Comparative Effectiveness in Melanoma

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Abstract

The worldwide incidence of melanoma continues to rise. It is a leading cause of cancer death and the second leading cause of loss of productive years of life. Although the diagnosis of melanoma is straightforward, there remain many controversies regarding treatment and surveillance. This chapter addresses important questions in melanoma treatment such as sentinel lymph node biopsy, what to do with a positive sentinel lymph node, margins of resection for melanoma, radiation for primary, nodal and metastatic melanoma, and routine use imaging. Through this chapter, the evidence for these controversial subjects and the barriers to resolution will be elucidated.

Keywords

Melanoma · Sentinel lymph node · Completion lymphadenectomy · Melanoma margins · Melanoma radiation · Imaging for melanoma

Contents

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1 Introduction

Melanoma remains one of the most confounding of solid tumors. Essentially refractory to cytotoxic chemotherapy, with a variable sensitivity to radiation, surgery remains the most effective tool in the armamentarium against this disease. While it may be one of the most well studied of malignancies from a surgical standpoint, with five radomized prospective clinical trials evaluating margin of excision, questions continue to abound about the appropriate application of therapies.

Though evidence-based medicine and cost are of paramount concerns for the clinician and the patient, many well-tested therapeutic interventions have never been proven to impact patients in a definitive manner. In addition, some of the newest therapies are so costly that their benefit has to be evaluated in the context of the patient's value system (i.e., what exactly is the cost of quantity and quality of life?). Perhaps more significantly, many interventions that have regularly been performed by clinicians, such as routine staging in asymptomatic patients, have *never* been shown to improve outcomes or quality of life in almost *any* malignancy. The driver of these procedures, however, continues to be the patient, and the false perception that these studies may offer early detection and improved outcomes.

The debate surrounding many of these questions may never truly be answered. Some argue that this is because the question will cost more to answer than just proceeding in a semi-blind dogmatic manner or that clinical judgment is sufficient to determine whether 1 or 2 cm margin would be optimal in a given location. It is incumbent upon us, however, to do our best to address these questions. At the very least it is imperative that we recognize the uncertainty around them, so that we can counsel our patients wisely, and preferably proceed thoughtfully and deliberately to answer them.

2 Sentinel Lymph Node

Lymphoscintigraphy was successfully used to identify regional draining nodal basins in melanoma patients in 1977 [1]. It would take another 15 years until results demonstrating the reliability and reproducibility of sentinel lymph node biopsy for

melanoma were documented and led to the initiation of a prospective, randomized clinical trial [2]. In 2006, the initial results of the Multicenter Selective Lymphadenectomy Trial-1 (MSLT-1) were published and sentinel lymph node biopsy became the standard of care for patients with intermediate-thickness melanoma or in patients with thin melanoma and high-risk features. It is regarded as a safe and accurate procedure that allows for the evaluation of draining lymph nodes without exposing the patient to the morbidity of elective lymphadenectomy.

Sentinel lymph node status is the strongest prognostic factor in patients with melanoma and is used to stage patients in the American Joint Committee on Cancer (AJCC) guidelines. The introduction of this procedure has corresponded with a shift in survival curves for stage III patients that are likely a direct result of the routine use of the technique [3, 4]. Despite these changes, controversy continues to surround the routine use of sentinel node biopsy in patients with either thin (<1 mm) or thick (>4 mm) melanomas. The risk of a positive node in patients with thin melanomas is low enough that the risk-benefit consideration may not support routine use and the likelihood of systemic failure regardless of sentinel node status is so high in patients with thick melanomas that the benefit of the procedure is less definitive in this subpopulation of patients as well [3, 5].

3 Thin Melanomas and Sentinel Lymph Node

Thin melanomas account for nearly 70 % of all melanoma. In general, this population has excellent outcomes with a 90 % survival at 10 years [3, 6, 7]. Despite this success, 3–7 % of patients will develop regional disease. Performing sentinel lymph node biopsies on *all* patients with thin melanoma is not cost effective and would subject patients to the risks, albeit small, associated with the procedure. Ideally, a trial could address the optimal selection of patients in this population who would benefit from undergoing the procedure. Unfortunately, the number of patients required to discern a difference and the number of variables which would have to be accounted for makes such a study impossible. Factors that have been variably shown to increase the risk of nodal metastases in patients with thin melanomas include Breslow thickness ≥0.75 mm, Clark's level IV, ulceration, mitotic rate of one or more, vertical growth phase, lymphovascular invasion, and tumor regression [8–15] (Table 1).

