Chapter 13
Melanoma

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Introduction

In 2014, the Canadian Cancer Society (CCS) reported that melanoma was the seventh most common diagnosed malignancy across Canada. Melanoma represents less than 5 % of all skin cancers, but accounts for the most attributable deaths from skin cancer. In 2014, 6500 new cases and 1050 deaths from melanoma were estimated to have occurred. Between 2001 and 2010, the incidence rates of melanoma increased by 2.2% per year for men and by 2.1 % per year for women [1].

Presentation	Prognosis 5-Year overall survival (OS)
• Localized disease (82–85 %)	90 %
• Regional metastasis (10–13 %)	30–75 %
• Distant metastasis (2–5 %)	15 %

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The American Joint Committee on Cancer (AJCC) 7th edition is the current recommended melanoma staging system.

Management

Primary Localized Melanoma

Management of melanoma in situ

Work-up	Wide local excision (margins) [2]	Lymph node assessment	Follow-up (F/U) [3–5]
• History and physical exam • No labs • No radiologic studies	• 5 mm clinical margin	• SLNB is not indicated	• Clinically: – Instruct patients on skin examinations (patient education) – Refer to dermatologist – One clinical visit per year

SLNB sentinel lymph node biopsy

Management of melanoma ≤ 1 mm (Breslow depth)

Work-up	Wide local excision (margins) [2]	Lymph node assessment	Follow-up (F/U) [3–5]
• History and physical exam • Clinical assessment of regional lymph nodes and in-transit lesions • No labs • No radiologic studies	• 1 cm clinical margin • Including skin and subcutaneous tissue to the fascia (but not the fascia)	• SLNB is not indicated in most cases (see below)	• Clinically: – Instruct patients on skin examinations (patient education) – Refer to dermatologist – Every 6–12 months for first 3 years, and then annually • No labs • No imaging

SLNB sentinel lymph node biopsy

Special Notes

- When melanoma 0.75–1 mm in depth, discuss the option of SLNB to patients with any of the following features [6–8]:
  - Ulceration (T1b)
  - Mitotic rate ≥ 1/mm^2 (T1b)
  - Microsatellitosis
  - Clark IV/V

- There is a lack of consensus regarding what should be considered a "high-risk feature" in melanomas < 1 mm in depth. Lymphovascular invasion, presence of regression >50 %, vertical growth rate, and absence of tumor infiltrating lymphocytes remain unclear predictors of lymph node positivity. The presence of one of these high-risk criteria in isolation cannot be interpreted as a clear indication for SLNB. Breslow thickness of >0.75 mm alone without any risk factor correlates with increased risk of positive SLN (8.8 %) and SLNB may be justified on the basis of tumor depth only [9].
- Mitotic rate is the most important prognostic factor after tumor thickness for stage I and II cutaneous melanoma and has a greater independent prognostic significance than tumor ulceration [10, 11].
- There is limited evidence to inform follow-up frequency and imaging.
- For subungual melanomas, the appropriate surgical management is a functional amputation (proximal to closest joint or ray amputation).

Management of melanoma 1–4 mm (Breslow depth)

Work-up	Wide local excision (margins) [2]	Lymph node assessment [2]	Follow-up (F/U) [4, 5]
• History and physical exam • Clinical assessment of regional lymph nodes and in-transit lesions • No labs • No standard radiologic studies • Further imaging only if clinically indicated	• 1–2 mm melanoma: – 1–2 cm clinical margin • 2–4 mm melanoma: – 2 cm clinical margin • Margins may be modified to accommodate functional or anatomic considerations • Consultation to plastic surgery if primary closure is compromised (i.e., lower arm/lower leg/high on the back)	• Discuss and offer SLNB	• Clinically: – Stage I: Every 6–12 months for 3 years and then annually – Stage II: Every 6 months for first 2 years, then annually – Stages III–IV: Every 3–6 months for first 3 years, then every 6–12 months for 2 years, and then annually – Patient education – Refer to dermatologist • No labs • No imaging

SLNB sentinel lymph node biopsy

Special Notes

- The updated available Level I evidence is insufficient to determine optimal excision margins for melanoma, including all Breslow thickness [12, 13]. Recommendations are based on consensus/guidelines.
- Excision of the fascia is not necessary except in the case of documented clinical or radiologic invasion. Margins are determined from the edge of the lesion or the incision excision/biopsy scar. Adequate margins are assessed clinically. Reexcision is recommended with involved margins.

