Surgical Management of the Groin Lymph Nodes in Melanoma in the Era of Sentinel Lymph Node Dissection

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Hypothesis: Intraoperative lymphatic mapping and sentinel lymphadenectomy (LM/SL) has become an increasingly popular surgical technique for staging the regional lymph nodes in early-stage melanoma. The technique of LM/SL has potentially great advantage for the groin, where the morbidity of superficial groin dissection or iliac dissection can be high. The surgical management of these basins is unknown for patients with tumor-positive sentinel lymph nodes (SNs).

Design: Cohort of successive patients undergoing LM/SL over 18 years. Those patients found to have tumor-positive SNs underwent sentinel complete lymph node dissection. Postoperatively, patients were followed up on a routine basis with serial examinations and chest radiography. The median follow-up was 50 months.

Setting: Tertiary cancer center.

Patients: The technique of LM/SL was performed for 431 consecutive patients. Sentinal lymph nodes were identified in each case. Patients with tumor-positive SNs underwent sentinel complete lymph node dissection.

Intervention: Cutaneous lymphoscintigraphy and blue dye with or without use of the gamma probe–directed LM/SL. Sentinel lymph nodes were examined by hematoxylin-eosin staining and immunohistochemistry staining with HMB-45 and S100 protein. Only patients with tumor-positive SNs had sentinel complete lymph node dissection.

Main Outcome Measure: Computer-assisted database with statistical analyses using log-rank tests and Cox regression models.

Results: Of the 431 patients, 264 (61%) were women and the median age was 50 years (age range, 15-89 years). A majority (86%) of the primary tumors were on the lower extremities, 54% were of Clark level IV or V, and there was a mean±SD thickness of 1.89±1.59 mm (range, 0.30-14.00 mm). Ninety-three patients (21%) were found to have tumor-positive SNs. After LM/SL and sentinel complete lymph node dissection, 62 patients (67%) were found to have a single tumor-positive lymph node, 25 (27%) had 2 tumor-positive lymph nodes, and 6 (6%) had 3 or more tumor-positive lymph nodes. Only 12 patients (4%) with tumor-negative SNs have had recurrence in the dissected basin. The 5-year overall survival was significantly better for patients with tumor-negative lymph nodes (mean±SD 5-year overall survival, 94%±5%) than for patients with tumor-positive lymph nodes (mean±SD 5-year overall survival, 75%±4%) (*P*<.01). The tumor status of the Cloquet lymph node was predictive of the tumor status of the iliac lymph nodes. Multivariate analyses with a Cox regression model identified tumor-positive SN (*P*=.001), primary tumor thickness (*P*=.03), and ulceration (*P*=.001) as being predictive of survival. Sex, age, Clark level, and primary site were not significant (*P*>.05).

Conclusions: Our results demonstrate the prognostic significance of LM/SL for early-stage melanoma draining to the groin basin. The accuracy of LM/SL measured by the rare recurrences suggests that this surgical procedure should become standard for patients with early-stage melanoma of the lower extremities and trunk. Sampling of the Cloquet node should be used to determine the need for iliac dissection when a tumor-positive SN is identified in the groin.

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THE MANAGEMENT OF THE REgional lymph nodes in patients with early-stage melanoma remains controversial. As yet, there is no definitive consensus regarding the optimum timing or extent of regional lymphadenectomy. Multiple retrospective single-institutional and prospective randomized clinical trials have failed to demonstrate a survival benefit for patients with early-stage melanoma with nonpalpable lymph nodes who undergo elective lymph node dissection (LND). Many investigators support the notion that regional lymph node metastases are an early sign of distant disease and that only patients with pathologically proven metastases should undergo

(therapeutic) LND even though many of the patients are probably not cured by the surgery alone.

Melanomas draining to the inguinal lymph nodes pose an additional problem since groin elective LND or therapeutic lymphadenectomy may be complicated by significant early and/or long-term morbidity, and the addition of deep groin dissection including iliac, hypogastric, and obturator lymph nodes (ilioinguinal LND [ILND]) may further increase the risk of additional complications.[1-3] Some investigators[1,4-6] report no survival advantage for the addition of ILND to inguinal dissection, stating that disease-specific factors negate any potential survival benefit, and reserve ILND for palliation only. Other investigators[7-11] have demonstrated a survival benefit for subgroups of patients undergoing ILND and believe that ILND is a superior procedure to superficial groin dissection (SGD).

