictable clinically, thus US screening could easily overlook relevant node fields and secondly we know that US has poor sensitivity (24%) for detecting nodal metastasis at presentation because about 70% of such nodal metastases are microscopic [16]. Finally any interval nodes would be missed unless palpable.

In the past when standard surgical treatment involved a completion node field dissection if patients had metastasis in the SLN, many studies were done to see if US of the SLNs after pre-operative LS could detect node metastasis that could be confirmed with fine needle aspiration under US guidance. This would then allow an elective dissection of the positive node field rather than proceeding to SLN biopsy followed by completion dissection at a later date. The best results came from the group led by Voit, where pre-operative US was able to identify abnormal lymph

nodes in 71%, and where US guided fine needle aspiration cytology (FNAC) was abnormal in 51% [18]. This high sensitivity has never been reproduced in any other institution. The rationale for this approach however, has been negated by the surgical move away from completion node field dissection when the sentinel node is positive. Standard of care is moving towards SLN biopsy with clinical and US follow up of the node field if SLN metastasis is present (see below) [19].

Some have attempted US mapping of the sentinel nodes with ultrasound contrast administered into the lymphatics [20] or with photoacoustic agents which allow intra-operative visualisation of the sentinel node [21], but these techniques are rarely performed and have not replaced the gold standard—sentinel node mapping done by lymphoscintigraphy using radiocolloids.

Teaching Point: US of the SLN mapped by LS has low sensitivity for detecting nodal metastasis at presentation.

Follow Up

Case Continued

The patient's US of the right axilla shows normal lymph nodes, including the two palpable lymph nodes. The palpable lesion in the left axilla turned out to be a prominent fat lobule. He has a wide excision of the right forearm primary site and biopsy of two sentinel nodes: one a right epitrochlear node and the other a right axilla node. Histopathology of the epitrochlear node was negative but the axilla node had a 0.5 mm rest of melanoma cells.

How Is US Used in Follow Up?

US is the best imaging procedure to detect metastatic disease in the regional node fields and surrounding subcutaneous tissues. It is more effective than CT and PET for detecting regional lymph node recurrence with a meta-analysis reporting a sensitivity of 60% (95% CI: 33–83), specificity of 97% (95% CI: 88–99), and diagnostic odds ratio of 42 (95% CI: 8.08–249.8) [22].

In patients with a positive SLN, many will not have undergone a completion node field dissection. These patients have about an 11% chance of harbouring metastasis in another lymph node in the field [19]. As melanoma recurrence is most frequent in the first 2–3 years after initial treatment, a number of surveillance protocols have the patient return for clinical and US follow up every few months during this period. US can detect metastasis down to a size of 1 mm depending on the node field [16], and long before any mass could be palpable clinically.

The frequency of follow up visits is decreased as the patient remains disease free.

US follow up will include examination of the draining node field as well as the excision scar and in thicker melanomas, a survey of the subcutaneous tissues between the original melanoma site and the draining node fields. When a probable

metastasis is found on US, FNA confirmation under US guidance is performed immediately (Fig. 5.4) and a positive result will lead to a therapeutic dissection of that node field or a WLE of the in-transit metastasis.

Teaching Point: US is an excellent method to detect nodal and in-transit metastases on follow-up. The frequency of follow up decreases as time passes without recurrence.

If the patient had undergone a node field dissection after a positive SLN biopsy, US remains useful in follow up to detect post-surgical scarring, haematomas or seromas that can introduce uncertainty to clinical palpation. In the case of a negative biopsy, node basin recurrence can still occur, i.e. a small false negative rate.

If US surveillance of clinical node negative patients is to be done rather than SLN biopsy, we think it is optimal when combined with a sentinel node mapping procedure (Fig. 5.5). The US follow up can then focus on the actual SLNs as well as checking the primary excision site and soft tissues between here and the draining node field to exclude in-transit metastasis especially in thicker melanomas.

Outside of scheduled US surveillance, the patient may present with a new mass lesion detected by him/herself or a medical practitioner, or with a new lesion detected by other imaging modalities such as Fluorine-18 labelled Fluorodeoxyglucose (FDG) PET/CT. If these new lesions can be accessed by US, it is the test of choice for assessment and to obtain a tissue diagnosis by guiding biopsy (Fig. 5.6).

Conclusion

Ultrasound is a simple non-invasive and widely available imaging modality. If a suspected melanoma metastasis is detected, it transitions into needle biopsy guidance easily. In expert hands, it is a versatile problem-solving tool at multiple time points in the diagnosis and treatment of melanoma.

Cross Sectional Imaging

Cross sectional imaging modalities relevant in the management of melanoma include CT, SPECT/CT, MRI and FDG PET/CT. Application of these imaging techniques currently relies on an empirical approach to stratify patients based on their perceived risk of loco-regional and distant metastases. The decision for imaging can be conceptualized within the settings of staging disease after diagnosis of melanoma, monitoring response to therapy, and after therapy has ceased during a period of active surveillance for recurrence.

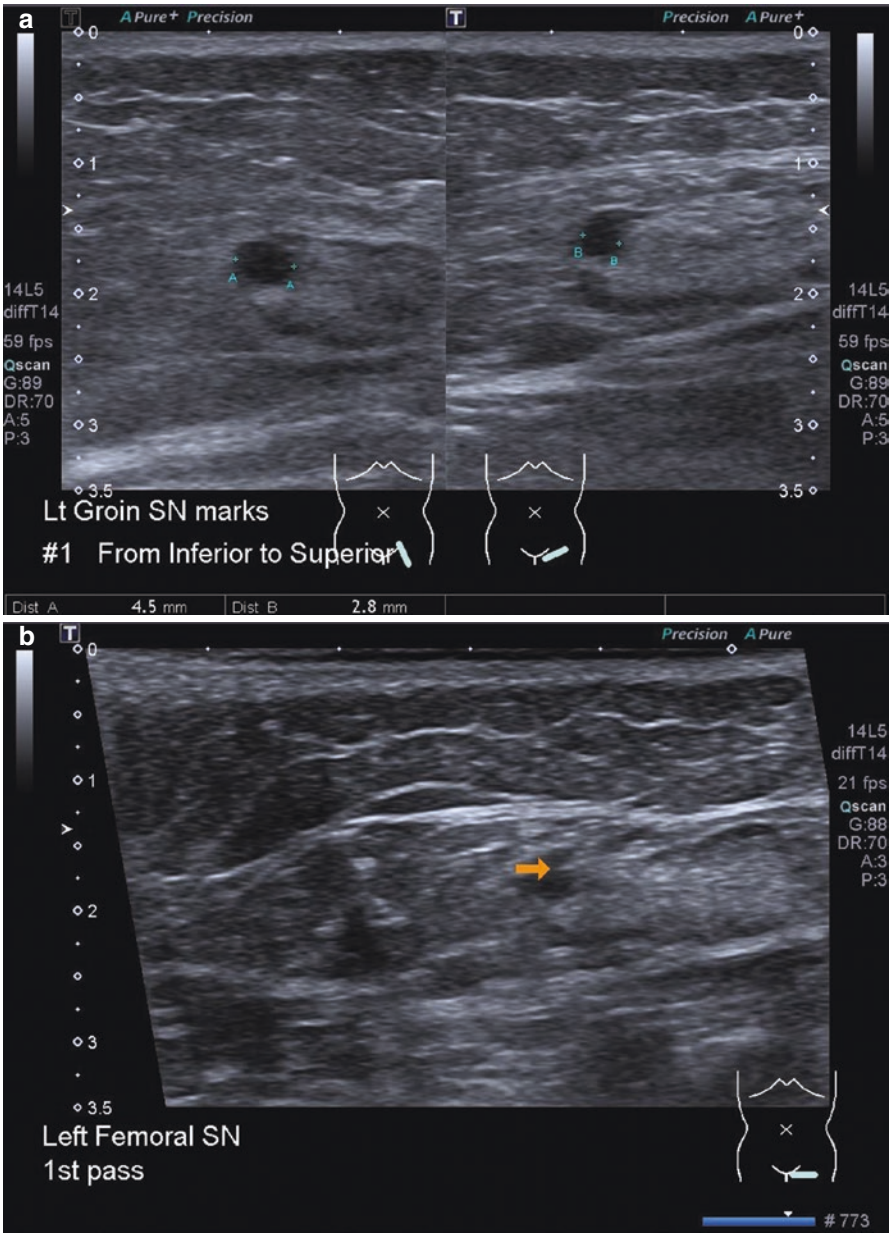

Fig. 5.4 (**a**) Focal 2–5 mm solid hypoechoic lesion in the cortex of a left femoral SLN in a patient with a left lower limb melanoma. This is a typical appearance of subcapsular metastasis. Longitudinal section in the left panel and transverse section in the right. (**b**) The small metastasis is subjected to FNA biopsy under US guidance. The tip of the 25G needle is seen in the metastasis (yellow arrow). (**c**) On-site cytology shows the typical findings seen in a melanomatous lymph node metastasis

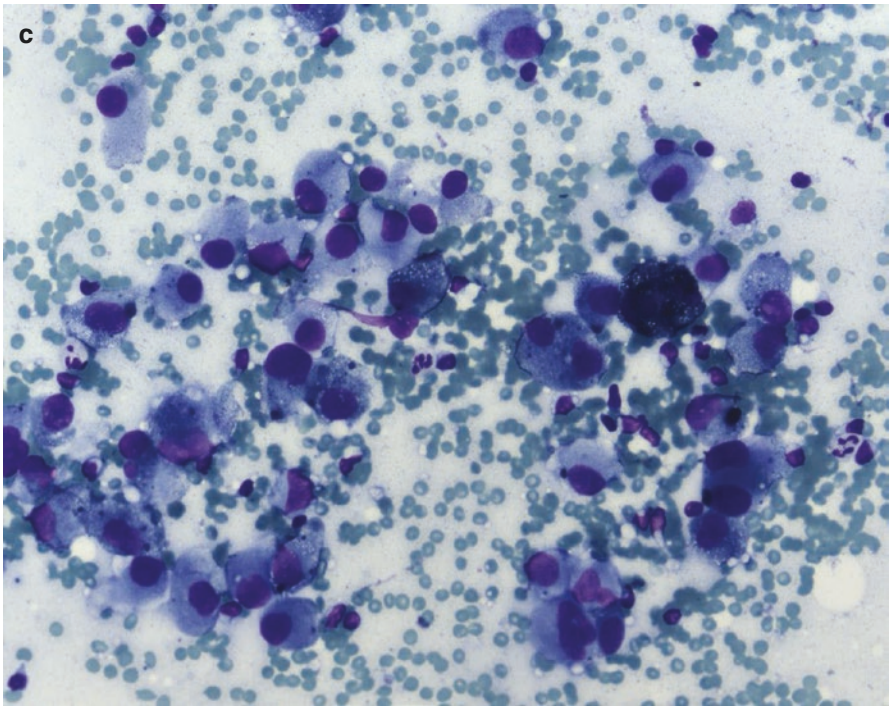

Fig. 5.4 (continued)

Staging

Early Stage Disease

SPECT/CT shows the precise location of SLNs in a node field as mentioned previously which facilitates surgical removal of these nodes. Also mentioned earlier in this chapter, targeted US of the SLN shown on LS can detect metastasis but the sensitivity is low [16]. The results of MSLTII have altered clinical practice so that the result of SLN biopsy is now the key to patient management.

In patients without regional nodal involvement, that is, Stage 1 or 2 disease [23, 24] or so-called early stage melanoma, the potential benefit of cross-sectional imaging is considered too low to warrant its routine use [25].

Both diagnostic CT and FDG PET/CT perform poorly in early stage melanoma where the volume of metastatic nodal and extra-nodal tumor deposits is usually low. False positive rates of 95% and 60% were reported with diagnostic CT and FDG PET/CT, respectively [26]. This extremely poor diagnostic performance is inextricably related to the low prevalence of metastatic disease in early stage melanoma in which SLN biopsy is recommended. The very high false positive rate resulting from unfettered use of cross-sectional imaging in this scenario would lead to unnecessary biopsy procedures and possibly unjustified treatment escalation.

Teaching Point: SPECT/CT is useful as part of LS prior to SLN biopsy but cross-sectional imaging is otherwise not recommended in early stage melanoma due to a high false positive rate.

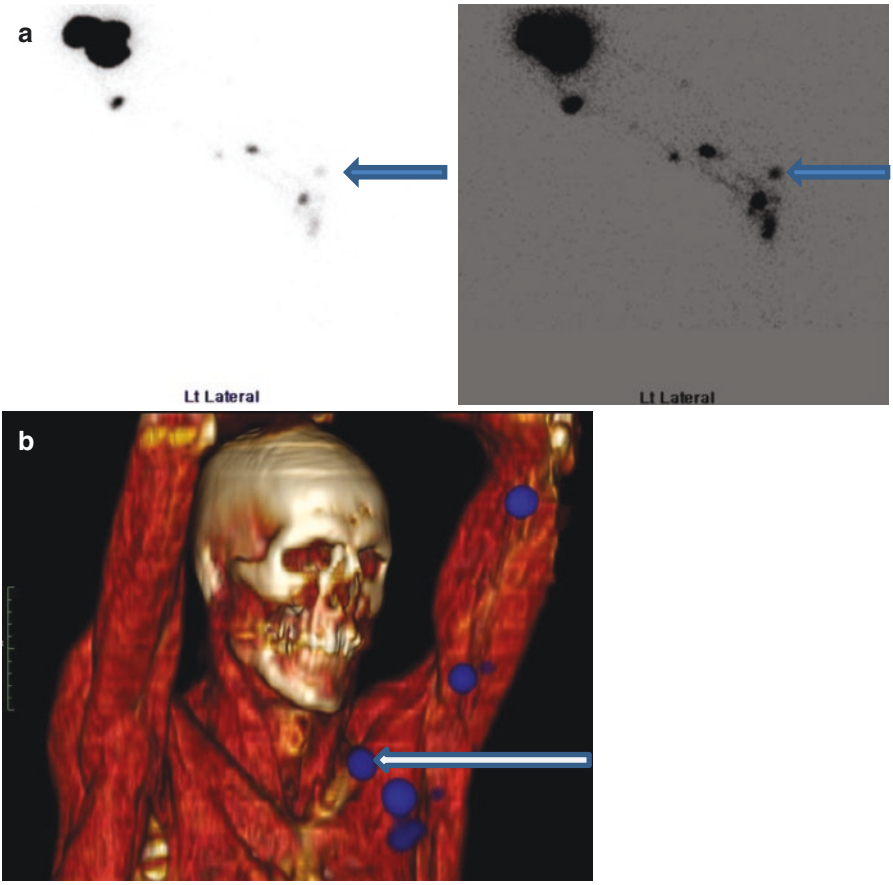

Fig. 5.5 (**a**) Lymphoscintigraphy from a left forearm melanoma. The injectate is the intense activity at the top left corner of the image. Lymph transit is seen easily in two bright collectors towards the right of the image. A faint third collector leading to a sentinel lymph node (arrows) could be missed if not inspected carefully. The image on the right is darkened to make it more visible. (**b**) Volume rendered image of lymphoscintigraphy SPECT and CT fusion. The blue dots represent radiolabelled lymph nodes. The sentinel lymph node from the faint collector is arrowed. (**c**) Left panel shows the lymphoscintigraphy SPECT/CT fusion of the faint SLN lying in the left deltopectoral groove. In the right panel this SNL is identified on US and has normal morphology. Without high quality LS it would be impossible to locate SLNs such as this on US when they lie in unusual locations

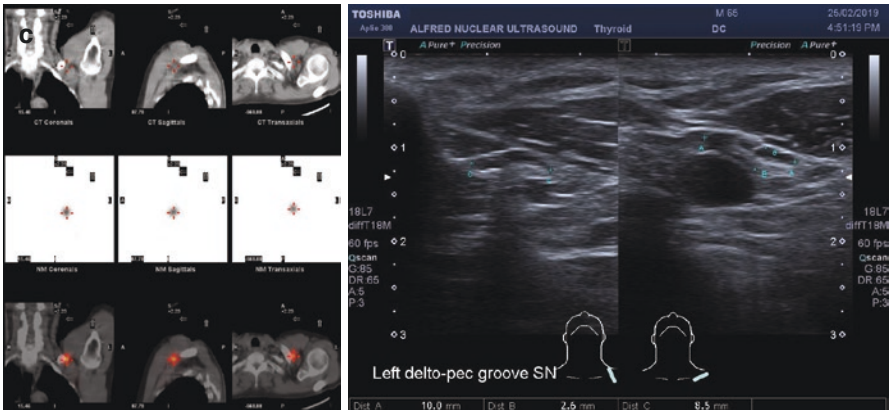

Fig. 5.5 (continued)

Later Stage Disease

In patients with Stage 3 disease, typically determined on SLN biopsy or regional nodal basin US with FNAC, cross sectional imaging is indicated to determine the extent of disease including possible upstaging to Stage 4 status.

The burden of nodal disease in stage 3 and 4 patients becomes great enough to realize the high diagnostic accuracy of FDG PET/CT. The sensitivity of FDG PET/CT in detecting nodal metastasis has been shown to increase from 81% to 100% in patients with stage 3 and 4 melanoma, respectively [27]. Moreover, meta-analyses have demonstrated sensitivities and specificities of 83–88% and 82–84%, respectively, for FDG PET/CT applied in stage 3 and 4 patients [25, 28].

FDG PET/CT has been shown to alter clinical decision making in 32% of patients with advanced disease [29]. It has also been shown to be comparable to MRI, and superior to CT and bone scintigraphy in detecting skeletal metastases [30]. Whole body FDG PET/CT is recommended prior to contemplating surgical resection of metastatic deposits (Fig. 5.7).

FDG PET/CT detection of cerebral melanoma metastases is hampered by intense physiologic metabolism within the cerebral cortex masking tracer uptake within cerebral melanoma deposits. The diagnosis of melanoma brain metastases relies on contrast enhanced MRI, or if MRI is contraindicated, contrast enhanced CT.

Diagnostic CT is a more convenient and less costly imaging modality compared to FDG PET/CT. It is often used to assess patients with melanoma, however, diagnostic CT has not been found to provide any significant diagnostic benefit above that obtained with FDG PET/CT [31] in patients with metastatic disease. The exception is in the assessment of lung metastases where FDG PET/CT is susceptible to factors including respiratory movement artifact that renders diagnostic thoracic CT more sensitive [32]. Modern PET/CT systems are able to perform diagnostic quality regional CT scans of the thorax during the whole-body attenuation CT acquisition. This enables a diagnostic quality CT scan of the lungs to be performed concurrently

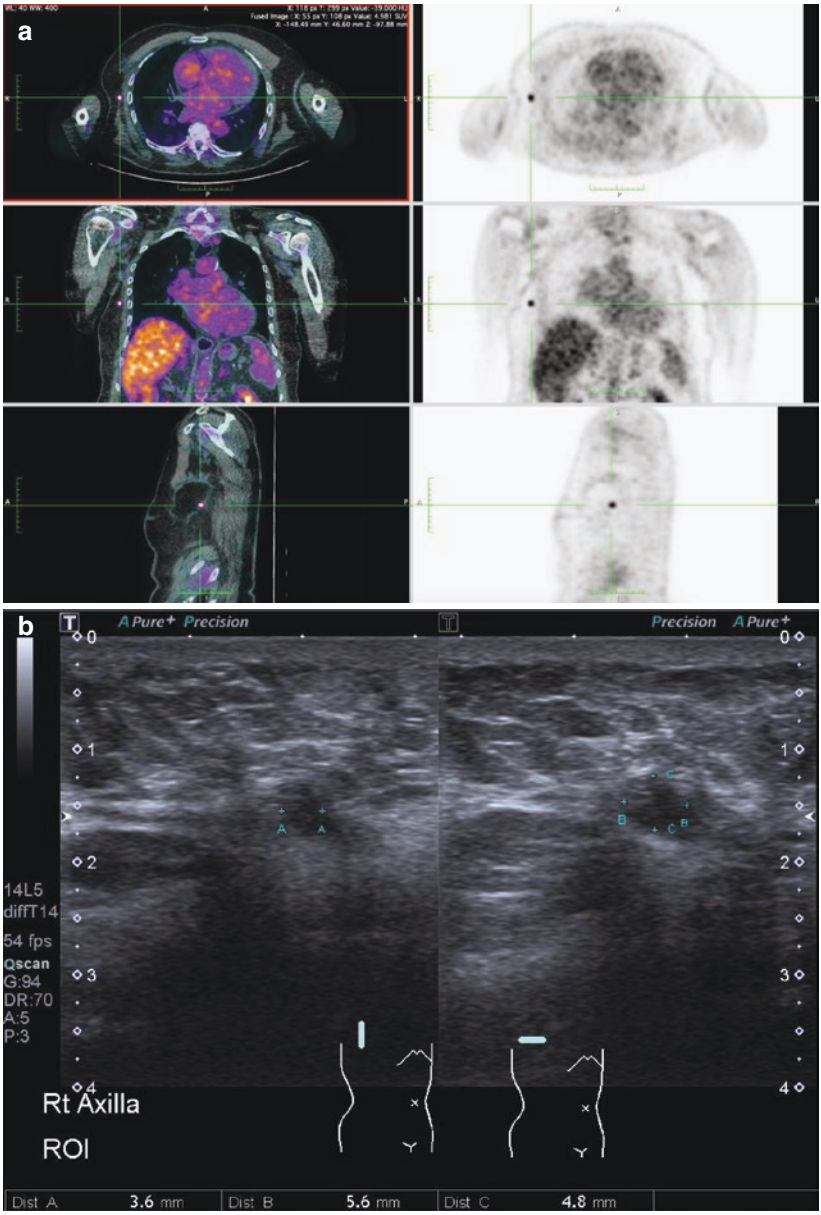

Fig. 5.6 (**a**) Surveillance FDG-PET/CT scan of a 56yo man who had past chest wall melanoma excision and therapeutic right axilla dissection. The cursors in this PET/CT fusion display are triangulated on a focal hypermetabolic lesion in the right axilla suspicious of node basin recurrence. (**b**) Targeted US localized this 3–6 mm solid hypoechoic metastasis. The lesion was not palpable. US guided FNA biopsy confirmed recurrent melanoma. (**c**) The patient returned a few days later to have skin marking and radioguided occult lesion localization (ROLL). Here US guides an intratumoral injection of radiocolloid (arrow). In addition to the skin mark and an indication of the tumor's depth, the surgeon uses a gamma probe to localize the tumor for removal. The gamma probe also confirms removal by clearance of radioactivity from the operative field

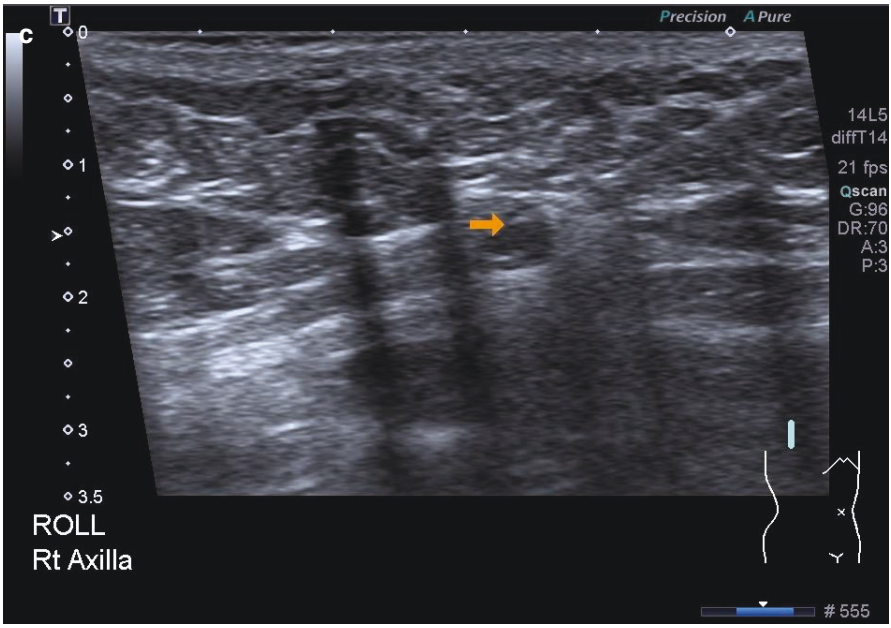

Fig. 5.6 (continued)

with a whole body FDG PET/CT scan thereby enhancing patient convenience and, in conjunction with cerebral MRI, delivers highly accurate staging information in patients with metastatic melanoma.