Management of melanoma ≥ 4 mm (Breslow depth)

Work-up	Wide local excision (margins) [2]	Lymph node assessment	Follow-up (F/U) [4, 5]
• History and physical exam • Clinical assessment of regional lymph nodes and in-transit lesions • No labs • Imaging: – CT or MRI of brain[a] + – CT chest, abdomen and pelvis – OR PET/CT ± MRI brain[a]	• 2 cm clinical margin • Margins may be modified to accommodate functional or anatomic considerations • Consultation to plastic surgery if necessary if primary closure is compromised	• Discuss and offer SLNB	• Clinically: – Stage II: Every 3–6 months for first 2 years, then every 6–12 months for 2 years, and then annually – Stages III–IV: Every 3–6 months for first 3 years, then every 6–12 months for 2 years, and then annually • No labs • No imaging

SLNB sentinel lymph node biopsy
[a]Depending on institutional preference or availability

Special Notes

- There is very limited data with no evidence about improved outcomes with standard metastatic work-up. This is left to the discretion of individual physicians.
- Controversy exists regarding clinical value of sentinel lymph node assessment for thick melanoma. T4 melanomas have higher risk of systemic metastases at initial diagnosis, and patients might not benefit from lymphadenectomy in terms of survival. However, for thick melanoma without distant metastases, SLNB remains useful for staging, prognostication, and locoregional control [14]. Thick melanomas have a 42 % risk of node positivity at 10 years and SLN status still represents the most important survival prognostic factor [15, 16]. Lymphadenectomy confers a 10-year disease-free survival benefit mostly for intermediate thickness melanoma. Among patients with intermediate thickness with nodal metastases, there is a benefit in 10-year melanoma-specific survival in the biopsy group (62.1 %) compared to the observation group (41.5 %) [15, 16].
- There is a lack of valid prospective studies of the efficacy of routine follow-up.
- No study has demonstrated an improvement in survival due to routine imaging surveillance.

Regionally Metastatic Melanoma

Clinical scenario	Work-up	Surgical approach [15, 17–19]
SLNB positive [15, 17–19]	• Metastatic work-up with: – CT head or MRI of brain + – CT chest, abdomen, and pelvis – OR PET/CT ± MRI brain	• Completion lymphadenectomy (CLND) is discussed and offered[a] • MSLT-2 trial—accrual completed • Observation + ultrasound monitoring (if patient refuses further surgery or not surgical candidate) • Refer to medical oncology for assessment of adjuvant therapy/clinical trial • Consider consultation to radiation oncology for adjuvant radiation therapy
Clinically positive lymph node	• FNA or lymph node biopsy • Imaging: – CT or MRI of brain + – CT chest, abdomen, and pelvis – OR PET/CT ± MRI brain	• Completion lymphadenectomy • Refer to medical oncology for assessment of adjuvant therapy/clinical trial • Consider consultation to radiation oncology for adjuvant therapy and/or for unresectable disease • Consideration of neoadjuvant therapy to enable resection
In-transit or satellite lesions [20–22]	• FNA or excisional/incisional biopsy • Imaging: – CT or MRI of brain + – CT chest, abdomen, and pelvis – OR PET/CT ± MRI brain	• Single lesion: – Surgical excision with clear margins + consider SLNB (if it has not been performed previously) – Refer to medical oncology for assessment of adjuvant therapy (interferon-α)/clinical trial • Multiple lesions (no consensus): – Resection if feasible – Isolated limb perfusion/infusion with melphalan ± dactinomycin. Possible improvement in DFS and OS with complete response. Similar overall response (50–85 %) rate between ILI and ILP. Increased toxicity with ILP. – Intralesional therapy with IL-2, interferon-α, or BCG. Phase III trial of intralesional VP10/Rose Bengal ongoing – Topical therapy with imiquimod or diphencyprone cream (DPCP) – T-VEC: viral vaccine talimogene laherparepvec. Objective response in 26 % and complete response in 11 % of cases. Clinical trials [23] – Radiation therapy for unresectable disease – Combination of systemic therapy with intralesional treatment/clinical trials

