General Information

The incidence of melanoma is increasing at a faster rate than any other human cancer, and the increase in its mortality rate is second only to lung cancer.\(^1\) It is the fifth most prevalent cancer in the U.S., and the incidence is increasing 7% annually. It comprises 5% of all skin cancer, but accounts for 75% of all skin cancer deaths.\(^2\) 1 in 75 people born in the year 2000 are projected to have melanoma in their lifetime compared with just 1 in 1500 born in 1935.\(^1\) 20% of melanoma occurs in the head and neck region: 51% in the facial region, 26% scalp, 16% neck, and 9% ear.

Development of Melanoma

Melanocytes are dendritic, neural crest-derived cells that normally inhabit the basal cell layer of the epidermis. Their purpose is the synthesis of photoprotective brown melanin pigment, and accordingly are dispersed in relatively low numbers, 1 melanocyte to 10 basal keratinocytes. Hyperplasias of melanocytes manifest clinically as diffuse hyperpigmentation (e.g. tanning) or macular foci of cutaneous darkening (e.g. lentigines). This is associated histologically with an increase in the ratio of melanocytes to basal keratinocytes. Nevus cell transformation refers to the poorly understood phenomenon whereby dendritic melanocytes become rounded cells that no longer tend to grow in lentiginous patterns but rather nest in aggregate, initially along the dermal-epidermal junction (junctional nevi). These cells may eventually "invade" the underlying dermis, first as nests and later as cords and single cells, to become compound nevi. Eventually, the junctional component is lost, producing a pure dermal nevi.\(^3\)

Melanoma may evolve from benign melanocytes or, more likely, from fields of progressive hyperplasia followed by dysplasia. Early melanoma tends to grow within the epidermis along the lines or radii of a circle (radial growth) and does not form expansive nests or nodules. This slow unrestricted
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phase of growth does not show any metastatic potential. With progression, tumor growth extends vertically into the underlying dermis (vertical growth), where melanoma cells form expansive and coalescent nests and nodules. This phase has metastatic potential with invasion into dermal lymphatic and vascular channels. Melanoma may show different growth patterns. The biphasic growth pattern is heralded by a slow radial growth phase of months to years followed by a relatively rapid vertical growth phase. Contrasting, monophasic growth is characterized by rapid vertical growth only.

Several general types of melanoma exist with many other variants described. Dysplastic nevi represent the border between melanocytic nevi and malignant melanoma. The clinical picture resembles that of malignant melanoma. Histologically, there is a lentiginous compound nevus with prominent bridging of nevus nests across adjacent epidermal rete ridges. Some nests also arise aberrantly in inter-rete spaces. The bridging nests are also associated with lamellar fibrosis of the underlying papillary dermis as well as a variable lymphoid response. Distinct types of malignant melanoma are classified, acral lentiginous, superficial spreading, lentigo maligna, nodular melanoma, and mucosal. Acral lentiginous melanoma involves the digits, particularly the nail bed. Superficial spreading melanoma is the most common head and neck melanoma, approximately 50%. It typically appears in the 4th to 5th decade. Clinically it appears as a mixture of colors brown/tan, pink/white with irregular borders. Microscopically it is characterized by irregular nests within the epidermis associated with an underlying lymphoid infiltrate; enlarged nests and single cells are present in all layers of the epidermis, whereas melanocytes in normal skin proliferate along the basal cell layer, and benign nevus cells form nests confined to the rete tips. Superficial spreading melanoma shows biphasic growth with the vertical phase heralded by elevation and surrounding erythema. Lentigo maligna subtypes comprises approximately 20% of head and neck melanomas. It shows the longest radial growth phase sometimes greater than 15 yrs. It typically occurs in the elderly in sun exposed facial skin. Clinically, they appear as a dark, irregular ink spot. Histologically, there is contiguous lintiginous proliferation of dyshesive, variably shaped, malignant melanocytes located within an atrophic epidermal layer and involving the infundibular basal cell layer of hair follicles. Nodular melanoma comprises approximately 30% of head and neck melanomas. They commonly occur in the 5th decade and show an aggressive monophasic growth pattern. They tend to occur in both sunexposed and nonexposed areas. They can appear well circumscribed and blue/black in color or show areas of nodularity and involution within an irregular plaque. Histologically, there is the appearance of downward tumorigenic growth of malignant cells, which expand the papillary dermis and extend into the reticular dermis. The dermal nests are considerably larger than ordinary nevus cell or melanoma cell nests that occur at the dermoeipidermal junction. A distinct clinical entity, mucosal melanoma of the head and neck constitutes 8% of all head and neck melanoma. The histologic staging systems of Breslow and Clark are of little use in assessing the extent of mucosal melanoma, mainly because of the lack of histologic landmarks analogous to the papillary and reticular dermis. Local control predicts better survival, and therefore aggressive resections should be performed when possible. A neck dissection is performed when nodes are either clinically palpable or are found to be positive by CT criteria. If nodal findings are histologically positive, postoperative radiotherapy is administered to the neck and retropharyngeal nodes. Adjuvant treatment with interferon alpha–2b is also recommended.

