

## Systematic Review

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# Management of cutaneous melanoma: update on current treatment from surgical perspective

Muhammad Salman<sup>1\*</sup>, Christina Meccano<sup>1</sup>, Mehwish Salman<sup>2</sup>

<sup>1</sup>Department of General Surgery, St. Bernard's Hospital, Gibraltar, British Overseas Territories

<sup>2</sup>Faculty of Medicine, Charles University, Prague, Czech Republic

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**\*Correspondence:**

Dr. Muhammad Salman,

E-mail: salman.dr@outlook.com

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## ABSTRACT

Incidence and mortality rate of cutaneous melanoma substantially varies across the globe depending upon early detection and management. Therapeutic developments have revolutionized the treatment. The aim of this paper is to discuss the treatment options for localized and advanced disease in the context of surgery, adjuvant, and neoadjuvant treatment. PubMed, Medline, Guidelines of European Society of Medical Oncology, National Institute of Clinical Excellence, American Joint Committee on Cancer on Melanoma, publications from 2012-2022 were searched. Low risk node negative disease (stage I and IIA) melanoma patients should have curative surgical wide local excision along with SLNB with no adjuvant therapy. High risk node negative disease (stage IIB and IIC) should be treated with curative surgery and SLNB followed by adjuvant immunotherapy. Low risk node positive disease (stage IIIA) surgical resection with SLNB followed by adjuvant systemic therapy, depending upon BRAF mutation status of tumour. High risk node positive microscopic disease (stage IIIB, IIIC, IIID) BRAF V600 mutation, primary resection with SLNB followed by nivolumab or combination of BRAF + MEK inhibitors. For BRAF wild-type tumours, adjuvant immunotherapy with programmed cell death-1 (PD-1) inhibitor. Patient with macroscopic disease that is resectable neoadjuvant combination immunotherapy followed by surgery with lymph node dissection. Metastatic disease (stage IV) regardless, adjuvant combination immunotherapy followed by maintenance nivolumab. Surgical excision is the treatment of choice for most patients with loco regional cutaneous melanoma and is curative in most cases. Checkpoint inhibitors and targeted therapies are important advances in adjuvant, neo adjuvant settings. Despite all the progress, melanoma remains challenging to treat.

**Keywords:** Melanoma, Sentinel lymph node, Lymph node dissection, Adjuvant therapy, Immunotherapy, BRAF mutation

## INTRODUCTION

Malignant melanoma account for less than 10% of skin cancer, being the deadliest due to its aggressive nature and mortality rate. The probability of developing melanoma in one's lifetime is 1 in 27 in male and 1 in 42 in female.<sup>1</sup> Last decade has seen substantial therapeutic developments in melanoma treatment particularly in advanced disease. Surgery remains the cornerstone of curative intent of melanoma treatment. Advanced melanoma with

multimodality treatment have also improved dramatically. The aim of the analytic paper is to investigate different treatment modalities for cutaneous melanoma according to stage of the condition as per American, European and UK guidelines and devise management plan of cutaneous melanoma. Many patients with melanoma remain at risk of poor outcome and future developments in multimodality management remain critical. Risk factors for developing cutaneous melanoma are multiple including sun exposure, tanning beds, family history of melanoma, advancing age, immunosuppression, fair colour, increased nevi count and

germ line mutations and polymorphisms predisposing to melanomas.<sup>1</sup>

#### ***Histological subtypes of melanoma***

##### ***Superficial spreading melanoma***

Most common variant with atypical epithelioid melanocytes in clusters.

##### ***Nodular melanoma***

Rapidly enlarging nodule, dermal mass of dysplastic tumour cells with upward epidermal invasion.

##### ***Lentigo malignant melanoma (LMM)***

Common in sun exposed parts of body. Slowly enlarging, irregular pigmented macule. It is precursor of melanoma in situ.

##### ***Lentiginous melanoma***

Slowly progressive melanoma presents in limbs and trunk. Histologically lentiginous hyperplasia with nests of melanocytes with cytological atypia.

##### ***Desmoplastic melanoma***

Slow growing non-pigmented lesion of head & neck in greater than 50% of cases. Tumour cells produce fibromucinous matrix.

##### ***Acral lentiginous melanoma (ALM)***

Arises from skin of soles, palms or under surface of nail. Subungual melanoma of thumb and great toe is commonest.<sup>2</sup>

In order of frequency acral lentiginous melanoma is most frequent followed by superficial spreading than nodular melanoma. The standard ABCDE criteria is not applicable to ALM, where CUBED acronym is applied - A: asymmetry of lesion, B: irregular, ragged, or indistinct border, C: lesion with more than one colour present, D: diameter of lesion greater than 6 mm, E: evolution change in size, shape, or colour of lesion.