Studies have reported an increased risk of nodal metastases in thin melanomas ≥0.75 mm when compared to <0.75 mm [8–10]. Han et al. [14] recently reported 6.3 % of melanomas ≥0.75 mm had positive lymph nodes, while only 2.5 % of melanomas <0.75 had positive lymph nodes. Other studies have reported rates of 5–15 % positive nodes for melanomas ≥0.75 mm, but 0–5 % for melanomas <0.75 mm [8–10, 12, 16–20] (Table 2). Positive nodes in melanomas <0.5 mm are even more unusual.

Table 1 Potential indications for sentinel lymph node biopsy in melanomas <1 mm

Biology	Depth	Patient
Ulceration	Positive deep margin	Excessive anxiety
Lymphovascular invasion	Regression	Age (younger)
Mitotic rate	Clark level IV or V	
Vertical growth phase	>0.75 mm	

Table 2 Rates of SLN positivity in thin melanomas and correlating characteristics

Study	Breslow thickness	Rate of SLN positivity (%)	Comments/other factors correlating with + SLN
Han et al. [8]	T1a < 0.76	0	Mitotic rate > 1/mm^2 ($p < 0.05$) Ulceration ($p < 0.05$)
	T1a ≥ 0.76	4.8	
	T1b < 0.76	18.2	
	T1b ≥ 0.76	12.5	
	T1 < 0.76	6	
	T1 ≥ 0.76	8.1	
Murali et al. [10]	0.51–0.74 mm	3.8	Lymphovascular invasion ($p = 0.018$)
	0.76–0.90 mm	5.3	
	0.91–1.00 mm	10.3	
Wright et al. [16]	<0.25 mm	8	Age < 50 ($p = 0.04$)
	0.25–0.50 mm	4	
	0.51–0.75 mm	4	
	0.76–1.00 mm	6	
Ranieri et al. [17]	<0.75 mm	2.3	Mitotic index > 6/mm^2 ($p = 0.006$) Clark level ($p = 0.01$)
	0.75–1.00 mm	10.2	
Wong et al. [18]	<0.75 mm	0	No other significant factors
	≤1 mm	3.6	
Hinz et al. [19]	<0.90 mm	0	No other significant factors
	0.90–1.00 mm	4.1	

SLN sentinel lymph node

Clark level has also been advocated by some as a predictor of nodal involvement in thin melanomas; however, the subjectivity of this classification has limited its utility. Ranges of SLN metastases in Clark level < IV are reported as 3.5–4.5 %, but this increases to 7.4–12.3 % in Clark level ≥ IV [14, 15, 17]. Additional studies have reported that Clark level is a predictor of disease when stratified by Breslow thickness to <0.75 and ≥0.75 mm [14]. Given this information, many continue to advocate for SLN biopsy with Clark IV tumors.

Although uncommon in thin melanomas, ulceration is a risk factor for more aggressive disease and secondarily, positive SLN. Yonick et al. [9] recently reported a five times increased risk in positive SLN in the presence of ulceration. Likewise, Han et al. [8, 14] reported ulceration increased the risk of a positive SLN. When stratified to Breslow thickness ≥0.75 mm, there was a 14.7% rate of nodal

positivity in patients with ulceration, whereas only 6 % of patients without ulceration had a positive SLN [8].

Mitotic rate was included in the most recent iteration of the AJCC staging system, being used to discriminate stage IB patients from stage IA [3]. Although correlative for metastatic potential and an independent predictor of survival, the overall contribution of mitotic figures to lymph node positivity is yet to be clearly defined [15, 21–23]. Other studies have found a slight but nonstatistically significant increases in SLN positivity or a significance only among patients with lymph node positive disease [8, 10]. This is an area where further research is necessary.

Tumor regression refers to the tumor loss associated with inflammatory stromal changes around a melanoma [12]. The prognostic significance of this phenomenon is not entirely clear and conflicting data abounds, but it remains another factor that may be considered when deciding if a SLN biopsy is necessary. While some studies have advocated for a more aggressive approach to sentinel lymph node biopsy in the setting of thin melanoma and mitotic figures, others have found this unwarranted [14, 24–26]. Although currently used at some sites to promote SLN biopsy, regression is not currently a criteria according to the National Comprehensive Cancer Network guidelines nor was it suggested by the consensus guidelines published jointly by the SSO and ASCO in 2012 [27, 28].

Despite a litany of histologic features which make a thin melanoma "high risk" the risk of nodal involvement, even in patients with these features, is low. Importantly, the risk of the procedure and the cost remain modest, at worst, and the impact of identifying disease early is significant on outcomes. The cost of delaying intervention in patients with nodal metastases is likely considerable, as well [29]. Given these considerations, the comparative effectiveness of sentinel node biopsy in thin melanoma patients is a question with an ambiguous answer and unfortunately, preconceived biases and limited alternative approaches deter additional studies attempting to review this question.

