

TITLE: Melanoma of the Head and Neck

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Introduction

Melanoma was first described by Rene Lannec in 1806. At that time the diagnosis was considered fatal. Since that time through advances in staging and early surgical treatment, the mortality of the disease has decreased, although it still remains the most deadly of the skin cancers. Advances have also shown that risk factors such as sun exposure to be a leading cause of melanoma; however, the incidence of melanoma has actually continued to increase at almost 5% per year even with warnings regarding sun exposure and widespread use of sunscreen. As of 2001 almost 47,000 new cases of melanoma occur each year. Many of these, if caught early may be amenable to surgical cure; but for later stage lesions it appears that modern treatments have done little to alter the final outcome.

Predisposing Factors

Sun exposure has long been known as a causative agent in the development of skin cancer. Debate still exists on whether acute intermittent exposure, early childhood exposure, or cumulative exposure over time is the most significant predictor of development of cutaneous malignancy; but it is well accepted that each of these are predisposing factors. Exposure to sunlight is harmful due its UVA and UVB components. UVB (280-320nm) light has long been considered to be the main factor, and has been shown to cause direct DNA mutations, however, several recent studies show that UVA (320-400nm) may play a more significant role. UVA is believed to act by the production of free radicals which secondarily induce DNA damage. Since the development of sunscreen, the incidence of cutaneous malignancy has failed to decline. Some studies have even suggested that use of sunscreen actually *increases* the incidence of cutaneous malignancy. This may be due to the lack of UVA protection in current formulations. It has been shown that burning is mostly a result of UVB exposure. Therefore, the SPF system, which is actually "the factor by which the sunlight exposure time is increased before burning," may only be an indicator of UVB protection.

Familial Syndromes

Familial melanoma, or dysplastic nevus syndrome, is thought to be an autosomal dominant syndrome. Family members usually have numerous nevi that may be irregular in outline and color. If biopsied, these lesions frequently will show nuclear atypia. These lesions may occur anywhere on the body, and are not exclusive to sun exposed areas. Although few studies have been carried out, it appears that family members affected with this syndrome have a probability of developing melanoma that is several thousand times that of the general population (1.4% - 5.4% per year).

Xeroderma pigmentosum is an autosomal recessive disease which is due to faulty DNA repair mechanisms. XP is not exclusive to melanoma, and also correlates with the development of squamous and basal cell malignancies. The risk of skin cancer is approximately 1000 times the general population and often occurs by the age of 10.

Types

Superficial Spreading Melanoma – This comprises about 75% of melanomas. As with most melanomas, it begins with a radial growth phase but eventually progresses to a vertical phase, which may be signaled by ulceration or bleeding. Tumor cells are atypical but uniform in appearance.

Nodular Melanoma – This comprises 10-15% of melanomas. Little to no radial phase is present resulting in very early invasion.

Acral Lentiginous Melanoma – This occurs on the palms or soles, and may be more frequent in blacks. Histology shows neoplastic cells with heavily pigmented dendritic processes in the basal layer.

Desmoplastic Melanoma – This type of melanoma may lack pigment. They are characterized by a “school of fish” appearance of spindle cells in a fibrous stroma. A hallmark of this lesion is its tendency for perineural invasion.

Lentigo Maligna Melanoma – This lesion usually appears in older persons. It has a prolonged radial phase which can last for years. The pre-malignant tumor may extend along sweat ducts and hair follicles, remaining in the dermal-epidermal junction until it invades the papillary dermis at which time it changes from lentigo maligna to lentigo maligna melanoma.

Diagnosis

The history should include details such as bleeding, itching, ulceration, pain. A history of dysplastic nevi or a family history of melanoma should also be sought. The physical exam should cover the standard ABCD's, as well as assess for other nevi. Common sites of presentation include sun exposed areas such as the arms and legs, as well as the back for men and the scalp for thin or balding patients. If a family history of melanoma is present, the physical should include all sun shielded areas as well, since melanomas can arise with minimal sun exposure.

- A – Asymmetry
- B – Border irregularities
- C – Color variegation
- D – Diameter (increase or > 6mm)

Any suspicious lesion requires a histologic examination. It is recommended that small lesions undergo *excisional* biopsy with 1-2 mm margins. Exceptions can be made for critical areas where minimal tissue removal is preferable. Excisional biopsy is not recommended for larger lesions due to deformity before diagnosis, and possible alteration of lymph draining patterns that may be needed later for sentinel lymph node mapping. When excision is not performed, a punch biopsy is recommended to assess the depth of the lesion. Needle and shave biopsies should not be done.