MSLT-2 multicenter selective lymphadenectomy trial 2 (NCT 00297895), *SLNB* sentinel lymph node biopsy, *FNA* fine-needle aspiration, *CLND* completion lymphadenectomy, *ILI* isolated limb infusion, *ILP* isolated limb perfusion, *BCG* Bacille Calmette-Guérin, *OS* overall survival

[a]No randomized trials have demonstrated the therapeutic value of completion lymph node dissection

Special Notes

- The rate of successful SLNB is 98.1 % with an overall false-negative rate of 12.5 %. In high-volume centers with >50 cases/year, a false-negative rate of 5 % (local recurrence rate 5 %) is achieved [24]. We recommend performing SLNB with preoperative lymphoscintigraphy and using both blue dye and radioactive dye. Approximately 15–20 % of patients with a positive sentinel lymph node will have melanoma metastases identified in completion lymphadenectomy [14, 25]. CLND has not been proven to increase overall survival after positive sentinel node and about 80–85 % of the time, SLN is the only positive node. These patients might be exposed to unnecessary morbidity [26]. MSLT-2 trial aims to define the therapeutic value of CLND versus observation after positive SLN.
- Completion lymphadenectomy in the axilla usually requires levels 1, 2, and 3 dissection with selective transection of pectoralis minor [27]. Some argue that level 3 axillary dissection should be performed only when palpable nodes are present [28, 29].
- In the groin, superficial inguinal lymphadenectomy remains the current standard of treatment with non-palpable positive SLN and absence of abnormal pelvic lymphadenopathy on imaging. Extent of dissection including deep iliac/obturator dissection is controversial. Deep iliac/obturator lymphadenectomy should be completed in the presence of pelvic node involvement on pre-operative imaging (CT scan or PET/CT). Deep iliac/ obturator lymphadenectomy should be considered in the presence of clinically detected superficial inguinal node disease, positive Cloquet's node and multiple positive (>= 3) positive sentinel nodes [30].
- Neoadjuvant therapies in the context of unresectable/borderline resectable regional disease have been studied. Chemotherapy such as temozolomide has been shown to be ineffective in the neoadjuvant setting in a small phase II study with a 15 % response rate, similar to what is seen in the metastatic setting [31]. Neoadjuvant high-dose interferon has shown a response rate of 55 %, but with high toxicity and 50 % recurrence at 18 months [32]. Biochemotherapy combining IL-2, interferon-alpha, and multiagent chemotherapy demonstrated high response rates (40 %) but with substantial toxicity [33]. Vemurafenib improved both DFS and OS in BRAF mutant metastatic melanoma patients. High response rate and low toxicity make vemurafenib an ideal neoadjuvant therapy; however currently no studies have been completed in this patient population [34].

- Intralesional interleukin-2 (IL-2) for the treatment of in-transit melanoma has an overall response rate of 82 %, with complete clinical response in 51–69 % of patients and complete pathologic response rate of 32 % [35]. When complete clinical response is achieved, an increase in 5-year overall survival can be obtained, compared to partial responders (80 % vs. 33 %, respectively) [36, 37]. However, this increase in survival might not necessarily represent a direct effect of intra-tumoral IL-2 and could be biased by selection of cases with less aggressive disease [38]. Unlike systemic IL-2, intralesional IL-2 is well tolerated with much less toxicity.

Rationale for sentinel lymph node biopsy	
Accurate staging • Allows a more rational follow-up strategy	
Prognostic factor • The 5-year overall survival for patients with nodal micrometastases is 67 % and with nodal macrometastases, 43 % [39]	
Better locoregional control • Complication rates of SLNB vs. lymphadenectomy: 4.6 % vs. 23.2 % [17, 40] • By identifying micrometastases (through SLNB), patients are less likely to require radiation to the nodal basin, and thus a lower chance of lymphedema • Lymphedema rate for axillary SLNB vs. complete lymphadenectomy: 1.7 % and 9 %, respectively [17, 41] • Lymphedema rate for groin SLNB vs. complete lymphadenectomy: 1.7 % and 26 %, respectively [17, 41]	
Potential/unclear survival benefit • In SLN-positive patients [16], to date, there is no definite evidence that SLNB followed by lymphadenectomy for positive nodes confers a survival benefit	
Impact in adjuvant therapy • Accurate nodal staging information is important in order to offer patients enrolment in ongoing clinical trials • Small benefit of interferon	
Tumor thickness likelihood of positive SN	
<0.8 mm	<1 %
0.8–1.5 mm	8 %
1.5–4.0 mm	23 %
>4.0 mm	42 %

