Journal of Surgical Oncology 2004;86:212–223

Lessons Learned From the Sunbelt Melanoma Trial

KELLY M. McMASTERS, MD, PhD,[1]* R. DIRK NOYES, MD,[2] DOUGLAS S. REINTGEN, MD,[3] JAMES S. GOYDOS, MD,[4] PETER D. BEITSCH, MD,[5] B. SCOTT DAVIDSON, MD,[6] JEFFREY J. SUSSMAN, MD,[7] JEFFREY E. GERSHENWALD, MD,[8] AND MERRICK I. ROSS, MD[8] FOR THE SUNBELT MELANOMA TRIAL

[1]*The Department of Surgery, University of Louisville, James Graham Brown Cancer Center and Center for Advanced Surgical Technologies (CAST), Louisville, Kentucky*
[2]*The Department of Surgery, LDS Hospital, Salt Lake City, Utah*
[3]*The Department of Surgery, Lakeland Regional Cancer Center, Lakeland, Florida*
[4]*The Department of Surgery, Cancer Institute of New Jersey, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School*
[5]*The Department of Surgery, Dallas Surgical Group, Dallas, Texas*
[6]*The Department of Surgery, Mobile Infirmary Medical Center, Mobile, Alabama*
[7]*The Department of Surgery, University of Cincinnati, Mobile, Alabama*
[8]*The Department of Surgery, University of Texas, MD Anderson Cancer Center, Houston, Texas*

The Sunbelt Melanoma Trial is an ongoing multicenter prospective randomized trial that involves 79 centers and over 3600 patients from across the United States and Canada. This is one of the first large randomized studies to incorporate molecular staging using reverse transcriptase polymerase chain reaction (RT-PCR). While the results related to the primary endpoints of the study are not yet available, several analyses have shed light on many aspects of sentinel lymph node (SLN) biopsy and melanoma prognostic factors. In particular, we have developed a practical definition of sentinel nodes based on the degree of radioactivity. We have established the low rate of postoperative complications associated with SLN biopsy as compared to complete lymph node dissection. We have identified factors that predict the presence of SLN metastases. In contrast, we have been unable to identify factors that indicate a low risk of non-sentinel node metastases in patients with a positive sentinel node, suggesting that completion lymphadenectomy is appropriate for such patients. We have further established the value of identifying interval or in-transit sentinel nodes, which can be the only site of nodal metastasis. We have evaluated the particular challenges associated with SLN biopsy of head and neck melanomas, have evaluated the patterns of early recurrence, and have identified an interesting correlation between increasing patient age and a number of prognostic factors. Future analyses will evaluate the benefit of early therapeutic lymphadenectomy and early institution of adjuvant interferon alfa-2b therapy, as well as the validity of molecular staging.
J. Surg. Oncol. 2004;86:212–223.

KEY WORDS: **melanoma; sentinel lymph node; adjuvant therapy; interferon α-2b; lymphadenectomy**

SENTINEL LYMPH NODE (SLN) BIOPSY DETECTS EARLY NODAL METASTASES

Since the pioneering work of Morton et al. [1], SLN biopsy has become a routine method for staging the regional lymph nodes of patients with cutaneous melanoma. Lymphatic mapping with intradermal injections of technetium sulfur colloid and isosulfan blue identifies the first draining, or ''sentinel'' node, which is usually the

Grant sponsor: Schering Oncology Biotech; Grant sponsor: Center for Advanced Surgical Technologies of Norton Hospital, Louisville, KY.
*Correspondence to: Kelly M. McMasters, MD, PhD, University of Louisville-Brown Cancer Center, 315 E. Broadway, Suite 308, Louisville, KY 40202. Fax: 502-629-3379.
E-mail: kelly.mcmasters@nortonhealthcare.org
DOI 10.1002/jso.20084
Published online in Wiley InterScience (www.interscience.wiley.com).

first site and often the only site of metastatic disease. Intensive pathological evaluation of the SLN with serial sectioning and immunohistochemistry (IHC) allows accurate detection of nodal micrometastasis and selection of patients for complete lymphadenectomy. Thus, SLN biopsy allows us to identify early nodal metastases that would not have been detected in the past, when we relied on clinical staging or elective lymph node dissection. By focusing the pathologist's attention on the node(s) most likely to contain metastatic disease, we now find very early nodal micrometastases. Thus, the entire spectrum of stage III melanoma has shifted—from a population of patients with predominantly bulky, palpable lymph node metastases, to patients whose entire volume of metastatic disease is represented by a single microscopic focus of cancer in a single sentinel node.

MOLECULAR STAGING OF MELANOMA

In addition to intensive histopathology, there has been much interest in molecular staging of sentinel nodes. Reverse transcriptase polymerase chain reaction (RT-PCR) analysis of lymph nodes is a very sensitive molecular staging test that can detect one melanoma cell in 1 million normal cells. RT-PCR detects specific mRNA expressed by melanoma cells. It has been reported that RT-PCR detection of melanoma cells in histologically negative sentinel nodes correlates with decreased disease-free and overall survival [2,3]. Routine RT-PCR analysis of sentinel nodes may improve our ability to predict those stages I and II melanoma patients who are at higher risk for recurrence. RT-PCR analysis can also detect circulating melanoma cells in the bloodstream [4]. The ultimate prognostic significance of RT-PCR-detected nodal and circulating melanoma cells remains uncertain. Even more unclear is whether any treatment decisions should be based on molecular staging.

NODAL STAGING AND ADJUVANT THERAPY FOR MELANOMA

What additional therapy should be given when nodal metastases are detected? At this point in time, interferon α-2b therapy remains the only United States Food and Drug Administration (FDA)-approved agent for adjuvant therapy of high-risk melanoma patients. Patients with nodal metastases comprise the largest group of high-risk patients. This drug was approved by the FDA based upon the Eastern Cooperative Oncology Group (ECOG) Trial E1684, which demonstrated a disease-free and overall survival benefit for treatment with high dose interferon α-2b [5]. A follow up study, E1690, confirmed a disease-free survival benefit but did not demonstrate an overall survival benefit for patients treated with high dose interferon α-2b [6]. A third study, E1694, in which patients were randomized to a ganglioside vaccine (GMK) versus high dose interferon α-2b, has been reported [7]. In this interim analysis, interferon α-2b was associated with significantly improved disease-free and overall survival versus the vaccine. Considering these results, should all melanoma patients with nodal micrometastases or molecular detection of melanoma cells in the SLN receive high dose interferon? This remains an unanswered question.

