Melanoma

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Introduction

Melanoma is the seventh most common diagnosed malignancy across Canada [1]. Melanoma represents less than 5% of all incident skin cancers but accounts for the most attributable deaths from skin cancer. In 2017, of all new cancers diagnosed, 3.9% in males and 3.1% in females were melanoma. Overall there were an estimated 7322 new cases, and 1240 deaths from melanoma in 2017. The incidence rates of melanoma continue to increase by approximately 2% per year for both men and women and the mortality rate by 1% per year for men and 0.3% for women [1].

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Similar trends in increasing incidence have been reported in the United States, United Kingdom, Sweden, and Norway [2]. Melanoma is the fourth most common cancer in adolescents and adults ages 15–49 [1].

Exposure to ultraviolet radiation through exposure to sunlight, tanning beds, and sun lamps are a major risk factor for melanoma. Other risk factors include having a fair complexion, the number and type of moles, personal and family history of skin cancer, a weakened immune system, and a history of severe blistering sunburn [3].

Historically, melanoma has been divided into four main subtypes: superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM), nodular melanoma (NM), and acral lentiginous melanoma (ALM) based on histopathological features of the intra-dermal component of the tumour adjacent to a dermal invasive component [4]. SSM is the most common subtype in European descent accounting for approximately 60% of cutaneous melanoma. They occur in younger patients (median age 5th decade) and arise in areas of intense intermittent sun exposure such as trunk and lower limbs [4–6]. SSM presents as a flat irregularly shaped macule with variation in colour (brown, black, pink, blue) and atypical reticular pattern on dermatoscopy [6, 7]. SSM subtype is the largest contributor to the increasing incidence of melanoma [8].

Lentigo Maligna Melanoma presents similarly to SSM, a large variegated macule with irregular edges. LMM tends to occur later in life (median 8th decade) and in chronically sun-exposed areas (head and neck, forearms). It is estimated to be 5–15% of all diagnosed melanomas but up to 25% of those diagnosed on head and neck [9, 10]. On histology there is evidence of severely sun-damaged skin with lentiginous proliferation of atypical melanocytes [4]. The 'ABCD' (asymmetry, border irregularity, colour variegation, diameter 6 mm) melanoma warning signs are hallmarks of SSM and LMM [11].

In contrast, NM and ALM do not fall into the 'ABCD' presentation. Nodular melanomas tend to occur in older patients (median age 7th decade), any location, and present as a rapidly expanding nodule often detected as changing lesions by patients. NMs account for 10–30% of diagnosed melanomas [8, 12]. Despite this, approximately half of all cutaneous melanomas >2 mm in depth are NMs, reflecting their increased vertical growth rate and resultant more advanced stage on presentation [12, 13]. In comparison with SSM, NM are more often ulcerated, have a higher mitotic index, and more frequently have an NRAS mutation [12, 14]. ALM appears as a pigmented lesion on non-sun–exposed extremities, specifically the palms of hands, soles of feet, and at the base of nail beds. The relative proportion of ALM varies across ethnicities. In white populations of European descent, ALM is reported to be 1–7% of all cutaneous melanomas; however, in Asian populations, ALM ranges from 18% to 47% and nearly 40% in African populations [15–17]. ALM has demonstrated lower overall 5 year and 10 year survival rates compared to other cutaneous melanomas of equivalent stage; however, given the rarity of the subtype and paucity of prospective data, it is unclear if this observation has been due solely to delay in diagnosis and later stages of presentation [15, 16].

Desmoplastic melanoma (DM) is a rare variant (<4%) of cutaneous melanoma and is most commonly located on the head and neck. Neurotropism and absence of BRAF mutation are common features of DM. Clinically it can be confused for lentigo maligna or more often be amelanotic. On histology it can often appear as an amelanocytic spindle with abundant collagen formation and is thought to be a

Table 16.1 Clinical presentation and prognosis

Presentation	Prognosis 5-Year overall survival (OS) [21]
Localized disease (82–85%)	82–99%
Regional metastasis (10–13%)	32–93%
Distant metastasis (2–5%)	20–30%[a]

[a]In the setting of checkpoint inhibitors and targeted therapy, 5 year OS for stage IV disease has increased from a historical 5 year OS of approx. 6%

sarcomatoid melanoma. There are two histological variants of DM, pure and mixed. In pure DM (pDM) the lesion is predominately desmoplastic and fibrosis is seen throughout. In mixed DM (mDM) fibrosis is limited and more cellularity is seen throughout the lesion. DM has higher rates of local recurrence compared to other melanoma histological subytpes [4, 18]. Additionally, pDM demonstrates higher rates of local recurrence, less frequent lymph node involvement, and overall better prognosis than mDM [18, 19]. In contrast, the rate of lymph node involvement and overall prognosis in mDM is similar to other melanoma histological subytpes [20]. Other uncommon melanoma subtypes include nevoid melanoma, (histologically resembles a nevus) and spitzoid melanoma (resembling a spitz nevus) [4].

Clinically melanoma can present a localized disease, with involved regional lymph node basins (regional metastatic disease), or with distant metastasis. Overall prognosis is reflective of extent of disease (Table 16.1).

Staging

The American Joint Committee on Cancer (AJCC) 8th edition is the current recommended melanoma staging system. In the 8th edition of the AJCC staging system, T1 thin melanomas (previously <1 mm) have been subcategorized into T1a <0.8 mm without ulceration and T1b <0.8 mm with ulceration, or 0.8–1 mm with or without ulceration [21, 22]. A significant decrease in 10 year melanoma-specific survival (MSS) was demonstrated for melanomas >0.8 mm with localized disease alone compared to melanomas <0.8 mm (73% vs. 86% $p < 0.01$) [23].

AJCC 8th edition no longer differentiates between satellite and in-transit lesions as 2 cm from the previous excision was an arbitrary cut-off.

While the extent of lymph node positivity is the greatest prognostic factor for MSS in the non-metastatic population, more accurate prognostic estimates are obtained by including tumour thickness [24]. This is reflected in the AJCC 8th edition which has expanded Stage III subcategories to reflect tumour thickness in addition to ulceration and the extent of nodal and/or in-transit disease [22, 24].

The AJCC 8th staging system has also re-categorized central nervous system (CNS) metastatic disease as M1d irrespective of other sites of disease. This reflects both the poorer prognosis of CNS metastasis compared to other sites of metastasis as well as the stratification in systemic therapy studies [22, 24]. Additionally, elevated lactate dehydrogenase (LDH) is no longer classified as M1c. LDH level is now combined with metastatic site such that each Ma-d has a subcategory designation (0 to indicate normal LDH and 1 for an elevated LDH).

Management

Primary Localized Melanoma

Notes: 5 mm margin is generally adequate particularly for MIS that is non-lentigo maligna (LM) type [28]. The borders of LM can be less distinct and have higher rates of incomplete excision [29]. In a large prospective study, 86% of MIS were completely excised with 6 mm margins, whereas 99% were completely excised with 9 mm margins [30]. Surgery is commonly performed to the depth of the deep subcutaneous fascia because occult invasive melanoma (generally less than 0.5 mm) has been reported in up to a third of MIS [31] (Table 16.2).

Special Notes

- Thin melanomas <1 mm in depth, discuss the option of SLNB to patients with any of the following features:
  - Between 0.8 and 1 mm (T1b)
  - Ulceration
  - Microsatellitosis
  - Clark IV/V
  - Higher mitotic count (>3)
- Once considered potential 'high-risk' features in thin melanomas, newer studies suggest that lymphovascular invasion, tumour regression >50%, vertical growth rate, and absence of tumour infiltrating lymphocytes are not independent risk factors for lymph node positivity. The presence of one of these criteria in isolation cannot be interpreted as a clear indication for SLNB [32–34].
- While most thin melanomas have <4.5% likelihood of a positive sentinel lymph node, the likelihood increases to 8.8% for melanomas 0.75–1 mm. Consideration for SLNB should therefore be given to patients based on Breslow thickness of >0.75 mm alone (rounded to 0.8 mm in AJCC 8th edition, T1b) [21, 32, 35–37] (Table 16.3).
- Ulceration is an independent prognostic factor for both melanoma-specific survival (MSS) and sentinel lymph node positivity. While ulceration in thin melano-

Table 16.2 Management of melanoma in situ

Workup	Wide local excision (margins) [25]	Lymph node assessment	Follow-up (F/U) [26, 27]
History and physical exam No labs No radiologic studies	5 mm clinical margin with the aim of achieving histological negative margins increase to 10 mm clinical margin if necessary	SLNB is not indicated	Clinically: Instruct patients on skin examinations (patient education) Refer to dermatologist One clinical visit per year with dermatologist (or more frequently as clinically indicated based on skin exam)

SLNB sentinel lymph node biopsy

Table 16.3 Management of melanoma ≤1 mm (Breslow depth)

Workup	Wide local excision (margins) [25]	Lymph node assessment	Follow-up (F/U) [26, 27]
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 <0.8 mm SLNB should be considered and discussed for melanoma 0.8–1 mm and <0.8 mm with ulceration	Follow-up is dependent on clinical stage based on the results of sentinel lymph node biopsy Stage IA Clinically: Instruct patients on skin examinations (patient education) Refer to dermatologist Every 6–12 months for first 3 years, and then annually with a dermatologist no oncologist follow-up is necessary No labs No imaging

SLNB sentinel lymph node biopsy

mas is seen predominately in those >0.8 mm, the presence of ulceration is an independent risk factor for sentinel lymph node positivity even in melanomas <0.75 mm [37–39]. For melanomas <0.8 mm with ulceration, consideration should be given to SLNB [35] (Table 16.3).

