Malignant Melanoma

Introduction

Melanoma is a malignant tumor of melanocytes, cells that are derived from the neural crest. There is an **increasing incidence** of melanoma, as well as an **increasing mortality**, despite our best efforts. Estimated new cases in the USA for the year 2015 will be 73 870, while deaths are estimated to be 9 940. This means 1 death per 7.43 diagnoses [1:8] – indicating the seriousness of this diagnosis. This is remains similar to the last 5 years of data, underscoring our lack of impact on the natural disease history.

While most melanomas arise in the **skin**, they may also arise from other sites to which neural crest cells migrate, such as rectum, vagina, oesphagus, nasopharynx, iris and oral cavity. **>50%** of the cases arise in apparently **normal** areas of the **skin –** so called *de novo* melanoma**s**. The rest arise from a precursor **pigmented lesion** such as dyplastic nevi. Multiple nevi indicate increased risk (see below). Presentation gender differences exist: Women tend to present with extremity melanomas, whereas men tend to present with trunk or head & neck lesions.

Usual Clinical Presentation – The Suspicious Pigmented Lesion

Many patients present with pigmented lesions and the vast majority are of no clinical concern. Experience in assessing pigmented lesions is the most important factor in accurate diagnoses, but have a systematic approach is exceptionally useful, even for experience dermoscopists. The clinical evaluation of a pigmented lesion of the skin is known as **dermatoscopy** (also known as **dermoscopy** or **epiluminescence microscopy**). These are indispensable tools for pigmented lesion evaluation. They consist of a polarized light source and a magnification lens (usually X10). The use of polarised light helps to cancel out skin surface reflections allowing a more unobstructed view of the 2mm below the surface. When the images or video clips are digitally captured or processed, the process is referred to as **"Mole Mapping",** which is currently considered the diagnostic standard as it allows retrospective image review and change over time.

A standardized dermoscopy report is also essential to the process as it allows independent review. The method of evaluation used by each practitioner is not relevant as they all have strengths and weaknesses. It is more important to be consistent and comfortable with you algorithm of choice. Some of the available algorithms include: ABCD rule, Menzies method, 7-point rule, C.A.S.H., CHAOS and clues, BLINCK algorithm and the 3 point check list. My personal choice is the C.A.S.H. method described by Kopf et al. and is presented below. Dermoscopy is a skill which, like auscultation, can be easily acquired but requires consistent practice to master. There are numerous books and interactive CDs as well as online resources for those who wish to enhance their skill set.

Suspicion for melanoma

	Low	Medium	High
Colours: Light brown, dark brown, black, red, white, blue Score 1 point for each colour	1-2 colours (1-2 points)	3-4 colours (3-4 points)	5-6 colours (5-6 points)
Architecture: Order vs disorder Score 0-2 points	None or mild disorder (no points)	Moderate disorder (1 point)	Marked disorder (2 points)
Symmetry: Consider contour, colours and structures Score 0-2 points	Symmetry in 2 axes (no points)	Symmetry in 1 axis (1 point)	No symmetry (2 points)
Homogeneity: Consider pigment network, dots & globules, blotches, regression, streaks, blue-white veil, polymorphous vessels Score 1 point for each structure	Only one structure (1 point)	2 types of structure (2 points)	3 or more structures (3-7 points)

Add up the scores for a total C.A.S.H. score (2 to 17). C.A.S.H. score of 7 or less is likely benign. C.A.S.H. score of 8 or more is suspicious of melanoma.

When in doubt, consider biopsy. An acceptable "hit-rate" for malignancy is 1 malignant biopsy in every 10. A higher "hit rate" should prompt the practitioner to excise more frequently. A lower "hit rate" should prompt the practitioner to consider a more thoughtful screening.

All pigmented lesions should undergo one of two clinical interactions – screening or excisional biopsy. Excisional biopsy should be performed with 1-3mm clinical margins and should be oriented in the same direction as a later excision would require. The reason for the narrow initial margins is to allow later lymph node mapping to be performed. In certain circumstances and in certain anatomical locations, excisional biopsy way not be appropriate and an incisional or punch biopsy may be done, with the caveat that sampling error remains a concern. Shave biopsies are never appropriate. Destructive treatment (laser, cautery or cryotherapy) of melanocytic lesions is **absolutely forbidden**.