IDENTIFICATION OF POPULATION THAT BENEFITS MOST FROM ADJUVANT INTERFERON α-2b

A significant concern regarding the E1684, E1690, and E1694 studies is that very heterogeneous patient populations were studied. The vast majority of patients had bulky, palpable nodal disease either synchronous with the primary tumor or recurrent at some time after the primary tumor had been previously excised. Very few patients had microscopically positive lymph nodes. These studies were performed prior to the widespread acceptance of SLN biopsy for nodal staging.

As SLN biopsy has become a standard practice in most major melanoma centers, very few patients with bulky palpable nodal disease are seen any longer. Therefore, the patients with stage III disease identified by SLN biopsy represent a significantly different population than that studied in E1684, E1690, and E1694. Such patients with very early SLN micrometastases in a single sentinel node appear to have a much better prognosis than patients with more advanced nodal disease (unpublished data). In fact, patients with a single microscopically positive SLN may not be truly ''high risk'' as defined in the past, but more ''intermediate risk'' for recurrent disease. Such a patient population has not truly been studied with high dose interferon. Because high dose interferon α-2b therapy is associated with significant toxicity and cost, it is appropriate to determine the degree to which patients with early nodal metastases benefit from the therapy. Even in light of the three randomized trials of high dose interferon α-2b, the risk/benefit ratio for patients with very early nodal metastases is not clear.

THE SUNBELT MELANOMA TRIAL

The Sunbelt Melanoma Trial is a multi-institutional, prospective randomized trial that integrates the advances in melanoma staging and adjuvant therapy. This study involves 79 centers in the United States and Canada. Over 3,600 patients have been enrolled in the study, which is now closed to new patient accrual. The principal goal is to use ultra-staging to identify those patients who will benefit most from adjuvant therapy. The central hypothesis is that adjuvant interferon α-2b therapy plus regional

lymph node dissection is more effective than lymph node dissection alone at prolonging disease-free and overall survival for patients with early nodal metastasis. Early nodal metastasis is defined as a single microscopically positive SLN only, or RT-PCR-only positive SLNs [8].

All patients less than 71 years old with melanoma ≥1.0 mm Breslow thickness, no palpable lymph nodes, no evidence of distant metastasis, and who are otherwise fit to receive interferon α-2b therapy are eligible (Fig. 1). At the time of lymphatic mapping and SLN biopsy, a portion of each SLN is frozen and stored for possible RT-PCR analysis at a later time. The remaining lymph node is examined by routine histology, serial sectioning, and IHC for S-100 protein. In addition, all patients undergo serial RT-PCR analysis of peripheral blood to detect circulating melanoma cells.

Patients with histologically or immunohistochemically positive SLNs are eligible for Protocol A. All patients undergo regional lymph node dissection. Patients with one histologically or immunohistochemically positive SLN as the only nodal metastasis are randomized to either observation or high dose adjuvant interferon α-2b therapy, with stratification by Breslow thickness (1.0–2.0 mm, >2.0–4.0 mm, or >4.0 mm) and ulceration.

Patients with more than one histologically or immunohistochemically positive SLN, any evidence of extracapsular extension of the tumor, or any non-SLN that contains metastatic melanoma are not randomized, but are treated with standard high dose interferon α-2b.

Patients with histologically and immunohistochemically negative SLNs are eligible for Protocol B. Markers analyzed include tyrosinase, MART1, Mage3, and gp100. A positive PCR test is defined as detection of tyrosinase, plus at least one other marker. If the SLN is negative by RT-PCR analysis, the patients are observed. If the SLN is positive by RT-PCR analysis, the patients are stratified by tumor thickness and ulceration, and randomized to one of three arms: observation, lymph node dissection, or lymph node dissection plus interferon α-2b (1 month, intravenous high dose only). Protocol B will not only define in a prospective fashion the natural history of patients with PCR-only positive SLNs, but will determine if adjuvant interferon α-2b therapy plus lymphadenectomy is superior to lymphadenectomy alone in terms of disease-free and overall survival.

This study offers a unique opportunity to use the advances in melanoma staging to determine the need for adjuvant therapy. In addition to the survival data related to the randomized treatment groups, a wealth of other important information will be generated from this

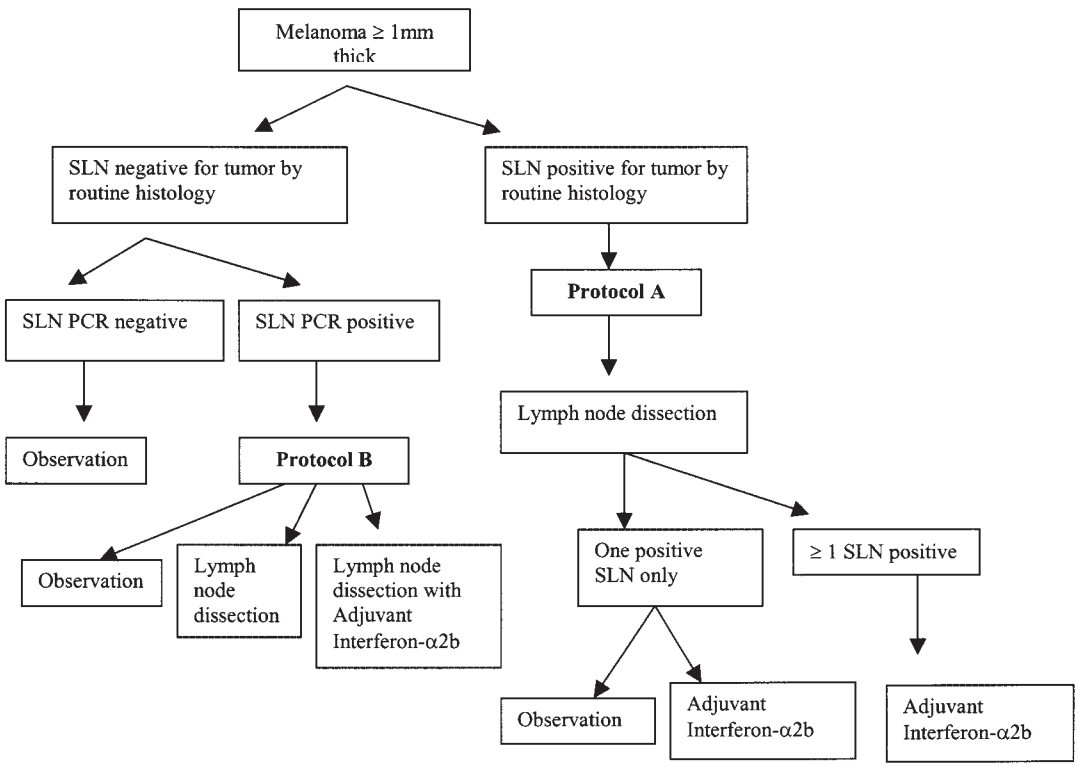

Fig. 1. Schema for the Sunbelt Melanoma Trial. Adapted from Ref. [8], with permission.

database. While we await the mature results regarding disease-free and overall survival of the randomized patients, which will require several more years of follow-up, we have performed several analyses that have improved our understanding of several features of SLN biopsy and melanoma.

