Introduction

The treatment for cutaneous melanoma is primarily surgical with a role for adjuvant treatment (interferon or radiation therapy) in select cases. Primary lesions are treated with wide local excision (WLE) and clinically evident regional lymph nodes are treated with lymph node dissection followed by adjuvant therapy. Currently, there is no highly effective systemic treatment for melanoma. Distant metastases and recurrent disease are difficult to manage. As a result, early detection and prompt surgical treatment of loco-regional disease before distant metastases occur are critical in reducing mortality. Twenty percent of patients with an intermediate thickness melanoma and no clinical evidence of nodal or distant spread will have occult regional metastasis (Morton 1991). Management of this group of patients has been controversial over the past few decades. In a population of patients with no evidence of spread beyond the primary site, the question remains: How much surgery should be performed? Elective lymph node dissection causes 80% of patients with a primary melanoma to undergo unnecessary surgery while a “watch and wait strategy” allows occult metastases to grow and spread to non-sentinel lymph nodes until they become clinically evident (Morton 1991). Sentinel lymph node biopsy was developed in an effort to identify which of these patients would benefit from additional surgical treatment beyond wide local excision. Its use in melanoma, particularly of the head and neck, has been a controversial topic of much ongoing research and debate.

Background

Cutaneous melanoma of the head and neck accounts for 20% of all melanomas. The lifetime incidence of cutaneous melanoma is now one in fifty-nine (up from 1/1500 in 1930), which has been increasing along with melanoma-related mortality over the past few decades (Rigel 2010). Melanoma is an aggressive cancer with unpredictable metastatic patterns making it more lethal than other solid tumors. Melanomas of the head and neck are more likely to recur and have a higher mortality rate in the head and neck.

TNM classification reflects the natural history of disease. Tumor depth determines T classification. Thicker tumors have a higher rate of spread. The histology also affects staging.
Ulcerated tumors have worse prognosis. Nodal classification also includes histology, meaning SLNB is necessary for staging. Stage I and II melanoma are confined to the primary site.

**Historical Treatment of the N0 Neck**

Prior to the advent of sentinel lymph node biopsy, surgical treatment of the clinically N0 neck (and other regional nodal basins) was controversial. Opinions about management of regional lymph nodes varied widely and the subject was hotly debated. Some surgeons preferred immediate elective lymph node dissection (ELND) while others adopted a “watch and wait” strategy. With the “watch and wait” approach, patients received only a wide local excision and were followed closely every few months. They only underwent a lymph node dissection if disease became clinically evident after excision of the primary lesion. It was known that depth of invasion correlated with disease spread and increased mortality. Based on retrospective analysis some experts argued using the depth of invasion as a cut-off for performing regional lymph node dissection. Proponents of an ELND argued that clinically negative regional lymph nodes may harbor occult metastases which could adversely affect survival. Rather than observation, they reasoned that a prophylactic lymph node dissection would increase the changes of long-term loco-regional control. Routinely, patients with intermediate thickness (1-4mm) lesions underwent an elective lymph node dissection. Morbidity and complications associated with these procedures included injury to the facial/spinal accessory nerves, chyle leak, skin flap necrosis, bleeding, lymphedema, and cosmetic deformity. O’brien et al. developed an algorithm for predicting drainage patterns of the head and neck in melanoma, although many patients received a modified radical neck dissection (Obrien 1995).

Two landmark studies-- the WHO and Mayo Clinic studies—conducted in the late 1970’s/early 1980’s questioned the utility of elective lymph node dissection in melanoma (Veronesi et al 1982 and Sim et al 1978). The WHO trial studied 573 patients with extremity melanoma. Patients were randomized into either WLE and observation vs WLE and immediate ELND (Veronesi 1982). The Mayo clinic trial include 173 patients with melanoma from all sites of the body. Patients were randomized into WLE with ELND and WLE plus observation. Both of these randomized controlled trials found no survival benefit from elective lymph node dissection. A retrospective case series limited specifically to patients with head and neck melanoma also found no survival advantage to ELND (Loree and Spiro 1989). Obrien also published a large retrospective case series of 631 head and neck melanoma patients and found no statistically significant survival advantage for ELND. Kane also published a large cohort study of 424 head and neck melanoma patients and found no difference in survival for ELND vs watch and wait.

More recently, Balch et al also published data from a large multi-institutional trial (Intergroup Melanoma Surgical Trial) in 1996 which included 740 patients. Stage I and II patients were randomized to ELND vs observation. Although no difference between the two groups were found overall, there was a statistically significant difference found in a subgroup of patients with 1-2mm tumor thickness (Balch 1996). This study was significant in that it showed N0 melanoma patients as a group would not benefit from ELND. There was, however, a sub-group of patients that are at high risk of undetectable regional spread (but not distant mets) who would benefit from lymphadenectomy (Balch 2000).

