Completion Lymph Node Dissection or Observation for Melanoma Sentinel Lymph Node Metastases: A Decision Analysis

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Erin E. Burke, MD

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Beth A. Virnig, PhD, Advisor
Karen M. Kuntz, ScD and Todd M. Tuttle, MD, Co-Advisors

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ABSTRACT

Objective: To determine whether melanoma patients with sentinel lymph node (SLN) metastases should undergo completion lymph node dissection (CLND).

Background: Randomized trial results comparing CLND with observation for patients with SLN metastases are not available.

Methods: We developed a Markov model to simulate the prognosis of hypothetical cohorts of patients with SLN metastases who underwent either immediate CLND or observation with delayed CLND if macroscopic disease developed. Model parameters were derived from published studies and included the likelihood of non-SLN metastases, risk of dying from melanoma, CLND complication rates, and health-related quality-of-life weights. Outcomes included 5-year overall survival (OS), life expectancy (LE), and quality-adjusted life expectancy (QALE).

Results: The projected 5-year OS for 50-year-old patients with SLN metastases who underwent immediate CLND was 67.2% compared to 63.1% for the observation group. The LE gained by undergoing immediate CLND ranged from 2.19 years for patients aged 30 to 0.64 years for patients aged 70 years. The QALE gained by undergoing immediate CLND ranged from 1.39 quality-adjusted life years for patients aged 30 to 0.36 for patients aged 70 years. In sensitivity analysis over a clinically plausible range of values for each input parameter, immediate CLND was no longer beneficial when the rate of long-term

complications increased and the quality-of-life weight for long-term complications decreased.

Conclusion: Immediate CLND following positive SLN biopsy was associated with OS and QALE gains compared with observation and delayed CLND for those who develop clinically apparent LN metastases.

Table of Contents

List of Tables

List of Figures

INTRODUCTION

Melanoma incidence is increasing in the Unites States with an estimated 76,100 new cases in 2014.[1] Patients with lymph node metastases have an estimated 5-year relative survival rate of 63% compared to 90% for those without lymph node metastases.[1-2] Presently, National Cancer Center Network (NCCN) guidelines recommend that a sentinel lymph node (SLN) biopsy be "considered" for patients with melanoma 0.75-1.0mm thick and that a SLN biopsy be performed if the primary melanoma is thicker than 1.0mm; for patients with SLN metastases, a completion lymph node dissection (CLND) is recommended.[2] These recommendations are largely based on the findings from the Multicenter Selective Lymphadenectomy Trial-1 (MSLT-1), a randomized controlled trial that compared survival between patients randomized to SLN biopsy versus those randomized to observation.[3] The melanoma-specific survival rates were not significantly different between the two randomized groups. However, for patients with lymph node metastases, the 5-year survival rate was significantly improved for patients who underwent a SLN biopsy and immediate CLND as compared to those who underwent a lymph node dissection when they developed macrometastases (72.3% versus 52.4%).[3]

Despite current recommendations many patients with SLN metastases don't undergo CLND. In an analysis from the National Cancer Data Base (NCDB), Bilimoria et al. reported that only half of the patients with SLN metastases

underwent CLND.[4] The use of CLND may be low because the procedure is associated with both early- and long-term morbidity. Since only about 15-30% patients with SLN metastases have non-SLN metastases, many patients will not benefit, and may actually be harmed by CLND.[5-11] Several retrospective non-randomized studies have reported no survival benefit from CLND for patients with SLN metastases.[12-15] These retrospective studies are limited by selection bias and small sample sizes. The prospective multicenter trial MSLT-II randomized patients with SLN metastases to either CLND or observation; unfortunately, the results of that trial will not be available for several more years.

The primary aim of this study was to determine the long-term survival and quality-adjusted survival for patients who have SLN metastases under two different treatment strategies: 1) immediate CLND and 2) observation with delayed CLND for those who develop clinically apparent (macroscopic) metastases. We chose to use a decision-analytic Markov model to overcome the limitations of previously published retrospective studies by making transparent the assumptions about the disease process, by incorporating information from different sources, and by conducting extensive sensitivity analyses.

