Sentinel Lymph Node Biopsies in Cutaneous Melanoma:
A systematic review of the literature

By

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Abstract

Cutaneous melanoma has become a growing health problem in the United States, affecting all age groups, ethnic groups, including both genders. The incidence rate of melanoma is rising faster than any other malignancy, with the American Cancer Society projecting nearly 60,000 new cases and over 8,000 deaths due to melanoma for the year 2007. One of the main components of diagnosis and management of cutaneous melanoma is staging of the patient. Given that the metastasis status of the lymph nodes is of great prognostic significance for melanoma, a new minimally invasive procedure called sentinel lymph node biopsy has become the preferred method of care for patients diagnosed with melanoma. However, to date, there has been no cumulative research looking at the evidence of sentinel lymph node biopsies in terms of overall survival and disease free survival. In addition, the theory that sentinel lymph node biopsies might increase the risk of in-transit metastases has been postulated. A systematic review was done evaluating the role of the routine use of sentinel lymph node biopsy in staging of melanoma to see if there is an overall benefit to patients diagnosed with melanoma in performing SLN biopsies.

The results of the comprehensive search revealed that there is fair evidence that the use of SLN biopsy in patients diagnosed with Stage I or II melanoma does not increase the risk of in-transit metastases compared to either WLE only, ELND, or delayed lymph node dissection of patients with clinically palpable nodes. Furthermore, the results in this paper demonstrates fair evidence that SLN provides a significantly better disease free survival but perhaps not an overall survival benefit. Given that there is no good treatment for advanced stage melanoma and sentinel lymph node biopsies do

not provide an overall longer survival, the decision to undergo a sentinel lymph node biopsy should be one of shared decision making.

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Introduction

Burden of Disease:

Cutaneous melanoma has become a growing health problem in the United States, affecting all age groups, ethnic groups, including both genders. Melanoma is a type of cancer that arises from specific cells in the skin called melanocytes. Malignant melanoma develops in these cells when melanocytes stop responding to normal cellular growth control mechanisms and become capable of local invasion or spreading to other organs. The incidence rate of cutaneous melanoma is on the rise, with the American Cancer Society projecting nearly 60,000 new cases and over 8,000 deaths due to melanoma for the year 2007.[1] The incidence rate of melanoma is rising faster than any other malignancy. Incidence rates between 1973 and 2002 have risen in all age groups, as well as in both men and women. Incidence rates in men between the ages of 55 and 64 years have increased four-fold, and five-fold for men 65 years and older.[2] The incidence of melanoma is lower among Hispanics and African Americans compared to whites, but rates are increasing among this population as well. Based on rates from 2003-2005, according to the data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, one in fifty-five men and women will be diagnosed with melanoma over their lifetime. The life-time risk of developing invasive melanoma is 3.15% for whites and 0.11% for African Americans.[3] Cutaneous melanoma is the sixth most common cancer in the United States, is the most common cancer in young women aged 25-29 years, and is second only to breast in women aged 30-34 years.[4] The median age at diagnosis is 57 years, affecting a younger patient population

than most solid tumors. Thus, cutaneous melanoma has become an increasingly common form of cancer.

The mortality rate from melanoma in men and women increased from 1975-1990, but since 1990 there has been no change in mortality among men and a decrease in mortality among women. The age-adjusted mortality rate for cutaneous melanoma from 2000-2004 was 2.6% per 100,000 men and women per year. In specific age groups, the highest mortality rate is seen in the age group 75 to 84, with 23.1% of men and women dying from melanoma.[3] The relative survival rates for melanoma are fairly good, compared to other malignancies. The five-year relative survival rate has increased since 1975 for all ages, races, and gender. Based on data from 1996-2003, the overall 5-year relative survival was 91.1%.[3] Although the relative survival rate for primary cutaneous melanoma is fairly good, it still represents a huge burden of disease among people in the United States, as well as around the world.

The rising incidence of melanoma also represents a huge economic burden to the healthcare system. One model found that the cost of diagnosing and treating new cases of invasive melanoma in 1997 was $560 million. Of the total cost, stage I and stage II were 5.5% of the total cost (%31 million); stage III was 34% ($191 million); stage IV was 55% ($309 million).[5] This is most likely a large underestimate of the true economic impact of melanoma on society given this analysis did not include the cost of screening, the cost of biopsies of suspect lesions, the cost of diagnosing and treating melanoma in situ, the cost of continued surveillance, and indirect costs, such as loss of income and employment.

Screening, diagnosis, management and treatment of melanoma varies considerably among healthcare providers. While some melanoma care is delivered via local physicians in community-based strategies, others are delivered via a multidisciplinary based approach. The Michigan Multidisciplinary Melanoma Clinic (MDMC) found that patients treated within the MDMC compared to patients treated within other sites in the Michigan community would save a third party payer roughly $1600 per patient, with equivalent rates of surgical morbidity, length of hospitalization, and long-term survival.[6] However, many patients are not treated in a multi-disciplinary based environment, and the costs of melanoma healthcare is high. If the incidence of melanoma continues to increase annually, the estimation of cost for melanoma treatment by Medicare may exceed $5 billion by the year 2010.[7]

Staging

Both environmental and genetic factors contribute to the development of malignant melanoma. The main environmental factor is sun exposure. There are clinical signs and symptoms that increase suspicions of possible melanoma. The ABCDE criterion for gross inspection of the skin is an acronym used by physicians and other health care professionals to aid in the early recognition of potential cutaneous malignant melanomas. Inspecting suspicious nevi lesions for asymmetry, border irregularity, color variegation, greater than 6 mm diameter, and evolving lesions over time for changes in size, shape, symptom, surface, and shades of color, aid in screening and diagnosis of malignant melanoma.[8]

Despite these clinical signs, the only way to accurately diagnose melanoma is by skin biopsy. After biopsy confirms melanoma, the next step is staging the patient.[4] In 2002, the American Joint Committee on Cancer published its 6th edition of the T,N,M melanoma staging system. Given that staging is associated with prognosis and treatment, it is critical to establish if there is local, regional, or distant metastasis at the time of diagnosis. The T classification is based on Breslow thickness (mm) and histologic evidence of ulceration, two of the most important prognostic indictors of the primary tumor.[4] However, Breslow thickness, measured from the top of the granular level of the epidermis to the deepest point of tumor penetration, is the best indicator of outcome.[7] The Clark level of invasion, or the level of depth penetration from the epidermis to the subcutaneous fat, is significant only for thin lesions (1.0mm or less). [9, 10] The N classification describes the extent of lymph node disease. N is based on the number of regional nodes with disease and the tumor burden in the nodes, either macroscopic or

microscopic. Macroscopic disease in the lymph nodes is clinically palpable disease or disease found by clinical imaging studies and verified by histology. Microscopic disease is disease that is not found clinically via physical exam or on imaging studies, but is detected only on histologic evaluation. Metastasis to a regional lymph node is the most important prognostic factor in early-stage melanoma. The final staging classification is M, which is based on the anatomic location of distant metastases and the level of serum lactate dehydrogenase.[4] Given that the strongest predictor of melanoma survival is the status of regional lymph nodes and up to one-fifth of patients diagnosed with a cutaneous melanoma will develop metastatic disease, revealing the status of the lymph nodes provides vital information for patient counseling, management, and treatment of cutaneous melanoma.[10]

History of Staging of Cutaneous Melanoma

Cutaneous melanoma commonly metastasizes to regional lymph nodes, with the regional nodal basin usually being the first site of metastasis. Before the acceptance of sentinel lymph node biopsy (SLN) as a staging mechanism, either elective lymph node dissection (ELND) or delayed lymphadenectomy with clinical palpable nodes was performed on patients with melanoma.[9] ELND has been the routine management of melanoma for the past twenty-five years because it was a way to stage the nodal basin. The major downside was that the majority of patients did not have metastatic disease. These patients had to go through the unnecessary procedure, suffering considerable morbidity and complications, without any therapeutic benefit. With these invasive procedures came many complications, such as lymphedema, nerve damage, and acute wound problems.[9] In addition, randomized control trials comparing ELND with delayed lymph node dissection at the time of clinical recurrence showed no significant overall survival benefit in patients undergoing ELND. [11]