Staging

Both the Clark and Breslow systems are commonly used in the staging of the primary lesion. The Clark stage is based on the tissue level of invasion, and absolute depth may differ depending upon the region of the body involved. The Breslow system is based upon the absolute depth, and has been shown in several studies to be the more reliable factor in predicting outcome. The definition of the levels in each system are given below.

Clark

- Level I Involves only the epidermis
- Level II Involves the basal layer and extends into the papillary dermis
- Level III Involves the papillary dermis to the boundary of the reticular dermis
- Level IV Involves the reticular dermis
- Level V Involves the subcutaneous tissues

Breslow

- Stage I < 0.75 mm
- Stage II 0.75 – 1.5 mm
- Stage III 1.5 – 4.0 mm
- Stage IV > 4.0 mm

Since the Breslow measurements are generally accepted as more reliable, they are the criteria used for the AJCC staging system below. With few exceptions, this system delineates the standard treatment for melanomas. Some exceptions of note can be found in the M.D. Anderson staging system, which generally treats lesions < 1 mm as Stage I and lesions > 1 mm as Stage II (rather than 1.5 mm in AJCC). It also gives significance to ulceration, so that lesions with measurements < 1 mm but with ulceration are treated the same as lesions with > 1 mm thickness. Both the AJCC and M.D. Anderson guidelines are given on the following page.

Treatment

Stage I

Surgery is the only recommended treatment. For these thin lesions, margins of 1 cm are acceptable. Minimal workup, including chest x-ray and LDH, is generally performed to rule out

metastasis. No neck dissection or lymph node biopsy is recommended due the low incidence of metastasis.

TABLE II.
American Joint Council on Cancer (AJCC) Staging.

Primary tumor (T)

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Melanoma in situ (atypical melanocytic hyperplasia, severe melanocytic dysplasia) (Clark's level I)
- T1: Tumor 0.75 mm or less in thickness and invades the papillary dermis (Clark's level II)
- T2: Tumor more than 0.75 mm but not more than 1.5 mm in thickness and/or invades to papillary-reticular dermal interface (Clark's level III)
- T3: Tumor more than 1.5 mm but not more than 4 mm in thickness and/or invades the reticular dermis (Clark's level IV)
 - T3a: Tumor more than 1.5 mm but not more than 3 mm in thickness
 - T3b: Tumor more than 3 mm but not more than 4 mm in thickness
- T4: Tumor more than 4 mm in thickness and/or invades the subcutaneous tissue (Clark's level V) and/or satellite(s) within 2 cm of the primary tumor
 - T4a: Tumor more than 4 mm in thickness and/or invades the subcutaneous tissue
 - T4b: Satellite(s) within 2 cm of the primary tumor

Regional lymph nodes (N)