**Why is head and neck ELND not effective?**

One proposed reason for the ineffectiveness of ELND particularly in the head and neck for melanoma is the complexity of head and neck lymphatic anatomy. Shah published a report of patients...
with head and neck melanoma who underwent radical neck dissection and found highly variable patterns of lymphatic spread (Shah 1989). Morton published a study in 1993 that found up to 10% of h&n lymphatic drainage patterns may drain to the contralateral side (1993). Correlation of lymphoscintigraphy in head and neck melanoma patients with clinical prediction of cervical lymph node spread found that over one in three patients would have a lymph node left behind if clinical predictions were used alone to decided which areas of the neck to dissect (O’brien 1995). These studies argue that head and neck lymphatic drainage is particularly complex and that previous selective lymph node dissections for occult metastases may have been directed to the wrong areas.

**Sentinel lymph Node biopsy technique**

During the controversy about the appropriateness of ELND, Morton et al described sentinel lymph node biopsy (Morton 1990 and 1992). Sentinel lymph node biopsy offered a much less invasive and less morbid method of staging the regional lymph node basin than ELND. The idea was based on the model that cancer cells spread through regional lymph nodes in a sequential fashion. Starting from the primary site they travel first to regional lymph nodes and then to distant sites. The sentinel lymph node is the first lymph node to receive direct lymphatic drainage from the primary site in a lymph node basin. There is a theoretical short window of time to remove regional micrometastases and remove the disease in its entirety in order to prevent distant metastasis (Morton 1991). The incubator hypothesis states that the primary melanoma sends immunosuppressive factors to the sentinel node which creates a favorable microenvironment for cancer growth. The tumor can then spread elsewhere (Morton 2003). This theory is controversial (and contrasts with the marker theory) and most likely does not apply to thick melanomas (Morton 2003).

The modern technique of sentinel lymph node biopsy involves a multi-disciplinary team which includes a nuclear medicine physician, surgeon, and pathologist (Morton 2012). Prior to the procedure (anywhere from 4 hours to 2 days) The skin surrounding the primary melanoma is injected with small volumes (0.05-0.1mL) of technectium 99-sulfer containing colloid. Lymphoscintigraphy is performed using a gamma camera to help identify which nodal basins drain the lesion and contain the sentinel lymph node(s). Alternatively, SPECT-CT can be used to locate candidates for SLNB. The patient is brought to the operating room and placed under general anesthesia. Blue dye is then injected into the dermis surrounding the lesion 10-20 minutes before the start of the procedure. A handheld gamma probe is then used to detect the previously injected technectium in the nodal basin which drains the lesion. An incision is made over the nodal basin. The blue dye and the gamma probe are used to identify which nodes is the sentinel node. Frequently multiple nodes are identified and removed. Generally all nodes that are greater than 10% of the radioactivity of the “hottest node” identified are removed to insure that the sentinel node is removed (McMasters 2004). The lymph node specimens are then sent to the pathologist for permanent section. H&E (hematoxyln and eosin) stains are performed. Any sample that is negative on H&E stain can then undergo further melanoma-specific immunohistochemistry stains such as S100, MelaninA, and HMB-45 (Wen 2011)

**Landmark SLNB Studies**

Since the invention of SLNB in 1992, a number of landmark studies have been performed. Some of all surgical sites, others of h&n alone.

The Multicenter Selective Lymphadenectomy Trial was an international NIH-funded prospective randomized, controlled surgical trial designed to evaluate the efficacy of SLNB. The goal was to
validate SLNB as a staging operation and to determine if there is a survival advantage to early CLND in the event of a positive SLNB. It randomized 2001 patients with a cutaneous melanoma of >1mm thickness and no evidence of regional or distant metastasis into two arms: wide local excision and observation vs wide local excision plus sentinel lymph node biopsy. If the sentinel lymph node biopsy was positive, patients underwent immediate complete lymph node dissection. The trial enrolled 2001 patients with intermediate-thickness cutaneous melanomas of all parts of the body from 1994-2002.

The Sunbelt trial is a multi-institutional, prospective randomized trial that examined the role of interferon adjuvant therapy in melanoma. Patients were recruited between 1997 and 2002. Final results were reported by McMasters et al in 2008 in which no benefit to adjuvant therapy with interferon was shown. The study included 321 H&N, 1141 trunk, and 1148 patients. This trial was particularly significant because Chao et al reported on the differences in technique and effectiveness of SLN by body area.

