Efficacy of Repeat Sentinel Lymph Node Biopsy in Patients Who Develop Recurrent Melanoma

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BACKGROUND: Even after negative sentinel lymph node biopsy (SLNB) for primary melanoma, patients who develop in-transit (IT) melanoma or local recurrences (LR) can have subclinical regional lymph node involvement.

STUDY DESIGN: A prospective database identified 33 patients with IT melanoma/LR who underwent technetium 99m sulfur colloid lymphoscintigraphy alone (n = 15) or in conjunction with lymphazurin dye (n = 18) administered only if the IT melanoma/LR was concurrently excised.

RESULTS: Seventy-nine percent (26 of 33) of patients undergoing SLNB in this study had earlier removal of lymph nodes in the same lymph node basin as the expected drainage of the IT melanoma or LR at the time of diagnosis of their primary melanoma. Lymphoscintography at time of presentation with IT melanoma/LR was successful in 94% (31 of 33) cases, and at least 1 sentinel lymph node was found intraoperatively in 97% (30 of 31) cases. The SLNB was positive in 33% (10 of 30) of these cases. Completion lymph node dissection was performed in 90% (9 of 10) of patients. Nine patients with negative SLNB and IT melanoma underwent regional chemotherapy. Patients in this study with a positive sentinel lymph node at the time the IT/LR was mapped had a considerably shorter time to development of distant metastatic disease compared with those with negative sentinel lymph nodes.

CONCLUSIONS: In this study, we demonstrate the technical feasibility and clinical use of repeat SLNB for recurrent melanoma. Performing SLNB cannot only optimize local, regional, and systemic treatment strategies for patients with LR or IT melanoma, but also appears to provide important prognostic information. (J Am Coll Surg 2014;218:686–694. © 2014 by the American College of Surgeons)

Sentinel lymph node biopsy has a well-established role in the management of primary cutaneous melanoma and provides prognostic information and a possible therapeutic benefit.[1,2] After initial appropriate management of the primary tumor, 2% to 10% of extremity melanomas will recur locoregionally as local recurrence (LR) or in-transit (IT) disease.[3,4] Because of the concern that LR/IT can be accompanied by distant metastatic disease, the role of performing SLNB in the management of patients who have LR/IT disease develop is less clear than in the case of primary tumors. However, a study from MD Anderson in the modern era of SLNB demonstrated that IT disease was the only site of recurrence in approximately 56% of patients.[3]

Patients in whom unresectable LR or IT extremity disease develop, and who have no evidence of systemic metastases, are often treated with regional chemotherapy in the form of hyperthermic isolated limb perfusion (HILP) or isolated limb infusion (ILI) with melphalan. Regional chemotherapy achieves complete response rates of 30% to 55%, with median duration of response ranging from 8 to 23 months.[5-7] Notably, ILI does not treat the regional nodal basin, as opposed to HILP, which can include a regional node dissection as part of the process of placing vascular cannulas. The prevalence of regional node involvement in patients with IT/LR has been explored briefly with the use of SLNB.[8,9] In the largest report of SLNB performed in patients with IT/LR, 47% (14 of 30) of patients had a positive sentinel lymph node (SLN),[7] suggesting that ILI alone or HILP

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Abbreviations and Acronyms

HILP = hyperthermic isolated limb perfusion
ILI = isolated limb infusion
IT = in transit
LR = local recurrence
SLN = sentinel lymph node
SLNB = sentinel lymph node biopsy

in the absence of an inguinal node dissection might be inadequate in nearly half of the patients with IT disease. Therefore, SLNB could be used to select the appropriate modality of regional chemotherapy delivery in patients with IT or LR, in addition to providing prognostic information and a possible therapeutic benefit. Previous reports, however, are limited because they lacked specific methodology in these complex patients who often have multiple lesions, and these studies do not include whether patients might have undergone SLNB or lymph node dissection at the time of primary melanoma diagnosis.