It is interesting to note that there is no prognostic loss when the definitive surgery is performed within 3 weeks of the initial diagnostic procedure, which allows adequate time for complete pathological reporting, even if immunohistochemistry methods are required.

Malignant Melanoma Diagnosed

Once the diagnosis of malignant melanoma has been secured, and the quality of the pathological report is suitable, the preliminary management of the patient starts (as always) with a history and examination as well as a focused and extensive dermatological examination and a specific assessment of the melanoma related risk factors. The clinical stage of the patient will then determine the further workup and specific treatment of the patient.

Melanoma Specific Risk Factors

- A patient who has had a **melanoma previously** is at risk of a second melanoma, or other non-melanoma skin cancer, this is the most important single risk factor, by 3 orders of magnitude (1500X risk).
- **A family history** of melanoma also indicates a significantly increased risk (150 – 700X – depending on the relationship). This is the second most important risk factor.
- The **atypical mole syndrome** (B-K Mole Syndrome, FAMM Syndrome) carries a 10% lifetime risk – this is the most important genetic factor.
- Epidemiological studies show an association between **melanoma and sun-exposure**, in particular **blistering sunburn** in childhood and adolescence.
- Certain sub-populations are at increased risk for melanoma – **fair skin and hair colour** other than black are risk factors (red is the most at 3.6X), but interestingly, eye colour has no significance.
- **Freckling** on exposure to sunlight is associated with 1.9X risk and **more than 20 nevi** is associated with a 3.4X risk.
- **Immunocompromised patients** such as chronic suppressive medication, HIV, Hodgekins etc are at increased risk due to poorer immune surveillance.
- Impaired DNA repair mechanisms (such as **Xeroderma Pigmentosa**) place patients at risk.
- A **melanocortin-1 receptor mutation** may confer an increased risk.

> “It remains critical to remember that melanoma may occur in **ANY** ethnic group and in **ANY** site which contains melanocytes, prior sun exposure notwithstanding”

Cellular Classification

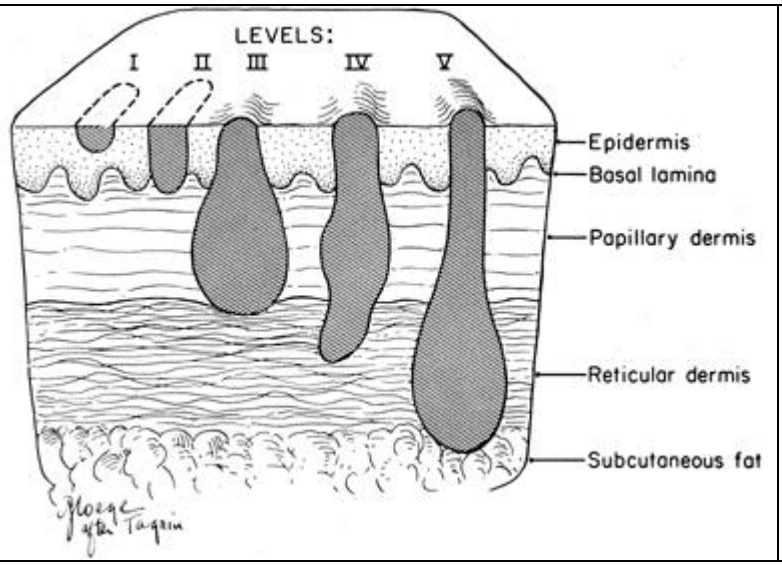
These are now considered descriptive terms and are of academic interest only as they have **no prognostic or therapeutic significance**.

- Superficial spreading. (70%)
- Nodular. (15%)
- Lentigo maligna. (5%)
- Acral lentiginous (palmar/plantar and subungual). (10%)
- Miscellaneous unusual types:
    - Mucosal lentiginous (oral and genital).
    - Desmoplastic.
    - Verrucous.
    - Spindle cell

Stage Information

The stage is determined on **histologic examination** by the vertical thickness of the lesion. It is measured in millimeters (to the nearest tenth) from the **upper granular layer of the epidermis to the deepest cell** and is known as the **Breslow’s depth. Clarke’s levels** are

no longer used in the present classification and were previously **only of significance in T1** melanoma.



Clark's Levels

Level I : In situ

Level II : Papillary dermis

Level III : Papillary-reticular junction

Level IV : Reticular dermis

Level V : Subcutaneous fat

Many older pathologists and surgeons still use the Clark Level classification and it would be wise to understand it.