Improvements in the management of cutaneous melanoma began in 1977 when Fee et al published their results on the role of lymphoscintigraphy in determining the lymphatic drainage patterns from a primary cutaneous melanoma.[12] In 1990, Dr. Donald Morton began working on studies using lymphoscintigraphy to identify the drainage patterns of truncal melanoma and then used mapping techniques to identify the SLN with a minimally invasive procedure. Morton believed that the primary tumor will first drain to one or more of the sentinel lymph nodes in the regional lymph node basin. Thus, because the sentinel lymph node is the first drainage site for tumor metastasis, the tumor status of the SLN can be used to predict the tumor status of the other lymph nodes in the

basin. In addition, he found that the status of the SLN reflected the status of the entire regional lymph nodal basin, with a low false-negative rate.[13] Many studies have confirmed that the success rate of sentinel lymph node biopsy procedure is very high, around 98%. [14-17] With the advent of sentinel lymph node biopsies, there have been several studies showing that the status of the sentinel lymph node is the most important prognostic factor of survival.[18, 19] Studies show roughly 88.5% of patients with a negative SLN biopsy are free of disease at three years with an overall survival rate of 93%, compared with 55.8% of patients with a positive SLN biopsy who have a 67% overall survival rate. [18, 20]

Sentinel Lymph Node Biopsy

The SLN biopsy is a procedure in which the sentinel lymph node is identified and removed; usually it is the first lymph node in the pathway from the primary tumor to the nodal basin. If the SLN is positive for tumor cells via histopathologic testing, other nodes in the basin are probably affected and need to be treated with a complete lymphadenectomy. If the node is negative, it is likely that the other nodes in the basin will not be positive and no further surgical intervention is warranted.[9] There are three methods used in the sentinel lymph node biopsy procedure: a preoperative lymphoscintigram, a blue-dye injection at the primary melanoma site immediately pre-operatively, and finally a intraoperative use of a gamma probe. [21] The intraoperative hand held gamma probe is beneficial because it allows for an easier search for the SLN resulting in a smaller incision site and shorter operating time, as well as ensuring a more complete removal of the SLN.[14] Using data from the Sunbelt Melanoma Trial, McMasters et al found the detection of sentinel nodes is best achieved by removing all nodes that stain blue and all nodes that show radioactivity greater than 10% of the count in the hottest node. [22, 23]

SLN biopsy is a less invasive procedure than ELND, but still has risks. For example, potential complications include excessive bleeding at the site of biopsy, pain or numbness at the site of biopsy, infection, lymphedema, nerve damage at the site of biopsy, and anaphylaxis in 1% of patients from the blue dye used during the procedure.[24] Many studies have shown that the complication rate from SLN procedures is lower than for complete lymph node dissection, with complication rates around 5%. [25, 26] Since the

only way to reliably stage and gather prognostic information is to see if the regional lymph nodes have disease, the SLN biopsy procedure has rapidly gained acceptance.[10]

Even though the rate for minor complications following SLN biopsy is small, there is a concern that the SLN biopsy procedure might increase the risk of in-transit metastases (ITM) by entrapment of tumor cells in the dermal lymphatic vessels during the procedure.[27] ITM's are subcutaneous metastases located between the site of the primary cutaneous melanoma and the regional lymph node basin. These represent a serious clinical problem as they are difficult to manage and very hard to eradicate. [28] A literature review of all studies calculating local/ITM recurrence as an outcome following SLN procedure by Thomas and Clark showed that the overall recurrence rate was 9.0%. They concluded that patients who had the SLN biopsy had double the incidence of local/ITM recurrence compared to patients treated solely with wide local excision; and patients who had the SLN biopsy followed by selective lymphadenectomy had four times the incidence of local/ITM recurrence compared to patients treated solely with wide local excision.[29] However, this review only looked at ITM recurrence in patients who had sentinel lymph node biopsies, not studies directly comparing the recurrence to other staging procedures. Thus, there remains a concern for an increased risk of ITM recurrence following SNL biopsy.

Even though lymphatic mapping with sentinel lymph node biopsy has become the procedure of choice for staging cutaneous melanomas of intermediate thickness, the procedure is underutilized. Between 1998 and 2000, Baxter and Tuttle, using Surveillance, Epidemiology, and End Results (SEER) data, found that 47% of patients with a melanoma of > 1.00 mm thick underwent lymphatic mapping and SLN biopsy.[30]

Similar results were found by Stitzenberg et al where only 48% of patients with intermediate thickness melanomas underwent lymphatic mapping and sentinel lymphadenectomy in North Carolina.[31] Thus, even though sentinel lymph node biopsy has become the preferred method for management of melanoma, its use is far from being widespread.

Although there is agreement that sentinel lymph node biopsy can reveal the status of the lymph node and has become the preferred method for staging melanomas by the National Comprehensive Cancer Network treatment guidelines[32], it is not clear whether the routine use of sentinel lymph node biopsies for diagnosed cutaneous melanomas leads to improved health outcomes, such as fewer recurrences, fewer surgeries and overall improved survival. A systematic review was done evaluating the role of the routine use of sentinel lymph node biopsy in staging of melanoma to see if there is an overall benefit to patients diagnosed with melanoma in performing SLN biopsies.

Methods

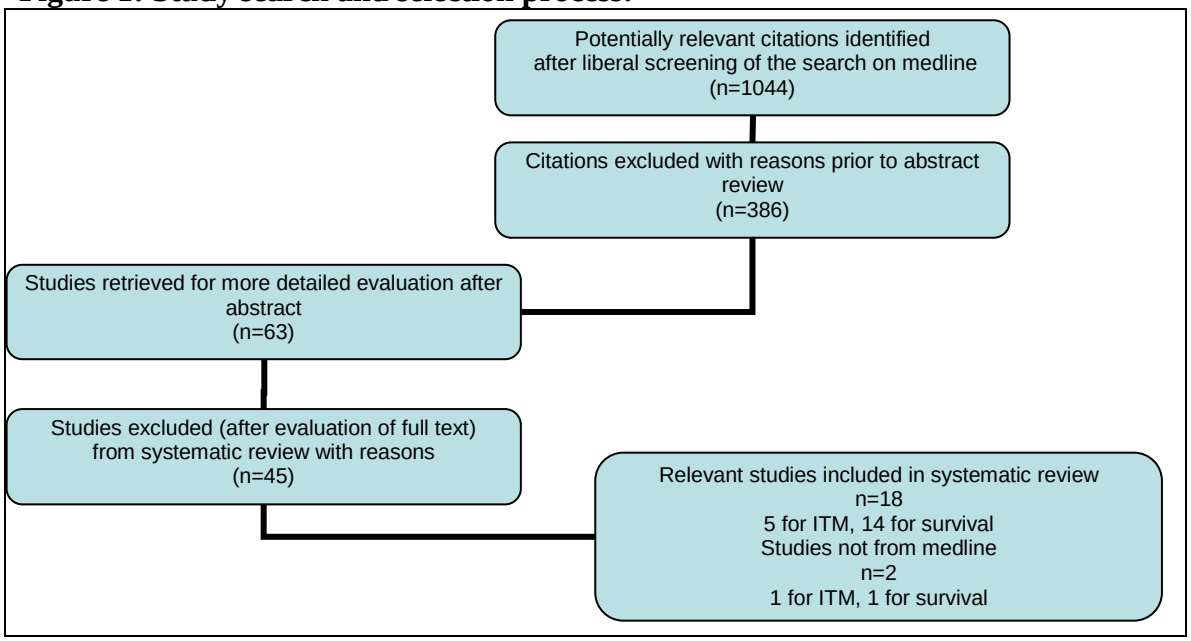
Search Strategy:

To identify relevant studies of the outcome of sentinel lymph node biopsies in staging of cutaneous melanoma, a MEDLINE database search using the MeSH terms "melanoma," "sentinel lymph node biopsy," "lymph nodes" and "biopsy" was completed. Since the introduction of sentinel lymph node biopsy was introduced in the early 90's by Dr. Morton, dates were limited from 1990 to present. Sentinel lymph node biopsy did not become a MeSH term until 2001 so the MeSH terms "lymph node" and "biopsy" had to be used to identify all relevant articles prior to 2001. Articles were limited to English and Humans. A MEDLINE search using the terms "melanoma" and "sentinel lymph node biopsy" as keywords with limits on studies being added to Medline in the last 180 days was also completed. The Cochrane database library was also searched using the search term "melanoma". References of all relevant papers found in the searches were reviewed, as well as review articles, which found an additional two studies.