WHICH NODES ARE REALLY SENTINEL NODES? THE 10% RULE

One very practical issue is that of defining which lymph nodes should be removed when SLN biopsy is performed. There is some controversy about the exact definition of a sentinel node. It has been suggested that the blue dye staining of the afferent lymphatic channel leading into the sentinel node is the sine qua non of a true sentinel node, because it indicates a direct lymphatic pathway from the site of the melanoma [9,10]. Yet it is clear that radioactive colloid injection with gamma probe detection frequently identifies sentinel nodes which would not have been detected with blue dye alone, and occasionally positive sentinel nodes are identified which have no evidence of blue dye staining. However, multiple sentinel nodes are often detected using the gamma probe. It is not clear whether these additional lymph nodes represent true sentinel nodes or second echelon lymph nodes, which have received radiocolloid particles that have passed through the true sentinel node.

We analyzed the Sunbelt Melanoma Trial database to determine the frequency with which these less radioactive lymph nodes contain metastatic disease when the most radioactive, or ''hottest'' node does not. In this analysis, 1,184 patients with cutaneous melanoma $\geq$1.0 mm Breslow thickness had SLNs identified. SLN biopsy was performed by injection of technetium sulfur colloid in addition to isosulfan blue dye in 99% of cases. Intraoperative determination of the degree of radioactivity of sentinel nodes (ex vivo) was measured, as well as the degree of blue dye staining [11].

Sentinel nodes were identified in 1,373 nodal basins in 1,184 patients. A total of 288/1,184 patients (24.3%) were found to have sentinel node metastases detected by histology or IHC. Nodal metastases were detected in 306 nodal basins in these 288 patients. There were 175 nodal basins from 170 patients in which at least one positive sentinel node was found and more than one sentinel node was harvested. Blue dye staining was found in 86.3% of the histologically positive sentinel nodes and 66.4% of the negative sentinel nodes. In 40/306 positive nodal basins (13.1%), the most radioactive sentinel node was negative for tumor when another less radioactive sentinel node was positive for tumor. In 20/40 cases (50%), the less radioactive positive sentinel node contained $\leq$50% of the radioactive counts of the hottest lymph node. The cervical lymph node basin was associated with an increased likelihood of finding a positive sentinel node other than the hottest node [11].

Table I demonstrates the impact of various definitions of a SLN on the detection of nodal metastases. Based on these data, we have defined the ''10% rule,'' which states that all blue lymph nodes, and all nodes that are $\geq$10% of the ex vivo radioactive count of the most radioactive (''hottest'') SLN should be harvested for optimal detection of nodal metastases. In addition, any palpably suspicious lymph nodes should also be removed at the time of SLN biopsy. If these guidelines are followed, it is very unlikely that nodal metastases will be missed. Despite concerns that the 10% rule would lead to removal of an inordinate number of radioactive lymph nodes that are not truly sentinel nodes, the average number of nodes removed is just over two per nodal basin. Interestingly, this 10% rule applies equally well to SLN biopsy for breast cancer [12].

TABLE I. Impact of Sentinel Node Definition on False Negative Results

Criteria for removal of sentinel nodes	No. of False negatives/no. of basins with positive nodes	False negative rate (%)[c]
A. Only hottest node removed	40/288[d]	13.9
B. Hottest node and all obviously blue nodes removed[a,b]	19/285[e]	6.7
C. Hottest node and all blue nodes removed[a]	6/285	2.1
D. 1st or 2nd SLN identified	5/288	1.7
E. All blue nodes and all nodes $\geq$10% of the hottest node	1/285	0.4

[a]This assumes that the faintly blue and/or obviously blue nodes would have been identified without the gamma probe, or that blue dye staining could be established prior to removing the node.
[b]Cases in which blue dye was not used have been excluded.
[c]The true false negative rate can only be determined by long term follow-up for recurrent nodal metastases in basins which are found to have negative sentinel nodes.
[d]All results are statistically different from category A and reduce the risk of false negative results ($P < 0.02$).
[e]Category B is statistically different from catetories C, D, E ($P < 0.01$).
Adapted from Ref. [11], with permission.

FACTORS PREDICTING SLN METASTASIS

Another important issue is to determine prognostic factors that predict the presence of SLN metastases, in order to better understand the population of patients most likely to benefit from SLN biopsy. Using the Sunbelt Melanoma Trial database, we performed univariate chi-square and multivariate logistic regression analyses to assess factors predictive of the presence of a positive SLN. Prognostic factors included in the statistical model were as follows: age, gender, site of primary tumor, Breslow thickness, Clark level, histologic subtype, vascular invasion, vertical growth phase, ulceration, regression, and number of draining nodal basins. Breslow thickness was examined as a categorical variable using the same classification as the AJCC/TMN staging system.

A total of 961 patients had complete data and were included in the statistical analysis. SLN were identified in 99.7% of patients. SLN were positive for tumor in 208/961 (22%) patients. Lymphatic drainage to more than one nodal basin was found in 14% of patients. By univariate analysis, age $\leq$60 years, increasing Breslow thickness, Clark level >III, unfavorable histologic subtype, lymphovascular invasion, vertical growth phase, ulceration, and greater than one nodal drainage basin were significantly associated with the presence of SLN metastasis. However, on logistic regression analysis, only age, Breslow thickness, Clark level, and ulceration were independently associated with the finding of a positive sentinel node (Table II). These covariates were entered into a stepwise logistic regression model, revealing that the independent predictors of SLN metastasis, in order of importance, were Breslow thickness ($P = 0.0008$), Clark level ($P = 0.0084$), ulceration ($P = 0.002$), and patient age ($P = 0.0091$). While Breslow thickness and ulceration have been demonstrated to be important prognostic factors predicting SLN metastasis in other series [14–16], the finding that Clark level and age were independent prognostic factors in this population of patients with melanomas $\geq$1.0 mm was novel [13].