Risk Factors and Initial Assessment

Early detection and diagnosis is probably the most critical factor accounting for the increase in overall survival of patients with melanoma during the past few decades. The risk factors for the development of melanoma include skin type I or II, the presence of atypical and congenital nevi, significant actinic
skin changes, history of melanoma, family history of melanoma or atypical nevi, and history of significant sun exposure (especially blistering sunburns). The most common signs of early melanoma include an increase in size or a change in color or shape of a pigmented lesion. The most common symptom is pruritus. Later signs and symptoms include tenderness, bleeding, and ulceration. The ABCDE’s (asymmetry, border, color, diameter, elevation, surrounding tissue) are a useful reminder of the clinical warning signs of melanoma, although early melanoma may lack these signs. Epiluminescence microscopy (ELM), use of a surface microscope in combination with oil immersion, is an evolving noninvasive technique that may improve the clinical diagnostic capabilities for early melanoma. Biopsy is indicated for any suspected pigmented lesion and only two techniques should be considered. If the lesion is small an excisional biopsy or saucerization can be performed of the entire lesion. Saucerization is similar to a shave biopsy except the depth of the biopsy is to the underlying adipose tissue. The wound is then left to granulate. If the lesion is large an incisional biopsy using an ellipse or punch can be performed. Removal of the most elevated or clinically suspect area should be performed to the level of the sub-Q fat. Regardless of the type of biopsy technique used the underlying principle is that the depth of the biopsy must be to the underlying adipose tissue to allow proper measurement of tumor thickness, which is the most important factor in deciding further treatment. If an excisional biopsy is performed and the diagnosis is malignant melanoma a second excision must be performed. The second stage consists of wide local excision to the fascia with margins ranging from 0.5 to 3 cm dependent on primarily on the tumor thickness.

**Pathology and Prognosis**

The pathology report must include diagnosis, tumor thickness measured in millimeters, and margins. Additional information that may provide important prognostic information includes histologic subtype, anatomic site, Clark level of invasion, mitotic rate, growth phase, and the presence or absence of ulceration, regression, host lymphocytic inflammatory response, angiolympathic spread, neurotropism, microsatellitosis, and precursor lesion. Many factors predict the prognosis of metastasis for melanoma. Tumor thickness measured in millimeters (Breslow depth of invasion) is the strongest predictor and single most important factor that determines management of patients and prognosis based on multifactorial analysis. In general, depth should be reported in Breslow thickness and Clark level of invasion, however, Breslow correlates much higher with prognosis. Clark’s level may add additional information in areas of thin skin such as the eyelid. In addition to tumor depth many studies have shown that anatomic site, ulceration, gender, histologic type, and nodal disease influence survival. In the head and neck, scalp lesions carry a worse prognosis; extremity lesions carry a better prognosis than trunk lesions, ulceration is poor, and in general women do better than men. In patients with lymph node metastasis several articles reported that Breslow thickness, presence of ulceration, and number of nodes positive influenced survival. Cohen reported that the most important prognostic indicator for 10-yr survival in patients undergoing lymphadenectomy for metastatic melanoma was the number of nodes positive.