Inclusion Criteria:

Randomized control trials, case-control trials, and observational and retrospective reviews that compared sentinel lymph node biopsies to either another form of staging of the regional lymph nodes or no dissection for staging in patients with primary cutaneous melanoma were included.. All types of trials were included, regardless of the number of participants or study duration. All patients with a diagnosis of primary cutaneous melanoma with no evidence of metastases at distant sites, regardless of their breslow thickness were also included. Trials that included only patients with melanoma of the head and neck were excluded. Trials whose patients were children or adolescents were also excluded.

Figure 1: Study search and selection process:



Data Extraction

Only one investigator independently extracted the data from relevant articles onto a standardized data collection form that included the following information: year of publication, inclusion and exclusion criteria, number of patients randomized or number of patients in study, number of patients lost to follow-up, staging procedure of melanoma, number of recurrences, survival, and mortality. The randomized control trials, articles were graded via quality grading of good, fair, or poor via the predefined criteria developed by the USPSTF and the National Health Service Centre for Reviews and Dissemination. For all other studies, quality was based on selection of cases or cohorts and controls, adjustment for confounders, methods of outcome assessment, length of follow-up and statistical analysis.

Results

Figure 1 illustrates the results of the study search and selection process of the included articles. Six articles were identified: one observation[33], four retrospective reviews[34-37] and one randomized control trial[38], addressing the risk of in-transit metastases following sentinel lymph node biopsies compared to other methods of staging, such as wide local excision (WLE) , elective lymphadenectomy (ELND) or delayed lymphadenectomy (DLND). Four studies compared either the overall ITM or ITM as a first recurrence rate in patients who had a WLE followed by a positive SLN biopsy to patients who had delayed lymph node dissection secondary to clinically palpable lymph node metastases.[33, 35, 36,38] Two studies compared overall ITM and ITM as a first

recurrence in patients who had either WLE only, WLE plus SLN biopsy or elective lymph node dissection.[34, 37]

Fifteen studies were identified, only one of which was a randomized control trial, that addressed survival of patients undergoing SLN biopsy compared to WLE only, DLND, and/or ELND. The majority of the studies were retrospective database reviews. The majority of the studies included patients who were either stage I and/or stage II. There was one study that included patients who were stage III[39] and one study that included patients who had thin melanomas with a breslow thickness of 0.76-1mm only.[40] The studies reported on different outcome measures of survival, including overall survival[39-49], disease free/recurrence free surviva,l[38-40, 43-45, 48, 50, 51] and melanoma specific survival[38, 40, 51] by creation of Kaplan-Meier survival curves. There was one study that calculated the relative risk of melanoma related death.[52] Five of the studies compared SLN biopsy to ELND[41-43, 50, 51]; six studies compared SLN biopsy to delayed lymph node dissection[38, 39, 46-49]; and four studies compared SLN biopsy to observation. [40, 44, 45, 52]

Does SLN biopsy increase the risk of in-transit metastases?

The six articles that addressed the rate of in-transit metastases are displayed in Table 1. [33-38] One of these studies was observation, one was a randomized control trial and the rest were done by retrospective data review from various melanoma databases. Only one study showed that the overall rate of ITM recurrence during the study period was statistically higher for patients who received a positive SLN followed by a complete lymphadenectomy compared to patients with clinically palpable nodes receiving a delayed lymph node dissection.[33] Another study showed a statistically significant higher rate of ITM as a first recurrence in patients receiving a SLN biopsy followed by CLND compared to patients with clinically palpable nodes receiving a DLND, but a non-significant higher rate of overall ITM recurrence rate.[35] Of the two studies looking at WLE, WLE + SLN biopsies, and ELND, only one study showed a statistically significant higher rate of ITM as a first recurrence in SLN compared with ELND[34], but both studies showed no significant difference in the overall ITM recurrence rate.[34, 37] The randomized control trial showed a non-significant overall rate of ITM recurrence of observation plus DLND compared to SLN.[38]

Given that all but two of the studies were retrospective, there is inherent selection bias and confounding to these studies. There was no randomization of groups so there will always be some confounding factors present that cannot be controlled for, even with statistical analysis. Some of the studies gave inclusion and exclusion criteria to determine which cases should be included, but none of the studies gave detail as to how many reviewers went through the database, as having multiple reviewers would ensure all correct cases were used. Also, there is no mention as to blinding of the people who

abstracted the outcomes from the cases. Bias would be limited if an independent reviewer measuring outcome was blinded to which surgical procedure the patient obtained.

Even though there was only one study that showed a significant higher rate of overall ITM recurrence during five years in patients with a positive SLN biopsy followed by a CLND (23% vs 8%, p=0.027), the overall quality of the study was poor.[33] This study suffered significantly from selection bias, confounding, and measurement bias. The observational study failed to reveal how the patients were selected to be included in the study. They stated they excluded patients with melanoma of the head and neck, and included patients who were Stage I and II. Also, there was no mention of patients who were potentially lost to follow-up. There was no mention of the procedure protocol for SLN biopsy, of the success rate of the SLN procedure, of how they assessed the histology of the lymph node biopsies, and if the same surgeon performed all surgical procedures. The two groups were statistically different at baseline with respect to breslow thickness and ulceration status of the primary lesion. Although the group who underwent SLN biopsy plus CLND had a deeper Breslow thickness as well as a greater percentage of ulcerations, logistic regression analysis did not show that Breslow thickness, age, sex, tumor location, tumor histology, or ulceration status had any statistically significant prognostic value. They found that the rate of ITM recurrence was increased in patients undergoing SLN biopsy + CLND compared to patients who underwent a delayed lymph node dissection. However, the patients who had SLN biopsy + CLND had more advanced disease at baseline with a poorer survival rate. This study is generalizable to patients who have clinically diagnosed Stage I or Stage II cutaneous melanoma, excluding melanomas of the head and neck.

Kretschmer et al found a statistically significant increased rate of ITM as a first recurrence in patients with a positive SLN biopsy compared to patients with clinically palpable nodes with DLND (27.3% vs 17.6%, p=0.03, and a 22.4% recurrence rate among + SLN plus CLND), but a non-significant overall ITM 5 year recurrence rate between the two groups, 33.75% and 33.3%, respectively.[35] In addition, this study also looked at overall and recurrence free survival of the types of nodal surgery, but failed to give significance values. Thus this study was not included in the analysis of the second question. The 5-year overall survival rate and the 5 year disease free survival rate for positive SLN was 54.4% and 38.6%, respectively, and 37.4% and 11.6% respectively for DLND. After controlling for several prognostic factors (breslow thickness, epidermal ulceration, age, location of primary lesion, gender), they noted that there was no significant difference in risk of developing ITM for the time of node dissection (SLN biopsy vs DLND). Overall, selection bias was not as strong in this study because the study gave specific inclusion and exclusion criteria. Patients with Stage I melanoma, patients with neck lymph node excision, patients with clinically palpable nodes, and patients with unknown primary tumors were excluded. In addition, at baseline, the groups were similar in regards to potential prognostic factors, such as site of primary tumor, breslow thickness, ulceration, and sex. The follow-up rate was complete for 97.8% of the patients, and the ten patients that were lost to follow-up all had negative SLN biopsies. Given that the study outlined their operative procedure and how they performed the SLN biopsy procedure (standard three method protocol), identified their definition of a sentinel node, and stated that they performed CLND and DLND according to established surgical protocol, measurement bias was kept to a minimum. Even though

they did not state their success rate of the SLN procedure, they did state that one surgeon performed 80% of all surgeries. Even though the authors assessed the two groups for initial comparability in regards to many prognostic factors, there is the potential for other confounders that they did not control for introducing bias.