- While mitotic rate was previously felt to be an independent prognostic factor for sentinel lymph node positivity in thin melanomas, recent data suggests that the impact of mitotic rate >1 mm is interdependent with Breslow thickness and depth >0.75 mm is a stronger predictor than mitotic rate [38, 40].
- 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).

Special Notes

- There have been no prospective randomized studies to date which compare 1 cm and 2 cm margins for intermediate thickness 1–2 mm melanoma. WHO Melanoma Group RCT 1 versus 3 cm for <2 mm melanoma demonstrated no difference in MSS but increased local recurrence with 1 cm excision [41]. A recent meta-analysis (although combines various tumour thickness) suggests that a narrow margin (1–2 cm) results in significantly worse local recurrence and MSS [42] compared to a wider margin (3–5 cm). This is the only publication that has demonstrated better survival with a wider margin of excision (Tables 16.4 and 16.10).
- RCTs for melanoma >2 mm have compared 1 versus 3 cm margins and 2 versus 4 cm margins. There was no significant difference in overall survival (OS) or local recurrence when comparing 2–4 cm margins [43, 44]. There was no difference in OS, but there was a significantly improved MSS in patients who had 3 cm margins compared to 1 cm margins [45] (Table 16.10).

Table 16.4 Management of melanoma 1.1–4 mm (Breslow depth)

Workup	Wide local excision (margins) [25]	Lymph node assessment	Follow-up (F/U) [26, 27]
History and physical exam Clinical assessment of regional lymph nodes and in-transit lesions No labs No routine radiologic studies Further imaging only as clinically indicated	1–2 mm melanoma: 1–2 cm clinical margin, 2 cm if feasible without compromising cosmetic or functional outcome or requiring reconstructive surgery 2–4 mm melanoma: 2 cm clinical margin Margins may be modified to accommodate functional or anatomic considerations Consultation with plastic surgery if primary closure is compromised (i.e., lower arm/lower leg/high on the back) No need to remove fascia	offer SLNB	Follow-up is dependent on clinical stage based on the results of sentinel lymph node biopsy Clinically: Instruct patients on skin examinations (patient education) Refer to dermatologist Stage IB/IIA: Every 6–12 months for 3 years and then annually with a dermatologist No oncologist follow-up is necessary No labs No imaging Stage IIB: Every 6 months with an oncologist (medical and/or surgical) for first 3 years, then annually Every 6–12 months with a dermatologist No labs No imaging Stages III–IV (see Tables 16.5 and 16.7)

SLNB sentinel lymph node biopsy

- The updated available Level I evidence is insufficient to determine optimal excision margins for melanoma [46]. Recommendations are based on consensus/guidelines.
- MelMarT-II (NCT 03860883) is an actively recruiting prospective trial randomizing patients 1–2 mm with ulceration and >2 mm with or without ulceration (pT2b-T4b AJCC 8th ed.) to 1 versus 2 cm resection to determine differences in disease-free survival (DFS) with narrow margins.
- May consider wider margins with desmoplastic melanoma (DM). Local recurrence rate (LRR) is higher than other cutaneous melanomas, 6.7–56% [47]. The increased LRR is believed to be due to both microscopic residual disease and neurotropism (seen 17–78%) [18, 47]. For pure DM lesions <2 mm resected with 1 cm margins cumulative index mortality was 25.2% higher than lesions <2 mm resected with 2 cm margins [48]. While there is no data specifically for DM, <1 mm current recommendations for excision all DM is 2 cm when feasible [18].
- Margins are determined from the edge of the clinically visible lesion or the incision excision/biopsy scar. Adequate margins are assessed clinically. Re-excision is recommended with involved margins.

Table 16.5 Management of melanoma > 4 mm (Breslow depth)

Workup	Wide local excision (margins) [25]	Lymph node assessment	Follow-up (F/U) [26, 27]
History and physical exam Clinical assessment of regional lymph nodes and in-transit lesions No labs Imaging: CT or MRI of brain[a] AND 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 with plastic surgery if necessary if primary closure is compromised	Discuss and offer SLNB	Follow-up is dependent on clinical stage based on the results of sentinel lymph node biopsy Clinically: Instruct patients on skin examinations (patient education) Refer to dermatologist Stage IIB/C: Every 6 months with an oncologist for first 3 years, then annually Every 6–12 months with a dermatologist No labs No routine imaging Refer to medical oncology for consideration of adjuvant clinical trial in Stage 2b/c Stages III–IV (see Tables 16.5 and 16.7)

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

- Based on limited data, it is recommended that the depth of excision should extend to the level of the fascia, but the fascia itself does not require excision except in the case of documented clinical or radiologic invasion [28, 49] (Table 16.4).

Special Notes

- There is very limited data with no evidence about improved outcomes with standard metastatic workup at the time of initial workup for patients with thick melanomas (>4 mm) and no evidence of nodal or in-transit disease. Imaging at initial presentation is left to the discretion of individual physicians (Table 16.5).
- Controversy exists regarding the clinical value of sentinel lymph node assessment for thick melanoma as T4 melanomas have higher risk of systemic metastases at initial diagnosis. However, for thick melanomas without distant metastases, SLNB remains useful for staging (and directing adjuvant treatment), prognostication, and locoregional control [35, 50, 51]. Thick melanomas have a 42% risk of node positivity at 10 years, and SLN status still represents the most important survival prognostic factor [50]. SLNB confers a 10-year disease-free survival benefit for intermediate and thick melanomas [50].
- 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. However, melanoma-specific survival for Stage IIB are lower than that of Stage IIIA and Stage IIC mirror that of IIIB suggesting that imaging as part of surveillance for high-risk Stage II patients might be warranted. The utility and implementation of routine imaging for surveillance in high-risk Stage II patients remain to be determined (Table 16.5).

- Surveillance imaging is currently left to the discretion of individual physicians. Some centres complete surveillance CT scans annually in the high-risk population while recognizing the current lack of data to support this.

Regionally Metastatic Melanoma

Special Notes

- The rate of successful SLNB is 98.1% with an overall false-negative rate of 12.5%. In high-volume centres with >50 cases, a false-negative rate of 5% (local recurrence rate 5%) is achieved [60, 61]. We recommend performing SLNB with preoperative lymphoscintigraphy and using both blue dye and radioactive dye [62]. Approximately 15–20% of patients with a positive sentinel lymph node will have melanoma metastases identified in completion lymphadenectomy [50, 61]. Table 16.7 desrcibes the rationale for sentinel lymph node biopsy.
- Based on retrospective data and the results of the MSLT-1 trial, there was controversy around the role of CLND after positive SLN alone. MSLT-1 demonstrated an improvement in disease-free survival in both intermediate and thick melanomas, but this translated into an improved MSS only for intermediate thickness melanomas when comparing SLNB positive with CLND to those patients who present with clinically palpable disease. This effect was not demonstrated for thick melanomas [50] (Table 16.11).
- Given that the SLN is the only positive node (i.e. no further positive lymph nodes identified on CLND) in 80–85% of patients, and the limited population in which CLND may confer survival benefit (MSLT-1), numerous patients undergoing routine CLND solely for SLNB positivity may be exposed to unnecessary morbidity [63, 64]. This was the basis for 2 RCTs prospectively examining the benefit of CLND after positive SLNB versus close observation, with CLND only in the setting of subsequently identified clinical or radiographic disease [52–54]. These RCTs demonstrated no difference in OS, MSS, or distant metastatic-free survival. MSLT-2 noted a higher disease free survival in the CLND group rather than observation group, but this did not translate into improved OS nor MSS, as patients underwent CLND at the time of lymph node disease progression [52] (Tables 16.6 and 16.11).
- Patients excluded from these RCTs included: concomitant microsatellitosis, immunosuppression of the patient, extracapsular spread/extension (MSLT-2 only), more than two involved nodal basins (MSLT-2 only), and disease >2 mm within the SLN (DeCOG-SLT only). Additionally, 66% positive SLNBs in both studies had <1.01 mm of lymph node disease [52, 54]. CLND, rather than close observation, can be considered for patients with the above features following discussion with the patient and MCC (Tables 16.6 and 16.11).
- In MSLT-2 subset analyses, no patients were seen to benefit from routine CLND including those with higher volume disease in the lymph nodes and higher number of nodes involved. Site of primary melanoma also did not affect outcome.

