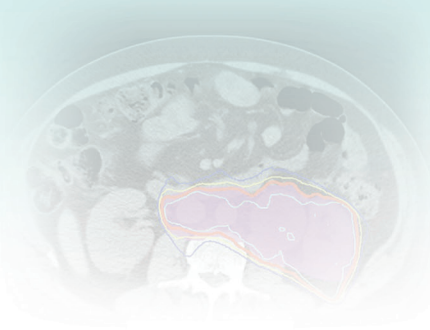
CHAPTER

42 Malignant Melanoma



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INCIDENCE

The incidence of melanoma continues to rise faster than that of any other cancer. It is estimated in 2015 that there will be 73,870 new cases of melanoma diagnosed and 9940 deaths in the United States.

BIOLOGIC CHARACTERISTICS

Sun exposure is clearly associated with the development of cutaneous melanoma. Inherited mutations may also play a role in some cases.

The natural history of melanoma is usually characterized by early, stepwise dissemination from a primary tumor to regional lymph node lesions and then to lesions at distant sites.

The main determinants of survival are the thickness of the primary tumor (measured in millimeters), the presence or absence of primary ulceration, the status of regional lymph nodes, and the sites of distant disease.

STAGING EVALUATION

For evaluating localized disease, a thorough history and physical examination including dermoscopy can suffice. For patients with nodal spread, the staging evaluation should include serum level measurement of lactate dehydrogenase and imaging with contrast-enhanced computed tomography (CT) and positron emission tomography (PET). Magnetic resonance imaging (MRI) of the brain should be considered, and it should be routine for patients with distant metastases.

PRIMARY THERAPY

Treatment of a primary melanoma lesion that is less than 0.75 mm thick is wide local excision alone. Sentinel lymph node biopsy is generally recommended for any lesion that is 1 mm or thicker or if ulceration or Clark level IV or V invasion exists in a lesion that is ≥0.75 mm and <1 mm. If the sentinel node is not involved, the patient may be observed, but if it is involved, complete lymph node dissection should be considered because it does offer a survival benefit in patients who are node positive.

If complete lymph node dissection is not possible because of medical comorbidities, elective radiation therapy to the involved nodal basin is preferred to observation.

ADJUVANT THERAPY

For patients at risk of nodal spread in whom sentinel lymph node biopsy will not alter subsequent management because of medical comorbidities, regional irradiation (i.e., elective irradiation) is preferred compared to observation.

Indications for postdissection nodal radiation therapy are high-risk pathological features including nodal extracapsular extension, lymph nodes measuring 3 cm or more in the widest diameter, at least two involved lymph nodes, and recurrent nodal disease after previous dissection for pathologically involved lymph nodes.

Adjuvant systemic interferon alpha-2b improves relapse-free survival for patients with thick, localized melanoma lesions and those with nodal metastases. It is however associated with significant toxicity.

LOCALLY ADVANCED DISEASE AND METASTASES

Palliative radiation therapy reduces symptoms in more than 80% of patients with inoperable disease or metastatic masses. Significant improvements in overall survival are seen in patients receiving systemic CTLA-4 blockers and BRAF inhibitors.

Malignant melanoma remains a predominantly surgically treated disease, and most patients with early-stage disease are cured by simple excision of the primary lesion. By the time growth of the primary tumor reaches a few millimeters, however, the risk of nodal and distant spread increases rapidly, and the role of adjuvant radiation therapy and systemic therapy takes on increasing importance. As for many diseases, radiation therapy is often recommended as an adjuvant to surgical dissection of locally advanced disease or as a palliative treatment of distant metastases. Until recently, the acceptance of radiation therapy as part of a standard treatment algorithm for patients with melanoma has been marred by controversy.

In the early 1930s, melanoma was considered to be categorically radioresistant. This belief was perpetuated by popular textbooks of the time until laboratory data showed that the reputed radioresistance of melanoma might reflect a broad shoulder in the low-dose portion of the cell survival curve. The data suggested that melanoma cells might be more sensitive to radiation delivered as a large dose per fraction (i.e., hypofractionation regimen). Although a randomized trial performed by the Radiation Therapy Oncology Group (RTOG) did not confirm clinical superiority for hypofractionation in a heterogeneous group of patients receiving palliative radiation therapy, these types of regimens are favored by clinicians specializing in melanoma radiation therapy.[1] Retrospective reviews of clinical experiences have suggested that the hypofractionated regimens are effective and can be safely delivered in a short period of time to a group of patients for whom survival is ultimately dictated by the risk of distant metastasis.[2,3]

Although hypofractionated radiation therapy has been shown to be effective in several clinical settings, the perceived risk of distant metastatic disease and concern over the rate of long-term radiation-related toxicity often precludes its use, regardless of effectiveness. In this chapter, we present the rates

of local failure, regional failure, distant failure, and long-term treatment-related toxicity for patients with melanoma and provide data supporting the use of radiation therapy in a defined group of patients. Only by balancing the competing risks of failure and treatment-related toxicity can physicians appropriately integrate radiation therapy into the management of patients with malignant melanoma.

ETIOLOGY AND EPIDEMIOLOGY

For 2015, 73,870 new cases of cutaneous malignant melanoma are estimated to occur in the United States, or 4.5% of all newly diagnosed cancers.[4] Although the incidence of malignant melanoma more than doubled between 1975 and 2000, new cases of melanoma are being diagnosed earlier in the course of the disease because of increased public awareness, and the mortality rate has steadily decreased.[4] The reason for the rise in incidence has not been explained. The number of deaths resulting from melanoma in 2013 was estimated to be 9480.

Several lines of evidence link sun or ultraviolet (UV) radiation exposure to the development of cutaneous melanoma.[5,6] There is a higher incidence of melanoma in populations with high levels of sun exposure, among sun-sensitive people, on sun-exposed body sites, in populations with high sun exposure, among people with other sun-related skin conditions,[7,8] and in those using artificial sources of UV radiation such as sunbeds. The development of melanoma may also be reduced by protection of the skin against sun exposure.[7]

Analysis of patients with familial clustering of melanoma has identified two genes, *CDKN2A* and *CDK4*, that confer increased susceptibility to melanoma development.[9] Although only a small percentage of patients with melanoma has a mutation in *CDKN2A*, carriers of this mutation have an almost 70% chance of developing melanoma by the age of 80 years.[10,11]

The presence of an increasing number of nevi also represents a well-accepted risk factor for the development of melanoma.[12] Whether the type of nevi (i.e., common, atypical, or dysplastic) is also important or merely reflects the degree of previous sun-related damage remains controversial.

PREVENTION AND EARLY DETECTION

Advocates of early detection and screening programs generally assume that early detection and treatment will significantly affect the mortality rate and the quality of life, particularly in melanoma, for which the association between tumor thickness and survival is well documented. Unfortunately, there are no randomized clinical trials to support routine screening of the general population. In the United States, routine screening of high-risk populations is still generally recommended, and educational efforts have been directed to clinicians and the public to promote early recognition of suspicious skin lesions. Periodic separate or mass screening for high-risk individuals consists of a total cutaneous examination and a 2- to 3-minute visual inspection of the entire integument by adequately trained physicians. Risk factors include a family history of skin cancer, fair skin, multiple nevi, and a history of melanoma or other skin cancers. Recognized signs of melanoma include the ABCDs of early diagnosis: A, asymmetry; B, border irregularity; C, color variation; and D, a diameter greater than 6 mm.