METHODS

Model Design

We developed a decision-analytic Markov model to project clinical outcomes for a hypothetical cohort of patients who have SLN metastases under two different treatment strategies: 1) immediate CLND and 2) observation with delayed CLND for those who develop clinically apparent (macroscopic) disease (Figure 1). A Markov model is a recursive decision tree that guides hypothetical cohorts of patients between mutually exclusive health states on the basis of transition probabilities obtained from published data.[16] In the immediate CLND arm, patients can enter one of the three disease states that are based on the number of lymph nodes (LN's) with microscopic metastases. Patients undergoing CLND will face risks of experiencing a short-term complication and/or long-term complications (not depicted in Figure 1). Each year patients face a chance of dying based on survival probabilities obtained from the literature. In the observation arm, patients can also enter one of three disease states. One state involves the patient never developing macroscopic disease and thus, they never undergo a delayed CLND. In the other two disease states, the patients develop macroscopic disease and thus undergo a delayed CLND. For ease of modeling all patients who developed macroscopic lymph node metastases, underwent a delayed CLND at 2 years. Thus, only in the two disease states where macroscopic disease develops do patients face the risks of short-term and long-term complications from undergoing a delayed CLND. Again these patients can

either remain in their assigned disease state or move to the “Dead” state based on survival probabilities. We chose to base the disease states on the number of lymph nodes with either macroscopic or microscopic metastases because the number of positive lymph nodes is strongly associated with survival; moreover, the survival data based on the number of positive lymph nodes are readily available from the comprehensive prospectively collected database of melanoma patients from the American Joint Committee on Cancer (AJCC).[17]

The model outcomes for each treatment strategy included 5-year overall survival (OS), life expectancy (LE) in years and quality-adjusted life expectancy (QALE) in quality-adjusted life years (QALY’s). The model was developed and analyzed using TreeAge Pro 2014 (TreeAge Software, Williamstown, MA).

Input Parameters

The base-case values and ranges for each of the input parameters used in our Markov model are listed in Table 1.

Lymph Node Status

Based on a systematic literature review and meta-analysis by the American Society of Clinical Oncology and Society of Surgical Oncology, about 20% of patients with SLN metastases will have non-SLN metastases.[10] Thus, we used a

base-case value of non-SLN metastases of 20% with a range from 15-30%, thus defining the expected range for this variable to be used in sensitivity analysis.[5-11]

The proportion of patients in each disease state defined by the number of positive LN's and the characteristics of LN metastases (microscopic vs. macroscopic) was obtained from a study by Balch et al. that used the American Joint Committee on Cancer (AJCC) melanoma staging database. This study provides information on the expected proportion of patients with 1, 2-3 and ≥4 LN's with either micrometastases or macrometastases.[17]

Survival Data

We derived annual disease-specific mortality rates from the five-year melanoma-specific survival curves reported for different levels of LN disease burden by Balch et al. using the AJCC melanoma staging database and assumed that these rates applied for five years.[17] For those patients who survive 5 years, the conditional survival rates were obtained from two large database studies. Those studies demonstrate that for patients with micrometastases in 1-3 LN's who survive 5 years, the 5-year conditional survival rate is about 90%. For patients with any macrometastases or ≥4 LN's with metastases who survive 5 years, the 5-year conditional survival rate is about 80%.[18,19] We derived annual disease-specific mortality rates from these estimates and assumed they applied to those patients who survived more than 5 years. To account for mortality due to non-

melanoma causes, we used annual all-cause mortality rates reported by the Centers for Disease Control and Prevention (CDC).[20]

Complication Rates

To account for the risks of undergoing a CLND, both short- and long-term complication rates were incorporated into our model. Short-term complications included those complications that occurred shortly after surgery and included surgical site infection, hematoma, seroma and wound dehiscence. Long-term complications included complications that could persist for a lifetime and included lymphedema and nerve injury. Based on data from two large prospective trials (MSLT-1 and Sunbelt Melanoma Trial) as well as smaller retrospective studies, we estimated base-case values and ranges for short- and long-term complication rates for CLND.[21-24]