From these data, we concluded that Breslow thickness, Clark level >III, the presence of ulceration, and patient age $\leq$60 years are independently associated with an increased risk of SLN metastasis. These factors should be taken into account when decisions regarding the need for SLN biopsy for nodal staging are made.

NODAL METASTASIS BEYOND THE SENTINEL NODES

The advantage of SLN biopsy in melanoma is that it spares approximately 80% of patients the need for complete regional lymphadenectomy while identifying those patients at highest risk. The presence of a positive sentinel node has been shown to be the single most important prognostic factor for recurrence and survival [17]. Those patients with positive SLN are appropriately selected for therapeutic completion lymph node dissection (CLND) and adjuvant therapy.

Previous studies have suggested that there may be some melanoma patients for whom CLND may not be necessary because nodal metastasis was never detected beyond the sentinel nodes [18–20]. We performed an analysis to determine, among patients with positive SLN, the frequency of nodal metastasis in the non-sentinel nodes (i.e., the nodes in the CLND specimen). Further, we sought to identify factors predictive of a minimal risk of non-sentinel node metastases.

TABLE II. Multivariate Logistic Regression Analysis of Factors Predictive of SLN Metastasis

Prognostic factor	Odds ratio	95% confidence intervals	*P* value
Breslow thickness			
1.0–2.0 versus >2.0–4.0	3.090	1.380–6.919	
1.0–2.0 versus >4.0	1.549	0.699–3.433	0.0005
Ulceration (absent vs. present)	2.224	1.441–3.432	0.0003
Clark level (II–III versus IV, V)	1.975	1.194–3.267	0.008
Age ($\leq$60 vs. >60 years)	0.520	0.322–0.842	0.008
Gender (male vs. female)	1.386	0.916–2.095	0.122
Primary site (axial vs. extremity)	0.737	0.483–1.125	0.157
Histologic subtype (all others vs. superficial spreading)	1.020	0.686–1.517	0.923
Lymphovascular invasion (absent vs. present)	1.592	0.916–2.765	0.099
Vertical growth phase (absent vs. present)	1.428	0.950–2.146	0.087
Regression (absent vs. present)	1.511	0.753–3.033	0.25
Number of Basins (1 vs. >1)	1.322	0.779–2.242	0.30

From Ref. [13] with permission.

This analysis included 274 patients with at least one positive SLN who underwent CLND of 282 involved regional nodal basins. Of the 282 SLN-positive nodal basins, 45 (16%) were found to have positive non-sentinel nodes in the CLND specimen. Breslow thickness, Clark level, presence of ulceration, histologic subtype, presence of vertical growth phase, evidence of regression, presence of lymphovascular invasion, number of positive SLN, age, gender, and presence of multiple draining nodal basins were not predictive of positive nodes in the CLND specimen. Patients with SLN metastases detected only by IHC for S100 protein had an equal likelihood of having positive non-sentinel nodes as those patients with positive SLN on standard hematoxylin and eosin (H&E) histopathological examination (Table III) [21].

From this analysis, we could not identify a patient population, based on standard clinicopathological factors, with minimal risk of non-SLN metastasis. Even patients with SLN micrometastases detected only by IHC had a significant (13.7%) risk of positive nodes in the CLND specimen. Therefore, it is our recommendation that, outside of a clinical trial, CLND should be performed routinely for patients with SLN metastases detected by H&E or IHC.

SENTINEL NODES OUTSIDE TRADITIONAL NODAL BASINS

Preoperative lymphoscintigraphy, a nuclear medicine scan, is performed routinely to identify the location of the SLN for patients with melanoma. Previous studies have demonstrated that lymphatic drainage patterns are not always accurately predicted on anatomic grounds, especially for melanomas of the trunk or head and neck [22,23]. While the majority of melanomas exhibit lymphatic drainage to traditional nodal basins (cervical, axillary, inguinal nodes), some patients have drainage to lymph nodes outside these basins [24–27]. Variously termed interval, in-transit, ectopic, or intercalated nodes, these lymph nodes outside traditional nodal basins sometimes contain metastatic disease, and may be the only site of nodal metastasis.

We analyzed the Sunbelt Melanoma Trial database to determine the frequency with which interval nodes are identified, and how often these nodes contain metastatic disease. SLN biopsy was guided by preoperative lymphoscintigraphy in all cases. Interval nodal sites, including epitrochlear and popliteal, as well as subcutaneous or intramuscular nodes outside of traditional basins, were evaluated for the presence of metastases.

SLN were identified in 2,332 nodal basins from 2,000 patients (Table IV). In 62/2,000 (3.1%) patients, interval SLN were identified. SLN metastases were found in 442/2,270 (19%) traditional nodal basins, and 13/62 (21%) interval sites. In 11/13 (85%) cases in which a positive interval node was found, it was the only site of nodal metastasis [28] (Table V).

Although interval SLN are identified infrequently, they contain metastatic disease at nearly the same frequency as SLN in cervical, axillary, and inguinal nodal basins. When a positive interval SLN is found, it is likely to be the only site of nodal metastasis. Therefore, we conclude that detailed preoperative lymphoscintigraphy and meticulous intraoperative search for interval nodes should be performed for all patients who undergo SLN biopsy for melanoma.

IS SLN BIOPSY REALLY LESS MORBID THAN COMPLETE REGIONAL LYMPH NODE DISSECTION?

The morbidity of regional node dissection is considerable. Studies have reported a complication rate from 25 to 61% following lymph node dissection [29–35]. Wound complications, lymphedema, and other complications are common. SLN biopsy is a minimally invasive procedure and is presumed to have the limited morbidity associated with a lymph node biopsy. Although it is often stated that SLN biopsy is associated with few complications, not much published evidence exists to substantiate this claim.

We analyzed the Sunbelt Melanoma Trial database to evaluate the morbidity associated with SLN biopsy. Patients underwent SLN biopsy, and were prospectively followed for the development of complications associated with this technique. Patients who had evidence of nodal metastasis in the SLN underwent CLND. Complications associated with SLN biopsy alone were

TABLE III. CLND Results in Patients With IHC-Only Positive SLN

Method by which SLN metastasis were detected	Positive non-sentinel nodes (%)
H&E	38/231 (16.5%)[a]
IHC only	7/51 (13.7%)

[a] $P = 0.63$, Chi-square.
From Ref. [21] with permission.