Also, C: change in colour which is not normal skin colour, U: uncertain diagnosis, B: bleeding lesion or chronic granulation, E: enlargement of lesion, ulceration despite treatment, and D: delay in healing of lesion beyond two months.

#### ***TNM cutaneous melanoma classification***

It is of the following types: localized disease (stage I-II), regional disease (stage III), and distant metastatic disease (stage IV).<sup>3,4</sup>

#### ***Stage I***

Stage I melanoma is limited to patients with low-risk primary melanomas (T1a, T1b, and T2a) without evidence of regional or distant metastases. Stage I subdivided into stages IA and IB based on the thickness of the primary tumour and the presence or absence of primary tumour ulceration.

#### ***Stage II***

Stage II disease includes primary tumours that are at higher risk of recurrence (T2b, T3a, T3b, T4a, and T4b) but do not have any evidence of lymphatic disease or distant metastases. Stage II subdivided into stage IIA, IIB, and IIC depending upon tumour thickness and the presence or absence of primary tumour ulceration.

#### ***Stage III***

Stage III disease includes pathologically documented involvement of regional lymph nodes and/or the presence of in-transit or satellite metastases (incorporated using N subcategory). Patients with stage III disease are sub-staged as having stage IIIA, IIIB, IIIC, or IIID disease depending upon the extent of lymphatic disease as well as the status of primary tumour ulceration and thickness (incorporated using T subcategory).

#### ***Unknown primary***

Patients with isolated metastases identified in the lymph nodes, skin, or subcutaneous tissue who do not have an identifiable primary cutaneous melanoma (T0) are classified as pathologic stage III, assuming no other sites of disease are identified after an appropriate staging evaluation. Other sites of metastases from an unknown primary melanoma are categorised as stage IV.

#### ***Stage IV***

The presence of distant metastases defines stage IV disease (M1a to M1d). Central nervous system metastases (M1d) are associated with a particularly poor prognosis. There are no subgroups.<sup>9</sup>

#### ***Breslow thickness***

Thin thickness melanomas (less than 0.85 mm to 1 mm) Tis to T1b, intermediate thickness melanomas (Breslow thickness 1 – 4 mm) T2-T3, and thick melanoma (Breslow thickness equal to and above 4 mm) T4.

#### ***Genetic classification***

Genetic basis of melanoma understanding progressed in last decade. Disease progression is associated with gene alterations. Multiple gene alterations observed in melanomas. Four different genetic melanomas subtypes on the basis activating gene mutations being identified, as

under: BRAF mutant melanomas (50%). BRAF mutation common in cutaneous sun damaged skin melanomas, N-Ras mutant melanomas, K-Ras mutant melanomas (25%), H-Ras mutant melanomas, NF1-mutant melanomas (15%), and triple wild type melanomas (10%).<sup>7,8</sup> Genetic alterations also include TERT-promoter mutations found in 30-80% melanomas. Tumour suppressor gene,

frequently altered in melanoma, are CDKN2A, PTEN, TP53, and ARID2. The aim of the analytic paper is to investigate different treatment modalities for cutaneous melanoma according to stage of the condition as per American, European and UK guidelines and devise management plan of cutaneous melanoma.

**Table 1: Comparison of histologic patterns of major subtypes of melanoma.<sup>2</sup>**

Variables	Superficial spreading melanoma	Lentigo malignant melanoma	Acral lentiginous melanoma	Nodular melanoma
<b>Pattern of RGP</b>	Diffuse pagetoid	Lentiginous	Lentiginous	Absent
<b>Dominant cell type in RGP</b>	Epithelioid	Epithelioid, spindle and uncommonly dendritic	Spindle, epithelioid or dendritic	Not applicable
<b>Epidermis of RGP</b>	Normal to hyperplastic	Atrophic	Hyperplastic	Not applicable
<b>Dominant cell type of VGP</b>	Epithelioid	Spindle and epithelioid	Spindle and epithelioid	Epithelioid
<b>Desmoplasia</b>	Rare	Common	Common	Uncommon
<b>Neurotropism</b>	Rare	Common	Common	Uncommon
<b>Frequency of regression</b>	Often partial regression	Common	Variable	Uncommon

RGP: radial growth phase, VGP: vertical growth phase

**Table 2: AJCC 8<sup>th</sup> edition melanoma TNM prognostic stage groups. Pathological stage 0 (melanoma in situ) and T1 do not require pathological evaluation of lymph nodes to complete pathological staging.<sup>3,5</sup>**

