Chapter 37
Head and Neck Melanoma

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Abstract The head and neck region, a sun-exposed area, is the site of up to one-third of all primary cutaneous melanomas. In addition, rare melanoma subtypes such as mucosal melanoma and desmoplastic variant occur more commonly in the head and neck than other regions of the body. Although the same general treatment principles that apply to melanoma at other body sites also apply to the management of melanoma of the head and neck, treatment in this region is complicated by the complexity of the regional lymphatic drainage pathways and the close proximity of lesions to structures of functional or esthetic significance. Early-stage melanoma of the head and neck can in many cases be effectively treated with surgery; however, the prognosis for patients with more advanced disease remains poor. In addition to complete excision of the primary tumor with adequate margins, for selected patients, radiotherapy, chemotherapy, and other adjuvant treatments can play a role in optimizing patient outcomes.

Keywords Cutaneous melanoma • Head and neck • Desmoplastic melanoma • Risk factors • Staging • Surgery • Immunotherapy • Sentinel lymph node biopsy • Neck dissection • Adjuvant radiation

Epidemiology, Risk Factors, and Etiology

Epidemiology

The incidence of cutaneous melanoma has increased dramatically worldwide over the last half century, with an estimated 160,177 new cases in 2008. For the USA there were an estimated 62,480 new cases [1, 2], and there has been an increase in melanoma incidence since 1992 equal to 3.1% per year in the Caucasian population in the USA [3]. As of 2004, the lifetime risk of developing melanoma was 1 in 41 for men and 1 in 61 for women in America [4]. This can be compared with a 1 in 53 risk for men and a 1 in 78 risk for women just 2 years prior, a 1 in 250 lifetime risk for individuals in 1980, and a 1 in 1,500 risk for individuals in 1935 [5].

Although the incidence of melanoma has steadily increased, the mortality rate has improved, with the 5-year disease-specific survival rates among melanoma patients increasing over the last 3 decades from 82 to 92% [4]. Worldwide deaths from melanoma in 2008 were estimated at 40,781 [2], with an estimate of 8,420 deaths occurring in the USA [2]. Despite improved mortality rates, the number of total deaths from melanoma continues to increase somewhat among American men as a result of the increased incidence of the disease. However, among American women, the death rates are decreasing slightly. Several theories for the increasing incidence of melanoma have been proposed, including increased environmental risk factors, changes in sun exposure behavior, earlier identification of melanomas, and increased reporting of low-risk melanomas to cancer registries [6–9]. The explanation of earlier melanoma detection as the reason for the increased incidence is an attractive one given the improvement in melanoma-specific survival.

Risk Factors

The primary environmental risk factor for the development of melanoma is sun exposure, particularly intermittent and intense exposures in childhood that lead to blistering sunburns [10–12]. This in part explains the high incidence of melanoma in the head and neck region, which has substantial exposure to sunlight, leading to an increased melanocyte density [13]. Interestingly, inherited melanoma occurs less frequently on head and neck skin, which is consistent with its propensity for sites with intermittent sun exposure, such as the trunk [14].

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Because the head and neck area tends to be continually exposed to the sun, the American Cancer Society recommends that this region should be protected with the combination of avoidance of sunlight during the peak hours from 10 AM to 4 PM, use of a hat, and generous and frequent application of sunscreen with an SPF of 15 or greater on uncovered areas. While there is some concern about the actual efficacy of sunscreens, and the potential misuse of sunscreens for the justification of even greater amounts of sun exposure, the recommendation for sunscreen usage stands, since most evidence suggests that sunscreens offer protection by blocking ultraviolet (UV) light in the UVA and UVB portions of the spectrum (310–400 and 290–320 nm, respectively). In fact, due to advancements in the development of sunscreens in the 1990s such as longer-lasting UV filters, and the development of better methods of assessing the UV protection of a formulation, sunscreens are currently about four times more effective at blocking UVA and UVB irradiation than the sunscreens of 10–20 years ago [15]. Other environmental risk factors, such as occupation and hobbies, geographic latitude, and tanning are surrogates for UV irradiation exposure.

Patient factors that contribute to the risk of melanoma include fair complexion, genetic predisposition, immune compromise, and the presence of pigmented nevi [16]. Whether pigmented nevi are precursors and not simply risk factors for the development of melanoma is controversial. The most convincing evidence supporting this precursor theory is the spatial association of nevi and melanoma histologically and clinically [17]. High nevus counts are strongly associated with melanoma of the trunk but less so in patients with melanoma of the head and neck [18]. The most important pigmented lesion associated with the development of melanoma is the dysplastic nevus, which is a variegated-colored lesion usually greater than 5 mm in diameter with an irregular border. Persons who have dysplastic nevi and no significant family history have a 6% lifetime risk of melanoma [19]. People who have both dysplastic nevi and a positive family history of melanoma have a 50% lifetime risk of melanoma [20]. However, the conversion of any single dysplastic nevus into melanoma is low [19]. In contrast to dysplastic nevi, the giant congenital nevus is associated with a 2–40% lifetime risk of transformation into melanoma and usually occurs before 5 years of age [21]. Lentigo maligna melanoma in situ is another premalignant melanocytic lesion that carries a 5–10% risk of progression to invasive disease [22]. The vast majority of these lesions occur on the head and neck, most commonly on the cheeks and nose [23].

