Published in final edited form as:

J Surg Oncol. 2015 June ; 111(7): 800–807. doi:10.1002/jso.23890.

Utility of Sentinel Lymph Node Biopsy for Solitary Dermal Melanomas

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Abstract

Background and Objectives—Solitary dermal melanoma (SDM) is melanoma confined to subcutaneous and/or dermal layers in the absence of a known primary cutaneous lesion. We hypothesized that sentinel node biopsy is an effective staging strategy for this rare disease.

Methods—A Markov decision model was constructed to represent two management strategies for SDM: wide local excision followed by observation, and wide local excision followed by sentinel node biopsy. Utilities, likelihood of positive sentinel node biopsy, and cancer progression rates during a five year time horizon were assigned based on institutional data and a review of existing literature. Estimated costs were derived using Medicare reimbursements.

Results—Excision followed by sentinel node biopsy provides greater utility, yielding 3.85 discounted quality-adjusted life years (dQALY) compared to 3.66 for excision alone. The incremental cost-effectiveness ratio for sentinel node biopsy is \$19,102 per dQALY. Sensitivity analyses demonstrated that observation is more cost-effective if greater than 23% of sentinel node biopsies are positive (16% reported), or if 5-year survival for observed patients is greater than 76% (69% reported).

Conclusions—Based on existing clinical evidence, sentinel node biopsy yields greater utility than excision alone and is cost-effective for patients presenting with solitary dermal melanoma.

Keywords

Solitary dermal melanoma; Decision analysis; Cost-effectiveness; Sentinel node biopsy; Melanoma

INTRODUCTION

Melanomas with an unknown skin primary site may present initially with nodal, visceral, or dermal disease, and comprise 2–6% of all melanomas [1–3]. The pathophysiology of these

cases is enigmatic, and therefore clinical staging may have several interpretations. These lesions may represent de novo malignancy originating from ectopic melanocytes (corresponding with stage II), in-transit disease with a spontaneously regressed primary (stage III), or distant metastasis with a regressed primary (stage IV) [4]. While some reports describe survival comparable to stage IV melanoma [5, 6], others note superior outcomes [2, 4, 7, 8].

Among these, the solitary dermal melanoma (SDM) subset comprises approximately 0.4–0.9% of all melanomas [2, 7, 9–11]. Due to unclear pathophysiology, the staging work-up for SDM is not standardized. Currently, the American Joint Committee on Cancer considers SDM a subset of stage III melanoma, a varied category that also includes regional and in-transit disease [12]. Sentinel lymph node biopsy (SNBx) is vital to the staging of intermediate thickness cutaneous melanomas. Not only is nodal status a strong prognostic indicator [13], recent data from the Multicenter Selective Lymphadenectomy Trial (MSLT-1) suggest that SNBx may improve disease-free survival [14]. More recently, SNBx for in-transit melanoma has received increasing attention, with early data suggesting prognostic and possibly therapeutic roles [15, 16]. Whether these promising results hold relevance to SDM's is unknown.

Outcomes data for SDM are dominated by small, single-center reports. Taken separately, the study sizes are too small to draw conclusions regarding the value of SNBx in SDM. However, in aggregate, this body of literature may provide adequate outcomes data to posit initial staging recommendations through decision analysis modeling. The purpose of this study is to combine institutional retrospective data with existing reports to assess the utility and cost-effectiveness of SNBx in the setting of SDM.

MATERIALS AND METHODS

Retrospective Data Collection

A review was performed of a prospectively collected database (IRB #10803) comprised of consecutive patients presenting with melanoma at the University of Virginia. The database was queried for patients whose primary site was unknown, yielding 135 cases. The diagnosis of SDM was defined by histologic evidence of melanoma limited to subcutaneous and/or dermal layers without epidermal involvement. Patients with more than one site of metastasis or concurrent visceral or nodal melanoma were excluded. Patients with a history of excisions for suspicious skin lesions were also excluded. The final cohort of 16 patients with SDM spanned the years 1996 to 2012. All patients underwent wide local excision, and were offered SNBx for regional staging. After resection, patients underwent follow-up every three months over the first year, then every six months thereafter. For all patients, demographic data, treatment course, and clinical outcomes were collected.

Literature Review

Outcomes and surgical staging data were gathered from articles referenced through the PubMed system using keywords “melanoma” and “unknown primary,” or “solitary dermal melanoma” to query all search fields. Of 491 articles returned, only original research articles

whose abstract presented long-term clinical outcomes of solitary dermal melanomas were included. Eight retrospective articles comprised the final dataset.