**Work-up and Staging**

Once the diagnosis of malignant melanoma is made a thorough history and physical exam should be performed including inspection of the entire skin surface and palpation of inguinal, axillary, supraclavicular, and head and neck lymph node systems with particular attention to the primary draining nodal areas. Attention to brain, bone, GI, and constitutional symptoms should be given. All suspicious palpable lymph nodes should undergo FNA. Laboratory and radiologic imaging vary from
institution to institution. Some recommend only a chest X-ray for stage I or II disease. \(^1\) Other institutions perform routine CT of the chest and liver function studies. \(^4\) For head and neck melanoma a CT of the neck should be routinely ordered. \(^4\) For patients with regional (stage III) or distant metastasis (stage IV), initial staging evaluation includes the aforementioned and computed tomographic scans of the head, chest, abdomen, and pelvis. Other studies should be aimed at specific complaints. \(^1\) FDG-PET scanning has shown some promise in locating areas of distant metastasis; however, for regional lymph node metastases, a recent study looking at the use of fluorodeoxyglucose-positron emission tomography in patients undergoing sentinel lymph node biopsy showed a sensitivity of only 16.7\% for regional lymph node metastases. Therefore, FDG-PET does not have a primary role for staging regional nodes in patients with clinically localized melanoma. \(^9\)

Clark’s classification is divided into five levels. Level 1 – in situ, tumor cells at level of basement membrane; Level 2 – through basement membrane and into the papillary dermis; Level 3 spread to papillary/reticular interface; Level- 4 spread into reticular dermis; Level- 5 invasion into subcutaneous tissue. Breslow’s classification correlates more strongly with prognosis and is defined as follows: Thin lesion < 0.76 mm in thickness; Intermediate lesion 0.76 mm to 1.49 mm and a separate break from 1.50 mm to 4.00; and Thick lesion > 4.00mm. \(^1,2\) Two staging systems exist, an older system which is broken down into clinical stage (CS) and pathological stage (PS). CS-I and PS-I are tumors with local disease only based on clinical and pathological evidence; CS-I, PS-II are lesions with occult lymph node metastasis without distant metastasis; CS-II, PS-II are clinically positive pathologically confirmed nodal disease; and CS-III – distant metastasis. The newer American Joint Commission on Cancer (AJCC) staging is complicated, but essentially broken down into Stage I and II representing local disease; Stage III regional lymph node and/or in-transit disease; and Stage IV distant disease. \(^1\)

### Surgical Treatment

Surgical margins for excision of the primary lesion vary from institution to institution; one suggested method based upon Breslow’s level is for lesions <0.75 mm in depth then excise a 1 cm margin, 0.76-1.49 then 1-2 cm (1 cm adequate for lesions <1mm), 1.5-4.00 then 1-2 cm (2 cm recommended for lesions >2mm), > 4.00 mm then 3 cm. \(^1\) Stated another way < 1.0 mm then 1cm, 1-4.0 mm then 2 cm, >4.0 mm then 3 cm. \(^2\) The depth of all excisions should be to the underlying muscle fascia.

Treatment of the regional lymphatics, especially the performance of an elective lymph node dissection, has been debated for decades. In general patients with clinically palpable or radiologically evident lymph nodes, clinical stage II, should have the regional lymphatics removed based upon location of the primary lesion and the presence or absence of distant metastasis. The primary debate exists for N0 patient.