Teaching Point: Cross sectional imaging is recommended in advanced stage melanoma to accurately diagnose the extent of metastatic disease.

Monitoring the Effects of Therapy

In patients with unresectable metastatic disease, treatment response using standard response evaluation criteria in solid tumors (RECIST) criteria remains the mainstay of response assessment [33]. The CT based RECIST criteria have been well validated in assessment of chemotherapy agents used in various solid tumors, with a reduction in number and size of lesions indicating a positive response [34] (Fig. 5.8).

The recently introduced molecular targeted and immunotherapeutic agents, however, produce the opposite effect in which a good response may be accompanied by an initial enlargement of lesions or the development of new lesions, in patients who go on to have an enduring therapeutic response. This is because these agents have their effect by stimulating the patient's own immune system to attack the cancer, which has resulted in development of a more complex CT-based assessment. The immune-RECIST (iRECIST) more accurately classifies therapeutic response by allowing for such a "flare response" [35].

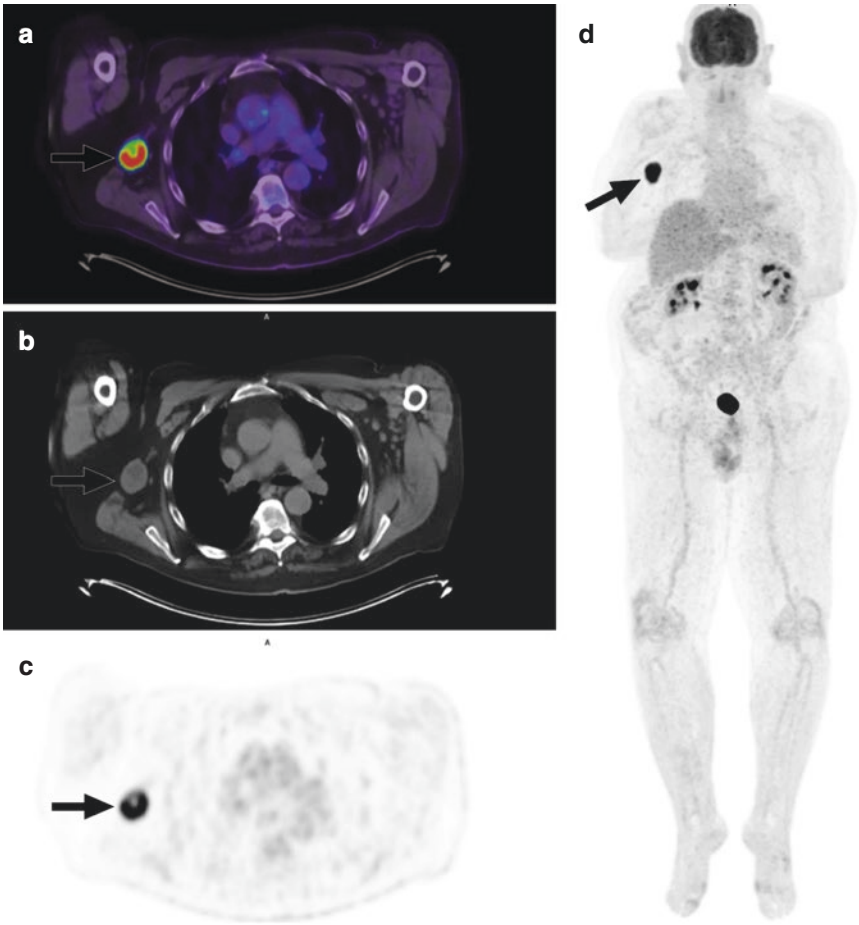

Fig. 5.7 72-year-old man with cutaneous melanoma excised from the right upper back 16 months previously. He developed palpable right axillary lymphadenopathy and the FDG PET CT is shown. Axial slices of the FDG PET/CT demonstrate intense metabolic activity in a metastatic 32 × 34 mm right axillary lymph node with central necrosis: (**a**) fused PET CT; (**b**) underlying low dose CT; (**c**) FDG PET; (**d**) SUVmax 12.45. The maximum intensity projection shows the FDG avid right axillary lymph node (arrow) but confirms no further loco-regional or distant metastases

Medical professionals caring for patients with metastatic melanoma receiving targeted molecular or immunomodulating agents must be aware of clinical trial requirements for CT based response assessment and ensure progress CT scans occur appropriately in conjunction with the trial co-ordinators.

FDG PET/CT holds promise for an accurate biomarker of treatment response in metastatic melanoma and has been studied using molecular targeted agents including BRAF inhibitors and immunotherapy including anti-PD1 agents.

Two reports using BRAF inhibitors showed a marked reduction in FDG avidity with therapy unrelated to progression free survival [36] and a mixed response on

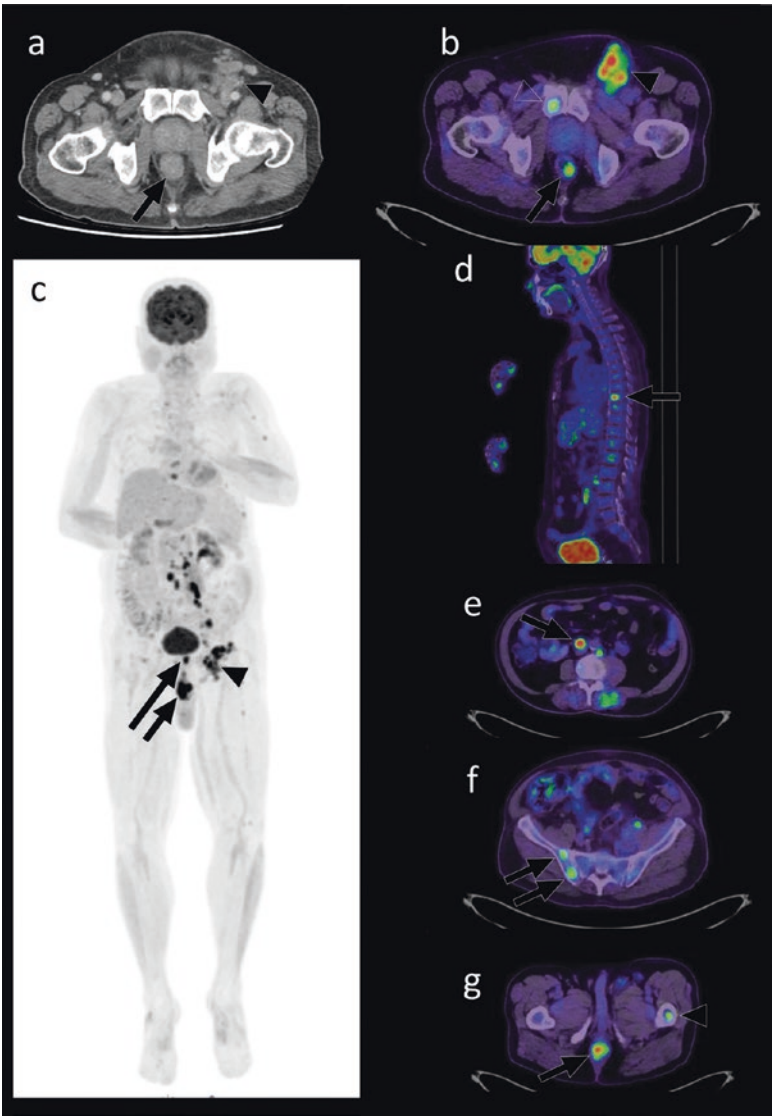

Fig. 5.8 77-year-old man presented with anal mass confirmed to represent melanoma. Contrast enhanced CT (**a**) shows a rectal mass (arrow) and matted left inguinal lymph node metastases (arrow head). The same axial slice of the staging FDG PET/CT scan shows (**b**) the rectal metastasis (arrow, SUVmax 9.64) and left inguinal lymph node metastasis (arrowhead, SUVmax 11.44) to both be highly metabolically active, in addition to a right pubic bone metastasis (open arrowhead, SUVmax 4.27). The maximum intensity projection of the staging whole body FDG PET/CT scan (**c**) demonstrates the intensely metabolically active primary anal melanoma (short arrow), the rectal (long arrow) and matted left inguinal lymph node metastases (arrowhead) in addition to widespread distant metastases involving T8 vertebral body (**d**, SUVmax 6.69), para-aortic lymph lymph nodes (**e**, SUVmax 10.40), the right iliac bone (**f**, SUVmax 4.83) and numerous other smaller osseous and extra-osseous metastases. The primary anal melanoma is also depicted (**g**, arrow, SUVmax 12.91; and a left femoral metastasis, arrowhead)

early FDG PET/CT able to predict earlier progression compared to patients with uniformly reduced FDG activity during therapy. On the other hand, studies using immunotherapeutic agents show increasing FDG activity in metastatic lymph nodes related to inflammatory infiltrates at sites of successfully treated disease [37]. This metabolic "flare response" is the corollary of the enlargement seen on CT when this occurs. The reporting physicians must take these differences into account to determine whether the disease has responded or progressed in each patient.

In summary, response assessment using cross sectional imaging during therapy for non-resectable metastatic disease uses both CT and FDG PET/CT. The precise role for each modality is being determined and requires more long-term survival outcome data from patients currently enrolled on clinical trials.

Teaching Point: Cross-sectional imaging is important for assessing response to therapy using both anatomic (CT) and metabolic (FDG PET) criteria.

Post Treatment Surveillance

Protocols for surveillance of patients with treated melanoma generally arise from expert opinion in conjunction with local availability of various imaging modalities. As such, and in the absence of evidence-based guidance, clinical practice varies widely [38]. As is the case with imaging strategies for staging of melanoma, imaging recommendations during surveillance are based on empiric assessment of the risk of recurrence informed by an understanding of patterns of melanoma recurrence.

After surgical treatment for early stage cutaneous melanoma, the peak time to first recurrence is 12 months, followed by 6 months and 3 months for the second and third recurrences, respectively [39]. Seventy percent of recurrences occur locally or in the regional lymph node basin [40] and therefore surveillance is best served by US as described earlier. In this context US has shown a sensitivity of 96% and specificity of 99% for detecting lymph node recurrence [41] and a follow up schedule of US every 3–4 months for 2 years such as employed in the MSLT-II trial is recommended [42]. The use of cross-sectional imaging in screening for recurrence is not warranted following treatment of early stage melanoma. However, in the case of US detected local or nodal recurrence, FDG PET/CT, CT and cerebral MRI should all be considered to fully re-stage the disease burden prior to salvage therapy.

Patients with treated advanced disease are more likely to recur than patients with treated early stage disease and therefore have more potential to gain from imaging strategies to detect recurrent disease. After recurrence has occurred and been diagnosed, there are possible beneficial effects of surgical resection of a single metastasis and immunotherapy may be more effective with lower volume disease—both of which support early detection to improve outcome.

A meta-analysis of FDG PET/CT employed for follow up in high risk melanoma patients determined that it had a sensitivity of 96% and specificity of 92% for the detection of recurrent melanoma when used in the surveillance setting, with 80% of

recurrences occurring in the first 3 years of follow up [43]. Similar studies using CT in patients with treated stage IIb–IIIc cutaneous melanoma have concluded limited utility in surveillance at 3 years after therapy [44].

Teaching Point: Surveillance of the regional node field using US is the preferred technique to detect small volume metastases. CT, FDG PET/CT and MRI have particular utility in follow up of more advanced disease.

Effect on Survival

Although no data exists to verify a survival benefit for any particular surveillance imaging protocol in patients with treated melanoma, FDG PET/CT holds the most promise due to its higher sensitivity compared with diagnostic CT. The empirical use of surveillance FDG PET/CT scans in treated advanced stage disease is a reasonable approach up to 3 years following therapy during which most of the recurrences are expected to occur. The aim is to detect low volume metastasis, however, the optimal timing of these scans to achieve this remains unclear.

As treatment patterns change, in particular the move away from routine completion lymph node dissection for SLNB positivity following on from the results of the MSLT-II trial [42], the role of cross-sectional imaging may also change. MSLT-II showed that survival of patients with SLNB positivity is not diminished by delaying nodal basin clearance surgery until the development of further regional nodal metastases. This conclusion relied upon early nodal recurrence detected by close follow up (3 monthly) with high quality US of the sentinel lymph node basins complementing the regular physician visits and patient self-examination.

Medical professionals caring for patients with melanoma must be careful not to empirically substitute cross sectional whole-body imaging modalities, including high sensitivity techniques such as FDG PET/CT, for US in their follow up regimen of SLNB positive patients because US is the most accurate technique to detect node field or subcutaneous soft tissue recurrence.

Teaching Point: The inclusion of cross-sectional imaging in surveillance has not been shown to improve survival but the early detection of low-volume metastasis is a worthwhile goal to enable earlier and possibly more effective initiation of systemic therapy.

Conclusion

Guidelines for the application of cross-sectional medical imaging in melanoma patients who may have occult disease are difficult to define in a way that covers all of the presentations that are possible in such patients. The individual patient's clinical situation must guide decision making on the specific merits of ancillary cross-sectional imaging. Factors such as the accessibility of imaging equipment, technical

expertise in image interpretation, and the economic burden to the patient and community will also require careful consideration when recommending an imaging protocol. When all factors are taken into account, the recommendation of cross-sectional imaging outside of standard protocols has to be tailored to the needs of the individual patient.

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Chapter 6
Primary Melanoma Treatment

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Learning Objectives

1. Understand the rationale and technique for wide excision of melanoma.
2. Review the recommended resection margins for wide excision and the supporting clinical evidence.
3. Identify specific areas of uncertainty pertaining to wide excision resection margins.
4. Recognize particularly challenging situations encountered during primary melanoma treatment and review the management options for each.
5. Review the non-operative options for primary melanoma treatment.

Case

A 69-year-old otherwise healthy Caucasian man is seen in your office for evaluation of a suspicious mole. Physical examination reveals a pigmented lesion with irregular borders and color variegation on the patient's upper back. A head-to-toe examination does not reveal any additional skin lesions or palpable lymphadenopathy. Punch biopsy demonstrates melanoma with a depth of 3 mm. The patient would like to know his treatment options at this time.

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Introduction

The incidence of melanoma has risen rapidly in the United States over the last 40 years. In 2018, an estimated 91,270 new cases of cutaneous melanoma will be diagnosed and 9320 patients will die of this disease [1]. Recent advancements in nodal staging practices and the development of local immunomodulatory therapies, immunotherapies, and targeted therapies have revolutionized the treatment of melanoma. However, the cornerstone of curative treatment for primary resectable melanoma is and will likely continue to be wide excision. In this chapter, the technique for wide excision and the recommended resection margins for primary melanoma are reviewed along with the clinical evidence behind these recommendations. While abundant clinical evidence exists concerning recommended excision margins in melanoma, there are still some areas of uncertainty as well as challenges in surgical treatment. Furthermore, non-operative treatments may be advisable in specific cases of primary melanoma. Options for non-surgical treatments have been increasing and include topical therapy, intralesional injections, radiation therapy, and systemic therapy. Knowledge of both surgical and non-surgical treatments for primary melanoma will aid clinicians in devising optimal treatment plans for their patients.

Operative Primary Melanoma Treatment

Wide Excision

Wide excision remains the mainstay of treatment for primary cutaneous melanoma. The objective of wide excision is to completely resect the primary tumor along with a margin of grossly uninvolved skin and subcutaneous tissue down to, but usually not including the deep fascia. The rationale for these wide excision margins is to prevent locoregional recurrence by removing the lymphatics immediately surrounding the tumor, which may harbor early microsatellite metastases [2, 3].

Technique

Depending on the extent of the planned resection, wide excision may be performed under local or general anesthesia. If sentinel lymph node biopsy will be performed, general anesthesia is typically used. Prior to incision, resection margins should be measured in all directions from the tumor biopsy site or the edges of the primary tumor if still present. After injection of local anesthetic, an elliptical skin incision is made encompassing these margins. The incision should have a length-to-width ratio of at least 3:1 and be oriented along Langer's lines or in any position that will optimize cosmesis and minimize tension for closure. As cutaneous melanoma tends not to violate fascial barriers, the resection is carried down to, but not through the deep

fascia. Upon removal, it is imperative to mark the surgical specimen for orientation in case re-excision is needed. After obtaining hemostasis, the wound is closed in layers with interrupted deep dermal stitches followed by running subcuticular or interrupted nylon stitches. Local advancement flaps may be needed to reduce tension for primary closure. More advanced reconstructive techniques may be required after extensive resections or operations in anatomically challenging areas.

Recommended Margins for Wide Excision

Historically, very wide 4–5 cm resection margins were practiced, often necessitating complex reconstruction and skin grafting. Breslow and Macht were the first to challenge this dogma, reporting favorable outcomes in a small series of patients who had thin melanomas resected with margins as small as 2 mm [4]. Since then, multiple prospective randomized trials have evaluated the adequacy of narrower margins for melanomas of varying thicknesses.

The first of these trials was conducted by the World Health Organization Melanoma Group and published by Veronesi et al. in 1988. The investigators randomized 612 patients with thin melanomas (<2 mm deep) to resection with 1 cm vs. 3 cm margins. At a mean follow-up of 90 months, there was no difference in overall survival (OS) or disease-free survival (DFS) between groups. Three patients had a local recurrence as their earliest site of relapse, all of whom had undergone excision with a 1 cm margin for tumors ≥1 mm thick. This led to the conclusion that 1 cm margins are safe for thin melanomas, particularly when lesions are <1 mm in depth [5, 6]. The Swedish Melanoma Study Group and the French Group of Research on Malignant Melanoma also completed trials directed toward patients with lesions ≤2 mm thick. Both trials found no difference in recurrence or survival after resection with 2 cm vs. 5 cm margins, confirming the safety of "narrow" 2 cm margins [7–9].

In 1993, Balch et al. published the 6-year outcomes of the Intergroup Melanoma Surgical Trial, which randomized 486 patients with 1–4 mm thick melanomas to resection with 2 or 4 cm margins. There was no difference in local recurrence rate or OS between groups, but patients in the 4 cm margin group had significantly longer hospital stays, attributed to increased need for skin grafting [10]. Ten-year follow-up data from this trial confirmed the long-term adequacy of 2 cm margins in preventing local recurrence and disease-specific mortality [11].

Later trials sought to establish appropriate resection margins for tumors of greater depth. In 2004, the United Kingdom Melanoma Study Group trial published their 5-year findings from 900 patients with lesions ≥2 mm thick who had been randomized to resection with 1 or 3 cm margins. The authors reported a significantly increased risk of locoregional recurrence with 1 cm margins [12]. Long-term follow-up also revealed an increased risk of melanoma-specific mortality after resection with 1 cm margins. Thus, the authors concluded that 1 cm margins are insufficient for melanomas ≥2 mm in depth [13].

Finally, Gillgren et al. reported the outcomes of 936 patients with melanoma >2 mm randomized to resection with 2 or 4 cm margins. After a median 6.7 years of

follow-up, the investigators found no difference in OS or recurrence-free survival between groups, confirming that 2 cm margins are safe for patients with melanoma >2 mm thick [14].

Data from the aforementioned trials, as well as a number of retrospective analyses [15–19], have led to the development of evidence-based recommendations for resection margins [20]. Each recommended margin is associated with a particular Breslow thickness, which is the most significant prognostic factor in a primary melanoma lesion. Breslow depth should be measured from the granular layer of the epidermis or, if ulcerated, from the ulcer base.

Clinical vs Pathologic Margins

It must be noted that all of the margins described above refer to clinical margins measured from the edge of a lesion or biopsy site by the surgeon as opposed to pathologic margins determined upon microscopic evaluation of the resected specimen. This distinction is important because the clinical margin underestimates the pathologic margin in nearly 30% of cases [21], and this discrepancy can affect a patient's risk for recurrence. The importance of pathologic margins was illustrated in a clinicopathologic analysis of 2131 cases of T2 melanoma from the Melanoma Institute of Australia, which found that pathologic margins <8 mm were associated with decreased disease-free survival, regional node recurrence-free survival, and distant recurrence-free survival [19].

Areas of Uncertainty

Despite the relative abundance of data pertaining to resection margins, several areas of uncertainty remain. In each of these cases, the treating clinician must weigh the individual patient's risk of local recurrence against the functional and anatomic consequences of a wider excision.