The present 7th AJCC classification (revised in 2010) is complex and confusing. It is not essential to know this by heart, but I have included it below as a reference for your later clinical use, as well as the previous 6th AJCC for comparison.

Primary tumor (T)

- TX: Primary tumor cannot be assessed (e.g., shave biopsy or regressed melanoma)
- T0: No evidence of primary tumor
- Tis: Melanoma in situ

HERE IS THE PREVIOUS "OLD" AJCC CLASSIFICATION (6th Edition) :

- T1: Tumor ≤1.0 mm in thickness **THIN**
  - T1a: **≤1.0 mm** (Clark's level II or III) with **no ulceration**
  - T1b: **≤1.0 mm** (Clark's level IV or V) **<u>or</u> with ulceration**
- T2: Tumor >1.0 mm but ≤2.0 mm in thickness **INTERMEDIATE**
  - T2a: **1.1 - 2.0 mm** with **no ulceration**
  - T2b: **1.1 – 2.0mm** and **with ulceration**
- T3: Tumor >2.0 mm but ≤4 mm in thickness **THICK**
  - T3a: **2.1 – 4.0 mm** with **no ulceration**
  - T3b: **2.1 – 4.0 mm** with **ulceration**
- T4: Tumor >4.0 mm in thickness **VERY THICK**
  - T4a: **>4.0 mm** with no ulceration
  - T4b: **>4.0 mm** with **ulceration**

HERE IS THE NEW AJCC CLASSIFICATION (7TH Edition)
** New for the 2010 classification - addition of number of mitoses per HPF (1mm^2)

T classification	*Thickness (mm)*	*Ulceration Status/Mitoses*
T1	≤1.0	a: NO ulceration AND mitosis <1/mm^2.
		b: with ulceration OR mitoses ≥1/mm^2.
T2	1.01–2.0	a: No ulceration.
		b: with ulceration.
T3	2.01–4.0	a: No ulceration.
		b: with ulceration.
T4	>4.0	a: No ulceration.
		b: with ulceration.

You can see that the major differences are the addition of mitoses per high power field (HPF) and that Clark's levels have been abandoned.

Regional lymph nodes (N)
***** The Regional node classification remains unchanged from the previous edition. The finding of melanoma cells away from the main tumour bulk, but less than 2cm from the tumour bulk is known as **a satellite lesion**, and more than 2 cm is known **as an in-transit metastasis**. The distinction is purely semantic as you can see that it makes no difference to stage or prognosis.

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis

N Classification	*No. of Metastatic Nodes*	*Nodal Metastatic Mass*
N1	1	a: Micrometastasis.
		b: Macrometastasis.
N2	2–3	a: Micrometastasis
		b: Macrometastasis.
		c: In transit metastases or satellites(s) *without* metastatic nodes.
N3	≥4 Metastatic nodes, or matted node OR in transit met(s) / satellite(s) *with* metastatic node(s).	

Distant Metastasis (M)
* The metastatic classification remains unchanged from the previous edition.

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

- M1a: Metastasis to **skin**, subcutaneous tissues, or **distant lymph nodes**
- M1b: Metastasis to **lung**
- M1c: Metastasis to other **visceral sites** or any site with raised serum **LDH**

Pathologic staging

Except stage 0 or stage IA patients (who have a low risk of lymphatic involvement and do not require pathologic evaluation of their lymph nodes), **pathologic staging** includes microstaging of the primary melanoma and the regional lymph nodes (**requires sentinel node biopsy** or **lymphadenectomy**).

Visual AJCC Staging

		T 1		T 2		T 3		T 4	
		A	B	A	B	A	B	A	B
N 0		I a	I b	I b	II a	II a	II b	II b	II c
N 1	A	III a	III b	III a	III b	III a	III b	III a	III b
	B	III b	III c	III b	III c	III b	III c	III b	III c
N 2	A	III a	III b	III a	III b	III a	III b	III a	III b
	B	III b	III c	III b	III c	III b	III c	III b	III c
	C								
N 3		IIIc		IIIc		IIIc		IIIc	
M 1		IV		IV		IV		IV	

Prognosis

The 3 most important factors in the prognosis of melanoma are clearly evident from the above staging system (and this you have to know – because it makes a clinical difference)

1. Presence of **Metastatic** disease
2. Tumour **thickness**
3. Presence of **ulceration**.

Despite these exceptionally important factors, a host of other less important factors may play a role in prognosis. They are divided into 3 groups:

1. Clinical prognostic factors include:

1. **Age.** Patients over the age of 45 tend to have a poorer prognosis.
2. **Gender**. Female patients tend to have a better prognosis, possibly related to site.
3. **Site**. Head and neck (esp scalp) as well as trucal melanoma have a worse prognosis than melanoma on the extremity. The acral surfaces of hands and feet however tend to a worse prognosis, possibly due to depth at presentation.