Health-related Quality-of-Life Weights

We used health-related quality-of-life (HRQoL) weights (i.e., utilities) to model the impact of having melanoma, undergoing a CLND, or having either a short-term or long-term complication from CLND. HRQoL weights are values that range from 0 to 1, with 0 being dead and 1 representing the best possible health. We used studies that estimated the HRQoL weight for a person with a history of melanoma but considered to be disease free as 0.96 (95% CI, 0.94-0.96).[25,26] HRQoL weights in the immediate post-operative period for those who undergo CLND are

less well defined. For our study, we used a value of 0.8 for the weight associated with the immediate post-operative time and this was applied for the period of one month after surgery.[27] The HRQoL weights for those who suffer complications are also less well defined and often taken from estimates of quality-of-life weights for those patients who experience lymphedema for any type of cancer surgery.[27,28] Based on those estimates we used a base-case value of 0.5 for short-term complications and 0.8 for long-term complications. For short-term complications the utility was assigned for a duration of one month, for long-term complications the utility was assigned for the remainder of the patient's life given the nature of the long-term complications that result after CLND.

Sensitivity and Threshold Analysis

We performed sensitivity analysis to determine the stability of our results when we varied the base-case parameter values within their plausible ranges. We performed one-way sensitivity analysis on all variables. For variables for which there was a published range, we performed sensitivity analysis over this range. For those values in which a clear range was not present in the literature, the sensitivity analysis was performed over a range of values that we considered clinically plausible. Additionally, we performed threshold analyses to determine what the base-case value would need to be to change the outcome from one treatment strategy being preferred to the other treatment strategy being preferred. To do this we varied the values for each input parameter over a wide

range that did not always include a clinically plausible value. Finally, we performed 2-way sensitivity analysis on those variables for which the analysis was most sensitive.

RESULTS

Five-Year Overall Survival

The predicted 5-year overall survival (OS) rates for each hypothetical cohort of patients defined by age who underwent either immediate CLND versus observation are presented in Table 2. For each cohort, the 5-year OS rate was higher for those who underwent immediate CLND rather than observation. The difference in percent survival ranged from 4.2% in patients age 30 to 3.8% in those age 70 (Table 2). The 10-year survival curves for a cohort of 50-year-old patients who underwent either CLND or observation is depicted in Figure 2.

Life Expectancy and Quality-Adjusted Life Expectancy

The predicted life expectancy (LE) was higher for those who underwent immediate CLND versus observation for each cohort (Table 3). The LE gained by undergoing immediate CLND ranged from 2.19 years in patients age 30 to 0.64 years in patients age 70.

The predicted quality-adjusted life expectancy (QALE) was also higher for those patients who underwent an immediate CLND for SLN metastases versus observation (Table 4). The QALE gained by undergoing immediate CLND ranged from 1.39 quality adjusted life years (QALY's) for patients age 30 to 0.36 QALY's for those age 70. In all cohorts the predicted QALE was less than the

predicted LE, since QALE estimates take into account the less-than-perfect health associated with having melanoma, surgery, and surgical complications.

Sensitivity and Threshold Analysis

Risk of Non-SLN Metastases

For a cohort of patients aged 50 years, the 5-year OS benefit gained by undergoing an immediate CLND rather than observation ranged from 3.1% when the risk of non-SLN metastases was 15% to 6.2% when the risk of having non-SLN metastases was 30%. Similar variations in the gains for LE and QALE with immediate CLND were observed when varying the risk of non-SLN metastases over the same range. For all age cohorts, CLND was always the preferred strategy when varying the risk of non-SLN metastases over the range found in the literature from 15-30%. For patients age 50, the preferred treatment strategy switched from immediate CLND to observation when the risk of non-SLN metastases was less than 7.8%.

Survival for Patients with 2-3 Macroscopic Lymph Node Metastases

We varied the 5-year melanoma-specific survival for those with 2-3 macroscopic lymph node metastases from 31.5% to 51.5% (Base-case value, 41.5%). Over this range of values, the preferred strategy was always immediate CLND for all age cohorts. A threshold analysis was performed on a cohort of patients aged 50

which showed that the 5-year melanoma-specific survival for those with 2-3 macroscopic lymph node metastases would have to be greater than 66.5% for observation to be the preferred strategy; this survival rate for macroscopic nodal metastases is unlikely because it exceeds the survival rate for patients with 2-3 microscopic lymph node metastases (63%).