Melanoma In Situ

No randomized clinical trials have evaluated the appropriate resection margin for melanoma in situ. An early consensus statement from the National Institutes of Health recommended 0.5 cm margins for melanoma in situ [22]. However, multiple retrospective studies have since suggested that 0.5 cm margins may be inadequate for complete tumor clearance [23–25]. A prospective analysis by Kunishege et al. that evaluated 1120 patients undergoing Mohs micrographic surgery for melanoma in situ found that the use of 6 mm margins resulted in the clearance of only 86% tumors, while 9 mm margins resulted in the clearance of 98.9% [26]. While 0.5 cm margins are helpful in sparing cosmetically sensitive areas, a preponderance of recent data suggests that margins closer to 1 cm may be necessary to achieve histologic clearance.

Melanomas 1–2 mm in Depth

A second area of uncertainty is the adequacy of 1 cm margins for melanomas 1–2 mm thick. The previously mentioned WHO trial reported a higher recurrence rate after resection of thin melanomas with 1 cm margins as compared to 3 cm margins, although this difference was not statistically significant [6]. Conversely, a recent retrospective analysis comparing 1–2 cm margins for melanoma 1–2 mm in depth found no difference in local recurrence or 5-year disease-specific survival between groups, and noted that 2 cm margins were associated with an increased need for skin grafts and cutaneous flaps. In the absence of level I or II data, a reasonable strategy may involve the use of 2 cm margins when feasible, but slightly smaller margins when needed to preserve function, facilitate wound closure, or maintain cosmesis [3].

Melanoma >4 mm in Depth

No randomized trial has specifically evaluated adequate resection margins for melanoma >4 mm deep. The recommendations for these tumors are largely extrapolated from the Intergroup and Swedish studies; however, the median tumor thickness in each of these trials was well under 4 mm (1.8 and 3.1 mm respectively), and both trials were underpowered to conduct subgroup analyses of patients with very deep lesions [10, 14]. Nonetheless, the best available evidence at this time suggests that 2 cm margins are adequate for melanoma >4 mm thick.

Lymph Node Involvement

All of the aforementioned trials pertaining to margin status excluded patients with known lymph node involvement [5, 8–10, 12, 14]. The risk of locoregional recurrence is likely increased in the setting of node positivity, and it is unknown whether a more extensive primary excision can help mitigate that risk [27]. For a detailed review of lymph node management, please refer to Chaps. 9 and 10.

Challenging Situations

Lentigo Maligna Melanoma

Lentigo maligna melanoma (LMM) and its in situ precursor, lentigo maligna (LM), comprise an uncommon melanoma subtype that typically occurs on the face and scalp of patients with chronic sun exposure. LM/LMM is characterized by indistinct clinical margins, corresponding to individual tumor cells that spread along the dermoepidermal junction [28, 29]. This lentiginous distribution of atypical melanocytes constitutes a "field defect" that makes complete resection challenging and likely contributes to the relatively high local recurrence rate of these lesions [30, 31]. The tendency for LM/LMM to arise in cosmetically sensitive areas such as the face and scalp further adds to

the complexity of managing this tumor. Fastidious margin evaluation using Mohs micrographic surgery or staged surgical excision has been used to obtain complete histologic clearance of LMM while minimizing disfigurement. Histologic identification of this type of melanoma may be challenging, particularly on standard frozen section processing of the Mohs' approach. While no prospective studies have compared these two approaches, the best available retrospective data suggests that staged excision may be superior for obtaining complete tumor clearance and minimizing recurrence rates [30, 32–34]. Skin mapping with punch biopsies has also been used delineate the radial spread of poorly-defined lesions after margin-positive resections. This method involves a ring of evenly-spaced punch biopsies taken 1 cm from a residual lesion or surgical scar. A positive biopsy prompts additional surrounding biopsies until a negative perimeter is established, at which point re-excision can be planned [35].

Topical imiquimod and radiation therapy are also efficacious in the treatment of LM/LMM due to their ability to cover the field defect associated with these tumors.

Acral Lentiginous Melanoma

Acral lentiginous melanoma (ALM) is a rare form of melanoma that typically affects the nail beds, palms, and soles and is the most common subtype of melanoma in patients of African or Asian descent. The treatment of choice for primary ALM is wide excision with the same margins used for cutaneous melanoma. Obtaining said margins can be challenging due to the anatomic complexity and functional import of the hands and feet [36, 37].

Subungual ALM usually requires amputation through the interphalangeal joint for upper extremity lesions, or the metatarsophalangeal joint for lower extremity lesions. However, modern reconstructive techniques may allow for digit preservation in the setting of melanoma in situ or minimally invasive (<0.5 mm thick) melanoma. In these cases, excision involves removal of the entire nail unit and underlying soft tissue down to the bone. Wound closure may be accomplished primarily with subcutaneous flaps in the case of amputations, or with a full thickness skin graft or pedicled flaps in the case of digit-preserving operations [38]. Resection of ALM of the palms and soles may require similarly complex reconstruction and should be planned in consultation with a reconstructive surgeon [37].

Non-operative Treatment for Primary Melanoma

Potential Reasons for Non-operative Management

Although the preferred treatment for melanoma is wide excision, there are several instances in which non-operative management is advisable. Non-operative management should be considered when the medical, functional, or cosmetic morbidity of resection may outweigh the potential benefits to the patient. This is obviously the case for patients whose medical comorbidities preclude a major operation but may

also apply to patients with large burdens of in-transit disease and those with LM/LMM arising in cosmetically sensitive areas of the face and scalp that might otherwise be amenable to topical, intralesional, or radiation therapy. While select patients may benefit from the resection of limited metastatic disease, those with widely disseminated metastases are also not surgical candidates and should be managed with systemic therapy and or palliative radiation.

Topical Therapies

Topical Imiquimod

Imiquimod is an immunomodulatory agent that acts by binding Toll-like receptor 7 on macrophages and dendritic cells [39]. Topical imiquimod is a valuable treatment option for LM/LMM, given its ability to cover the wide field defect associated with this melanoma subtype without compromising cosmetically sensitive areas of the face and neck. Early retrospective studies investigating imiquimod as first-line therapy for LM demonstrated impressive pathologic complete regression (pCR) rates ranging from 64% to 86% [40–42]. However, a recently published phase II trial enrolling 28 patients with lentigo maligna demonstrated pCR of only 37%, which was too low to justify a phase III trial comparing imiquimod to wide excision [43].

Topical imiquimod has also been used to treat extensive in-transit melanoma metastases with favorable results. Several small case series have documented complete regression of cutaneous melanoma metastases and even regression of visceral metastases after treatment with topical imiquimod [44–46]. An open-label pilot study comparing topical imiquimod to topical diphencyprone for cutaneous melanoma metastases is currently accruing patients [47].

Topical Diphencyprone

Diphencyprone (DPCP) is an immunomodulatory drug whose mechanism of action is thought to involve a Th17 lymphocyte-mediated contact hypersensitivity reaction. Like imiquimod, DPCP has been used in the treatment of extensive in-transit melanoma metastases [48–50]. An Australian retrospective study of 50 patients with locally recurrent or in-transit metastatic melanoma treated with topical DPCP demonstrated a 46% rate of complete clearance of cutaneous melanoma metastases [51].

Intralesional Injections

Bacillus Calmette-Guerin (BCG) Injection

BCG was the first agent used for the intralesional treatment of melanoma in-transit metastases. In 1974, Morton et al. published their experience with 151 patients treated with intralesional BCG, reporting a 90% regression rate amongst

injected lesions as well as a 17% regression rate in uninjected lesions. Subsequent studies also reported very high response rates in injected dermal lesions of up to 90% [52–54]. Therefore, BCG is still listed as a category 2B recommendation in NCCN guidelines as an intralesional treatment for microsatellite or in transit disease. Despite this, the use of BCG intralesional injections can have a relatively high incidence of adverse effects including severe injection site reactions and occasionally systemic adverse effects and have been supplanted by other newer local intralesional injection agents.

Talimogene Laherparepvec (T-VEC) Injections

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a secreted glycoprotein that stimulates the development of dendritic cells and macrophages and the subsequent activation of T cells [55]. Early studies of intralesional GM-CSF demonstrated response rates ranging from 23% to 28% [56, 57]. T-VEC injections enable the localized overexpression of GM-CSF using a HSV I virus modified for selective tumor cell infection, immunogenicity, and the expression of the GM-CSF gene [55]. A randomized phase III trial published in 2015 compared T-VEC to GM-CSF for the treatment of 436 patients with unresectable stage IIIB and IV melanoma. The investigators demonstrated a 16.3% durable response rate (defined as complete response or partial response lasting ≥6 months) for patients treated with intralesional T-VEC compared to 2.1% for patients treated with GM-CSF ($p < 0.001$). Interestingly, objective responses were also documented in uninjected lesions, including 15% of measurable visceral tumors. Median OS was greater in the T-VEC arm, although this did not reach statistical significance (23 months vs 19 months, $p = 0.051$) [58]. Current guidelines recommend the consideration of T-VEC injection for the treatment of in-transit metastases and local satellite or in-transit recurrence [20].

Interleukin-2 (IL-2) Injections

IL-2 has been used as both a systemic therapy and an intralesional agent in the treatment of melanoma. Intralesional IL-2 is associated with an excellent response rate and a much more favorable side-effect profile compared to its intravenous use [59–61]. A phase II trial including 48 patients with dermal or subcutaneous melanoma metastases demonstrated a complete response in 70% of injected metastases that was durable over at least 6 months [62]. The NCCN guidelines recommend the consideration of intralesional IL-2 for the same indications as intralesional T-VEC injection [20].

Rose Bengal/PV-10

Rose Bengal is a xanthine dye that has recently been investigated as a chemoablative agent for use in intralesional injection. A phase II study enrolling 80 patients with advanced melanoma refractory to standard therapy reported a target lesion overall response rate of 51% and a complete response rate of 26% after injection with PV-10. This response was durable for a median duration of 4.0 months [63]. A phase III trial comparing intralesional PV-10 to temozolomide or dacarbazine for locally advanced melanoma is currently accruing patients.

Radiation Therapy

The role of radiation therapy (RT) in the primary treatment of melanoma is largely limited to LM/LMM. As mentioned above, the subclinical lentiginous spread exhibited by LM/LMM makes this subtype of melanoma particularly amenable to coverage in a radiation field. Both superficial radiotherapy (SRT) and Grenz ray therapy have been used effectively in the treatment of this disease. A systematic review of nine studies including 537 patients treated with definitive RT for LM reported a 3-year recurrence rate of only 5%. The majority of the patients with recurrent LM underwent successful salvage RT or surgery. The later development of LMM was documented in only 1.4% of patients. The included studies used both SRT and Grenz ray therapy with a variety of dosing schedules and no clear indication of an optimal technique [64]. Another retrospective study that was not included in the above meta-analysis included 593 patients treated with Grenz ray therapy for LM/LMM and demonstrated an 88% rate of complete disease clearance. The rate of clearance was higher (90%) in the patients who underwent RT after partial resection of their lesion [65]. To date, no optimal radiation type or dosing regimen for LM/LMM has been established.

Systemic Therapy

Melanoma is one of the few solid tumors that can actually be cured or obtain long-term durable responses by a systemic treatments such as IL-2 or new immunotherapy agents [66]. However, systemic therapy is not recommended as the definitive treatment for primary melanoma unless the disease is widely metastatic and unresectable or the patient's medical comorbidities preclude surgical excision. Systemic treatment options include immune checkpoint inhibition, targeted BRAF/MEK therapy, and cytotoxic chemotherapy. The use of these agents in the adjuvant and palliative settings are discussed in detail in subsequent chapters.

Conclusion/Case Discussion

Wide excision is the cornerstone of primary melanoma treatment. In this case, the patient's 3 mm thick lesion should be excised with 2 cm margins on all sides. As the lesion has well-defined borders and does not exhibit in-transit metastases, topical therapy and radiation therapy are not indicated. Management of the axillary lymph nodes is indicated in this patient and will be discussed in another chapter.

Critical Take Home Points

- Wide excision is the mainstay of treatment for primary melanoma.
- Appropriate excision margins are dictated by the Breslow depth of the lesion being excised.
- Particular attention to margin control must be practiced when excising lentigo maligna and lentigo maligna melanoma due to these lesions' tendency for subclinical radial spread.
- Non-operative treatment should be considered when the medical, functional, or cosmetic morbidity of an operation outweigh the potential benefits to the patient.
- Non-operative options for melanoma include topical therapies, intralesional injection, radiation therapy, and systemic therapy.

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Chapter 7
Regional Nodal Staging: Clinically Node Negative

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Introduction

The incidence of malignant melanoma has increased over the past few decades, and melanoma now represents the fifth most common cancer in the United States [1]. Prognosis following diagnosis is highly dependent on disease stage, as determined by Breslow thickness, primary tumor ulceration, and the presence of regional lymph node (LN), satellite/in-transit, or distant metastases [2]. In patients with clinically localized melanoma, sentinel lymph node biopsy (SLNB) is an important staging and prognostic tool used to evaluated the pathologic status of the regional LN basin.

History

First introduced to the surgical community by Morton et al. in the early 1990s, SLNB quickly replaced elective LN dissection (ELND) in determining whether tumor cells have spread beyond the primary site to the regional nodal basin [3].

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Routine ELND in patients with early-stage melanoma was controversial for several reasons. Large multi-institutional prospective studies failed to demonstrate a significant survival benefit of ELND compared to nodal observation except in certain subgroups of patients [4, 5]. Clinically occult LN metastases were histologically identified in only about 15–20% of patients who underwent ELND, while patients were exposed to the potentially significant morbidity associated with ELND without a definite clinical benefit [3, 5].

In the initial report of SLNB published by Morton et al., SLNs were successfully identified in 194 (82%) of 237 specimens, ranging from 81% for cervical basins to 89% for the groin [3]. Among the 259 SLNs from the 194 specimens, 18% harbored microscopic melanoma metastases. In contrast, only 0.06% of non-sentinel nodes were found to be tumor-bearing (false-negative rate 1%), corroborating the notion that the SLNs were the initial sites of regional LN spread and confirming the high sensitivity of the technique [3].

The role of SLNB in the management of clinically localized melanoma was further assessed prospectively through a large randomized trial, the Multicenter Selective Lymphadenectomy Trial-1 (MSLT-1), which was initiated by Morton et al. in 1994 [6]. Ten-year survival outcomes were published in 2014 (Table 7.1) [7]. The phase III trial included 2001 patients diagnosed with localized cutaneous melanoma of Breslow thickness ≥1.2 mm. Patients were randomized to undergo wide local excision (WLE) of the primary tumor with SLNB, followed by immediate completion lymphadenectomy (CLND) for those with a positive SLN, versus wide excision of primary alone with nodal observation and therapeutic lymphadenectomy at time of nodal recurrence. While the trial found no significant difference between randomized groups for the primary study endpoint (melanoma-specific survival), SLNB was associated with improved 10-year disease-free survival in patients with intermediate-thickness melanomas, defined as 1.2–3.5 mm in Breslow thickness (SLNB vs. observation, Hazard Ratio [HR] 0.76, P = 0.01), and thick melanomas, or >3.5 mm (HR 0.70, P = 0.03). This was driven largely by higher regional recurrence rates in the observation arm of the trial. The trial reaffirmed the strong prognostic value of the SLN; nodal metastasis was associated with decreased melanoma-specific survival (intermediate-thickness, HR 3.09, P < 0.001; thick, HR 1.75, P = 0.03). Furthermore, earlier intervention with SLNB and immediate CLND, compared to therapeutic lymphadenectomy after nodal recurrence, appeared to be associated with improved melanoma-specific survival in the subgroup of patients with intermediate-thickness melanomas with nodal disease (HR 0.56, P = 0.006). A similar treatment-related response with early nodal intervention was not observed among patients with thick melanomas and LN metastases (HR 0.92, P = 0.78).

The important prognostic information provided by SLNB led to the incorporation of regional nodal micrometastases in the sixth edition of the American Joint Committee on Cancer staging system for melanoma in 2001 [8]. Historically, the distinction between clinical and pathologic staging was not emphasized. With the widespread use of SLNB, and increased upstaging of clinically node-negative patients, clinical and pathologic staging led to distinct populations of patients with disparate survival outcomes. The difference in survival conferred by the pathologic nodal status was most pronounced for clinically node-negative patients with melanomas >1.0–4.0 mm in Breslow thickness (P < 0.0001) [8].

Table 7.1 Ten-year survival outcomes from the Multicenter Selective Lymphadenectomy Trial-1: clinically node-negative patients with melanoma who underwent sentinel lymph node biopsy (SLNB) versus nodal observation [7]

	Intermediate-thickness melanomas (1.2–3.5 mm Breslow thickness)		Thick melanomas (>3.5 mm Breslow thickness)	
	HR (95% CI)	P value	HR (95% CI)	P value
Primary outcome				
Melanoma-specific survival	N = 1270		N = 290	
Observation	Reference		Reference	
SLNB	0.84 (0.64–1.09)	0.18	1.12 (0.76–1.67)	0.56
Secondary outcomes				
Disease-free survival	N = 1270		N = 290	
Observation	Reference		Reference	
SLNB	0.76 (0.62–0.94)	0.01	0.70 (0.50–0.96)	0.03
Node-positive patients: melanoma-specific survival	N = 209		N = 101	
Observation with nodal recurrence	Reference		Reference	
SLNB positive	0.56 (0.37–0.84)	0.006	0.92 (0.53–1.60)	0.78
Node-positive patients: distant disease-free survival	N = 209		N = 101	
Observation with nodal recurrence	Reference		Reference	
SLNB positive	0.62 (0.42–0.91)	0.02	0.96 (0.56–1.64)	0.88
Node-negative patients: melanoma-specific survival	N = 1025		N = 177	
Observation without nodal recurrence	Reference		Reference	
SLNB negative	0.89 (0.61–1.29)	0.54	1.18 (0.63–2.18)	0.61

HR hazard ratio, *CI* confidence interval, *SLNB* sentinel lymph node biopsy

Patient Selection for Sentinel Lymph Node Biopsy

Guideline Recommendations

SLNB is recommended for certain populations of patients presenting with clinically node-negative invasive melanoma with appreciable risk of regional nodal metastasis. It is not recommended for patients diagnosed with melanoma *in situ* or those with clinically-evident nodal disease (for which nodal microstaging is unnecessary). Clinical guidelines continue to evolve over time with respect to precise patient selection criteria, but generally are concordant in recommending SLNB for patients with intermediate-thickness melanomas >1.0–4.0 mm in Breslow thickness.

Current guidelines set forth by the American Society of Clinical Oncology (ASCO) and the Society of Surgical Oncology (SSO) recommend the performance of SLNB in patients with intermediate-thickness melanomas (>1.0–4.0 mm in Breslow thickness) (Fig. 7.1a) [9]. Furthermore, a SLNB may be considered after a

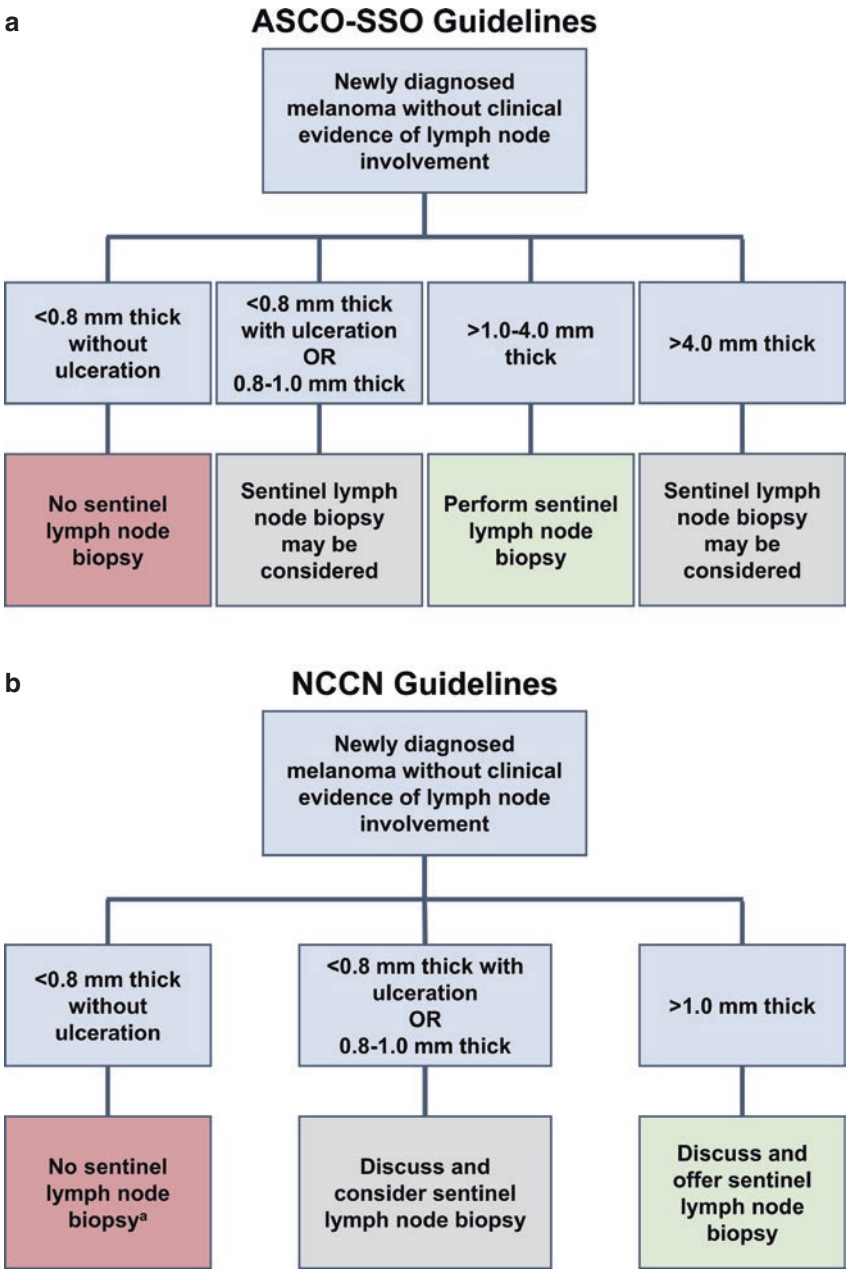

Fig. 7.1 National guidelines for patient selection for sentinel lymph node biopsy. (**a**) American Society of Clinical Oncology (ASC) and Society of Surgical Oncology (SSO) guidelines [9]. (**b**) National Comprehensive Cancer Network (NCCN) guidelines [10]. [a]Sentinel lymph node biopsy may be considered if other high-risk features are present, such as a very high mitotic rate (≥2 per mm^2), especially in a young patient, lymphovascular invasion, or a combination

thorough discussion of potential benefits and risks in patients with T1b melanomas (<0.8 mm in Breslow thickness with ulceration, or 0.8–1.0 mm in thickness irrespective of ulceration status). Similarly, it may be considered in patients with thick melanomas (>4.0 mm in thickness), who harbor a significant risk of regional LN metastasis. SLNB is not routinely recommended for patients with thin, non-ulcerated tumors <0.8 mm.