2. Histological prognostic factors include:

1. **Pigmentation**. Amelanotic melanomas tend to evade diagnosis and present at a more advanced stage and thus have a worse prognosis.
2. **Lymphocytic infiltrate**. An infiltrate is associated with thinner lesions and better prognosis.
3. **Regression (halo)**. Controversial – some claim an increased rate of metastatic disease.
4. **Mitotic index** and **nuclear aneuploidy**. These are associated with poorer prognosis.

5. **Vertical growth phase**. Also associated with poorer prognosis.

3. Molecular prognostic factors are an emerging frontier and include:

1. **p53**. Expression of this tumour suppressor gene is associated with a better prognosis
2. **Akt**. This may allow invasive growth patterns
3. **c-Myc**. Over-expression of this oncogene is associated with a worse prognosis
4. **Ki-67**. Expression of this epitope is associated with metastatic disease and poor prognosis.
5. **HMB-45**. This melanoma reacting antibody is associated with poorer prognosis.

The following survival rates are based on nearly 60,000 patients who were part of the 2008 AJCC Melanoma Staging Database. These are *observed* survival rates. They include some people diagnosed with melanoma who may have later died from other causes, such as heart disease. Therefore, the percentage of people surviving the melanoma itself may be higher.

Stage IA: The 5-year survival rate is around 97%. The 10-year survival is around 95%.

Stage IB: The 5-year survival rate is around 92%. The 10-year survival is around 86%.

Stage IIA: The 5-year survival rate is around 81%. The 10-year survival is around 67%.

Stage IIB: The 5-year survival rate is around 70%. The 10-year survival is around 57%.

Stage IIC: The 5-year survival rate is around 53%. The 10-year survival is around 40%.

Stage IIIA: The 5-year survival rate is around 78%. The 10-year survival is around 68%.

Stage IIIB: The 5-year survival rate is around 59%. The 10-year survival is around 43%.

Stage IIIC: The 5-year survival rate is around 40%. The 10-year survival is around 24%.

Stage IV: The 5-year survival rate for stage IV melanoma is about 15% to 20%. The 10-year survival is about 10% to 15%. The outlook is better if the spread is only to distant parts of the skin or distant lymph nodes rather than to other organs, or if the blood level of lactate dehydrogenase (LDH) is normal.

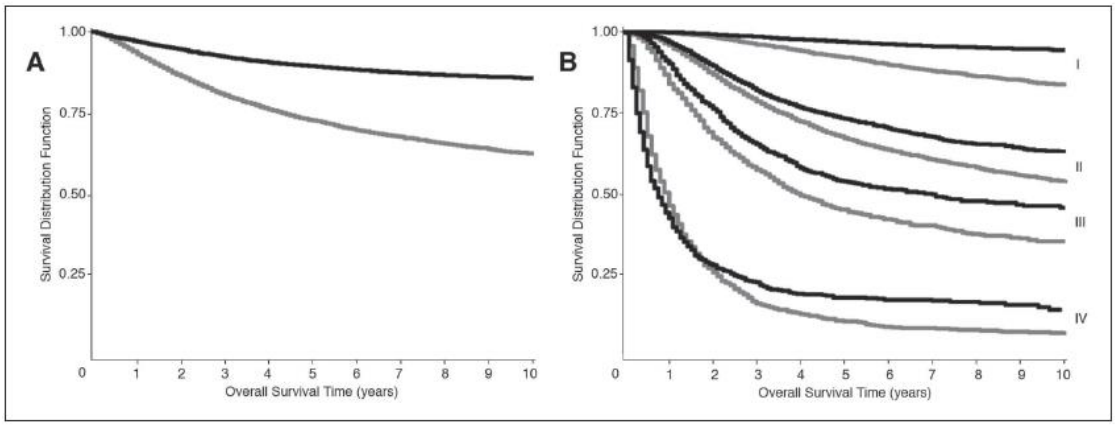


Fig 1. Kaplan-Meier survival curves for time to melanoma-specific death. (A) Overall survival distributions and (B) American Joint Committee on Cancer (AJCC) stage-specific survival distributions for Surveillance, Epidemiology, and End Results cancer registry (black) and AJCC (gray) cohorts.