Long-term Complication Rates and Associated Quality-of-Life Weights

When varying the long-term complication rates from 2.3-41% based on values found in the literature, the QALE gained by undergoing immediate CLND for a cohort of 50 year olds ranged from 1.22 QALY's to only 0.07 QALY's respectively. On threshold analysis, the rate of long-term complications had to be greater than 43.4% for the preferred strategy to become observation for a cohort aged 50 years. However, given the minimal QALE gains as the complication rates approached 41%, further sensitivity analysis was performed on other age groups. When varying the rate of long-term complications from 2.3-41%, the QALE gained favored immediate CLND for all age cohorts except those who were aged 70 years. For, the cohort aged 70 years, immediate CLND was no longer associated with QALE gains when the rate of long-term complications was greater than 38.5%.

Our analysis was somewhat sensitive to the HRQoL weight associated with long-term complications. If this value were less than 0.50, then observation would be the preferred strategy for the cohort aged 50 years. For patients aged 60 years, a HRQoL weight less than 0.52 resulted in observation being favored; and for patients aged 70 years, a quality-of-weight less than 0.55 favored observation.

Other Input Parameters

Sensitivity analysis on the remaining input parameters demonstrated that the optimal strategy did not change even with wide variations in these input parameters.

Two-way Sensitivity Analysis

Our results were most sensitive to changes in the input parameters when the probability of long-term complications and the utility of long-term complications were varied at the same time. With this two-way sensitivity analysis, observation became the preferred strategy for patients aged 50 under some situations. For example, when the probability of long-term complications was 41%, the utility of having a long-term complication had to be greater than 0.80 for CLND to be preferred. Our results were also modestly sensitive to changes in the probability of long-term complications when the probability of having positive NSLN's was varied at the same time. Similarly our results were modestly sensitive to changes in the utility of long-term complications when the probability of having

positive NSLN's was varied at the same time. CLND continued to remain the preferred strategy for all values when the probability of having positive NLSNs and probability of survival with 2-3 macroscopically positive lymph nodes were varied at the same time.

DISCUSSION

Our study used a decision-analytic Markov model to project 5-year OS, LE and QALE for hypothetical cohorts of melanoma patients with SLN metastases who underwent either immediate CLND or observation. Using the base-case values defined in Table 1, we found that immediate CLND was associated with 5-year OS, LE and QALE gains for all age cohorts. The QALE gains were smaller than the LE gains, but were still appreciable. The survival gains and quality-adjusted survival gains were smaller for the older age groups but were still present. We also performed several sensitivity analyses and found that immediate CLND remained the preferred strategy even when varying the base-case values for these parameters dramatically. However, the model outcomes were sensitive to variations within a clinically plausible range for both long-term complication rates and quality of life weights associated with having long-term complications. In both cases, the preferred strategy switched to observation in older cohorts (60 or 70 years).

The projected survival benefit associated with CLND is based on the observation that about 20% of melanoma patients with SLN metastases will have non-SLN metastases that would be left untreated. Furthermore, the survival rates of patients with microscopic lymph node metastases are substantially higher than for those patients with macroscopic lymph node metastases.[3,17] Nevertheless, the potential survival benefit associated with CLND for all patients is diluted by

the 80% who do not have non-SLN metastases; in fact, such patients may be harmed by CLND. The confusion regarding the optimal management of regional lymph node nodes is illustrated by the observation in the NCDB study that only half of the patients with SLN metastases underwent CLND.[4] Yet, in an international survey study of melanoma surgeons, performed by Pasquali et al., 92% of respondents recommended CLND for SLN metastases.[29]

Although several retrospective studies have reported no survival benefit from CLND, most studies are limited by selection bias and small sample size.[12-15] In the multicenter randomized clinical trial MSLT-II, patients with SLN metastases are randomized to either CLND or observation with nodal ultrasound. The primary outcome measurement is melanoma-specific survival. Unfortunately, the results from this trial won't be available for several years, and the estimated primary completion date is September 2022.[30] There is some concern that patients enrolled in MSLT-II will have a lower risk of non-SLN metastases and may not be representative of patients with SLN metastases in general due to reluctance to randomize high-risk patients to the observation arm. For instance, in the international survey study by Pasquali et al., 47.4% of responders did not consider it appropriate to randomize patients with more than one positive SLN. In addition, 33.3% of responders thought it appropriate to consider implementing an upper limit to the size or area of the SLN metastases in MSLT-II.[29] If the patients

enrolled in MSLT-II have a lower rate of non-SLN metastases, the survival benefit of CLND may be considerably attenuated.