Guidelines from National Comprehensive Cancer Network (NCCN) recommend offering SLNB for patients with a risk of positive SLN of 10% or higher [10]. This would include patients with melanomas ≥1.0 mm in Breslow thickness, regardless of ulceration status. Unlike the ASCO/SSO guidelines, the NCCN guidelines do not differ in their recommendations for intermediate-thickness and thick melanomas. SLNB should be considered in those with 5–10% risk, such as patients with melanomas <0.8 mm with high-risk features (ulceration, mitotic rate ≥2 per mm^2 [particularly in patients of young age], lymphovascular invasion, or a combination) or 0.8–1.0 mm in thickness. The guidelines further state that, among patients for whom SLNB should be considered or offered, individual clinical decisions depend on patient comorbidities, patient preferences, and other factors. SLNB is not recommended for those with <5% risk, such as patients with melanomas <0.8 mm in Breslow thickness without ulceration or other high-risk features. Additionally, the presence of microsatellitosis or in-transit disease at initial melanoma presentation already defines stage III disease, and while SLN status does have prognostic value, the importance of SLNB in this patient population has not been clearly defined [10, 11].

Evidence for Intermediate-Thickness and Thick Melanomas

Guideline recommendations for SLNB are based in part on the results from MSLT-1 and several other retrospective studies. Similar to MSLT-1, many retrospective studies demonstrated an improvement in disease-free survival, but not melanoma-specific survival, in patients with intermediate-thickness who underwent SLNB (Table 7.2) [12–14]. One retrospective study using data from the Surveillance Epidemiology and End Results (SEER) demonstrated worse melanoma-specific survival in patients with intermediate-thickness melanomas who underwent nodal observation compared to SLNB (HR 1.18, 95% Confidence Interval [CI] 1.04–1.34, P = 0.009) [15]. However, the authors noted that the absolute difference in survival was small (1.7%). Retrospective studies have identified increasing Breslow thickness, ulceration, mitoses, and lymphovascular invasion to be associated with SLN positivity in patients with intermediate-thickness melanomas (Table 7.3) [16–18].

Unlike for intermediate-thickness melanomas, the MSLT-1 did not demonstrate that early nodal intervention among patients with thick melanomas and nodal metastases was associated with improved melanoma-specific survival (SLNB positive vs. observation with nodal recurrence, HR 0.92, P = 0.78) [7]. Similar to MSLT-1, multiple retrospective studies have not demonstrated an improvement in

Table 7.2 Multivariable analyses of survival outcomes in retrospective studies comparing sentinel lymph node biopsy (SLNB) and nodal observation in patients with clinically node-negative malignant melanoma

Study	Breslow thickness	Data source	Cohort (N)	Disease-free survival Adjusted HR (95% CI)	P value	Melanoma-specific survival Adjusted HR (95% CI)	P value
Karakousis et al. [27]	Thin	Institutional	Observation with clinical nodal recurrence (426)	–	–	3.29 (1.83–5.93)	<0.001
			SLNB positive (91)	–	–	Reference	
Kachare et al. [15]	Intermediate	Surveillance epidemiology and end results	Observation (matched 3955)	–	–	1.18 (1.04–1.34)	0.009
			SLNB (matched 3955)	–	–	Reference	
van der Ploeg et al. [13]	Intermediate and thick	Institutional	Observation (2931)	1.40 (1.23–1.58)	<0.001	1.04 (0.88–1.22)	0.642
			SLNB (2909)	Reference		Reference	
Kachare et al. [12]	Thick	Surveillance epidemiology and end results	Observation (1825)	–	–	1.09 (0.95–1.25)	0.20
			SLNB (2746)	–	–	Reference	
Ribero et al. [19]	Thick	Institutional	Observation (172)	Reference		Reference	
			SLNB (178)	0.59 (0.43–0.79)	0.001	0.77 (0.53–1.12)	0.176
Boada et al. [20]	Thick	Multi-institutional	Observation (matched 376)	Reference		Reference	
			SLNB (matched 376)	0.74 (0.61–0.90)	0.002	0.84 (0.65–1.08)	0.165
Sperry et al. [14]	Thin (≥0.76–1 mm)	Surveillance epidemiology and end results	Observation (matched 552)	–	–	Reference	
			SLNB (matched 552)	–	–	1.53 (0.75–3.13)	0.24
	Intermediate		Observation (matched 1404)	–	–	Reference	
			SLNB (matched 1404)	–	–	0.87 (0.66–1.14)	0.31
	Thick		Observation (matched 354)	–	–	Reference	
			SLNB (matched 354)	–	–	0.80 (0.56–1.15)	0.23

HR hazard ratio, *CI* confidence interval

Table 7.3 Multivariable analyses of clinicopathologic characteristics associated with sentinel lymph node positivity in retrospective studies

Characteristic	Study	Comparison	Adjusted OR (95% CI)	P value
All patients				
Age	Balch et al. [34]	<40 vs. ≥60 years	1.8 (1.5–2.1)	<0.0001
		40–59 vs. ≥60 years	1.4 (1.3–1.7)	<0.0001
Location	Balch et al. [34]	Upper extremity vs. head/neck	1.1 (0.9–1.4)	0.2554
		Trunk vs. head/neck	1.7 (1.4–2.1)	<0.0001
		Lower extremity vs. head/neck	1.8 (1.4–2.2)	<0.001
Breslow thickness	Balch et al. [34]	1.01–2.0 vs. ≤1.0 mm	2.1 (1.6–2.7)	<0.001
		2.01–4.0 vs. ≤1.0 mm	4.3 (3.3–5.6)	<0.001
		>4.0 vs. ≤1.0 mm	6.5 (4.8–8.8)	<0.001
Clark level	Balch et al. [34]	III vs. II	1.8 (1.0–3.4)	0.0674
		IV vs. II	2.7 (1.4–5.0)	0.0023
		V vs. II	2.5 (1.3–5.0)	0.0065
Ulceration	Balch et al. [34]	Present vs. absent	1.4 (1.2–1.6)	<0.0001
Lymphovascular invasion	Balch et al. [34]	Present vs. absent	3.0 (2.4–3.6)	<0.001
Thin melanomas				
Age	Sinnamon et al. [28]	<40 vs. ≥65 years	2.04 (1.44–2.90)	<0.001
		40–64 vs. ≥65 years	1.59 (1.19–2.11)	0.001
	Conic et al. [29]	30–39 vs. <30 years	0.82 (0.56–1.22)	N/A
		40–49 vs. <30 years	0.64 (0.43–0.96)	N/A
		50–59 vs. <30 years	0.63 (0.43–0.92)	N/A
		60–69 vs. <30 years	0.52 (0.35–0.77)	N/A
		≥70 vs. <30 years	0.56 (0.38–0.84)	N/A
Sex	Sinnamon et al. [28]	Female vs. male	1.26 (1.00–1.58)	0.04
	Conic et al. [29]	Male vs. female	1.32 (1.07–1.63)	N/A
	Karakousis et al. [32]	Male vs. female	2.5 (1.2–5.0)	0.01

(continued)

Table 7.3 (continued)

Characteristic	Study	Comparison	Adjusted OR (95% CI)	P value
Breslow thickness	Cordeiro et al. [30]	≥0.75 vs. <0.75 mm	1.90 (1.08–3.33)	N/A
	Sinnamon et al. [28]	≥0.76 vs. 0.50–0.75	1.74 (1.36–2.23)	<0.001
	Piazzalunga [31]	>0.75 vs. <0.75	2.02 (1.25–3.26)	0.004
	Conic et al. [29]	≥0.8 vs. <0.8	1.24 (1.02–1.51)	N/A
Clark level	Cordeiro et al. [30]	IV/V vs. II/III	2.24 (1.23–4.10)	N/A
	Sinnamon et al. [28]	III vs. II	2.07 (1.17–3.63)	0.01
		IV/V vs. II	2.27 (1.30–3.96)	0.003
	Conic et al. [29]	IV/V vs. II/III	1.48 (1.19–1.85)	N/A
Ulceration	Cordeiro et al. [30]	Present vs. absent	2.27 (0.98–5.24)	N/A
	Sinnamon et al. [28]	Present vs. absent	1.58 (1.11–2.24)	0.01
	Piazzalunga [31]	Present vs. absent	2.94 (1.36–6.31)	0.006
	Conic et al. [29]	Present vs. absent	1.64 (1.21–2.18)	N/A
	Karakousis et al. [32]	Present vs. absent	7.6 (2.2–26.6)	0.002
Mitoses	Cordeiro et al. [30]	≥1 per mm^2 vs. absent	6.64 (2.77–15.88)	N/A
		≥1 vs. <1 per mm^2	1.46 (0.61–3.49)	N/A
	Sinnamon et al. [28]	≥1 per mm^2 vs. absent	1.46 (1.13–1.89)	0.003
	Conic et al. [29]	Present vs. absent	1.95 (1.54–2.49)	N/A
	Mozillo et al. [26]	≥1 per mm^2 vs. absent	6.44 (2.17–19.15)	<0.001
	Karakousis et al. [32]	Present vs. absent	3.3 (1.5–7.4)	0.003
Lymphovascular invasion	Sinnamon et al. [28]	Present vs. absent	2.07 (1.06–4.04)	0.03
Vertical growth phase	Karakousis et al. [32]	Vertical vs. radial growth phase	7.9 (1.7–36.8)	0.009

Table 7.3 (continued)

Characteristic	Study	Comparison	Adjusted OR (95% CI)	P value
Intermediate-thickness melanomas				
Age	Bartlett et al. [16]	≥60 vs. <60 years	0.69	0.047
	Chang et al. [17]	60–74 vs. <60 years	0.45 (0.30–0.67)	<0.001
		≥75 vs. <60 years	0.48 (0.28–0.82)	0.007
	Hanna et al. [18]	Continuous, every 10 years	0.80 (0.78–0.83)	<0.0001
Sex	Hanna et al. [18]	Female vs. male	0.857 (0.79–0.93)	0.0002
Location	Chang et al. [17]	Lower extremity vs. head/neck	2.15 (1.20–3.86)	0.010
		Upper extremity vs. head/neck	1.65 (0.86–3.16)	0.132
		Trunk vs. head/neck	2.12 (1.21–3.71)	0.009
	Hanna et al. [18]	Lower extremity vs. head/neck	1.81 (1.59–2.06)	<0.0001
		Upper extremity vs. head/neck	0.98 (0.86–1.11)	0.71
		Trunk vs. head/neck	1.74 (1.55–1.95)	<0.0001
Breslow thickness	Bartlett et al. [16]	1.01–1.49 vs. 1.50–4.00 mm	0.29	<0.001
	Chang et al. [17]	2.00–2.99 vs. 1.01–1.99 mm	2.31 (1.57–3.41)	<0.001
		3.00–4.00 vs. 1.01–1.99 mm	3.04 (1.93–4.79)	<0.001
	Hanna et al. [18]	Continuous	1.56 (1.48–1.63)	<0.0001
Clark level	Hanna et al. [18]	III vs. II	1.41 (1.02–1.87)	0.03
		IV/V vs. II	1.49 (1.03–1.94)	0.009
Mitoses	Bartlett et al. [16]	Absent vs. present	0.47	0.093
	Hanna et al. [18]	Present vs. absent	1.63 (1.42–1.86)	<0.0001
Ulceration	Hanna et al. [18]	Present vs. absent	1.35 (1.24–1.47)	<0.0001

(continued)

Table 7.3 (continued)

Characteristic	Study	Comparison	Adjusted OR (95% CI)	P value
Tumor infiltrating lymphocytes	Bartlett et al. [16]	Present vs. absent	0.60	0.018
Lymphovascular invasion	Bartlett et al. [16]	Absent vs. present	0.46	0.010
	Hanna et al. [18]	Present vs. absent	3.18 (2.77–3.66)	<0.0001
Microsatellites	Bartlett et al. [16]	Absent vs. present	0.44	0.010
	Chang et al. [17]	Present vs. absent	2.31 (1.09–4.89)	0.029
Thick melanomas				
Location	Yamamoto et al. [25]	Trunk vs. head/neck	4.60 (2.03–10.42)	0.0003
		Extremities vs. head/neck	3.17 (1.35–7.42)	0.008
Histology	Yamamoto et al. [25]	Desmoplastic vs. superficial spreading	0.09 (0.02–0.36)	0.001
Microsatellites	Yamamoto et al. [25]	Present vs. absent	10.31 (1.98–53.83)	0.006

OR odds ratio, *CI* confidence interval, *N/A* not available

melanoma-specific survival with receipt of SLNB in patients with thick melanomas [12, 14, 19, 20], where the frequency of occult systemic metastases may be appreciable [21]. SLN positivity rates for thick melanomas are quite high, reported as 32.9% in MSLT-1 [7] and ranging from 30% to 51.2% in retrospective series [12, 19, 21–26]. However, even despite the lack of any demonstrable survival benefit of the SLN procedure in this high risk population, retrospective studies have found the SLN status to be prognostic, with SLN positive patients experiencing worse disease-free [19, 20, 22, 23, 25], distant disease-free [24], melanoma-specific [19, 20, 25], and overall survival [22, 24–26] (Table 7.4). Reported factors associated with decreased likelihood of SLN positivity in patients with thick melanomas have included identified head/neck location, desmoplastic histology, and absence of satellitosis (Table 7.3) [25]. Other studies found the presence of ulceration [22, 24] and lymphovascular invasion [24] to be associated with SLN positivity by univariable analysis.

Evidence for Thin Melanomas

Evidence supporting SLNB in patients with thin melanomas are limited to retrospective studies as there are no randomized trials comparing SLNB to nodal observation for this lower risk patient population. Using data from SEER, Sperry et al.

Table 7.4 Multivariable analyses of survival outcomes in retrospective studies comparing sentinel lymph node positive and negative patients with melanomas >4.0 mm in Breslow thickness

Study	Data source	Cohort (N)	Disease-free survival Adjusted HR (95% CI)	P value	Melanoma-specific survival Adjusted HR (95% CI)	P value
Ribero et al. [19]	Institutional	Observation (172)	Reference		Reference	
		Negative (94)	0.47 (0.33–0.68)	<0.001	0.62 (0.39–0.96)	0.03
		Positive (84)	0.78 (0.54–1.12)	0.18	1.03 (0.66–1.62)	0.87
Gershenwald et al. [22]	Institutional	Negative (77)	Reference		Reference[a]	
		Positive (49)	2.03 (1.36–2.70)	0.039	3.24 (2.26–4.21)	0.018
Ferrone et al. [23]	Institutional	Negative (88)	Reference		–	–
		Positive (38)	3.3 (1.8–6.0)[b]	<0.001	–	–
Gajdos et al. [24]	Institutional	Negative (120)	Reference[c]		Reference[a]	
		Positive (107)	3.95 (2.11–7.41)	<0.0001	2.28 (1.37–3.77)	0.0014
Yamamoto et al. [25]	Institutional	Negative (251)	Reference		–	–
		Positive (161)	1.39 (1.03–1.86)	0.029	–	–

HR hazard ratio, *CI* confidence interval
[a]Overall survival
[b]Relative risk
[c]Distant disease-free survival

demonstrated an improvement in disease-free survival for patients with high-risk, thin (≥0.76–1.00 mm with ulceration or ≥1 mitoses per mm^2) melanomas of the head and neck who underwent SLNB compared to observation, similar to the findings for patients with intermediate-thickness and thick melanomas (Table 7.2) [14]. In a two-center study of patients with thin melanoma, receipt of SLNB was associated with improved survival outcomes (5-year melanoma-specific survival 88% vs. 72%, $P < 0.0001$) in patients with identified SLN metastases compared to those who developed clinical nodal disease [27]. Further prospective study would be needed to delineate the influence of patient selection and other potential biases in these observed results. Among patients with thin melanomas, increasing Breslow thickness is a strong risk factor for SLN positivity, with most studies using a depth of 0.75 or 0.80 mm as the cutpoint for comparison [28–31] (Table 7.3). Other primary tumor factors, such as the presence of ulceration [28–32], mitoses [28–30, 32], and lymphovascular invasion [28], have also been associated with increased risk for SLN positivity, supporting the consideration of SLNB in patients with thin melanomas and these high-risk features.

In addition to tumor factors, patient age appears to be associated with SLN status (Table 7.3). Multiple studies have demonstrated lower rates of positive SLNs in older patients, regardless of other clinicopathologic features [16–18, 28, 29, 33, 34]. Paradoxically, however, older age is also associated with decreased melanoma-specific survival [33]. However, patient age is not included as a factor for consideration in current clinical practice guidelines, which focus on tumor factors.

Technical Performance

Lymphoscintigraphy and Tracer Injection

First developed in 1977, preoperative lymphoscintigraphy is the commonly accepted technique for identifying the regional draining LN basin in anatomic areas with variable drainage patterns, such as the head, neck, and trunk (Fig. 7.2) [35]. In truncal melanomas, for example, contralateral rather than ipsilateral nodal basins may be involved, and in head and neck melanomas, pre-auricular, parotid, or suboccipital sites rather than the cervical chain or supraclavicular nodes may serve as the primary draining basin. Information from lymphoscintigraphy helps to guide the

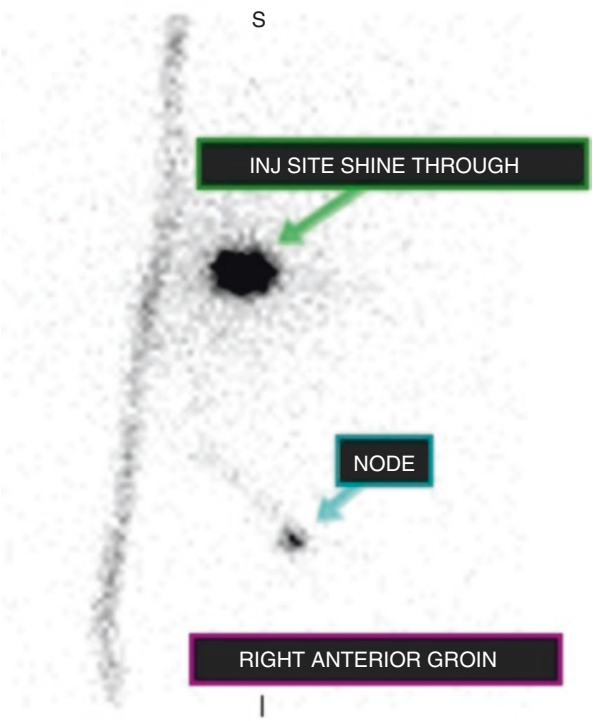

Fig. 7.2 Preoperative lymphoscintigram demonstrating a sentinel lymph node located in the right inguinal basin in a patient with a right lower back melanoma

biopsy of all involved regional LN basins. While it is typically performed on the day of surgery just prior to SLNB, surgery can be performed up to 24 h later without significant dissipation of radiolabeled colloid [36].

Lymphoscintigraphy typically begins with a four-point intradermal injection of 0.05–1 mCi of technetium 99-labeled sulfur colloid just adjacent to the primary melanoma biopsy site or clinical residual lesion [37]. It should be injected in wheels, 0.1 mL per aliquot, with a 25- to 27-gauge needle. Drainage to the nodal basin is usually brisk, within 10–30 min. Inadequate tissue tension in the wheel can lead to delayed drainage, and injected volumes larger than 0.1 mL risk obstructing dermal lymphatics [9, 38]. Also, increased pressure from the wheel can cause leakage when the needle is removed, leading to interference on gamma imaging. In some areas, such as the head and neck, the caudal injection is held as it may interfere with imaging of the nodal basin. Subcutaneous injection should be avoided, as drainage from subcutaneous lymphatics may not represent lymphatic drainage from the cutaneous melanoma. The radiation dose from a SLNB to the surgeon and other personnel is minimal. It is estimated that the radioactive dose from a single biopsy is one-thirtieth of the annual whole-body absorbed dose from background radiation [38].

Most centers implement planar gamma camera imaging following radiocolloid injection to identify the appropriate nodal basins and sentinel nodes. Some centers implement dynamic imaging to visualize nodes close to the injection site that receive direct lymphatic drainage. This technique captures images immediately after injection at 30 s per frame for 2–30 min. It is recommended that head and neck melanomas be evaluated by single-photon emission computed tomography (SPECT-CT) in addition to planar lymphoscintigraphy when available, as it has been shown to find an additional nodal basin in 38% of patients, increase the yield of positive SLNs, decrease local recurrence rates, and alter surgical approach in 20–50% of cases (Fig. 7.3) [39–42]. Other techniques used to assist with node localization include the use of a cobalt-57 flood source or other hot source to trace the outline of the patient. Furthermore, some centers perform skin markings over identified nodes in the appropriate operative position, occasionally from both the anterior and lateral views.

After lymphoscintigraphy, the patient can proceed to the operating room. Additional SLN localization may be performed by injection of blue dye with the identification of any blue-colored LNs as SLNs. Prior to injection of the blue dye, it is important to outline the margin for the WLE, as the dye may obscure a small biopsy scar. A four-point intradermal injection with up to 1–2 mL of blue dye is performed at the primary melanoma site. Five to ten minutes are needed for the blue dye to reach the nodal basin. Commercially available dyes include isosulfan blue and methylene blue. Both dyes are effectively taken up by the dermal lymphatics, but have different side effect profiles. In one study, 1.5% of patients had an adverse reaction to isosulfan blue, including a significant rate of anaphylaxis in 0.75% of patients [43]. Methylene blue has been associated with tissue necrosis, so care must be taken in anatomic regions where the dye might not be fully resected, such as the ankles, wrists, and face. Small amounts of blue dye left at the excision site may rarely result in permanent tattoo.