4 Thick Melanomas and Sentinel Lymph Node

Thick melanomas are described as Breslow thickness ≥4 mm. These patients have a significant risk of regional metastases (60–70 %) but an equally high risk of systemic disease (70 %). The high risk of systemic disease in this population has therefore led many authors to question the utility of sentinel lymph node biopsy in patients with melanomas greater than 4 mm in depth rationalizing that their prognosis is more strongly linked to progression to stage IV illness than to lymph node status [30, 31]. Because the survival of these patients is poor overall, Balch et al. [32, 33] initially hypothesized that locoregional management via nodal dissection was unlikely to confer survival benefit. However, two recent studies advocated that sentinel lymph node status—even in patients with thick melanoma—was found to be an independent predictor of survival [30, 31]. Gershenwald et al. [31] looked at 116 patients with melanoma >4 mm thick and found that sentinel lymph node status was still the most powerful predictor of overall survival by univariate and multivariate analyses.

Ferrone et al. [34] likewise looked at 126 patients with thick melanoma and found comparable rates of positive SLN (30 % vs. 39 %) and 3-year recurrence-free survival (76 % vs. 72 %). In the presence of conflicting data, many institutions routinely perform SLN biopsy even in those with thick primary tumors. With the advent of more robust therapeutic options for visceral disease and investigations demonstrating promising early results for genetic profiling of tumors, the role of surgical staging via sentinel lymph node biopsy becomes more ambiguous, generating a greater series of questions. The opportunity for early intervention in high-risk patients without the potential morbidity of surgical lymphadenectomy may pose a better alternative than the current paradigm in a subset of patients.

5 Overall Benefit of Sentinel Lymph Node Biopsy

The MSLT-1 trial has proven that early detection of regional metastases improves survival (Fig. 1); however, because the ability to select patients to undergo sentinel lymph node biopsy is impeded by the limitations of using histologic characteristics to determine biology, the procedure itself does not afford an overall survival benefit for all comers (intervention can only impact survival in the 17 % of patients who actually have nodal disease). This is compounded by the significant heterogeneity observed in the node positive group, which–with increasing recognition of microscopic and immunohistochemically detected disease, is likely to become more diverse. Survival in this group can range from 64 to 91 % depending on the population [35]. The resulting limitation of the sentinel lymph node procedure therefore, is that even in patients who are at the highest risk for having nodal metastases, nearly two-thirds will be undergoing a procedure that they do not need and, therefore, can derive no benefit. Within this context, the optimal improvement in this procedure will not be a technical one, but rather an intervention which aids in improving selection. Unfortunately, the ability to make this improvement will likely rely upon techniques other than histology such as genetic analyses or similar. Likewise, improvments in selection will be dependent on an ability to accrue large numbers of patients in order to discern even small differences in study groups. There is still much work to be done to define the group most likely to benefit from sentinel node biopsy.

To work this direction, we could use large database studies, using propensity scoring to match those undergoing sentinel- lymph node biopsy with similar controls. While pooling of clinical data from multiple institutions has been done by the American Joint Committee on Cancer (AJCC), using a larger data set and standardizing the pathology variables (in which there was previously wide variability), could help us find an answer. Decision analyses could also assist in this process, and could effectively summarize the costs, benefits, and probabilities of each branch point. Though it may be difficult to assign accurate probabilities to some of the more qualitative outcomes, such as quality of life and patient satisfaction, application of the decision sciences could be very productive in defining the proper use of sentinel lymph node biopsies.