The technical aspects of performing SLN mapping of a primary melanoma are well described, with a success rate identifying SLN using vital blue dyes plus radiocolloid and intraoperative use of the hand-held gamma probe approaching 99%.[10] Performing SLNB in patients in whom IT or LR develops, many of whom have undergone previous lymph node biopsies or completion dissections, can pose challenges not encountered when performing SLNB for primary melanoma. In a study from MD Anderson, independent predictors of IT recurrence after primary excision included Breslow depth, ulceration, and SLN status.[3] Many patients with IT disease had intermediate or thick primaries and likely underwent SLNB (in the SLNB era) at the time of the primary diagnosis. Additionally, as suggested by the MD Anderson study, many patients who had IT disease develop also had SLN involvement with the primary; these patients have historically been offered completion node dissection. As a result, the success rate of identifying the SLN in patients who have had previous lymph nodes removed might be considerably lower. Additionally, there are no established criteria for determining which lesions to map in patients presenting with $\geq$2 IT lesions. The aims of this study were to describe our technique for performing SLNB in patients with LR or IT disease, determine positivity rate of SLNB in a wider range of patients with IT disease, and assess the clinical use of performing SLNB in this patient population.

METHODS

A prospective database identified 33 patients from 2005 through 2013 with LR or IT extremity melanoma undergoing SLNB. Local recurrences were defined as solitary lesions within 0.5 cm of the primary melanoma lesion or scar (Fig. 1). Before SLNB, all patients had physical examination and whole-body PET/CT imaging. Any patient with distant metastatic disease or concern for regional node involvement on physical examination or PET/CT was not considered for SLNB. After therapy, which included wide local excisions, SLNBs, lymph node dissections, or regional chemotherapy treatments, patients in this study were followed every 3 months for 1 year with physical examination and whole-body PET/CT, every 6 months for 5 years, and yearly thereafter to detect both local and distant metastases.

The day before SLNB, patients underwent lymphoscintigraphy. When >1 IT lesion was present (Fig. 1), the most proximal lesion was mapped by injecting 0.9 to 1.0 mCi total technetium 99m sulfur colloid in 4 equal aliquots around the site of the tumor deposit. If multiple lesions were present at the same level, the largest lesion was mapped. Immediate images, 3- to 4-hour delayed images, and 23- to 24-hour delayed images were subsequently obtained.[11] A hand-held gamma probe was also used intraoperatively in all cases.

Once in the operating room, approximately 1 to 2 mL isosulfan blue dye was injected into the lesion only if a resection of the mapped IT/LR was planned. For patients with $\leq$3 lesions and no single lesion >5 cm (small-volume disease), resection was usually performed at the time of SLNB (Fig. 1). However, if the small-volume disease was a second, rapid recurrence (<6 months), and the patient had not received any regional chemotherapy treatments previously, regional chemotherapy was planned and these patients did not get resection of their low-volume disease at the time of SLNB. Lymph nodes were removed using similar guidelines for SLN removal for primary melanoma; all blue lymph nodes and all nodes measuring $\geq$10% of the ex vivo radioactive count of the hottest sentinel node were harvested.[12] This study was approved by the IRB at Duke University and informed consent was obtained from all subjects.

Summary statistics were derived using established methods and presented as either percentages for categorical values or medians with ranges for continuous variables. A comparison of time to distant metastatic disease between those with a positive SLNB vs negative SLNB was assessed with the log-rank test, and Kaplan-Meier curves were used display the results of these tests.

RESULTS

The characteristics of patients' (n = 33) primary melanomas are listed in Table 1. Median thickness was 1.79