Table 16.6 Management of regional metastatic melanoma

Clinical scenario	Workup	Treatment approach	Follow-up
Sentinel lymph node biopsy (SLNB) positive [35, 52–54]	Mutational analysis Metastatic work-up with: CT head or MRI of brain AND CT chest, abdomen, and pelvis (C/A/P) OR PET/CT ± MRI brain	Completion lymphadenectomy (CLND) is no longer offered routinely to all patients based on the results of MSLT-2 and deCOG-SLT Rather than CLND: clinical exam + ultrasound (U/S) monitoring of SLNB positive lymph node basins q 4–6 months for the first 2 years. then q6 months for 3 years Discussion and consideration of CLND for those patients: who are unable to go onto close surveillance and/or did not meet inclusion criteria for MSLT-2 and deCOG-SLT Refer to medical oncology for assessment of adjuvant therapy	Clinically: Instruct patients on skin examinations (patient education) Stage III: Every 3–6 months with an oncologist for first 3 years, then every 6 months for 2 years, then annually Every 6–12 months with a dermatologist U/S of SLNB positive basins q4–6 months for first 2 years then q 6 months for 3 years Consider imaging: CT C/A/P q 6–12 months or as clinically indicated CT/ MRI brain as clinically indicated -no role for routine bone scan No routine labs
Clinically Positive Lymph Nodes[a] [35, 52–54]	FNA or lymph node biopsy Mutational analysis Imaging: CT or MRI of brain AND CT chest, abdomen, and pelvis OR PET/CT ± MRI brain	Therapeutic lymphadenectomy, or completion lymphadenectomy if previous SLNB, of involved basin(s) Consideration of neoadjuvant therapy to enable resection and potentially improve survival Refer to medical oncology for assessment of neoadjuvant or adjuvant therapy Consider consultation with radiation oncology for adjuvant therapy to nodal basin and/or for unresectable disease	
Local recurrence, in-transit or satellite lesions[b] [27, 55, 56–59]	Excisional/incisional biopsy or FNA Mutational analysis Imaging: CT or MRI of brain AND CT chest, abdomen, and pelvis OR PET/CT ± MRI brain	*Local recurrence* Surgical excision with negative margins *One to four in-transit/satellite lesion*: Surgical excision with clear margins Refer to medical oncology for assessment of adjuvant therapy *Multiple lesions* (no consensus): Local surgical therapy options Resection if feasible Amputation (very rarely necessary) Intralesional therapy with IL-2, interferon-α, BCG, VP10/Rose Bengal ORR 69–87% and CR rates for IL-2 range from 32% to 69%. CR correlated with improved PFS and OS. Addition of topical therapies to IL-2 has increased the CR to 60–100% T-VEC[c]: viral vaccine talimogene laherparepvec. Phase 3 RTC T-VEC vs.G-CSF. 15% with TVEC in injected lesions, 8% in uninjected (bystander) and 3% in visceral lesions. Median OS response improved with T-VEC (23.3 months vs. 18.9) Topical therapy with imiquimod or diphencyprone cream (DPCP). OR 60–100% and CR rates 40–100% have been reported with imiquimod. OR 13–46% and CR rates 40–80% have been reported with DPCP Radiation therapy for unresectable disease has demonstrated up to 66% CR and 100% ORR for subcutaneous metastasis Regional therapy options Heated isolated limb perfusion (HILP)/infusion (ILI) with melphalan ± TNF-α. Possible improvement in DFS and OS with complete response. Higher CR and ORR with HILP than ILI (26–69% CR and 67–95% ORR with HILP a 25–38% CR and 45–77% ORR with ILI). Similar 5 year OS rates 49% with HILP and 46% with ILI. Increased toxicity with HILP Combination of systemic therapy with intralesional treatments are ongoing in clinical trials	

(continued)

Table 16.6 (continued)

SLNB sentinel lymph node biopsy, *FNA* fine-needle aspiration, *CLND* completion lymphadenectomy, *ILI* isolated limb infusion, *HILP* heated isolated limb perfusion, *BCG* Bacille Calmette-Guérin, *OS* overall survival, *CR* complete response, *ORR* overall response rate (complete + partial response)

[a]Clinically palpable lymph nodes should be managed as described even in the setting of no obvious primary melanoma

[b]Local recurrence is thought to represent persistent disease and presents at the margin of the WLE scar, therefore recommendation is for re-excision to negative margins. Satellite (within 2 cm of the WLE scar)/ in-transit metastases (> 2 cm from the WLE excision) represent intralymphatic spread of melanoma and can present as cutaneous or subcutaneous masses between the WLE scar and the regional lymph node basin

[c]T-VEC is currently unavailable in Canada outside of a clinical trial

Table 16.7 Rationale for sentinel lymph node biopsy

Accurate staging Allows a more directed treatment planning (ex. adjuvant therapy) and rational follow-up strategy [52]	
Prognostic factor The 5-year overall survival for patients with nodal micrometastases (<2 mm) is 67% and with nodal macrometastases 43% [82]	
Better locoregional control Among patients with intermediate thickness melanomas, MSS is improved when regional metastasis was identified via SLNB rather than clinical presentation (62.1% vs. 41.5%) [50, 83]	
Decreased complication rates Complication rates of SLNB vs. lymphadenectomy: 4.6% vs. 23.2% [62] Lymphedema rate for axillary SLNB vs. complete lymphadenectomy: 1.7% and 9%, respectively [52, 62] Lymphedema rate for groin SLNB vs. complete lymphadenectomy: 1.7% and 26%, respectively [52, 62]	
Potential survival benefit SLNB has been associated an increase in DFS for both intermediate and thick melanomas [50] SLNB has been associated with an increase in MSS for patients with an intermediate thickness melanoma that have metastases in their lymph nodes	
Impact in adjuvant therapy Accurate nodal staging information is important in order to offer patients adjuvant targeted therapy or checkpoint immunotherapy and/or enrolment in clinical trials	
Tumour thickness likelihood of positive SN [84]	
<0.75 mm[a]	1–3.6%
0.76–1.5 mm	7–9.8%
1.5–4.0 mm	20.9–24.6%
>4.0 mm	31.4–39.7%

[a]Without evidence of ulceration

- As the role for CLND in the setting of positive SLNB has decreased, most lymphadenectomies in the groin will be performed either as a CLND for clinically/ radiographically diagnosed disease or therapeutic lymph node dissection (TLND; i.e. clinically identified lymph node involvement without previous SLNB). In the pre-MSLT-2/de-COG setting of CLND for only positive SLNB

(without evidence of further disease), lymphadenectomy was limited to the superficial inguinal LN basin and deep (iliac/obturator) dissection was reserved for clinically palpable disease or radiographic pelvic node involvement [65] (Tables 16.6 and 16.11).

- In the setting of CLND (for clinically palpable)/TLND, the rates of deep (iliac and/or obturator) LN involvement are approximately 30–35% [66, 67]. In the setting of palpable lymphadenopathy or recurrent disease after SLNB, both a superficial and deep groin dissection is currently offered at our centre.
- It is not known whether in the setting of radiographically detected involvement of the superficial compartment (while on surveillance for a resected positive sentinel lymph node) one can safely omit the deep dissection. This is currently under investigation in a multi-centre RCT EAGLE-FM (NCT02166788).
- Completion/therapeutic lymphadenectomy in the axilla usually requires levels 1, 2, and 3 dissection with selective transection of pectoralis minor [68, 69]. In the setting of clinically diagnosed disease, rates of level 3 lymph node involvement are 18–31% and 100% when presenting with bulky disease (defined by a large fixed axillary mass or matted nodes presenting in all three levels) [70, 71].
- Neoadjuvant therapies in the context of unresectable/borderline resectable regional disease are being studied. Phase II trials using both targeted therapies (dual BRAF and MEK inhibitors) as well as checkpoint inhibitors (CTLA-4 and PD-1 inhibitors) in the neoadjuvant setting have demonstrated complete pathological responses between 25% and 58% with higher rates of near-complete and partial pathological responses. This has translated into an improved event-free survival and absolute overall survival of 18–23% [72–75]. Currently there are multiple ongoing studies to determine the comparative utility of neoadjuvant versus adjuvant therapies for clinically/marginally resectable disease, the optimal duration of neoadjuvant therapy, as well as the optimal therapeutic regime (Table 16.12).
- 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% [57]. When complete clinical response is achieved, an increase in 5-year overall survival can be obtained, compared to partial responders (80% vs. 33%, respectively) [76, 77]. 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 [78]. Unlike systemic IL-2, intralesional IL-2 is well tolerated with much less toxicity. 58–100% complete pathologic response has been demonstrated when IL-2 injections are combined with topic imiquimod and retenoids [79–81] (Table 16.6).