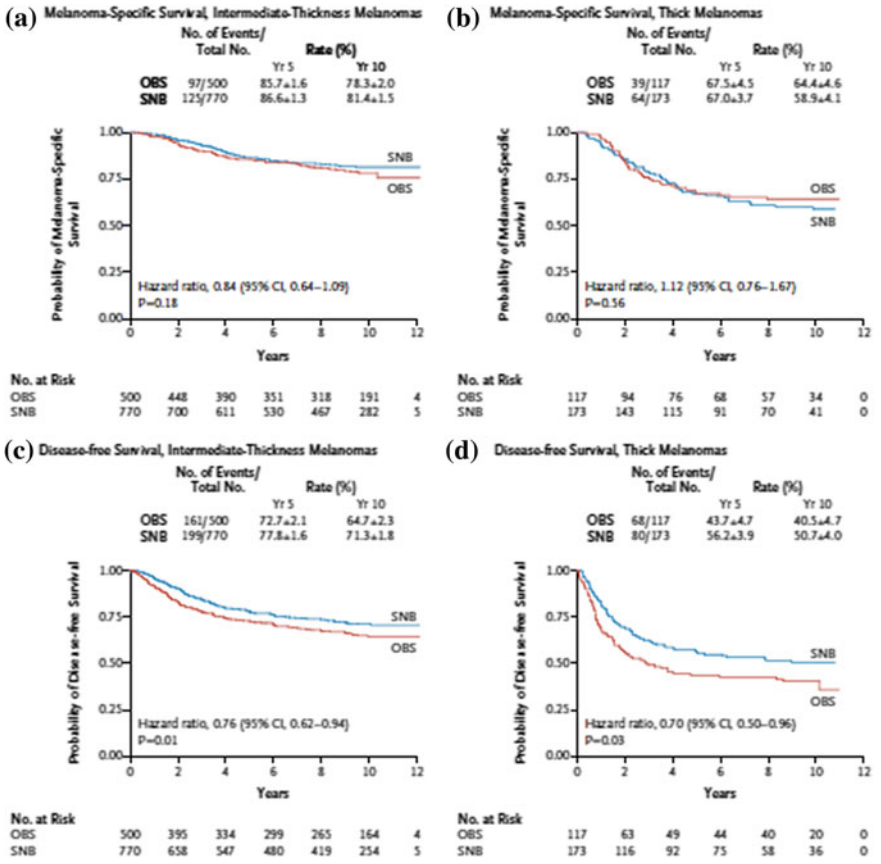

Fig. 1 Melanoma selective lymphadenectomy trial I (MSLT-1) results demonstrating both improved melanoma-specific survival and disease-free survival [29]. **a** Melanoma-specific survival, intermediate-thickness melanomas. **b** Melanoma-specific survival, thick melanomas. **c** Disease-free survival, intermediate-thickness melanomas. **d** Disease-free survival, thick melanomas

6 Completion Lymphadenectomy

The advent of sentinel node biopsy has made the management of nodal metastases even more controversial than the detection of nodal metastases. It is well recognized that in many diseases, management of regional disease is controversial (breast cancer, gastric cancer) and melanoma is similarly challenged. Using conventional histologic evaluation, only 20 % of patients undergoing CLND will have additional nodal disease, implying that as many as 80 % of SLN positive patients may be exposed to the risks of a second, more morbid procedure with potential long-term effects, without benefit. There are differences in the detection of metastatic deposits in sentinel nodes versus nodes in a completion lymphadenectomy specimen given

the more rigorous examination with immunohistochemistry and serial sectioning applied to sentinel nodes. One could argue, that without the more intense scrutiny of the completion lymph nodes that is applied to sentinel nodes, the true incidence of nodal involvement in CLND specimens is not known. As a result, regional disease management after a positive sentinel lymph node remains a discussion point.

Although one might extrapolate from the MSLT trial that there may be survival benefit to clearing the nodal basin with completion lymphadenectomy (early detection of disease impacts outcome which would imply some potential benefit to regional disease control), other studies have not been so forthcoming. Outside of MSLT, there fails to be a proven survival advantage for undergoing a completion lymphadenectomy. Van der Ploeg et al. [36] recently evaluated 1,174 patients with sentinel node positive melanoma, 61 of whom did not undergo completion lymph node dissection. Completion lymphadenectomy did not show any influence on survival (HR 0.86, 0.46–1.61; $P = 0.640$). Another multicenter trial examined 134 SLN positive patients at 16 centers who did not undergo completion lymphadenectomy and compared them against a cohort of patients from Memorial Sloan Kettering Cancer Center who had a positive SLN and underwent completion lymphadenectomy [37]. There was no difference in nodal recurrence-free survival between the groups ($P = 0.07$) or in the disease-specific survival between the groups ($P = 0.65$). Other studies have documented similar results with no difference in recurrence-free or disease-specific survival [4, 38].

Other studies have attempted to delineate characteristics of the sentinel lymph node which may predict involvement of nonsentinel lymph nodes. Additional factors such as tumor burden, depth of invasion from capsule, microanatomic location, and maximum diameter of the largest tumor have all been considered as predictors of additional lymph node disease [4, 39–41]. Nagaraj recently published a metaanalysis to determine clinicopathologic variables most predictive of nonsentinel node metastases in the setting of a positive sentinel node [42]. There were nine factors including ulceration, satellitosis, neurotropism, >1 positive SLN, angiolymphatic invasion, extensive locations, macrometasases >2 mm, extranodal extension, and capsular involvement which predicted additional positive nodes beyond the sentinel lymph node. Unfortunately, this makes for a complex set of prognosticators when attempting to decide on completion lymphadenectomy and may not be as useful practically. Van der Ploeg et al. published a more straightforward study demonstrating that the burden of disease and allocation of tumor within the sentinel lymph node influences melanoma-specific survival. Patients with metastases <0.1 mm and found in the subcapsular area had a 5-year overall survival of 91 %. Nonsentinel lymph node rates for these patients was 2 %. The study concluded that completion lymph node dissection in these patients may be overtreating patients who have a survival that is equivalent to SLN negative patients [43].