This study is also generalizable to patients diagnosed with Stage I or II cutaneous melanoma, excluding those with palpable lymph nodes or neck lymph node dissections. They found that the median interval between primary tumor excision and palpable nodal metastases was 12 months in the DLND group whereas the median time interval to the occurrence of a first distant or nodal recurrence was 47.5 months in the positive SLN group. Thus, the time during which ITM may manifest as a first recurrence is almost four times longer if nodal recurrences are avoided by using the SLN biopsy procedure. Given that the overall ITM reoccurrence rate was not different between the groups, they concluded that sentinel lymph node biopsy does not increase the risk of ITM.

The final study that compared ITM recurrence of positive SLN plus CLND with DLND in patients with clinically palpable nodes showed no significant difference in ITM as a first recurrence (20.1% vs 17.0%, no p value reported). [36] However, they found a significant lower rate of ITM recurrence in patients who received DLND compared to SLN plus CLND when only comparing patients who relapsed (25.9% vs 37.3%, p=0.02). The difference in the median time to ITM recurrence was not significant in the CLND group (231 days) vs. the DLND group (240 days). Given that the study specified inclusion and exclusion criteria for the cases they chose form the database, selection bias was minimized. However, the two groups were different in regards to the location of the primary site and the DLND group had a higher number of lymph node(s) with

metastases. The bias from measurement was reduced by having the Pathology department confirm measurement of both Clark level and Breslow thickness. Also, the SLN biopsy procedure was according to standard protocol and the false-negative rate of the procedure was 4.9%, similar to other studies. They also defined ITM and excluded patients from the DLND group who already had ITM, which limits measurement bias. Although they used statistical analysis to find which prognostic factors influenced the rate of ITM in the entire SLN group, they did not use statistical analysis to control for potential confounders between the SLN group and the DLND group, which were different at baseline. Furthermore, the results of this study are only applicable to patient with melanoma with a breslow thickness $\geq$ 0.75mm or Clarks level $\geq$ IV. Given that there was no significant difference in overall survival using Kaplan Meier graphs between DLND and CLND in patients who developed ITM and there was no difference in rate of ITM as a first reoccurrence in the groups, the authors concluded that the SNL biopsy procedure does not increase the risk of ITM. Furthermore, the estimated overall 3 year survival (from the date of relapse) in ITM patients was better when compared to other types of relapses after CLND and DLND.

Two studies compared WLE only, WLE plus SLN biopsy or ELND. Kang et al found a significantly higher rate of ITM as a first recurrence in patients undergoing ELND, without controlling for potential confounders, but no difference in overall ITM recurrence.[34] In their study they found the overall incidence of ITM increased with depth of primary lesion, and thus matched patients within the study by T stage. In the 1,875 patients who were matched (625 in each group) for T stage, they found no significant difference in overall ITM or ITM as a first recurrence for WLE, SLND, or ELND. They

also controlled for confounding by matching patients from each treatment group by age, sex, breslow depth, and primary site location. Again, from the analysis of 1,680 patients (560 in each group) they found no significant difference in ITM overall or as a first recurrence in the treatment groups. From their Kaplan-Meier survival curves, there was no significant treatment-related differences in rate of ITM as a first recurrence, however, patients with WLE and SLND did better with respect to overall ITM than the ELND group. With matching of patients for T stage and again for potential confounders, there was no statistical difference between the two groups on Kaplan Meier curves.

Given that this study used matching of potential prognostic factors, confounding was minimized, but not eliminated. Selection bias was high because the study did not state specific inclusion or exclusion criteria. There was also incomplete data for the patients on ulceration status of primary lesion, with 45.9% melanoma of unknown ulceration. This is of great significance because ulceration status is a prognostic factor for melanoma. Since almost half of the ulceration status of the melanomas was unknown, this prognostic factor could not be controlled for in statistical analysis. The three groups were not comparable at baseline, with the SLN biopsy group having the highest percentage of patients over 50 years of age and the ELND group having a greater percentage of melanomas with a breslow thickness > 2mm (no mention of significance). In addition, the SLN biopsy and ELND group had more patients with a higher Clarks level. From the beginning, the patients in the ELND group had a poorer prognosis, with higher breslow thickness and Clark's level. However, the authors did control for thee potential confounders in matched pair statistical analysis. The authors defined their outcome of interest, ITM, but they did not give any details on operative procedures,

histology of the SLN, or success rate of the SLN procedure, leading to potential measurement bias. This study is only generalizable to patients with a stage I or II cutaneous melanoma, since this was the only inclusion criteria for the study. In conclusion, the authors state that there is not an increased incidence of ITM after SLN biops vs WLE or ELND and there is no survival disadvantage, either disease free or overall, in those SLND patients who did develop ITM.

The final study by Van Poll et al also showed no significant difference in ITM as a first recurrence between patients in WLE, SLND, and ELND upon univariate analysis.[37] Even after multivariate analysis adjusting for Breslow thickness, ulceration, age, sex, and follow-up time there was no difference in ITM recurrence. When comparing nodal disease in the groups, univariate analysis showed that tumor negative SLN group had a significantly lower rate of ITM as a first recurrence (1.7% vs 4.5%, p=0.03) and overall ITM (2.5% vs 5.5% p=0.04) than tumor negative ELND. However, for tumor positive disease there was no significant difference. The authors performed another subgroup analysis in patients with evidence of regional metastatic disease, a group with WLE followed by a delayed lymph node dissection of clinically palpable metastatic nodes to a group with WLE with SLN biopsy followed by a completion lymph node dissection within 3 to 4 weeks. From this analysis, the total ITM rate was significantly lower in the SLN with CLND compared to DLND (10.8% vs 24.3% p=0.008). Although the authors minimized selection bias by stating inclusion and exclusion criteria prior to database review, the groups were not initially comparable. The WLE group had a higher proportion of men and the patients were older at age of diagnosis. The breslow thickness and ulceration rates were higher in the WLE plus

ELND group. The authors stated that the treatment for all three groups used the same surgical protocols over the 10 year study period and defined their outcome measurement definitions of local, in-transit, regional, and distant melanoma recurrences. Even though the groups had varying prognostic factors as baseline, the authors did control for many potential confounders (age, sex, tumor thickness, ulceration status, Clark's level, primary tumor site location, and follow-up period) via multivariate analysis and multiple regression. This study is generalizable to patients diagnosed with cutaneous melanoma with a breslow thickness >1mm. The group of patients who received immediate regional lymph node dissection because of a positive SLN biopsy had a lower incidence of ITM compared to patients treated with WLE followed by delayed lymph node dissection at time of clinically palpable lymph node metastases. Thus, the authors concluded that their results did not support the hypothesis that mechanical entrapment of tumor cells in lymphatic channels due to surgical interference with the regional nodes causes ITM. The risk of developing ITM was not increased by SLN biopsy or ELND.

In conclusion, from the results of these trials, there seems to be fair evidence that the use of SLN biopsy in patients diagnosed with Stage I or II melanoma does not increase the risk of in-transit metastases compared to either WLE only, ELND, or delayed lymph node dissection of patients with clinically palpable nodes.

Is the survival in favor of patients undergoing SLN biopsy?

The fifteen articles that address survival in patients who underwent sentinel lymph node biopsy are displayed in Table 2. The majority of the articles found were retrospective database reviews comparing SLN biopsy patients to either ELND, DLND, or WLE and observation only. Given the limitations and bias inherent to retrospective database reviews, there is not strong evidence to make a valid conclusion on SLN biopsies and overall survival and disease free survival from the studies analyzed in this review. There was one randomized control trial[38] that looked at the primary outcome of overall survival. This RCT was only given a quality rating of fair as well due to bias in its internal validity.

Five retrospective database review articles were identified comparing SLN biopsies to ELND[41-43, 50, 51]. Three of these studies reported overall survival (OS) as their primary endpoint[41-43] and two studies reported disease free or recurrence free survival (DFS/RFS) as their endpoints[50, 51]. The study by Essner et al found no significant difference in OS at five years when comparing all patients who received a SLN ± CLND compared to patients receiving an ELND, nor was there a significant OS when comparing only node positive SLN patients + CLND to node positive patients who received ELND[43]. This analysis was after a matched-pair analysis on age, gender, location of primary lesion and breslow thickness. However, the analysis failed to control for ulceration status, Clarks level, and type of histological melanoma, all of which affect prognosis.