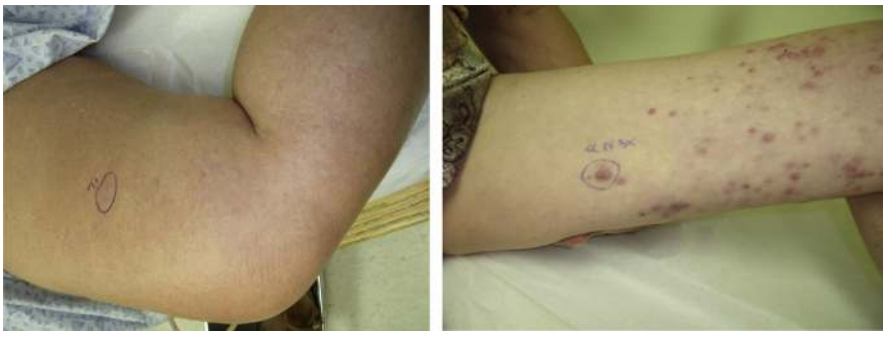

Figure 1. A local recurrence (left). This single lesion is mapped using methods described plus vital blue dye as resection of the lesion is planned with SLNB. Right: A patient with unresectable in-transit disease. The most proximal lesion (circled) is mapped using described methods and no blue dye is used.

mm (n = 23). There were 8 upper-extremity melanomas, 2 back melanomas, and 23 lower-extremity primary lesions. Twenty-four (73%) patients had undergone SLNB at the time of their primary melanoma diagnosis. One patient had also undergone resection of one regional lymph node at the time of primary diagnosis, which was in 1994; the node was negative for malignancy, but no imaging or dye techniques were used. Of the patients (n = 24) who underwent SLNB of the primary melanoma, 3 had a positive lymph node in the inguinal nodal basin. Two of those patients underwent completion inguinal lymph node dissection and the remaining patient underwent systemic treatment. One additional patient had a negative inguinal SLNB at the time of primary diagnosis, IT disease developed, and the patient was treated with ILI followed by HILP. Iliac (0 of 5) and obturator (0 of 5) lymph nodes removed during HILP were negative for malignancy. After achieving complete response to HILP, a single, isolated extremity recurrence developed in this patient, SLNB of the recurrence was performed, and the patient was included in this study. In total, 26 of 33 (79%) patients undergoing SLNB in this study had some earlier removal of lymph nodes in the same lymph node basin as the expected drainage of the IT or LR.

Table 1. Primary Melanoma Characteristics

Category	Data
Primary tumor Breslow depth	
Median (range), mm	1.79 (0.9–10.8)
n	23
Previous SLNB, n (%)	24/32 (73)
Previous positive SLNB, n (%)	3/23 (13)
Previous lymph node dissection, n (%)	3/32 (9)
Time to IT/LR	
Median (range)	25.7 mo (7.7 mo to 16 y)
n	30

IT, in transit; LR, local recurrence; SLNB, sentinel lymph node biopsy.

Median time to IT or LR was 25.7 months (Table 1), and 3 patients had melanoma of unknown primary. Four patients had LRs and 29 patients had IT extremity melanoma. Of the patients with ≤5 recurrent lesions (n = 20), 18 had recurrent disease excised concurrently with planned SLNB, and in 2 patients lesions were not resected because these patients were considered appropriate for regional chemotherapy treatments due to the rapid or repeat nature of the recurrences. We generally require candidates for regional chemotherapy at our institution to have clinically or radiologically measurable disease at the time of the procedure to determine the true efficacy of the treatment; as such, even patients with low-volume disease did not have resections if regional chemotherapy was planned. As discussed in the Methods, for the 22 patients who underwent resection of the recurrence, isosulfan blue dye was used in addition to lymphoscintigraphy to identify SLNs as outlined in Figure 2.

Successful identification of at least 1 lymph node was visualized by imaging after lymphoscintigraphy in 94% (31 of 33) of patients. Both failures were in patients who had undergone earlier SLNB at the time of their primary melanoma. The first failure was in an LR of a back melanoma, where lymphoscintigraphy identified >8 foci of activity in multiple anatomic sites, and a decision was made not to perform SLNB, and resection only of the LR was carried out. The second failure was also in a patient with locally recurrent back melanoma and no nodes were identified on lymphoscintigraphy, and excision only of the LR was performed. Notably, in the 2 patients with previous inguinal lymph node dissections, an iliac node was identified on imaging as the draining lymph node. Additionally, a third patient, who had 2 of 5 inguinal lymph nodes positive for melanoma during SLNB at the time of the primary melanoma but did