The current guidelines of the 2008 National Comprehensive Cancer Network recommend either CLND or participation in a clinical trial for a positive sentinel lymph node. Despite these recommendations, only 50 % of patients in the National Cancer Data Base with a positive sentinel lymph node actually undergo CLND, clearly indicating some disconnect between recommendations and practice [44].

Reasons for lack of CLND in SLN positive patients are variable. Kingham et al. looked at over 2,000 patients who had undergone SLN biopsy, where 317 patients had positive SLN followed by lymphadenectomy and 42 patients with positive SLN did not. The patients not undergoing CLND were older (median age 70 vs. 56 years, $p < 0.01$) and had a trend toward thicker melanoma (Breslow 3.5 vs. 2.8 mm, $p < 0.06$). Additionally, as expected, there were a higher percentage of lower extremity melanomas in the group that did not undergo CLND (40 % vs. 13 %; <0.01) since many surgeons avoid groin dissections secondary to their high risk of complications and lymphedema. Bilimoria et al. and Cormier et al. [44, 45] found similar reasons for lower than expected rates of CLND such as older age, lower extremity melanoma, thin melanomas, and African-American race.

Perhaps most importantly, these studies, when analyzed in the context of the others, provide an ambiguity to the overall benefit to the patient undergoing completion lymphadenectomy. A survival benefit has not been proven, morbidity from many lymphadenectomies is high, and few patients in the sentinel node era actually recur in the nodal basin making palliative interventions a low priority. It is a challenge to demonstrate an overall comparative effectiveness to completion lymphadenectomy and it will be a long time before any data is available to provide any insight. Obstacles to our understanding this in greater detail include inherent bias toward the MSLT-2 trial (patients are only referred for possible observation if they are perceived as "lower risk"), low incidence of events in this population necessitating a large patient population with extended follow up, and finally a long "tail" in which events can occur before data is conclusively determined to represent a comprehensive review. With these obstacles, there will be a considerable delay before the questions surrounding lymphadenectomy can be answered.

Similar to the issues regarding the optimal use of sentinel lymph node biopsy, the uncertainty around completion lymph node dissections need to be explored using alternative research methods. Studies that make use of large databases and pooled multi-institutional clinical data will help us avoid the bias inherent in MSLT-2 and the long follow-up time required for meaningful results. Decision analyses can also help us examine how we should guide our patient through the process of choosing a completion lymphadenectomy or not.

7 Margins of Resection

7.1 1 versus 2 cm Margins

Until the 1970s, wide excision of all melanoma with 3–5 cm margins was the standard [46]. In the 1970s, there was recognition that different Breslow's thickness and Clark's levels may guide the need for a wider excision. In 1980s, the World Health Organization (WHO) melanoma group organized a randomized prospective clinical trial to determine optimal margin resection (1 cm vs. 3 cm) for thin melanoma <2 mm thick [47, 48]. There was no statistically significant local recurrence

Table 3 Randomized trials in primary melanoma excision margins

Trial	Melanoma thickness (mm)	Margins of resection	Local recurrence	Overall survival
WHO [46–48]	<2	1 cm versus 3 cm	12 year	12 year
			1 cm—2.6 %	1 cm—85.1 %
			3 cm—0.1 %	3 cm—87.2 %
				$p = 0.77$
Intergroup trial [49, 50]	1–4	2 cm versus 4 cm	10 year	10 year
			2 cm—2.1 %	2 cm—79 %
			5 cm—1 %	5 cm—7.6 %
				$p = 0.07$
Swedish melanoma study group [53]	0.8–2	2 cm versus 5 cm	10 year	10 year
			2 cm—0.6 %	2 cm—79 %
			5 cm—1.0 %	5 cm—76 %
French cooperative group [52]	<2.1	2 cm versus 5 cm	10 year	10 year
			2 cm—0.62 %	2 cm—87 %
			5 cm—2.4 %	5 cm—86 %
				$p = 0.56$
United Kingdom melanoma study group [51]	>2	1 cm versus 3 cm	5 year	5 year
			1 cm—3.3 %	1 cm—68.2 %
			3 cm—2.8 %	3 cm—70 %
				$p = 0.60$