The study by Doubrovsky[42] also found no significant OS in patients treated with SLN biopsy ± CLND vs ELND at five years. Furthermore, when this study used

multivariate analysis, the type of operation (SLN vs ELND) had no significant affect on patient survival (p=0.24). In this study, the two groups were different from baseline, with the SLN group being older, but having fewer ulcerative lesions and not as high of a breslow thickness. However, the study performed by Dessureault et al found a significant OS difference in patients treated with SLN vs ELND vs observation alone (p<0.0001) at five years. However, this study was rated as poor, as data was collected from 12 institutions with no standardization of diagnosis, staging, or treatment techniques and there was a difference in follow-up time. In addition, there was no baseline comparison of the groups and no statistical analysis controlling for potential confounders. From the results of these three trials, it seems that there is poor to fair evidence resulting from retrospective reviews that performing SLN biopsies results in no difference in overall survival compared to ELND.

From the two studies looking at DFS/RFS, Tsutsumida[50] found no significant DFS at 3 years in patients treated with SLN vs ELND, or in patients who had a positive SLN biopsy vs patients who had a positive ELND result. Clary et al [51] also found no difference in DFS at 3 years when comparing SLN patients to ELND. However, Clary et al performed a subgroup analysis on all high risk patients, defined as patients who had breslow thickness > 3.0mm, the presence of nodal metastases and age >50. In analyzing all of the patients who were at high risk, the RFS for breslow thickness > 3.0 mm and for age > 50 years was significantly better for ELND patients compared to SLN patients at 3 years. For node negative high risk patients, the RFS was also significantly better for ELND patients compared to SLN patients. These results point towards a disadvantage of performing SLN biopsies. However, these results are from a retrospective designed study

with several limitations, such as short follow-up period and its design. From the five studies comparing ELND to SLN biopsy, it seems there is no difference in OS or DFS. Although, it seems that there might be a negative risk by decreasing DFS in node negative patients by performing SLN biopsy.

The literature search identified four studies comparing SLN biopsy to observation. Three of these studies, all retrospective, reported OS and one of the studies, an observational cohort, reported relative risk. The studies by Gutzmer et al[44], Koskivuo et al[45], and Starz et al[40], found no significant OS difference in patients treated with SLN biopsy vs observation. However, in a subgroup analysis performed by Kosviuo of patients with a positive SLN compared to observation, there was a significant difference in OS, with more patients benefiting from observation. These studies also point towards SLN biopsies offering a significantly better DFS compared to observation (see table 2). The study performed by Mohrle et al[52] found that the relative risk of melanoma related death to be 0.8, but was not statistically significant, comparing patients who had undergone SLN to observation. The relative risk did not change when comparing patients who had positive or negative SLN biopsies to observation. In conclusion, these overall fair quality articles point towards no difference in OS for performing SLN biopsies, but perhaps point towards an advantage for regional control in improving DFS.

The literature review revealed six articles comparing SLN biopsy to DLND when clinically palpable nodes were present. Given that SLN biopsy has replaced ELND in the management of melanoma, comparing SLN biopsy to DLND is more imperative. All six of these studies reported OS as an endpoint[38, 39, 46-49]. Rutkowski et al[39] found that there was no difference in OS or DFS at 5 years, when calculated from the date of primary

tumor excision, for patients treated with positive SLN biopsy plus CLND compared to DLND. However, they found a significant OS difference favoring SLN biopsy plus CLND when calculated from the time of lymphadenectomy (48% vs 38%, p=0.02). This article does not support an improved OS, or even a DFS, in patients who are stage III and have clinical disease in lymph nodes undergoing SLN biopsy plus CLND compared to DLND. Van Akkooi et al also found that there was no significant difference in OS at 5 years, when calculated from date of primary tumor excision, for patients treated with SLN biopsy plus CLND vs. DLND[49]. Even when patients with nodes containing submicrometastases were excluded from analysis, there was still no difference in OS. The authors are in agreement with Rutkowski et al and conclude there is no survival benefit in performing SLN biopsies. The main bias in the both of these studiess is that the two study groups were different at baseline, and they do not factor differences during their statistical analysis for OS survival.

On the other hand, Kretschmer et al found a significant 13% OS difference at 5 years, calculated from time of primary tumor excision, in patients treated with positive SLN biopsy plus CLND compared to DLND. This study represented cases from five different clinical centers, with one of the centers not performing DLND. One of the main bias with this study is that the data came from 5 different centers. There was no way of making sure everyone was treated the same, and thus the measurements were most likely not equal, valid, and reliable given that many different surgeons performed the procedures. Another bias in this study is that ulceration status was not available for all patients because three sites did not measure ulceration status. Since ulceration status is a prognostic factor in melanoma, this introduces confounding. In Morton et al's

retrospective review, a matched pair analysis was performed on 287 patients, matched for pT stage, ulceration, sex, age, and total number of tumor-involved nodes, using a computer program. This analysis revealed 5, 10, and 15 year significant OS, calculated from time of primary tumor excision, in favor of positive SLN biopsy plus CLND compared to DLND. The authors conclude that the result from this study indicate that melanoma behaves according to the incubator hypothesis, where melanoma metastasis first to lymph nodes where it remains latent before metastasizing further (as opposed to the marker hypothesis, where melanoma metastases via lymphatics and blood simultaneously. Thus, finding tumors cells in the SLN is merely a marker that the melanoma has already metastasized and removal of tumor in the lymph nodes is unlikely to have a therapeutic effect) Thus, there is a clinical window where the tumor can be removed before it spreads. The authors calculated the proportion of patients who would benefit from an early lymphadenectomy based on the matched pair analysis (if these patients represented the entire population of patients with melanoma). They calculated 7.4% of patients would benefit from early lymphadenectomy.

Finally, the study by Starz et al compared SLN biopsy ± CLND to DLND in melanoma patients with breslow thickness greater than 0.75mm[48]. For all patients who had undergone SLN compared to DLND, there was a significant OS difference favoring SLN biopsy. When comparing only patients who had positive SLN biopsy plus CLND compared to positive DLND, there was barely a significant difference in OS favoring SLN plus CLND ($p=0.0419$). Differences in follow-up times were not taken into consideration in calculating the OS time, which leads to measurement bias. A subgroup analysis was performed on patients with intermediate thickness (0.76mm-4mm) and OS

was significantly better in the SLN biopsy group compared to DLND (p=0.0076). The authors conclude that early removal of lymph nodes is beneficial in the management of melanoma.

In summary, there are two retrospective reviews which show no overall survival benefit for performing SLN biopsies and three retrospective studies showing a potential overall survival benefit in performing SLN biopsies. Given that these are retrospective reviews, they suffer from confounding, selection bias, and measurement bias. Many of the studies do not control for all potential confounders, such as age, differences in length of follow-up time, histology, breslow thickness, site of primary lesion, and ulceration status. Given that many of the studies do not contain equal comparison groups, it would be important to control for differences, although some studies do not. Many suffer from selection bias because they do not state guidelines as to how patients were selected. Many also are subject to measurement bias because some do not explain techniques of performing SLN biopsies or the SLN success rate. Thus, many authors conclude in their studies that a randomized control trial is needed to answer the question of an overall survival benefit.

Only one of the fifteen articles was a randomized control trial by Morton et al.[38] This multi-center trial included patients from the United States, Australia, and Europe, which randomized patients to either 1) wide local excision and SLN biopsy with immediate lymphadenectomy if patients had a positive SLN biopsy or to 2) wide local excision and observation with lymphadenectomy if patient had clinically palpable lymph nodes. The third interim results of this trial are reported in the paper. Patients who received SLN biopsy had a significantly better disease free survival at 5 years compared

to patients who had observation only (78.3±1.6% vs 73.1±2.1% 95%CI of 0.59-0.93, p=0,009). The subgroup analysis comparing patients who had a positive SLN biopsy with CLND to patients with WLE and DLND also showed a significantly better five year survival rate for patients who received the SLN biopsy (72.3±4.6% and 52.4±5.9%, 95% CI of 0.32-0.81, p=0.004). There was no significant difference in overall survival between the two groups at the 3rd interim analysis. Perhaps one of the reasons that the SLN group showed no difference in overall survival was because they had more distant recurrences compared to the observation group. At the 4th of the 5th planned interim analysis, melanoma specific survival is now significant (HR 0.74, $p < 0.001$) and the DFS remains significant (HR 0.74, $p < 0.001$). This is the first RCT to look at SLN vs DLND. At the 3rd interim analysis there was significant difference in DFS, but not OS. In the 4th interim analysis there seems to be a significant difference in OS as well.