When T is...	N is...	M is...	Then the clinical stage group is...
<b>Tis</b>	N0	M0	0
<b>T1a</b>	N0	M0	IA
<b>T1b</b>	N0	M0	IB- low risk node negative
<b>T2a</b>	N0	M0	IB- disease
<b>T2b</b>	N0	M0	IIA
<b>T3a</b>	N0	M0	IIA
<b>T3b</b>	N0	M0	IIB- high risk node negative
<b>T4a</b>	N0	M0	IIB- disease
<b>T4b</b>	N0	M0	IIC
<b>Any T, Tis</b>	≥N1	M0	III – high risk node positive
<b>Any T</b>	Any N	M1	IV- disease

Bold line represents cut off three groups

**Table 3: Common mutations associated with melanoma and its mimickers.<sup>7,8</sup>**

Gene	Characteristic association
<b>CDKN2A</b>	Familial melanoma
<b>BRAF</b>	Most common mutations in sporadic melanoma
<b>PTEN</b>	Common
<b>NRAS</b>	Enriched in nodular melanoma
<b>HRAS</b>	Present in some Spitz nevi, distinguishing them from spitzoid melanoma
<b>ALK</b>	ALK fusions in subset of Spitz neoplasms
<b>KIT</b>	Predilection for Lentigo Maligna melanoma, Acral lentiginous & mucosal melanoma
<b>GNAQ, GNA11</b>	Uveal melanoma, blue nevi
<b>BAP1</b>	Associated with epithelioid Spitz tumours, uveal melanoma, mesothelioma, renal cell ca
<b>TERT</b>	Encodes for telomerase, can be associated with high-risk spitzoid melanoma
<b>NTRK</b>	Gene fusions frequently associated with infantile fibrosarcoma; TRK inhibitors available
<b>NF1</b>	Occurs with mutations in RAS genes
<b>IDH1</b>	3 to 5% of melanomas
<b>RAC1</b>	Common

## METHODS

PubMed, Medline, Clinical key, latest guidelines from European society of medical oncology (ESMO), National institute of clinical excellence (NICE), American joint committee on cancer (AJCC) on melanoma along with publications published in English from June 2012 to August 2022 were searched. The medical subject heading (MeSH) terms used was melanoma AND sentinel lymph node AND immunotherapy OR adjuvant treatment. Articles searched were narrowed down by abstract, with emphasis on papers that focused on treatment options of cutaneous melanoma, excluding cutaneous melanoma involving head and neck. Studies that dealt with recommendations for staging, workup, and follow up were also included.

## RESULTS

Surgical management is critical for diagnosis, staging, and optimal treatment of primary cutaneous melanoma. Surgical goals include histological confirmation by biopsy, pathological staging of primary tumour, regional nodal basin by sentinel lymph node biopsy (SLNB), in transit metastasis and distant metastatic disease. Thickness of melanoma (Breslow thickness) is the key factor in clinical staging in relation to wide local excision (thin, moderate, and thick).

### ***Stage 0 to stage IA melanoma (Tis to T1A<0.8 mm without ulceration) thin melanoma wide local excision of primary tumour***

#### *Low risk node negative disease*

Asymptomatic patient with stage 0 (TisN0M0) does not require routine imaging like CT, PET CT or MRI or laboratory evaluation. In case of equivocal findings, ultrasonography of nodal basin is required. Screening regional lymph nodes with ultra-sonography before SLNB showed high sensitivity (60%) and specificity (97%) respectively. Tumour thickness, ulceration. Mitotic rate and lympho-vascular invasion are strong predictors for SLNB positivity. Treatment is wide excision (WLE) of primary melanoma site with appropriate margin of normal tissue around the primary site to minimize the risk of local recurrence.

Recommendations from National Comprehensive Cancer Network (NCCN) and American Academy of Dermatology (AAD) is 0.5 to 1 cm margin, followed by evaluation by histopathology to ensure clearance.<sup>4-6,9</sup>

#### *Role of Mohs micrographic surgery (MMS)*

Hand and foot melanomas were managed with either amputation or WLE, causing functional, loss of digit and affecting quality of life. WLE can leave margin involvement. MOH micrographic surgery (MMS) technique evolution as treatment modality encompasses

excision of primary lesion followed by complete microscopic evaluation of lateral and deep margins with maintaining tissue orientation. It has advantage of tissue conservation, optimal margin control and high cure rate. It has 100% peripheral margin evaluation. Maintaining function and cosmesis of hand, feet, or digit after MMS can be difficult. This may require skin graft, flap for defect closure. MMS may be beneficial, but topic is controversial.<sup>12,13</sup>

Sentinel lymph node biopsy (SLNB) is not routinely recommended for stage T1a for tumour thickness less than 0.8 mm and no ulceration. SLNB can be discussed in T1a in special cases like mitosis 3 or greater/mm<sup>2</sup>, positive deep margin or Breslow thickness cannot be measured (Tx), and ulceration.