Adjuvant Therapy

Recent studies have demonstrated the utility of adjuvant checkpoint inhibitors or targeted therapy in the setting of lymph node positivity (either following detection

of microscopic disease on SLN biopsy or after resection of clinically involved lymph nodes). For those patients with a BRAF V600E/K mutation,dual targeted therapy (dabrafenib + trametinib) has demonstrated an improved 4-year recurrence-free survival, decreased relapse rate, improved distant metastasis-free survival (compared to placebo), and an estimated 4-year cure rate of 54% (vs. 37% with placebo) [85, 86] (Table 16.12). In patients both with and without a BRAF mutation, immune checkpoint inhibitors have also demonstrated an improvement in recurrence free survival and overall survival (for ipilimumab). Ipilimumab (a CTL4-A inhibitor) demonstrated an improved 5 year recurrence-free survival (40.8%), distant metastasis-free survival, and overall survival (65.4%) compared to placebo (54.4%) [87] (Table 16.12). Nivolumab (a PD-1 Inhibitor) has demonstrated an improved 18 month recurrence-free survival in comparison to ipilimumab (70.5% vs. 60.8%); however, overall survival has not yet been reported [88] (Table 16.12). Pembrolizumab (a PD-1 Inhibitor) has also demonstrated an improved 18 month recurrence-free survival (71.4%) compared with placebo (53.2%); however, OS has also not been reported [89] (Table 16.12).

Patients with Stage IIB/IIIC and high-risk stage IIIA should routinely be considered for adjuvant immunotherapy. It is unclear whether the benefits outweigh the potential toxicities of immunotherapy for Stage IIIA patients with a low burden of disease (1 SLN positive with <1 mm and no evidence of ulceration) as these patients were excluded from the stage III RCTs [27]. Table 16.8 presents a comparison of the current adjuvant therapies.

There is limited data around the role for radiation therapy (RT) in the setting of effective adjuvant immunotherapies. Prior to the advent of effective immunotherapy, adjuvant RT to the site of primary WLE was considered in desmoplastic melanoma with high-risk features (>4 mm, extensive neurotropism/perineural

Table 16.8 Comparison of adjuvant therapies

	Nivolumab vs. Ipilimumab (Checkmate 238) [88]	Dabrafenib + Trametinib vs. placebo (Combi-AD) [86]	Pembrolizumab vs. placebo (Keynote 054) [89]	Ipilimumab vs. placebo (EORTC 18071) [87]
Patients	IIIb/c, IV (no brain mets)	IIIa (>1 mm), IIIb, IIIc	IIIa (>1 mm), IIIb, IIIc (no intransits)	IIIa (>1 mm), IIIb, IIIc (no intransits)
Duration of Therapy	1 year	1 year	1 year	1 year
RFS	1 year 70% vs. 60% HR 0.65	4 year 54% vs. 38% HR 0.57	1 year 75% vs. 61% HR 0.57	5 year 40% vs. 30% HR 0.75
DMFS	HR 0.73	HR 0.53	N/A	5 year 48% vs. 38%
OS	N/A	3 year 86% vs. 77% HR 0.57	N/A	5 year 65% vs. 54%

invasion, and narrow resection margins, located on head and neck) [27, 90]. Adjuvant RT to the lymph node basins has been demonstrated to reduced nodal recurrence (but not relapse-free or overall survival) in patients at high risk of nodal recurrence including gross/macroscopic extranodal extension, ≥1 positive parotid LN, ≥2 cervical LNs, ≥3 axillary or ilioinguinal LNs [27, 91]. Adjuvant RT is also associated with a higher rate of lymphedema especially for patients receiving inguinal radiation. In the current era of adjuvant therapy, the role RT as an adjuvant treatment is unclear.

Distant Metastatic Melanoma

Special Notes

- Most common causes of death with metastatic melanoma are respiratory failure and intracranial metastases.
- No head-to-head trials have been conducted on the use of targeted therapy compared to immunotherapy in BRAF mutated patients. The use and sequencing of targeted and/or immunotherapies in the metastatic setting is dependent on multiple factors including the extent of disease, rapidity of growth, location of disease (CNS involvement), symptoms, tolerability of potential adverse events, and drug funding (Tables 16.8 and 16.13).
- Similarly, the utility of surgical resection in the setting of metastatic disease in the era of immunotherapy is dependent on the extent of disease, responsiveness of disease to targeted/immunotherapy, location of disease, and patient symptoms (Tables 16.9 and 16.13).
- 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 [93]. 5-Year survival of 40% has also been reported for complete metastasectomy when tumour-free margins are obtained [110]. Prior to the advent of immunotherapy when resection of melanoma metastases ± systemic therapy was compared to systemic medical therapy alone, median survival was 15.8 versus 6.9 months and surgical treatment conferred a 4-year survival of 20.8% versus 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 [96].
- In the era of immunotherapy while the number of metastatectomies does not appear to have increased, the nature of the metastatectomies has increased from predominately resection of in-transit disease to predominately intra-abdominal surgery. There was a significant increase in potentially curative surgery for residual oligometastatic disease [95]. Optimal sequencing of metastasectomy with targeted and immunotherapies remains unclear (Table 16.9).

Table 16.9 Management of distant metastatic disease

Workup	Surgical approach [92–95]	Systemic therapy
Labs: Serum LDH CBC, lytes, BUN, Cr, LFTs, TSH Mutational Analysis/ BRAF and next-generation sequencing testing Imaging: CT or MRI of brain CT chest, abdomen, and pelvis PET/CT scan to identify otherwise occult metastatic disease if considering surgical intervention	Role of metastasectomy has evolved in the setting of systemic targeted and checkpoint immunotherapies Consider mastectomy as an adjunct after initiation of systemic therapy. Evolving evidence for resection of residual or active oligometastatic disease (<3 sites) after treatment with immunotherapy or targeted therapy as 'curative intent' surgery. Increased resection of intra-abdominal disease for non-palliation purposes. Prior to advent of effective systemic immunotherapy, complete resection of highly selected patients with oligometastatic disease resulted in 20–30% 5 year OS including: [92–94, 96] Pulmonary metastases –most common site of solid organ metastasis Symptomatic or isolated GI (4% of stage IV) metastases Subcutaneous metastases Distant lymph node basins Liver, adrenal, and pancreas Symptomatic brain metastases (surgery, stereotactic radiosurgery, or whole-brain radiation) Palliation of symptoms (bleeding, bowel obstruction, neurologic sequelae) 75–90% can obtain symptom relief	Targeted therapies dependent on mutational status (BRAF, KIT, MEK, NRAS genes) [3] V600E/K BRAF mutation positive (43–50% of cases) Combination-targeted therapy (BRAF inhibitor + MEK inhibitor) has demonstrated improved sustained long-term response (OS, PFS,) compared to monotherapy [97–100] BRAF inhibitor (vemurafenib, dabrafenib, encorafenib) + MEK inhibitor (trametinib, cobimetinib, binimetinib) rapid tumour response, but common progression of disease within 12 months of treatment NRAS is mutated in approximately 15–30% of melanomas. There is limited data around targeted therapy for NRAS mutated melanoma. Binimetinib (MEK inhibitor) has demonstrated a mild improvement in progression-free survival in stage IV disease [101] BRAF and NRAS mutations are mutually exclusive (occurring together <0.5%) KIT mutations occur in 2–8% of all cutaneous melanomas: more common in acral (25%) and mucosal (22%) melanoma tyrosine kinase inhibitors demonstrate approx. 20% response rate in the metastatic setting [102–104] Checkpoint inhibitors Ipilimumab (CTLA-4 Inhibitor): Slow but durable response in 20% of patients [105] Anti-PD1: Pembrolizumab and Nivolumab Pembrolizumab: 5 year OS in Stage IV is 34%, (41% when used as 1st line) [106] Nivolumab: 3 year OS 51.2% when used 1st line [107] Combined immunotherapy (Ipilimumab + Nivolumab) – 3 year OS was 58% in the Nivo + Ipi, Treatment-related adverse events grade 3/4 occurred in 59% with combination verses 21–28% with single agent immunotherapy [108, 109] Systemic chemotherapy (dacarbazine, temozolomide, carbo/taxol and abraxane): used after progression on checkpoint inhibitors ± targeted immunotherapy. Limited clinical response rate. Consider clinical trial whenever available and appropriate