Even though this was a well-designed RCT, the study suffered from several bias' and resulted in a overall quality grading of fair. The main problem with the RCT by Morton was their analysis of the post-hoc subgroup survival benefit. When they did this subgroup analysis, the randomization of patient characteristics for the two groups was lost, thus confounding and selection bias were introduced. Another potential bias is they did not include patients with false-negative results in the group who underwent lymphadenectomy. Another problem with this study is that they only present the results on a subgroup of patients with melanomas 1.2-3.5mm, but fail to report the overall results.

Discussion

Sentinel lymph node biopsy was adopted as the preferred method of care in the United States by the World Health Organization and by National Comprehensive Cancer Network treatment guidelines[32]. The reason is because studies show patients who have a negative sentinel lymph node biopsy have a better prognosis compared to patients who have a positive sentinel lymph node. Thus, SLN biopsy offers a minimally invasive staging procedure resulting in a prognostic indictor. Due to the morbidity and lack of overall survival advantage of elective lymph node dissection, sentinel lymph node biopsies replaced ELND as a staging procedure and became the preferred method even though there were no studies showing a therapeutic advantage of SLN biopsy.

One of the main concerns raised about SLN biopsy procedure was the fear that SLN biopsy increases the risk of in-transit metastasis by mechanically disrupting the flow of lymph to the regional nodes. If SLN biopsy did increase the risk of ITM, the procedure would essentially eliminate or reduce any survival or therapeutic advantages because ITM confer a poor prognosis with a worse 5 year survival rate of 25% and are more difficult to manage. [28] However, from the analysis of the articles identified from my comprehensive search, there is fair evidence pointing towards the use of SLN biopsy in patients diagnosed with Stage I or II melanoma does not increase the risk of in-transit metastases compared to either WLE only, ELND, or delayed lymph node dissection of patients with clinically palpable nodes. There is little evidence from these studies that early nodal removal by SLN biopsy has any impact on the natural history of ITM. The fear of increased risk of ITM with SLN biopsy was one of the main arguments against

the widespread use of SLN. From my review, it seems that ITM should not be a concern of mechanical disruption but perhaps of the biology of ITM.

Another question raised with the implementation of SLN biopsies was if the procedure resulted in a subsequent increase in disease free survival and overall survival. From the fifteen articles found during this comprehensive literature search, SLN provides a significantly better disease free survival but perhaps not an overall survival benefit. There were three retrospective reviews pointing towards an OS benefit in patients undergoing SLN biopsy compared to DLND, but two retrospective reviews that lacked to find this same benefit. The one randomized control trial, considered to be the gold standard but only given a fair quality grade, showed a significant improvement in DFS and the newest results show an improvement in OS as well. However, this RCT only shows the results from a small subgroup of the entire patients included in the MSLT-1 trial. Biologically, it makes sense that patients undergoing SLN biopsies with subsequent complete lymphadenectomy would have a prolonged disease free survival period because the patient is given an early stage III diagnosis with detection and removal of metastasis in the lymph nodes. However, strong evidence is lacking in the possibility that performing SLN biopsies results in an overall survival benefit.

Perhaps one reason that studies have failed to show an overall survival for patients treated with SLN biopsy is because not all melanoma metastasis are present in the regional lymph nodes. In about 2/3rd of cases of melanoma, metastatic disease develops as locoregional metastasis, and in 1/3rd of cases it presents as distant metastasis. SLN biopsy will detect and remove only regional lymph node metastasis. In one study, 50% of patients developed metastasis not in the regional lymph nodes. Distant metastasis

in this study appeared to be an early event in metastatic spread and could have occurred via hematogenous spread, resulting in support of the marker hypothesis.[53] Thus, SLN biopsy might not show a significant improved overall survival in studies because hematogenous spread has already occurred in a majority of patients. Perhaps SLN biopsy will become only one part of the staging technique in the future where other modalities might be able to identify metastasis that have bypassed the regional lymph nodes.

Another possible reason the studies failed to show an improvement in overall survival with SLN biopsy is because it represents a lead-time bias. The studies identified showed an improvement in disease free survival, but not of overall survival, except for the newest results of the 4th interim analysis of the MSLT-1 Trial. The SLN biopsy procedure is detecting melanoma metastases early in the asymptomatic period. Thus, the patients who get a SLN biopsy procedure are being upstaged earlier than patients who have a delayed lymphadenectomy. However, since the overall survival between the two groups is the same, the SLN biopsy patients are not actually living longer than the observation patients but are merely finding out about their disease at an earlier point.

One of the main hopes of the SLN biopsy was to identify patients who have positive sentinel lymph nodes so they could be treated further, either with completion lymphadenectomy and/or adjuvant therapy. All patients with positive sentinel lymph nodes are additionally treated with a completion lymphadenectomy to remove any further possible metastasis. It is assumed that all positive sentinel nodes will go on to cause overt disease. Thus, by performing a completion lymphadenectomy it will provide the patient with a survival advantage. However, this might not be the case as some studies have suggested that not all positive sentinel lymph nodes will go on to cause overt nodal

disease if not removed early. Starz et al concluded that perhaps only deposits greater than 1 mm (SIII) were of adverse prognostic significance. [48] In this study, patients' S classification, or the maximum distance from the interior margin of the lymph node capsule, provided better prognostic information compared to the mere presence of a positive SLN, as patients with an SIII classification had a significantly worse overall survival rate. Another study suggested that perhaps only micrometastases found by immunohistochemical analysis were not of prognostic significance.[54] There is evidence that not all occult nodal disease will progress to overt clinical disease; some micrometastases in the SLN will either be destroyed by host-immune processes or become dormant.[55] Thus, research is still being done to help shed light on prognostic factors to determine which patients would be better suited for the SLN biopsy procedure.

Approximately 15-20% of patients with a positive SLN are found to have additional disease with CLND[56], which means 80% of patients with a positive SLN do not require this procedure. In addition, the CLND procedure is more invasive than a SLN procedure, causing complications in roughly 37.2% of patients in the MSLT-1 trial. In this trial, the procedures were performed by experienced surgeons, and thus most likely underestimate the true complication rate of CLND on patients who might not need CLND. [57] A multi-institutional study evaluated patients who were SLN positive but did not undergo a CLND compared to a contemporary series of melanoma patients who had CLND[56]. They found the overall disease specific survival of patients with a positive SLN who did not undergo CLND was not significantly different from patients who had a positive SLN who underwent CLND. Thus, the authors concluded obtaining a CLND after SLN made no difference on survival. Given this study was retrospective review,

more studies need to be performed to definitely answer this question. A recent retrospective study by Roka et al attempted to identify clinico-pathological features to predict which positive SLN patients will have additional disease present in CLND in hopes of identifying high-risk patients.[58] They concluded that clinico-pathological features can not reliably be used to identify patients who will have additional disease on CLND, and thus all patients with a positive SLN biopsy require a CLND. The therapeutic utility of CLND after a positive SLN is still largely unknown and is currently being tested in the Multicenter Selective Lymphadenectomy Trial (MSLT II) randomized control trial. If there is a survival benefit for CLND after SLN biopsy, then it would favor performing SLN biopsies on all patients with melanoma.