Length of follow-up, overall survival and rate of regional progression were abstracted from each article. Where available, data were subdivided into two groups: patients who underwent SNBx and those who did not. The rate of sentinel node positivity and survival outcomes within node-positive and node-negative subgroups were collected for patients who underwent SNBx. Annual rates of survival up to 5 years following resection were obtained from each article's narrative and/or Kaplan-Meier curves where available. Survival outcomes at each time point were averaged and weighted by sample size. Annual survival rates were converted to monthly rates by assuming a constant monthly rate of survival within each postoperative year. Identical methods were used to calculate monthly rates of regional recurrence. These data were pooled with institutional retrospective data to provide composite baseline estimates of model variables (Table 1).

Introduction to Markov Decision Models

A Markov decision model compares the expected utility and cost of two or more interventions by simulating the treatment and follow-up process [17]. Hypothetical patients representing a disease of interest are assigned to one of several treatment arms, and are then followed for a predetermined amount of time. Each increment of time during follow-up—i.e., one month, one year, etc—is represented by a Markov cycle. During follow-up, patients occupy various health states, such as disease-free survival, stage III disease, or death. Each health state is associated with utilities and costs that are derived from published literature and established cost structures. After each Markov cycle, patients may move from one health state to another. The likelihood of such moves are determined by transition variables (for example, rate of regional recurrence). By accruing the costs and utilities for each Markov cycle over the follow-up period, a decision model produces an expected total cost and utility associated with each treatment option.

Model Construction

For our study, a Markov decision model was created to simulate two management strategies for patients presenting with SDM: 1) wide local excision (WLE) followed by observation for recurrence and 2) WLE followed by SNBx (Figure 1A). In the baseline scenario, patients present with SDM of the upper extremity or chest draining to an axillary nodal basin. Subjects assigned to SNBx undergo surveillance for recurrence if sentinel node(s) are negative (N0), or completion lymph node dissection (CLND) followed by observation if at least one sentinel node is positive. For subjects assigned to observation, the development of regional macrometastatic disease (stage IIIC) prompts therapeutic lymph node dissection. Any patient who undergoes completion or therapeutic lymph node dissection may develop chronic lymphedema. Only the reported rates of moderate to severe lymphedema were applied to this model, as marginal lymphedema may not have a significant impact on quality of life [18–20]. In the baseline model, all patients with regional metastases (stage III) receive systemic high-dose interferon. However, while it is generally accepted that high-dose interferon confers a benefit to disease-free survival, data are conflicting regarding

impact on overall survival [21]. Acknowledging that some patients may forgo this therapy, a second model excluding interferon's benefits and disutilities was also analyzed.

Following either WLE plus SNBx or WLE alone, patients are followed for five years with each Markov cycle representing 1 month. Figure 1B depicts the available health states during follow-up. Transition rates, such as survival rate and progression rate, were derived from institutional data combined with data from published sources (Table 1) [1–3, 7, 9–11, 22]. All clinical transition rates were modeled in a time-dependent manner based on published Kaplan-Meier curves and textual reports where available. When data from primary literature were inadequate to posit SDM-specific transition rates (for example, rate of regional recurrence following negative SNBx), values were extrapolated from the known-primary melanoma literature [12, 14]. Follow-up terminated with either death or 5-year survival. Thus far, there are no reliable outcomes data for SDM beyond five years. The primary outcome was the expected number of discounted quality-adjusted life years (dQALY) over the first five years following treatment.

Costs and Utilities

Cost-effectiveness was the model's secondary outcome. Relevant costs are presented in Table 1. In concordance with National Comprehensive Cancer Network guidelines [23], patients undergoing surveillance for recurrence receive clinician follow-up every three months for the first six months, followed by every six months thereafter. Computed tomography of the chest, abdomen and pelvis is performed every six months, and magnetic resonance imaging of the brain is performed annually. Costs for WLE, SNBx, axillary CLND, clinician follow-up and radiographic imaging were derived from the Medicare physician fee schedule and Hospital Outpatient Prospective Payment System [24, 25]. Patients who experience chronic lymphedema incur additional management costs [26], while patients with regional metastases incur costs associated with high-dose systemic interferon therapy [27].

Disease-free survival, overall survival, and progression were the primary determinants of utility in the model. More mercurial outcomes such as psychosocial effects were not incorporated. The American Joint Committee on Cancer currently classifies SDM as regional disease [12]. Therefore, because 0.98 is the expected utility of melanoma with regional nodal metastases [28], this value was used as the utility for the node-negative health state. Disutilities associated with stage III disease, CLND, chronic lymphedema, and systemic interferon were assigned based on established literature when available [18, 19, 28–31], or expert investigator approximation (Table 1). These disutilities were allowed to change with time based on reports on temporal trends in morbidity and side-effect profiles.