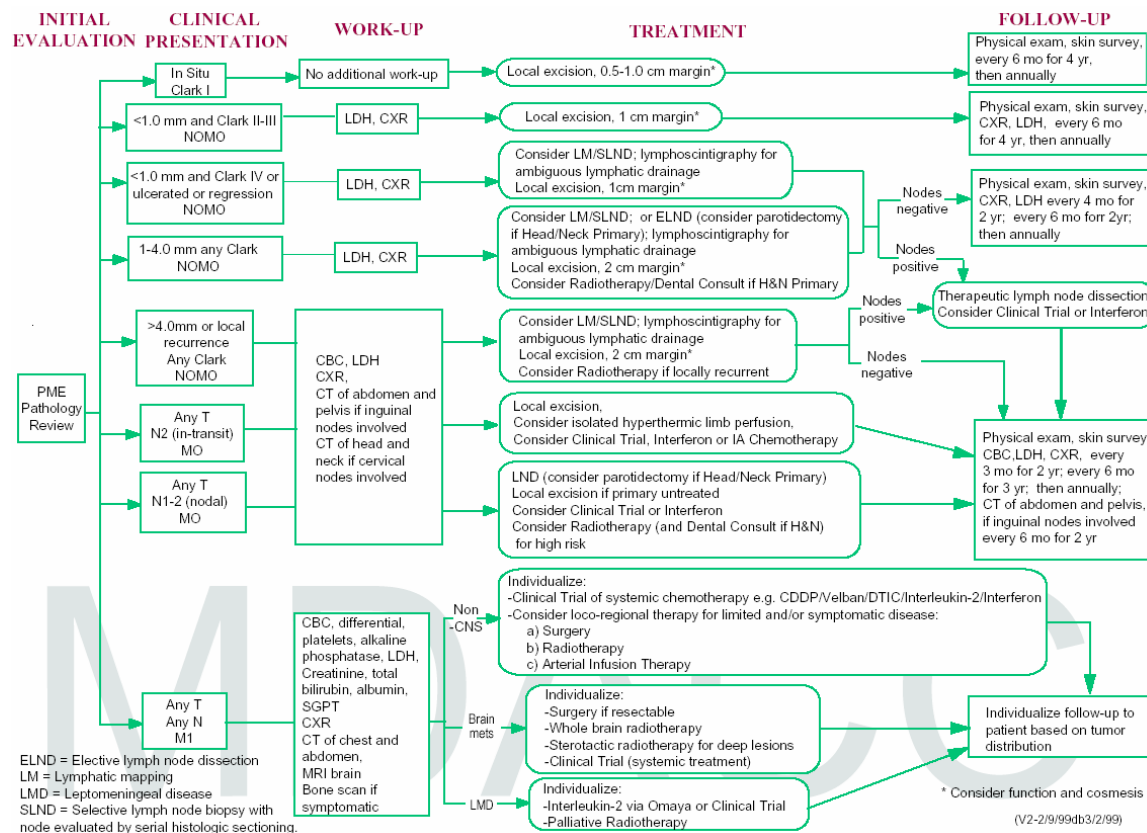
- NX: Regional lymph nodes cannot be assessed
 - N0: No regional lymph node metastasis
 - N1: Metastasis 3 cm or less in greatest dimension in any regional lymph node(s)
 - N2: Metastasis more than 3 cm in greatest dimension in any regional lymph node(s) and/or in-transit metastasis
 - N2a: Metastasis more than 3 cm in greatest dimension in any regional lymph node(s)
 - N2b: In-transit metastasis
 - N2c: Both (N2a and N2b)
- Note: In-transit metastasis involves skin or subcutaneous tissue more than 2 cm from the primary tumor but not beyond the regional lymph nodes.

Distant metastases (M)

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis
 - M1a: Metastasis in skin or subcutaneous tissue or lymph node(s) beyond the regional lymph nodes
 - M1b: Visceral metastasis

Stage grouping

- Stage 0
 - Tis, N0, M0
- Stage I
 - T1, N0, M0
 - T2, N0, M0
- Stage II
 - T3, N0, M0
 - T4, N0, M0
- Stage III
 - Any pT, N1, M0
 - Any pT, N2, M0
- Stage IV
 - Any pT, Any N, M1



Stage II

Workup for stage II lesions includes CXR and LDH as with stage I lesions. Some authors recommend lymph node mapping and a CT metastatic workup in cases such as ulcerative lesions or recurrent disease. The treatment of stage II lesions is probably the most complicated. This difficulty stems from the significant percentage of occult metastasis present with these lesions. While higher stage lesions require more complex and invasive therapies due to their obvious clinical findings, treatment of stage II lesions involves controversial therapies with inherent morbidity to treat a low yet statistically significant percentage of metastasis. The primary therapy for stage II lesions is surgical, with a wide local excision and 2 cm margins. If 2 cm margins cannot be obtained due to location, then combined surgery and radiotherapy should be instituted. Adjuvant therapies employed for stage II lesions include elective neck dissection, elective neck irradiation, and sentinel lymph node biopsy.

Elective neck dissection has been used frequently in stage II lesions. One of the inherent difficulties with this method is defining the route of lymph drainage. Tumors of the occipital area and the posterior scalp (separated by a vertical line through the EAC), are considered to drain posteriorly into the postauricular and suboccipital nodes. These lesions should undergo a posterolateral neck dissection. Lesions on the forehead and scalp anterior to the line are believed to drain into the periparotid and upper jugular nodes. A dissection for these lesions should a parotidectomy and a lateral neck dissection. Lesions which arise on the anterior face generally spread to the submental, submandibular, and deep cervical nodes. A supraomohyoid neck dissection is generally recommended.