Formed in 2003, the Sentinel Lymph Node Working Group (SLNWG) was a head and neck melanoma database of 614 patients. Each patient with H&N melanoma underwent WLE of the lesion plus SLNB. The study, published in 2006 was the largest head and neck melanoma database with respect to SLNB.

**Complications/Morbidity**

SLNB is a relatively safe and low-morbidity procedure, especially when compared with ELND. Since 80% of SLNB’s will be negative, most patients can avoid the morbidity of neck dissection (Morton 2012). The patients undergoing SLNB in the MSLT-I trial experienced complications 10% of the time. In the same study, patients undergoing immediate lymphadenectomy experienced a 37% complication rate (Morton 2005). The Sunbelt Trial similarly found a much lower complication rate for patients undergoing SLNB vs lymphadenectomy (4.6% vs. 23%). Common complications in both of these trials included hematoma/seroma, wound dehiscence, and lymphedema (Boland and Gershwin 2008).

Morton/MSLT-I trial compared early vs. delayed neck dissections and found a statistically lower rate of lymphedema and shorter hospital stay with early neck dissection (Morton 2010).

**Prognostic Value**

SLNB yields important clinical information for staging, prognosis, and clinical decision making. Histologic status of the sentinel lymph node has been shown to be the most important independent predictor of overall 5 year survival in patients with stage I and II melanoma; more important than Breslow depth and histologic ulceration (Morton 2006). The 5 year survival of SLN-negative patients was 90% in the MSLT-I trial (Morton 2005).

**Overall Accuracy/False Negative Rate for SLNB**

The “success” of a SLNB procedure overall for all parts of the body is usually high. The SLN is identified 93-100% of the time (Leong 2011). In addition, the status of the sentinel lymph node accurately reflects status of the entire nodal basin. In Morton’s initial study in 1992, patients received SLNB’s and then underwent CLND regardless of the status of the SLN. Out of 3079 non-sentinel lymph nodes identified by their CLND, only 2 contained tumor (0.06%) when the SLN was negative (Morton 1992).
Controversy Over Head/Neck SLNB Accuracy

The accuracy of head and neck SLNB has been controversial over the past 10 years. Chao conducted a sub-analysis of head and neck patients from the Sunbelt Trial. Conducted by McMasters et al, the Sunbelt Trial was a multi-institutional prospective randomized trial (McMasters 2004). Patients underwent WLE of a primary cutaneous melanoma and SLNB. If the SLNB was positive, patients underwent CLND. Chao found a lower rate of identifying the SLN in the head and neck than in the trunk/extremities (97% vs 100%). The rate of identifying a positive SLN was also lower in the head and neck region (15% head/neck vs 23% for trunk). The false negative rate was also higher in the head/neck region (1.9% vs 0.5%). Although complications overall were low, the only motor nerve injuries that occurred in the series were in the head/neck region (Chao 2003). Other trials during the 2000’s published results that questioned the utility of head and neck SLNB. Published in 2005, the MSLT trial found an 85% success rate of identifying the SLNB in the head and neck. This was lower than the overall success rate of 95% when all sites were considered (Morton 2005). Carlson et al found no difference in nodal recurrence rates in the head/neck region between positive and negative SLNB’s (Carlson 2003).

Several explanations for the comparatively poorer results obtained in head/neck SLNB were proposed by Chao. First, washout occurs faster in the head/neck region. Fewer head/neck lymph nodes were stained blue in the Sunbelt trial due to the increased vascularity of the region. Second, lymph nodes are smaller in the head/neck than other areas of the body. Third, regional lymph node basins are closed to the primary site. This could allow greater shine-through effect in head/neck melanomas. Fourth, the head/neck region contains intricate and complicated anatomy which makes dissection more difficult. A significant percentage of head/neck melanomas drain to the parotid. Finally, head and neck melanomas may have an increased rate of in-transit metastases (Chao 2003).