As a result of the controversy in the care of patients with early-stage melanoma, Morton et al[12] in 1992 described a minimally invasive alternative to elective LND or delayed therapeutic dissection: intraoperative lymphatic mapping (LM), sentinel lymphadenectomy (SL), and sentinel complete LND (SCLND). This procedure is based on the concept that regional lymph node metastases occur by passage of melanoma cells through afferent lymphatics to the regional basin and to particular identifiable sentinel lymph nodes (SNs). Experiments with cutaneous lymphoscintigraphy and subsequent work with several vital dyes in an animal model demonstrated that SN technology was valid.[13,14] A large body of literature supporting the concepts of the original work by Morton and colleagues has accumulated over the past 13 years.[15]

Although a defined role of LM/SL/SCLND in patient care is unknown, LM/SL has become an increasingly popular alternative to elective LND.[16] The attraction of LM/SL/SCLND to both surgeons and patients is that the technique is minimally invasive with little morbidity and is highly accurate for determining lymph node status for staging and directing adjuvant therapy. Patients who have a tumor-positive SN undergo SCLND whereas those with tumor-negative LM/SL are spared the costs and potential morbidity of complete LND.[17] The technique of LM/SL/SCLND is particularly attractive for managing patients with primary tumors on the lower extremities and trunk that show lymphatic drainage to the groin lymph nodes. However, there are few data available to demonstrate the accuracy of this technique for the groin basin.

METHODS

Four hundred thirty-one patients with clinical stage I (American Joint Committee on Cancer stage I or II) melanoma who underwent LM/SL and SCLND for tumor-positive SNs between January 1985 and July 2003 were identified from our computer-assisted database. Data were analyzed by patient sex and age as well as by primary tumor site, Breslow thickness, ulceration, and histology of the primary melanoma.[18]

Preoperatively, patients were routinely evaluated by complete history and physical examinations, chest radiography, and blood profiles, including lactate dehydrogenase levels. In some cases, computed tomography scans of the chest, abdomen, and pelvis, magnetic resonance imaging, or positron emission tomography were used when there was clinical suspicion of dis-

tant metastases.[19,20] If metastases were identified, patients were excluded from LM/SL. Lymphatic mapping and SL were performed according to the techniques we previously described.[12,21,22] In brief, patients underwent cutaneous lymphoscintigraphy either several days prior to or on the day of the operative procedure.[23] The skin site identified by lymphoscintigraphy was marked by the nuclear medicine physician. At the time of surgery, 1.0 to 2.0 mL of isosulfan blue (Lymphazurin 1%; Tyco International, Exeter, NH) was injected intradermally at the primary site. The skin was gently massaged to enhance the drainage of isosulfan blue into the regional lymphatics. An incision was made over the skin site marked by the nuclear medicine physician. The afferent lymphatics were examined for blue staining followed from the edge of the wound to the first SN.

Since 1993, we have routinely used radiolymphoscintigraphy as an adjunct to the blue dye to improve the accuracy of LM/SL. Blue-stained or radioactive SNs were excised and examined for the presence of metastases either by review of frozen sections (early in our experience) or, more commonly, by permanent sections with hematoxylin-eosin staining. If metastases were not demonstrated by hematoxylin-eosin staining of the first sections, additional sections were cut from the bivalved lymph nodes and stained with murine monoclonal antibodies HMB-45 and S100.[24] If metastases were identified in the SN, SCLND was recommended and usually performed. Lymph nodes removed by SCLND (either SGD alone or with ILND) were examined only by conventional hematoxylin-eosin staining.

Patient records were reviewed to confirm all of the clinical data, including the location (ie, inguinal or iliac) of the nodal metastases, number of lymph nodes with metastasis, pathologic status of the Cloquet node, and operative procedure performed. The Cloquet node has been defined as the lymphatic tissue medial to the femoral vein at the superior aspect of the femoral canal and is thought to represent the leading lymph node into the pelvis from the inguinal basin.[10] The Cloquet lymph node was evaluated by hematoxylin-eosin staining only.

Postoperatively, patients were followed up by routine clinical examination, blood work, and chest radiography. Follow-up time was calculated from initial diagnosis until last follow-up or death. Follow-up ranged from 4 to 198 months (median, 50 months). All of the LM/SL and SCLND procedures occurred within 3 months of diagnosis of the primary melanoma. Survival curves were constructed using Kaplan-Meier estimates.[25,26] Differences in survival distributions were tested by the log-rank method. Differences in frequency distributions and proportions were made using either χ^2 analysis or Fisher exact test. $P<.05$ was considered statistically significant.

RESULTS

Most patients (61%) were women, a majority (53%) of the patients were aged 50 years or younger (range, 15-89 years), and 86% of the patients had primary tumors on the lower extremities. Primary tumors ranged in thickness from 0.30 to 14.00 mm (mean, 1.89 mm). Fifty-four percent of the primary tumors were of Clark level IV or V, and 15% were ulcerated. Forty-four percent of the primary tumors were superficially spreading histologic abnormalities. Patients with tumor-positive SNs tended to have primary tumors that were of a higher Clark level and were thicker than those in patients with tumor-negative SNs (**Table 1**).