Our study is the first to utilize a decision-analytic Markov model to address the question of whether or not to perform immediate CLND for those patients with SLN metastases. By using a Markov model, we can overcome some of the limitations associated with the published retrospective studies by incorporating data from a variety of studies to inform a framework of this disease process. In addition, Markov modeling allows for inclusion of quality-of-life measures that take into account that all patients in the CLND group are subjected to the complications of the procedure even though only 20% have non-SLN metastases would derive any survival benefit from a CLND. Finally, this methodology provides timely information on the expected survival benefits and risks of performing immediate CLND given the best data available and in the absence of results from prospective randomized trials.

This study has several important limitations. First, this study depends on input parameters available from the published literature. To limit inaccuracies, data included in this model were taken from large prospective studies and high quality databases, whenever possible. Furthermore, sensitivity analyses were performed to demonstrate the stability of this model's outcomes when input

parameters were varied. Second, a number of assumptions were required when creating the model, which is true when creating any decision model. For example, we assumed that all patients with microscopic lymph node metastases in non-SLN's who are observed will develop macrometastases. This assumption is supported by findings from MSLT-1.[3] We also assumed that CLND will only benefit those patients who have non-SLN metastases. Intuitively this assumption makes sense because removing unaffected lymph nodes is unlikely to improve survival. We also assumed that each patient had only one positive SLN; therefore, our results may not be reflective of patients with more than one positive SLN. Another limitation of our study is that we didn't consider other factors (ulceration, tumor thickness, volume of metastases in SLN) that influence the risk of non-SLN metastases. However, our sensitivity analysis included a broad range of risk of non-SLN metastases, and thus, minimized this limitation. Finally, we considered the morbidity of CLND as a single procedure. However, the early and late complications differ substantially for lymph node dissections of the neck, axilla, and groin.

Despite these potential limitations, this study provides important information about the absolute survival and quality-adjusted survival gains for patients who undergo immediate CLND for SLN metastases rather than observation. Presently, such information is not available from published studies. Furthermore, our study presents this information in a way that can be tailored to individual

patients based on age and risk factors such as likelihood of having non-SLN metastases or surgical complication. The OS, LE and QALE outputs from this model provides physicians with data that can be used in counseling patients of varying age regarding their expected benefits and risks for each treatment strategy.