TABLE IV. Frequency of Interval SLN by Site of the Primary Tumor

Primary tumor site	No. of Patients	No. of patients with in transit sites (%)
Upper extremity	423	16 (3.8%)
Lower extremity	457	9 (2.0%)
Trunk	901	24 (2.7%)
Head and neck	219	15 (6.8%)
Total	2,000	64 (3.2%)

From Ref. [28] with permission.

TABLE V. Comparison of Nodal Metastasis in Traditional Nodal Basins versus Interval Nodes

Primary tumor site	SLN positivity in conventional nodal basins (cervical, axillary, and inguinal) Positive SLN/total nodal basins (%)	SLN positivity at interval nodal sites Positive interval SLN/total interval nodal sites (%)
Upper extremity	68/425 (16%)	1/16 (6%)
Lower extremity	100/463 (22%)	2/9 (22%)
Trunk	243/1,149 (21%)	5/24 (21%)
Head and neck	31/233 (13%)	5/15 (33%)*
Total	442/2,270 (19%)	13/62 (21%)

*$P < 0.05$ versus conventional nodal basins, Fisher's Exact Test.
Adapted from Ref. [28] with permission.

compared to those associated with SLN biopsy plus CLND.

A total of 2,120 patients were evaluated, with a median follow-up of 16 months. Overall, 96/2,120 patients (4.6%) developed major or minor complications associated with SLN biopsy, while 103/444 patients (23.2%) experienced complications after CLND (Table VI). There were no deaths associated with either procedure [36].

While SLN biopsy is not without morbidity, most of the complications associated with SLN biopsy are minor. One previous study of 200 consecutive SLN biopsies for melanoma identified a 9% complication rate [37]. Our study found a somewhat lower complication rate, at 4.6%. Hematoma and seroma formation is the most frequent complication, which usually is of no long-term consequence. Lymphedema after SLN biopsy alone appears to be rare. One study reported a 1.7% incidence of lymphedema associated with SLN biopsy for melanoma [38]. We found a 0.7% risk of lymphedema among patients undergoing axillary or inguinal SLN biopsy. It should be noted that, in the Sunbelt Trial, lymphedema was not evaluated by prospective evaluation of limb volume or circumference, but was defined as clinically apparent swelling of the extremity based on history and physical examination. Nevertheless, the rates of lymphedema reported in the Sunbelt Melanoma Trial following axillary and inguinal CLND were 4.6 and 31.5%, respectively, within the ranges reported in other studies [29–35].

Allergic reactions to isosulfan blue dye reportedly occur in about 1.5% of cases, although most are mild allergic reactions. Leong et al. [39] reported a 1% incidence of anaphylaxis to isosulfan blue dye: three cases in a series of 406 patients during lymphatic mapping for melanoma. To date, we have had only one allergic reaction, attributed to blue dye, in over 3,600 patients in the Sunbelt Melanoma Trial.

Overall, this analysis indicated that the morbidity of SLN biopsy is substantially less than that of CLND. Most complications of SLN biopsy are minor, and easily managed. This was the first large report from a large

TABLE VI. Complications Associated With SLN Biopsy and CLND

Complication[a]	SLN Complications no. (%)	CLND Complications no. (%)	*P* value[b]
Total patients with complications	98/2,120 (4.6%)	103/444 (23.2%)	<0.0001
Wound separation	5 (0.24%)	7 (1.58%)	0.001
Wound infection	23 (1.08%)	31 (6.98%)	<0.0001
Severe infection	0	6 (1.35%)	<0.0001
Hemorrhage	2 (0.09%)	2 (0.45%)	0.12
Lymphedema	14 (0.66%)	52 (11.7%)	<0.0001
Hematoma/seroma	49 (2.31%)	26 (5.9%)	0.0002
Skin graft requirement	0	0	—
Thrombophlebitis	2 (0.09%)	0	0.68
Deep venous thrombosis	2 (0.09%)	1 (0.23%)	0.36
Pneumonia	0	0	—
Urinary tract infection	0	1 (0.23%)	0.17
Cardiac complication	0	0	—
Pulmonary complication	3 (0.14%)	0	0.57
Sensory nerve injury	3 (0.14%)	8 (1.8%)	<0.0001
Motor nerve injury	2 (0.09%)	2 (0.45%)	0.12
Other	9 (0.42%)	18 (4.1%)	<0.0001

[a]Because some patients had more than one complication, the percentages for individual complications are calculated from the total number of complications.
[b]Fisher's Exact Test.
From Ref. [36] with permission.

multicenter study to substantiate the claim that SLN biopsy is less morbid than regional lymphadenectomy.

SLN BIOPSY FOR HEAD AND NECK MELANOMAS

Melanomas of the head and neck (H&N) pose unique surgical challenges. The very rich and complex lymphatic and vascular drainage in this region of the body may account for the well-known but not well-understood phenomenon: H&N melanomas are associated with increased likelihood of recurrence and diminished overall survival compared to other sites [1].

With the advent of lymphoscintigraphy, it became apparent that anatomic predictions of nodal drainage are not always reliable. This is especially true of H&N melanomas. Discordance between clinically predicted basins and actual drainage basins is commonly attributed to complex lymphatic drainage patterns [22,41–43]. We hypothesized that because SLN staging for H&N melanomas may be more challenging due to the variable lymphatic drainage, same-basin recurrence rates after a negative SLN biopsy (false negative results) may be higher compared to melanomas in other sites. The purpose of this analysis was to compare SLN biopsy results and same-basin recurrence rates in H&N melanomas with those for truncal and extremity melanomas.

A total of 2,784 patients were evaluated with a median follow-up of 18 months. The mean number of SLN per nodal basin was 2.8, 2.7, and 2.1 for H&N, truncal, and extremity melanomas, respectively. Median Clark level, Breslow thickness and presence of ulceration were similar among the groups. Peri-parotid SLN were identified in 25% of cases; there were no facial nerve injuries. SLN biopsy for H&N melanoma had higher false negative rates at 1.5% (vs. 0.5% for trunk or extremity) but fewer histologically positive SLN at 15% (vs. 23.4 and 19.5%; $P < 0.001$) compared with truncal and extremity melanoma (Table VII). Blue dye was visualized less frequently in SLN of H&N melanoma patients compared to those with trunk or extremity melanomas [44].