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

Table 16.10 Wide local excision-margins

Melanoma (Breslow thickness)	Study	Methods	Results
In situ (MIS) No RCTs	Kunishigie et al. [30]	Prospective case series 1982–2008 *N* = 1120 MIS All moh's microsurgery (3 mm margin + additional 3 mm) If positive margin additional 3 mm resected	All patients have a minimum of 6 mm margins 86% had negative margins with 6 mm increased to 97% with 9 mm margins Local recurrence with negative margins 0.3% at 3 years 0.8% at 5 years
	Akhtar et al. [29]	Retrospective case series 2001–2009 *N* = 192 MIS (75 lentigo maligna - LM) All excised ≥2006 had 5 mm margins (58%)	29.3% of LM were incompletely excised on initial excision 7/75 left incompletely excised with recurrence rate of 29% 2 (1%) recurred of completely excised, also LM margins 0.8 and 1.4 mm
<1 mm	French Cooperative Surgical Trial [111]	*N* = 337 (melanoma < 2.1 mm) RCT Excision margins: 2 cm vs. 5 cm Excluded acral lentiginous Median F/U: 16 years	No difference in OS (87% vs. 86%) Time to recurrence was 37.6–43 months 10-year disease-free survival was 85% with 2-cm margin and 83% with 5-cm margin. LRR 5.6%
	Swedish Cooperative Surgical Trial [112]	*N* = 989 (melanoma 0.8–2.0 mm) RCT Excision margins: 2 cm vs. 5 cm Median F/U: 11 years	No difference in 10 year OS (79% vs. 76%) 5-year recurrence-free survival was 81% with 2 cm and 83% with 5 cm (no difference). LR: <1% overall
	WHO Melanoma Program Trial [113] [41]	*N* = 612 (melanoma ≤ 2 mm) RCT Excision margins: 1 cm vs. ≥3 cm (3–5 cm) Median F/U: 15 years	No difference in OS 8 year OS 89.6% 1 cm vs. 90.3% ≥ 3 cm and 12 year OS were 85.1% and 87.2% respectively Differences (not significant) in LR narrow And wide excision (2.6% 1 cm excision vs.0.1%, ≥ 3 cm

(continued)

Table 16.10 (continued)

Melanoma (Breslow thickness)	Study	Methods	Results
1–4 mm French, Swedish and WHO trials plus:	Intergroup Melanoma Surgical Trial [44, 114]	*N* = 740 (melanoma 1.0–4.0 mm) RCT Excision margins: 2 cm vs. 4 cm on trunk and proximal extremity Median F/U: 10 years	No difference in 10 year OS 70% with 2 cm vs. 77% with 4 cm No difference is LR with 2 cm vs. 4 cm margins whether the comparisons were made as first relapse 0.4% vs. 0.9%) or anytime (2.1% vs. 2.6%)
	British Cooperative Group Trial [45, 115]	*N* = 675 (melanoma 2.0–4.0 mm) RCT excision margins: 1 cm vs. 3 cm Median F/U: 8.8 years	No difference in OS Melanoma-specific survival improved with 3 cm margins compared to 1 cm margins HR 1.24 Cumulative incidence of death due to melanoma at 8.8 years was 47.9% with 1 cm and 38.1% with 3 cm margins Lower LR with 3 cm margins ($p = 0.05$)
	Swedish Melanoma Study Group + Danish Melanoma Group [43]	*N* = 936 (melanoma ≥2 mm) RCT 1:1 Excision margins: 2 cm vs. 4 cm (50% >3 cm) Median F/U: 6.7 years (11.8 in Swedish cohort)	No difference in OS at 5 years (65% vs. 65%) or 10 years No difference in MSS at 5 years Difference (non-significant $p = 0.06$) in local recurrence 1 cm (4.3%) vs. 3 cm (1.9%)
>4 mm	British Cooperative Group Trial [45, 115]	*N* = 225 (melanoma > 4 mm) Excision margins: 3 cm vs. 1 cm Median F/U: 8.8 years	No difference in OS (as above)

F/U follow-up, *RCT* randomized controlled trials, *WLE* wide local excision, *OS* overall survival, *NS* not significant, *LRR* locoregional recurrence, LR local recurrence (within/adjacent to the scar). *CLND* completion lymphadenectomy – previous SLNB, *DFS* disease-free survival, *TLND* therapeutic lymphadenectomy – palpable or radiographic disease without previous SLNB, *SLN* sentinel lymph node

Table 16.11 Sentinel lymph node biopsy and completion lymphadenectomy

Study	Methods	Results
Multicenter Selective Lymphadenectomy Trial (MSLT-1) [50]	Phase III Multicentre RCT $N = 1347$ (melanoma 1.2–3.5 mm), 314 with thick melanoma Groups: WLE + SLNB (with CLND if SLNB positive, observation if SLNB negative) vs. WLE and observation alone (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 MSS 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
Multicenter Selective Lymphadenectomy Trial (MSLT-2) [52]	Phase III multicentre RCT $N = 1939$ Intermediate and thick melanomas ($\geq$1.2 mm) with positive SLNB (all underwent WLE and SLNB) 1:1 Randomization to either: Completion lymph node dissection Close observation with clinical exam and ultrasound and completion dissection with additional nodal disease	Median f/u 43 months 3 year MSS did not differ between the CLND group and the nodal observation group (86% vs. 86%) Sub-group analysis did not identify any group with improved MSS with CLND vs. observation 3 year DFS higher with CLND (68%) vs. observation (63%) 2nd to decreased nodal recurrence at 3 years (92% with CLND vs. 77% with observation) No difference in distant metastasis-free survival Median thickness in both groups 2.1 mm, 69–72% had only one SLN positive, median size of metastasis in SLN 0.61–0.67 mm, approx. 65% had $\leq$1 mm of disease in SLN
De-COG SLT [53, 54]	Phase III multicentre RCT $N = 438$ (trial closed early 2nd to limited accrual) Intermediate and thick melanomas ($\geq$1 mm) with positive SLNB (all underwent WLE and SLNB) 1:1 Randomization to either: completion lymph node dissection close observation with clinical exam and ultrasound and completion dissection with additional nodal disease	Median f/u 72 months No difference in Distant metastasis-free survival (DMFS) at 3 years 77% with observation and 74.9% with CLND, or 5 years 68% with observation and 65% with CLND No difference in OS at 3 years (81.7% observation and 81.2% CLND) or 5 years No difference in recurrence free survival (RcFS) at 3 years (67.4% observation vs. 66.8% CLND) and 5 years Median thickness in both groups 2.4 mm, 91–93% had only one SLN positive, approx. 65% had $\leq$1 mm of disease in SLN

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, RcFS recurrence-free survival, *DMFS* distant-metastasis-free survival

Table 16.12 Adjuvant systemic therapy

Drug	Study	Methods	Results
Dual targeted therapy: Dabrafenib (BRAF inhibitor) + Trametinib (MEK inhibitor)	Hauschild et al., Long et al. [85, 86] *N* = 870	Phase 3 RCT (COMBI-AD) Resected Stage III (IIIA only if >1 mm of disease in ≥1 lymph node), BRAF V600E/K mutated All patients had completion lymphadenectomy prior to trial enrollment RCT 1:1 adjuvant Dabrafenib + Trametinib 12 months vs. placebo Post-hoc subgroup analysis (AJCC 7th vs. AJCC 8th staging) to assess for RcFS (recurrence + death)	3- and 4-year RcFS rates 59% and 54% dabrafenib (Dab) plus trametinib (Tram) vs. 40% and 38% placebo Dab + Tram median recurrence not reached at 44 months, vs. 16.6 placebo Relapse rates 40% Dab + Tram vs. 59% placebo DMS with Dab + Tram HR 0.53 3-year OS 86% with combination vs. 77% with placebo (not significant) Estimated 54% Dab + Tram vs. 37% placebo will never recur (estimated cure rate) RcFS improved across all stages (both 7th and 8th staging) with Dab-Tram
Checkpoint inhibitors:			
Ipilimumab (CTLA-4 inhibitor)	Eggermont et al. [87] *N* = 951	Phase 3 RCT (EORTC 18071) Resected Stage III (IIIA only if >1 mm of disease in ≥1 lymph node) All patients had completion lymphadenectomy prior to trial enrollment RCT 1:1 ipilimumab (Ipi) 10 mg/kg q 3 weeks * 4 cycles then q3 months for up to 3 years vs. placebo	5-year RcFS rates 40.8% Ipi vs. 30.3% placebo Ipi improved RcFS in both micro- and macrometastasis Overall survival was significantly longer with Ipi 5 year OS was 65.4% Ipi vs. 54.4% placebo 5 year DMS 48.3% Ipi vs. 38.9 placebo (HR 0.76)
Pembrolizumab (PD-1 inhibitor)	Eggermont et al. [89] *N* = 1014	Phase 3 RCT (Keynote 054) Stage III patients stratification via Stage IIIA (only if >1 mm of disease in ≥1 lymph node) /IIIB/IIIC (<4 lymph nodes) and IIIC(>4 nodes) All patients had completion lymphadenectomy prior to trial enrollment 1:1 Pembrolizumab (Anti-PD-1) 200 mg q 3 weeks *18 weeks (1 year) vs. placebo	Median f/u 15 months 12-month RcFS was 75.4% with pembrolizumab (Pembro) and 61.0% with placebo (HR 0.57) 18-month RcFS significantly higher with pembro vs. placebo 71.4% vs. 53.2%, Benefit of Pembro was similar across stages IIIA, IIIB, IIIC, and microscopic and macroscopic nodal ds Adverse events grades 3 to 5 with pembro were 14.7% vs. 3.4% with placebo