Sentinel lymph node biopsy is a relatively new technique. Recent studies have shown that using a combination of dye and a radioisotope can yield first order lymph nodes in > 95%. These studies have also shown that the status of the sentinel lymph node highly correlates with the metastatic status and overall outcome of the patient. However, many of the current studies cited involve regions other than the head and neck. It has also been shown that a learning curve exists for adequate performance of this procedure. A more thorough discussion of SLNB is held for later.

Stage III

Stage III lesions harbor in-transit nodal disease. The workup of these lesions requires CXR, LDH, and a CT of the neck. A CT to evaluate for distant metastasis should be considered. The surgical excision should attempt 2 cm margins. If a node is present distant to a lesion, all in-transit node basins should be addressed. This means for lesions of the temple, cheek, or anterior scalp region, a parotidectomy should be performed. As mentioned before, an appropriate neck dissection, i.e. posterolateral, lateral, or supraomohyoid, should be performed. Radiotherapy has been shown to decrease local recurrence rates. Chemotherapy may be considered.

Stage IV

Workup for these lesions includes CXR, LDH, CT of the abdomen, MRI of the brain, and some recommend a CBC and liver panel. Primary excision with 2 cm margins should be attempted. Radiotherapy for local control should be considered. Chemotherapy for palliation should be considered.

Follow-up

TABLE V.
Recommendations for Follow-up on the Basis of Stage.

Stage	PE	Radiology	Labs
Melanoma-in-situ	Every 6 mo × 4 y then annually	None	None
Stage I or II (no ulceration, thickness <1.0 mm)	Every 6 mo × 4 y then annually	CXR	LDH
Stage I or II (with ulceration or thickness >1.0 mm)	Every 4 mo × 2 y, then Every 6 mo × 2 y, then annually	CXR	LDH
Stage III or recurrent primary	Every 3 mo × 2 y, then Every 6 mo × 3 y then annually	CXR	LDH, CBC
Stage IV	Individualize	Individualize	Individualize

CXR = chest x-ray; LDH = lactate dehydrogenase; CBC = complete blood count.

SLNB

For all types of cancer it is known that occult metastasis may exist in the absence of clinically identifiable disease. In cases such as melanoma, where the presence or absence of these metastasis will drastically effect the course of treatment and the prognosis, diagnostic SLNB is often employed. Before sentinel node biopsy was used, the alternatives were neck

dissection, which has inherent morbidity, or clinical follow-up. SLNB has the benefit of allowing for pathologic analysis of the first order lymph nodes while incurring minimal surgical morbidity.

The technique of SNLB involves injecting both a radioisotope and a visible dye into the area of the tumor and examining the drainage basin for dye and isotope uptake. The radioisotope is commonly Tc99, which may be injected several hours prior to surgery. Localization of this isotope is carried out intraoperatively by use of a handheld gamma counter. The dye is typically isosulfan blue, which can be injected in the operating room before the start of the procedure. Once the patient is asleep, a dissection of the first order lymph node basin is carried out, which can be guided by the gamma counter. If the radioisotope fails to localize adequately, the isosulfan dye can be tracked to the first set of stained nodes. A node is considered to be a “sentinel node” if it localizes a high amount of isotope, takes up the dye, or both. Early in the development of the SLNB technique, when only the vital dye technique was employed, the rates of identification of a sentinel node were only 60-80%, even with experienced surgeons. Today, with the combination of both methods, identification of sentinel nodes is commonly reported as 96-100%.

The utility of SLNB has been under investigation since its development, specifically regarding the following areas: 1) How often are SLN's identified, 2) How often are the nodes positive for metastasis, 3) How often are positive nodes not identified by SLNB, and 4) What prognostic or treatment data can be deduced from a positive node?

The rate of identification of a sentinel lymph nodes, as described above, have been quoted by several studies to be near 100%. While many studies focus on truncal and extremity sites for melanoma, it has been shown in site-specific studies to be an equally effective procedure in the head and neck. In a review by Alex, he cites thirteen studies which focus on the head and neck, with success rates of 88-99%, with the average occurring in the mid nineties.

In localized and removed sentinel nodes, it has been found that the incidence of positive nodes is approximately 12%. Early studies into SNLB stressed performing a neck dissection following SNLB whether positive or negative, since the accuracy of the procedure had not been determined. In cases where a SNLB has been positive for malignancy, the SLN will be the only positive node found in the completed neck dissection in approximately 80%. After removal of only the sentinel nodes, completion neck dissection found positive remaining nodes in only 2%.