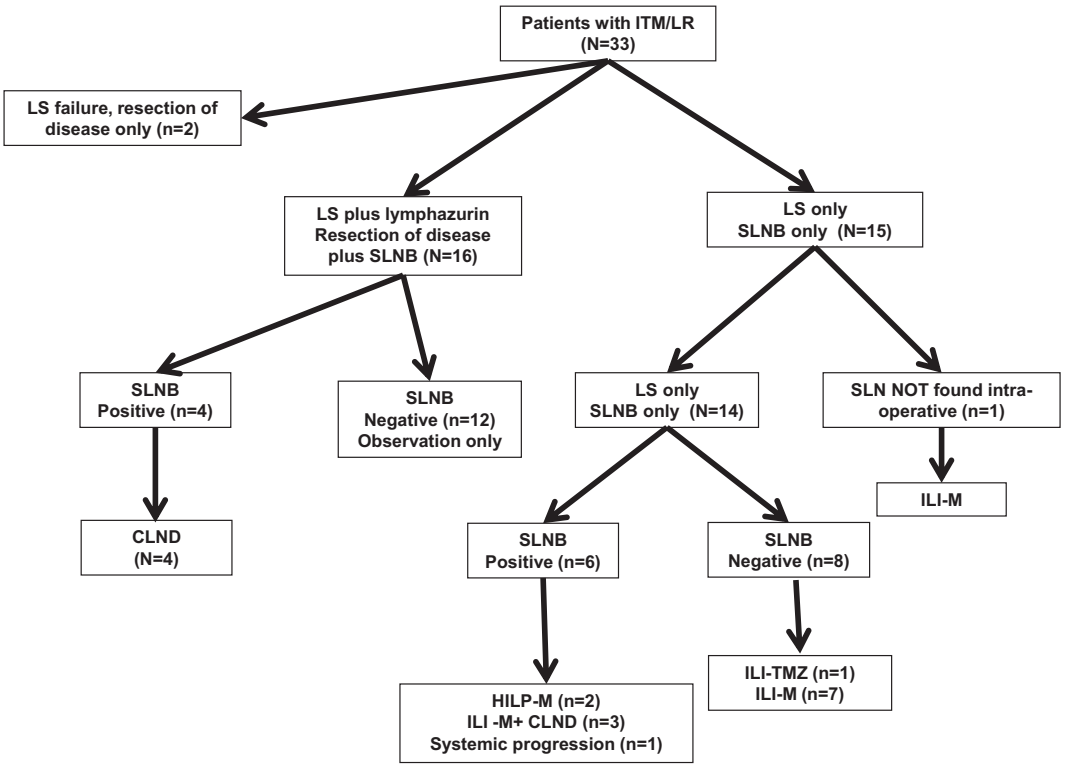

Figure 2. Flow diagram of study patients. CLND, completion lymph node dissection; HILP, hyperthermic isolated limb perfusion; ITM, in-transit melanoma; ILI-M, isolated limb infusion melphalan; LR, local recurrence; LS, lymphoscintigraphy; SLNB, sentinel lymph node biopsy; TMZ, temozolomide.

not undergo completion nodal dissection, also had an iliac node identified as the draining node. Finally, 1 patient with a primary melanoma on the distal arm underwent axillary SLNB at the time of the primary melanoma, which was negative, and had antecubital fossa and axillary draining lymph nodes identified when the LR on the distal upper extremity was mapped.