Etiology

Although the overwhelming majority (90%) of cases of melanoma is sporadic, familial syndromes with a high risk of development of melanoma, such as dysplastic nevus syndrome or xeroderma pigmentosa, have been studied and have provided some insights into the etiology of melanoma. Patients with familial melanoma have been found to have primary germ-line mutations, which include CDKN2A (cyclin-dependent kinase inhibitor 2A) on chromosome 9p21, CDK4 (cyclin-dependent kinase 4) on chromosome 12q14, and the MC1R (melanocortin-1 receptor) [16]. The CDKN2A gene encodes the $p16^{INK4a}$ and $p14^{ARF}$ tumor-suppressor genes, which induce G1 cell-cycle arrest and p53-dependent apoptosis, respectively. $P16^{INK4a}$ exerts its effect by inhibiting CDK4/6-mediated phosphorylation of the Rb protein. When dephosphorylated, Rb associates with E2F, preventing E2F from inducing progression of the cell past the G1 checkpoint. $P14^{ARF}$ exerts its effect by inhibiting HDM2-induced ubiquitination of p53, thus preventing p53 degradation, and allowing p53's DNA-damage sensing, cell-cycle pausing, and pro-apoptotic effects [24]. The MC1R protein is a G-protein-coupled receptor that is activated in response to MSH (melanocyte-stimulating hormone) to ultimately promote a switch of production from red/yellow-type melanin to a brown/black-type melanin by melanocytes. MCR1 mutants do not make the switch from the red/yellow type melanin to the brown/black type, and persons with such mutations are phenotypically Fitzpatrick grade I, that is, possessing extreme sun sensitivity that puts them at higher risk for development of melanoma [24]. Somatic mutations in CDKN2A and CDK4 have also been identified in some sporadic cases of melanoma [24]. Other genes frequently mutated in sporadic melanoma include the kinase BRAF; the tumor suppressor PTEN; and cKIT, the tyrosine kinase responsible for melanocyte differentiation. Several other proteins are upregulated in melanoma, including Bcl-2, AKT, and p53 [16].

Presently, neither GenoMEL (the Melanoma Genetic Consortium) nor the American Society of Clinical Oncology recommends using clinical genetic testing of CDKN2A, even though it is thought to be the highest-risk mutation associated with the development of melanoma. Reasons for the hesitation to use this genetic test include the fact that less than half (39%) of patients with a strong family history of melanoma will test positive for CDKN2A mutation, with the majority having germ-line mutations in other genes or independent sporadic events. Thus, the utility of directed screening of family members with a strong family history of melanoma for CDKN2A mutations is unclear [25, 26].

There is evidence to suggest that there are different etiologies of melanoma depending on the pattern of sun exposure and the area of skin on which the melanoma lesion arises. For instance, mutations in BRAF have been found to be significantly more common in melanomas occurring on skin subject to intermittent sun exposure, such as the trunk, compared with those occurring on areas chronically exposed to the sun, such as the extremities or face [27]. Patients with melanomas in areas of chronic sun exposure most commonly

have wild-type BRAF but frequently also have increased copy numbers of the CCND1 gene and the cKIT gene [28, 29]. Also expression of the tumor suppressor p53 has been found to be greater in patients with head and neck melanoma than in patients with melanoma on the trunk [30].

Diagnosis and Evaluation

Diagnosis

Patient history is the key to early diagnosis of melanoma. The majority of melanomas are suspected by the patient and his or her family members, with fewer than 25% detected by physicians during the course of examination [31]. Patients with melanoma frequently complain of color change, growth, or the development of itching, bleeding, pain, or ulceration in a lesion that was previously present. While obtaining the patient history, the physician should take particular note of current occupational and recreational risks for excessive sun exposure, and history of sunburns especially as a child, as well as a history of melanoma or other skin cancer in family members.

A thorough physical examination is focused on risk stratification of the suspicious lesion, to determine whether biopsy is indicated, and the identification of additional suspicious lesions. It is important not to miss a second lesion, since development of a pigmented lesion in one area is likely a marker for overall for excessive sun exposure. Patients with one melanoma lesion are known to have a significantly increased risk of synchronous melanomas and nonmelanoma skin cancers (e.g., basal cell and squamous cell carcinomas) compared with the general population [32–36]. Proper examination requires adequate light and magnification and should include all skin and mucosal surfaces of the head and neck, including the scalp. The ABCDE mnemonic describes a checklist that can be useful for physicians in assessing pigmented lesions: *A*symmetry in growth, *B*order irregularity, *C*olor abnormality (variation in color in a single mole), *D*iameter greater than 6 mm, and *E*levation or raised from the skin. Of these characteristics, border irregularity most strongly predicts malignancy [37, 38]. Evidence suggests that physician observation of a change, or evolution, in a lesion is very important in increasing physician-suspicion that a pigmented lesion is a melanoma [39]. The importance of lesion observation over time in predicting development of melanoma was reflected in the incorporation of an alternative E, for "evolving," into the previously mentioned ABCD mnemonic for describing a changing pigmented lesion [40]. Other features to note on physical examination that have bearing on the stage of a melanoma include skin ulceration, satellite lesions, in-transit metastases, and lymphadenopathy in draining nodal basins. Patients with suspicious lesions or photo-damage in the head and neck region should be referred to a dermatologist for full-body screening and long-term follow-up, as a dermatologist's visual examination is 89–97% sensitive, with a 35–75% positive predictive value [41].

Suspicious pigmented lesions must be biopsied in a manner that allows pathologic examination of the point of maximum depth. Excisional biopsy with 1- to 3-mm margins is recommended for small lesions in favorable locations. Excisional biopsy (as opposed to wide local excision) has been shown to leave lymphatic drainage pathways unaltered including drainage to sentinel lymph nodes. In addition, patients who have had excisional biopsy for small lesions have improved survival compared with those who have not [42]. However, it is recommended that large lesions, or those that encroach on cosmetically unfavorable areas, be evaluated with incisional biopsy, such as via punch biopsy, ensuring that the thickest part of the lesion is included. Needle or shave biopsy in the evaluation of suspicious pigmented lesions is not recommended as they may miss the full depth of the lesion. The decision as to which pigmented lesions are suspicious enough to warrant biopsy is based on the ABCDE criteria and should take into account all the patient's risk factors for melanoma, keeping in mind that most dysplastic nevi will never progress to melanoma [43]. Although supportive data are lacking, some recommend that dysplastic nevi in areas that are difficult to follow clinically, such as the hair-bearing scalp, be prophylactically excised [44].

Further Evaluation

Once the diagnosis of malignant melanoma is confirmed by biopsy, the focus of further workup is on identifying any regional or distant metastases, as these have a great impact on prognosis and further treatment planning. A multidisciplinary evaluation and a cooperative approach to disease management in this disease includes involvement of multiple specialties such as radiology, nuclear medicine, radiation therapy, medical oncology, plastic and reconstructive surgery, dermatology, and other specialists to guide an individual's treatment plan.