The U.S. Preventive Services Task Force (USPSTF)[13] performed a thorough review of the medical literature and issued a practice policy statement regarding skin cancer prevention counseling. Recommended preventive measures include avoidance of sunlight exposure—particularly limiting time spent outdoors between 10 AM and 3 PM—and wearing protective physical barriers such as hats and clothing and sunscreens that are opaque or that block UV A and B radiation.

CLINICAL MANIFESTATIONS, PATHOBIOLOGY, AND PATHWAYS OF SPREAD

Clinical Presentation and Pathology

Primary cutaneous melanoma may develop in or adjacent to one of the precursor lesions (e.g., lentigo maligna, dysplastic nevus) or in normal skin, and it can manifest clinically in four major growth patterns.[14] The most prevalent variant is *superficial spreading melanoma,* which constitutes approximately 70% of cases.[15,16] Superficial spreading melanoma often arises in a junctional nevus, where it first appears as a deeply pigmented area, progressing gradually to a flat induration, generally over several years. As the lesion grows, the surface and perimeter may become irregular with amelanotic patches. On histologic examination, it is characterized by a prominent intraepidermal proliferation of malignant melanocytes similar to Paget's disease; hence, this pattern is called *pagetoid melanoma*.[17] The malignant cell may be confined to the lower portion of the epidermis or may spread up into the granular cell layer of the epidermis, which is frequently hyperplastic. As the lesion enlarges, clusters of malignant cells invade the dermis and subcutaneous tissues.

Nodular melanoma is the second-most common variant (15% to 25% of melanoma lesions).[15,16] Nodular melanoma develops more frequently de novo on the trunk, head, or neck of middle-aged individuals. In contrast to superficial spreading melanoma, the nodular variant affects men more than women. It manifests as a raised or dome-shaped, blue-black lesion, which is usually darker than superficial spreading melanoma. Approximately 5% of nodular variants manifest as nonpigmented, fleshy nodules, and therefore, this type of lesion is called *amelanotic melanoma*. Histologic testing shows that nodular melanoma is characterized by an expansile nodule centered at the papillary dermis, with little or no epidermal component, composed of epithelioid cells. Spindle cells, small epithelioid cells, and mixtures of cells may be present. Deeper invasion of the dermis and subcutis occurs as the lesion grows.

Lentigo maligna melanoma is seen in less than 10% of malignant melanoma lesions.[16,18] This variant occurs most frequently on the face or neck of Caucasians older than 50 years, and it arises from a precursor lesion of melanoma in situ called *lentigo maligna* (i.e., *Hutchinson's melanotic freckle*).[19] It manifests as a relatively large (>3 cm), flat, tan-colored (with different shades of brown) lesion that often has been present for more than 5 years. The border becomes irregular as the lesion enlarges. On histologic examination, an invasive tumor is usually composed of spindle-like cells. These cells may be embedded in a fibrous stroma (i.e., desmoplastic pattern) or may form fascicles displaying neural features and infiltrating endoneural and perineural structures of the cutaneous nerves.[19,20]

Acral lentiginous melanoma occurs characteristically on the palms or soles or beneath nail beds.[21-23] The relative frequency of acral lentiginous melanoma varies substantially with race. It represents about 5% of melanomas in Caucasians and 35% to 60% in dark-skinned individuals.[24,25] Most acral lentiginous melanomas occur on the foot sole in individuals older than 60 years. They generally start as tan or brown stains and evolve over a period of years to reach an average diameter of 3 cm before a diagnosis is established.[22,23] Histologic testing reveals that early-stage acral lentiginous melanoma is composed of large, highly atypical, pigmented cells along the dermoepidermal junction in an area of hyperplastic epidermis. At the

invasive stage, infiltrating cells may be epithelioid or spindle shaped.[20] Sometimes, infiltration to deeper structures occurs, predominantly through the eccrine ducts.[17]

Biology and Patterns of Spread

Superficial spreading and lentigo maligna melanomas generally grow slowly over many years (i.e., radial growth phase). Left untreated, however, these lesions gradually invade the dermis and subcutis (i.e., vertical growth phase) and acquire metastatic potential. Acral lentiginous melanomas and, particularly, nodular melanomas have a shorter natural history, with rapid progression to the vertical growth pattern.

Previously, two microstaging systems were used. The Breslow system classifies lesions by the vertical thickness between the granular layer of the epidermis and the deepest part of invasion, measured with an ocular micrometer. In ulcerated lesions, measurements are made from the surface to the deepest part.[26] The Clark method categorizes lesions into five groups by the level of dermal or subcutis invasion: level I, confined to the epidermis; level II, invasion to the papillary dermis; level III, invasion to the papillary-reticular dermal interface; level IV, invasion to the reticular dermis; and level V, invasion to the subcutaneous tissue.[15] Of the two systems, tumor thickness is more accurate in predicting outcome, although level of invasion remains prognostic for patients with lesions less than 1 mm thick.[27]

In an analysis of 17,600 patients with melanoma, several clinical and histologic variables were found to be of prognostic value, and they formed the basis for an updated American Joint Committee on Cancer (AJCC) staging system[27,28] (Table 42-1). For patients without clinical evidence of nodal spread, primary thickness and ulceration were the most important prognostic features. The 10-year melanoma-specific mortality increased proportionally as the thickness of the primary tumor increased (Figure 42-1), and the survival of patients with ulcerated primary lesions diminished to a level equivalent to that of patients with thicker primary lesions that were not ulcerated[27] (Figure 42-2). There was significantly inferior 10-year disease-specific survival (DSS) according to site of the primary lesion (i.e., worse for trunk, head, and neck lesions than extremity lesions), gender (i.e., worse for patients who were male than for those who were female), and age (i.e., worse for patients who were older than for those patients who were younger).[27]

For patients with documented nodal metastases, the most important prognostic feature was the number of involved lymph nodes, but primary tumor ulceration and burden of nodal disease (microscopic compared to macroscopic) remained of prognostic significance on multivariate analysis[27] (Table 42-2). Patients with skin, subcutaneous, and distant lymph node metastases fared better than those with visceral metastases.[27]

PATIENT EVALUATION AND STAGING

Suggested staging guidelines for patients with melanoma are shown in Table 42-3. Clinical evaluation of patients with melanoma consists of inspection and palpation of the involved area of skin and the regional lymph nodes. Patients with primary lesions 1 mm thick or larger are generally staged at the time of wide local excision with sentinel lymph node biopsy. Patients with thinner lesions may still be at risk of nodal disease and may benefit from sentinel lymph node biopsy if the primary lesion is ulcerated, is associated with satellitosis, or is Clark level IV or V. If the sentinel node is involved, CT scanning of the lungs, abdomen, and pelvis is warranted as a baseline evaluation.[29]

Chest radiography plays little or no role in the initial management of patients with localized disease. PET scans and MRI