Sensitivity Analysis

Because model variables may not accurately represent reality, sensitivity analyses for all transition variables, treatment variables, and utilities were performed across wide ranges of potential values. Using one-way sensitivity analyses, we tested whether the relative cost-effectiveness of the model's treatment strategies change as each variable's assigned value is allowed to fluctuate. In order to perform probabilistic sensitivity analyses, each variable's

baseline value was replaced with a probabilistic distribution. These distributions were defined by values 50% above and below the baseline value. By randomly sampling from these distributions and repeatedly processing the model, a confidence interval representing the likelihood of cost-effectiveness could be depicted. Willingness to pay (WTP) was set at \$50,000/dQALY. All analyses were conducted using TreeAge Pro 2014 (TreeAge Software, Inc). Retrospective data collection was approved by the University of Virginia Institutional Review Board (IRB protocol #10803).

RESULTS

Clinical Outcomes

Among the institutional cohort of 16 patients, 11 underwent SNBx. Median (interquartile range) follow-up was 3.4 years (1.4 – 6.3). Demographics and clinical outcomes are shown in Table 2. Three out of 11 SNBx's (27%) yielded at least one positive node. Among node-negative patients, one experienced late regional recurrence (12.5%). The Kaplan-Meier estimate for overall survival was 60% at 5 years. Estimates for survival at years one through five were incorporated into weighted averages from existing literature. Taken in aggregate, the 5-year survival rate for sentinel node-positive, sentinel node-negative, and observation-only patients across primary reports were 67%, 74%, and 69%, respectively (Table 3). The weighted average of the rate of sentinel node positivity was 0.158 [7, 10].

Utility and Cost-Effectiveness

In the baseline scenario, patients who choose SNBx accrue 3.85 dQALY over the first five years following intervention, compared to 3.66 dQALY for patients choosing observation. By the end of the five year time horizon, patients in the SNBx arm are more likely to reside in a disease-free state and less likely to have died than patients in the observation arm (Figure 2). Total cost associated with selecting SNBx is \$26,221, compared to \$22,557 for observation. Thus, SNBx is cost-effective, with an incremental cost-effectiveness ratio (ICER) of \$19,102/dQALY relative to observation. When the model is processed without interferon, SNBx remains the more effective strategy, yielding 3.86 dQALY versus 3.50 for observation with an ICER of \$11,876/dQALY.

Sensitivity Analysis

Sensitivity thresholds calculated with a WTP of \$50,000 are presented in Table 1. For example, SNBx is no longer cost-effective if greater than 23% (vs 16% reported) of procedures yield positive node(s), or if greater than 15% (vs 3.4% reported) of sentinel node-negative patients experience regional recurrence (false negative). The cost-effectiveness plane representing the distribution of probabilistic sensitivity analysis results is shown in Figure 3A. The results indicate that the likelihood that SNBx is cost-effective compared to observation is 78–95% over a WTP range of \$50,000 to \$100,000/dQALY (Figure 3B).

DISCUSSION

Results of this decision model support SNBx for surgical staging. Disutilities classically associated with SNBx, such as the adverse effects of adjuvant interferon, are offset by utility gained from accurate early staging and avoidance of morbidities associated with lymphadenectomy for macrometastatic disease [32]. Moreover, SNBx is cost-effective with a modest ICER when compared to observation for regional progression.

These results are built upon important assumptions. First, the baseline model incorporates a treatment algorithm that calls for completion lymph node dissection and high-dose interferon for micrometastatic disease. Although CLND is the current standard of care for such patients, high-dose interferon is not as widely recommended due to treatment-related morbidity. The supplementary model excluding interferon shows that SNBx remains relevant for patients forgoing this therapy. Indeed, avoiding the early cost and morbidity of interferon actually causes SNBx to be even more cost-effective. This finding is not unexpected, as prior works have shown the ICER of high-dose interferon to be greater than \$75,000 [27].