Four hundred thirty-one patients underwent LM/SL, with identification of SN in all of the cases. Three hun-

dred thirty-eight patients (78%) had tumor-negative SNs; 12 (4%) of these patients have subsequently had recurrence in the nodal basin (**Table 2**). Ninety-three patients (21%) had tumor-positive SNs. Sentinel complete LND was performed in all but 4 cases with tumor-positive SNs. Sixty-two patients (67%) had 1 tumor-positive lymph node, 25 (27%) had 2 tumor-positive lymph nodes, and 6 (6%) had 3 or more tumor-positive lymph nodes identified. Thirty-seven (40%) of the 93 patients with tumor-positive dissections have had recurrence. Forty-nine (11%) of the 431 patients have died. Patients with tumor-positive inguinal SNs underwent SCLND by removal of the entire superficial (inguinal) basin alone (SGD) (n=20), with sampling of the Cloquet lymph node to determine the need for ilioinguinal dissection (n=31), or ilioinguinal dissection (ILND) as routine management (n=38). Four patients with tumor-positive SNs did not undergo SCLND as a result of either patient or physician choice. Sixteen (17%) of the 93 patients with tumor-positive SNs had primary tumors on the trunk. One patient with bilateral tumor-positive inguinal lymph nodes refused SCLND. One patient had an SGD alone. Ten patients had an SGD with sampling of the Cloquet lymph node. In 4 cases, both inguinal and iliac lymph node dissections were performed without knowing the tumor status of the Cloquet node.

Seventy-six patients had tumor-positive SNs arising from primary melanoma on the lower extremities. Three patients with tumor-positive SNs refused SCLND. In 19 cases, SGDs were performed. In 21 cases, patients had an SGD performed with sampling of the Cloquet node to determine the need for deep groin dissection. In 33 cases, SGD and deep groin dissection were performed as a single procedure.

The mean ± SD 5-year disease-free survival was significantly worse for patients with tumor-positive dissections (52% ± 9%) than for those with tumor-negative dissections (82% ± 7%) (*P* < .001) (**Figure 1**). The difference in disease-free survival translated to a lower mean ± SD overall 5-year survival (75% ± 4% vs 94% ± 5%, respectively; *P* < .001) (**Figure 2**). Only Clark level and thickness correlated with greater risk for patients having tumor-positive lymph nodes.

Fifty-five (16%) of 338 patients with tumor-negative SNs have had recurrence. Nearly half of all (22/25) first-site recurrences were to in-transit sites. Twelve patients (4%) had recurrences to the dissected basin, and 43 (13%) had recurrences to distant sites. The median time to recurrence in the lymph node was 28 months; however, 1 patient had recurrence 132 months after tumor-negative LM/SL.

Thirty-seven (40%) of 93 patients with tumor-positive SNs have had recurrence. Most (31 [84%] of 37) of these recurrences have been to distant sites; they have less commonly been to regional lymph nodes, in-transit sites, or at the wide excision. The median time to distant recurrence for tumor-positive dissections was 7.6 months.

Multiple clinicopathologic features were examined for their role in predicting overall survival. Only tumor thickness, tumor status of the SN, and ulceration were significant (*P* < .05) (**Table 3**).

A variety of operative procedures were used to manage the regional lymph nodes after LM/SL (**Figure 3** and **Table 4**). The decision for the operative procedure was based on surgeon and perhaps patient choice. The positive predictive value for the tumor status of the Cloquet node to determine the status of the deep groin lymph nodes was 66% (4/7 cases) whereas the negative predictive value was 97% (46/47 cases).

Table 1. Comparison of 431 Patients With Tumor-Negative and Tumor-Positive Sentinel Lymph Nodes

Factor	Patients With Tumor-Negative Sentinel Lymph Nodes, No. (%)	Patients With Tumor-Positive Sentinel Lymph Nodes, No. (%)	χ^2 *P* Value
Sex			
Men	129 (30)	38 (9)	.92
Women	209 (48)	55 (13)	
Age, y			
≤50	168 (39)	52 (12)	.39
>50	170 (39)	41 (9)	
Primary tumor site			
Trunk	45 (10)	16 (4)	.49
Lower extremity	293 (68)	76 (18)	
Clark level*			
I/II	41 (9)	2 (<1)	
III	127 (29)	13 (3)	
IV	154 (36)	60 (14)	.004
V	14 (3)	6 (1)	
Unknown	80 (18)	11 (31)	
Histologic abnormality†			
Superficial spread	157 (36)	41 (9)	
Other	111 (26)	31 (7)	.90
Unknown	70 (16)	21 (5)	
Ulceration status‡			
Without ulceration	147 (34)	137 (32)	
With ulceration	42 (8)	8 (2)	.90
Unknown	49 (11)	48 (11)	
Thickness (continuous)			.004
≤2.0 mm	173 (42)	21 (5)	<.001
>2.0 mm	139 (34)	77 (19)	

*Clark level missing for 14 primary tumors.
†Histologic analysis data missing for 91 primary tumors.
‡Ulceration data missing for 97 primary tumors.