The incidence of same basin nodal recurrences after a negative SLN biopsy has ranged from 0 to 25% in other studies [22,45–47]. In our study, the incidence was 1.9% with a median follow-up of 18 months. This was significantly higher than the incidence of same basin recurrences in trunk and extremity melanomas (0.5% each, $P < 0.05$). Technical variations, differing types of radioactive colloid, and differences in the follow-up period in these studies may explain, in part, the differences in results. The relatively short follow-up period in the Sunbelt study also must be considered, and the differences in these same basin recurrence rates may become more pronounced with further follow-up. Although the incidence of same basin recurrences was slightly greater for H&N melanomas versus other locations, the degree of accuracy of nodal staging for H&N melanomas was acceptable.

In summary, H&N melanomas are associated with a lower rate of positive SLN, even though most primary tumor prognostic factors (i.e., Breslow thickness and ulceration) are not different compared to truncal and extremity melanomas. SLN from patients with H&N melanomas are less likely to contain visible blue dye staining. H&N melanomas are associated with a slightly greater risk of false negative results, despite removal of a greater number of SLN. This study underscores the importance of attention to the technical aspects of SLN biopsy in H&N melanomas: detailed preoperative lymphoscintigraphy, prompt search for blue nodes, and thorough knowledge of the anatomy of the region. Such technical factors are likely to improve the results of SLN staging of H&N melanomas.

PATTERNS OF EARLY RECURRENCE

In yet another analysis, we sought to establish the patterns of early recurrence after SLN biopsy for melanoma. Overall, there were 1,183 patients with a median follow-up of 16 months. SLN were positive in 233/1,183 patients

TABLE VII. SLN Mapping and Metastasis by Primary Site

Variable	H&N	Trunk	Extremity	*P* value
SLN Pos by H&E[a]	38/287 (13.2%)	225/1,104 (20.4%)	186/1,098 (16.9%)	$P \leq 0.01$
SLN Pos by IHC only[a]	5/287 (1.7%)	33/1,104 (3.0%)	28/1,098 (2.6%)	$P =$ NS
Total SLN Pos by H&E or IHC[a]	43/287 (15.0%)	258/1,104 (23.4%)	214/1,098 (19.5%)	$P \leq 0.01$
Mean no. of nodal basins/pt	1.17	1.29	1.05	$P \leq 0.01$
Mean no. of SLN/pt	2.83	2.72	2.14	$P \leq 0.01$
% SLN stained blue[b]	59.2%	68.6%	74.0%	$P \leq 0.01$
"False Negative"[c]	6/321 (1.9%)	6/1,141 (0.5%)	7/1,148 (0.5%)	$P < 0.05$

NS, not significant.
[a]The smaller denominators in these categories reflect the inclusion of only evaluable cases in which complete H&E and IHC data were available.
[b]Among patients injected with blue dye.
[c]"False negative": tumor recurrence in a basin staged to be SLN negative.
Adapted from Ref. [44], with permission.

(20%). The recurrence rate was greater among patients with histologically positive SLN than those with negative SLN (15.5 vs. 6.0%, respectively, $P < 0.05$). Patients with positive SLN were more likely to have distant metastases (as opposed to locoregional recurrence) than those with negative SLN (67 vs. 46%, respectively, $P < 0.05$). By multivariate analysis, SLN status, Breslow thickness, Clark level, and ulceration were significant independent factors associated with early recurrence (Table VIII). Completion lymphadenectomy after finding a positive SLN effectively prevented early regional lymph node recurrence [48].

From this analysis, we concluded that patients with positive SLN are more likely than those with negative SLN to develop both local/in-transit recurrence and distant metastases within a short follow-up period. Nodal status, Breslow thickness, Clark level, and ulceration are independent predictors of early recurrence. Longer follow-up is necessary to determine the factors associated with overall survival.

AGE AND PROGNOSTIC FACTORS

It has been shown previously that age of patients with melanoma varies directly with mortality and inversely with the presence of SLN metastasis [49]. To gain further insight into this apparent paradox, we analyzed the relationship between age and other major prognostic factors.

A total of 3,076 patients were enrolled in the study with a median follow-up of 19 months. Five age groups were examined: 18–30, 31–40, 41–50, 51–60, 61–70 years. A strong linear correlation between age and several key prognostic factors was identified (Figure 2): As age increased, so did Breslow thickness (ANOVA, $P < 0.001$), the incidence of ulceration ($P < 0.001$), the incidence of regression ($P < 0.001$), and the proportion of male patients ($P < 0.001$). The incidence of SLN metastasis, however, declined with increasing age ($P < 0.001$) [50].

TABLE VIII. Logistic Regression/Multivariate Analysis of Factors Predicting Early Recurrence

Variable	Odds ratio (95% confidence intervals)	*P* value
Age		
<60 versus >60 years	0.861 (0.546–1.357)	0.5188
Gender		
Male versus female	0.976 (0.624–1.526)	0.9146
Breslow thickness		
1–2 versus >4	2.477 (1.369–4.485)	0.0111
2–4 versus >4	1.718 (0.968–3.050)	
Clark level		
I–III versus IV–V	2.231 (1.148–4.333)	0.0179
Ulceration		
No versus yes	2.209 (1.424–3.427)	0.0004
Vertical growth phase		
No versus yes	0.885 (0.556–1.409)	0.6071
Primary melanoma site		
Extremity versus non-extremity	1.347 (0.870–2.085)	0.1822
SLN		
Positive versus negative	2.763 (1.797–4.249)	<0.0001
Number lymph node positive		
1 versus ≥2	2.706 (1.367–5.357)	0.0043

From Ref. [48], with permission.

As age increases, so does Breslow thickness, the incidence of ulceration and regression, and the proportion of male patients—all poor prognostic factors. However, the frequency of SLN metastasis declines with increasing age. It is not known whether this represents a decreased sensitivity of the SLN procedure in older patients or a different biological behavior of melanomas in older patients. These data suggest a hypothesis that with increasing age, melanoma may metastasize more frequently via hematogenous spread without concomitant nodal metastasis. This hypothesis will be evaluated with longer follow-up for patterns of recurrence and overall survival.