In the absence of evidence on physical examination of regional or distant spread of melanoma, thickness of the primary cutaneous lesion is used to determine the need for additional diagnostic evaluation, since tumor thickness is known to strongly influence the risk of metastasis [45]. Thus, the stage of the melanoma, which is based on the thickness of the cutaneous melanoma, is the primary determining factor for the extent of the metastatic workup. According to the National Comprehensive Cancer Network

(NCCN) guidelines, the choice of diagnostic tests to determine extent of disease and possible regional spread varies greatly among institutions. This variation is likely due to the lack of prospective data demonstrating the most appropriate work-up of the patient with melanoma. For this reason, the NCCN makes suggestions for work-up but largely leaves the choice of diagnostic test to the discretion of the treating physician [46]. Most physicians who treat melanoma would agree that for patients with in situ disease, no additional testing is needed. At The University of Texas M.D. Anderson Cancer Center, all thin (≤1 mm) melanomas, require only a chest X-ray and measurement of serum lactate dehydrogenase (LDH) as a screen for distant disease. Intermediate-thickness melanomas (>1 to 4 mm) are at greater risk of regional spread of melanoma and are thus candidates for preoperative lymphoscintigraphy and subsequent intraoperative sentinel lymph node biopsy (SLNB) to aid with pathologic staging. Patients with thick (>4 mm) or recurrent disease are at very high risk for distant disease, and consideration should be given to a more extensive metastatic work-up including CT scan of the neck as well as CT of the chest, abdomen, and pelvis and a brain MRI. Patients with clinically evident regional disease or ulceration of the primary melanoma should have preoperative neck CT or ultrasound imaging to help in treatment planning. The role of PET scanning is unclear, with many studies reporting low yield and a significant false-positive rate in patients with early-stage melanoma [47]. There may be an emerging role for PET imaging in the work-up of patients with more advanced melanoma, especially when potentially mutilating surgery is planned. However, it is unclear if the diagnostic yield of PET is better than that of traditional imaging techniques [48, 49].

Melanoma in rare cases can be found in the cervical or parotid nodes in patients with no evidence of a primary melanoma (metastatic melanoma of unknown origin), leading to the possibility that the primary melanoma had spontaneously regressed. In this case, more extensive diagnostic testing than would normally be done should be undertaken in the search for a head and neck primary melanoma, including ocular and mucosal sites. Physical examination and endoscopy are the first steps in the search for a primary. If physical examination and endoscopy do not identify the primary lesion, a PET scan may be considered, although there is a paucity of evidence of its effectiveness in this case. If no primary is located, patients should be treated with regional lymphadenectomy (neck dissection) appropriate to the nodal level(s) involved, with or without parotidectomy, plus adjuvant radiotherapy with or without chemotherapy (more below). In general, the outcome for patients with melanoma of unknown primary is the same or better than that for patients with regional nodal metastases from a known primary lesion [50].

Staging

The current AJCC staging system was revised in 2009 to better reflect factors proven to worsen prognosis and decrease the chance of survival. The current staging system, which has been validated, is detailed in Table 37.1 [51]. This latest staging system incorporates several variables proven to influence survival of patients with melanoma. Thus survival

Table 37.1 Melanoma of the skin: TNM classification and anatomic stage/prognostic groups

Definitions of TNM

Primary tumor (T)

TX	Primary tumor cannot be assessed (e.g., curettaged or severely regressed melanoma)
T0	No evidence of primary tumor
Tis	Melanoma in situ
T1	Melanomas 1.0 mm or less in thickness
T2	Melanomas 1.01–2.0 mm
T3	Melanomas 2.01–4.0 mm
T4	Melanomas more than 4.0 mm

Note: a and b subcategories of T are assigned based on ulceration and number of mitoses per mm^2 as shown below:

T Classification	Thickness (mm)	Ulceration status/mitoses
T1	≤1.0	a: w/o ulceration and mitosis <l/mm^2
		b: with ulceration or mitoses ≥l/mm^2
T2	1.01–2.0	a: w/o ulceration
		b: with ulceration
T3	2.01–4.0	a: w/o ulceration
		b: with ulceration
T4	>4.0	a: w/o ulceration
		b: with ulceration

Regional lymph nodes (N)

NX	Patients in whom the regional nodes cannot be assessed (e.g., previously removed for another reason)
N0	No regional metastases detected
N1-3	Regional metastases based upon the number of metastatic nodes and presence or absence of intralymphatic metastases (in-transit or satellite metastases)

Note: N1-3 and a–c subcategories assigned as shown below:

N classification	Number of metastatic nodes	Nodal metastatic mass
Nl	1 node	a: micrometastasis[a]
		b: macrometastasis[b]
N2	2–3 nodes	a: micrometastasis[a]
		b: macrometastasis[b]
		c: in-transit met(s)/ satellite (s) without metastatic nodes

(continued)

Table 37.1 (continued)

N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s)

[a]Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed)

[b]Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension

Distant metastasis (M)

M0	No detectable evidence of distant metastases
M1a	Metastases to skin, subcutaneous, or distant lymph nodes
M1b	Metastases to lung
M1c	Metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH

Note: Serum LDH is incorporated into the M category as shown below:

M Classification	Site	Serum LDH
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

Anatomic stage/prognostic groups

Clinical staging[a]				Pathologic staging[b]			
Stage 0	Tis	N0	M0	0	Tis	N0	M0
Stage IA	T1a	N0	M0	1A	T1a	N0	M0
Stage IB	T1b	N0	M0	1B	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
Stage IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
Stage IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
Stage IIC	T4b	N0	M0	IIC	T4b	N0	M0
Stage III	Any T	≥Nl	M0	IIIA	T(1 – 4)a	N1a	M0
					T(1 – 4)a	N2a	M0
				IIIB	T(1 – 4)b	N1a	M0
					T(1 – 4)b	N2a	M0
					T(1 – 4)a	N1b	M0
					T(1 – 4)a	N2b	M0
					T(1 – 4)a	N2c	M0
				IIIC	T(1 – 4)b	N1b	M0
					T(1 – 4)b	N2b	M0
					T(1 – 4)b	N2c	M0
					Any T	N3	M0
Stage IV	Any T	Any N	Ml	IV	Any T	Any N	M1

[a]Clinical staging includes micro staging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases

[b]Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 or Stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes

varies depending on the stage of disease (Fig. 37.1) [51]. Of note, the current staging system incorporates microscopic lymph node metastases, such as those found upon sentinel lymph node biopsy, into the definition of pathologic staging. One prognostic factor that was not included in the 2002 AJCC melanoma staging revisions was mitotic count of the primary tumor. This index reflects the proliferative potential of the melanoma at the time of resection. The importance in the mitotic index in predicting survival had been examined previously, and since then even more data has emerged pointing to its importance [52].