In the last 2 years, several studies have been published to support the usefulness of head and neck SLNB. Leong conducted a meta-analysis of head/neck SLNB’s for melanoma. He found a 93-100% success rate of identifying the SLN in 16 different studies conducted from 1993-2006. The positivity of the SLN ranged from 10-21% with a mean of 16% (Leong 2011). Erman et al. published a 10 year operative experience of head and neck SLNB’s conducted at the University of Michigan. It was the largest single-institution study for head and neck SLNB. 353 patients underwent WLE and SLNB with a 99.7% success rate of identifying the SLN. The study also yielded a 95.8% negative predictive value for head/neck SLNB (Earman 2012). This figure mirrored the 98.1% negative predictive value published by Miller et al from Oregon in 2010 (Miller 2010). Furthermore, Earman found a 19.7% positivity rate in head/neck SLN’s which compares favorably to the 21.4% positivity rate found in the trunk/extremity in the Sunbelt trial (Earman 2012). No facial nerve, cranial nerve, or bleeding complications were recorded. Earman concedes the unique challenges of head/neck SLNB and attributes the success of the Michigan experience to surgical familiarity of the head/neck. All surgeons participating in the Earman study were full-time head and neck cancer surgeons (Earman 2012).

SLNB and Survival

Based on the third interim analysis of the MSLT, the study found no statistically significant difference in overall survival between the two groups (Morton 2005). It did, however, show that patients with intermediate thickness melanoma showed a statistically significant increase in disease-free survival with a 5 year disease free survival in the SLNB group of 78% vs 72% in the observation group (P=0.0074). It did also showed that patients with intermediate thickness melanoma (1.2-3.5mm) who
developed nodal disease in the SLNB group had a fewer number of positive nodes (1.9 vs 3.2) (Morton 2005).

Who should receive SLNB (Indications)?

NCCN recommendation states SLNB is indicated for patients with stage Ib or stage II (no evidence of spread outside the primary lesion). This correlates to patients with primary melanomas less than 1 mm thick with ulcerated histology or high mitosis rate. Thinner melanomas have a lower propensity for spread and SLNB may be unnecessary.

Thick melanomas (>4mm) have been shown to be associated with early distant metastasis. A SLNB and subsequent regional LND would not address distant metastases and would not improve survival (Morton 2003)

Future areas of study

Currently, most patients who undergo SLNB with a positive node then undergo immediate complete neck dissection. Only 12 percent of patients with a positive SLN will have an additional positive non-sentinel node (Morton 2012). Since such few non-sentinel nodes will be positive, is SLNB a therapeutic as well as a diagnostic procedure? The second multicenter selective lymphadenectomy trial (MSLT-II) strives to answer that question. MSLT-II is a prospective randomized surgical trial comparing SLNB plus CLND vs SLNB plus ultrasound observation of lymph nodes. The trial opened in 2005 and aims to enroll nearly 2000 patients (Morton 2012).

Conclusions/Summary

Elective Lymph node dissection in melanoma is controversial and rarely performed. As shown by Erman et al, sentinel lymph node biopsy is an accurate and relatively safe procedure (low-morbidity) for staging in experienced hands. The accuracy/false negative rate for SLNB for the head/neck region specifically is currently being debated in the literature. Finally, SLNB has not been shown to increase overall survival in melanoma in a randomized control trial. It has, however, been shown to increase disease-free survival. There continues to be ongoing research and debate in this area.

Faculty discussion – Drs. McCanmon, Bruce Leintz on Dr. Patton’s presentation on Sentinel Nodes In Malignant Melanoma-

Dr. Leintz:

We must always think of skip metastases and that we don’t always know whether they are going to be distant or regional. The whole understanding of doing a sentinel lymph node biopsy requires that there be step-wise metastases from the primary tumor and yet you are now thinking that doing a lymph node biopsy might give you better information for doing an elective neck dissection. Why would anyone think that that would be the case?

But the traditional literature says that it should be a radical or at most a modified radical neck dissection. So why wouldn’t the sentinel lymph node have been more often than not? My last comment is that I think it’s inappropriate to be talking about the complications that related to the various procedures that are available to treat melanoma when you don’t know which is the better treatment. I also think that the complication rate related to who should be doing those procedures was unacceptably high for hematoma of
over twenty percent in one of your larger series. I would hope that anyone here in this room who is doing elective neck dissection would have a much lower rate of hematoma. We should be getting five percent or less.

**Dr. McCammon:**

I would add to the utility of the sentinel node localization in melanoma, like cutaneous (skin) cancers, which have a broader distribution than upper aerodigestive cancers anatomically and so you have things on the ear which may go to the occipital region. You have the higher rate of contralateral metastases which only lymphosintigraphy will indicate that you should do a contralateral dissection or a bilateral dissection and I think that the whole question of the parotid is important because the sentinel lymph node...(inaudible) if you are going to use your radical or your modified radical paradigm to get the complete lymph node base from something up here then that kind of en-bloc dissection would include the parotid whereas if you do lymphosintigraphy and your sentinel node is below the parotid and it’s negative then you can spare any searching around in the parotid bed. So those are ways that I would find it more useful than just a completion lymphadenectomy.

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