Several studies have tried to resolve this conflict. A nonrandomized study performed by Balch and others found that the 5 and 10 year survival of patients with intermediate thickness melanoma (0.76 – 3.99 mm) doubled in patients who had ELND at the time of primary excision. The 5 and 10 year survival for patients with thin (<0.76 mm) and thick (4.0 mm) did not change with ELND. \(^5\) Four prospective randomized studies have been published looking at immediate lymph node dissection and delayed lymph node dissection, for N0 melanoma. The Mayo Clinic published an article in 1986 which showed no significant survival difference between three treatment groups: 1) immediate lymph node dissection 2) delayed lymphadenectomy (became clinically positive) 3) no lymphadenectomy. This study did however find more subsequent complications occurred from melanoma in the no
lymphadenectomy group.\textsuperscript{10} This study has been criticized for not addressing any sub-groups of patients who may have benefited from ELND.\textsuperscript{11} The WHO conducted a study which also did not show any survival benefit, however this study was also criticized for not delineating any subgroups based on prognostic factors and being largely confined to extremity melanomas in females, a lower risk lesion.\textsuperscript{11} Another study by Balch in 1996 found no overall 5-yr survival difference for patients who received ELND vs. nodal observation for stage I and II melanoma. However, the study did find an improved survival for patients less than 60 yrs of age with ELND. Of these patients, those with tumors 1 to 2 mm thick, without tumor ulceration, and with both those features showed improved survival with ELND. These findings are criticized on the grounds that when more subsets or subclasses of data are analyzed the chances of finding data that looks significant when it is actually not increases.\textsuperscript{11} A second study by the WHO published in 1998 looked at trunk melanomas 1.5 mm or more in thickness with two treatment arms, immediate and delayed lymphadenectomy. The study found no significant 5-year survival benefit between the two groups; it did however find a significant survival benefit between those patients who underwent ELND that had occult metastasis and those who later developed metastasis and had delayed lymphadenectomy.\textsuperscript{12}

Based on these studies and other data, the rationale for ELND is based on the hypothesis that microscopic metastases may disseminate sequentially from primary melanoma to the regional lymph nodes and then to distant sites. 30\% of stage I and II melanomas will have occult lyphatic disease. By the time these lymph nodes become palpable 70-80\% of these patients will have distant metastases with a 10-yr survival of 15-25\%, while the 5-yr survival of those individuals with 1-2 nodes positive containing only micrometastases is 65\%. Additionally, Balch’s nonrandomized study showed a significant survival benefit with intermediate thickness melanoma.\textsuperscript{2,13} The rationale against ELND is founded on the data from randomized prospective studies from the WHO, Mayo clinic and Balch’s multi-center trial, that no survival benefit is gained when comparing ELND with no ELND without further subset consideration. Additionally, 70\% of patients will have no occult metastases and therefore undergo an unnecessary procedure with its concomitant morbidity. Lastly, the theory of distant hematogenous spread arising from occult lymph node metastasis has not been proven.\textsuperscript{2,13}

Balch made recommendations for ELND based upon the data presented by breaking melanoma patients into three groups based upon local tumor thickness and the chances for regional and distant metastatic disease. The three groups are 1) those patients with melanoma localized to the primary lesion site; 2) those with local disease plus possible regional node micrometastases; and 3) those with local disease plus distant micrometastases, irrespective of whether they have nodal micrometastases as well. The use of tumor thickness provides a quantitative estimate of the risk for occult metastatic melanoma at regional and distant sites; it is the most important, but not the sole factor that should be used in determining whether or not to perform ELND. Balch’s recommendations are as follows. Thin melanomas (0.76 mm) are associated with localized disease and a 95\% or greater cure rate. An ELND would provide no therapeutic benefit in such patients. Intermediate thickness melanomas (0.76 to 4.0 mm) have an increasing risk (up to 60\%) of harboring occult regional metastases, but have a relatively low risk (<20\%) of distant metastases. Patients with these lesions might therefore benefit from and ELND. Thick melanomas (>4mm) not only have a high risk of regional node micrometastases (>60\%), but also are associated with a high risk (>70\%) of occult distant disease at the time of initial presentation. These patients do poorly, since the distant metastases in most instances negate the benefit of surgically excising the lymph nodes. The goal of treating these nodes is palliative, and the operation might be deferred until nodal metastases become clinically evident. He then goes on to state, "tumor thickness should not be the sole criterion for making surgical treatment decisions. Other factors such as
the presence or absence of tumor ulceration, the patient’s sex and age, the anatomical location of the melanoma, and the operative risk should all be considered when making the decision to perform ELND in any individual patient. In addition to the direct benefits on survival of ELND, some authors additionally state that especially in the head and neck region where the morbidity of selective dissection is low that an indirect benefit may be obtained by identifying and stratifying those patients with regional micrometastases to receive post-op adjuvant therapies.