Management

General Principles

The treatment of malignant melanoma of the head and neck follows the same overall guidelines of melanoma treatment as for other sites of the body. In general, the treatment of cutaneous melanoma includes complete resection of the primary tumor with sufficient margins, with the decision to perform adjuvant treatment based on stage of disease. However, the complex anatomy of the head and neck requires consideration of the important esthetic and functional defects that may result from treatment, and requires that planning for appropriate reconstruction be incorporated into treatment planning. For these reasons, melanoma of the head and neck is more likely to necessitate multispecialty assessment and frequently multimodality therapy than melanoma at other sites of the body. A synopsis of treatment recommendations according to stage is given in Table 37.2 [53].

Treatment of the Primary

The keystone of treatment for nearly any resectable primary is the complete wide local excision (WLE) of the tumor complete with adequate margins. However, the definition of an "adequate" surgical margin is often controversial and a matter of compromise. On the basis of studies of melanoma of non-head-and-neck sites, 5-mm margins of excision have been recommended for in situ disease, 1-cm margins for thin melanomas (<1 mm), 1- to 2-cm margins for intermediate lesions (1–2 mm), and 2-cm margins for thick melanomas (>2 mm) [54]. Surgical margins greater than 2 cm have not been shown to improve overall survival or local-regional control [55]. In the head and neck, the surgeon is often unable to take a wide local margin of 1–2 cm without causing substantial esthetic or functional disability. Considering the potentially adverse effect on quality of life that may result

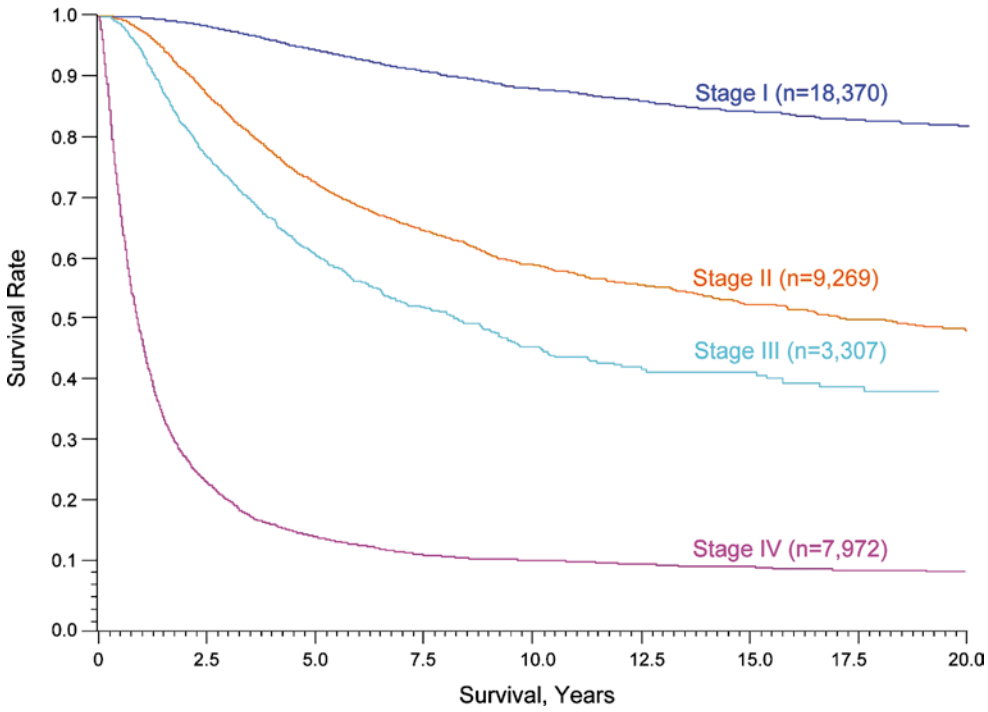

Fig. 37.1 Twenty-year survival curves for patients with localized melanoma (Stages I and II), regional metastases (Stage III), and distant metastases (Stage IV). The *numbers* in *parentheses* are the numbers of patients from the AJCC Melanoma Staging Database used to calculate the survival rates. The differences between the *curves* are highly significant ($p < 0.0001$). Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, http://www.springer.com

Table 37.2 Recommendations for treatment, on the basis of stage

Stage	Treatment
I	Primary tumor – WLE
II	Primary tumor – WLE
	Regional lymphatics – observation vs. END vs. SLNB vs. ENI
III	Primary tumor – WLE
	Regional lymphatics – neck dissection ± parotidectomy
	Consider postoperative radiotherapy
	Consider systemic adjuvant therapy trials
IV	Primary tumor – WLE
	Regional lymphatics – neck dissection ± parotidectomy if N+
	Metastasis – site-directed surgery or radiotherapy
	Consider systemic adjuvant therapy trials
	Supportive care

END elective neck dissection, *ENI* elective neck irradiation, *N+*, node positive, *SLNB* sentinel lymph node biopsy, *WLE* wide local excision
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from oncologic resection, it is best to discuss the treatment options with the patient before surgery and obtain his or her thoughts on how to best balance competing functional and oncological concerns.