Treatment Options Overview

Stage 0 Melanoma

Stage 0 melanoma (in situ) may be treated by excision with microscopically free margins. Most surgeons recommend margins of 0.5cm. No further work up is required, but continued screening for a second malignancy is critical. The lifetime risk of a second melanoma is in the order of 10-15%.

Stage I Melanoma (GOAL = CURE)

Surgery of the Primary Lesion : Stage I melanomas are treated with **adequate radial excision margins.** Recent evidence has shown no improved benefit between 1cm and 2cm for stage 1a. **For T1 lesions, 1cm** margins appear adequate, while **T2 lesions should have radial margins of 2cm**. In addition, excision depth should be **limited to the subcutaneous tissue**, and not include the deep fascia as this has shown no added benefit, and may possibly result in metastatic spread.

Lymph Node Surgery : **Elective regional lymph node dissection** is of **no benefit** for patients with stage I melanoma. However, lymphatic mapping and **sentinel lymph node biopsy** for patients who have tumors **with ulceration (Stage Ib),** may allow the identification of individuals with occult nodal disease (**clinically node negative,** but stage III nonetheless) who might benefit from regional lymphadenectomy and adjuvant therapy – these patients have shown unquestionably higher survival rates. Stage Ia patients do not require SNLB. A previously controversial point is SLNB in stage Ia patients with poor tumour biology such as Ki-67 or HMB-45, or adverse clinical and histological parameters, or truncal lesions especially in males. Presently, SLNB is recommended in such patients.

Further Workup: CT scans, in the absence of clinically positive nodes has a low detection rate. Even lower rates are found for chest x-rays, bone and liver scans and ultrasonography. Even PET scans have a low detection rate. Blood workup is similarly of low prognostic significance. Thus, **NO** additional investigations are required

Stage II Melanoma (GOAL = CURE)

Surgery of the Primary Lesion : Stage II melanoma requires the surgical **margins to be 2 cm**. The reduction in margins from 4 cm to 2 cm was associated with a reduction in surgical morbidity, but no change in survival. Patients treated with 1 cm margins of excision had a higher rate of locoregional recurrence, suggesting that **1 cm margins are not adequate**. In **melanomas >4mm thick**, there was controversy about whether to extend the margins to 3cm. Recent literature (Surgical Clinics or North America, 2010) suggest the margins should be reduced to **2 cm** even for thick lesions.

Lymph Node Surgery : Lymphatic mapping (**lymphoscintigraphy**) and **sentinel lymph node biopsy** is specifically recommended to assess the presence of occult metastasis in patients with stage II disease (positive nodes makes them stage III). This **identifies** patients who **may benefit from adjuvant therapy** and spares majority of individuals the morbidity of regional lymph node dissection. Survival is better among those patients who undergo immediate (interval usually 3 weeks) **therapeutic regional lymph node dissection** for micro-metastatic disease, than it is among those who delay lymphadenectomy until clinical positive nodes appear.

Bio-Chemotherapy: A **relapse-free survival** advantage was shown for all patients who received **high-dose interferon** (including stage II patients) when compared with the observation, as was a statistically significant **overall survival benefit**. The greatest benefit was seen in the node-negative (stage IIB) subset. A **vaccine** of conjugated GM2 melanoma antigen has been shown to be **inferior** compared to treatment with interferon. Low and intermediate doses have shown no benefit. Pegylated interferon is not FDA approved, but trials have shown increased side effects without increased benefit.

Further Workup : CT scans in patients with T4 lesions may be of benefit to detect occult mets, but in T2 and T3 lesions the detection rate is well below the false positive rate and it is not indicated. **PET scans (CT/PET combination) have revolutionized the hunt** for metastatic disease in T2 and T3 lesions and it is presently the investigation of choice. Further investigations are not warranted.