**Sentinel Node Theory**

The major problem in the debate of whether to perform ELND or not stems around identifying only those subjects whom actually harbor occult lymph node metastases, thereby avoiding unnecessary lymph node dissection in 70% of patients without occult lymph node disease. To help resolve this problem, Morton developed the sentinel node theory. The sentinel node is defined as the first node in a particular nodal group to receive regional lymphatic flow from the tumor site. If this sentinel node can be identified, the decision to perform an ELND is then based on the pathologic evaluation of this node.

The procedure involves injecting isosulfan blue dye around the primary lesion or biopsy site and then following the lymphatic channels to the sentinel lymph node. Initial studies which also included an ELND, found that a sentinel lymph node could be identified in greater than 80% of basins and that the false negative rate, that is the sentinel node being histologically negative and another node being positive, was less than 1%. A more recent article using pre-operative lymphoscintigraphy, intra-operative radiolymphoscintigraphy, and isosulfan blue dye showed blue dye apparent in 69.5% of sentinel lymph nodes (SLN) excised, gamma probe “hot” nodes in 83.5%, but more importantly the success rate using the combined techniques was 96%. Success rates as high as 98% have been quoted.

Different lymph node regions have shown different success rates with the groin being the most successful and the axilla and head and neck regions being less successful. A recent study of sentinel lymph node biopsy for the head and neck region using pre-operative lymphoscintigraphy, blue dye, and intra-operative gamma probe reported a success rate of 90% with 8 nodes being positive and a false negative result in 2 cases yielding a sensitivity of 80%. The following unique difficulties with the procedure in the head and neck region were reported. It is more difficult to visualize the lymphatic drainage with lymphoscintigraphy because the sentinel nodes are often close to the highly radioactive site where the tracer is injected. The tracer travels fast; if more than 1 node is visible within a few minutes after injection, it is difficult to distinguish sentinel nodes from non-sentinel nodes. In addition, sentinel nodes may be small and located in sites that are not easily accessible, for example in the parotid gland. Due to the difficulty and unproven benefit of sentinel node biopsy in the head and neck region, and the low morbidity of superficial parotidectomy and selective neck dissection in this region, some authors continue to advocate the use of selective LND for intermediate lesions until further data is available on the use of sentinel lymph node biopsy.

Another advantage to identifying sentinel lymph node status has recently been studied as a prognostic indicator. In 580 patients in whom SLN mapping was successful, SLN status was the most significant prognostic factor with respect to disease-free and disease-specific survival by univariate and multiple covariate analyses.

One variable in the utility of sentinel lymph nodes is the ability of the pathologist to determine the presence of metastatic melanoma cells. The usual techniques used to evaluate lymph nodes for
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melanoma include H &E staining and immunohistochemical staining with antibodies against S-100 protein or HMB-45 melanoma antigen. The problem with these methods is that the rate limiting step is the number of sections cut and examined. A method of cell culture has proven more sensitive than routine histology in detecting melanoma cells in tissue, however this assay has been criticized because of the delay of 4-6 weeks to receive the results and the potential limited applicability to the community hospital setting.

A new technique using reverse transcription coupled with polymerase chain reaction (RT-PCR) has been described to detect melanoma cells in peripheral blood as well as lymph nodes. The procedure involves using PCR to detect the messenger RNA (mRNA) of tyrosinase. Tyrosinase is a key enzyme during melanin synthesis in melanocytes and melanoma cells. Because melanocytes normally are not present in peripheral blood or lymph nodes, the detection of transcription of the tyrosinase gene is an indication that there are metastatic melanoma cells present. A recent study evaluated lymph node samples from 29 clinically stage I and II melanoma patients undergoing ELND. 11 of 29 (38%) lymph node samples were pathologically positive. 19 of 29 lymph node preparations (66%) were RT-PCR positive.