between the two margins. A follow-up study from 1998 confirmed an insignificantly higher (2.6 % vs. 0.98 %) risk of local recurrence in the narrow margin group with no difference in overall survival [46]. Meanwhile the Intergroup Melanoma Surgical Trial randomized 1–4 mm melanomas to 2 cm versus 4 cm excisions [49]. Neither the local recurrence (0.8 % vs. 1.7 %) nor the 5-year survival (79.5 % vs. 83.7 %) were statistically significant. A follow-up study in 2001 confirmed that neither 10-year local recurrence (2.1 % vs. 2.6 %) nor overall survival (70 % vs. 76 %) was statistically significant in the narrow excision or wide excision groups [50]. Finally, the United Kingdom Melanoma Study Group Trial found no difference in local recurrence (3.3 % vs. 2.8 %) or overall 5-year survival (68.2 % vs. 70 %) in 1 cm versus 3 cm resection margins in melanomas >2 mm [51]. When combining local and regional disease recurrence, however, there was a significant difference (37.1 % vs. 31 %; $p = 0.05$) between the groups. In overlapping these trials, the recommendations of a 1–2 cm wide local excision for a 1–2 mm melanoma were created, allowing clinicians the liberty of taking a 1 cm margin in cosmetically sensitive locations (Table 3).

Two additional trials looked at even wider margins (Table 3). The French cooperative group randomized patients with thin or intermediate melanomas to 2 cm versus 5 cm local excision and found there was no difference in tumor recurrence, disease-free survival or overall survival for lesions <2 mm [52]. This was again confirmed in the Swedish Melanoma Study Group which looked at 2 cm

Table 4 Current recommendations for margins of excision

Breslow thickness	Margin of excision
In situ	5 mm
<1 mm	1 cm
1–2 mm	1 or 2 cm
2–4 mm	2 cm
>4 mm	2 cm

versus 5 cm margins in melanoma ≤2.1 mm thick [53]. There was no difference in overall survival or disease-specific survival at 10 years.

No randomized trials have ever examined 1 cm versus 2 cm margins and, while an international trial has been written and proposed, accrual to this trial is considered to be an obstacle. This concern is largely based on the fact that most clinicians have a predisposition to use a 1 cm margin where anatomically or physically constrained. A single institution study recently validated these data [54]. Hudson et al. reviewed 2,118 patients with T2 melanoma who underwent 1 cm versus 2 cm wide local excision. With a median follow-up of 38 months, the local recurrence was 3.6 months in the 1 cm group and 0.9 % in the 2 cm margin group ($p = 0.044$); however, on multivariate analysis, this difference was no longer significant ($p = 0.368$). Overall 5-year survival, likewise, was not statistically significant (29.1 months vs. 43.7 months). This validated the current NCCN recommendations; however, given the biases and uncertainty of retrospective analyses, a randomized controlled trial is required to put this question to rest.

For lesions greater than 2 mm, there remained controversy over margins of excision. Thomas et al. [51] published the results of a multi-institutional randomized trial of 1 versus 3 cm surgical margins in melanoma >2 mm. In the 900 patient trial, a 1 cm margin was associated with a statistically significant risk of recurrence but no difference in overall survival. Unfortunately, this trial did not use sentinel lymph node biopsy, had a poor definition for what constituted "local recurrence," and greater than 60 % of the recurrences were actually nodal in nature, which makes its modern applicability questionable. Still dissatisfied with the question of a 2 versus 4 cm resection margin for lesions >2 mm, Gillian et al. [55] published a trial specifically looking at these margins to determine overall survival. They found no difference in overall survival or in the risk of recurrence or death due to melanoma when using a 2 cm resection margin versus a 4 cm resection margin.

Thus, while the studies have compared different margins of excision based on Breslow depth of tumor, it has been globally accepted that a 2 cm margin is acceptable for melanomas >2 mm (Table 4). There appears to be no change in survival or recurrence with this margin. Importantly, the rate of primary closure with these resection margins is much higher than a 4 cm margin, which is associated with increased rates of skin grafts and their associated complications.

Despite the consensus regarding these approaches, there is increased morbidity with larger excisions, greater cost to the patient, and more days off from work. The goal of an excision is to perform complete removal of the tumor, and as has been noted with other malignancies, we have frequently overshot that mark. There is a

considerable amount of data available on melanoma, but we are yet to find the smallest safe margin—which may even be less than 1 cm. At present, it will be extremely difficult to answer this question as biases have been set and although risks are definitely higher with larger excisions, the perceived morbidity is well tolerated.