Distant Metastatic Melanoma

Work-up	Surgical approach [42–45]	Systemic therapy [46]
• Labs: – Serum LDH – CBC, lytes, BUN, Cr, LFTs • Imaging: – CT or MRI of brain – CT chest, abdomen, and pelvis – PET/CT scan if considering surgical intervention	• Metastasectomy—careful consideration of complete resection in: – Pulmonary metastases (survival benefit)—5-year OS of 20 % if complete metastasectomy compared to 4 % if incomplete resection – Symptomatic GI metastases – Symptomatic brain metastases (surgery, stereotactic radiosurgery, or whole-brain radiation) – Symptomatic adrenal metastases – Liver metastases—survival benefit only shown in retrospective studies from ocular melanoma when complete metastasectomy – Subcutaneous metastases – Palliation of symptoms	• Clinical trial whenever available and appropriate • Targeted therapies dependent on mutational status (BRAF, cKIT, MEK, NRAS, GNAQ genes) – V600 BRAF mutation positive (43–50 % of cases): offer clinical trial or BRAF inhibitor – BRAF inhibitor (vemurafenib, dabrafenib): rapid tumor response, but common progression of disease within 6–12 months of treatment. Preferred option for symptomatic or rapidly progressive disease – MEK inhibitor—alone or in combination with BRAF inhibitor/clinical trials. Combined treatment offers a longer PFS – cKIT: featured in acral and mucosal melanoma • Immunotherapy – Ipilimumab: Slow but durable response in 20 % of patients – Systemic IL-2: objective response in 20 % of cases, complete response in 7 % [42]. Significant toxicity. – Anti-PD1: monoclonal antibody against PD-1. Preferred option for stage IV disease – Anti-PDL1—antibody against PD-1 ligand. Clinical trials • Systemic chemotherapy (dacarbazine, temozolomide, carbo/taxol and abraxane): Dacarbazine and temozolomide have a clinical response rate of 15–20 % and a complete response rate of 3–5 % [42]

LFT liver function test, *PET* positron emission tomography, *OS* overall survival, *PFS* progression-free survival

Special Notes

- Most common causes of death with metastatic melanoma are respiratory failure and intracranial metastases. A phase II trial of complete resection for stage IV melanoma (SWOG, S9430 trial) reported a 4-year OS of 31 % with median survival of 21 months [47]. 5-Year survival of 40 % has also been reported for complete metastasectomy when tumor-free margins are obtained [42]. When resection of melanoma metastases ± systemic therapy was compared to systemic medical therapy alone, median survival was 15.8 vs. 6.9 months and surgical treatment conferred a 4-year survival of 20.8 % vs. 7.0 %. Distant disease-free interval of more than 12 months, M1a, and lower number of organ sites of metastases were associated with improved survival [48]. Optimal sequencing of recent systemic therapies with metastasectomy remains unclear.

Landmark Trials

Wide Local Excision: Margins

Melanoma (Breslow thickness)	Study	Methods	Results
• In situ	• No RCTs	–	–
• <1 mm – No specific RCTs	**French Cooperative Surgical Trial** [49]	• $N=337$ (melanoma < 2.1 mm) • Excision margins: 5 cm vs. 2 cm • Median F/U: 16 years	• No difference in OS • LR not reported
	Swedish Cooperative Surgical Trial [50]	• $N=989$ (melanoma 0.8–2.0 mm) • Excision margins: 5 cm vs. 2 cm • Median F/U: 11 years	• No difference in OS • LR: <1 % overall
	WHO Melanoma Program Trial [51]	• $N=612$ (melanoma ≤ 2 mm) • Excision margins: 3–5 cm vs. 1 cm • Median F/U: 15 years	• No difference in OS • No difference in LR
• 1–4 mm – French, Swedish and WHO trials plus:	**Intergroup Melanoma Surgical Trial** [52, 53]	• $N=740$ (melanoma 1.0–4.0 mm) • Excision margins: 4 cm vs. 2 cm • Median F/U: 10 years	• No difference in OS • No difference is LR
	British Cooperative Group Trial [54]	• $N=675$ (melanoma 2.0–4.0 mm) • Excision margins: 3 cm vs. 1 cm • Median F/U: 5 years	• No difference in OS same • Lower LR with 3 cm margins ($p=0.05$)