Performing SLN biopsies on patients with melanoma is thought to improve patient care by identifying patients in which adjuvant treatment would be helpful. However, this would be the case only if adjuvant treatment existed for melanoma that increased overall survival and/or disease free survival. A recent systematic review found no systematic adjuvant therapy (interferon, levamisole, vaccine or chemotherapy) that conferred a significant overall survival benefit in patients with high-risk primary melanoma.[59] However, there was a significant improvement in disease-free survival (DFS) for patients treated with high-dose interferon[60]. Even though DFS is improved with high-dose interferon, the medication also causes at least grade three toxic effects in most patients. Thus, the benefits of additional months of disease free survival, yet ultimately no effect on overall survival, have to be weighed against the year-long toxic effects of interferon therapy. SLN biopsy would identify patients who have positive nodal disease status, but these patients may or may not benefit from adjuvant treatment.

If sentinel lymph node biopsy with completion lymphadenectomy does not confer any sort of survival advantage and there is no conclusive evidence that adjuvant treatment is beneficial, then why use this procedure on patients diagnosed with melanoma? Given that SLN biopsy is minimally-invasive with minor side effects, some patients may wish to go through this procedure simply to know their lymph node status, and thus their prognostic status. Patients may feel reassured knowing that if they have a negative sentinel lymph node, their survival will be better than if they are positive. Even though there is roughly a 4% failure rate and being sentinel lymph node negative is not a 100% guarantee for no recurrences (around 13% of SLN negative patients will develop recurrence by 3 years[18]), patients will still have a better idea of their long-term outcome. On the other hand, if a patient has a false-positive SLN, this information can be devastating and lead to unnecessary completion lymphadenectomy and/or adjuvant therapy.

In a questionnaire survey with patients who underwent SLN biopsy, 91% believed that they gained some benefit from the procedure, such as peace of mind or the ability to plan for the future, both of which were independent of the outcome of the biopsy.[61] However, this benefit seemed to be only short-term. Regardless, the majority of patients approved of the procedure and would recommend it to others. One advantage of the SLN biopsy, even though there is still not universal agreement that it has a therapeutic advantage, is that it may provide patients with psychosocial benefits necessary to cope with the diagnosis of cutaneous melanoma.

SLN biopsy is the only minimally invasive staging technique that is available for cutaneous melanoma. Several studies have looked at the use of CT, PET and ^{99m}Tc-MIBI

scintigraphy as possible alternatives. However, none of these modalities are as sensitive as SLN biopsy at detecting microscopic positive nodal metastasis.[62-65] There has been further research on other screening alternatives. One study compared methallothioneines over-expression to SLN biopsy and found that it was comparable to SLN as a prognostic marker, but cheaper and easier.[66] Other research has looked at the prognostic information of tumor-infiltrating lymphocytes[67] and p-cadherin[68]. The information that SLN biopsy, a one time procedure, provides may be considered important to both the clinician and patient in terms of management options and psychosocial factors. Yet there is still further research being done on other potential alternatives.

The use of ultrasound with fine needle aspiration in management of cutaneous melanoma has shown potential promise for an additional role in melanoma management. Given that ultrasound has a lower sensitivity and high false negative rate, ultrasound cannot completely replace SLN biopsies. However, studies have shown using US with FNA allows 10%-16% of patients to be spared the SLN biopsy procedure. [69, 70] Another newly published study highlight the potential promise of use of inductively coupled plasma-mass spectrometry (ICP-MS) with FNA as a means of nonsurgical evaluation of sentinel lymph nodes.[71] Perhaps by using US with FNA, the SLN biopsy procedure can be limited to only high risk patients, or even using a non-surgical alternative such as ICP-MS, thus reducing the number of unnecessary SLN biopsies.

Even though the SLN biopsy is the preferred method for the treatment of melanomas, widespread use of this procedure has not been obtained, with roughly one-half of patients receiving this standard.[28-29] A retrospective review of a cancer registry at a teaching hospital in Greenville, South Carolina, showed that only 60% of patients

diagnosed with melanoma received a SLN biopsy, and the non-universal adherence to standards did not appear to have an effect on overall survival, although the study was not powered to show this outcome. [72] Concerns have been raised that this procedure might not be feasible for management of all patients presenting with melanoma. Given that SLN is a multi-disciplinary approach, with the need for surgeons, pathologists, and nuclear medicine physicians, it is not surprising that the national standards have not been universally met.

Another potential barrier to wide-spread implementation of SLN biopsies is because of the learning curve of the procedure, with 20-30 cases needing to be performed prior to independent utilization to achieve success rates greater than 90%[73, 74]. Thus, only experienced surgeons should be performing this technique. However, the SLN biopsy procedure is not limited to high volume specialty institutions as one study proved the feasibility of the SLN procedure in a community-based institution with comparable technical success rates and false-negatives rates.[75] Another study compared performing SLN biopsy as an inpatient procedure to an outpatient day surgery and found that there were no significant differences in time between diagnosis and surgery, prolonged hospital stay and complication rates.[61] The patients had a greater satisfaction with outpatient surgery and it reduces cost and use of hospital inpatient beds. Regardless of the setting, the key to successful SLN procedure is quality control of the various multi-disciplines. Given that SLN biopsy is the preferred method, and it is feasible not only at high volume specialty clinics, more research looking at the barriers to access of care for patients presenting with cutaneous melanoma should be pursued.

In light that the evidence for SLN biopsy is one of clinical equipoise, the cost-effectiveness of this procedure must also be considered. For melanomas less than 1 mm in thickness, there is much controversy over whether or not SLN biopsy should be performed, given only a very small percentage of patients would benefit from this procedure. The SLN biopsy procedure costs $10,096 to $15,223, compared to $1,000 to $1,720 for wide local excision alone. In one quantitative method analysis of cost-effectiveness for performing SLN biopsies in patients with melanomas less than 1.2 mm in thickness found that a large number of SLN biopsies would need to be performed to identify one patient with regional disease. The estimated the cost per life saved ranged between $627,000 to $931,000 for melanomas less than 1.2mm and even greater for melanomas less than 1mm, up to $153,00 annual cost per life saved. These authors conclude by raising the question as to whether or not it is cost-effective to perform SLN biopsies in this population group. [76]

Another study looked at the cost-effectiveness, including treatment, toxicity, follow-up and relapse cost, using a decision analytical model comparing four treatment strategies in patients with Stage II melanoma (greater than 1 mm). Their primary outcome was cost in US dollars per quality-adjusted relapse-free life year saved. They found that using interferon treatment was more cost-effective than no treatment. The most cost-effective was to perform SLN and treat only those with positive disease with high dose interferon at $18,700/QALY.[77] Currently, it appears that it might not be cost-effective to perform SLN on all melanomas less than 1mm. For melanomas greater than 1 mm, the SLN biopsy might be cost-effective in determining which patients to treat with adjuvant interferon, although treatment with interferon remains controversial.

Even if the SLN biopsy procedure does not drastically improve survival, it is a diagnostic procedure that allows for nodal staging of melanoma. At this stage, it seems highly unlikely that the AJCC will revert back to clinical staging of nodal disease because the SLN biopsy procedure does provide better control of regional disease, thus improving disease free survival. Wide local excision with delayed lymphadenectomy when a patient has clinically palpable disease is not the best option for management of regional nodal disease of cutaneous melanoma. By the time the DLND is performed, extracapsular extension, invasion of neurovascular structures makes regional disease control more difficult than performing a SLN biopsy +/- complete lymphadenectomy.[78] Thus, even though there is not widespread agreement that SLN improves overall survival, it does control local disease, providing patients with a significantly better chance of remaining disease free without recurrences. SLN biopsy remains the best option currently available. Perhaps with further research on other modalities, such as ultrasound and/or molecular markers, the use of SLN biopsy can be limited to only high-risk patients, thus minimizing unnecessary procedures.

SLN biopsy can identify the 15-20% of patients with melanoma that have clinically negative lymph nodes but occult regional nodal metastasis, thus who would might benefit from a lymphadenectomy. The majority of patients will undergo this procedure and not have negative SLN biopsies. Many studies have recently been done attempting to create a model that incorporates the factors that are important in determining of the SLN is positive.[79-83] The majority of the models studied looked at prognostic factors beyond breslow depth, such as mitotic rate, age, angiolymphatic invasion, regression and microsatellitosis. These models will allow for an improved

ability to predict the presence of SLN metastasis, which can help with individual patient risk estimation and decision making to help the patient make an informed decision on if SLN is right for them. One of these models was a nomogram that when tested against predictions based on the AJCC clinical staging system was found to be more accurate and discriminating. [79] Hopefully, models such as these can help reduce the number of SLN biopsies so that patients only at high risk for regional nodal mets will be subject to this minimally invasive procedure.