However, if we could overcome these pre-conceptions, we could design a clinical trial similar to previous studies of wide local excisions, targeting cosmetically sensitive areas and patient populations that may be more willing to compromise in order to avoid wound healing issues or large grafts or flaps. There should also be efforts to design a trial that will tell us how deep a margin we truly need for a melanoma excision. In certain patients, on certain areas of the body (e.g., an obese patient with a thigh melanoma), it may not be necessary to excise all subcutaneous tissue down to the fascial level.

8 Radiation

8.1 Primary Cutaneous Melanoma

While the primary treatment of melanoma is surgical resection, radiation is often considered in both the primary and adjuvant setting. As the population ages, there are some elderly patients who are not candidates for surgical resection. In this scenario, there can be consideration for primary radiation therapy (RT) in patients with lentigo maligna and lentigo maligna melanoma. Small studies have shown that while the 5-year local recurrence rates are higher in patients treated with RT in head and neck melanoma, the difference may not be statistically significant (13.2 % vs. 6.8 %) [56]. This treatment is more often considered in Europe than in the United States.

Rates of local recurrence for cutaneous melanoma after appropriate wide local excision are approximately 5 %. However, there are certain conditions in which adjuvant radiation is considered including desmoplasia, neurotropism, microsatellites, positive resection margin not amenable to additional resection and recurrence after previous excision. Radiation is especially considered in cases of head and neck melanoma where further resection may simply not be feasible. Additionally, local control of lentigo maligna melanoma may be augmented with hypofractionated radiation [57]. Rao et al. [58] report that they are more likely to use radiation in patients with satellitosis because of the high risk of recurrence.

8.2 Radiation to Regional Nodal Basin

Studies have demonstrated benefit to adjuvant radiotherapy to regional nodal basins. Accepted criteria for this therapy include multiple positive nodes, large nodes, extracapsular extension, and recurrent disease. Recurrence rates of 60–80 % are reported for multiple nodes or nodes 6 cm or larger [59]. Likewise, extranodal extension is associated with an approximate 60 % recurrence rate [59, 60]. Finally, there are higher rates of relapses in the neck (35–45 %), whereas rates in the axilla

(25–35 %) and the groin (10–20 %) tend to be lower [59]. There are recent trials demonstrating decreased recurrence in high-risk nodal beds (multiple positive nodes, extracapsular extension, large nodes, or recurrent disease) [61, 62]. Burmeister et al. demonstrated a significant difference in reduced risk of lymph node field relapse to 16.3 % from 26.8 % (Hazard Ratio 0.56, 95 % confidence interval 0.32–0.98; $p = 0.41$), but no difference in relapse-free survival or overall survival in their randomized controlled trial.

Radiation is not without complications. Although cervical radiation is fairly well tolerated, complications are not infrequent in other sites. Complications following axillary radiation can be as high as 30 % at 5 years [58, 63]. In a study from the Melanoma Institute of Australia, arm lymphedema rates after axillary dissection with radiation were 53 % [64]. A similar study from MD Anderson demonstrated a 20 % incidence of lymphedema that necessitated medical treatment [65]. Complications in the groin after radiation and groin dissection can similarly be substantial, especially in those with a body mass index greater than 30 kg/m^2 [63]. Ballo et al. [66] demonstrated a 23 % incidence of clinically significant lymphedema after inguinal lymph node dissection and RT and a 40 % rate of clinically significant treatment-related complications of wound breakdown and healing complications. In the TROG study, Burmeister et al. [67] reported a 9 % incidence of lymphedema in patients with axillary disease undergoing lymphadenectomy and radiation. This number increases to a 19 % incidence of grade 3 lymphedema after ilioinguinal dissection and radiation. Although significant reductions in local recurrence are demonstrated, given these high complication rates, appropriate consideration should be given prior to instituting RT following lymphadenectomy. To balance the possible morbidity of this treatment against its benefits, more trial data would be helpful. Randomizing patients at a high risk of nodal disease (e.g., advanced Stage II) may help to delineate the limits of utility of this treatment in the clinical setting.

8.3 Brain Metastases

Up to half of patients with metastatic melanoma develop brain metastases [68]. Once brain metastases develop, the 1-year survival is less than 15 % [69]. Options for therapy include surgery, systemic therapy, whole brain radiation (WBR), and stereotactic radiosurgery. Although there are many studies on treatment of brain metastases, these often include multiple primary sites so applicability to metastatic melanoma in particular, may be limited.