Table 2. Distribution of First-Site Recurrences for 431 Patients With Primary Melanoma of the Lower Extremities and Trunk*

Sentinal Lymph Node Status	Local Recurrence, No. (%)	In-transit Recurrence With or Without Lymph Node Tumor Recurrence, No. (%)	Recurrence in Lymph Nodes, No. (%)	Distant Recurrence, No. (%)
Tumor negative (n = 338)	2 (0.6)	34 (10.1)	12 (3.6)	43 (12.7)
Tumor positive (n = 93)	2 (2.2)	13 (14.0)	3 (3.2)	31 (33.3)

*Total patients with first-site recurrences included 55 patients with tumor-negative sentinel lymph nodes and 37 patients with tumor-positive sentinel lymph nodes.
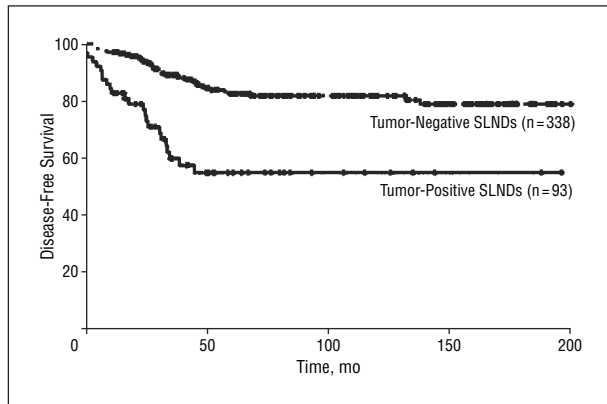
Figure 1. Overall 5-year disease-free survival estimates for patients with tumor-negative (mean±SD overall 5-year disease-free survival, 82%±7%) and tumor-positive (mean±SD overall 5-year disease-free survival, 52%±9%) sentinel lymph node dissections (SLNDs). Patients with tumor-negative sentinel lymph nodes had significantly better disease-free survival than those with tumor-positive sentinel lymph nodes (*P*<.001).
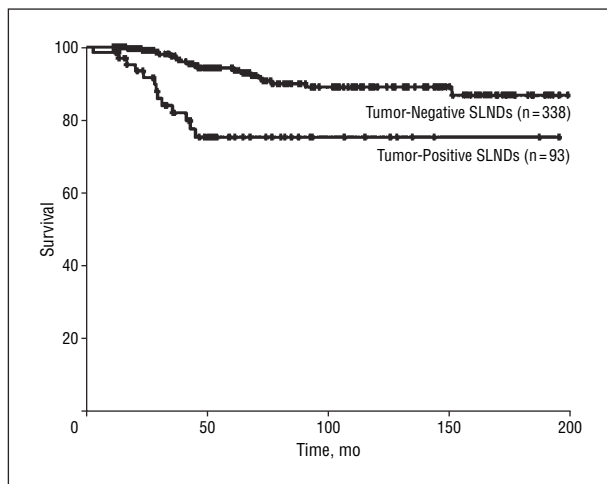

Figure 2. Overall 5-year survival estimates for patients with tumor-negative (mean±SD overall 5-year survival, 94%±5%) and tumor-positive (mean±SD overall 5-year survival, 75%±4%) sentinel lymph node dissections (SLNDs). Patients with tumor-negative sentinel lymph nodes had significantly better survival than those with tumor-positive sentinel lymph nodes (*P*<.001).

Table 3. Univariate and Multivariate Analyses of Factors Predicting Overall Survival of 431 Patients Undergoing Lymphatic Mapping and Sentinel Lymphadenectomy for Primary Tumors on the Lower Trunk and Extremities