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Melanoma (Breslow thickness)	Study	Methods	Results
• >4 mm	**British Cooperative Group Trial** [54]	• *N* = 225 (melanoma > 4 mm) • Excision margins: 3 cm vs. 1 cm • Median F/U: 5 years	• No difference in OS

F/U follow-up, *RCT* randomized controlled trials, *WLE* wide local excision, *OS* overall survival, *NS* not significant, *LR* locoregional recurrence, *CLND* completion lymphadenectomy—immediate, *DFS* disease-free survival, *TLND* therapeutic lymphadenectomy—delayed, *SLN* sentinel lymph node

Sentinel Lymph Node Biopsy

Study	Methods	Results
Multicenter Selective Lymphadenectomy Trial (MSLT-1) [15, 16]	• RCT • *N* = 1347 (melanoma 1.2–3.5 mm), 314 with thick melanoma • Groups: WLE + SLNB (with CLND if positive) vs. WLE and observation (with TLND when clinically nodal relapse) • Median F/U: 10 years	• 5-year DFS 78 % vs. 73 % ($p = 0.009$) • 10-year DFS SLNB vs. observation for intermediate thickness: 71.3 % vs. 64.7 % ($p = 0.01$) and for thick melanoma: 50.7 % vs. 40.5 % ($p = 0.03$) • No significant difference in 10-year melanoma-specific survival in intermediate-thickness melanoma (81.4 % in SLNB group vs. 78.3 % in observation group, $p = 0.18$) and in thick melanoma (58.9 % vs. 64.4 %, $p = 0.56$) • Subgroup analysis in positive sentinel node patients: – Better 10-year OS in those who were SLN+ and had CLND vs. those who had TLND (62.1 % vs. 41.5 %, $p = 0.006$) • Node-negative patients have 10-year OS of 85.1 % vs. 62.1 % for those with node-positive disease ($p < 0.001$) • In multivariable analysis, sentinel node status is the strongest predictor of disease recurrence and death from melanoma

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Study	Methods	Results
Multicenter Selective Lymphadenectomy Trial (MSLT-2) NCT00297895	• Phase III multicenter RCT • Groups: Sentinel Lymphadenectomy and Complete Lymph Node Dissection Versus Sentinel Lymphadenectomy Alone in Cutaneous Melanoma Patients With Molecular or Histopathological Evidence of Metastases in the Sentinel Node • Accrual completed in 2014 • Estimated study completion date : 2022	

RCT randomized controlled trial, *WLE* wide local excision, *OS* overall survival, *LR* locoregional recurrence, *NS* not significant, *CLND* completion lymphadenectomy—immediate, *TLND* therapeutic lymphadenectomy—delayed, *SLN* sentinel lymph node, *DFS* disease-free survival

Systemic Therapy

Drug	Study	Methods	Results
Vemurafenib	Chapman PB et al. [55]	• RCT • Vemurafenib (BRAF inhibitor) vs. dacarbazine in previously untreated metastatic melanoma with the BRAF V600E mutation	• At 6 months, OS was 84 % for vemurafenib group vs. 64 % for dacarbazine • Relative reduction 63 % in risk of either death and 74 % in risk of disease progression as compared with dacarbazine • PFS of 5.3 vs. 1.6 months with dacarbazine
Dabrafenib	Hauschild A et al. [56]	• RCT • Dabrafenib (BRAF inhibitor) vs. dacarbazine in previously untreated unresectable stage III or IV BRAF-mutated melanoma	• Median PFS 5.1 months for dabrafenib vs. 2.7 months for dacarbazine (HR 0.30, $p<0.0001$) • Adverse events 53 % dabrafenib group vs. 44 % dacarbazine group
Trametinib	Flaherty KT et al. [57]	• RCT • Trametinib (MEK inhibitor) vs. dacarbazine vs. paclitaxel in previously untreated BRAF-mutated metastatic melanoma	• 6-month OS 81 % trametinib vs. 67 % chemotherapy • Median PFS 4.8 months in trametinib vs. 1.5 months in chemotherapy groups (HR 0.45, $p<0.001$)