### ***Stage IB- stage II A, T1b to T2b (0.8 mm with ulceration to 1-2 mm) thin to intermediate melanoma***

#### *Low risk node negative disease*

WLE with one cm margin for T1 lesion while T2 lesion again 1 cm to 2 cm margin, but studies showed 1 cm margin is adequate. A WHO trial 612 patients with tumour thickness <2 mm randomly assigned to 1 cm and 3 cm margin. Swedish Melanoma study group assigned randomly 989 patients with melanoma thickness 0.8 to 2 mm for 2 to 5 cm resection margin while another French study of 362 patients with melanoma thickness less than 2 mm were randomly assigned to 2 versus 5 cm margins. All the three above studies showed no difference between the groups in risk of local recurrence, overall survival, and disease-free survival. One cm resection margin is acceptable by NICE, ESSO guidelines. SLNB is recommended in T1b melanomas (0.8-1.0 mm or <0.8 mm with ulceration). 5% patients with thin melanomas have SLNB metastases. Melanomas greater than 0.75 mm have SLN positivity in 6.3% and 8.8%. Consideration of clinicopathologic risk factors is recommended when considering SLNB in patients with T1b disease.<sup>10,16,17</sup>

### ***Stage II a – II C, T3 (2mm-4 mm thickness /intermediate thickness) high risk node negative disease***

Melanomas >2 mm thick NCCN and AAD guidelines recommend a 2 cm margin.

Multicentre European trial at 53 sites comprising 936 patients with melanomas of trunk and extremity greater than 2 mm thick were randomly assigned to 2-4 cm resection margin to calculate effect of resection alone from 1992 to 2004. Melanoma specific survival, overall survival or recurrence free survival showed no statistically significant difference between two resections. Similar results were obtained from another melanoma trial of 468 patients with intermediate thickness (1-4 mm). In conclusion, 2 cm resection margin is recommended. Avoid reconstruction whenever possible.

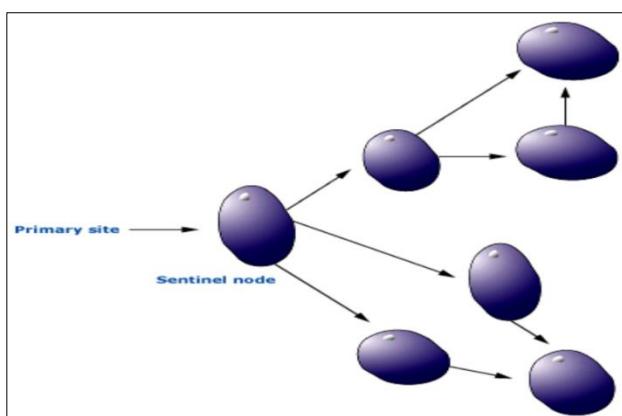
**Table 4: Randomized trials examining optimal surgical margin width for cutaneous melanoma.<sup>22-28</sup>**

Study	n	Median follow-up	Melanoma thickness (mm)	Margin (cm)	Local recurrence (%)
World Health Organization <sup>24</sup>	612	12 years	0 to 1	1	3/186 (1.6)
			1.1 to 2	1	5/119 (4.2)
			0 to 1	3	1/173 (0.6)
			1.1 to 2	3	2/134 (1.5)
Swedish <sup>25</sup>	989	11 years	0.8 to 2	2	3/476 (0.6)
				5	5/513 (1)
French cooperative	326	16 years	<2.1	2	1/181 (0.05)
				5	4/185 (0.2)
Melanoma intergroup trial <sup>27</sup>	468	8 years	1 to 4	2	(2.1)
				4	(2.6)
British trial <sup>28</sup>	900	60 months	≥2	1	15/453 (3.3)
				3	13/457 (2.8)
Europe <sup>28,29</sup>	936	6.7 years	>2	2	20/465 (4.3)
				4	9/471 (1.9)
			19.6 years	>2	2
					Not reported
					4

**Table 5: Recommended excision margin as per Breslow thickness.**

Breslow thickness	Recommended excision margin (cm)
<b>Melanoma in situ</b>	0.5 to 1
<b>≤1 mm (T1)</b>	1
<b>&gt;1 to 2 mm (T2)</b>	1 to 2
<b>&gt;2 mm (T3 to T4)</b>	2

SLNB is recommended, which helps to improve regional disease control and decision regarding adjuvant therapy.<sup>18</sup> Rate of nodal metastases in this group of patients ranges from 16-20%. Rate of complications from SLNB is approximately 5%. Please see the outcome of multicentre selective lymphadenectomy trial (MSLT-I and (MSLT-II) described in detail in section of discussion.