Both superficial and deep margins need to be kept in mind in order for the surgeon to appropriately resect the primary tumor in all three dimensions. Adequate margins in the scalp most commonly extend to the galea and potentially include the periosteum or portions of the calvarium for more extensive disease. Facial melanoma often requires resection down to the deep layer of the subcutaneous fat, and potentially up to and through the muscles of facial expression. Tumors overlying the parotid gland are excised down to the parotidomasseteric fascia. If the lesion extends into this fascial barrier, parotidectomy is recommended. Because the skin of the external ear is thin and adherent to the underlying cartilage, sufficient margins in this region often necessitate resection of the underlying cartilage or partial or complete auriculectomy. Extension medially into or beyond the external auditory canal requires a temporal bone resection [53]. Surgical extirpation of mucosal melanoma of the head and neck often resembles those surgeries performed for squamous cell carcinomas of the upper aerodigestive tract, and frequently require local, regional, or vascularized free flaps for reconstruction.

Frozen section control of resection margins may sometimes be helpful in minimizing unnecessary tissue loss if there is good communication between the surgeon and a pathologist who is comfortable with this technique in the setting of melanoma. Otherwise, there is a significant potential for false-negative results [56]. Therefore, our preferred practice in an area that will require complex reconstruction is to excise a lesion and then cover it with a bolster dressing, followed by expedited histopathologic review of the formalin-fixed, paraffin-embedded tissue with subsequent additional resection if necessary. In this scenario, margin status can be confirmed within 24 h, and definitive reconstruction is delayed until after adequate margins are ensured. Moh's

micrographic surgery is another technique utilized by specially trained dermatologic surgeons for sparing tissue in areas of functional or cosmetic significance. While Moh's surgery has been described in the literature, particularly in thin melanomas, long-term results are unclear, and it is not presently the standard of melanoma care [57].

While all primary melanomas should be surgically excised, there is evidence that postoperative radiotherapy can be employed to improve local-regional control in certain cases, such as when the adequacy of surgical margins is compromised by the proximity of key structures or there is extensive peri-neural invasion by tumor within the specimen. This is further addressed below.

Desmoplastic melanoma is an infrequent variant of cutaneous melanoma that is most often found in the head and neck, with about 50% of cases of desmoplastic melanoma arising above the clavicles. It tends to occur in older male patients and to present with greater depth of invasion at the primary site compared with nondesmoplastic melanoma. Importantly, desmoplastic melanoma has a propensity for perineural spread, with reported rates ranging from 17 to 94% [58, 59]. Desmoplastic melanoma also has a high rate of amelanosis, or lack of pigmentation (about 40–73%), compared with non-desmoplastic cutaneous melanoma (~7%), which may lead to a delay in clinical diagnosis of melanoma [60]. Additionally, desmoplastic melanoma can be a challenge to diagnose histologically by conventional hematoxylin and eosin staining. In fact, one study showed that patients with pure desmoplastic melanoma were incorrectly diagnosed on initial biopsy or excision in 28% of cases, with 10% of mixed desmoplastic melanoma cases being misdiagnosed initially on histopathology [61]. All of these factors have been implicated as contributing to desmoplastic melanoma's high rate of local recurrence (up to 56%) [62]. For this reason, adjuvant radiation is recommended for the desmoplastic variant of melanoma and has been shown in retrospective data to decrease local recurrence rate and improve recurrence-free survival [63, 64].

Treatment of the Neck

The neck should be treated surgically in patients with clinical evidence of spread of tumor to regional lymph nodes (stage III). For patients with positive lymphadenopathy by physical examination or imaging, a neck dissection is almost always performed. In most cases, a comprehensive neck dissection sparing all nonlymphatic structures is sufficient, with resection of all the most likely lymphatic drainage basins of the primary site including additional areas, such as the parotid gland, as well as the peri-facial, occipital, and peri-auricular nodes as needed [65]. Figure 37.2 depicts the nodal regions, or "levels" of the neck.

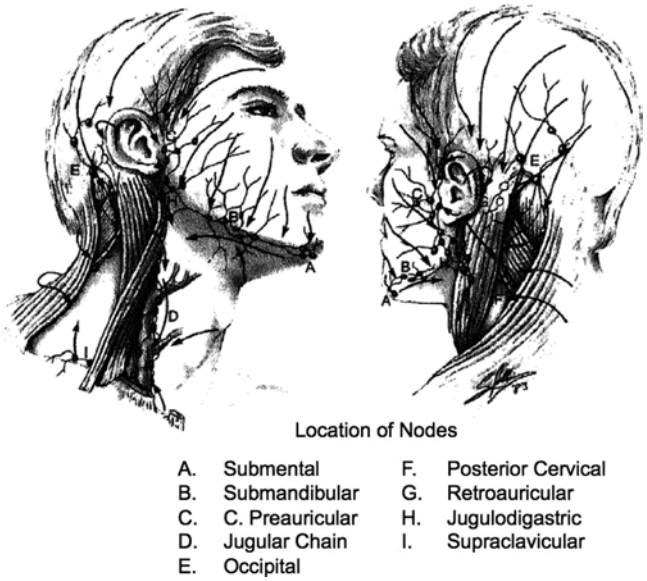


Fig. 37.2 Cutaneous lymphatic drainage of the head and neck. The usual patterns of lymphatic drainage from cutaneous regions of the head and neck are shown in this drawing, along with the major corresponding lymph node basins. In general, lymph node level I corresponds to the submental and submandibular nodes (A, B). Additionally levels II, III, IV, and V correspond to the jugulodigastric (H), jugular (D), supraclavicular (I), and posterior cervical (F) nodal areas, respectively. Used with permission from Balch CM, Houghton AN, Milton GW, et al., editors. Cutaneous melanoma. 2nd ed. Lippincott; 1992

While the role of neck dissection in treatment of macroscopic lymphadenopathy is well established, substantially more controversy surrounds the management of the N0 neck, in which there may be occult spread of melanoma to regional lymph nodes. Options for treatment of the neck include observation, elective neck dissection (END), sentinel lymph node biopsy (SLNB), and elective neck irradiation. An argument favoring observation of the N0 neck is that neither elective neck dissection nor SLNB has been shown to substantially improve overall survival [66]. Currently, patients with thin melanomas (T1a) are considered to be at minimal risk for regional lymph node metastasis, and as such are routinely treated with observation without any surgical intervention. However, patients with T1b or stage II disease are at substantial risk for nodal metastasis and have been traditionally considered candidates for END and more recently for SLNB.