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Drug	Study	Methods	Results
Ipilimumab	Robert C et al. [58]	• RCT • Ipilimumab (Anti-CTLA-4) + dacarbazine vs. dacarbazine + placebo in previously untreated metastatic melanoma	• OS significantly longer in Ipi + D vs. D + placebo—11.2 vs. 9.1 months with higher survival rates at: – 1 year (47.3 % vs. 36.3 %) – 2 years (28.5 % vs. 17.9 %) – 3 years (20.8 % vs. 12.2 %)
Interferon-alpha	Kirkwood JM et al., 1996—Eastern Cooperative Oncology Group (EGOG 1684) [59]	• RCT • High-dose IFN alpha-2b vs. observation in stage IIB and III primary or recurrent regional nodal metastases	• 5-year RFS 37 % vs. 26 % • 5-year OS 46 % vs. 37 % • Dose modification in majority of patients due to toxicity
	Kirkwood JM et al., 2000—Eastern Cooperative Oncology Group (EGOG 1690) [60]	• RCT • High-dose IFN-alpha for 1 year vs. low-dose IFN-alpha for 2 years vs. observation in stages IIB and III or recurrent regional nodal metastases	• RFS benefit of IFN alpha is dose dependent (44 % vs. 40 % vs. 35 %) • No significant survival benefit (5-year OS 52 % vs. 53 % vs. 55 %)
	Wheatley K et al. [61]	• Meta-analysis • 12 trials, comparisons of IFN-alpha with controls	• Absolute difference in DFS of 7 % with IFN-alpha • OS benefit is not significant, but absolute survival difference of 3 % with IFN-alpha • The difference in treatment effect is dependent on doses of IFN-alpha. Benefit of IFN-alpha tends to increase with increasing total scheduled dose ($p = 0.05$)
Combined BRAF and MEK inhibitors	Long GV et al. [62]	• RCT • Dabrafenib (BRAF inhibitor) + trametinib (MEK inhibitor) vs. dabrafenib + placebo in previously untreated unresectable stage IIIC or stage IV melanoma with BRAF mutation	• Median PFS 9.3 months in combination group vs 8.8 months in dabrafenib-alone group • Overall response rate: 67 % vs. 51 % • At 6 months, OS 93 % vs. 85 % ($p = 0.02$) • Similar adverse events
	Larkin J et al. [63]	• RCT • Vemurafenib (BRAF inhibitor) + cobimetinib (MEK inhibitor) vs. vemurafenib + placebo in untreated unresectable locally advanced or metastatic BRAF mutation-positive melanoma	• Median PFS 9.9 months in combination group vs. 6.2 months in vemurafenib-alone group • Overall response rate: 68 % vs. 45 % • At 9 months, OS 81 % vs. 73 % ($p = 0.046$) • Higher rate of adverse events Grades 3–4 with combination group

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Drug	Study	Methods	Results
Anti-PD1	Wolchok JD et al. [64]	• Phase 1 trial • Nivolumab (Anti-PD1) + ipilimumab intravenously, combined or sequenced regimens	• Objective response in 40 % and 20 % of cases in combined and sequenced regimens, respectively
	Topalian SL et al. [65]	• Retrospective • *N* = 107 • IV Nivolumab q 2 weeks for up to 96 weeks in advanced melanoma	• Median OS 16.8 months, 1- and 2-year OS 62 % and 43 %, respectively • Median PFS 3.7 months • Objective response rate 31 %
	Hamid O et al. [66]	• Retrospective • *N* = 135 • IV Lambrolizumab q 2–3 weeks in advanced melanoma	• Median PFS > 7 months • Objective response rate 38 %

RCT randomized controlled trial, *PFS* progression-free survival, *OS* overall survival, *D* dacarbazine, *RFS* relapse-free survival, *DFS* disease-free survival, *IFN* interferon

Referring to Medical Oncology (Patients with High-Risk Melanoma)

1. Primary melanoma with Breslow thickness > 4 mm
2. Node-positive melanoma
3. In-transit or satellite lesions
4. Metastatic disease
5. Recurrent disease
6. Unknown primary melanoma

Patients with metastatic melanoma should be referred for clinical trials whenever possible. Metastatic melanoma of the unknown primary site is diagnosed in approximately 2–9 % of all melanoma cases. It is usually diagnosed if metastatic melanoma is confirmed clinically and pathologically, and if no cutaneous, uveal, or mucosal melanoma primary can be found. Data suggests that unknown primary melanoma can be accurately staged using the AJCC staging system, and have equal survival stage per stage [70].