Nivolumab (PD-1 Inhibitor)	Weber et al. *N* = 906 [88]	Phase 3 RCT (Checkmate 238) Stage IIIB, IIIC or resected Stage IV (including brain metastasis) All patients had completion lymphadenectomy prior to trial enrollment 1:1 Nivolumab (Nivo) 3 mg/kg q 2 weeks for 1 year or Ipilimumab (Ipi) 10 mg/kg q 2 weeks * 4 dose then q 12 weeks for 1 year total	18 month median f/u, median recurrence-free survival not reached in patients with stage III or stage IV disease, irrespective of disease stage more benefit with nivo than ipi 12-month RcFS 70.5% with Nivo vs. 60.8% with Ipi, 18-month RcFS were 66.4% and 52.7%, respectively Grade 3/4 adverse events were 14.4% with Nivo and 45.9% with Ipi
Neoadjuvant trials			
Dual targeted therapy: Dabrafenib (BRAF inhibitor) + Trametinib (MEK Inhibitor)	Amaria et al. *N* = 21 [72]	Phase 2 randomized trial Stage IIIB/C or Stage IV resectable oligometastases 1:2: upfront surgery vs. Dab + Tram 8 weeks pre-op and 44 weeks post-op Only one patient in the surgery arm received adjuvant treatment with a 5 drug combination regime	DFS at 18.6 months 71% dual therapy vs. 0% with surgery alone Median event-free survival 19.7 months dual therapy vs. 2.9 months surgery alone Trial stopped early due to longer than expected event-free survival with Dab + Tram 58% complete response and 17% partial response
Dual Checkpoint Inhibition: Ipilimumab (CTLA-4 Inhibitor) + Nivolumab (PD-1 Inhibitor)	Blank et al., Rozeman et al. [74, 75] *N* = 20 Ipilimumab 3 mg/kg + Nivolumab 1 mg/kg	Phase 2 randomized trial (OpACIN) Palpable stage 3 1:1: Ipi + Nivo either 4 cycles after surgery or 2 cycles pre-op, 2 cycles post-op 90% of patients developed grade 3 or 4 adverse events Based on A/Es neo-OpACIN being undertaken to identify optimal dosing	78% with >50% necrosis on pathology (7/9) (3 with <10% viable tumour and 3 with pCR) 31 month f.u 0/7 patients with path response developed recurrent disease Neoadjuvant arm: 30 month recurrence-free survival 80%, OS 90% Adjuvant arm: 30 month recurrence-free survival 60%, OS 67%
	Amaria et al. [73] *N* = 23 Nivolumab 3 mg/kg vs Ipilimumab 3 mg/kg + Nivolumab 1 mg/kg	Phase 2 randomized trial Stage IIIB/C or Stage IV resectable oligometastases 1:1 Nivo alone 4 cycles q2 weeks pre-op, VS. Nivo + Ipi 3 cycles q3 weeks pre-op post-op both arms Nivo alone 3 mg/kg q2 weeks Trial stopped early bc of disease progression events in Nivo only arm and high rate of A/Es in the combo arm	2 pts in Nivo arm progressed and were unresectable pCR 25% in Nivo alone, 45% in Nivo + Ipi PFS at 15 months 82% in combo vs. 58% Nivo alone OS at 22 months 100% in combo vs. 76% in Nivo alone PFS and OS not significant (? 2nd to small sample size) Improved PFS and OS in patients who achieved pCR vs. those who did not

Table 16.13 Systemic therapy for metastatic disease

Drug	Study	Methods	Results
Targeted immunotherapy:			
Dabrafenib (BRAF inhibitor) + Trametinib (MEK inhibitor)	Long, G. et al. [116] *N* = 423	Phase 3 RCT (Combi-D) BRAF V600E/K mutation unresectable stage III or IV 1:1 Dabrafenib + Trametinib vs. Dabrafenib alone No prior systemic tx for Stage IV disease, excluded untreated brain metastasis	3-year PFS was 22% with combination therapy versus 12% with monotherapy 3-year OS was 44% vs. 32%, respectively Greatest 3 year OS benefit in pts with baseline LDH ≤ ULN and <3 organ sites with metastasis 62% vs. 25%
	Robert, C. et al. [99, 117] *N* = 704	Phase 3 RCT (Combi-V) BRAF V600E/K mutation unresectable stage III or IV 1:1 Dabrafenib + Trametinib vs. Vemurafenib alone No prior systemic tx for Stage IV disease, excluded untreated brain metastasis	3-y PFS, 25% with combination therapy vs. 11% with monotherapy 3-year OS, 45% vs. 32% respectively Greatest 3 year OS benefit in pts with baseline LDH ≤ ULN and <3 organ sites with metastasis 70% vs. 46%
Vemurafenib (BRAF inhibitor) + Cobimetinib (MEK inhibitor)	Ascierto et al. [97] *N* = 495	Phase 3 RCT (CoBRIM) BRAF V600E/K mutation, unresectable stage III or IV RCT 1:1 Vemurafenib + Cobimetinib vs. Vemurafenib alone No prior systemic tx for Stage IV disease, excluded untreated brain metastasis	Median progression-free survival was 12.3 months for combined therapy vs. 7.2 months for monotherapy Median overall survival was 22.3 months versus 17.4 months respectively
Encorafenib (BRAF Inhibitor) + Binimetinib (MEK Inhibitor)	Dummer et al. [98] *N* = 577	Phase 3 RCT (Columbus Trial) BRAF V600E/K mutation, unresectable stage III or IV 1:1:1 Encorafenib + Binimetinib vs. Encorafenib alone vs. Vemurafenib alone No prior systemic tx for Stage IV disease, excluded untreated brain metastasis	median progression-free survival was 14·9 months with combination therapy vs. 9.6 months with encorafenib alone vs. 7·3 months with vemurafenib alone median follow-up 16.6 months, median OS not yet reached
Checkpoint inhibitors:			
Ipilimumab (CTLA-4 Inhibitor)	Robert C et al. [118] *N* = 502	Phase 3 RCT tx naive unresectable stage III or IV Ipilimumab 10 mg/kg + dacarbazine vs. dacarbazine + placebo	OS significantly longer in Ipi + D vs. D + placebo—11.2 vs. 9.1 months with higher survival rates at: 1 year 47% vs. 36%, 2 year 28% vs. 18%, and 3 year 20.8% vs. 12.2%

Table 16.13 (continued)

Drug	Study	Methods	Results
	Hodi et al. [119] *N* = 676	Phase 3 RCT previously treated unresectable stage III or IV, HLA-A*0201 positive 3:1:1 ipilimumab 3 mg/kg + gp100, vs. ipilimumab 3 mg/kg vs. gp100	median overall survival was 10 months among patients receiving ipilimumab ± gp100 vs. 6 months with gp100 alone progression-free survival was highest in the ipi alone group 57.7% at 12 weeks (vs. 49% with combination and 49% with gp100 alone Ipi alone group had best ORR 10.9%
	Schadendorf et al. [105]	Patient level OS-analysis, 1861 patients unresectable stage III or IV, previously treated (1257) or treatment naive (604) 2 trials, (10 prospective and 2 retrospective including 2 phase III trials) comparisons of ipilimumab with controls (3 mg/kg in 52%, 10 mg/kg in 40% of patients)	median OS was 11.4 months 3 year OS rates were 22% for all patients 26% for treatment-naive patients, and 20% for previously treated patients
Nivolumab (PD-1 inhibitor)			
	Weber et al. [120] *N* = 631	Phase 3 RCT (Checkmate 037) Unresectable stage III or IV progressed on ipilimumab ± BRAF/MEK inhibitor 2:1 nivolumab 3 mg/kg q2 week vs. cytotoxic chemotherapy (ICC) (dacarbazine/paclitaxel)	ORR 31. 7%, in the nivolumab group vs. 10. 6%, in the ICC group Median duration of response had not yet been reached at 8.4 months with nivolumab vs. 3·5 months with ICC
	Ascierto et al. [107] Robert et al. [121] *N* = 418	Phase 3 RCT (Checkmate 066) unresectable stage III or IV, treatment naive BRAF wt 1:1 nivolumab 3 mg/kg q2 week vs. dacarbazine q3 week	3-year OS 51.2% with nivolumab vs. 21.6% with Dacarbazine median OS was 37.5 vs. 11.2 months Complete and partial responses were 19.0% and 23.8% with Nivo

(continued)