8.4 Whole Brain

WBR has been described for many years in the treatment of metastatic lesions to the brain. When used alone, WBR does not have an appreciable survival benefit, but it can help with reducing symptoms and halting progression to allow for salvage

therapy. Median survival after WBR is 3–5 months [70–72]. The addition of temozolomide may afford a slightly higher median survival of 6 months with an approximate 10 % response rate [73]. Finally, a recent phase 2 study evaluated temozolomide, thalidomide, and WBR to patients with brain metastases from melanoma and found only a 7.6 response rate with a median time to progression of 7 weeks and a median overall survival of 4 months [74]. Complications from WBR include neurocognitive toxicity and progressive dementia [58, 75].

8.5 Stereotactic Radiosurgery

Both gamma knife and linear accelerator-based radiosurgery have been used for cerebral melanoma metastases. TROG 9508 was a randomized trial of patients with one to three brain metastases (5 % melanoma primary) to WBR with or without the addition of SBRT and found an improvement in performance status at 6 months for those that received both therapies, but no survival advantage with the addition of SBRT. In patients with a single lesion, there was a benefit to adding SBRT to WBR [76]. Other studies have shown an improvement in relapse-free survival with the combination of WBR and SBRT [77, 78]. Finally, several studies have retrospectively evaluated melanoma-specific brain metastases and found SBRT to be beneficial for local control of melanoma, especially in those with a good performance status and a limited number of lesions, as well as control of extracranial metastases [79].

In summary, radiation is rarely used as the primary treatment of melanoma. Its use in control of high-risk lesions, as well as high-risk nodal basins after surgical resection remains in evolution, but has not shown definitive survival benefit. RT for central nervous system metastases could become more standard of care as newer techniques such as intensity modulated RT and image-guided RT enable more precise delivery to tumor with avoidance of normal tissue.

9 Staging and Follow up

Perhaps one of the least controversial yet equally minimally evidence-based aspects of the care of melanoma patients is routine imaging and patient follow up. Several studies have demonstrated little utility to routine exams and there is no evidence that radiographic imaging benefits patients in any manner [80–83]. Of all endeavors in the care of patients with a history of malignancy, radiographic imaging may be the most costly and the least proven. It is important to note that the timing of imaging rarely impacts therapeutic decision-making and the majority of scans performed in asymptomatic patients are negative. Furthermore, there is growing concern regarding the side effects from the radiation associated with repeated thin-cut CT scans.

In melanoma, as with many malignancies, the routine physical exam in follow up rarely yields a significant finding. Patients are instructed to contact providers to let them know of changes in between routine appointments. It is most often these

interval evaluations that prompt further examination and investigation. Consider the scenario: in order for a routine visit to be the mechanism by which a patient identifies a recurrence or new lesion, the timing has to be that the lesion was first noticed within close proximity of the scheduled visit. Therefore, it is often the interval visits scheduled at the request of the patient that prompt additional testing for new concerns.

Perhaps most striking is that even with published NCCN guidelines many clinicians still routinely perform staging evaluations inclusive of aggressive radiographic imaging modalities in asymptomatic patients [83]. Even the most educated physicians who are aware of the evidence against routine scans will often acquiesce to radiographic studies "just to be sure." The solution to this is dependent on the education of the public—the public will need to understand that the routine scan has little benefit in the absence of symptoms—before the clamor for scans will begin to quiet. Despite these arguments against scanning, one cannot apply a value to the reassurance (false or real) provided by cross-sectional imaging. The ability to take a sigh of relief is an intangible, immeasurable quality that benefits patients and their families, despite the evidence against routine scans.

To determine the clinical utility of this practice, however, we need to perform rigorous cost-effective analyses and decision analyses. If findings of these speak against routine physical exam and imaging follow-up, the clinical conversation between surgical oncologist and patient will have to be accordingly tailored. Assessments of outcomes should then be performed; a recent Patient-Centered Outcomes Research Institute (PCORI) grant was giving to a project looking at patient self-management of distressing symptoms in centers treating breast, lung, prostate, and colon cancer. More projects in this vein could help to ease the anxiety that accompanies any cancer diagnosis.

10 Conclusion

As oncologists, we are faced with the challenges of decision-making in a less than informed environment. Charged with the task of applying evidence-based medicine in a field with a paucity of evidence and an enormous burden of bias, the challenge of making the right choices for our patients is overwhelming. It is unlikely that many of the questions in melanoma can be answered due to the complexity of the variables and the marginal differences expected. There are, however, opportunities for improving our understanding, enhancing our decision-making, and for the application of known data in a more effective manner. Importantly, these decisions cannot be made in the lay press and in the court of public opinion. It is imperative that knowledge be shared and choices be driven by data and not impression. Opportunities abound for investigation and the development of a better understanding of this disease and those must be pursued if we endeavor to provide the best care possible for patients.

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