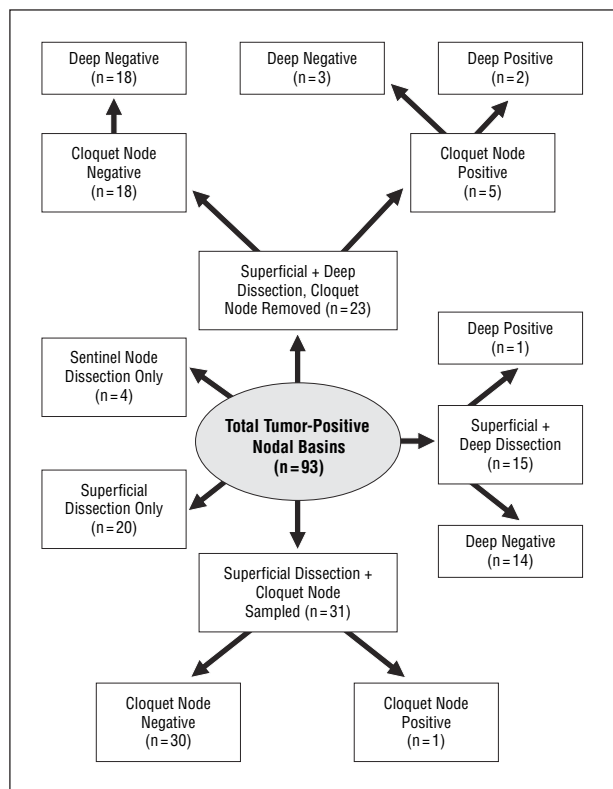| Factor	Univariate Analysis	Multivariate Analysis
Age <50 y	0.611	NA
Sex	0.270	NA
Primary tumor site	0.910	NA
Clark level (II/III vs IV/V)	0.188	NA
Thickness, mm	0.0006	0.003
Ulceration status	0.016	0.0035
Sentinel node status	0.0003	0.045

Abbreviation: NA, not applicable.

Figure 3. Summation of tumor-positive dissections and lymph areas dissected. A variety of surgical approaches were used by surgeons based on individual decision.

COMMENT

The development of LM/SL has revolutionized the management of patients with early-stage melanoma. The technique allows surgeons to identify the pattern of lymphatic drainage from the primary site to the regional lymph node basin; it provides a basis for removal of the SN and a focused pathologic assessment of the specimen. The staging of the regional lymph nodes in this fashion has led to more homogeneous staging than traditionally expected in these patients. Numerous retrospective studies[12,13,15,18] prior to the development of LM/SL have shown that the 5-year survival of patients with lymph node metastases (American Joint Committee on Cancer stage III) can range between 15% and 70%. This wide range in outcome reflects the historical heterogeneity of patients presenting with American Joint Committee on Cancer stage III disease. The prognostic factors for stage III disease have been defined as patient related, primary tumor related, and lymph node related.[9,18] With the exception of thick primary tumors (>4 mm) of the trunk,[27] it is generally accepted that lymph node–related variables are the most important determinant of survival following development of nodal disease. The most important prognostic variables include number of tumor-containing lymph nodes,[5,9] percentage of tumor-positive lymph nodes,[28] presence of extracapsular extension,[29] macroscopic vs microscopic evidence of disease,[29] clinically tumor-positive lymph nodes,[5,30] ulceration of the primary tumor, and highest level of tumor-involved nodes.[9] The survival of patients with tumor-negative lymph nodes has been reported to be in the range of 70% to 90%.[17,18,30]

Table 4. Additional Tumor-Positive Lymph Nodes Identified by the 4 Operative Procedures and Recurrence Patterns*

Type	Patients, No.	Recurrence in Superficial Groin, No. (%)	Recurrence in Deep Groin, No. (%)	Recurrence in Cloquet Node, No. (%)
SGD	20	6 (28)	3 (15)	NA
SGD and deep (iliac and obturator) groin dissection	38	7 (18)	3 (9)	NA
SGD with intraoperative analysis of Cloquet lymph node	31	10 (32)	1 (0)	1 (3)
LM/SL only for tumor-positive sentinel nodes	4	2 (50)	2 (50)	NA
LM/SL for tumor-negative sentinel nodes	341	10 (3)	2 (<1)	NA

Abbreviations: LM, lymphatic mapping; NA, not applicable; SGD, superficial groin dissection; SL, sentinel lymphadenectomy.
*Each of the 4 operative procedures were used for the 431 patients following LM/SL.

The development of LM/SL has clearly advanced the methods by which the regional lymph nodes are staged. A majority of patients with tumor-positive SNs will have only a single lymph node with metastases, thereby making the prognosis of most patients with lymph node metastases very uniform; however, these data call for question as to the role of SCLND. Pathologically proven superficial groin nodes are associated with a 30% to 75% 5-year survival.[4,6,31] Our 75% 5-year survival compares favorably with previous findings.[27-30] Regardless of other prognostic factors, the decision for performing a deep groin dissection hinges on the clinical and pathologic status of the superficial inguinal nodes. Clinically tumor-positive inguinal nodes are predictive of pathologically tumor-positive iliac nodes in 15% to 100% of cases.[2,4,21] Sterne et al[31] have found that the degree of clinical nodal involvement is important in predicting iliac node tumor positivity. In their series of 25 patients who underwent ILND, 1 mobile superficial groin lymph node was associated with pathologically tumor-positive iliac nodes in 8 (36%) of cases whereas multiple mobile nodes or fixed nodes were always associated with positive iliac nodes. The incidence of iliac node tumor positivity is also directly related to the number of pathologically tumor-positive inguinal nodes. Finck et al[7] have shown that the incidence of tumor-positive iliac nodes increases from 14% when 1 inguinal node is pathologically tumor positive to 50% when 4 or more nodes are involved. Other investigators[32] have shown a 100% incidence of iliac node tumor positivity when 3 or more inguinal nodes contain metastatic disease. However, the number of tumor-containing nodes is not easily determined at surgery and is not useful for making decisions on performing ILND after identifying a tumor-positive SN.