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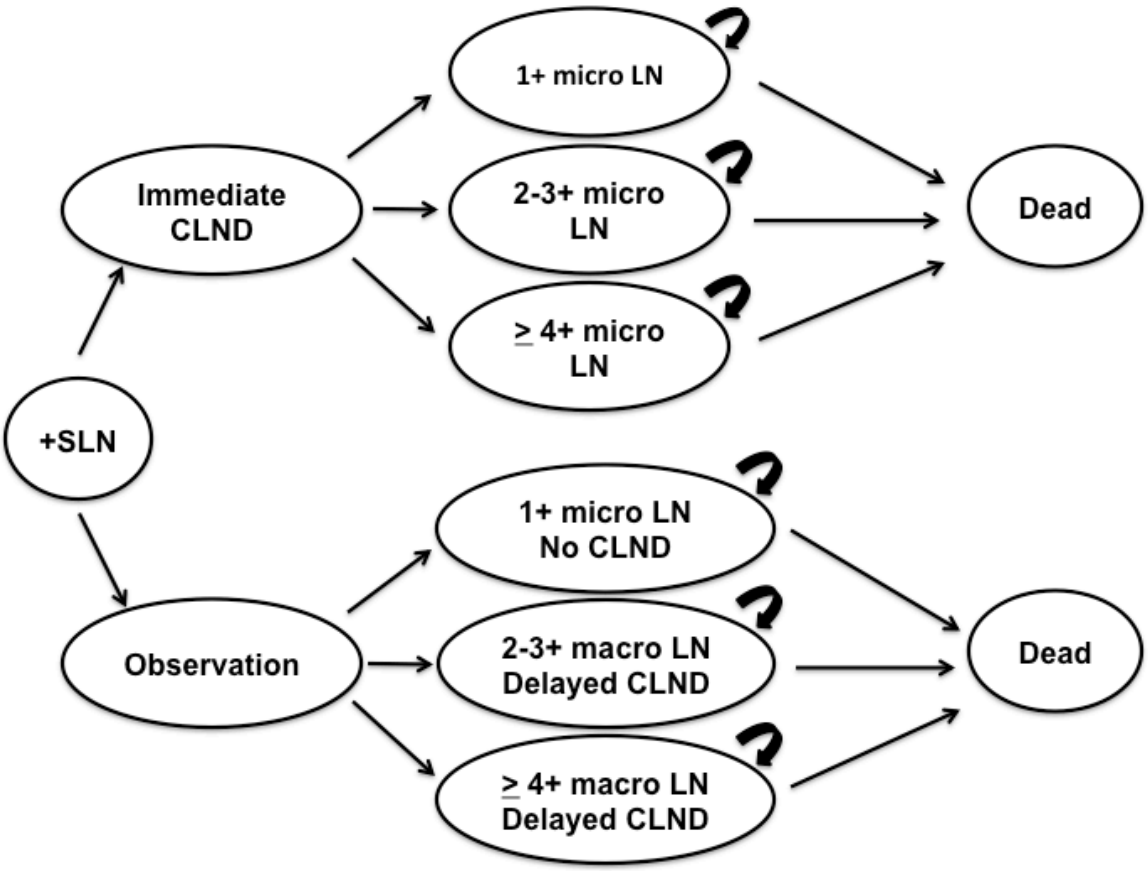

Figure 1. State Transition Diagram for Markov Model. Abbreviations: + SLN = sentinel lymph node metastases, CLND = completion lymph node dissection, LN = lymph node, Micro = micrometastases, Macro = macrometastases. Patients enter each disease state based on number and size of lymph node metastases. They can then remain in that disease state or die from melanoma or die from other causes and thus move to the dead state. Each cycle of this Markov model is one year in length.