OTHER IMPORTANT LESSONS FROM THE SUNBELT MELANOMA TRIAL

Despite all the interesting findings detailed above, and the promise of much more important information to come, there is another lesson that has been learned from this endeavor that has broader implications. The Sunbelt Melanoma Trial developed as a truly grass roots effort in the surgical oncology community to study SLN biopsy and adjuvant therapy for melanoma. The Sunbelt Melanoma Trial and Dr. Donald Morton's Multicenter Selective Lymphadenectomy Trial (MSLT) [51], represented the first large surgeon-led studies in melanoma since the Intergroup Melanoma Surgical Trial, directed by Dr. Charles Balch [52]. These were important developments, re-establishing surgical oncologists' involvement in defining the appropriate direction for clinical research in the field of melanoma. Because surgical oncologists often remain involved in patient follow-up for a lifetime, it only makes sense that they should remain intimately involved in adjuvant therapy studies.

Yet the surgical oncologists often found themselves only peripherally involved in clinical research. When the Sunbelt Melanoma Trial was initiated in 1997, few of the Sunbelt surgical oncologists participated in any other clinical studies. The Sunbelt Melanoma Trial provided their first opportunity to develop a clinical trial infrastructure to enter patients into randomized trials.

What we have learned since then is that surgical oncologists are exquisitely interested, willing, and able to perform clinical trials in an attempt to improve the outcome of their patients. Although accrual to the Sunbelt

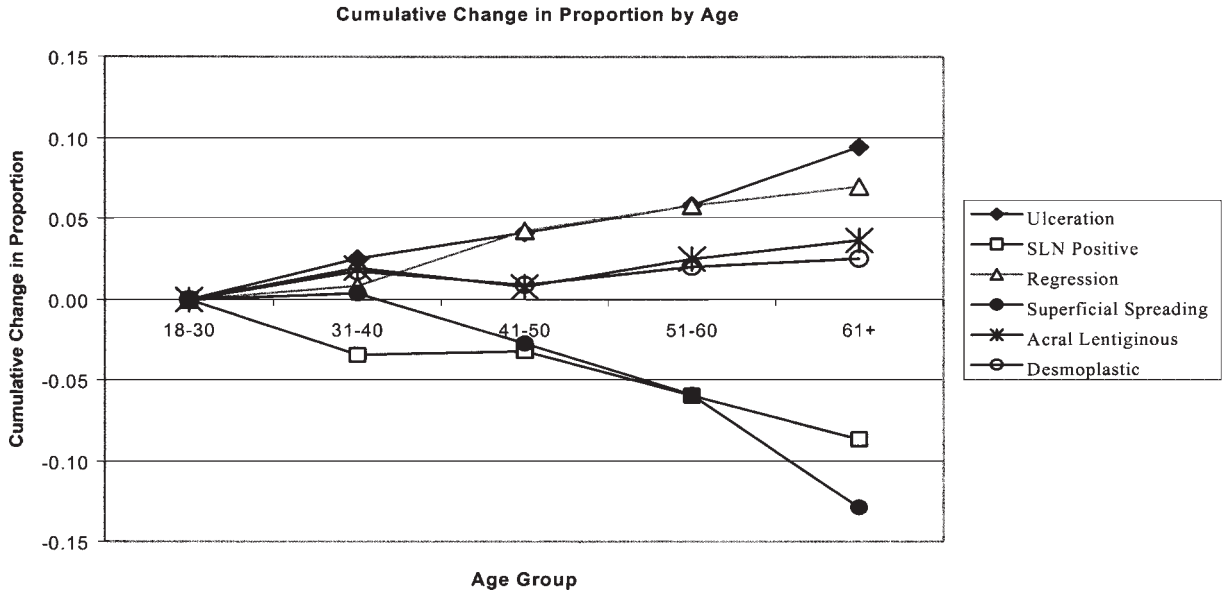

Fig. 2. Correlation between age and various prognostic factors. From Ref. [50], with permission.

Melanoma Trial has now been discontinued, and we ultimately fell short of our extended accrual goals in terms of randomized patients, the fact that over 3,600 melanoma patients were entered into a highly complex clinical trial in 6 years is rather remarkable. It is even more remarkable when one considers that much of this work was supported by the surgical oncologists and their institutions, because the level of funding was often not sufficient to cover the costs of enrolling patients. This indicates an extraordinary level of motivation on the part of the surgical oncology community to participate in clinical research. It also implies that that the same spirit that inspired creation of the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Intergroup Melanoma Surgical Trial [52] is alive and well in the surgical oncology community.

This, therefore, is perhaps the most important lesson from the Sunbelt Melanoma Trial. Surgical oncologists can and should perform clinical research. Surgical oncologists should be involved in adjuvant therapy studies. It is hoped that the same level of enthusiasm and participation demonstrated in the Sunbelt Melanoma Trial will extend to the American College of Surgeons Oncology Group, which now is available to support such large scale clinical studies.

ACKNOWLEDGMENTS

We thank Deborah Hulsewede, Debra Williams, Sherri Matthews, and Kristy Greenwell, and Lee Hagendoorn for their exceptional efforts in running the Sunbelt Melanoma Trial Operations Center. We are grateful for the active and ongoing participation of all the Sunbelt Melanoma Trial investigators: Gerald Aranha, MD, Loyola University Medical Center, Maywood, IL; Stephan Ariyan, MD, Yale University, New Haven, CT; Frederick Aronson, MD, Maine Center for Cancer Care, Scarborough, ME; Michael B. Atkins, MD, Beth Israel Deaconess Medical Center, Boston, MA; Bruce Averbook, MD, Metro Health Medical Center, Cleveland, OH; Yona Barash, MD, Mercy San Juan Hospital, Carmichael, CA; Paul Baron, MD, Roper Hospital, Charleston, SC; Derrick Beech, MD, University of Tennessee-Memphis Medical Center, Memphis, TN; Mansoor H. Beg, MD, North Shore University Hospital, Great Neck, NY; Peter D. Beitsch, MD, Dallas Surgical Group (St. Paul Med), Dallas, TX; John L. Bell, MD, UT Medical Center, Knoxville, TN; Marc Boisvert, MD, Washington Cancer Institute, Washington, DC; Richard A. Bold, MD, UC Davis Cancer Center, Sacramento, CA; Ralph Broadwater, MD, Arkansas Cancer Research Center, Little Rock, AR; Ned Z. Carp, MD, Lankenau Hospital, Wynnewood, PA; A. Lawrence Cervino, MD, Summa Health Systems/Akron, Akron, OH; David Z.J. Chu, MD, City of Hope National Center, Duarte, CA; Rosa Cuenca, MD, East Carolina University, Greenville, NC; Paul S. Dale, MD, Southeastern Surgical Oncologists, Macon, GA; George W, Daneker, MD, Northside Hospital, Atlanta Regional CCOP, Atlanta, GA; Ronald DeConti, MD, Moffitt Cancer Center, Tampa, FL; Marie France Demierre, MD, Boston Medical, Boston, MA; Mukund S. Didolkar, MD, Sinai Hospital of Baltimore, Baltimore, MD; Raza Dilawari, MD, Methodist Hospitals of Memphis (Boston Baskin), Memphis, TN; Larry Dillon, MD, Memorial Hospital Colorado Springs, Colorado Springs, CO; Paul S. Dudrik, MD, UT Medical