Melanoma of the head and neck spreads to the neck along relatively predictable lymphatic pathways, and therefore the site of the primary has been used to determine the type of elective neck dissection performed in treatment of the neck. In general, patients with a neck or scalp primary melanoma posterior to a vertical line through the external auditory canal require postero-lateral neck dissection that encompasses levels II–V of the neck plus the retroauricular and suboccipital

lymph nodes [67]. Patients with a scalp or neck primary anterior to that vertical line through the external auditory canal typically undergo a lateral neck dissection (levels II–IV) and a parotidectomy. Melanoma primary lesions on the face are treated with a supraomohyoid neck dissection (levels I–III). Because cutaneous cancers may spread to nodal groups other than levels I–V, which are the nodal areas more commonly involved in mucosally derived head and neck tumors such as squamous cell carcinoma, it is important that the clinician have a high index of suspicion for involvement of the facial, peri-auricular, and especially parotid lymph nodes. The parotid is a frequent site of metastasis from the temple, peri-auricular, and anterior scalp areas. As a general rule, parotidectomy must be considered when the parotid lies between the primary melanoma lesion and the site of clinically evident nodal metastasis. For very anterior lesions occurring on the central face, chin, and neck, the parotid lymph nodes are usually not likely to be a site of melanoma metastasis [53].

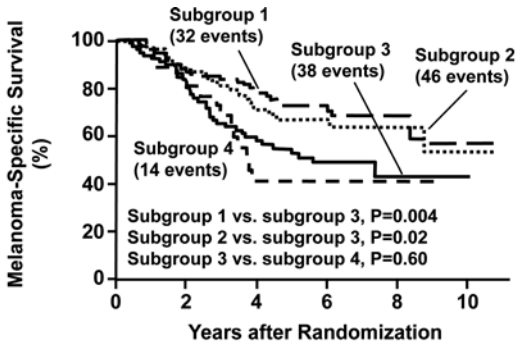
The justification for elective neck dissection is that it removes the nodal groups at risk before the appearance of clinical evidence of metastases, theoretically reducing the risk of regional or distant spread. Although this reasoning seems sound, only limited prospective data support the use of END to improve local-regional control or overall survival. Even among the subsets of patients with intermediate-thickness and nonulcerated melanomas shown in prospective studies to have improved survival after END [51, 68], a significant number of patients would have never developed neck disease and yet are subjected to the morbidity of END when it is performed routinely. Sentinel lymph node biopsy addresses this dilemma. This technique is based on the principle that initial lymphatic spread from a given primary site is to a very limited subset of lymph nodes before wider dissemination occurs. Thus, by injecting the primary site of the melanoma with tracer substances, it is possible to use preoperative nuclear imaging, intraoperative blue dye localization, and intraoperative lymphoscintigraphy to find the sentinel node or nodes and perform a very limited lymphadenectomy with increased pathologic investigation of the sentinel nodes to determine the presence of nodal metastasis with greater sensitivity [70, 71].

The validity of SLNB is well-established for melanoma on the trunk or extremities. However, its role in the treatment of cutaneous melanoma of the head and neck is still being refined. Identification and removal of sentinel lymph nodes in the head and neck can be difficult because (1) the primary and metastatic sites are often very close to each other, (2) routes of lymphatic drainage can be complex, (3) central lesions can potentially spread bilaterally, and (4) sentinel nodes can be found at several neck levels concurrently, or within the parotid gland. Despite this, numerous studies have shown that one or more sentinel nodes can be located in the vast majority of patients (>95%) if both vital dye staining and lymphoscintigraphy are used [69, 72]. Considering the evidence that the lymphatic drainage patterns from cutaneous melanoma of the head and neck do not always occur in a predictable way, one could see how using SLNB initially to map out the first echelon lymph nodes most likely at risk would be an attractive alternative to the traditional staging END [73–75]. Approximately 2–3 sentinel nodes are usually identified, often in nonadjoining lymph node areas. Despite a very low average false-negative rate in trials where SLNB is followed by END, some of studies have found higher than expected rates of lymph node metastases in patients with negative SLNB [75].

The prognostic power of SLNB in head and neck melanoma is supported by several retrospective and prospective studies. Data from a retrospective study of SLNB performed on 113 patients at a large cancer center followed for a median of 34 months verified successful sentinel node identification in 96% of patients [76]. While the rate of regional recurrence in the 23% of patients with positive sentinel nodes was 13%, it was 5% in patients with negative sentinel nodes. The overall rate of all types of recurrences was 48% in patients with a positive sentinel node biopsy, and 23% in those with negative sentinel nodes. Despite the higher recurrence rate in patients with positive SLNB, sentinel node status was not significantly associated with survival on multivariate analysis; the only variables associated with decreased disease-free survival and overall 5-year survival were Breslow thickness, and age greater than or equal to 60 years, respectively.

Results from a Sentinel Lymph Node Working Group trial consisting of 614 patients accrued from 13 centers demonstrated significantly worse 5-year disease-free survival for patients with positive sentinel nodes (about 50%) compared with patients with negative sentinel nodes (about 80%) and found that sentinel lymph node status was the most significant predictor of disease-free survival by multivariate analysis [77].

The prognostic value of SLNB was quite convincingly demonstrated in the landmark prospective Multicenter Selective Lymphadenectomy Trial (MSLT I), the results of which were published in 2006 [66]. In this trial, 1,269 patients with intermediate-thickness melanomas from multiple sites including the head and neck, with no evidence of regional spread at presentation (N0), were randomly assigned to WLE with SLNB, or WLE alone with performance of a delayed lymph node dissection (LND) if nodal metastases became clinically apparent. Taking into account all patients in the study, there was an improvement in the 5-year disease-specific survival rate for the WLE–SLNB group (78%) compared with the WLE alone group (73%), although melanoma-specific and overall survivals showed no difference. In a subset analysis of only the patients who had micrometastases on SLNB or developed lymph node metastases, however, the 5-year melanoma-specific survival was significantly better in the WLE–SLNB-early LND group (72%) than in the WLE-delayed LND group (52%) (Fig. 37.3) [66].