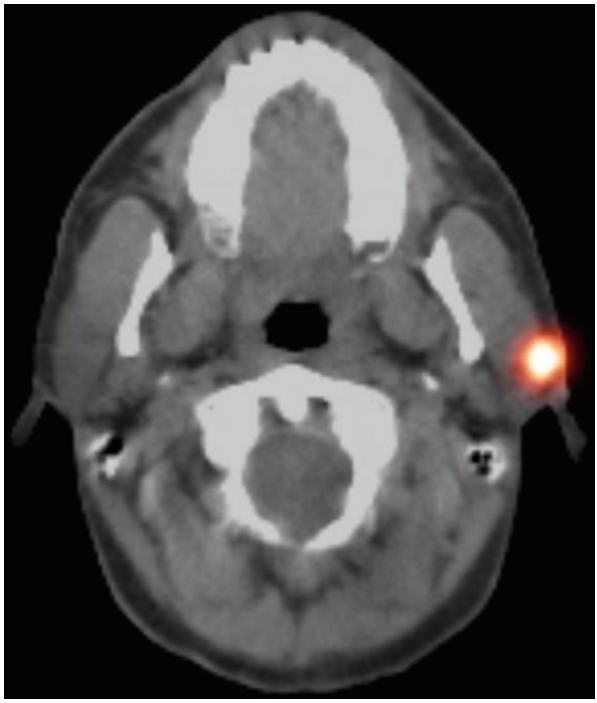

Fig. 7.3 Preoperative single-photon emission computed tomography (SPECT-CT) demonstrating sentinel lymph node located superior to the left superior parotid gland in a patient with a primary melanoma located on the left side of the face

Two other SLN tracers used in the care of patients with melanoma include indocyanine green and tilmanocept (Lymphoseek®). Indocyanine green is used in conjunction with infrared fluorescence for detection of SLNs. While studies have shown that indocyanine green detects SLNs more efficiently than traditional methods, there is no long-term evidence that suggests its use improves outcomes [44]. The use of tilmanocept, a molecule specifically engineered as an ideal radiotracer for SLN detection with binding capacity to CD206 receptors on the surface of macrophages and dendritic cells, has been promising. In a clinical trial involving patients with clinically node negative melanoma, tilmanocept was found to have increased sensitivity compared to conventional SLN dyes [45].

Performance of Sentinel Lymph Node Biopsy

A gamma probe is placed in a sterile sleeve and used to identify areas of radiotracer uptake in nodal basins identified on preoperative lymphoscintigraphy. If there is significant radiotracer interference from the primary melanoma injection site, WLE of the primary tumor can be performed first to decrease interference. Otherwise, SLNB is usually performed prior to the excision of the primary site, to prevent potential cross-contamination and allow for more time for lymphatic drainage to the

nodal basin. A small incision is made across the nodal basin and the dissection is carried down using instrument dissection and electrocautery. The incision is typically made such that it can be extended should a CLND ultimately be performed. Blue-stained lymphatics and the gamma probe are used to direct the dissection towards the SLN(s). Small lymphatics or vessels entering the node are ligated or clipped as necessary. Care is taken not to disrupt the capsule of the SLN using instruments or electrocautery, as it can affect pathological assessment [46]. In general, additional dissection should be avoided in the nodal basin other than that required to remove the SLNs.

All blue nodes, grossly abnormal nodes, or nodes with at least 10% of the *ex vivo* maximum radiotracer count of the hottest node are removed. This recommendation extends from a study from McMasters et al. that found that in 13.1% of positive nodal basins, the most radioactive SLN was negative for tumor, while another less radioactive LN was positive for tumor [47]. Furthermore, in 50% of those cases, the radioactive count of the positive node was ≤50% of the radioactive count of the hottest node. Approximately one to three SLNs are typically identified per dissection following these criteria.

In most cases, WLE and SLNB are completed during the same operation. However, some patients are referred for SLNB only after their WLE has been completed. A series of publications have evaluated the feasibility and accuracy of lymphoscintigraphy and SLNB in this setting [48–51]. In a large study of this type by Gannon et al., lymphatic mapping and SLNB were successful in 103 of 104 patients who had WLE prior to SLNB [50]. A comparison to a cohort of over 1000 patients who underwent concomitant WLE and SLNB at the same institution revealed no significant differences in the SLN identification rate, incidence of a positive SLN, or number of SLNs identified. Interestingly, more patients with axial primaries who underwent prior WLE were found to have multiple LN basin drainage, but this did not reach statistical significance ($P = 0.07$). Due to these findings, it is recommended that patients undergo concomitant WLE and SLNB whenever possible to provide patients with a single operation, lower costs, and avoid the risk and morbidity of a potentially larger second operation to accomplish accurate staging.

Further studies are needed to fully validate the accuracy of SLN mapping by tracking long-term false negative recurrences. The overall accuracy of SLNB depends on anatomic location, with likely increased accuracy for truncal and extremity locations where lymphatic drainage is more predictable, and a higher false negative rate in head and neck locations where drainage is more complex [52, 53].

Specimen Handling

SLN specimens should be intact with ideally a rim of adjacent adipose tissue present and without crush deformities or diathermic injury [46, 54]. Once removed, the length, width and height of the LN are measured and an *ex vivo* maximum

radiotracer count is obtained by scanning the node with the gamma probe. Additionally, it is important to note the presence or absence of blue dye discoloration and additional markings, including collections of melanin and carbon pigment.

The method of choice for tissue preservation is routine processing with fixation in 4–10% buffered formalin [54–61]. Frozen sectioning is not preferred as it provides suboptimal morphology, has poor sensitivity, and does not adequately incorporate the subcapsular region of the LN, a site of frequent micrometastases [54–61]. When fixing tissue from the SLN in buffered formalin, the solution should be allowed to sit at room temperature for at least 12 h, although some institutions have advocated for 48 h of incubation [54, 59]. This allows the technetium-labeled sulfur colloid in the radiotracer to decay [59].

Pathologic Assessment of the Sentinel Lymph Node

Specimen Sectioning

Pathologic investigation of the SLNs, and the identification of micrometastases, is critical to the accurate staging of cutaneous melanoma, and ultimately, the determination of treatment options and prognosis. Following fixation, the specimen is dissected in order to embed in paraffin. Two methods have been proposed for the dissection of the SLN: bivalve and bread-loafing dissection. Bivalve bisection cuts the LN longitudinally along its longest axis and bread-loafing dissection slices the node perpendicular to the longitudinal axis. Of these techniques, bivalve dissection is considered to be the standard of specimen sectioning among institutions [54–57, 60, 61]. Bisection along the longitudinal axis allows the specimen to be transected through the hilum. By bisecting at the level of the hilum, a large number of lymphatic vessels, including efferent lymphatic vessels, and the subcapsular region are exposed. This increases the rate of detection of micrometastases in the SLN [54–56, 60].

Additional sectioning of the LN has been a topic of debate among institutions. At this time, there is no consensus on the number of sections or levels necessary for SLN analysis [54]. The majority of institutions employ sectioning into 2–4 mm slices with each block of tissue being further sectioned into 1–3 levels to be analyzed by hematoxylin-eosin (H&E) staining [58–60]. More levels are necessary for immunohistochemistry (IHC) analysis. Some institutions have advocated for utilizing serial-sectioning of samples to obtain more level as this has the potential for revealing occult metastases with minimal additive labor or cost [57].

Specimen Staining and Tumor Burden Assessment

Sections obtained from SLN specimens are analyzed histologically using H&E and IHC (Fig. 7.4). It is sometimes difficult to accurately interpret histology shown on H&E staining alone due to hypercellularity within the LN and similarities in morphology between melanoma and normal nodal cells. As many as 12% of metastases will be missed in the absence of IHC [62, 63]. Traditionally, S-100, a marker for metastatic melanoma, has been the primary target for staining in SLN specimens due to its high sensitivity (95–100%) [59, 60]. Additionally, HMB-45, a target of the antigen gp100, and MART-1, a melanoma-associated antigen recognized by T cells, are often used for staining. HMB-45 is reactive with 50–80% of metastatic melanoma cells, but often negative in an intracapsular nevus, which makes it useful in distinguishing intracapsular nevi from melanoma [59, 60, 62]. Tyrosinase, a marker specific for melanocytic differentiation, has a similar sensitivity and specificity profile as these other markers, and is useful in detecting false negatives following HMB45 and MART-1 staining. An antibody combination of these three markers, HMB-45, MART-1, and tyrosinase, is currently in circulated use with increased sensitivity compared to each antibody alone [60]. Lastly, SOX10, a transcription factor in neural crest cells, has, in limited studies, been shown to be sensitive and specific to melanoma metastases, but is not widely used at this time.

There is little consensus on a specimen protocol for SLNs for melanoma, but several institutions and organizations are in support of their own single-site protocols. Cochran et al. was first to propose a protocol where SLNs are bisected and sectioned serially into ten sections; four discontinuous sections are stained with H&E, one section is stained with S-100, and one section is stained with HMB45 [55, 64]. Moffitt Cancer Center sections the node in 2–3 mm intervals and forms section blocks at one to three levels; one section is used for H&E and one section is used for S-100 [64]. At the Massachusetts General Hospital, three serial sections are taken from the

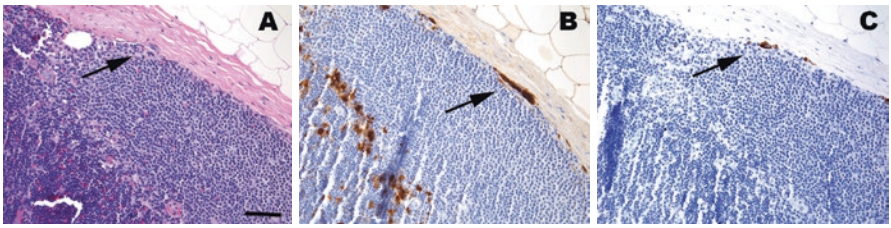

Fig. 7.4 Representative photomicroscopy of melanoma sentinel lymph node. (**a**) Histology (H&E stain). Rare melanoma cells in the subcapsular area of this sentinel node. (**b**) S-100 stain. Rare subcapsular melanoma cells are positive for S-100. (**c**) HMB-45 stain. Rare subcapsular melanoma cells are positive for HMB-45. Bar indicates 80 μm. Arrows point to the melanoma cells

specimen block at three different levels measuring 80–100 μm apart and 1–2 mm in thickness: (1) the second, fifth, and eighth levels are stained with H&E, (2) the third, sixth, and ninth levels are stained with S-100 and HMB-45, and (3) the first, fourth, and seventh levels are stained with NK1C3, a protein present on activated granulocytes, and MART-1 [64]. At the Hospital of the University of Pennsylvania, sections are taken from the specimen at four different levels. The first and fourth levels are used for histology and the second and third levels are stained with S-100 and HMB-45. The European Organization for Research and Treatment of Cancer protocol, modified from the Cook et al. protocol, involves an initial full-face section, similar to the Cochran bivalving technique, followed by five step sections 50 μm apart with staining of the subsections with H&E, S-100, and HMB-45, respectively [54, 65]. While there are minute differences between various pathologic protocols, all protocols share a common understanding that bivalving of the node, in order to evaluate the subcapsular sinus, in combination with serial sectioning leads to the best positive predictive value for the identification of melanoma micrometastases [64].

Following section preparation, specimens are examined with particular attention to the subcapsular sinus region [54]. Positive SLNs are identified in the subcapsular region 86% of the time, so it is critical to preserve and examine this section pathologically [66]. Higher power magnification (400×) is typically utilized to confirm findings noted on low magnification. Melanoma cells can, at times, be difficult to differentiate from underlying cells present in LNs, including macrophages, dendritic cells, and nevus cells. All of these cells are positive for S-100, but can be distinguished based on size, nuclear and cytoplasmic characteristics, and distribution within the node. Nevus cells, benign and small nevomelanocytic cells, are usually negative for HMB45 and Ki67, and are typically intracapsular or trabecular [54, 66]. Melanoma cells are larger than nevus cells and contain larger nucleoli with a higher nuclear to cytoplasmic ratio [54, 63, 66]. Macrophages can be differentiated by noting the coarse melanin granules in contrast to the fine melanin granules of melanoma cells [54, 63].

When evaluating sections, there is limited consensus on a single scoring algorithm, but there is consensus on the assessment parameters for the SLNs. All specimens should be evaluated for the location of the tumor deposit within the LN (whether this be subcapsular, intraparenchymal, or trabecular), the presence or absence of extracapsular invasion, and the size of the tumor deposit [54, 67]. Extracapsular invasion should be documented as this has been associated with poor prognosis [63]. Extension of tumor cells into the central portion of the SLN indicates a worse prognosis, as location within the non-subcapsular location is sensitive for additional non-sentinel nodal metastases during complete LN dissection [54, 63, 66]. In fact, micrometastases within the subcapsular region only have a non-sentinel lymph node positivity rate of 2% and a melanoma-specific survival rate of 95%, making this biology more akin to negative SLNs and clinically insignificant [68]. The Rotterdam criteria suggests that tumor burden within the SLN <0.1 mm, particularly within the subcapsular region, may predict very low likelihood of additional non-sentinel LN disease in the nodal basin [68].

Reverse transcriptase polymerase chain reaction (RT-PCR) for molecular detection of melanoma tumor markers has been evaluated as a method for identifying positive SLNs [69]. However, RT-PCR status of histologically negative SLNs has not been associated with statistically different disease recurrence and survival outcomes, suggesting that RT-PCR positivity may not provide clinically valuable prognostic information [69, 70]. As such, histologic examination using a combination of H&E and IHC remains the gold standard for SLN assessment.

Summary

- SLNB is a technique to evaluate the pathologic status of the regional nodal basin in patients diagnosed with clinically node-negative malignant melanoma. It is not performed for patients with melanoma *in situ* or those with clinically-evident nodal metastases.
- The evidence for performing SLNB is strongest for patients diagnosed with intermediate-thickness melanomas (>1.0–4.0 mm in Breslow thickness). MSLT-1 demonstrated improved disease-free survival, but no difference in melanoma-specific survival, in patients with melanoma 1.2–3.5 mm in thickness. Among patients with nodal metastases, there was improved melanoma-specific survival associated with early nodal intervention in this population.
- SLNB should also be offered to patients with thick melanomas (>4.0 mm), for which SLN status is strongly associated with disease-specific survival outcomes.
- In patients with thin melanomas <0.8 mm with high-risk features (ulceration, very high mitotic rate, lymphovascular invasion, or a combination) or those ≥0.8–1.0 mm in Breslow thickness, SLNB may be considered.
- Lymphoscintigraphy with radiolabeled colloid should be performed prior to SLNB in order to accurately identify the regional draining nodal basin. In patients with melanoma involving the head and neck, SPECT-CT may improve identification of the draining basin.
- Intradermal injection of blue dye may be used in conjunction with the radioactive tracer for SLN identification. All blue nodes, grossly abnormal nodes, or nodes with at least 10% of the *ex vivo* maximum radiotracer count of the hottest node are removed.
- For thorough pathologic evaluation, SLNs should be bivalved and serially sectioned.
- A combination of H&E and IHC are used to identify nodal metastases. Stains for S-100, HMB-45, and MART-1 are typically utilized.
- SLN specimens should be evaluated for location of the tumor deposit within the LN (subcapsular, trabecular or intraparenchymal), presence or absence of extracapsular invasion, and size of the tumor deposit.

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Chapter 8
Regional Melanoma Therapy: Positive Sentinel Lymph Node

Mark B. Faries

Case

A 68-year-old man presents to your office after biopsy of a pigmented lesion of the skin of the left temple. The biopsy revealed a melanoma that was 1.5 mm in thickness, mitotic rate of 2/mm^2, non-ulcerated. The lesion did not exhibit lymphovascular invasion. You recommend and perform a wide excision of the primary lesion together with lymphatic mapping and sentinel lymph node biopsy. You identify two sentinel lymph nodes in the pre-auricular and submandibular region. One of these demonstrates metastatic melanoma.

- *What clinical and pathologic characteristics are related to his risk of melanoma-related death?*
- *Should this patient consider completion lymph node dissection?*
- *What clinical and pathologic characteristics are related to his risk of non-sentinel node metastases.*
- *If a completion node dissection is done, what nodal areas should be included?*
- *How should this patient be followed into the future?*
- *How should this follow up be different if he forgoes completion dissection?*
- *Should he consider adjuvant radiation therapy?*
- *Should he consider adjuvant medical therapy?*

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Introduction

Lymphatic mapping with sentinel lymph node biopsy is a critical component of the initial treatment of patients with clinically-localized melanoma who are at significant risk of nodal metastasis. For patients whose lymph nodes are clear of metastasis, no further surgical therapy is required, and consideration of systemic medical therapy is generally limited. However, patients with melanoma discovered in one or more sentinel nodes are candidates for additional regional and/or systemic therapy. Management decisions in this situation are not always straightforward, but may be guided by several principals. The most appropriate therapy for any individual patient will be determined by their staging or prognostic work up, available therapeutic options, and the risks of those therapies. A thorough discussion of these factors for each patient will enable them to weigh the advantages and disadvantages of each approach and select the one that suits their situation best.

Prognostic Assessment

An individualized risk assessment for each patient with a sentinel node metastasis is essential before appropriate clinical decisions can be made. This assessment will include both clinical and pathologic variables. Since decisions need to be made regarding both the management of regional lymph nodes and the use of systemic adjuvant therapy, estimation of the risk of both regional relapse and of melanoma-related death should be done. Pathologic staging for Stage III disease now requires data derived from not only regional lymph nodes but also the primary tumor. These combinations are demonstrated in the most recent update to the American Joint Commission on Cancer (AJCC) staging system (eighth edition) [1] (see Table 8.1). Specific Stage III classifications are categorized based upon the number of involved nodes, the presence or absence of extra-nodal regional metastases (in-transit or satellite metastases) and characteristics of the primary tumor, and any substage is possible with sentinel node-detected regional metastases (see Table 8.2). Stage IIIA patients have T1a/b or T2a tumors with N1a or N1b nodal metastases. This

Table 8.1 Possible N stages (AJCC eighth edition) for sentinel node metastasis patients

N Stage	# Positive nodes[a]	Satellite/in-transit
N1a	1	None
N2a	2–3	None
N2c	1	Present
N3a	≥4	None
N3c	≥2	Present

[a]All nodal metastases clinically occult

Table 8.2 Possible pathologic stages for sentinel node metastasis patients[a]

Stage	T Stage	N Stage	5-year MSS
IIIA	T1a/b-T2a	N1a, N2a	93%
IIIB	T2b/T3a	N2c, N3a	83%
IIIC	T3b/T4a	N1a, N2a, N2c, N3a, N3c	69%
IIIC	T4b	N1a, N2a, N2c	
IIID	T4b	N3a, N3c	32%

[a]All are M0: no distant metastases

translates to primary tumors no thicker than 1 mm with ulceration or no thicker than 2 mm without ulceration and with no more than three clinically occult metastatic lymph nodes. Clearly, there is an enormous prognostic spectrum for these patients, which makes estimation of the long-term outlook an important first step in taking care of them.

Other factors may also be important in determining prognosis, such as the patients' age and gender [2, 3]. Older age and male gender are associated with worse outcomes. Risk calculators have been developed, which may add value and will likely improve in the coming years. Molecular profiling of primary melanomas is also being developed with some testing now commercially available. However, the robustness of these assays and the value they add to the current, refined staging system are yet to be fully determined.

It is important to note that all staging systems, including the current AJCC eighth edition, were developed using the complete pathologic data of not only the sentinel node, but the completion dissection specimen following full removal of the regional nodal basin [1, 4]. As discussed below, such completion dissection surgery is no longer a universally performed, so the staging information derived from the completion dissection will not be available for all patients in the future. For those patients who do not undergo dissection, the total number of positive nodes will not be known, making their definitive stage unknown. In addition, multiple retrospective series and prospective data from the second Multicenter Selective Lymphadenctomy Trial (MSLT-II), demonstrate a significant, prognostic value of non-sentinel node status, independent of the total number of positive nodes [5]. A reliable method of reproducing that prognostic discrimination without the completion dissection has not been established [6].

As noted above, all this discussion assumes the absence of detectable distant metastases. The use of radiographic imaging to confirm this absence in the setting of a positive sentinel node has been controversial. It is rare to find distant metastases on imaging at the time of a positive sentinel node biopsy. Series have reported rates of 1.9–5% true positive tests for imaging [7–9]. The rate of false positive findings, sometimes requiring biopsy to confirm, exceed true positives by a considerable amount leading to legitimate questions about the cost-effectiveness of imaging. The rate of true positive exams appears to be higher in patients with

thicker primary melanomas and more extensive sentinel node involvement, adding to the rationale for imaging in those patients. One reasonable rationale for initial imaging by contrast-enhanced CT scan after discovery of a sentinel node metastasis is to establish a baseline for future comparison.

Completion Lymph Node Dissection

Two initial clinical treatment decisions must be made for the patient with a positive sentinel node: whether to undergo additional regional therapy (surgery and/or radiation) and whether to receive adjuvant systemic medical therapy (Fig. 8.1). These two management questions are independent of each other for the most part. That is, a patient might elect not to undergo completion dissection but choose to receive systemic therapy, or vice versa. In the past, completion lymph node dissection was standard therapy for all such patients. In fact, sentinel node biopsy was initially developed solely as a means of determining who should undergo dissection [10]. However, it became evident over time that a large majority of patients with positive sentinel nodes had no additional disease detected in the completion dissection [11, 12]. In other words, most patients have all regional disease removed with the sentinel node biopsy. The utility of completion dissection was put to the test in two prospective randomized trials in which patients were randomly assigned either to standard dissection or to observation of the nodal basin and dissection if a regional nodal recurrence was detected [5, 13] (Table 8.3).

Both trials showed that early intervention with lymph node dissection did not result in any discernable difference in melanoma-specific survival or distant disease-free survival. This was in contrast to the difference in survival seen in the first Multicenter Selective Lymphadenectomy Trial (MSLT-I), which compared sentinel node biopsy with completion dissection for node positive patients to nodal observation without sentinel node biopsy [14]. In that trial, patients with intermediate-thickness melanomas who had early removal of nodal disease had a doubling of melanoma-specific survival time compared to those whose nodal disease was removed later at the time of clinical recurrence. The more recent trials evaluating CLND for node-positive patients suggest that that benefit was likely derived from removal of the sentinel node disease rather than the completion dissection. It appears that patients with non-sentinel node metastases exhibit similar biology to patients with thick primary melanomas. In those categories, some patients may be salvaged by surgery, but the timing of operative intervention does not seem to be an important consideration.