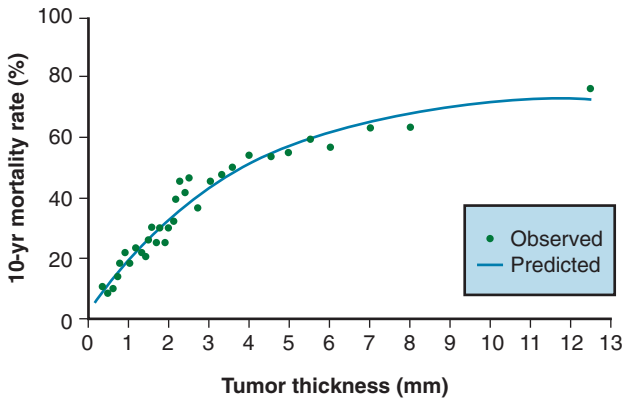
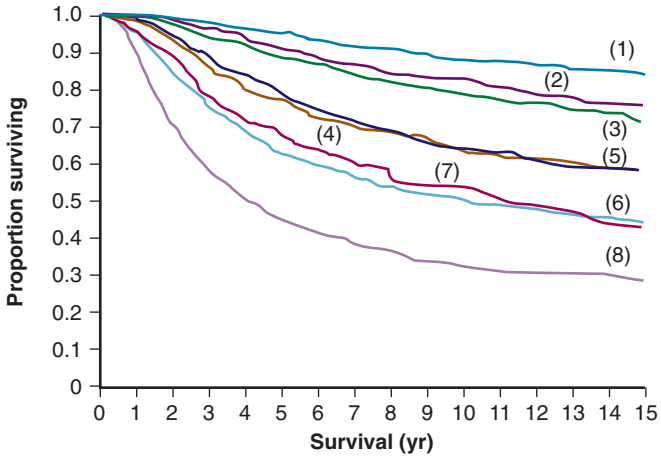


Figure 42-1 Observed and predicted 10-year mortality rate of 15,320 patients with clinically localized melanoma based on the mathematical model $f(t) = 1 - 0.998e(-211t = 0.009\ t_2)$, which is derived from the melanoma database of the American Joint Committee on Cancer (AJCC). t is the measured thickness (mm), and $f(t)$ is the 10-year melanoma-specific mortality rate ($p < 0.0001$).
From Balch CM, Soong S, Gershenwald JE, et al: Prognostic factors analysis of 17,600 melanoma patients. Validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol 19:3622–3634, 2001.



	Thickness (mm)	Ulceration	No. Patients
(1)	= <1.0	No	4510
(2)	= <1.0	Yes	1380
(3)	1.1–2.0	No	3285
(4)	1.1–2.0	Yes	958
(5)	2.1–4.0	No	1717
(6)	2.1–4.0	Yes	1523
(7)	>4.0	No	563
(8)	>4.0	Yes	978

Figure 42-2 Survival curves for 14,914 patients with localized melanoma stratified by melanoma thickness and presence or absence of ulceration. The correlation of the subgroups used for defining melanoma TNM staging with melanoma-specific survival is significant ($p < 0.0001$).
From Balch CM, Soong S, Gershenwald JE, et al: Prognostic factors analysis of 17,600 melanoma patients. Validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol 19:3622–3634, 2001.

TABLE 42-1 American Joint Committee on Cancer Staging System for Melanoma of the Skin

Primary Tumor (T)		Clinical Stage Grouping	
TX	Primary tumor cannot be assessed (e.g., shave biopsy, regressed melanoma)	Stage 0	TisN0M0
		Stage IA	T1aN0M0
T0	No evidence of primary tumor	Stage IB	T1bN0M0
Tis	Melanoma in situ		T2aN0M0
T1	Melanoma ≤1 mm thick, with or without ulceration	Stage IIA	T2bN0M0
T1a	Melanoma ≤1 mm thick, and mitosis <1/mm^2, no ulceration		T3aN0M0
		Stage IIB	T3bN0M0
T1b	Melanoma ≤1 mm thick, and mitosis >1/mm^2, or with ulceration		T4aN0M0
		Stage IIC	T4bN0M0
T2	Melanoma 1.01-2 mm thick, with or without ulceration	Stage III	TanyN1M0
			TanyN2M0
T2a	Melanoma 1.01-2 mm thick, no ulceration		TanyN3M0
T2b	Melanoma 1.01-2 mm thick, with ulceration	Stage IV	TanyNanyM1
T3	Melanoma 2.01-4 mm thick, with or without ulceration		
T3a	Melanoma 2.01-4 mm thick, no ulceration		
T3b	Melanoma 2.01-4 mm thick, with ulceration		
T4	Melanoma >4 mm thick, with or without ulceration		
T4a	Melanoma >4 mm thick, no ulceration		
T4b	Melanoma >4 mm thick, with ulceration		
Regional Lymph Nodes (N)		**Pathologic Stage Grouping**	
NX	Regional lymph nodes cannot be assessed	Stage IA	T1aN0M0
N0	No regional lymph node metastasis	Stage IB	T1bN0M0
N1	Metastasis in one lymph node		T2aN0M0
N1a	Clinically occult (microscopic) metastasis	Stage IIA	T2bN0M0
N1b	Clinically apparent (macroscopic) metastasis		T3aN0M0
N2	Metastasis in two or three regional nodes or intralymphatic regional metastasis without nodal metastases	Stage IIB	T3bN0M0
			T4aN0M0
		Stage IIC	T4bN0M0
N2a	Clinically occult (microscopic) metastasis	Stage IIIA	T1-4aN1aM0
N2b	Clinically apparent (macroscopic) metastasis		T1-4aN2aM0
N2c	Satellite or in-transit metastasis without nodal metastasis	Stage IIIB	T1-4bN1aM0
			T1-4bN2aM0
N3	Metastasis in four or more regional nodes, or matted metastatic nodes, or in-transit metastasis, or satellite(s) with metastasis in regional nodes(s)		T1-4aN1bM0
			T1-4aN2bM0
			T1-4aN2cM0
Distant Metastasis (M)		Stage IIIC	T1-4bN1bM0
MX	Distant metastasis cannot be assessed		T1-4bN2bM0
M0	No distant metastasis		T1-4bN2cM0
M1	Distant metastasis		TanyN3M0
M1a	Metastasis to skin, subcutaneous tissues, or distant lymph nodes	Stage IV	TanyNanyM1
M1b	Metastasis to lung		
M1c	Metastasis to all other visceral sites or distant metastasis at any site associated with elevated lactic dehydrogenase		

From Edge SB, Byrd DR, Compton CC, et al: AJCC cancer staging manual, ed 7, New York, 2010, Springer.