Stage III Melanoma (GOAL = DISEASE FREE TIME)

Surgery of the Primary Lesion: Stage III melanoma (positive nodes but no distant mets) is surgically treated with **wide local excision** of the primary tumor with **1 cm or 2 cm margins**, depending on tumor thickness and location, as above.

Lymph Node Surgery: In these patients with positive nodes, a surgical clearance of the involved basin is **mandatory**.

Bio-Chemotherapy: **All stage III patients** require adjuvant therapy. Multi-centre trials have presented conflicting reports regarding the overall survival benefits with **high dose interferon therapy**, but disease free survival is improved by its use. As mentioned previously **GMK vaccine is inferior** to interferon therapy. High-dose chemotherapy has **not** been shown to improve survival.

For patients with in-transit/satellite lesions (stage IIIC) of the extremities, **isolated hyperthermic limb perfusion (ILP) with melphalan** (L-PAM) with or without tumor necrosis factor-alfa (TNT-alfa) has resulted in high tumor response rates and **palliative benefit**. The addition of interferon-gamma has not been of any benefit.

2 Exciting, novel strategies are currently undergoing trial: Intra-tumoral injections of replication-competent oncolytic viruses and the monoclonal therapy, ipilimumab.

Stage IV Melanoma and RECURRENT Melanoma (GOAL = PALLIATION)
Most often this is diagnosed by PET scans. Blood LDH levels may be used as a baseline marker to assess response rates and recurrence in patients with liver or GIT mets.

Isolated metastases to the lung, gastrointestinal tract, bone, or occasionally the brain may be **palliated by resection** with occasional (very occasional) long-term survival. The primary tumour (if it can be found) and the local lymph nodes (if involved) are resected for palliative benefit only.

Radiation therapy may provide **symptomatic relief** for metastases to brain, spinal cord, bones, and viscera. Melanoma is a radio-resistant tumour and high dose-per-fraction therapy is required.

Biochemotherapy: Advanced melanoma is **refractory to most standard chemotherapy**. However, drug development in melanoma is changing. Significant strides have been made in cataloguing the genetic abnormalities that permit the formation and dissemination of melanoma and in better understanding immunologic checkpoints.

Chemotherapy: The response rate to dacarbazine (DTIC) is poor and usually **short-lived**, ranging from 3 to 6 months – overall survival is unchanged. Multi-drug combination regimens have not demonstrated any advantage over dacarbazine. The much touted drug, temozolomide has not been shown to be better than dacarbazine and was thus not approved by the FDA.