Immediate dissection does reduce the risk of regional nodal recurrence, since disease excised in the dissection never has the opportunity to become clinically apparent as a recurrence. Recurrence in the basin is still possible, but the risk is reduced by nearly 70% [5]. This reduction in nodal recurrence results in a modest, but statistically significant reduction in recurrence overall.

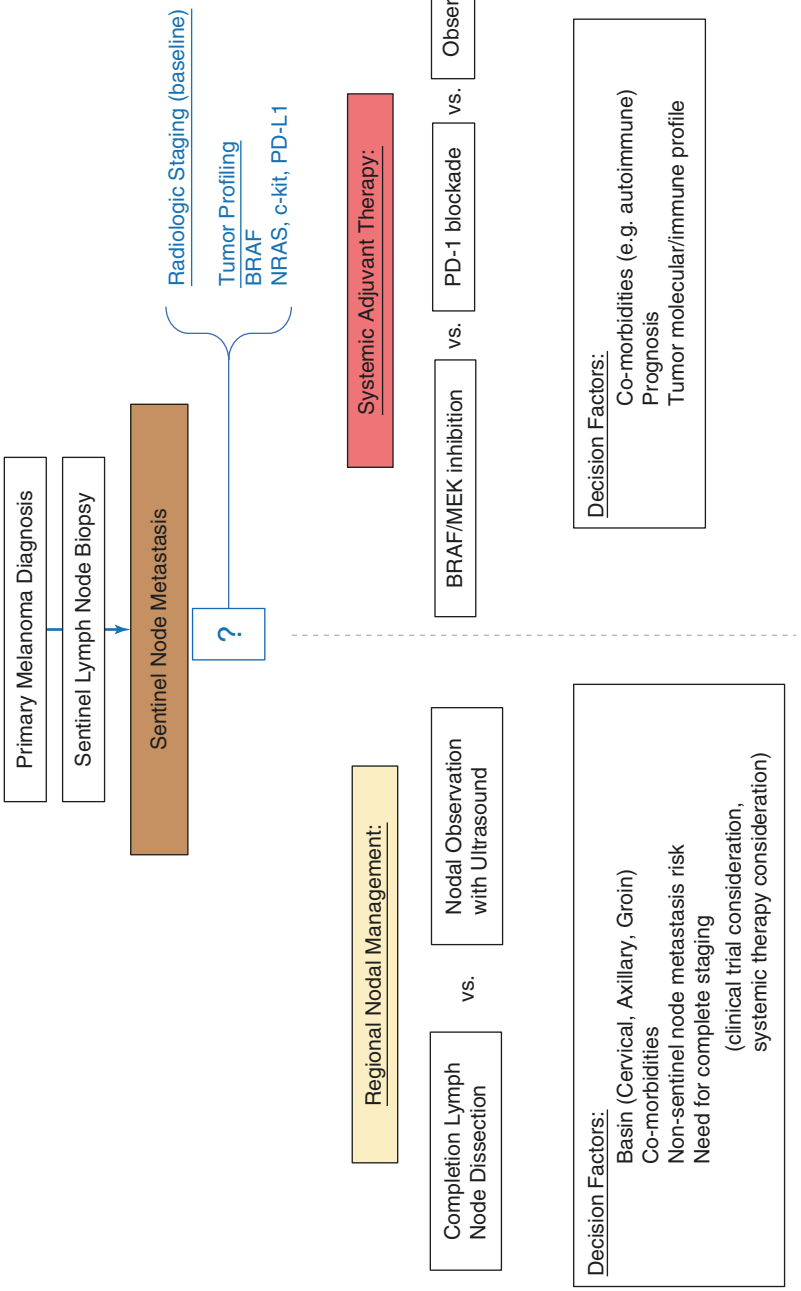

Fig. 8.1 Decision tree for patients with SLN metastasis: two, largely independent decisions are needed. One (left panel) is with regard to completion lymph node dissection. the other (right panel) is whether and which systemic adjuvant therapy to use

Table 8.3 MSLT-II and DeCOG-SLT trials

Trial	Number randomized	Primary endpoint	HR	Secondary Endpoints	Notes
DeCOG	483	DMFS	1.03 (p = 0.87)	DFS (NS) OS (NS) Nodal DFS (8% vs. 15%)	Head/neck melanoma excluded
MSLT-II	1939	MSS	1.08 (p = 0.42)	DFS (p = 0.04) OS (NS) DMFS (NS) Nodal DFS (HR 0.31, p < 0.001)	

DeCOG-SLT German Cooperative Oncology Group selective lymphadenectomy trial, *MSLT-II* second multicenter selective lymphadenectomy trial, *HR* hazard ratio, *DMFS* distant metastasis-free survival, *MSS* melanoma-specific survival, *DFS* disease-free survival

If completion node dissection is pursued, a thorough dissection of the basin is indicated. In the head and neck region, a full, modified radical neck dissection should be performed. For primary melanomas of the forehead or anterior scalp, a superficial parotidectomy should also be considered, given the potential for parotid drainage from those areas. Because the location of the primary melanoma may vary considerably, selective dissection of limited nodal stations in the neck should be avoided. In the axilla, typically level III nodes are removed in addition to levels I and II. In the inguinal region, a dissection of the superficial (femoral) nodes is performed. With the exception of radiographic evidence of pelvic nodal metastases, indications for inclusion of the deep (pelvic) nodes in the completion surgery are not uniform among melanoma centers. Factors include number of positive superficial nodes (three or more), metastasis in Cloquet's node, and pelvic drainage on the pre-sentinel node lymphoscintigram [15, 16].

Although there are apparent staging and regional recurrence benefits to immediate dissection, there is a cost as well, which includes the short and long-term morbidity associated with the procedure. These toxicities vary based on the involved basin, but include infection, bleeding, wound healing problems, seroma, nerve injury and lymphedema [17, 18] (Fig. 8.2). The lowest risk in general is with the cervical basin. In that area, any long-term toxicity would be most likely related to nerve injury. Some numbness is to be expected in the lateral neck and supraclavicular region, though this is seldom clinically significant. However, injury to motor nerves including the spinal accessor and facial nerve branches may occur, and that risk must be considered.

Axillary dissection is intermediate in most toxicity risks. Though injury to the long thoracic or thoracodorsal nerves is possible, it should be quite rare. Lymphedema is a significant concern for the arm, though it occurs only in a minority of patients. Reported rates of lymphedema vary greatly across series, most likely related to the intensity of the assessment of the morbidity. However, overall rates appear to be

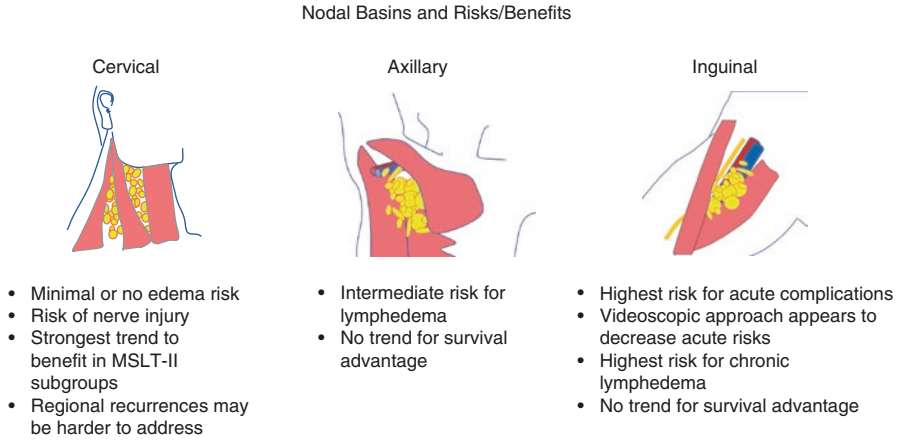

Fig. 8.2 Variation in risks and advantages of complete lymph node dissection in the major lymph node basins

significantly less than those seen in breast cancer with dissection, though the reason for this difference is not entirely clear [19]. Inguinal dissection is the most difficult basin with regard to morbidity. Both acute and chronic morbidities have been reported as fairly common in numerous series. Relatively recently, a minimally-invasive, videoscopic approach has become more commonly used [20]. This technique appears to result in much lower rates of acute complications. The effect of this advance on chronic toxicity, particularly lymphedema is yet to be determined.

An estimation of the risk of additional, non-sentinel lymph node metastases is critically important to patients deciding whether to have additional surgery. Several attempts have been made to be able to predict non-sentinel node metastases [12, 21–26]. These schemes have generally included primary tumor characteristics (particularly tumor thickness) and the amount of disease found in the sentinel node(s). However, there has been generally little consistency in the final predictive models and validation of any particular model has been difficult. In addition, it appears that models that rely on detection of non-sentinel node metastases by standard pathology techniques will miss a considerable portion of involvement of the residual basin. When immunohistochemistry is applied to non-sentinel nodes, approximately 10% more patients are found to have metastases [21]. This is a similar percentage to the excess of non-sentinel node metastases seen in the observation arm of MSLT-II when compared to the immediate dissection arm [5].

Overall, each patient will need to weigh the risks and benefits of the additional surgery. As prognostic models improve, the staging information derived from the total number of positive nodes and non-sentinel lymph node status may be able to be reproduced through other sources, which will diminish further the rationale for completion dissection.

Clinical Follow Up

Regardless of the decision a patient makes regarding additional nodal surgery, patients with positive sentinel nodes are at substantially increased risk of subsequent recurrence and require close clinical follow up. There is not consensus, though, about the frequency and modalities to be used in routine clinical follow up. For patients who are Stage IIIA, there is a very low probability of a true positive finding on initial radiographic imaging. However, baseline imaging may be performed in order to facilitate subsequent comparison, for example in the setting of subcentimeter pulmonary or hepatic nodules. Current recommendations are to consider baseline imaging for sentinel node positive patients who are Stage IIIA and to perform it in patients who are Stage IIIB or higher [27]. Baseline imaging may be most useful when anatomic (e.g. CT scan) rather than functional imaging (e.g. PET) is used.

Later follow up imaging protocols also vary among centers. In principle, the intensity and frequency of imaging should be tailored to suit an individual's disease characteristics. For patients who elect not to have completion dissection surgery, ultrasound of the at-risk nodal basin is indicated to replicate the conditions of randomized trials demonstrating the safety of active surveillance. In addition, imaging should be used as needed to investigate new or unexplained symptoms that might be indicators of recurrence. MRI is the most sensitive study to evaluate the brain and should be used for that purpose when possible. In patients who are unable to undergo MRI, contrast enhanced CT may be used, though the sensitivity of that modality will be lower.

Adjuvant Therapy

Radiation Therapy

Radiation is another local modality with some similarities to surgery. It can treat a larger amount of tissue than can be practically removed at operation. Although melanoma has traditionally been felt to be a "radio-resistant" tumor, there is good evidence that radiation can be effective in reducing or eliminating microscopic residual disease. A prospective, multicenter clinical trial has evaluated the value of radiation to regional nodal basins after dissection for nodal metastases [28]. Patients were eligible for the trial if they had a single positive parotid node, two positive cervical or axillary nodes or three positive inguinal nodes. The trial demonstrated a clear reduction in the risk of subsequent recurrence in the nodal basin, but did not demonstrate a significant reduction in the overall risk of recurrence and absolutely no indication of benefit for disease-specific or overall survival. For this reason, it is relatively unusual to recommend radiation as an adjuvant after sentinel node biopsy.

Medical Therapy

Adjuvant treatment with medical therapy has been a long-standing area of controversy in melanoma. However, recent advances in the available treatments have led to less controversy with improvements in the efficacy and toxicity profile of current agents. This area continues to rapidly evolve as new drugs and combinations demonstrate activity in the more advanced, metastatic setting are brought to evaluation as adjuvants.

Principles of adjuvant therapy include an estimation of recurrence and mortality risk, predictive tumor biomarkers, and patient comorbidities and preferences. The first approved adjuvant medical therapy was interferon-α. High and low-dose regimens were evaluated in clinical trials and the high-dose regimen was approved in the United States in 1997. The balance of efficacy and toxicity for this agent was not optimal and many eligible patients elected not to pursue this treatment. There was clear and reproducible improvement in disease-free survival with interferon-α, but the impact on overall survival was harder to consistently show [29]. Meta-analyses found a small benefit for overall survival, but this was balanced by common and significant side effects [30]. Subsequently a pegylated formulation of the agent was also approved with a similar pattern of disease-free survival benefit without convincing overall survival improvement. Some studies found ulceration of the primary tumor to be a predictive biomarker correlated with survival benefit to interferon, but agents with substantially improved risk/benefit ratios became available shortly after the availability of pegylated interferon, reducing its appeal [31].

These new agents include checkpoint inhibitors and targeted therapies. Immune checkpoints are regulatory mechanisms within the immune system, present to prevent overactivity of the immune system and/or autoimmunity. Checkpoint blockade removes one or more of these brakes on immune activity, enabling greater immune recognition of tumor cells. These drugs first demonstrated significant activity in the metastatic setting [32, 33]. Though response rates are not generally high, durable responses and durable stable disease do occur, resulting in long-term survival among a significant number of patients whose prognosis was previously very limited. The two checkpoints that have been targeted with approved adjuvant therapies are the cytotoxic T-lymphocyte antigen-4 (CTLA-4) and the programed death-1 (PD-1)/programmed death ligand-1 (PD-L1) proteins. Both agents have demonstrated clinical activity in the adjuvant setting as well [34–36]. There are clear disease-free survival benefits to both drugs, suggesting a strong likelihood of an overall survival advantage as well. Side effects are autoimmune toxicities, which can vary considerably. Serious and even fatal toxic reactions have been reported. Most toxicities are reversible with adequate management, though some toxicities such as endocrinopathies may be permanent. Comparing the two immune targets, it appears targeting PD-1 results in better response with less toxicity than CTLA-4 blockade, making PD-1 blockade the treatment of choice [36].

For patients whose melanomas have mutations in the BRAF gene, targeted therapies with small molecule agents designed to interfere with the mutant protein and its

signaling pathway have also demonstrated utility as adjuvants. The most effective strategy combines inhibition of mutant BRAF and of MEK. This has demonstrated improvement in both disease-free and overall survival in a prospective clinical trial [37]. The combination of BRAF and MEK inhibition seem to be associated with less toxicity than BRAF inhibition alone, strengthening the rationale for the combination even further. Common side effects include fever and fatigue as well as mild nausea and headache. These are uniformly reversible upon stopping the drugs.

The trials that led to approval of these agents included higher risk patients. For anti-PD-1 therapy, only Stage IIIB (AJCC v7) or higher patients were eligible. For the BRAF/MEK combination patients with IIIA (AJCC v7) disease were allowed, but only if their sentinel node disease burden was >1 mm in largest dimension. This means there is no directly applicable clinical experience with these drugs in many current Stage III melanoma patients who have low volume nodal disease. The data that are available suggest the proportional benefits will be similar in these lower-risk groups, but the absolute benefit will likely be quite small for many. For such patients, optimal risk-stratification, possibly including the pathologic status of non-sentinel nodes, will be important for treatment planning.

Conclusion

Overall, in the modern era, most Stage III melanoma patients are diagnosed by sentinel lymph node biopsy. Our understanding of the disease in these patients had improved considerably in recent years as have our options for non-surgical therapy. The most likely areas for improvements into the future include increasingly accurate prognostic assessments using more detailed pathologic and molecular data, and application of more efficacious or less toxic medical treatments based upon coming improvements developed for more advanced metastatic situations. Significant optimism appears justified.

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Chapter 9
Regional Therapies: Clinically-Apparent Nodal Disease

Nabil Wasif

Case

A 58 year old man is referred to your clinic by his dermatologist. He was seen for a lesion on his left lower extremity calf area that was noticed by his spouse to become larger and discolored. Shave biopsy was performed and read out as a 3.5 mm, Clark IV, ulcerated (T3b) nodular melanoma extending to the base of the biopsy. On clinical exam the patient has a healing shave biopsy site in the middle of his posterior left calf. Palpation of the popliteal fossa is normal but he has a palpable lymph node measuring 2 cm in his left groin.

- *How commonly does cutaneous melanoma present with synchronous lymph node metastases?*
- *What is the appropriate initial diagnostic work-up?*
- *Is systemic staging indicated and if so what test(s)?*
- *What should be the initial management of this patient?*
- *What is the optimal technique for regional nodal dissection?*
- *Have there been any surgical advances in surgical lymphadenectomies?*
- *Is there any role for adjuvant radiation therapy?*
- *Is there any role for adjuvant systemic therapy?*

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Epidemiology

In the United States, it is estimated that 84% of patients with melanoma will have localized disease, 9% regional disease and 4% distant metastatic disease at the time of presentation [1]. Overall the incidence of melanoma is increasing at a rate of 33% for men and 23% for women from 2002 to 2006 [2]. Patients presenting with clinically-apparent disease will likely remain a distinct subset of the population with the potential to increase in number not only due to an increased incidence overall but also in response to the results of the second Multicenter Selective Lymphadenectomy Trial (MSLT-2) [3]. As has been detailed elsewhere, the results of this trial did not show a survival advantage in patients who underwent immediate lymphadenectomy compared to those who underwent observation following a positive SLNB. This is likely to result in a greater proportion of patients with a positive SLNB opting for surveillance and a potential increase in delayed presentation of clinically apparent nodal disease referred for salvage lymphadenectomy.

Diagnosis

Tissue diagnosis of regional disease is recommended prior to commencing therapy. The least invasive way to do this while maintaining high diagnostic accuracy is via fine needle aspiration guided by physical examination or under image guidance. In experienced hands the sensitivity and specificity of FNA biopsy is 97% and 99% respectively [4, 5]. Alternatives are core biopsy or excisional biopsy. Excisional biopsy for diagnosis is discouraged as it is often performed with improper orientation of the incision. In patients without an antecedent history of melanoma or a melanoma of unknown primary an excisional biopsy may be appropriate, but should be performed with consideration to the need for further surgical intervention.

Staging

Once regional disease is confirmed, systemic staging is recommended to rule out distant metastases. Asymptomatic patients with clinically positive nodes have a 4–16% yield of routine cross-sectional imaging [6–8]. However, this must be weighed against the 8–22% rate of indeterminate or false positive findings [6, 7]. Current evidence suggests that PET/CT may be the most effective imaging modality in this setting, with sensitivity ranging from 68% to 87% and specificity 92% to 98% [9]. Additional information provided by PET/CT may result in changes in management of upto 30% of patients [10, 11]. Although these changes were

traditionally mostly surgical, they may now also influence medical management decisions such as enrollment in neo-adjuvant trials. Even if no additional disease is found, a baseline study serves as a frame of reference in these patients who are at risk for subsequent development of metastases. In patients with Stage IIIC disease a brain MRI is recommended, even for asymptomatic patients, mainly due to the 11% risk of CNS disease [12]. Early detection of brain metastases is important as treatment outcomes are improved in patients with lower CNS tumor burden or asymptomatic disease.

Management

Wide local excision of the primary lesion and resection of the regional nodal basin in the form of a surgical lymphadenectomy is recommended for the following reasons. Firstly, to remove all clinically apparent and occult disease in the regional nodal basin. Secondly, to appropriately stage and risk stratify the patient. A third reason that may become more important with personalized therapy is to obtain an adequate amount of tissue for biobanking and gene sequencing. In the rare patient with loco-regional disease that is advanced enough to be unresectable upfront, consideration should be given to enrollment in a clinical trial of neo-adjuvant therapy. The surgical technique and anatomic boundaries for lymphadenectomy depend on the site of regional involvement.

Cervical Lymphadenectomy

Involvement of the cervical nodes can be from a primary melanoma of the head and neck or upper truck/shoulders. The standard recommendation to perform a modified neck dissection involving removal of lymph nodes in levels II, III, IV and V while preserving the spinal accessory nerve, the sternocleidomastoid muscle (SCM) and the internal jugular vein. Level I lymph nodes should be included in dissections resulting from primary melanomas located on the frontal scalp or face. In the rare case of a palpable parotid lymph node a concurrent superficial parotidectomy should be performed. Parotidectomy may also be considered in patients with melanomas of the anterior scalp or upper face. Direct involvement of motor nerves is uncommon except in cases of desmoplastic melanoma, and branches of this important nerve can generally be salvaged during dissections. Some branches of the cervical sensory plexus are typically removed with the specimen. The greater auricular nerve should be preserved if possible, as sensory deficits on the ear may be more noticeable to patients.

Figure: (The Neck Dissection Manual, Thurnher et al. or Color Atlas of Head and Neck Surgery, p. 172, Dubey et al.)

Axillary Lymphadenectomy

The operative technique of axillary dissection is familiar to most general surgeons, since it is used frequently in the treatment of axillary breast cancer metastases . Unlike breast cancer, in which level I and II nodes are dissected, in melanoma levels I, II and III should all be included. Level I lymph nodes lie in the low axilla lateral to the pectoralis minor muscle, Level II lymph nodes lie beneath or posterior to the pectoralis minor muscle and also include Rotter's or inter-pectoral lymph nodes, and Level III lymph nodes lie in the high axilla medial to the pectoralis minor muscle.

Care should be taken to preserve the long thoracic and the thoracodorsal nerves. Typically in the case of palpable disease, branches of the intercostobrachial nerves will be sacrificed with the specimen. This results in areas of numbness on the posterior upper arm but should not result in any significant functional consequence.

During the procedure the ipsilateral arm should be prepped into the field to allow manipulation during the procedure. Primarily this includes anterior extension of the arm, which allows greater anterior mobilization of the pectoralis muscles and improved access to the medial portions of the basin.

Figure: (Chassins Operative Strategy in General Surgery Axillary Dissection, p. 1029.)

Superficial and Deep Groin Lymphadenectomy

The superficial inguinal basin includes lymph nodes located in the femoral triangle, bounded by the sartirous laterally, the inguinal ligament superiorly and the adductor muscles medially. In addition, soft tissue and nodes located superior within 5 cm superior to the inguinal ligament should be included in the dissection. The femoral vessels should be skeletonized and preserved during the dissection. The saphenous vein may be preserved if such preservation will not compromise the completeness of the procedure.