TABLE 42-2 Five-Year Survival Rates for Patients with Stage III (Nodal Metastases) Disease Stratified by Number of Metastatic Nodes, Ulceration, and Tumor Burden

	Microscopic Nodal Disease (No. Involved)						Macroscopic Nodal Disease (No. Involved)					
Melanoma Ulceration	**1 Node % ± SE**	**No.**	**2-3 Nodes % ± SE**	**No.**	**>3 Nodes % ± SE**	**No.**	**1 Node % ± SE**	**No.**	**2-3 Nodes % ± SE**	**No.**	**>3 Nodes % ± SE**	**No.**
Absent	69 ± 3.7	252	63 ± 5.6	130	27 ± 9.3	57	59 ± 4.7	122	46 ± 5.5	93	27 ± 4.6	109
Present	52 ± 4.1	217	50 ± 5.7	111	37 ± 8.8	46	29 ± 5.0	98	25 ± 4.4	109	13 ± 3.5	104

From Balch CM, Soong SJ, Gershenwald JE, et al: Prognostic factors analysis of 17,600 melanoma patients. Validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol 19:3622-3634, 2001.
SE, standard error.

of the brain are indicated for patients with multiple or clinically palpable nodal metastases and for all patients with documented distant disease.

PRIMARY THERAPY AND RESULTS

Primary Tumor

Standard treatment for localized melanoma (stages I and II) is wide local excision. Wide local excision is a therapeutic intervention, but it also establishes tissue diagnosis and provides accurate microstaging. Six randomized trials have examined the appropriate width of excision for primary melanoma.[30-34] The recommended skin margins vary from 1 cm to 2 cm depending on lesion thickness and location.[34,35]

Sentinel lymph node biopsy is recommended according to the aforementioned criteria (see "Patient Evaluation and Staging" section). This diagnostic procedure involves injection of the primary site with a dye and radiotracer-tagged colloid that localizes to the first draining lymph node or nodes after a short period of time. These nodes are then removed, serially sectioned, and examined with immunohistochemical staining techniques. Patients without involved lymph nodes are spared a comprehensive lymph node dissection. The procedure provides accurate nodal staging, but it should be followed by complete lymph node dissection or nodal radiation therapy if the sentinel node is involved. The rate of nodal spread according to primary thickness is shown in Table 42-4; it is less than 5% for lesions 0.75 mm or smaller, 10% for lesions 0.76 mm to 1.5 mm, 20% for lesions 1.51 mm to 4 mm, and 30% to 50% for lesions larger than 4 mm.[36-47]

Radiation therapy is not indicated as definitive management of primary malignant melanoma. An exception to this rule is large facial lentigo maligna melanomas for which wide surgical resection may require extensive reconstruction. In a series of 25 patients treated at the Princess Margaret Hospital with primary radiation therapy using orthovoltage x-rays (100 KeV to 250 KeV) and followed for a period of 6 months to 8 years (median, 2 years), local control was achieved in 23 patients (92%).[48] Regimens used were 35 Gy in 5 fractions over 1 week for lesions smaller than 3 cm, 45 Gy in 10 fractions over 2 weeks for primary tumors of 3 cm to 4.9 cm, and 50 Gy in 15 to 20 fractions over 3 to 4 weeks for tumors 5 cm or larger.

Radiation therapy is rarely recommended as an adjuvant to wide local excision as local recurrence rates are generally low (<10%). High-risk features such as primary thickness greater than 4 mm, head or neck primary site, and primary ulceration or satellitosis have been reported to significantly increase the risk of local recurrence, but few series report recurrence rates much higher than 15%[32,49-60] (Table 42-5).

One variant of melanoma, the desmoplastic subtype with neurotropism, has historically been associated with recurrence rates as high as 50% after wide local excision alone.[61-68] In a nonrandomized series specifically examining the role of radiation therapy in 150 patients with desmoplastic melanoma, a

TABLE 42-3 Staging Guidelines and Diagnostic Algorithm

Disease Presentation	Workup
Primary lesion <1 mm, and Clark levels II-III, and not ulcerated	History and physical examination*
Primary lesion ≥1 mm, or Clark levels IV-V, or ulcerated	History and physical examination* Sentinel lymph node biopsy
Microscopic nodal metastases	History and physical examination* Chest radiograph and serum LDH level Further imaging if warranted
Macroscopic nodal metastases	History and physical examination* Serum LDH level CT imaging of chest, abdomen, pelvis CT imaging of head and neck if primary tumor above clavicles Consider brain MRI Further imaging if warranted
Distant metastases	History and physical examination* Chest radiograph and serum LDH level CT imaging of chest, abdomen, pelvis CT imaging of head and neck if primary tumor above clavicles Brain MRI Further imaging if warranted

CT, *Computed tomography;* LDH, *lactate dehydrogenase;* MRI, *magnetic resonance imaging.*
**Attention to comprehensive skin and nodal basin examination.*

TABLE 42-4 Percentage of Patients with Positive Sentinel Lymph Nodes by Primary Melanoma Thickness

	Patients (%) by Tumor Thickness (mm)							
Study	**≤0.75**	**0.76-1.5**	**1.51-4**	**>4**	**≤1**	**1.01-2**	**2.01-4**	**>4**
Krag et al[36]	4	3	22	27	—	—	—	—
Joseph et al[37]	0	7	18	30	—	—	—	—
Mraz-Gernhard et al[38]	—	—	22	28	—	—	—	—
Haddad et al[39]	0	15	19	29	—	—	—	—
Gershenwald et al[40]	5	5	19	34	—	—	—	—
Statius Muller et al[41]	0	15	26	57	—	—	—	—
Bachter et al[42]	—	7	21	44	—	—	—	—
Blumenthal et al[43]	—	9	64	27	—	—	—	—
Caprio et al[44]	2	4	17	39	—	—	—	—
Vuylsteke et al[45]	—	—	—	—	6	16	34	55
McMasters et al[46]	—	—	—	—	—	15	30	45
Rousseau et al[47]	—	—	—	—	4	12	28	44
Weighted average (%)	1	7	21	33	4	14	29	45

From Bonnen MD, Ballo MT, Myers JN, et al: Elective radiotherapy provides regional control for patients with cutaneous melanoma of the head and neck. Cancer 100:383-389, 2003.

TABLE 42-5 Local Recurrence after Surgery Alone for Primary Tumor According to High-Risk Pathologic Characteristics

Characteristic	%	References
Breslow thickness ≥4 mm	6 to 14	35,49-53
Head and neck location	5 to 17	32,49,50,52,54-58
Ulceration	10 to 17	32,35,50,52
Satellitosis	14 to 16	59,60

Adapted from Ballo MT, Ang KK: Radiotherapy for cutaneous malignant melanoma. Rationale and indications, Oncology 18:99–107, 2004.

recurrence rate of 24% (14 of 59 patients) was reported without irradiation and 7% (5 of 71 patients) with irradiation.[67]

Regional Nodes

Elective Nodal Treatment

The role of elective nodal therapy at the time of wide local excision of the primary tumor has been disputed extensively. Advocates of elective lymph node dissection argued that melanoma progresses in a stepwise fashion from the primary lesion to regional nodes and then to distant sites, whereas opponents suggested that positive regional lymph nodes are only indicators of systemic spread. Results of an early nonrandomized study by the Sydney Melanoma Unit[69] involving 1319 patients suggested that elective lymph node dissection improved the survival rates of patients with intermediately thick melanomas (0.76 mm to 4 mm), however, four prospective Phase III trials did not confirm these results.[70-73]

The surgical community has embraced sentinel lymph node biopsy with selective lymph node dissection as a replacement to elective lymph node dissection, despite no reported therapeutic benefits in terms of overall survival (OS). This choice depends on several lines of reasoning.[74,75] The status of the sentinel lymph node is a powerful determinant of subsequent survival and provides prognostic information to the patient; it identifies patients with early regional lymph node metastases that might benefit from nodal dissection as a way of avoiding advanced regional recurrence; and it identifies patients who may be candidates for investigational systemic therapy trials.