No. at Risk						
Subgroup 1	122	100	65	38	15	2
Subgroup 2	148	120	73	43	18	2
Subgroup 3	78	63	37	23	5	1
Subgroup 4	26	20	8	5	3	0

Fig. 37.3 Melanoma-specific survival among patients with nodal metastases. Subgroup 1 is comprised of patients with a tumor-positive sentinel node. Subgroup 3 contains patients with nodal recurrence during observation who underwent delayed lymphadenectomy. Subgroup 4 is comprised of patients with nodal recurrence after a negative sentinel lymph node biopsy result. Subgroup 2 contains patients in subgroup 1 plus those in subgroup 4. The 5-year survival rate of subgroup 1 was significantly better than that of subgroup 3 at 72.3±4.6% and 52.4±5.9%, respectively (hazard ration for death, 0.51; CI, 0.31−0.81; $p=0.004$ by log-rank test and $p=0.007$ by the Cox model). Used with permission from [66]. Copyright 2006 Massachusetts Medical Society. All rights reserved

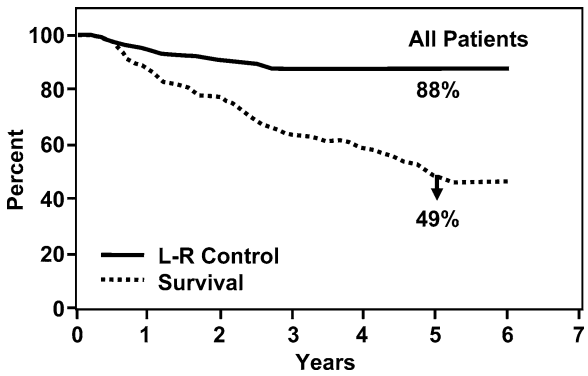


Fig. 37.4 Actuarial local-regional control and survival rates of 174 patients treated with hypofractionated postoperative radiotherapy for high-risk cutaneous melanoma. The adverse features evaluated in this study were thickness ≥1.5 mm or Clark level IV/V (79 patients), palpable lymphadenopathy (32 patients), and nodal relapse after previous excision of melanoma (63 patients). The local-regional control rate was 88% at 5 years following hypofractionated postoperative radiotherapy in high risk cutaneous melanoma patients. This is substantially improved compared to similar historical controls not treated with adjuvant radiotherapy. Used with permission from [86]. Copyright 1994 Elsevier

Additionally, the number of tumor-positive nodes in the delayed LND group was greater than twice that of the positive SLNB-early LND group (3.3 vs. 1.4, respectively). Given these observations, and other studies showing similar results, the use of SLNB with subsequent early lymph node dissection if positive, as opposed to delayed neck dissection when nodal involvement becomes clinically apparent, is recommended [78].

Considering the retrospective nature of available data, the role of SLNB in predicting the prognosis of clinically N0 patients with thick (>4 mm) primary melanomas is not clear. However, since several of these studies show that SLNB is predictive of either recurrence or survival, the routine use of SLNB is recommended for this group of N0 patients with thicker lesions [79–83].

A special situation in the management of the N0 neck arises when the histopathology is that of desmoplastic melanoma. A retrospective study examining a major cancer center's experience with desmoplastic melanoma over a 25-year period showed that the regional spread of this variant of melanoma depends upon the degree of desmoplasia within the tumor, with the pure form of desmoplastic melanoma being much less likely than the mixed form to metastasize to regional lymph nodes (1 vs. 18%, respectively) [61]. Additionally, the melanoma-specific mortality was significantly greater for patients with the mixed form compared with the pure form of desmoplastic melanoma and conventional melanoma. Consequently, elective lymphadenectomy and sentinel lymph node biopsy are not recommended in patients with pure desmoplastic melanoma.

In approximately 80% of SLNB-positive patients, the removed sentinel nodes are the only tumor-containing nodes found at completion lymphadenectomy. Given this relatively high rate of a second positive lymph node, completion lymphadenectomy is currently the standard of care to ensure regional control in those patients with a positive SLN. However, this issue is being further investigated in the MSLT II trial that was designed to determine whether serial nodal ultrasound can be used to select for those SLNB-positive patients who will need completion lymphadenectomy [84]. The results of this ongoing trial may further help guide the use of sentinel lymph node dissection to maximize survival and minimize unnecessary morbidity.

Although melanoma was historically thought to be radioresistant, some studies have shown that an enhancement in local-regional control of cutaneous melanoma with adverse features (≥1.5-mm thickness, Clarks level IV/V, nodal metastases, or recurrence after excision) in the head and neck is possible using a hypofractionation regimen [85, 86]. This hypofractionation scheme consisted of large-dose fractions of 6 Gy delivered in five fractions, or 30 Gy total, to the primary site and regional lymph node basins. This regimen has been shown to achieve local-regional control rates of up to 88% when administered postoperatively, which is a definite improvement over historical control rates in this population (~50%) (Fig. 37.4) [86]. Although this percentage is based

on retrospective data with historical controls, the substantial degree of the benefit suggests that this altered fractionation radiotherapy regimen is appropriate as an adjuvant local-regional therapy. Although the hypofractionated scheme described is used most commonly, there is some evidence that conventional fractionation can be as efficacious as hypofractionation in the adjuvant treatment of cutaneous melanoma of the head and neck [87]. Additionally, adjuvant and primary radiotherapy have been suggested to improve local-regional control in both mucosal melanoma and desmoplastic melanoma of the head and neck, although overall survival is not improved [88, 89].

Prevention and Treatment of Distant Metastases

Patients with stage III melanoma are at elevated risk for development of distant metastatic melanoma, even when local-regional control is achieved. Stage IIB and IIC patients also have a considerable risk, albeit smaller than that for stage III patients, of developing distant metastases [90]. Several approaches have been developed to decrease the risk of distant metastases in high-risk patients. While many show promise, none have consistently reduced the risk of distant metastases in prospective studies.