**Figure 1: Sentinel node concept.<sup>18</sup>**

Radical lymph node dissection is recommended for cases of clinically detected lymph node metastases in resectable

stage III disease after pathological assessment (cytology/histology) preoperatively along with adequate staging. Another point to mention is that in absence of neoadjuvant therapy radical node dissection is recommended over node picking for clinically palpable lymph nodes in resectable disease. Dissection of groin if iliac involvement is present otherwise inguinal lymphadenectomy is sufficient. In case of axillary involvement, level 3 axillary clearance is recommended. In case of neck nodes, involvement Modified radical neck dissection is recommended. Opinion differs on all the above lymph node dissections.

**Stage III – stage IV, T 4 OR any T, Any N M +ve melanoma low risk (III A) to high-risk node positive disease**

Melanomas thicker than 4 mm, survival and local recurrence outcomes depend upon the presence of regional or distant disease. Studies from Europe, UK showed similar overall survival and local recurrence with 2 cm clear margin and 4 cm clear margin. In stage III, clinically resectable disease primary melanomas should be removed with clear margin to ensure local control. Primary closure and avoid reconstruction whenever possible with 1-2 cm margin. In clinical stage IV disease in the absence of symptoms or need for diagnostic tissue, there is no need to resect the primary tumour. If there is, indication to resect the primary lesion resection should be with clear margin without any additional safety margins. In most circumstances in stage IV disease, no surgical treatment of primary melanoma is recommended since patient will be receiving systemic therapy.

## DISCUSSION

Surgical excision is treatment of choice & curative in patients with locoregional melanoma. Some patients

relapse with disseminated disease, and some presented with disease recurrence. Checkpoint inhibition immunotherapy and targeted therapies is used in adjuvant and neoadjuvant setting. Factors that influence the decision to offer adjuvant or neoadjuvant therapy and choice of agent, include risk of disease recurrence, stage at diagnosis, degree of lymph node involvement, BRAF mutation status and characteristics of patient such as age, comorbidities and treatment preferences or enrol in clinical trial.

The physical examination of regional lymph nodes is often inaccurate since 20% of clinically node negative patients have metastatic involvement and vice versa. Definitive information about the status of the regional nodes can be obtained from ultrasound guided fine needle aspiration cytology or fine needle biopsy of suspected pathological lymph node. When SLNB is indicated for surgical staging, wide local excision and SLNB should be carried out in same operative setting. Lymphatic mapping and SLNB is carried out by different techniques such as use of radioisotope technetium 99 with or without blue dye, fluorescent indocyanine green, superparamagnetic iron oxide magnetic tracer method. Sentinel lymph biopsy (SLNB) is therapeutic for regional control in most patient with regional metastases. This allows us to determine prognosis, select patient who benefit from adjuvant therapy, and select candidates for clinical trials.

#### ***Multicentre selective lymphadenectomy trial-1 (MSLT-1) and (MSLT-2)***

Largest trial to address the role of lymphatic mapping with SLNB in determining prognosis and its impact on survival. A subsequent multicentre selective lymphadenectomy trial-2 deals with management of patients found to have a positive sentinel lymph node. MSLT-1 trial, 2001 patients were randomly assigned to lymphatic mapping with SLNB (60%) and to observation (40%) between 1994 to 2002. The results of MSLT-1 confirmed the role of lymphatic mapping with SLNB as a prognostic tool. Trial also demonstrated significant survival benefit in patients with intermediate thickness melanoma with microscopic lymph node involvement, assigned to lymphatic mapping with SLNB and underwent early regional lymphadenectomy compared to those who had only wide local excision without SLNB. MSLT-1 trial are supported by larger retrospective series of 5840 patients in the melanoma institute Australia database treated between 1992-2008. MSLT-2 trial included 1934 patients who had positive SLNB as well as WLE of primary tumour with Breslow thickness equal, greater than 1.20 mm, or greater with Clarke level III-V, regardless of Breslow thickness or ulcerative tumour or Clark level. Patients were randomly assigned to completion lymph node dissection (CLND) or observation. Each follow up visit was covered with ultrasound of lymph node basin. Melanoma specific survival was same for both groups. Disease-free survival was better in lymph node dissection group. Melanoma specific survival was worse in thicker primaries,

ulceration, positive lymph nodes. No subgroup could be identified in whom completion lymph adenectomy provided benefit.

#### ***DE COG-SLT trial***

Multi-centre trial 483 patients with cutaneous melanoma of trunk or extremities were randomly assigned to immediate CLND or observation, including ultrasound of primary and appropriate lymph node basins. Most patients had low volume metastasis in SLN. After 72 months of median follow up, lymph node metastasis was more frequent in observation arm (16.3%) compared to CLND group (10.8%). Difference in regional node recurrence rate, distant metastasis free survival, relapse free survival and overall survival at five years were similar between the groups. Complication rate was higher in CLND group. SLNB is not offered to patients with stage 0 to stage IA. Patients with melanoma with Breslow thickness of 0.8-1.0 mm with at least one of the features like ulceration, lympho-vascular invasion, or mitotic index of 2 or more, SLNB should be considered. Melanoma with Breslow thickness greater than 1 mm SLNB should be considered. Pregnant patients with the above should have SLNB carried out as delayed procedure after pregnancy.