Center, Knoxville, TN; David Dunning, MD, Northern Virginia Oncology Group, PC, Fairfax, VA; J. Benton Dupont, MD, Baton Rouge General Medical Center, Baton Rouge, LA; Burton L. Eisenberg, MD, Fox Chase Cancer Center, Philadelphia, PA; Robert K. Finley, III, MD, Dayton Clinical Oncology Program, Dayton, OH; Thomas G. Frazier, MD, Bryn Mawr Hospital, Bryn Mawr, PA; George Fuhrman, MD, Ochsner Clinic, New Orleans, LA; Michele Gadd, MD, Massachusetts General Hospital, Boston, MA; Charles E. Geyer, JR, MD, Joe Arrington Cancer Center, Lubbock, TX; W. Larry Gluck, MD, Cancer Centers of the Carolinas, Greenville, SC; James S. Goydos, MD, Cancer Institute of New Jersey, New Brunswick, NJ; Keith Heaton, MD, Park Nicollet Clinic/HealthSystem Minnesota, St. Louis Park, MN; Richard A. Hoefer, JR, DO, FACS, Oyster Point Surgical Associates, PC, Newport News, VA; Ryan F. Holbrook, MD, Sacred Heart Med Ctr/Deaconess Med Ctr, Spokane, WA; James Howe, MD, University of Iowa, Iowa City, IA; Lisa Jacobs, MD, University of Missouri Ellis Fischel Cancer Center, Columbia, MO; William Jewell, MD, Kansas University Research Institute, Kansas City, KS; Denise L. Johnson, MD, Stanford University Medical Center, Stanford, CA: Richard Keidan, MD, William Beaumont Hospital, Royal Oak, MI; Mark C. Kelley, MD, Vanderbilt University Medical Center, Nashville, TN; V. Suzanne Klimberg, MD, Arkansas Cancer Research Center, Little Rock, AR; Mark Kozloff, MD, Ingalls Hospital, Harvey, IL; William G. Kraybill, MD, Roswell Park Cancer Institute, Buffalo, NY; Joseph A. Kuhn, MD, Baylor University Medical Center, Dallas, TX; Jeffrey E. Lee, MD, M.D. Anderson Cancer Center, Houston, TX; D. Scott Lind, MD, University of Florida College of Medicine, Gainesville, FL; Jose Lutzky, MD, Mount Sinai & Miami Heart Institute, Miami Beach, FL; Paul F. Mansfield, MD, M.D. Anderson Cancer Center, Houston, TX; Kelly Marc McMasters, MD, University of Louisville, Louisville, KY; Greg P. Midis, MD, UT Medical Center, Knoxville, TN; Richard C. Montgomery, MD, Lexington Clinic/St. Joseph Hospital, Lexington, KY; Don Morris, MD, University of New Mexico, Albuquerque, NM; Edward Newsome, MD, Tulane University Medical Center, New Orleans, LA; Michael Nolen, MD, O U C M -T, Tulsa, OK; James H. North, MD, Eisenhower Army Med Ctr, Fort Gordon, GA; R. Dirk, Noyes, MD, LDS Hospital, Salt Lake City, UT; Thomas Olencki, D.O., The Cleveland Clinic Foundation, Cleveland, OH; Steven Pandelidis, MD, York Hospital/ PA, York, PA; David B. Pearlstone, MD, Cancer Centers of the Carolinas, Greenville, SC; Roger R. Perry, MD, Sentara Cancer Institute/EVMS, Norfolk, VA; E. Phillip Polack, MD, Wheeling Hospital West Virginia, Wheeling, WV; Maurice Rawlings, Jr., MD, Memorial Hospital, Chattanooga, TN; Neal Ready, MD, Rhode Island Hospital, Providence, RI; Douglas Reintgen, MD, Lakeland Regional Cancer Center, Lakeland, FL; Calvin Ridgeway, MD, Albuquerque Surgical Group, PA, Albuquerque, NM; Lee B. Riley, MD, PhD, St. Luke's Hospital, Bethlehem, PA; David C. Ritter, MD, Lee Memorial Cancer Ctr, Naples, FL; Catherine Ronaghan, MD, Joe Arrington Cancer Center, Lubbock, TX; Merrick I. Ross, MD, M.D. Anderson Cancer Center, Houston, TX; Elizabeth Saettler, MD, CancerCare/ Manitoba, Wpg. Manitoba, Canada; Armando Sardi, MD, St. Agnes Healthcare, Baltimore, MD; Donna Schade, MD, M.D. Anderson Cancer Center Orlando, Orlando, FL; Elin R. Sigurdson MD, Fox Chase Cancer Center, Philadelphia, PA: David A. Sloan, MD, University of Kentucky, Lexington, KY; Jeffrey Sussman, MD, University of Cincinnati, Cincinnati, OH; Kenneth K. Tanabe, MD, Massachusetts General Hospital, Boston, MA; Peter Tate, MD, Central Baptist Hospital, Lexington, KY; Clifford Thompson, MD, Mima Century Research Associates, Melbourne, FL; Roderick Tompkins, MD, Kings Daughters-Ashland, Ashland, KY; Courtney M. Townsend, Jr., MD, University of Texas Med Br/Galveston, Galveston, TX; Todd Tuttle, MD, University of Minnesota Cancer Center, Minneapolis, MN; Douglas Tyler, MD, Duke University Medical Center, Durham, NC; Marshall M. Urist, MD, University of Alabama, Birmingham, Birmingham, AL; Charles N. Verheyden, MD, PhD, Scott and White Memorial Hospital, Texas, Temple, TX; Gaylord Walker, MD, Cancer Center at Providence Hospital & Mobile Infirmary Medical Center, Mobile, AL; Geoffrey Weiss, MD, University of Texas HSC / San Antonio, San Antonio, TX; Richard L. White, Jr., MD, Carolinas Medical Center, Charolotte, NC; Eric Whitman, MD, The Melanoma Center of St. Louis, St. Louis, MO.

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