Given that all the important questions surrounding the use of SLN melanoma are still unanswered and data is currently being collected for the MSLT I and II trials, I think it is important for physicians to have a discussion with their patients who are diagnosed with cutaneous melanoma. I think it is important for the patient to know that the sentinel lymph node biopsy is stated as the preferred method of care by the AJCC and the WHO, but there are still questions that remain unanswered. Patients need to be aware that SLN biopsy does not increase the risk of in-transit metastases. They also need to be aware that undergoing the SLN biopsy probably does not improve overall survival, as provided by the results of current studies. The patient also needs to be aware of all the facts surrounding the procedure: the false-negative rate is around 10%; the false-positive rate is about 20%; there is a 10% minor complication rate with the procedure, but this increases to 40% with a completion lymphadecetomy, and not every patient with a positive SLN will have additional disease found with their completion lymphadecetomy; and it is controversial if the microscopic disease in the SLN will actually progress and cause clinically detectable disease; and finally, there are no adjuvant therapies that improve overall survival in patients with high-risk melanoma. Patients should be aware of the pros

and cons of each option, discuss them with their physician provider and family/friends, and make their own decision given that this is a preference-sensitive decision with clinical equipoise. Perhaps new research will shed light on the ability to identify high-risk melanoma patients who would be more likely to benefit from a SLN biopsy. Until this research becomes available, shared decision making with the patient should be done surrounding this topic.

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Table 1: Studies measuring ITM recurrence as outcome

Author, Year	Study Design	Intervention	ITM as a first recurrence	P value	Overall ITM recurrence rate	P value	Quality Grading
Estourgie, 2004[33]	Observational	61 + SLN + CLND	--	--	23%	0.027	poor
		60 DLND + palpable nodes			8%		
Kretschmer, 2005[35]	Retrospective[+] database review	244 +SLN + CLND	27.3%	0.03	33.75%	0.38	fair
		199 DLND + palpable nodes	17.6%		33.3%		
Rutkowski, 2006[36]	Retrospective database review	963 SLN -	4.8%	ns (not given)	--	--	fair
		224 + SLN + CLND	20.1%				
		DLND + palpable nodes	17.0%				
Van Poll, 2005[37]	Retrospective database review[£]	1035 WLE	2.5%	0.24	4.9%	0.27	fair
		754 WLE + SLN	2.4%		3.6%		
		229 WLE + ELND	4.4%		5.7%		
Kang, 2005[34]	Retrospective[*] database review	2,2271 WLE	1.59%	0.0008	3.36%	0.2405	fair
		1,016 WLE + SLND	1.67%		3.64%		
		625 WLE + ELND	2.56%		6.56%		
Morton, 2006[38]	RCT	814 SLN ± CLND	--	--	7.7%	0.38	good
		533 WLE ± DLND			8.4%		

* Results show in the table are for unmatched analysis. Overall incidence and ITM as first recurrence rates for matched analysis are not shown in table.

+ Results do not show the overall and ITM first recurrence rate for SLN negative biopsies

£ Results do not show subgroup analysis.

Table 2: Studies measuring survival: overall survival (OS), disease free survival (DFS), recurrence free survival (RFS), melanoma specific survival (MSS)

Note: ~ refers to my interpretation of the Kaplan Meier Curve if not stated in the study

Author, Year	Study Design	AJCC stage	Intervention	Type of Survival	Survival (%)	P value	Type of Survival	Survival	P value	Time period	Quality Grading
Essner, 1999[43]	Retrospective Database review	Stage I	267* SLN ± CLND	OS	--	0.98	DFS	--	0.25	5 year+	fair
			267* ELND								
			Node positive patients 42+SLN/CLND	OS	--	0.08£					
			32 ELND								
Clary, 2001[51]	Retrospective Database review	Stage I/II	152 SLN	RFS	71%	0.12	MSS	--	0.87	3 year	fair
			329 ELND		80%						
			All high risk patients SLN	RFS for breslow > 3mm	~ 47%	0.04	RFS for age > 50 years	~ 65%	0.01		
			ELND		~ 75%			~ 82%			
			node negative high risk∫ 90 SLN	RFS	~ 70%	0.04					
			167 ELND		~ 82%						
Dessureault, 2001[41]	Retrospective Database review	Stage IB/IIA€	5, 156 - observe	OS	69.8%	< 0.0001				5 year	poor
			2,032 - SLN		90.5%						
			1,836 - ELND		77.7%						

Doubrovsky, 2004[42]	Retrospective database review	> 1.5-mm thick	672 SLN ± CLND 793 ELND	OS	--	0.139				5 year	fair
Tsutsumida, 2007[50]	Retrospective	> 1.5 mm	30 SLN 72 ELND 12 + SLN 19 + ELND	DFS	87.2% 72.7% 82.5% 72.2%	0.280 0.90				3 year	fair
Rutkowski, 2003[39]	Retrospective database review	Stage III	145 +SLN + CLND 205 DLND	OS	41% 42%	ns	DFS	35% 31%	ns	5 year	fair
Morton, 2003[47]	Retrospective database review	Stage I/II	287 SLN+CLND 287 DLND	OS[§]	73% / 69%/ 69% 51% / 37% / 32%	< 0.001				5/10/15 year	fair
Kretschmer, 2004[46]	Retrospective database review	Stage I/II	314 SLN+CLND 623 DLND	OS	62.5% 50.2%	0.002				5 year	fair
Van Akooi, 2007[49]	Retrospective database	Stage I/II	64 SLN + CLND 124 DLND	OS	13% difference	0.1115				5 year	fair
Starz, 2004[48]	Retrospective database review	Breslow > 0.75mm	324 SLN ± CLND 274 WLE ± DLND 70 + SLN ±	OS	~ 65% ~ 30% ~ 65%	0.03 0.0419	RFS (distant mets)	~ 75% ~ 35% ~75%	0.006 0.0048	8 year	fair

			CLND 57 + DLND		~ 35%			~ 38%			
Morton, 2006[38]	RCT	1.2-3.5 mm	814 SLN ± CLND	DFS	78.3±1.6%	0.009	Melanoma specific survival	87.1±1.3%	0.58	5 year	fair
			533 WLE ± DLND		73.1±2.1%			87.1±1.3%			
			SLN+CLND					72.3±4.6%	0.004		
			WLE+DLND					52.4±5.9%			
Möhrle, 2004[52]	Observational cohort	Stage I/II	271 +/-SLN 2,617 observe	RR of melanoma-related death	0.8	0.37					fair
			238 - SLN 2,617 observe	RR	0.75	0.36					
			33 + SLN 246 observe	RR	0.73	0.38					
Gutzmer, 2005[44]	Retrospective database review	Stage I/II	296 SLN 377 no SLN	OS	--	0.32	RFS	~ 78% ~ 65%	0.0064	4 year	poor
Koskivuo, 2007[45]	Retrospective case-control cohort	Stage I/II	305 SLN 616 control	OS	87.8% 82.5%	0.66	DFS	85.1% 79.0%	0.42	5 year	fair
			+ SLN control		~ 76% ~ 82%	< 0.001					
Starz, 2007[40]	retrospective	Breslow 0.76-1mm	87 WLE + SLN 61 WLE	OS		0.99	Melanoma specific survival RFS		0.03 0.01		fair

*****The 267 patients were matched based on gender, age, site of primary tumor, and the breslow thickness.
+ The difference in follow-up times for the two groups was statistically significant (p=0.001) but was controlled for via statistical methods.
∫ There was no sig difference b/w ELND and SLN/CLND for patients that were node positive.
£ Nonsignificant trend favoring of SLN/CLND
€ This shows subgroup analysis of patients w/ breslow thickness >1mm only. All patients with positive nodal disease were excluded from analysis.
§ Analysis is based on 287 pairs matched on pT stage, ulceration, age, sex, and total number of involved nodes.