Table 16.13 (continued)

Drug	Study	Methods	Results
Pembrolizumab (PD-1 inhibitor)	Robert et al. [122] *N* = 173	Phase 1 trial (Keynote-001) unresectable stage III or IV progressed on ipilimumab Pembrolizumab 2 mg/kg q3 week vs. 10 mg/kg q3 week	ORR 26% at 8 months f/u in both groups A/E rate was the same in both groups
	Hamid et al. [106], Robert el al [123]. *N* = 655	Phase 1b trial, (Keynote-001) unresectable stage III or IV Pembro 2 mg/kg q3week vs. 10 mg/kg q3 week vs. 10 mg/kg q2 week 151 treatment naive, 496 had previous systemic treatment (excluding PD-1 inhibitors)	5 year OS 34% in all patients and 41% in treatment (tx)-naive patients Median OS was 23.8 months in all patients and 38.6 months in tx naïve patients 16.0% achieved CR at median 12 months, 2 year sustained DFS 90% and sustained CR 88% at 30 months
	Schacter et al. [124] Robert et al. [125] *N* = 834	Phase 3 RCT (Keynote-006) unresectable stage III or IV 1:1:1 Pembrolizumab 10 mg/kg q 2 weeks vs. Pembrolizumab 10 mg/kg q 3 week vs. Ipilimumab 3 mg/kg Prior systemic tx for Stage IV disease (excluding PD-1 and CTLA-4 inhibitors)	ORR 36% in pembro group vs. 13% in ipi group median OS not reached in pembro at 23 months, median OS with ipi 16 months 2 year OS was 55% in the pembro arms vs. 43% in ipi arm
Combination therapy:	Hodi et al., Wolchok et al. [108, 109] *N* = 94	Phase 3 RCT (Checkmate-067) tx naive unresectable stage III or IV 1:1:1 Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg q 3 weeks * 4 doses then Nivolumab alone 3 mg/kg q 2 weeks vs. Nivolumab alone 3 mg/kg q 2 weeks vs. Ipilimumab alone 3 mg/kg q 3 weeks * 4 doses	median OS was not reached at 48months in the Nivo + Ipi group vs. 36.9 months with Nivo vs. 19.9 months with Ipi 3 year OS was 58% in the Nivo + Ipi group vs. 52% in the Nivo group vs. 34% in the Ipi group Treatment-related adverse events grade 3/4 occurred in 59% with combination, 21% with Nivo alone and 28% with Ipi alone

RCT randomized controlled trial, *PFS* progression-free survival, *OS* overall survival, *D* dacarbazine, *RFS* relapse-free survival, *DFS* disease-free survival, *IFN* interferon, *Ipi* ipilimumab, *Nivo* nivolumab, *Pembro* pembrolizumab, *RcFS* recurrence-free survival

Landmark Trials

Systemic Therapy

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

1. Primary melanoma with Breslow thickness >4 mm
2. Node-positive melanoma (palpable and sentinel node positive)
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 [126].

Referring to Radiation Oncology [90, 91]

1. Unresectable or gross residual nodal disease
2. Extracapsular nodal extension
3. ≥1 parotid, ≥2 cervical, ≥2 axillary, ≥3 inguinal palpable lymph nodes involved
4. Cervical lymph node ≥2 cm, axillary and inguinal lymph node ≥3 cm
5. Metastatic disease – if symptomatic from focal disease; treatment of brain metastases with stereotactic radiosurgery
6. Pure desmoplastic melanoma with narrow margins, locally recurrent or extensive neurotropism
7. Multiple local recurrences at the primary site (after resection), positive margins around primary site from microsatellites
8. In transit/satellite disease unsuitable for surgery, intralesional, or topical therapies or systemic therapy

Referring to Multidisciplinary Cancer Conference (MCC)

1. Bulky nodal disease
2. New metastatic disease
3. In-transit or locoregional recurrence

4. Any consideration of non-standard multimodal therapy
5. Consideration of available clinical trials

Technical Aspects of Melanoma Defect Reconstruction

There are various coverage options following melanoma excision. The decision-making process for selection of the best coverage method is dependent on the following factors: defect location, size, adjacent skin laxity, history of radiation or need for adjuvant treatment, and the patient's medical comorbidities. In general, the simplest closure method is used that will provide optimal function and cosmesis.

Generally, a full-thickness circular tissue defect, going down to fascia, periosteum, or paratenon, is present after a melanoma excision. The commonly used coverage options are listed below with a brief description of their appropriate use and important perioperative care.

Primary Closure

Primary closure is the simplest closure available and is recommended whenever possible. It requires adequate laxity in the surrounding tissue and can be used in any part of the body. It is also easily done in a clinic setting with the use of local anesthetics.

As for technical tips, a preoperative elliptical excision marking allows a linear closure without a dog-ear formation that would otherwise result from closing a circular defect. It may be necessary to undermine both sides of the skin flaps at the pre-fascial level to allow adequate advancement. It is recommended to suture the incision in a layered fashion to approximate the superficial fascia where present, the deep dermis, and finally the skin closure.

Skin Graft

When primary closure is not possible, skin graft may be useful in areas where there is a lack of adjacent skin laxity. A skin graft is a fast procedure, but it takes longer to heal, requires postoperative wound care, and has worse aesthetics than flap coverage. Furthermore, a skin graft should not be used in a previously irradiated tissue or in an area that will likely receive adjuvant radiation.

There are two types of skin grafts: (1) full thickness skin graft (FTSG) that consists of epidermis and the full thickness of dermis and (2) split thickness skin graft (STSG) that consists of epidermis and a partial thickness of dermis.

The FTSG may be useful across a joint as it does not undergo significant secondary contraction like STSG. However, it is important to remember that an FTSG has a limitation to the size that can be harvested since the donor site requires a primary closure (i.e. groin, supraclavicular region, etc.), and an FTSG takes less readily than

the STSG. Intraoperatively, it is pie-crusted using a scalpel to prevent hematoma or seroma formation under the graft, and it is sutured to the defect skin edges with gut sutures.

The STSG is useful in a larger surface area over any soft tissue (muscle, fascia, fat), periosteum, perichondrium, paratenon, and medullary bone. Frequently harvested using a dermatome from any healthy skin (i.e. commonly thighs), the common thickness used is 0.012″ and STSGs may be used as a pie-crusted sheet graft or meshed to enlarge the surface area and improve its ability to conform to irregular contours. The STSG may be sutured or stapled to the recipient site, and the donor site undergoes secondary healing over the course of approximately 2 weeks.

Postoperative care is necessary to allow adequate graft healing. This may be achieved using a bolster dressing using a Reston foam or a VAC dressing, which is necessary for approximately 5 days postop to provide compression, avoid shear, and avoid fluid accumulation under the graft. After removal of the initial dressings, daily non-adherent dressing changes are required for approximately 2 weeks afterwards until the skin graft has fully healed. Patients may require splints during the immediate postoperative graft healing period if skin grafts are placed in extremities and do not have a VAC dressing on in order to prevent tendon or muscle movement below the graft.

Local Flaps [1]

Local flaps may be a better option over skin grafts when the coverage requires better tissue colour and contour match and durability. Local flaps consist of skin, subcutaneous tissue, and superficial fascia, where the tissues in the immediate vicinity of the primary defect are raised and transferred to the defect size. There are a variety of local flaps, and the commonly used types in melanoma defect coverage include advancement, transposition, rotation, and keystone flaps. It is important to note that after a local flap is performed, it may interfere with accuracy of sentinel lymph node mapping and make re-excision more challenging.

Advancement Flap

Advancement flap as shown in Fig. 16.1 is a unidirectional linear advancement of tissue. There are many varieties of this flap. The single advancement flap, which demonstrates the general principle of this flap design, is demonstrated below. The flap is designed by making parallel incisions along a tangent to the defect at the depth of the defect. Tension may be reduced by undermining both opposing wound edges and by utilizing Burrow's triangle excisions.

Transposition Flap

An example of a transposition flap is the classic rhomboid flap as shown in Fig. 16.2. A defect is shaped into a rhombus shape with angles of 60 and 120 degrees. The flap is designed as an extension of the short axis of the rhomboid in the region of the maximal adjacent skin laxity. The flap is lifted and transposed into the defect as the tension vector changes by 90 degrees, and the donor site is closed primarily.