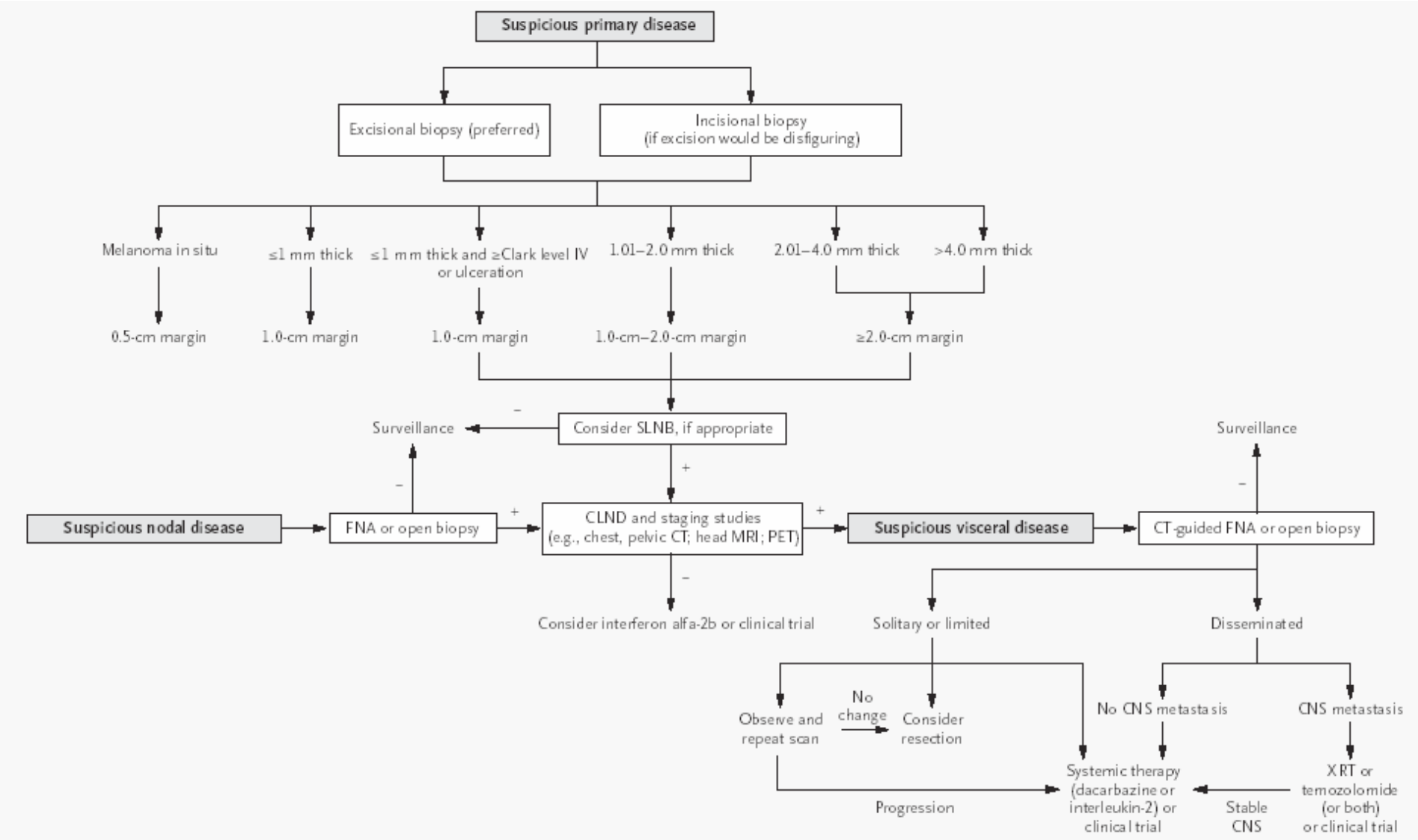
Immunotherapy: Response to **IL-2 regimens** is in the 10% to 20% range. Approximately 5% of patients may obtain a complete remission and be long-term survivors. Attempts to improve on this therapy have included the addition of lymphokine-activated killer cells, but only Level III data exist for this strategy

Monoclonal Antibodies: Among patients receiving ipilimumab, a survival benefit was shown at 1 year for stage IV. Side effects and treatment mortality remain high however. Recently ipilimumab have gained SA registration and even a spot on Carte Banche (!) but is VERY expensive and unlikely to gain general funding approval.

Cellular inhibitors : These novel and very exciting therapies are still in their infancy, although they show promise for the future. Currently several large trials are underway investigating : Multikinase inhibitor sorafenib (Nexavar), BRAF Inhibitors (Vemurafenib – undergoing SA trial presently - should be available soon, but will likely be VERY expensive), Kit Inhibitors, MEK, AKT and P13 Kinase Inhibitors.

Closing Comments

Melanoma is a serious diagnosis to present to a patient. As rates are increasing, a high index of suspicion is required. Poor initial management of a suspicious lesion can destroy the opportunity for valuable (and often life saving) diagnostic and therapeutic interventions. Thus, although a **thorough working knowledge of melanoma** is required of all doctors, it is essential to refer such patients to specialist care for any interventions.


Suspicious primary disease
Excisional biopsy (preferred)
Incisional biopsy (if excision would be disfiguring)
Melanoma in situ
≤1 mm thick
≤1 mm thick and ≥Clark level IV or ulceration
1.01–2.0 mm thick
2.01–4.0 mm thick
>4.0 mm thick
0.5-cm margin
1.0-cm margin
1.0-cm margin
1.0-cm–2.0-cm margin
≥2.0-cm margin
Consider SLNB, if appropriate
Surveillance
Suspicious nodal disease
FNA or open biopsy
CLND and staging studies (e.g., chest, pelvic CT; head MRI; PET)
Suspicious visceral disease
CT-guided FNA or open biopsy
Surveillance
Consider interferon alfa-2b or clinical trial
Solitary or limited
Disseminated
Observe and repeat scan
No change
Consider resection
No CNS metastasis
CNS metastasis
Systemic therapy (dacarbazine or interleukin-2) or clinical trial
XRT or temozolomide (or both) or clinical trial
Progression
Stable CNS