Morton et al[76] randomly assigned 1269 patients with intermediate-thickness primary melanoma to wide excision and postoperative observation of regional lymph nodes with lymphadenectomy if nodal relapse occurred, or to wide excision and sentinel lymph node biopsy with immediate lymphadenectomy if nodal micrometastases were detected on biopsy. This trial, known as the Multicenter Selective Lymphadenectomy Trial (MSLT-I), reported improved 5-year disease-free survival (DFS) when patients undergoing sentinel lymph node biopsy with selective lymph node dissection were compared with patients who were observed. There were no differences in melanoma-specific survival. In a subgroup analysis confined to patients with nodal metastases, there was improved melanoma-specific survival in patients undergoing immediate lymphadenectomy compared with those in whom delayed lymphadenectomy was required for recurrent disease. Although the validity of this postrandomization analysis has been questioned by many,[77] the prognostic information provided by sentinel lymph node biopsy was confirmed. A second Multicenter Selective Lymphadenectomy Trial (MSLT-II) is currently examining the role of ultrasound in the staging of patients who are clinically node negative and randomizing patients with involved sentinel lymph nodes to completion lymph node dissection or observation with periodic ultrasonography.

Although sentinel lymph node biopsy remains the standard approach to patients with early-stage melanoma, there are some patients with significant medical comorbidities for whom detailed prognostic information is of little relevance and enrollment in a clinical trial is unlikely. For these patients, elective nodal irradiation is superior to observation, which places the patients at unnecessary risk of regional recurrence.[78] In a retrospective analysis from the M. D. Anderson Cancer Center, Bonnen e al[79] reviewed 157 patients with stage I or II cutaneous melanoma of the head and neck who received elective regional irradiation instead of lymph node dissection after wide local excision of the primary site. Indications for regional irradiation included primary thickness of 1.5 mm or greater or Clark level IV or V disease. There were 15 regional failures (89% regional control at 10 years) despite estimation that 33 to 40 patients had microscopically involved regional nodes (based on data from Table 42-4). Six percent of patients required medical care for a clinically significant complication, with moderate hearing loss being the most common complaint (5 patients). Although elective nodal irradiation has the same limitations as elective lymph node dissection, it can effectively provide regional control for patients at risk for regional recurrence while avoiding surgical dissection.

Therapeutic Nodal Approaches

For most patients, nodal dissection results in more than an 80% likelihood of regional control. For patients with certain clinicopathologic features, however, the surgical literature suggests regional recurrence rates as high as 80% and, therefore, a need for additional regional therapy. Although nodal extracapsular extension remains the strongest predictor of subsequent regional recurrence after surgery alone, several series have reported elevated recurrence rates if at least four lymph nodes are involved, the lymph nodes measure at least 3 cm in diameter, they are located in the cervical basin, or they are detected during a therapeutic dissection (as opposed to elective dissection or at the time of sentinel lymph node biopsy).[80-85] Although less well described in the literature, nodal recurrence after previous dissection for involved regional nodes also places the patient at increased risk of subsequent relapse. Patients with one of these six clinicopathologic features have a 30% to 50% rate of subsequent regional recurrence after nodal dissection alone (Table 42-6).

There are substantial retrospective data supporting the effectiveness of regional radiation therapy for patients with one of the aforementioned high-risk features. Relapse rates after adjuvant radiation therapy range from 5% to 20%, compared with the much higher range seen without adjuvant irradiation.[83,86-96] The Trans-Tasman Radiation Oncology Group and the Australia and New Zealand Melanoma Trials (TROG/ANZMTG) group completed a randomized trial comparing nodal observation with radiation therapy after lymphadenectomy in patients with palpable nodal disease and high-risk features.[97] High risk features included one or more involved parotid nodes, two or more involved cervical or axillary nodes, or three or more involved inguinal nodes; presence of extranodal tumor spread; or the maximum diameter of the largest metastatic lymph node was 3 cm or more (for a cervical node) or 4 cm or more (for an axillary or inguinal node). Patients received 48 Gy in 20 fractions over 4 weeks to standard conventional fields. Although there was no improvement in overall survival, this trial reports acceptable acute toxicity and 5-year regional control of 77% with radiation therapy compared with 60% without it ($p = 0.023$).

Tolerance to adjuvant radiation therapy is generally excellent and early toxic effects are infrequent and minor. Most patients receiving comprehensive neck irradiation experience transient parotid swelling after the first radiation fraction that

typically lasts 1 day. For most sites, brisk erythema with patches of moist skin desquamation, particularly within the axilla and the groin, are common. In the TROG/ANZMTG randomized trial, late radiation-related complications were distinctly uncommon, except for an increase in subcutaneous fibrosis in the adjuvant radiation therapy arm. Clinically significant extremity lymphedema (requiring some form of medical management such as a compressive sleeve or physical therapy) occurs in a minority of patients. It is more common after groin dissection than after cervical or axillary dissection, and it appears to moderately increase further in the setting of adjuvant irradiation, particularly for patients with locally advanced groin metastases[85,93-102] (Table 42-7). In one series examining the timing of lymphedema, however, half of the patients had developed lymphedema before starting adjuvant groin irradiation.[95] This suggested that the higher rate of lymphedema was to some extent a consequence of locally advanced disease and its surgical treatment and not solely the result of the radiation therapy. In this same series, there was a correlation between body mass index and the development of chronic lymphedema, suggesting that patient factors need to be incorporated into rational treatment guidelines.[95] In the randomized trial there were no differences in quality of life, although regional symptoms were worse in those patients receiving radiation therapy.

TABLE 42-6 Regional Relapse Rates after Surgery Alone for Nodal Disease According to High-Risk Pathologic Characteristics

Nodal Characteristic	Study	Year	Relapse Rate (%)
Extracapsular extension	Calabro et al[80]	1989	28*
	Lee et al[81]	2000	63*
	Monsour et al[82]	1993	54
	Shen et al[83]	2000	31*
≥4 Involved lymph nodes	Calabro et al[80]	1989	17 to 33*
	Lee et al[81]	2000	46 to 63
	Miller et al[84]	1992	53*
Lymph node ≥3 cm	Lee et al[81]	2000	42 to 80
	Shen et al[83]	2000	14
Cervical lymph node location	Bowsher et al[85]	1986	33
	Lee et al[81]	2000	43*
	Monsour et al[82]	1993	50
Therapeutic dissection	Byers[55]	1986	50
	O'Brien et al[57]	1991	34
	Lee et al[81]	2000	36
	Shen et al[83]	2000	20

Significant on multivariate analysis.