#### ***Imaging***

Different imaging modalities are in practice in preoperative and post-operative setup. Stage IA to IIA ultrasound of lymph node basin to pick enlarged suspicious nodes and carry out FNAC/ultrasound guided biopsy of suspected node, if positive proceed to SLNB. Consider whole body CT and brain CE-CT for stage IIB to stage IV. Consider brain MRI if locally available instead of CE-CT brain.

In addition, children, young adults less than 24 years of age and women with pregnancy having stage IIB to stage IV melanoma should have MRI brain instead of CE-CT brain. Patients with stage IIIC to IV with primary melanoma located in scalp or with mitotic index of 5 or more should also have brain MRI instead of CE-CT brain.<sup>16-19</sup>

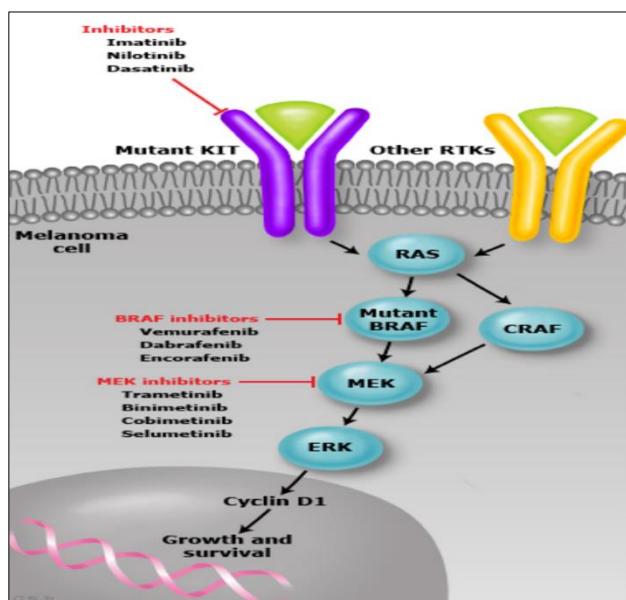
However, patients may present with metastatic disease or develop metastasis after initial definitive treatment. Development of immunotherapy using checkpoint inhibitors, targeted therapy against mitogen activated protein-kinase (MAPK) pathway. The choice of therapy is based upon extent of disease, molecular characteristics of the tumour, patient performance status and co morbidity. If targeted systemic therapy is indicated, genetic testing be carried out on melanoma tissue sample. BRAF analysis should not be offered to stage IA and IB, except as part of clinical trial. BRAF analysis of melanoma tissue should be offered to stage IIA to stage IV. BRAF V600E should be checked first by immunohistochemistry and if it is negative or inconclusive, a different BRAF genetic test should be applied.

### BRAF mutation

Patients with high-risk microscopic node positive disease that harbours BRAF gene, particularly a BRAF V600 mutation, have the option of adjuvant therapy with either immunotherapy or targeted therapy (BRAF + MEK inhibitors). Patients with metastatic melanoma lacking BRAF mutation (BRAF wild-type disease) have option of systemic therapy such as checkpoint inhibitor immunotherapy, the agents that inhibit cytotoxic T lymphocytes associated antigen 4 (CTLA-4) and programmed cell death receptor-1 (PD-1).

### BRAF mutations (MAPK pathway)

Approximately one-half of cutaneous melanomas have a V600 mutation in the BRAF gene. In combination with downstream MEK, BRAF activates the mitogen-activated protein kinase (MAPK) pathway, resulting in oncogenesis. In most patients with BRAF V600 mutation-positive melanoma, BRAF inhibition produces rapid tumour regression. The addition of MEK inhibition reduces resistance and decreases cutaneous toxicity seen with single-agent BRAF inhibition.<sup>29</sup>



**Figure 2: Mitogen-activated protein (MAP) kinase pathway.**

### Adjuvant and neoadjuvant therapy for cutaneous melanoma

#### Low risk node negative disease

Low risk node negative disease patients' stage I to IIA (less than or equal to 2 mm to 4 mm thick without ulceration) but no lymph node involvement. Perform surveillance alone after surgery without adjuvant therapy. This group has low risk of disease recurrence and surgery alone is usually curative.<sup>9,10,16,17,20,21,29,30</sup>

#### High risk node negative disease

Patients with stage IIB and IIC disease with tumour >2 mm with ulceration to >4 mm with or without ulceration. Adjuvant immunotherapy with either pembrolizumab or nivolumab rather than surveillance. Surveillance and enrolment in clinical trial is reasonable alternative particularly in stage IIB disease, given the likely low recurrence rate.