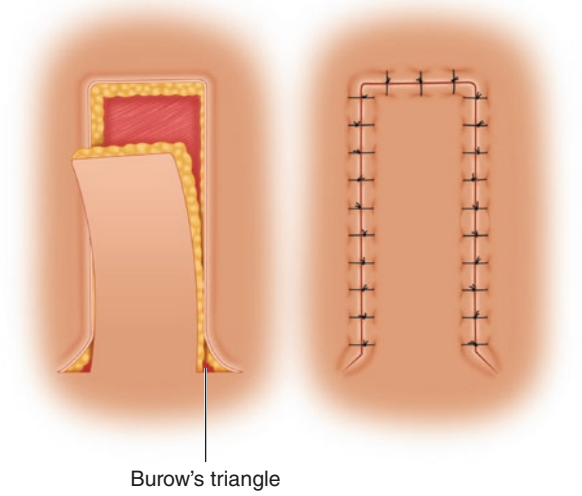


Fig. 16.1 Single advancement flap

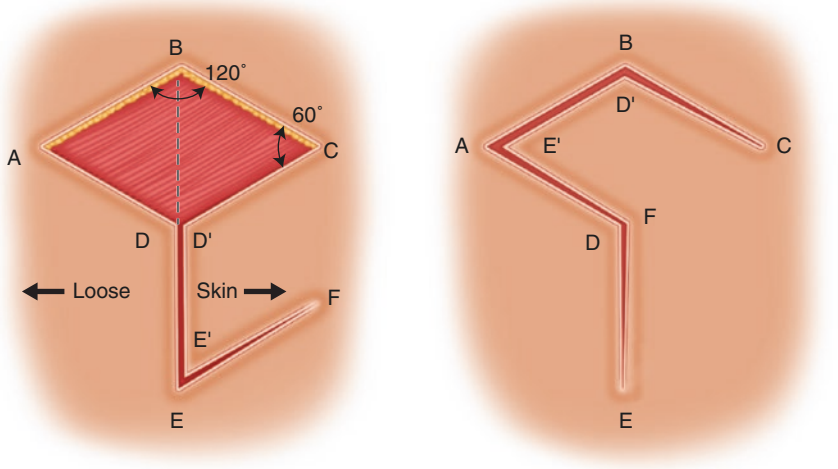
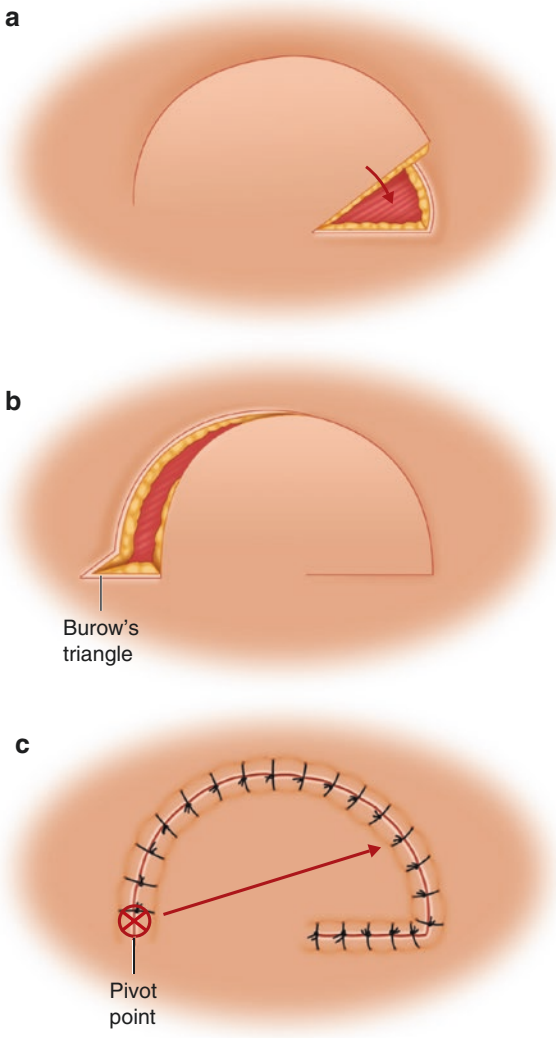


Fig. 16.2 Rhomboid flap

Rotation Flap

Rotation flaps repair defects that cannot be closed along a single tension vector by an advancement flap as shown in Fig. 16.3. It is designed by extending an arc from beyond the base of the defect (of approximately 5–6 times the base of the triangulated defect), with a pivot point about 2 times in length of the triangulated defect. The rotation results in a secondary defect along the arc of rotation, which is often closed by re-distribution of the elevated flap over this defect and the defect form the

Fig. 16.3 Rotation flap



melanoma excision. Alternatively, a Burrow's triangle allows a closure without a dog ear and by eliminating the secondary defect. A Burrow's triangle may also be used to relax the line of maximal tension of the flap, to avoid ischemic compromise to the flap.

Keystone Flap

Keystone flap as shown in Fig. 16.4 is a fasciocutaneous flap based on muscular perforators that can be considered in most parts of the body, and is particularly useful in back, chest, abdomen, and longitudinally oriented leg or arm defects. It requires having intact fascia with intact perforators supplying it. When designing a

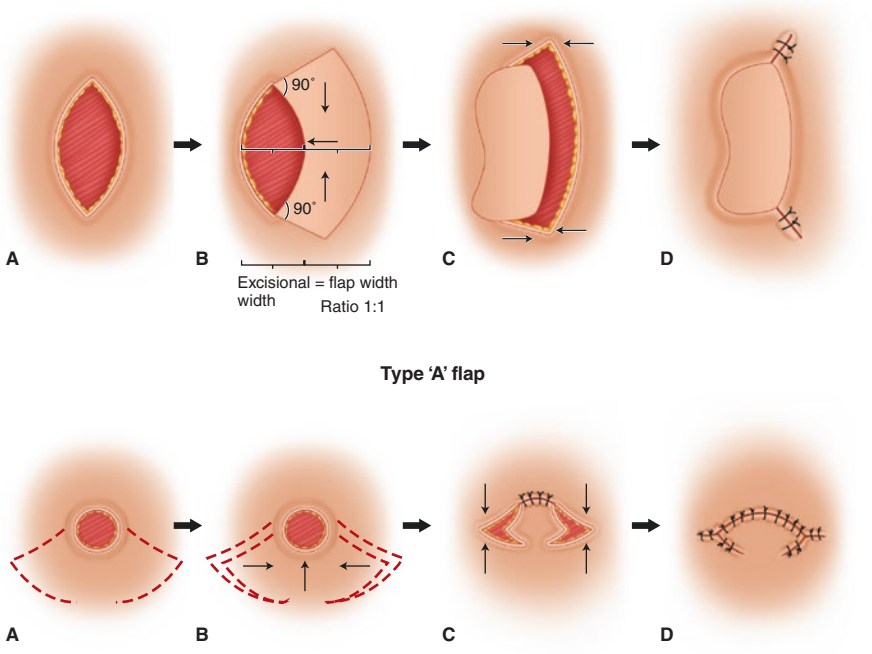


Fig. 16.4 Keystone flap and its modification (Type 'A' flap) [2]

keystone flap, it is important to take the flap from area of maximal laxity. Below diagrams demonstrate the classic keystone flap design and a modification of it below to optimize blood supply. While it is a flap design that may be considered in most parts of the body, it is not ideal in the following situations:

- Distal medial leg where the flap is designed over the bone
- Midline of back is in the flap design
- Fascial septum is in the flap
- Skin has been elevated off the fascia perforators already (i.e. if an advancement flap has been attempted and didn't reach)

Regional Flaps

Regional flaps, which are tissue with its own blood supply, are used for larger defects. They are useful in irradiated defects or defects that may have exposed critical structures, such as major vessels, nerves, bones and/or tendons; for example, in a larger defect with exposed axillary vessels, a pectoralis muscle flap or a latissimus dorsi flap may be indicated. Free flaps, which are distant transfers of tissue with its own blood supply using microsurgical techniques, are less commonly performed in

melanoma and non-melanoma coverage situations. In situations where regional flaps would be needed or when local flap options are not straightforward, early plastic surgery consultation is recommended to allow operative planning and coordinated surgery.

Toronto Pearls

- Groin dissection flaps should preserve Scarpa's fascia with the flap.
- Saphenous vein preservation during groin dissection could be considered.
- Level 3 axillary dissection should be completed in the presence of palpable axillary disease.
- Superficial and deep groin dissection should be completed in the presence of palpable disease.
- If patient does not undergo completion lymphadenectomy after a positive SLNB, perform ultrasound monitoring of the axilla and/or groin every 4–6 months for 3 years and then yearly to 5 years.
- Pembrolizumab is the preferred adjuvant therapy in non-BRAF mutated patients (2nd to q3 week drug dosing) over nivolumab.
- Consider radiation for multiple local recurrences at the site of primary disease following re-excision.
- Currently we do not have access to VP10, T-VEC, or interferon-α as injectable treatment for in-transit disease.
- Our centre routinely uses IL-2 intra-tumoral injection and aldara and retinoid creams (triple therapy) in the management of multiple in-transit metastases as first-line treatment after surgery.
- Topical immunotherapy (diphencyprone – DPCP) or systemic immunotherapy is 2nd line after triple therapy for ongoing in-transit disease.
- Radiation is rarely used for in-transit disease.

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