Coit et al[9] previously reported the status of the Cloquet node to be 79% predictive of occult iliac node metastasis. Our results suggest both the positive and negative predictive values of using the Cloquet lymph node for evaluating the deep groin basin. Although most surgeons would agree that SGD is the mainstay for treatment of groin node metastases, the role of ilioinguinal dissection remains controversial. Some investigators[23] have reported that the addition of a deep node dissection is not warranted when the inguinal nodes contain occult metastatic disease since the likelihood of deep node metastases is small. Others[5,6] have found this to not be the case. Deep node dissections are most often performed in the presence of clinically evident iliac metastases. Opponents of deep node dissection believe that the high potential morbidity outweighs any survival benefit and that deep node positivity is just a marker of disseminated disease. Previously published 5-year survival rates in patients with pathologically proven deep node metastasis ranged from 0%[1] to 34%.[2,3] In the modern era of LM/SL, even patients with 2 to 4 tumor-positive lymph nodes have survival estimates of 40% to 50%.[18]

A review of 294 patients with American Joint Committee on Cancer stage III melanoma to the groin was performed to determine the utility of our management algorithm for deep groin nodes. Superficial groin dissections provided a survival benefit in those patients selected for low-risk factors. However, a 29% 5-year survival following deep groin dissections in patients with histologically tumor-positive deep nodes would seem to indicate that some patients treated by SGD and deep groin lymph node dissection derive a therapeutic benefit from the procedure and that systemic disease is not a universal finding in patients with deep node metastases. Multivariate analysis identified female sex, younger age, and low tumor burden as good prognostic factors associated with survival. The pathologic status of the Cloquet node was superior to the clinical status of the superficial groin nodes for predicting occult iliac node metastases.

Our results demonstrate the importance of LM/SL for staging the regional lymph nodes in early-stage melanoma. These data are consistent with a number of other studies verifying the accuracy of this minimally invasive operative technique. The technique of LM/SL reduces the morbidity and costs of lymph node staging compared with SGDs (with or without deep groin dissections). Although only 3% of the patients had recurrence in the lymph node basin after tumor-negative LM/SL, these recurrences may cause significant morbidity because of the high incidence of synchronous in-transit disease (Table 2).[33] Similarly, recurrences following a tumor-positive superficial groin may occur with in-transit disease and potentially increase the risk of patients developing chronic lower extremity pain or lymphedema as a result of treatment. Although the therapeutic value of SCLND is unknown and is being tested (in the Multicenter Selective Lymphadenectomy Trial II), our data suggest that tumor status of the Cloquet node may be the most useful approach to evaluating the tumor status of the deep groin lymph nodes following LM/SL.[34]

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DISCUSSION

Stanley Leong, MD, San Francisco, Calif: The authors listed have contributed significantly in the development of lymphatic mapping and sentinel lymphadenectomy in the staging of melanoma. To date, about 80% of the melanoma patients with a negative sentinel lymph node can be spared a more morbid procedure of a regional lymph node dissection. Numerous studies by others have confirmed the utility of this important staging procedure. Thus, lymphatic mapping and sentinel lymphadenectomy for melanoma has been adopted as the standard of care in the staging of melanoma (Leong SP. *Curr Treat Options Oncol*. 2004;5:185-194).

In this study, Dr Essner and colleagues have summarized a large melanoma database regarding the lymphatic mapping and the sentinel lymphadenectomy in the groin nodal basin, a difficult area to work with and very aptly brought up by the authors that if you do a radical dissection, the morbidity is significant.

They have confirmed their previous publications that 5-year overall survival of patients with primary trunk and extremity melanoma was significantly better for patients with tumor-negative than tumor-positive sentinel lymph nodes. The most important finding perhaps in this study is that only 3.5% (12 of 338) of the patients who had negative sentinel lymph nodes developed nodal basin recurrence. Thus, the false-negative rate is 3.5%, attesting to the fact that the procedure is highly accurate. Further, in the group of 90 patients with positive sentinel lymph nodes, most patients developed distant metastasis (84%) and, less commonly, to regional lymph nodes, in-transit sites, or at the local excision sites. On the other hand, the recurrence rate for the negative sentinel lymph node group is significantly lower. These data suggest that melanoma progression in general is orderly rather than the fact that at inception, it is systemically widespread. The spectrum theory by Hellman says that cancer development is progressive. Before it starts

to metastasize, we are able to excise the cancer and potentially cure the patient—a provocative thought. Both the breast cancer and melanoma data in the sentinel lymph node era suggest that the spectrum theory is the most compatible one rather than the Fisher concept that cancer is systemic at the onset or the Halstedian concept that only lymph nodes are involved before systemic spread. The spectrum theory indicates that at an early point of proliferation, it is probably lymphatic bound, and then later, the cancer may become systemically bound (Leong SP. *Ann Surg Oncol.* 2004;11:192S-197S).