Practice regarding inclusion of the deep or pelvic portion of the basin (i.e. ilioinguinal groin dissection) varies among centers, but the presence of bulky or clinically-apparent disease in the superficial basin has been used as a selection criterion in many instances. This may be performed by dividing the inguinal ligament to reach the deep nodes in continuity, or by approaching the nodes through a separate retroperitoneal approach through the anterior abdominal musculature, preserving the ligament. The deep dissection involves skeletonization of the external iliac vessels up to the bifurcation of the common iliacs and dissection of the obturator nodes overlying the obturator nerve and vessels. Both the obturator nerve in the pelvis and the motor components of the femoral nerve in the superficial groin should be preserved. Some sensory branches of the femoral nerve may be included in the dissection specimen.

Figure: (Atlas of Operative Procedures in Surgical Oncology, Karakousis, p. 237.)

Adequacy of Lymphadenectomy

In contrast to lymphadenectomies in other parts of the body, there is no consensus on the minimum number of lymph nodes for each basin. This is likely because the number may vary according to the nodal basin of interest and the exact technique used. More important than the absolute number of nodes evaluated on pathology are the anatomic boundaries of the dissection and the thoroughness of the removal of soft tissues within those boundaries. The operative report of any lymphadenectomy should clearly describe the boundaries of the dissection so as to enable an assessment of completeness to be made. A separate issue to be considered is whether the extent of dissection can be modified safely according to the underlying indication, i.e. for a positive SLNB, for a palpable node, or for bulky nodal disease in the setting of metastatic disease [13–16]. There is little data to guide decision making in these situations, and in general a complete dissection is recommended.

Morbidity of Lymphadenectomy

Morbidity from regional lymphadenectomy ranges from 20% to 40% and consists mainly of lymphedema, wound healing issues, seromas and infections [17, 18]. Both short and long term sequelae of nodal dissection are seen. The frequency of these morbidities varies a great deal with the basin site and occur most commonly with groin dissections. Several modifications have been attempted to reduce some of the morbidity associated with groin dissection. In particular saphenous vein preservation and minimally invasive techniques.

Minimally Invasive Lymphadenectomy

In an effort to reduce the particularly high morbidity associated with groin dissections a minimally invasive technique for groin lymphadenectomy was developed [16, 19]. The procedure involves the use of videoscopic techniques and three ports placed inferior to the femoral triangle on the thigh. The minimally invasive technique is contraindicated in the setting of tumor involvement of the skin but can be performed for other micrometastases. Following a formalized training program for surgeons this technique has been shown to decrease the incidence of serious short-term complications and can be performed with a reproducible and standardized technique. The approach also leads to removal and pathologic assessment of similar numbers of lymph nodes to the open approach. An online video for the technique is available at: http://medprofvideos.mayoclinic.org/videos/minimally-invasive-inguinal-lymph-node-dissection-milnd

Adjuvant Systemic Therapy

Interferon-α was the first systemic adjuvant therapy approved for melanoma, followed by pegylated interferon-α [20]. However, these treatments provided modest clinical benefits at the cost of significant toxicity. The development of modern immune and targeted therapies has now supplanted interferon in this setting. The cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibitor ipilimumab first demonstrated clinical efficacy in the metastatic and then the adjuvant setting [21–23]. This was followed by the programmed death 1 (PD-1) inhibitors, which not only demonstrated efficacy in the metastatic and adjuvant setting but also were less toxic than CTLA-4 inhibitors. Finally, for the 40–60% of patients with mutation in the BRAF gene, targeted therapy with BRAF inhibitors, with concurrent MEK inhibition, is an approved adjuvant therapy option having demonstrated relapse-free and overall survival benefits. It is important to note that patients with palpable lymph nodes are distinct from those with microscopic disease identified on SLNB, although both are classified as Stage III disease. Although there is some debate as to the risk/benefit ratio of adjuvant therapy for Stage IIIA melanoma, most physicians would agree that Stage IIIB and higher patients constitute a high risk subset that should undergo therapy.

Radiation Therapy

In patients at high risk of nodal relapse following regional lymphadenectomy, radiation therapy has been used as an adjunct to affect regional control. Retrospective analyses of the utility of radiation in this setting were somewhat contradictory, which is not surprising given the strong potential for selection bias for radiation among high-risk patients. A prospective, randomized trial was undertaken to better address this issue. This trial demonstrated a clear reduction in the risk of in-basin failure among radiated patients but did not suggest any overall survival benefit [24]. The improvements in regional disease control came at the cost of increased morbidity. Eligible patients included those with ≥1 parotid, ≥2 cervical or axillary or ≥3 groin positive lymph nodes, maximum nodal diameters ≥3 cm in the neck and ≥4 cm in the axilla or groin, or extracapsular extension. Patients were randomized following lymphadenectomy to either adjuvant radiation (48 Gy delivered in 20 fractions) or observation. Regional nodal recurrence was significantly decreased in the adjuvant radiation group after a mean follow up of 73 months (HR 0.54, 95% CI 0.33–0.89). There were no differences in recurrence-free survival or overall survival among the two groups. The rate of grade 2–4 toxicities in the adjuvant radiation group was 74% and consisted primarily of wound healing issues, pain and joint stiffness.

Outcomes

Patients with clinically positive nodes are staged as having IIIB or higher disease in the eighth edition of the AJCC staging for melanoma. Prognostic factors in these patients include the number of positive nodes, extranodal extension, primary tumor ulceration and patient age [25–28]. The 5-year survival rate for patients with Stage IIIB, IIIC and IIID disease are 83%, 69% and 32% respectively although this is likely to improve as the effect of the introduction of adjuvant therapies over the last 5 years becomes evident.

Surveillance

Recommendations for surveillance are based on retrospective reviews and expert consensus and should be tailored to each patient's risk of recurrence. It is also important to note that the most frequent mode of recurrence detection is by patient self-report [29].

Following completion of treatment, patients should undergo a history and physical (with emphasis on nodes and skin) every 3–6 months for the 2 years, followed by every 3–12 months for 3 years. After 3 years annual surveillance exam should be conducted. Surveillance imaging in the form of a chest X-ray, CT, brain MRI and/or PET/CT every 3–12 months could be considered to screen for recurrent disease at the discretion of the physician and should be directed by the conditional probability of recurrence and symptoms. Due to the fact that most recurrences manifest in the first 3 years, routine imaging for asymptomatic recurrence is not recommended after 3–5 years.

Future Directions

As the focus shifts from adjuvant to neo-adjuvant therapy for loco-regionally advanced melanoma, multi-modality management of patients with clinically apparent nodal disease at presentation is also likely to change. Pilot studies have been and continue to be conducted in Stage III melanoma. These include trials of immune therapy, targeted therapy and intralesional therapy with oncolytics. If trials currently underway demonstrate efficacy for neo-adjuvant therapy then treatment sequencing will shift towards systemic therapy first followed by surgery, as seen in management of loco-regionally advanced breast cancer. With more effective systemic therapy available for use in the neoadjuvant setting it is not inconceivable that complete eradication of nodal disease with medical therapy may lead to trials of observation

versus surgery, similar to the 'watchful waiting' approach for rectal cancer. However, for the foreseeable future the role of surgical lymphadenectomy remains central in the management of clinically apparent nodal disease in patients with a newly diagnosed cutaneous melanoma.

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Chapter 10
Surgery for Stage IV Melanoma

Norman G. Nicolson and Dale Han

Learning Objectives

1. To understand the prognosis of patients with stage IV melanoma in the era of effective systemic therapies.
2. To understand the indications for surgery in stage IV melanoma patients.
3. To understand which patients with stage IV melanoma may potentially benefit from surgery and the appropriate selection of stage IV melanoma patients for metastasectomy.
4. To understand the role of non-surgical interventions in the management of stage IV melanoma.

Clinical Case

A 66-year-old woman presents to your office for discussion of her options for metastatic melanoma. She is now 3 years status post wide local excision and therapeutic lymph node dissection for a thick melanoma on the left upper extremity with palpable left axillary nodal disease. She was treated with adjuvant ipilimumab for 2 years, with no treatment-related side effects. She recently had routine surveillance imaging which revealed a mass lesion in the descending colon (Fig. 10.1). She

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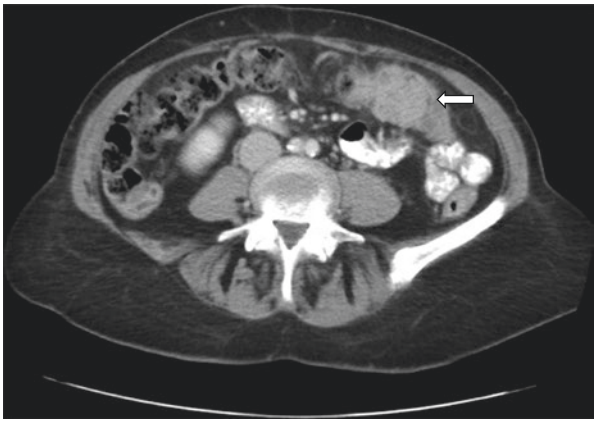

Fig. 10.1 Clinical case: colon mass. Staging CT scan demonstrates a 3.7 cm solid lesion in the distal transverse colon, as shown by the arrow, which is new compared with the patient's prior CT scan 6 months earlier

underwent colonoscopy with polypectomy, which confirmed metastatic melanoma. Imaging with whole-body PET/CT and brain MRI revealed no other suspicious sites of disease, and she is asymptomatic.

- Is the patient a candidate for colectomy for metastatic disease?
- Will metastasectomy improve her survival?
- What are the indications for metastasectomy in patients with melanoma?
- Should she undergo additional systemic therapy before or after surgery?

Introduction

Melanoma is the most common cause of skin cancer-related death in the United States [1]. Approximately 4% of all melanoma cases are diagnosed as stage IV at presentation, but an additional 20% of all patients with localized melanoma will eventually develop distant metastatic recurrences, and the rate varies considerably depending on the initial stage of the disease [2, 3]. According to the AJCC eighth edition staging system, stage IV melanoma is categorized as M1a (distant skin, soft tissue, or lymph node metastasis), M1b (lung metastasis), M1c (other visceral organ metastasis aside from central nervous system), or M1d disease (central nervous system metastasis) [4]. Patients with metastases in multiple categories, are staged according to the most advanced site. Additionally, each M category is subdivided on the basis of whether or not LDH is elevated [4].

Prior to the introduction of current systemic therapies, the median survival of stage IV melanoma patients was only 6–10 months while 5-year survival was approximately 5% [5]. Given the poor prognosis of stage IV melanoma patients and the lack of effective systemic therapies, the use of surgery in patients with distant metastases was relatively limited in the past. Even patients with oligometastatic disease that was amenable to resection were felt to have a high risk of harboring

other sites of occult metastases. The risk for disease progression soon after surgery, along with the lack of effective systemic approaches, were thought to limit the potential benefit of surgery in this population.

However, over the past decade, the increased availability of newer effective systemic treatments, including targeted therapies and immunotherapy, has radically changed the outlook for patients with stage IV melanoma. More of these patients are now potentially becoming candidates for surgery, but not all patients with distant metastatic melanoma will benefit from metastasectomy [6, 7]. Careful patient selection is crucial in order to provide the greatest benefit while minimizing risks. In this chapter, we will examine the potential indications for surgery for stage IV melanoma patients, present prognostic factors for appropriately selecting patients for metastasectomy, and review the available evidence for these treatments.

Evolution of Surgical and Systemic Therapy for Stage IV Melanoma

Historically, the mainstay of treatment for metastatic melanoma was cytotoxic chemotherapy. However, response rates to dacarbazine or temozolomide-based regimens were generally disappointing. Response rates were approximately 10–20%, and most responses were short lived at <6 months [8]. In the absence of any other useful systemic treatments, these agents remained standard of care. The addition of some early immune-modulating agents, such as interleukin-2, used by itself or in combination with chemotherapy (biochemotherapy), provided the first evidence for durable responses using immune-based therapies [9]. However, survival was not improved with these therapies and toxicity was relatively high.

During this earlier era of systemic therapy, surgical treatment of metastatic melanoma was viewed cautiously, but was seen as the only curative option for eligible and appropriately selected patients given the limited efficacy of available systemic agents [10]. Earlier studies on metastasectomy for melanoma reported 5-year overall survival (OS) that varied widely (5–40%), although most studies demonstrated 5-year OS in the range of 15–30% (Table 10.1). These studies suggested that some patients with stage IV melanoma could benefit from metastasectomy, but it should be noted that these patients represented a highly selected population [11–35]. Importantly, in this era, the median survival for patients treated with systemic therapies was approximately 6–12 months, while survival of surgically treated patients appeared to be better in most studies evaluating metastasectomy at that time, with several reporting median survival as long as 20–40 months [11, 28, 30, 36]. However, the true benefit of surgery in these patients was difficult to establish, as most of these early studies were retrospective case series and were subject to significant selection bias.

Subsequently, data from Multicenter Selective Lymphadenectomy Trial (MSLT)-I further supported the idea that select patients had improved survival after

Table 10.1 Historical studies evaluating metastasectomy for melanoma [5]

Study	# of surgical patients	5-Year overall survival (OS)	M-stage of surgically treated patients
Markowitz et al. (1991) [11]	72	38%	M1a
Gadd and Coit (1992) [12]	23	22%	M1a
Barth et al. (1995) [13]	281	14%	M1a
Eton et al. (1998) [14]	57	5%	M1a
Meyer et al. (2000) [15]	75	18–20%	M1a
Karp et al. (1990) [16]	22	4.5%	M1b
Gorenstein et al. (1991) [17]	54	25%	M1b
Harpole et al. (1992) [18]	98	20%	M1b
Karakousis et al. (1994) [19]	39	14%	M1b
Tafra et al. (1995) [20]	106	27%	M1b
La Hei et al. (1996) [21]	83	22%	M1b
Ollila et al. (1998) [22]	45	16%	M1b
Meyer et al. (2000) [15]	83	10–15%	M1b
Leo et al. (2000) [23]	282	22%	M1b
Andrews et al. (2006) [24]	86	33%	M1b
Petersen et al. (2007) [25]	249	21%	M1b
Neuman et al. (2007) [26]	26	29%	M1b
Ricaniadis et al. (1995) [27]	23	28%	M1c
Ollila et al. (1996) [28]	46	41%	M1c
Haigh et al. (1999) [29]	27	Median OS: 26 months	M1c
Agrawal et al. (1999) [30]	19	38%	M1c
Wood et al. (2001) [31]	60	24%	M1c
Rose et al. (2001) [32]	24	29%	M1c
Collinson et al. (2008) [33]	23	2-year OS: 39%	M1c (adrenal)
Reddy and Wolfgang (2009) [34]	11	27%	M1c (pancreas)
Fife et al. (2004) [35]	205	Median OS: 9 months	M1d

M1a: Distant skin, soft tissue, lymph node metastasis; M1b: Pulmonary metastasis; M1c: Gastrointestinal/adrenal metastasis; M1d: Central nervous system metastasis

Table 10.2 Contemporary studies of metastasectomy for melanoma

Study	# of surgical patients	Overall survival	Systemic therapy utilized[a]
Sosman et al. (2011) [10]	77	4-year: 31%	Mixed[b], varying agents
Howard et al. (2012) [37]	161	4-year: 21%	Mixed[b], varying agents
Faries et al. (2014) (liver) [42]	58	5-year: 30%	Mixed[c], including CPI and targeted therapy
Deutsch et al. (2017) [43]	392	Median: 18 months	Mixed[c], including CPI and targeted therapy
Klemen et al. (2017) [71]	26	5-year: 57%	Adoptive cell transfer
Faries et al. (2017) [38]	303	5-year: 43%	Vaccine trial
Hanna et al. (2018) (pulmonary) [72]	99	5-year: 21%	Mixed[c], including CPI and targeted therapy
Smith et al. (2018) (modern era cohort) [45]	69	Median: 16 months	Mixed, including CPI and targeted therapy
Bello et al. (2019) [46]	237	Median: 21 months	All treated with CPI therapy

CPI checkpoint inhibitor

[a]Modern systemic therapy includes checkpoint inhibitor treatment with anti-PD-1 and/or anti-CTLA-4 agents and targeted therapy using BRAF and MEK inhibitors

[b]Checkpoint inhibitors and targeted agents were not in routine use but received by some patients on clinical trial. Routine systemic therapies included interferon, IL-2, vaccine therapy, chemotherapy, or biochemotherapy

[c]Includes patients from before and after the era of modern systemic therapies

metastasectomy (Table 10.2). Patients from MSLT-I who developed distant metastases were evaluated, and the 4-year survival was significantly improved at 20.8% for patients treated with metastasectomy compared with only 7% for patients treated with medical therapy alone [37]. The MMAIT-IV clinical trial also reported high 5-year OS in surgically treated stage IV melanoma patients. In this phase III trial, stage IV melanoma patients had complete resection of up to five distant metastatic sites and were then treated with either adjuvant BCG with Canvaxin or BCG with placebo. There was no difference in survival with the addition of Canvaxin, but 5-year OS was over 40% in both surgically treated arms [38].

The last decade has seen dramatic changes in the prognosis of patients with metastatic melanoma as a result of the development of much more efficacious systemic therapies. A detailed review of these agents is beyond the scope of this chapter, but, for example, treatment with checkpoint inhibitor (CPI) agents has revolutionized the care of patients with advanced melanoma. The seminal trial of combination CPI therapy reported overall response rates of 40–60%, with complete responses seen in 10–20% of patients, many of whom experienced durable responses [39]. Similarly, combination targeted therapy using *BRAF* and *MEK* inhibitors have also shown high response rates, although many tumors eventually become resistant to treatment, and responses are generally less durable than those seen after CPI treatments [40, 41].

As these new systemic therapy options improve the outcomes of patients with distant metastatic melanoma, additional consideration has been given to the role of

surgery in stage IV disease. Studies are now starting to show that survival of stage IV melanoma patients can be dramatically improved in select patients who are treated with both these newer systemic therapies and surgery (Table 10.2) [10, 37, 38, 42–46]. For instance, the Royal Marsden Melanoma Unit published their experience in melanoma metastasectomy before (2003–2007) and after (2011–2015) the era of effective systemic therapy (EST). In this study, patients had significantly improved survival after metastasectomy in the after EST era versus before the EST timeframe (median: 16 vs. 6 months, $p < 0.001$), and more operations in the after EST era were done for curative intent [45]. Furthermore, a study from Memorial Sloan Kettering Cancer Center evaluated patients with stage III or IV melanoma who were treated with CPI therapy and surgery. Approximately 88% of patients had stage IV disease, and the majority of patients were treated with anti-CTLA-4 alone (62%) [46]. Patients who were resected to no evidence of disease (NED) had a 5-year survival of 75%, while resection of a stable or responding lesion resulted in a 5-year OS of 90%. Even resection of one progressing site was associated with a 5-year OS of 60%, but surgery in patients with multifocal progressive disease was associated with poor outcomes. However, even in the contemporary era, studies of metastasectomy for melanoma have shown some conflicting results and selection bias [47]. For instance, in the largest series on abdominal melanoma metastases, the timeframe of treatment did not significantly affect survival, although a cut-point of 2003 was used which was prior to the introduction of most ESTs. Of note, treatment with metastasectomy was still significantly correlated with improved OS, particularly for patients with gastrointestinal tract metastases [43].

As systemic treatments improve in melanoma, more patients who would once have been considered to have unresectable disease are becoming potential candidates for metastasectomy. Furthermore, the availability of ESTs provides a means to treat occult metastases and thereby determine which cases have tumor biology favorable for metastasectomy. These developments allow for better selection of patients who are most likely to benefit. In addition, the role for metastasectomy is expanding. For instance, surgery for stage IV melanoma can be used for resection of isolated non-responding lesions in a patient with additional metastases but overall disease control using other therapies (e.g. EST), or for consolidation of remaining disease after a favorable response to ESTs [42, 48]. Also, the scope of patients considered for palliative procedures has broadened, as the life expectancy of even patients experiencing modest benefit from systemic therapies make such interventions more worthwhile in terms of risk and benefit.

Patient Selection for Metastasectomy

A multi-disciplinary approach in managing stage IV melanoma patients is crucial given the complex treatment considerations in this population. In considering metastasectomy for a patient with stage IV disease, patient selection is key. Although there are no perfect prediction systems, some general principles will help to determine which patients are most likely to benefit from metastasectomy (Fig. 10.2).