Adjuvant Therapy

Radiation therapy if given in high-dose fractions (400to 500 cGy) may be used to treat patients who have bulky disease, residual or recurrent disease, unresectable lesions, or those who are too ill to undergo surgical resection. Superficial lesions such as lentigo maligna melanoma may also be treated with radiotherapy in cases which surgery would be disfiguring or debilitating. The 5 year cure rate for lentigo maligna melanoma using radiotherapy is approximately 80%. Radiotherapy given adjunctively in situations in which the risk of recurrent disease is high, such as disease in the neck, has been shown to prevent recurrent regional disease. In a non-randomized, prospective study, of 152 dissected necks or parotids, with 45 receiving radiation and 107 not, regional recurrence rate was 6.5% in the irradiated group, compared with 18.7% in the non-irradiated group. (p = 0.55) However, the irradiated group had more extensive nodal involvement, and extracapsular spread. This trend toward improved regional control needs to be studied further. Radiation can also be used to palliate metastatic disease, especially that to bone.

Chemotherapy has been used in the systemic therapy of melanoma. Response rates in general are around 25% with a durable control rate of around 1%. Adjunctive chemotherapy may be considered in CS I lesions with Breslow thickness > 1.5 mm, or in CS II patients post WLE and therapeutic LND. Adjunctive therapy to date has not shown survival advantage. The most common single agent used is dacarbazine (DTIC) which produces objective responses in about 20% or patients. One of the common combination regimens used more frequently is the so-called Darmouth regimen consisting of carmustine (BCNU), cisplatin, DTIC, and tamoxifen. Initial reports described response rates of 50%. Many trials using variations of this regimen are currently underway.

Melanoma often behaves in unusual fashion showing involution of areas or complete involution of primary lesions with later lymphatic metastasis. The belief is that the immune system plays an important role in the pathogenesis of this tumor. Because of this fact many forms of immunotherapy have been tried including specific immunotherapy with vaccines intended to induce or augment immunity against melanoma-associated antigens; and immunotherapy with non-specific stimulants such as BCG, a tuberculosis prevention agent; C.parvum, an anaerobic, gram-positive, diphtheroid
bacillus with immunostimulatory properties; and levamisone, an antihelminthic drug noted to potentiate many immunologic reactions. So far none has shown a survival benefit, however many trial are currently in progress and this area may eventually prove very useful.\textsuperscript{1,22}

Interferon has demonstrated biologic activity in metastatic melanoma, including antiproliferative activity, enhancement of the immune elimination of melanoma, and activity indirectly mediated through the host immune system. The recently publishes Eastern Oncology Group (ECOG 1684) study compared 1 year of adjuvant high-dose interferon alfa-2b (IFN-a 2b) to observation, randomizing 280 patients with (1) depth of primary tumor of 4 mm or more or (2) positive nodes that were either palpable or detected of lymph node dissection. With a median follow-up of 6.9 years, the study showed improved disease-free and overall survival rates for the treated group. The benefit, confined to patients with nodal metastases, rose the disease-free survival compared to the control group from 1 to 1.7 years and for overall survival from 2.8 to 3.8 years. The high doses of interferon used in this trial, however, had significant toxicity leading to a 26% drop-out rate. These positive survival results of ECOG 1684 prompted the FDA to approve high-dose interferon alpha "as adjuvant treatment to surgery in patients with malignant melanoma who are free of disease but at high risk for systemic recurrence." Many trials using interferon are currently under way.\textsuperscript{20} Interferon-gamma however has proved to be of no current benefit.\textsuperscript{23}

\textbf{Summary} Melanoma incidence is increasing as well as the number of deaths from melanoma. However, the survival rates are increasing due to early detection and prompt, thorough treatment. Many factors must be considered when designing a treatment plan for a patient, but the most important single factor used for determining therapy beyond local excision is pathologic tumor depth. This emphasizes the importance of appropriate biopsy technique. The debate over the usefulness of elective lymph node dissection continues and may never be fully elucidated, however, the usefulness of sentinel node biopsy with newer laboratory identification techniques may allow the decision to be made on more scientific grounds. This would allow optimal treatment of the patient with minimal morbidity from unneeded procedures. While surgery is currently the mainstay of treatment, many other areas under research, and may someday prove useful.

\textbf{References}


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