#### Low risk node positive disease

For patient with stage IIIA disease having non-ulcerated tumour <2 mm in thickness & SLN metastases, surveillance rather than systemic therapy as these patients have lower risk of disease recurrence less than 20%. For all other patients with resected stage IIIA melanoma, one year of systemic adjuvant therapy based upon BRAF mutation status of tumour.

#### High risk node positive disease

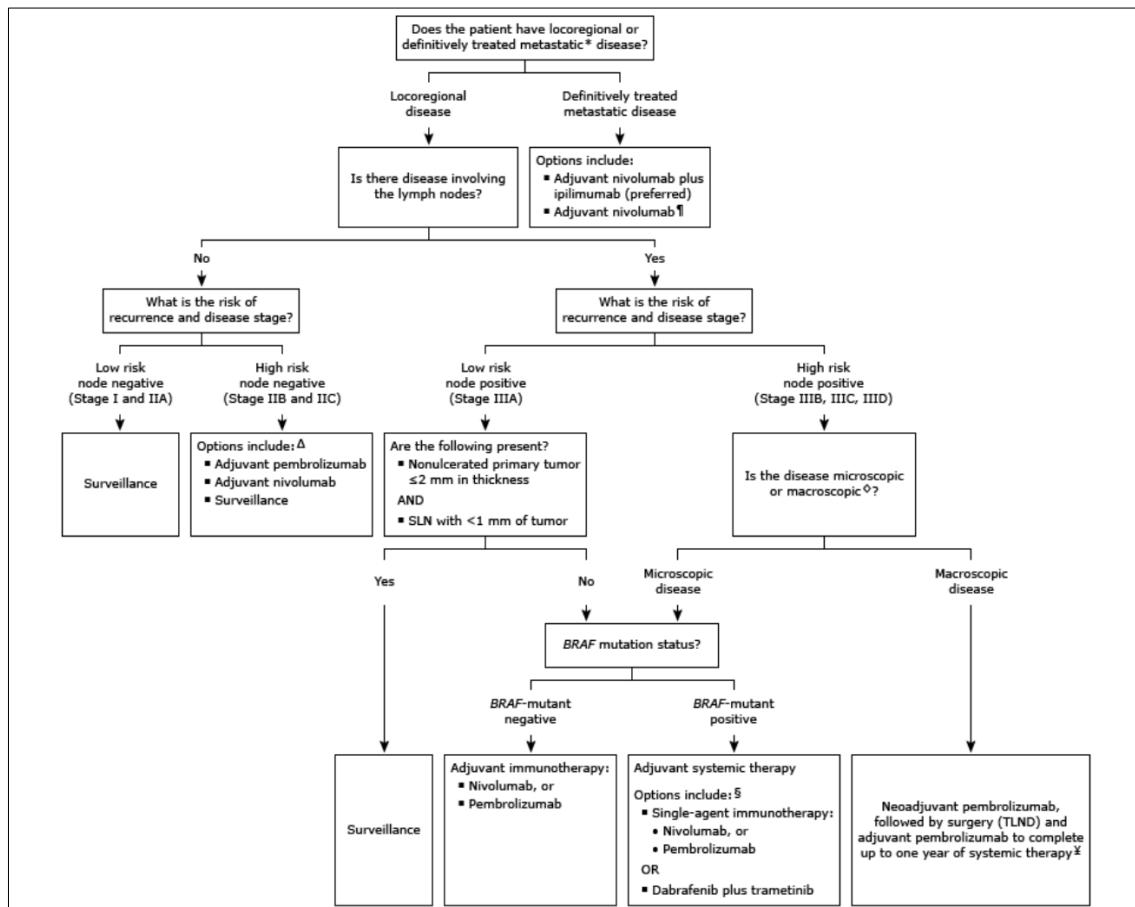
For stage IIIB, IIIC and IIID melanoma, patients should be divided into two subgroups.

#### Microscopic disease

Microscopic disease is tumour burden detected on SLNB. Patients with resected microscopic disease with no prior neoadjuvant therapy, option of adjuvant systemic immunotherapy or targeted therapy for BRAF V600 mutated tumour. BRAF wild type tumour one year of adjuvant immunotherapy with programmed cell death 1 inhibitors (PD-1) rather than other systemic therapies or surveillance. Alternate is nivolumab or pembrolizumab. For BRAF mutated tumours option include one adjuvant immunotherapy with nivolumab or pembrolizumab or one year of targeted therapy with combination of BRAF plus MEK inhibitors dabrafenib and trametinib. It improves overall survival as compared to surveillance. Nivolumab is an alternative in case of potential toxicities. Combined BRAF plus MEK inhibitor therapy has replaced the use of single-agent BRAF inhibitors. Options include dabrafenib plus trametinib, vemurafenib plus cobimetinib, and encorafenib plus binimetinib. Simultaneous inhibition of BRAF and MEK improves response rates and survival compared with BRAF inhibition alone. The rapid tumour regression is especially important for patients with extensive tumour burden and disease-related symptoms.