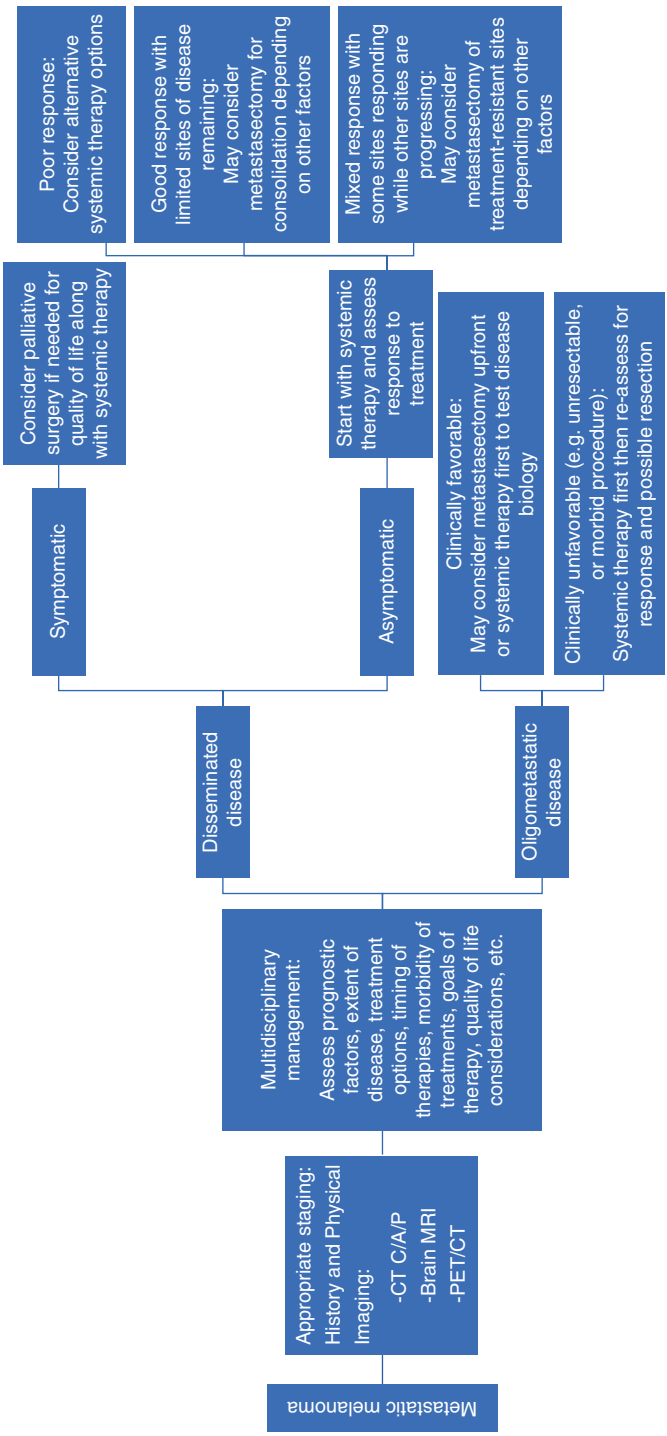

Fig. 10.2 Treatment approach for evaluating for potential metastasectomy. General algorithm for evaluating stage IV melanoma patients for potential metastasectomy. *CT* computed tomography, *C/A/P* chest, abdomen, and pelvis, *MRI* magnetic resonance imaging, *PET* positron emission tomography

Staging

Patients must first have appropriate staging to determine the extent of the metastatic disease. All stage IV patients should be evaluated with complete history and physical and imaging studies, such as CT scans of the chest, abdomen, and pelvis, and brain MRI, prior to considering a surgical procedure [49]. The distribution and number of metastatic lesions provide prognostic information, and the resectability of a metastatic tumor is based in part on these factors as well as involvement of specific organs or contiguous structures (Figs. 10.3 and 10.4). It is clear that the ability to eradicate all disease and render a patient NED is correlated with better outcomes, while cytoreductive or debulking surgery is of minimal benefit [15]. However, with the current ESTs, isolated resection of treatment-resistant lesions may also provide benefit in a patient with other sites of disease that appear to be responding to or controlled by other therapies.

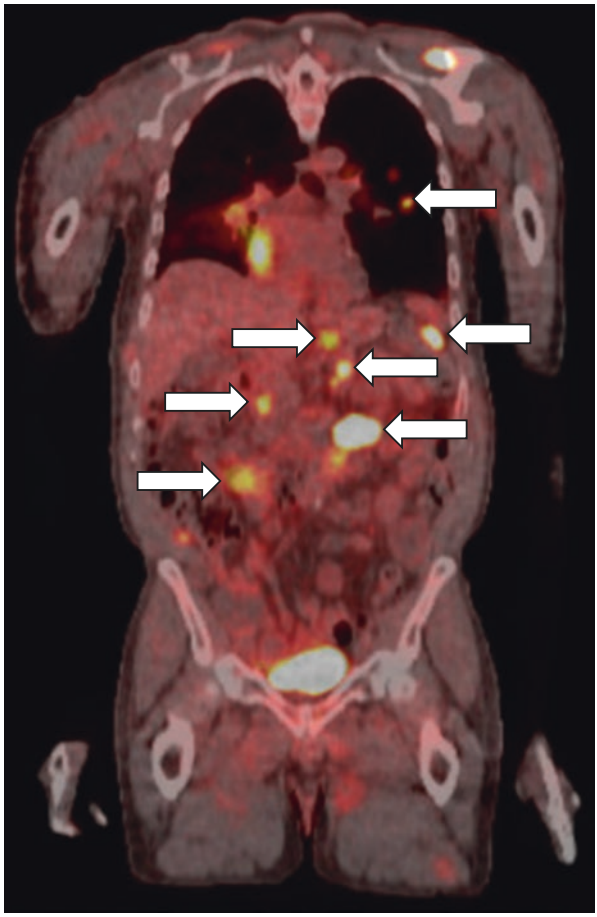

Fig. 10.3 Disseminated disease. PET/CT demonstrates pulmonary, retroperitoneal, and abdominal metastases as shown by the arrows. Given the number of metastatic lesions, volume of disease, and sites of metastases, this patient should start treatment with systemic therapy and would not benefit from upfront surgery

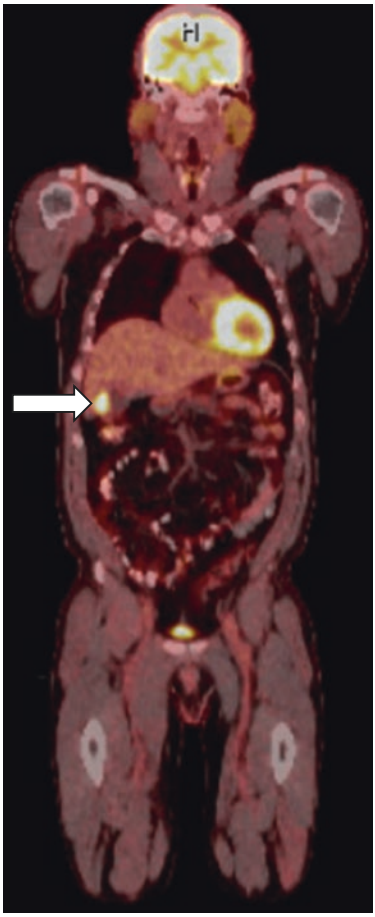

Fig. 10.4 Oligometastatic disease. PET/CT demonstrates a single hypermetabolic focus in the gallbladder, as shown by the arrow, in a patient who presented 16 months prior with isolated lymph node disease from an unknown melanoma primary. The patient had oligometastatic melanoma and underwent cholecystectomy for consolidation metastasectomy. Pathology revealed a deposit of metastatic melanoma in the gallbladder. The patient remains on anti-PD-1 therapy with no evidence of disease 15 months later

Prognostic Considerations

A number of clinicopathologic characteristics are also prognostic, which can influence the decision of whether or not to offer metastasectomy (Table 10.3). For instance, the type of stage IV disease is important to note since prognosis varies by anatomic site of the metastasis [50]. In particular, patients with only M1a disease have the best prognosis, while patients with M1c and M1d disease have the worst prognosis [50, 51]. Furthermore, resection of M1a disease is associated with the best outcomes, with a 4-year OS of 69% reported from the MSLT-I study [37]. The number of metastatic lesions and volume of disease are also important considerations given that prognosis generally worsens with increasing number of lesions and greater volume of disease, although multi-centric disease is not necessarily a contraindication for metastasectomy [47].

Table 10.3 Factors to consider when evaluating stage IV melanoma patients for metastasectomy

Type of stage IV disease (staging)
Complete resectability of known sites of disease
Distribution and anatomic sites of metastases
Number of metastatic lesions and volume of disease
Length of disease-free interval
Tumor volume doubling time
Response to systemic therapy
Morbidity of procedure
Timing with other therapies
Purpose of metastasectomy

Tumor biology is a crucial factor to consider. For instance, tumor volume doubling time (TDT) and disease-free interval (DFI) are factors that are correlated with prognosis, the rapidity of tumor growth, and biologic aggressiveness [19, 22]. Patients who have a short TDT or DFI are more likely to have progressive disease soon after surgery and are less likely to benefit from metastasectomy [19, 22, 25]. In contrast, patients who have had a DFI of >12 months or TDT >60 days are more likely to gain a survival benefit [22, 37]. In addition, how a tumor responds to systemic therapy provides important prognostic information. Patients who respond to systemic treatments and have regression of distant disease have better outcomes compared with patients who continue to progress on therapy [42]. For those patients who have a good response, surgical consolidation for curative intent may be performed for patients who have a limited number of remaining disease sites that are all able to be surgically resected. Metastasectomy can also be performed to remove persistent treatment-resistant areas that are either progressing or stable in size in a patient with other sites of disease that are responding to or controlled by other therapies such as EST. In contrast, patients who do not respond to systemic therapy are less likely to achieve durable disease control after surgical resection [42].

Morbidity

The patient's ability to tolerate an operation, the morbidity of the procedure, and effects on quality of life must be taken into account when planning treatment approaches. This is particularly important in cases with stage IV disease given that survival is decreased in these patients, and it is important to maintain quality of life and minimize morbidity during that potentially shortened lifespan. The benefit of a procedure must be weighed against the risks, types of morbidity, and potential effects on quality of life after surgery. For instance, a patient with other significant

life-limiting comorbidities is less likely to benefit from a surgical resection if there are higher risks for perioperative complications, morbidity, and mortality from the procedure.

Timing of Therapies

If surgical resection is considered, the order of therapies utilized may vary. Given the paucity of high-quality data on the topic, no specific protocol can be recommended regarding the pre-operative or post-operative use of systemic therapy [48]. In most cases, the biology of the stage IV disease is considered aggressive or the metastatic sites are unresectable or would require potentially morbid surgical procedures, and most patients will be treated with upfront systemic therapy. Most stage IV patients are at relatively high risk for developing other sites of metastases, and up-front systemic therapy has the benefit of allowing assessment of tumor response and potential disease progression, which can aid in selecting patients with favorable biology for metastasectomy. In contrast, patients with a single site of distant metastasis that can be resected with low morbidity could conceivably be rendered disease-free with an up-front operation. Up-front surgery may also be considered for palliative purposes such as for brain or bowel metastases to either control symptoms (e.g. bleeding) or to prevent later issues (e.g. obstruction). Systemic therapy is often utilized after upfront surgery in these cases, depending on the risk for developing additional distant metastases or whether there are other known sites of disease.

Purpose of Surgical Intervention

Patients with stage IV melanoma may be considered for surgical resection based on extent of disease, prognostic and morbidity considerations, and availability of other therapies, but the goals and purpose of metastasectomy should be carefully delineated. Surgery can be performed for consolidation (curative-intent), resection of treatment-resistant lesions, or palliation.

- Consolidation (Fig. 10.5): Patients who are treated with systemic therapy and either respond, such that a few sites of disease remain, or have stable disease in a limited number of remaining sites, may have all known remaining sites of metastatic disease fully resected for curative-intent, rendering the patient NED.
- Selective resection of treatment-resistant sites (Fig. 10.6): Some patients may have different types of responses to systemic therapy at varying sites. If these patients have an overall favorable response pattern, but have a limited number of

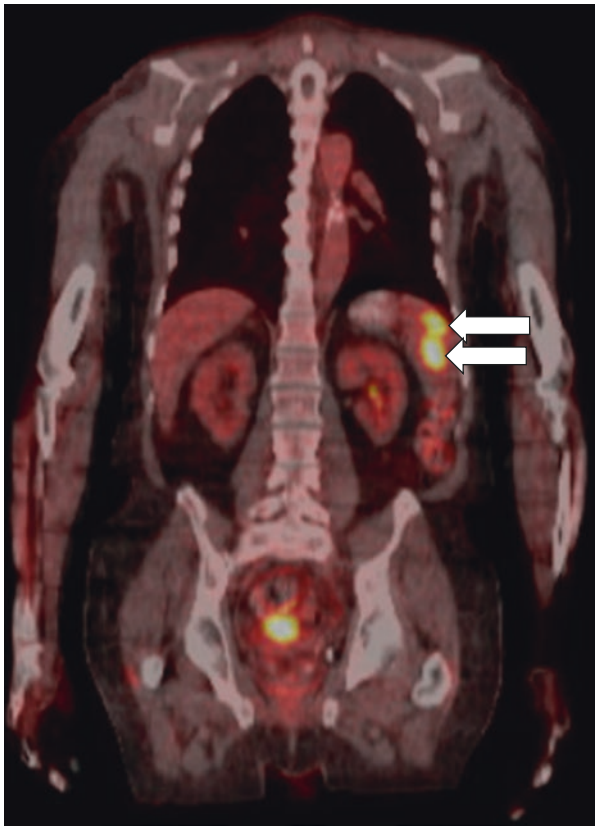

Fig. 10.5 Consolidation for curative intent. PET/CT demonstrates two hypermetabolic lesions in the spleen, as shown by the arrows, in a patient undergoing immune checkpoint inhibitor therapy for stage IV melanoma. The patient had no other sites of metastatic disease, and the splenic lesions were stable on systemic therapy for at least 12 months. He underwent splenectomy for curative intent. Pathology demonstrated metastatic melanoma in the spleen. Three years after his consolidation metastasectomy, the patient remains with no evidence of disease

metastases that are resistant to systemic treatment, these treatment-resistant sites may be resected. The remaining metastatic sites would continue to be treated and controlled with other therapies (e.g. EST) [45].

- Palliation: metastasectomy can be considered for palliative purposes, which consists of surgery done to improve quality of life or relieve symptoms in patients who would be left with disease and are considered incurable. In the era before EST, surgery for metastatic melanoma was often palliative [45]. In the gastrointestinal tract, palliative resections may be performed for lesions which are obstructing or bleeding, while skin and soft tissue palliative metastasectomy may be considered for large lesions that are bleeding, painful or have become infected [52]. Symptomatic brain or spinal cord metastases can be considered for surgical palliation as well.

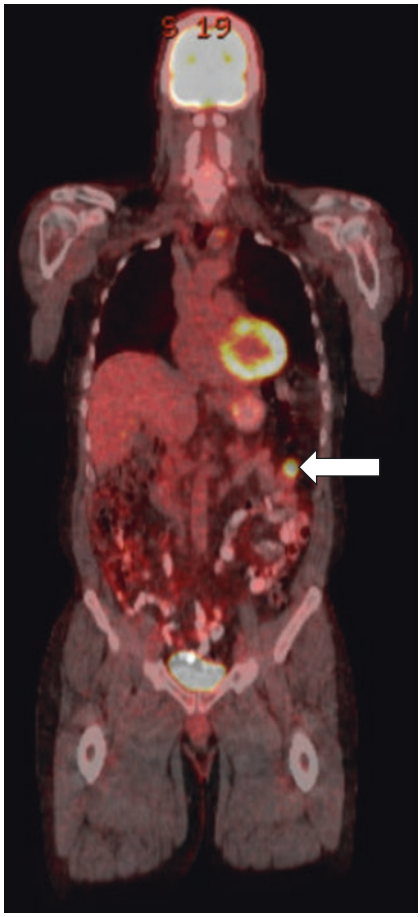

Fig. 10.6 Selective resection of treatment-resistant sites. PET/CT demonstrates a hypermetabolic focus in the left upper quadrant of the abdomen, as shown by the arrow, which was an omental implant of metastatic melanoma. The patient had several sites of stage IV metastatic melanoma, and he was treated with immune checkpoint inhibitor therapy. His additional sites of disease (hypermetabolic foci in the thyroid and the right middle lobe of the lung) had remained stable for 21 months on the patient's regimen of combination immunotherapy. However, the omental implant grew over a 3-month interval. The intra-abdominal lesion was resected, and pathology showed metastatic melanoma. The patient has been followed for 3 years, and his disease has remained stable. Recently, the thyroid lesion was also resected and was revealed to be metastatic melanoma

Site-Specific Considerations

M1a Disease

Approximately 25–40% of all patients with distant melanoma metastases will have M1a disease [53]. These patients have the best prognosis of all stage IV melanoma patients, approaching a 5-year survival of 50% or greater in some studies after surgical resection [37, 38]. In addition, morbidity and mortality after resecting these lesions is typically low, and metastasectomy can be considered in appropriately selected M1a patients [52]. Although national guidelines about margins used for metastasectomy of distant skin and soft tissue metastases are not available, a margin of 1 cm is commonly employed [54]. For extensive metastatic lesions of the extremity, regional therapy techniques such as isolated limb perfusion or infusion have also been used [55]. Metastases to distant lymph node basins are typically managed with

a therapeutic lymphadenectomy in select patients, although there is limited evidence to guide practice in this regard, particularly given the relatively high morbidity associated with lymphadenectomy in certain nodal basins such as the groin.

M1b Disease

Many of the early reports on metastasectomy for melanoma evaluated resection of isolated pulmonary lesions [25, 26, 56]. The lung is the most common site of visceral metastasis at 15–35% of all stage IV melanoma patients. M1b disease is also associated with the second-best prognosis, and these patients have a 20–30% 5-year survival [5, 37]. Numerous factors are correlated with better prognosis after pulmonary metastasectomy, including smaller tumor size, R0 resection, and no extrathoracic disease [26, 57]. Resection of metastatic pulmonary lesions may be done as a wedge resection in many cases, although lobectomy may be required, and some institutions are performing pulmonary metastasectomy via minimally invasive approaches [58]. Of note, additional considerations must be made in evaluating patients for pulmonary metastasectomy. For instance, patients must be able to tolerate a lung resection and should be evaluated for sufficient pulmonary reserve.

M1c Disease

Liver metastasis is seen in approximately 15–20% of stage IV melanoma patients [59]. Of note, for biological reasons that are incompletely understood, ocular melanoma has a particular propensity to metastasize to the liver [60]. Owing in large part to the reported successes in resecting colorectal liver metastases, liver resection for metastatic melanoma has been pursued in high-volume centers since even prior to the advent of ESTs. Furthermore, the morbidity of liver surgery has decreased and surgical techniques have improved over time such that more liver metastasectomies are being performed, particularly in higher-volume institutions that have appropriate expertise. The John Wayne Cancer Institute reported their experience treating melanoma patients with liver metastases and showed a significantly higher 5-year OS of 30% after surgical therapy compared with patients who were not treated with surgery (5-year OS: 6.6%) [42]. Other liver-directed therapies include ablation techniques (e.g. radiofrequency, microwave, etc.), and this same study showed that outcomes did not appear different between patients treated with ablation versus liver resection [42]. Furthermore, a meta-analysis of 22 studies of hepatectomy for metastatic melanoma confirmed that patients who underwent resection had significantly improved overall survival compared with non-surgical patients (median: 14–41 vs. 4–12 months), although the possibility of significant selection bias was noted in all the included studies [47]. Additional liver-directed treatments are being evaluated, including percutaneous hepatic perfusion (PHP) [61]. A randomized trial

demonstrated positive results on progression-free survival but not OS for patients treated with PHP for unresectable melanoma liver metastases [62].

Bowel metastasis is relatively uncommon and develops in only 2–4% of patients with melanoma [5]. However, melanoma is the most common cancer resulting in small bowel metastasis, and the small bowel is the most common site affected (75% of cases with bowel metastases) [52]. Bowel metastases often cause symptoms, resulting in bleeding, obstruction, intussusception, and pain. Resection of bowel lesions may be performed for palliative purposes in many cases even if the patient is not a candidate for a curative approach. In contrast, patients who have bowel metastases that are amenable to resection may benefit from metastasectomy for either consolidation or resection of an isolated treatment-resistant lesion [43]. Resection of bowel metastases may be done through either open or minimally invasive techniques, depending on the available expertise. The site of bowel metastasis should be completely resected with adequate margins and a portion of the feeding mesentery should be resected with the specimen due to the risk for spread of melanoma to draining lymph nodes.

Treatment of melanoma metastatic to other intra-abdominal sites, such as the spleen and adrenals, has also been reported [43]. Splenectomy or adrenalectomy may be performed in appropriately selected patients to treat metastases in these sites. In general, patients with abdominal metastases from melanoma had improved median OS with surgery compared with non-surgical management (18 vs. 7 months), with the greatest benefit seen after surgery for gastrointestinal tract metastases [43].

M1d Disease

Metastasis to the brain and spinal cord is one of the most feared developments for melanoma patients and occurs in 5–20% of melanoma cases across all stages [63]. Even small lesions may have abrupt and profound impacts on patients' functional status and life expectancy, and a high index of suspicion is required when working up any neurological complaints. The median survival for patients with melanoma brain metastases was historically <6 months, although a recent phase 2 study of combined immunotherapy demonstrated much higher survival, with complete responses seen in 26% of patients and an OS of 82% at 1 year [64, 65]. Brain metastases, particularly if bleeding, may require urgent surgical decompression and resection, often followed by adjuvant radiation [66]. Although in the past adjuvant whole brain radiation was routine, this practice has been recently questioned, as neurocognitive side effects can be significant [67]. In addition, patients with isolated brain metastases may benefit from metastasectomy, particularly if they have shown signs of a favorable response to systemic treatment [68]. In the past, surgical resection of brain metastases has been associated with a median survival of 6–9 months, although this was in the era before ESTs [66, 69]. Large brain metastases, particularly in patients who are symptomatic, which are isolated or in surgically approachable locations are often managed with resection if feasible, while

multiple lesions may be treated with radiation [66, 70]. As an alternative to surgical resection, many patients have been successfully treated with stereotactic radiosurgery, which is often used for unresectable lesions or multiple brain metastases [70].

Summary and Conclusion

Improvements in systemic therapy over the past decade have offered many patients with stage IV melanoma a chance at improved survival and possibly cure. Importantly, in the era of EST, more patients with stage IV melanoma are becoming potential candidates for surgery for consolidation of response, for resection of treatment-resistant foci, or for palliation. Furthermore, studies continue to show that appropriately selected patients gain a survival benefit after metastasectomy, and criteria for selecting patients for metastasectomy are becoming better defined. Given the complex treatment considerations for stage IV melanoma patients, a multi-disciplinary approach and appropriate patient selection for metastasectomy are critical in order to provide these patients optimal outcomes.

Clinical Case: Conclusion

After discussion with the patient, you recommend a left hemicolectomy for her single site of metastatic melanoma, given the patient's limited sites of disease and prolonged disease-free interval. The patient wished to proceed and pathology from surgery showed no remaining melanoma in the colon, although two draining lymph nodes were positive for metastatic melanoma. Her recovery was uneventful, and she continued treatment with immune checkpoint inhibitors. At 5 years of follow up, she has had no evidence of disease recurrence.

Take Home Messages

- Systemic treatment of stage IV melanoma has been revolutionized by the introduction of immune checkpoint inhibitors and targeted therapy.
- Surgical treatment of stage IV disease may improve survival in select patients.
- Careful patient selection, with particular attention to staging data, prognostic and morbidity considerations, and timing with other therapies, will help the treatment team identify stage IV patients most likely to benefit from metastasectomy.
- Surgery for patients with stage IV disease may be done for consolidation of remaining disease for curative intent, resection of treatment-resistant foci, or for palliation.

Conflict of Interest The authors declare that they have no financial conflicts of interest relevant to this work.

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