Distant Disease and Adjuvant Systemic Therapy

A great amount of resources has been directed toward developing effective systemic therapy for patients with melanoma. Although surgical resection with selective use of adjuvant radiation therapy results in satisfactory local and regional control for most patients, even thin melanomas have significant metastatic potential. Most research initiatives have focused on interferon alpha-2b (IFN) or vaccines, or combinations of both. European investigators have examined the role of low-dose IFN therapy, and U.S. investigators have focused primarily on high-dose regimens. Three randomized Eastern Cooperative Oncology Group (ECOG) trials are used to support the use of adjuvant IFN for patients with a high risk of recurrence.[103-105]

The first trial (ECOG 1684) enrolled 287 patients with primary melanomas thicker than 4 mm without palpable nodes, lymph node metastasis detected at elective lymph node dissection, a clinically palpable regional lymph node with primary melanoma of any stage, or regional lymph node recurrence at any interval after appropriate surgery for primary melanoma of any depth.[103] This prospective study revealed a significant prolongation of relapse-free survival (RFS) (5-year actuarial, 37% versus 26%; $p = 0.002$) and OS (5-year, 46% versus 37%; $p = 0.02$) associated with high-dose IFN therapy (i.e., intravenous administration five times per week for 4 weeks, then subcutaneous administration three times per week for 48 weeks). The overall benefit of treatment in this trial was correlated with the tumor burden and the presence of microscopic nonpalpable and palpable regional lymph node metastases. The benefit of therapy with IFN was greatest among recipients with palpable regional nodal metastases or nodal recurrences.

The second trial (ECOG 1690) compared high-dose IFN for 1 year or low-dose IFN for 2 years versus observation.[104] Intent-to-treat analysis revealed 5-year RFS of 44% and 40% for the high-dose and low-dose IFN arms, respectively, compared with 35% in the observation arm ($p = 0.05$ for high-dose IFN versus observation, and $p = 0.17$ for low-dose IFN versus observation). Most of the benefit was observed for patients with two to three involved lymph nodes. For OS, there was no difference demonstrated for the three treatment arms (52%, 53%, and 55% for high-dose IFN, low-dose IFN, and observation, respectively).

TABLE 42-7 Clinically Significant Lymphedema According to Site of Regional Disease and Treatment

	Surgery Alone*			Surgery and Radiation*		
Nodal Basin	Study	Year	%	Study	Year	%
Cervical	Urist et al[98]	1983	0	Ballo et al[93]	2002	0
	Wrightson et al[99]	2003	0	Burmeister et al[102]	2002	0
				Burmeister et al[96]	2006	0
Axilla	Urist et al[98]	1983	1	Ballo et al[94]	2003	16
	Wrightson et al[99]	2003	5	Burmeister et al[102]	2002	7
	Bowsher et al[85]	1986	3	Burmeister et al[96]	2006	9
Groin	Bowsher et al[85]	1986	18	Burmeister et al[102]	2002	45
	Karakousis et al[100]	1994	10	Ballo et al[95]	2004	27
	Hughes et al[101]	2000	19	Burmeister et al[96]	2006	19
	Wrightson et al[99]	2003	32			

Clinically significant lymphedema required some form of medical management (e.g., compressive device or physical therapy).

The third trial (ECOG 1694) compared high-dose IFN with a ganglioside GM2 melanoma vaccine.[105] After 880 patients were randomized to one of the treatment arms, an interim analysis indicated inferiority of the ganglioside vaccine with respect to RFS and OS. In a subgroup analysis, however, the beneficial effects of IFN were seen only in the patients with stage T4N0 disease and not those with nodal disease.

Debate over the merits of routine IFN therapy has focused on the inconsistent subgroup analysis findings and concerns about the toxicity of IFN, but it is not unreasonable to recommend one year of IFN for patients with thick tumors (>4 mm thick), ulceration, a high mitotic rate (≥1 per mm^2), or nodal metastases.[106]

Frequently observed regression of primary melanoma and even occasionally metastatic disease has suggested an important role for the immune system. This has fueled a long-standing search for active immunotherapies against melanoma. Interleukin-2 has shown durable response rates in 15% of patients and is considered a reasonable first option for patients with metastatic disease with sufficient performance status to tolerate its significant toxicity.

Until recently, none of the immunologic approaches had demonstrated clinical efficacy in terms of OS. However, the U.S. Food and Drug Administration recently approved new drugs as treatment for metastatic melanoma based on Phase III trial data reporting improvement in OS.

The BRAF kinase inhibitor vemurafenib blocks the mitogen-activated protein kinase (MAPK) signaling pathway that normally promotes cell proliferation and contains BRAF kinase as one of its components. Oncogenic (i.e., abnormal) BRAF kinase has been reported in almost 50% of cutaneous melanomas resulting in uncontrolled activation of the MAPK pathway. In 675 patients randomized to either vemurafenib or dacarbazine there was an improvement in the 6 month OS (84% versus 64%, $p < 0.001$) with vemurafenib and a response rate of 48%.[107] Vemurafenib should be considered in patients with untreated metastatic disease, but genetic mutation analysis is essential to verify the appropriate BRAF mutation (V600E) is present. A second BRAF inhibitor, dabrafenib, was also tested against dacarbazine in 250 patients with the V600E mutation and resulted in improved progression-free survival.[108]

The human monoclonal antibody Ipilimumab blocks cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and stimulates an antitumor T-cell response. In 676 patients with stage III or IV disease ipilimumab was given either alone or with gp100 vaccine and compared to a third group receiving gp100 vaccine alone. The median survival was improved in both groups receiving the ipilimumab when compared to the gp100 group (10 months versus 6.4 months, $p < 0.001$).[109] In a second trial of 502 patients with untreated metastatic melanoma ipilimumab was given with dacabazine and compared to dacarbazine plus placebo and resulted in significantly improved OS at 3 years (20.7% versus 12.2%, $p < 0.001$).[110] Ipilimumab should be considered in patients with untreated receptor negative (e.g. BRAF, cKit) metastatic disease. When temporally combined with radiation ipilimumab has been reported to result in regression of disease distant from the irradiated site suggesting the possibility of an immunologically mediated abscopal effect.[111] Trials involving combinations of targeted therapy and radiation therapy are under way to determine if responses can be improved.

LOCALLY ADVANCED DISEASE AND PALLIATION

Radiation therapy can reduce symptoms for more than 80% of patients with advanced inoperable or metastatic disease. The recommended dose-fractionation schedule for external beam therapy depends on the tumor's location and the patient's life expectancy. The most frequently used regimens are 30 Gy given in 10 fractions over 2 weeks for skeletal or multiple cerebral metastasis, 36 Gy in 12 fractions for pathologic fracture of extremity bones (after internal fixation), 50 Gy in 25 fractions for solitary metastases after resection or radiosurgery (brain), and 36 Gy in 6 fractions over 3 weeks (twice each week) for dermal or subcutaneous melanoma masses or for neck node metastasis. Conventional fractionation schedules may always be considered if tumor lies near critical structures. The use of stereotactic ablative radiation therapy has gained considerable attention recently for the management of oligometastases from melanoma in the brain, lung, bones, spine, and liver. Dose schedules vary according to the tumor volume and site of disease but are generally well tolerated.

RADIATION THERAPY TECHNIQUES

Target Volume

Adjuvant radiation therapy for primary melanoma should encompass the primary site scar with a 3-cm to 4-cm margin, depending on the anatomic site and surrounding critical structures.