The only FDA-approved adjuvant systemic therapy for melanoma patients at high risk for metastasis is interferon-alpha-2b (IFN-alpha-2b). However, the conflicting results of multiple randomized controlled trials evaluating adjuvant IFN-alpha-2b for melanoma patients at high risk for metastasis have created confusion regarding its usefulness in patients. To summarize these results, the data support a small increase in average disease-free survival for patients with stage III and high-risk stage II disease who take high-dose IFN-alpha-2b without a consistent benefit in overall survival [91]. IFN-alpha-2b therapy is administered for a 1-year period and can lead to considerable toxicity, such as nausea, fatigue, depression, and influenza-like illness. These disadvantages must be weighed against the mild benefit in disease-free survival when deciding whether or not to recommend IFN-alpha-2b to a patient. Other adjuvant therapies are considered experimental and include biochemotherapy (immunotherapy plus antimelanoma chemotherapy) and melanoma vaccines [90]. To date no prospective data support a consistent benefit for any of these therapies, nor for chemotherapy alone, and are thus best administered to a patient in the context of a clinical trial [92–94]. Our practice is to refer patients with stage III disease who have completed their local-regional therapy to a medical oncologist with experience in treatment of melanoma for a candid discussion of all available systemic adjuvant therapy options.

Patients with stage IV (distantly metastatic) disease have a poor prognosis that has not been shown to be substantially improved by any treatment. Dacarbazine (DTIC) is the only chemotherapeutic agent recommended for stage IV melanoma. In fact, no combination regimen has been show to be significantly more efficacious than dacarbazine alone in increasing disease-free or overall survival, despite modest improvements in the <20% response rate seen with dacarbazine alone [95]. Temozolomide, an agent closely related to DTIC, has shown efficacy equivalent to that for DTIC and has the added benefit of greater blood–brain barrier penetration, which is important in patients with melanoma metastases to the brain [96]. Continued evaluation of new chemotherapeutic agents and immunotherapeutic approaches in the treatment of disseminated disease remains experimental, and thus far such approaches have not been reliably beneficial in most patients [95]. Some trials combining chemotherapeutic drugs such as vinblastine, cisplatin, tamoxifen, and dacarbazine with the biochemotherapeutic agents interferon-alpha-2a and interleukin-2 have shown increased response rates in the combination arms compared with chemotherapy alone [97–100]. Overall, however, the conclusion can be drawn that the results are conflicting and that these regimens are best used primarily in the setting of a clinical trial.

The combination of chemotherapy with various targeted therapies is being studied in metastatic melanoma more frequently given the lack of an effective treatment for this disease. Sorafenib is an agent that was designed to inhibit the ATP-binding site of the BRAF kinase. It has also been found to inhibit CRAF, VEGFR2, PDGF-beta, p38, flt-3, and c-KIT [101]. In the phase II trial setting, sorafenib has shown modest activity in refractory metastatic melanoma [102]. In a phase III trial looking at sorafenib combined with carboplatin and paclitaxol, given after failed treatment of advanced melanoma with dacarbazine or temozolomide regimens, there was no improvement in progression-free survival, overall survival or response rate with the addition of sorafenib to the chemotherapeutic regimen [103]. Thus in the second-line setting, sorafenib added to paclitaxol and carboplatin is not recommended. The trial evaluating the efficacy of this regimen as a first-line agent for advanced melanoma is ongoing [103]. Another targeted agent currently being studied is oblimersen sodium, which is an anti-Bcl-2 antisense oligonucleotide designed to induce apoptosis by inhibiting expression of the antiapoptotic product of the Bcl-2 gene. When combined with DTIC in a phase II trial in patients with metastatic melanoma, overall survival and progression-free survival were significantly improved compared with the use of DTIC alone [104]. Sorafenib and oblimersen sodium are just two of many promising targeted agents currently being tested in the clinical trial setting for the treatment of metastatic melanoma.

Table 37.3 Recommendations for follow-up, on the basis of stage

Stage	Physical examination	Radiology	Laboratory tests
Melanoma in situ	Every 6 months × 4 years, then annually	None	None
Stage I or II (with ulceration, or thickness >1.0 mm)	Every 6 months × 4 years, then annually	CXR	LDH
Stage I or II (with ulceration, or thickness >1.0 mm)	Every 4 months × 2 years, then every 6 months × 2 years then annually	CXR	LDH
Stage III, or recurrent primary	Every 3 months × 2 years, then every 6 months × 3 years, then annually	CXR	LDH, CBC
Stage IV	Individualize	Individualize	Individualize

CBC complete blood count, *CXR* chest X-ray, *LDH* lactate dehydrogenase

Treatment of Recurrent Disease

Whether it is local, regional, or distant, recurrence of melanoma is a poor prognostic sign. Re-excision is the treatment of choice for local or regional recurrences, with strong consideration given to recommending adjuvant radiotherapy. Patients with local recurrences that cannot be excised may be evaluated for palliative systemic treatment with or without a subsequent attempt to resect the recurrence. In the case of isolated distant metastatic melanoma, particularly to the lung, it might be prudent to excise the distant recurrence, as aggressive treatment occasionally results in a long-term progression-free interval or even cure. Brain and liver metastases have a worse prognosis, which is reflected in the M3 categorization of such visceral distant metastases in the melanoma staging system delineated by the AJCC [51, 105]. Although the majority of patients with recurrence will die of their disease, quality of life can be preserved by maintaining local-regional control.

Posttreatment Follow-Up

Because melanoma tends to occur in relatively younger patients, extended periods of follow-up are the norm. It has been reported that 28–56% of melanoma recurrences are discovered by a physician, indicating that a schedule of routine physical examination is an important aspect of follow-up [106, 107]. The routine use of laboratory and radiographic tests in follow-up is controversial, with little reliable data to guide their use. A summary of a recommended follow-up protocol based on stage of disease is in Table 37.3 [53].

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