The authors should be congratulated for developing and maintaining a large melanoma sentinel lymph node database to provide evidence-based information to allow us to understand better the biology and clinical outcome of melanoma. Further, it helps us to develop new hypotheses to be tested in clinical trials.

Despite the large database being presented, the subgroups, as you can see in that very busy slide, are still of small numbers and therefore make statistical conclusions difficult. Perhaps such subgroups can be better analyzed with pooled data from multiple sentinel lymph node databases.

I have several questions: (1) Can the authors rely on preoperative lymphoscintigraphy to determine the location of groin sentinel lymph nodes, ie, the superficial inguinal vs iliac nodal basin? (2) What is the identification rate of sentinel lymph nodes in the superficial inguinal vs external iliac basin by blue dye, radiotracer, or a combination? (3) How do you define a harvested Cloquet lymph node? Which is more important: Cloquet vs sentinel lymph nodes? Sometimes, it is not easy to find the Cloquet lymph node. When you are at the inguinal ligament, there is no lymph node there. (4) How do you follow the iliac lymph nodes, as they are deep and not easily palpable for those patients for whom you only do a superficial inguinal lymph node dissection? (5) How do you address the issue of separate channels draining into the superficial inguinal vs iliac sentinel lymph nodes? This is particularly relevant for the trunk melanoma, which may bypass the Cloquet lymph node. (6) The exact algorithm of management of groin lymph nodes in melanoma is somewhat unclear from this manuscript. I wonder if the authors could clarify and construct a flowchart to indicate the algorithm and its rationale.

Theodore X. O'Connell, MD, Los Angeles, Calif: The authors recommend that we use Cloquet's node as an additional sentinel lymph node to indicate whether we should do an iliac-pelvic node section, but the major question is, what is the benefit to the patient of this additional treatment given the increased operative time and long-term morbidity, ie, lymphedema, etc? Obviously, if the iliac nodes are negative, the patient cannot benefit from a node dissection, and it appears that over 50% had negative iliac nodes, even with a positive Cloquet's lymph node. Second, what is the survival benefit for the patients who do have positive nodes? Do positive iliac nodes in addition to positive superficial and deep inguinal nodes really indicate systemic disease, and therefore, further lymph node dissection produces no survival benefit?

Jan K. Horn, MD, San Francisco: I was wondering if the authors could comment on their morbidity from the groin dissections and contrast whether the deep vs the superficial dissections faired differently.

Jon M. Greif, MD, San Diego, Calif: I also want to congratulate the authors on utilizing their very extensive database to provide practical algorithms for management. I have 2 questions. One relates to what Dr Leong asked, how do you identify Cloquet's lymph node? It looked like in 1 of your diagrams, you were actually injecting blue dye in the groin, and I wondered if that is something that you do. My second question is, how do you follow your patients who have positive superficial groin nodes but negative Cloquet's node? Are you us-

ing serial CT [computed tomography] scans? Is there a role for PET [positron emission tomography] scanning? And, when do you proceed with the deep node dissection? I personally, this year, have had a patient who on CT scan had a 2-cm iliac node that looked very suspicious. We went in, we did the deep dissection and specifically identified that 2-cm node, removed it, studied it very extensively, and it and the other nodes were negative. Of course, the good news for the patient was he didn't have cancer, but I wonder how or if we could have avoided that negative exploration.

James E. Goodnight, Jr, MD, Sacramento, Calif: In identifying a positive sentinel lymph node, springing from the discussion of breast cancer, do you distinguish from a metastasis that is H&E [hematoxylin-eosin] positive from cells identified only by immunohistochemistry, and is there a minimum number of melanoma cells appearing in the sentinel node in which you would declare a nonmetastasis?

Dr Essner: Dr Leong has raised a question regarding the use of a single-institutional database for evaluating patient outcome. Any time you perform a single-institutional study, it's always useful to validate the data with larger cooperative group data sets. Dr Leong and his colleagues have organized the Sentinel Node Working Group and created a very large melanoma database, which will allow us to validate our single-institutional data. Even more importantly, we may be able to address additional clinical questions from the larger database.