The target volume for patients receiving *elective nodal irradiation* for *head and neck primary sites* includes the primary lesion, the preauricular and postauricular lymph nodes (for high facial and scalp primary tumors), and the ipsilateral lymph nodes from levels I through V, including the ipsilateral supraclavicular fossa (Figure 42-3). For patients receiving therapeutic nodal irradiation for one of the aforementioned high-risk nodal features, the target volume is essentially the same, including the dissection scar, except that the primary tumor bed is irradiated only if regional relapse occurred less than 1 year after excision of the primary disease.

For *axillary nodal metastases,* radiation fields include the axillary lymph nodes from levels I through III (Figure 42-4). The supraclavicular fossa and low cervical lymph nodes may be included if there is bulky high axillary disease but otherwise do not need to be treated.

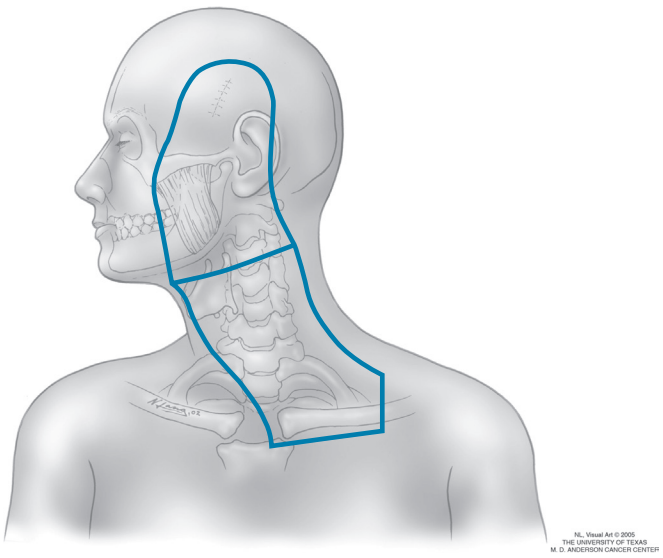


Figure 42-3 Typical external beam radiation treatment field for a patient with cervical lymph node metastases. A similar field is used for a patient requiring elective irradiation.
Courtesy NL Visual Art © 2005, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

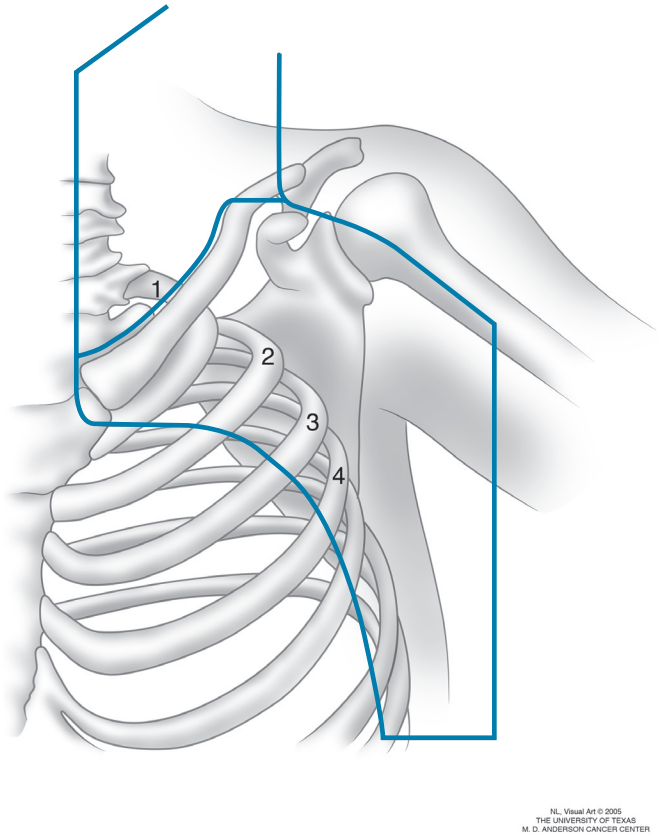


Figure 42-4 Typical external beam radiation treatment field for a patient with axillary lymph node metastases. Numbers correspond to the ribs. The upper border of the field typically ends at the superior aspect of the clavicle, but the supraclavicular and cervical lymph nodes may be irradiated if clinically involved.
Courtesy NL Visual Art © 2005, University of Texas M. D. Anderson Cancer Center, Houston, Texas.

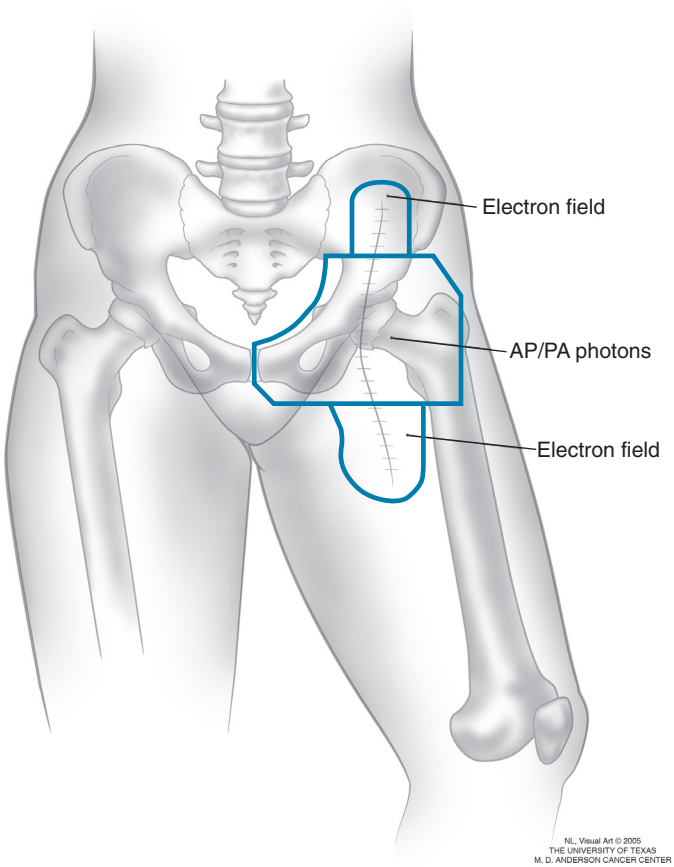


Figure 42-5 Typical external beam radiation field for a patient with groin lymph node metastases.
Courtesy NL Visual Art © 2005, University of Texas M. D. Anderson Cancer Center, Houston, Texas.

At a minimum, a field for groin lymph node metastases covers the nodal regions that have pathologically confirmed nodal disease and usually includes the entire surgical scar (Figure 42-5). Judgment must be used regarding elective irradiation of adjacent nodal regions (i.e., external iliac coverage in the setting of confirmed inguinal disease) because of concern about the increased toxicity associated with groin irradiation, particularly for patients who are obese. Unlike the cervical or axillary regions, where electrons and flashing photon fields, respectively, generally deliver a full dose to the skin, special attention must be paid to delivering a full dose to the groin scar.