In the prediction of overall survival, Gershenwald found that 3-year disease-specific survival for a negative biopsy was 96.8%, while a positive biopsy was 69.9%. While it was also found that sentinel nodes were more likely to be positive with increasing Breslow measurements (T1, T2 4.8%; T3 19.2%; T4 34.4%), covariate analysis of tumor thickness, Clark level, and status of SLNB found that the status of the sentinel node was the most significant prognostic factor for survival. Gershenwald also noted that 11% of his patients developed a recurrence following a negative sentinel node biopsy. It was noted that regional recurrence was the primary site. In 80% of the patients that had regional recurrence following negative SLNB, it was found that nodal disease was missed by conventional histologic techniques; and that the application of serial sectioning and immunostaining with S-100 or HMB-45 increases the yield.

Radiotherapy

Although melanoma was once considered to be a radioresistant tumor, several studies have recently shown that treatment of the lymphatic basins can result in a significant decrease in local and regional control. This improvement in local control is not confined to early stage lesions, and has been found to equally effect stage II-IV lesions, as well as patients with recurrent melanoma of the head and neck, making local recurrence rates almost 88% at five years. It must be noted though, that even with improved local control, there was no statistical significance in survival in any of the groups. However, since local recurrence can be debilitating and cosmetically deforming, this treatment should be considered more therapeutic rather than palliative.

Chemotherapy

Chemotherapy is reserved for proven systemic spread beyond regional lymphatics. According to Braud et al., there is no role for chemotherapy or immunotherapy in stage III disease, and no studies yet have shown any benefit. Although several common regimens exist for stage IV melanoma, including interferon, interleukin, and several multi-drug regimens, none have shown any significant improvement in outcome. Systemic therapy for these lesions are generally considered experimental, and many authors recommend that if patients who elect for chemotherapy be referred to an appropriate oncologist for enlistment in a current clinical trial.

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Diagrams in this paper were taken from the article by Lentsch and Meyers and from the M.D. Anderson web site.

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Questions

Any relationship to previous questions on other exams is *purely* coincidental.

1. A genderless person of some age has a small melanoma of the forehead which is 0.6 mm deep on histologic section. Minimal appropriate margins for resection would be:
 - a. 2 mm
 - b. 5 mm
 - c. 1 cm
 - d. 2 cm
 - e. 3 cm

2. A lesion is removed from the temple of a X year old person. Histologic examination with H&E stain is inconclusive. Which of the following stains could be used to evaluate for melanoma?
 - a. Cytokeratin
 - b. Vimentin
 - c. Integrillin
 - d. HMB-45
 - e. GFAP

3. On examination of sections from excisional biopsy of a cutaneous melanoma it is found that an area of peri-neural tissue tests positive for S-100 protein. The most common type of melanoma associated with this lesion would be:
 - a. Superficial spreading
 - b. Nodular
 - c. Acral Lentiginous
 - d. Lentigo maligna
 - e. Desmoplastic

4. A 4.5 mm melanoma is found over the right temple. A 1.5 cm node is found in the right level II area. Appropriate therapy would be
 - a. Only excision with 2 cm margins
 - b. Excision with 2 cm margins, right neck dissection,
 - c. Excision with 2 cm margins, right neck dissection, parotidectomy
 - d. Excision with 2 cm margins, right neck dissection, parotidectomy, interferon alpha.
 - e. Excision with 2 cm margins, bilateral neck dissections, radiation, chemotherapy.

5. A lesion measuring 5x3 mm which is suspicious for melanoma is found on the forehead. The recommended method for diagnosis is
- Excisional biopsy
 - Incisional biopsy
 - Punch biopsy
 - Shave biopsy
 - Needle biopsy
6. Which of the following statements regarding sentinel lymph node results is correct.
- SLN negative – Chances of a missed metastasis are < 5 %
 - SLN negative – 5 year survival is > 95 %
 - SLN positive – 5 year survival likely < 70 %
 - SLN negative – further sectioning of specimen or special stains may be required to confirm diagnosis
 - All of the above
7. Radiation therapy is useful for which of the following reasons?
- It can be used on anterior midline areas like the upper lip
 - It can be used as sole therapy for nasal tip lesions
 - It decreases long-term mortality for stage III lesions
 - It decreases long-term morbidity for stage III lesions