Cancer Care Ontario (CCO) and the Melanoma Disease Site Group recommend that high-dose interferon alpha-2b therapy for 1 year should be discussed with and offered to patients with high-risk melanoma for adjuvant therapy. Pegylated IFN can be used as an alternative to high-dose IFN-alpha [71]. Meta-analyses and randomized controlled trials demonstrated increased recurrence-free survival rate with IFN-alpha (7 % absolute risk reduction at 5 years), but little effect on overall survival (3 % absolute benefit in 5-year OS) [61, 72]. Tumor burden in lymph nodes and ulceration of the primary tumor have been reported as predictors for benefit from adjuvant IFN-alpha [73]. Because the actual overall survival benefit with systemic therapy is relatively small (3 %), patients should be encouraged to participate in available clinical trials.

Referring to Radiation Oncology [74–76]

1. Gross residual disease
2. Extracapsular nodal extension
3. ≥2 cervical, ≥2 axillary, ≥3 inguinal lymph nodes involved
4. Cervical lymph node ≥ 2 cm, axillary and inguinal lymph node ≥ 3 cm
5. Therapeutic lymph node dissection not possible after positive sentinel node
6. Unresectable in-transit/satellite metastases and isolated limb perfusion/infusion is not effective or not possible [22]
7. Metastatic disease—if symptomatic from focal disease; treatment of brain metastases with stereotactic radiosurgery or whole-brain radiation therapy
8. Pure desmoplastic melanoma with narrow margins, locally recurrent or extensive neurotropism [77]

Referring to Multidisciplinary Cancer Conference (MCC)

1. Melanoma with Breslow thickness < 1 mm
2. Bulky nodal disease
3. New metastatic disease
4. In-transit or locoregional recurrence
5. Any consideration of non-standard multimodal therapy
6. Consideration of available clinical trials

Desmoplastic Melanoma

Desmoplastic melanoma (DM) constitutes less than 4 % of all primary cutaneous melanomas and is most commonly located on head and neck. Neurotropism and absence of BRAF mutation are common features of DM. DM is pathologically characterized by spindle-shaped cells with atypical melanocytic proliferation and abundant collagen stroma [78]. Desmoplastic melanoma is classified into pure and mixed subtypes. Pure subtype DM is defined by a predominance of stromal fibrosis with >90 % desmoplasia while mixed DM is characterized by the presence of desmoplasia within 10–90 % of the tumor [79].

DM has favorable survival prognosis compared to conventional melanoma subtypes with a lower risk of distant metastases. However, DM has an increased risk of local recurrence (5-year local recurrence rate of 17 %). Radiation therapy may improve the rate of local recurrence [77]. Recommendation on SLNB is controversial, with overall rate of positive SLN ranging between 0 and 15 %, but should be considered and discussed with patients [77, 79]. DM featuring mixed subtype has a 24.6 % rate of SLN positivity vs. 9 % with pure subtype [79].

Toronto Pearls

- Groin dissection flaps should preserve Scarpa's fascia with the flap.
- Saphenous vein preservation during groin dissection could be considered if micrometastatic nodal disease only.
- Consider IL-2 intra-tumoral injection in the management of multiple in-transit metastases as first-line treatment.
- For patients at high risk for local failure and those who only underwent superficial groin dissection, consider postoperative surveillance with CT of the abdomen/pelvis to identify patients who could develop iliac/obturator node recurrence and be candidates for further salvage surgery.
- Consider radiation therapy for pathologic positive margins from satellitosis or lymphovascular invasion around the primary site.
- If patient declines completion lymphadenectomy after a positive SLNB, perform ultrasound monitoring of the axilla and/or groin every 6 months for 3 years and then yearly to 5 years.
- Level 3 axillary dissection should be completed in the presence of palpable axillary disease. In the presence of positive axillary SLNB, level 1–2 dissection can suffice.

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