Dr Leong also asked a question regarding the role of lymphoscintigraphy as a technique to identify additional tumor-positive nonsentinel lymph nodes. Yes, we did look at lymphoscintigraphy as a method to try to predict where secondary draining lymph nodes were located, ie, if you had a lymphoscintigraphy that demonstrated the sentinel node in the superficial groin, would delayed lymphoscintigraphy images provide information to the location of secondary tumor–draining lymph nodes either in the superficial or deep groin? Overall, lymphoscintigraphy did not appear to be a reliable method of determining if there were secondary nodes in the deep pelvis that would be tumor positive or not.

We typically select patients with primaries greater than a millimeter thick for sentinel lymph node dissection. Patients who have thinner primaries are also eligible depending on individual features of the tumors and patients. Sometimes, patients will travel specifically to our institution and desire to have a sentinel node dissection performed. But, as you can see from our data, even patients with very thin primaries and low Clark levels will have tumor-positive sentinel lymph nodes. We published a paper several years ago (Bleicher et al. *J Clin Oncol.* 2003) demonstrating our experience with patients with thin primaries who underwent sentinel lymph node dissections, and indeed, we do find patients with very low-risk primaries with tumor-positive nodes. The thinnest primary with tumor-positive lymph nodes was 0.3 mm. The long-term outcome of these patients is unknown.

The identification of Cloquet's node (described by Cloquet in the 1800s), defined as the lymph node at the site at the entrance of the femoral triangle at the inguinal ligament, can be found by a number of approaches. The manner in which we perform superficial groin dissections is that we elevate the lymph nodes over the external oblique fibers and as you enter into the cribiform fascia, usually Cloquet's node is identified adjacent to the femoral vein. Sometimes, Cloquet's node will be adherent to the remainder of the superficial groin dissection, so occasionally you actually will dissect it with the remainder of the superficial groin nodes. Other times, you have to retract Cloquet's node through the femoral canal after the superficial groin nodes have been removed. We do find the Cloquet's node in the majority of cases. This study did not prospectively perform and record the location and tumor status of Cloquet's node

in all cases. Four surgeons performed the vast majority of procedures. There was a variety of surgical techniques used, and in some cases, it was the patients who decided if they would have a deep groin dissection performed or not.

How do we follow these patients? Typically we follow them with hybrid CT-PET scans. We think this combination is the single best approach. What is the optimal timing for imaging? Nobody really knows. We tend to perform scans once a year (and chest x-rays with clinical examinations on a more frequent basis) unless other factors suggest scanning should be done more often. Yes, I do agree there are lymphatic channels that go from the inguinal region directly to the iliac nodes, and I do believe there are some patients in which the Cloquet's node is the sentinel node. It's hard even with our prospectively collected database to try to determine exactly the location of the sentinel node and if it was the same as Cloquet's node. This could be studied a little bit more closely using larger cooperative data sets.

How did we select our patients for different operations? The choice was made by the surgeons and the patients. Some patients refused deep groin dissection because of the risk of lymphedema. Most of the clinical data that have been generated regarding the morbidity of deep groin dissections were published 10 to 30 years ago when many of the deep iliac lymph node metastases were found by clinical examination or patient-directed symptoms, and so many of the patients had large tumor burdens, which alone puts them at risk for lymphedema. We have reviewed our data at John Wayne [John Wayne Cancer Institute, Saint John's Health Center, Santa Monica, Calif] to determine if there is a survival advantage for patients when surgeons performed both superficial and deep groin dissections as compared with superficial groin dissections alone. Yet, there is inherent difficulty analyzing these data as patients who undergo superficial groin dissection without performing a deep groin dissection lack staging of the deep regional basin; thus, patients' prognosis may not truly be comparable when trying to determine potential benefits of deep groin dissection.

The morbidity of the procedures: our paper did not describe it. We do have data from the MSLT I trial [Multicenter Selective Lymphadenectomy Trial I] (prospective randomized trial of sentinel lymph node dissection), where we prospectively recorded short-term morbidity from groin dissections and the low-term rate of chronic lymphedema. In our experience, the rate of clinically relevant lymphedema is about 5%, which contrasts significantly from older medical literature where rates of chronic morbidity and lymphedema are up to 60%. These older studies represent a different patient population than we normally see now, as many of these groin dissections were performed for clinical palpable lymph node metastases.

Dr Goodnight asked a question about how we define a tumor-positive sentinel node. If you review the medical literature for melanoma, which may be different than in breast cancer, it suggests that an H&E-stained tumor-positive sentinel node is equivalent to an IHC [immunohistochemistry]–stained tumor-positive node, and more recent studies suggest that finding tumor-positive sentinel nodes by RT-PCR [reverse-transcriptase polymerase chain reaction] is equivalent to finding metastases by the other approaches, suggesting the prognosis of these patients is relatively the same. Exactly how these 3 techniques will be used in the future for staging the sentinel node is unclear.