Second, disease state transition rates are derived from weighted averages of small, single-center retrospective studies. Because these studies report a wide range of clinical outcomes, sensitivity analyses are crucial. It is important to note, for example, that the threshold 5-year survival rate for patients choosing observation is 76%. This means that if additional reports show that patients who forgo SNBx experience 76% 5-year survival, then SNBx may no longer be the optimal strategy. In reality, it is unlikely that the model conclusions would change with new survival data. This is because an increase in the survival rate of patients forgoing SNBx will likely be associated with a concurrent increase in the survival rate of node-negative patients, thereby maintaining the utility advantage of SNBx. Similarly, although the rate of chronic lymphedema varies by dissection site [29, 33], sensitivity analyses show that this rate does not have an impact on model results. This insensitivity is due to reports that nodal dissections for palpable regional disease have a higher rate of lymphedema than completion dissections performed secondary to positive sentinel nodes [34]. A particularly under-represented variable is regional recurrence following negative SNBx. Only one prior study reported this value, noting one recurrence out of 30 at 5 years (3.3%) [10]. Given this paucity of data, outcomes from the known-primary literature were adopted, which may underestimate the true regional recurrence rate in SDM. Although model diagnostics suggest that the cost-effectiveness of SNBx is likely robust to potential amendments in outcomes data, sensitivity analyses are critical in identifying specific variables—such as regional recurrence—which are deserving of focused research.

Considering only those variables that have a realistic sensitivity threshold, the most important clinical variables are the rate of SNBx positivity and the likelihood of regional recurrence after a negative SNBx. These factors are intuitively relevant. The pathologic assessment of sentinel nodes is not widely standardized [35], and the clinical relevancy of micrometastases in sentinel nodes has recently come under focused attention [36]. If a large proportion of SNBx's yield positive nodes—i.e., increased sensitivity for micrometastases—a larger portion of patients may be subjected to CLND procedures which may not offer

meaningful therapeutic benefit. Existing data suggest that the rate of node positivity in SDM is likely less than the threshold value of 23%. With additional reporting, this statistic can be refined. Similarly, if a large fraction of negative SNBx's terminate in regional progression, then its utility as a staging tool is questionable. Regional recurrences in the setting of negative sentinel nodes are rare for melanomas with known primary [14, 37, 38]. Although similar trends exist for SDM [7, 10], additional reporting is necessary to improve data reliability.

This study's outcomes may be contextualized through prior works pertaining to melanomas of known primary. Using single-institution retrospective data, Agnese and colleagues reported an ICER of \$42,284 for SNBx in thin melanomas [39]. This population had a positive node identification rate of only 1.4%, compared to 16% in the present model. Certainly, the cost per life saved of a screening tool increases dramatically as pretest prevalence decreases. Morton and colleagues adopted MSLT-1 outcomes data to extrapolate 20-year utilities of SNBx for intermediate-thickness melanoma using a Markov decision model. Sentinel node biopsy was found to be cost-effective, yielding 0.44 additional dQALY over 20 years with an ICER of roughly \$2,500 [40]. Given its primary function as a staging tool, most of the benefit of SNBx should be realized over a prolonged follow-up period. As Figure 2 shows, distribution states increasingly favor SNBx over time. Therefore, it is not surprising that a decision model extrapolated to 20 years yields a lower ICER for SNBx than a 5-year model. As long-term SDM clinical outcomes become available, the cost-effectiveness of SNBx should be reassessed.

This study has several limitations. First, due to its rarity, SDM clinical outcomes are highly variable. However, sensitivity analyses indicate that the model's results are robust to potential deviations from baseline values. Nevertheless, revisiting the analysis after more data regarding SDM prognosis become available would be worthwhile. Second, the decision model is grounded within a set treatment and follow-up algorithm. Extrapolating the results for non-compliant patients or alternative surveillance protocols may be unsubstantiated. Third, the utility impact of CLND, lymphedema, and interferon may vary across individuals [28, 30]. While the present model captures the time-dependent nature of these variables, it does not simultaneously accommodate patient-level variations, as risk-adjustment models do not yet exist for SDM. It is also important to note that SNBx's potential benefits in this model are chiefly determined by survival, disease-free survival, and treatment morbidities. Less tangible corollaries of SNBx such as psychological or social effects may further increase the effectiveness of this procedure. Finally, due to the paucity of data pertaining to the rate of distant metastases from SDM, a Stage IV disease state was not modeled. Because SNBx has been associated with improved disease-free survival [14], the addition of a Stage IV disease state would most likely further inflate the utility advantage of SNBx.

CONCLUSIONS

Clinical data regarding solitary dermal melanoma are currently limited. Collaborative reporting of outcomes—most importantly the rate of positive sentinel node biopsy—is necessary to further solidify an optimal management strategy. However, existing evidence

supports sentinel lymph node biopsy as an adjunct to wide local excision for patients presenting with this infrequent disease.

ACKNOWLEDGEMENTS

This study was funded by NIH T32 CA163177 (to YH and PS).

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Figure 1.