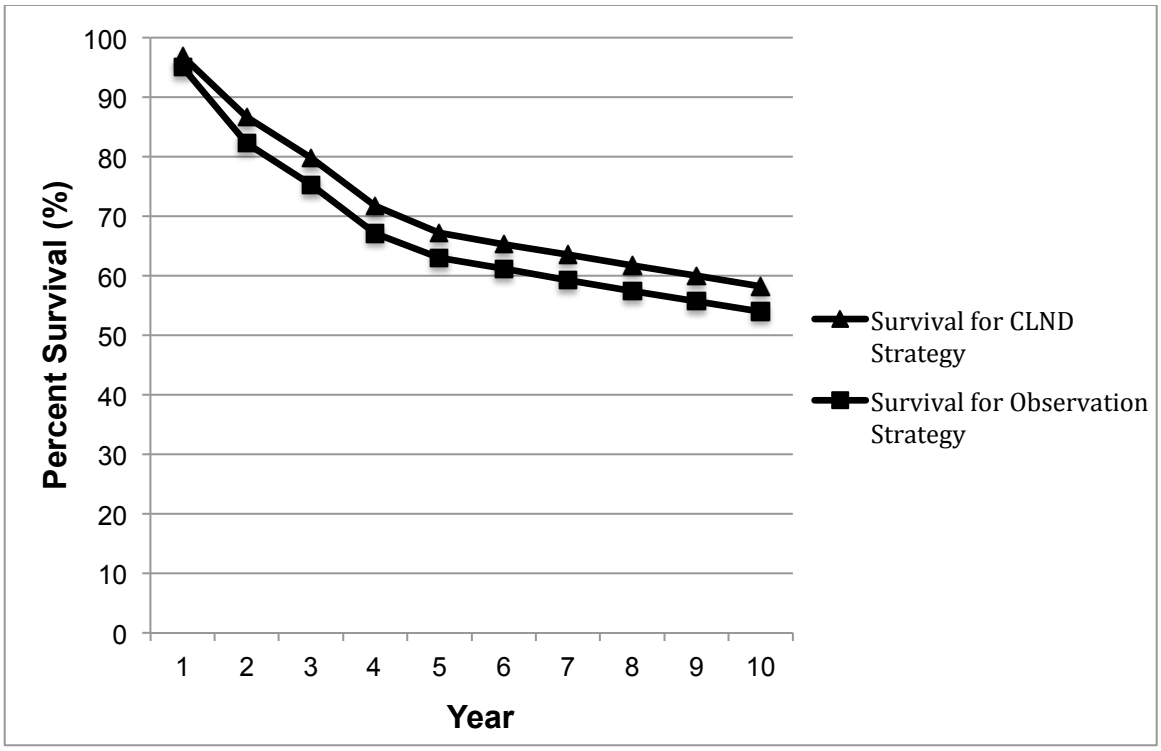

Figure 2. Projected 10-year Survival Curve for 50-year-old Patients Undergoing Either Completion Lymph Node Dissection (CLND) or Observation for Lymph Node Management.

Table 1. Input Parameter Base-Case Values and Ranges from the Literature for the Markov Model.

Input Parameters	Base-Case Value (Range)	Sources
Percent of Patients by Non-SLN Status		
Percent with non-SLN Metastases	20 (15-29)	
Percent of Patients by LN Number & Metastasis Size (Includes SLN)		
Micrometastasis		
1	80 (71-85)	5-11,17
2-3	17.6 (13.2-26.4)	
≥4	2.4 (1.8-3.6)	
Macrometastasis		
0 (only have SLN metastasis)	80 (71-85)	
2-3	11.5 (8.6-17.3)	
≥4	8.5 (6.4-12.7)	
5-Year Melanoma Specific Survival (%)		
Micrometastasis		
1	71	
2-3	63	
≥4	36	
Macrometastasis		
0 (only have SLN metastasis)	71	
2-3	41.5	
≥4	36	17-20
Conditional Melanoma Specific Survival (%)*		
1-3 LN's with micrometastases	90	
≥4 LN's with micrometastases or any macrometastases	80	
Death Due to Other Causes		
All Cause Mortality	Age Dependent	
Percent with Surgical Complications (%)		
Short-term Complications	30 (23-37)	21-24
Long-term Complications	15 (2.3-41)	
Health-Related Quality-of-Life Weights		
Melanoma	0.96 (0.94-0.96)	
Immediately post-operative state	0.8	25-28
Short-term complication	0.5	
Long-term complication	0.8	

*Conditional on surviving the first 5 years

Abbreviations:

Non-SLN = Non-sentinel lymph node, SLN = Sentinel lymph node, LN = Lymph node

Table 2. Five-year Overall Survival (OS) for Immediate Completion Lymph Node Dissection (CLND) or Observation.

Patient Cohort by Age (Years)	Immediate CLND (% Alive)	Observation (% Alive)	Difference in 5-yr OS (Immediate CLND - Observation)
30	68.6	64.4	4.2
40	68.2	64.0	4.2
50	67.2	63.1	4.2
60	65.3	61.3	4.1
70	60.8	57.0	3.8

All patients have sentinel lymph node metastases based on SLN biopsy.

Table 3. Life Expectancy (LE) for Immediate Completion Lymph Node Dissection (CLND) or Observation.

Patient Cohort by Age (Years)	Immediate CLND (Years)	Observation (Years)	LE Gained in Years (Immediate CLND - Observation)
30	32.01	29.82	2.19
40	26.15	24.38	1.77
50	20.53	19.18	1.35
60	15.32	14.35	0.97
70	10.61	9.97	0.64

All patients have sentinel lymph node metastases based on SLN biopsy.

Table 4. Quality-Adjusted Life Expectancy (QALE) for Immediate Completion Lymph Node Dissection (CLND) or Observation.

Patient Cohort by Age (Years)	Immediate CLND (QALY's)	Observation (QALY's)	QALY's Gained (Immediate CLND - Observation)
30	29.94	28.55	1.39
40	24.45	23.35	1.10
50	19.20	18.36	0.84
60	14.32	13.73	0.59
70	9.91	9.55	0.36

Abbreviations: QALY's = quality adjusted life years
All patients have sentinel lymph node metastases based on SLN biopsy.