Setup, Field Arrangement, and Dose-Fractionation Schedule

For patients with cervical disease, an open neck position provides access to the primary site and parotid and cervical lymphatics, and it allows treatment delivery with electrons of appropriate energy. Lesions of frontal, temporal, and preauricular areas; the auricle; and the cheek are usually treated with two or three fields, depending on the distance between the primary tumor and the parotid nodes. Matching electron fields are used to treat the primary site, the parotid and lower neck nodes. The junctions between the fields are moved (0.5 cm to 1 cm) after the second and fourth treatments to improve dose homogeneity. A tissue-equivalent bolus is placed over a line connecting the lateral canthus and the mastoid tip to spare the temporal lobe, and an additional piece of bolus may be placed over the larynx. The thickness of this bolus depends on the electron energy used. Elective or adjuvant radiation treatment is administered to a total dose of 48 Gy in 20 daily fractions (Monday through Friday) or 30 Gy at 6 Gy per fraction, twice each week (Monday and Thursday or Tuesday and Friday) over 2.5 weeks. Electron doses are specified at D_{max} (maximal depth dose) and care is always taken to ensure that the dose to the spinal cord does not exceed 40 Gy at 2.4 Gy per fraction or 24 Gy at 6 Gy per fraction.

For axillary treatment, the patient is immobilized in a supine position with the treatment arm akimbo. Laser lines that include the upper and lower torso ensure a reproducible treatment setup. Typically, anterior and posterior photon fields are used to deliver the dose to the levels I, II, and III axillary lymph nodes. Dose homogeneity is ensured using a field-within-a-field technique (using multileaf collimators). The radiation dose is 48 Gy in 20 daily fractions or 30 Gy at 6 Gy per fraction, twice each week over 2.5 weeks. If necessary the dose may be prescribed to a volume such that the isocenter dose is 3% to 6% lower than the prescribed dose as dose heterogeneity can result in unacceptable toxicity at these doses per fraction.

To irradiate the groin, patients are immobilized in a unilateral frog-leg position, eliminating any inguinal skin folds.

Photons or electrons can be used depending on the patient's contour, extent of surgical bed and whether the pelvic nodes are included as part of the target volume. Lower-energy electron fields can be used superiorly and inferiorly to cover the full extension of the scar. If a photon technique is selected, a tissue-equivalent bolus is used over the scar, and the dose is weighted anteriorly. Doses are either 48 Gy in 20 daily fractions or 30 Gy at 6 Gy per fraction, twice each week over 2.5 weeks. Appropriate reductions are made to limit the small bowel dose to 40 Gy at 2.4 Gy per fraction or 24 Gy at 6 Gy per fraction.

For all sites of regional disease, intensity-modulated radiotherapy (IMRT) may also be used to cover the aforementioned regions. IMRT is currently under investigation as an alternative technique aimed at reducing toxicity.

Radiation Therapy for Bulky or Inoperable Nodal Disease

Radiation therapy can be considered for bulky or inoperable nodal disease in which surgery is likely to be incomplete or the extent of the nodal disease would predict a poor OS. Similar techniques used in the postoperative setting can be used with surgery to follow 10 to 12 weeks later if the patient continues to have localized disease.

Patient Care during and after Radiation Therapy

Patients are informed of the specific acute side effects of treatment, such as mucositis and parotiditis after irradiation of the cervical basin and moist desquamation after irradiation of the axilla or groin. After moist desquamation occurs, cleaning the area with mild soap and water to prevent secondary infection is recommended.

Regular follow-up examinations include evaluation of the treated area for late complications and a search for potential relapse. The most common late side effects include hypopigmentation, hyperpigmentation, telangiectasia, and skin and subcutaneous tissue atrophy. After cervical irradiation, monitoring for subclinical hypothyroidism and the signs and symptoms of hearing loss, although relatively uncommon, is essential. Acute lymphedema is managed early and aggressively with physical therapy and compressive devices to avoid chronic lymphedema.

TREATMENT ALGORITHMS AND CLINICAL TRIALS

Elective Nodal Treatment

Sentinel lymph node biopsy has obviated routine elective treatment of the draining lymphatics of patients with thick primary melanomas. Although retrospective studies of elective irradiation have verified the effectiveness of this approach, sentinel lymph node biopsy with complete lymph node dissection has become accepted as the standard of care. For patients whose medical comorbidities preclude sentinel lymph node biopsy (and the required comprehensive dissection if the sentinel node is involved), elective nodal irradiation is favored over observation, which reduces the risk of regional recurrence with its associated morbidity. Although this approach is still investigational, it is suggested that patients with a positive sentinel lymph node biopsy result who refuse subsequent dissection be referred for regional irradiation. Observation in the setting of an involved sentinel lymph node is not appropriate, and systemic therapy is not a substitute for completing regional therapy.

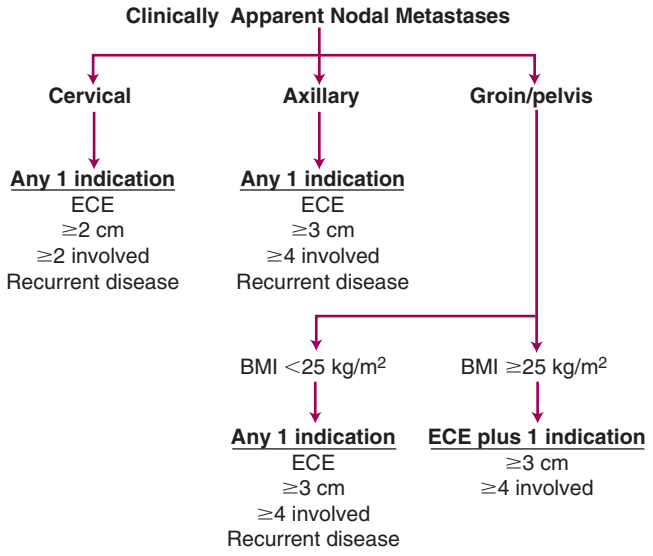


Figure 42-6 Treatment algorithm for patients with nodal metastases from melanoma. Typically, the threshold for irradiating patients with cervical lymph node metastases is lower than for those with inguinal lymph node metastases, for which the risk of long-term lymphedema is higher. *BMI*, Body mass index; *ECE*, extracapsular extension.

Therapeutic Nodal Approaches

Therapeutic nodal dissection is the standard treatment for patients with lymph node metastases, and available data support the use of systemic, high-dose adjuvant IFN. Adjuvant postoperative irradiation is also indicated to reduce the regional recurrence rate in patients with high-risk clinicopathologic features. Although some of the same features that predict regional failure, such as extracapsular extension and number of involved lymph nodes, also predict distant failure, the importance of regional control should not be underestimated, and radiation therapy should not be systematically avoided because the risk of distant metastasis is perceived to be too high.

We have developed radiation treatment guidelines that account for the complex clinical interaction between the risk of regional recurrence, the risk of regional toxicity, and the risk of distant metastatic disease (Figure 42-6). For patients with cervical disease, the threshold for irradiation may be lowered to include those with at least two involved lymph nodes or those with tumors measuring at least 2 cm in diameter. For patients with groin metastases, the threshold may be raised so that combinations (two or more) of the high-risk features must be present before adjuvant irradiation is given.

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To K. Kian Ang for demanding excellence.

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A full list of cited references is published online at www.expertconsult.com.

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