A) Decision tree for solitary dermal melanoma (SDM). Each path terminates in a Markov model. B) Markov design. Patients undergoing observation following wide local excision (WLE) enter the model through surveillance. Those who undergo sentinel node biopsy (SNBx) enter via surveillance or completion lymphadenectomy (CLND) based on sentinel node status. Macronodular recurrence necessitates CLND. Following CLND, patients enter Stage IIIa or IIIc, with or without chronic lymphedema. Each non-operative disease state is associated with a corresponding monthly mortality rate.

Figure 2.

Markov disease state distributions. Over time, patients belonging to the sentinel node biopsy (SNBx) decision arm experience a higher likelihood of disease-free survival and a lower likelihood of death than patients in the observation (Obs) arm.

Figure 3.

A) Cost-effectiveness of sentinel lymph node biopsy (SNBx) relative to observation under probabilistic sensitivity analysis. Ellipse demarcates 95% confidence interval of results. Dashed lines indicate two thresholds of willingness-to-pay (WTP): \$50,000 and \$100,000. Markers to the right of each line represent estimates for which SNBx is cost-effective relative to observation. B) Cost-effectiveness acceptability curve for SNBx relative to

observation. Using a conservative WTP of \$50,000, SNBx has a 78% likelihood of being cost-effective.

Table 1

Model variables and sensitivity thresholds

Variable	Baseline Value	Sensitivity Threshold	Reported Range	Reference
5Y rate of progression:				
WLE regional recurrence	0.23	-	0.20 – 0.24	[10], ^b
SNBx (-) regional recurrence	0.034	< 0.15		[30]
WLE survival	0.69	< 0.76	0 – 1.00	[2, 3, 9–11, 15, 18], ^b
SNBx (-) survival	0.74	> 0.67	0.67 – 1.00	[7, 10], ^b
SNBx (+) survival	0.67	-	0.67	[10], ^b
Macronodules (IIIc) survival	0.40	-		[19]
Treatment variables:				
SNBx positive rate	0.16	< 0.23	0 – 0.27	[7, 10], ^b
Chronic lymphedema rate	0.18	-	0.08 – 0.30	[15, 16, 27, 37]
Utilities				
N0 resected surveillance	0.98	-		[25]
NX resected surveillance	0.96	-		^a
Resected regional disease (IIIA)	0.92	> 0.68		[25]
Resected regional disease (IIIC)	0.89	-		^a
CLND (month 1–12)	-0.05	> -0.46		^a , [27, 28]
Chronic lymphedema	-0.05	-		^a , [14, 15]
Interferon-α				
month 1–6	-0.15	> -0.45	0.04 – 0.19	[25, 29]
month 6–12	-0.08			
month 12–24	-0.04			
Costs (USD)				
Clinic follow-up	121.7			[22]
CT body	1208.4			[21, 22]
MRI head	542.3			[21, 22]
Lymphedema (monthly)	619.9			[23]
Wide local excision	880.4			[21, 22]
SNBx	2908.6			[21, 22]
CLND	4948.3			[21, 22]
Interferon, drug				
month 1	20670			[24]
month 2–12	2035			
Interferon, administration	1380			[24]

^aInvestigator approximation;^bInstitutional review

WLE: wide local excision; SNBx: sentinel node biopsy;

CLND: completion lymph node dissection

Table 2

Patient demographics and clinical outcomes

Variable	Median/N	IQR/%
Total	16	
Follow-up (years)	3.4	1.4 – 6.3
Age	64.9	55.4 – 70.7
Female	8	50.0%
Site of solitary dermal melanoma		
Upper Extremity	4	25.0%
Lower Extremity	5	31.3%
Chest/Abdomen/Back	5	31.3%
Head/Neck	2	12.5%
Sentinel biopsy performed	11	68.8%
Positive	3	27.3%
Recurrence		
Total	9	56.3%
Local	2	22.2%
In-transit	1	11.1%
Regional	2	22.2%
Distant	4	44.4%
5Y Disease-free survival		34.3%
Time to recurrence (months)	15.0	11.6 – 26.9
Kaplan Meier-Survival (all patients)		
Year 1		100%
Year 2		82%
Year 3		78%
Year 4		67%
Year 5		60%

Table 3

Time-dependent survival rates

Disease State	N	Survival Rate (Years after surgery)					Reference
		1	2	3	4	5	
WLE and observation	134	0.92	0.86	0.85	0.72	0.69	[1, 3, 9–11, 18, 37], <i>a</i>
SNBx (-)	86	1.00	0.90	0.80	0.74	0.74	[7, 10], <i>a</i>
SNBx (+)	23	0.91	0.91	0.74	0.67	0.67	[10], <i>a</i>
Macronodule (IlIc)	720	0.85	0.64	0.53	0.47	0.40	[19]

a Institutional review

WLE: wide local excision; SNBx: sentinel node biopsy