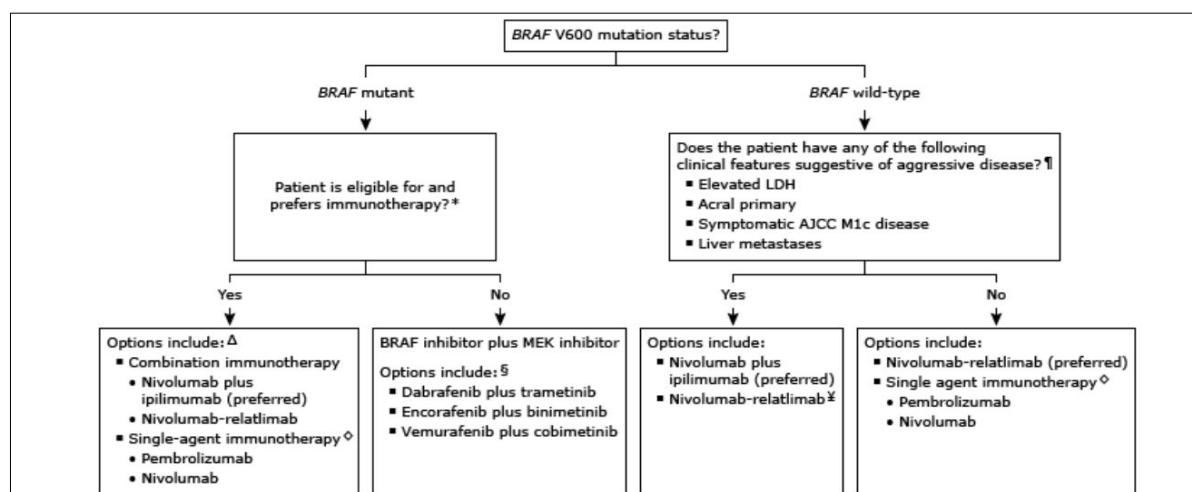
#### Macroscopic disease

Node positive disease on physical/imaging or satellite metastasis on pathology FNAC, which is resettable initial treatment with neoadjuvant pembrolizumab rather than primary surgery reported event free survival in randomized trial. Alternate option is neoadjuvant therapy with nivolumab plus ipilimumab or clinical trial enrolment investigating other neoadjuvant regimens.



**Figure 3: Selection of adjuvant and neoadjuvant therapy for resectable cutaneous melanoma.**

\*All sites of disease treated with either surgery or radiation therapy; † adjuvant nivolumab is an option for those who are unable to tolerate the potential toxicities of combination nivolumab plus ipilimumab; △ surveillance is an appropriate alternative to adjuvant therapy; ◊ microscopic disease / macroscopic disease; § immunotherapy and targeted therapy with dabrafenib plus trametinib are both effective options with different toxicity profiles; ‡ alternative options include neoadjuvant nivolumab plus ipilimumab or clinical trials investigating other neoadjuvant regimens.



**Figure 4: Approach to selecting initial systemic therapy in patients with extracranial metastatic cutaneous melanoma.**

LDH; Lactate dehydrogenase; PFS; Progression free survival. This algorithm reveals the initial systemic therapy patient with extra cranial metastatic cutaneous melanoma it is based on tumour BRAF mutation status, clinical presentation of aggressive disease, performance status, comorbidities and preferences. \*Eligibility for immunotherapy, ! brain metastases, ^ patient with BRAF V600 mutant melanoma

### Metastatic disease

Patients with stage IV metastatic disease regardless of BRAF V600 mutation status who have gone through primary definitive treatment of all sites of metastatic disease, adjuvant nivolumab plus ipilimumab followed by maintenance nivolumab. It improves overall survival as compared to surveillance. Nivolumab is an alternative in case of potential toxicities. In a retrospective analysis of survival data from two large phase III trials, 34% of patients with BRAF V600 mutations treated with the combination of dabrafenib and trametinib were alive at five years, and approximately 20 percent were progression free at five years. Lactate dehydrogenase (LDH) appears to be a critical prognostic factor. As an example, 43% of patients with normal LDH were alive at five years. Other prognostic factors for improved survival include higher performance status and <3 organ sites with metastases.<sup>20,21,29</sup>

### CONCLUSION

Surgical excision is treatment of choice for locoregional cutaneous melanoma and curative in most cases. There is shift towards targeted therapy and immune checkpoint inhibitors with selective use of completion lymph node dissection. Neoadjuvant therapy for challenging melanoma is promising and progressing.

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