Ninety-seven percent (30 of 31) of patients underwent removal of at least 1 blue or radioactive node. The procedure was well tolerated with no major complications. One patient who had undergone a previous inguinal lymph node dissection had an iliac node identified on imaging, but no lymph node was identified intraoperatively. Of 30 patients who had an SLN removed, 10 (33%) had evidence of metastatic melanoma involving the lymph node, as outlined in Figure 2. Of the 3 patients with positive inguinal SLNBs at the time of primary melanoma, 2 patients had positive iliac nodes when the IT lesion was mapped and, in 1 patient, the iliac node could not be found at the time of surgery. Three patients who did not have SLNB at the time of primary diagnosis (n = 1 melanoma unknown primary, n = 2 SLNB not performed) had evidence of melanoma in the inguinal SLNB performed for IT disease. Finally, the remaining 5 patients who had positive SLNBs when the LR or IT lesion was mapped had negative SLNBs at the time of the primary melanoma. Patients in this study with a positive SLN at the time the IT/LR was mapped had a considerably shorter time to development of distant metastatic disease compared with those with negative SLNs, as shown in Figure 3. Time to distant metastatic disease

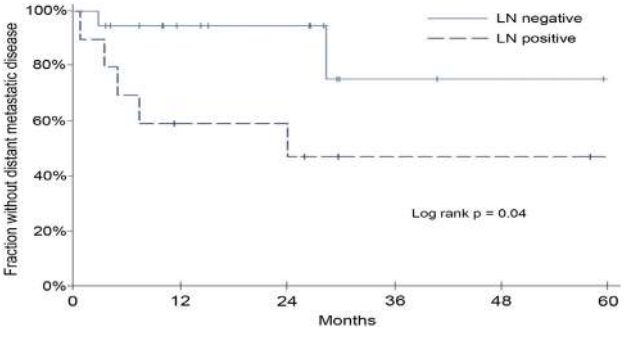

Figure 3. Kaplan-Meier curve for time to development of distant metastatic disease for patients who were SLNB negative (solid line) and positive (dashed line).

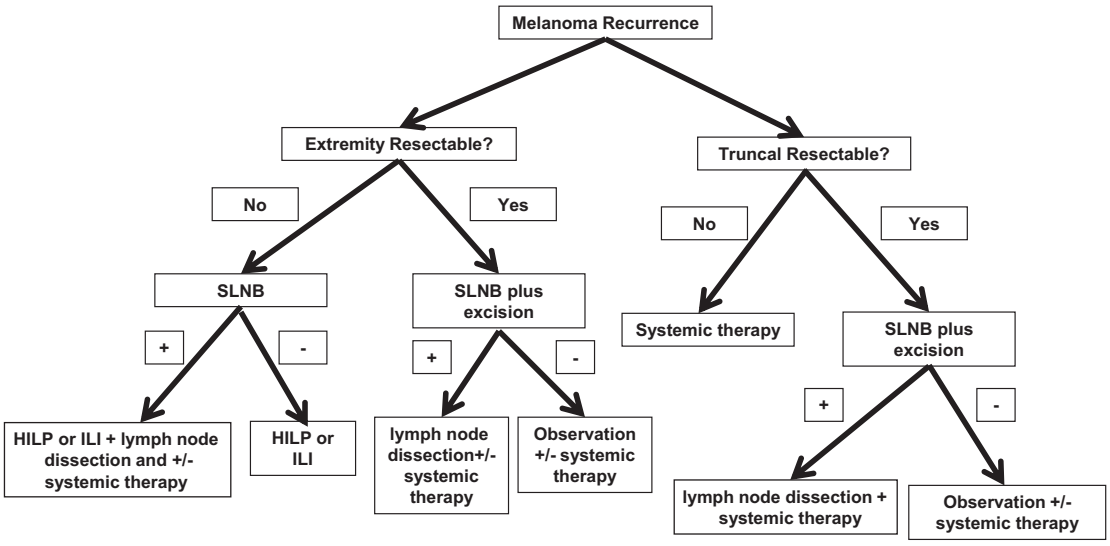

Figure 4. Algorithm for use of SLNB in patients presenting with recurrent melanoma. HILP, hypothermic isolated limb perfusion; ILI, isolated limb infusion; SLNB, sentinel lymph node biopsy.

was calculated from the time of SLNB to development of any stage IV disease (above the regional nodal basin).

After SLNB-positive/negative excision of the IT or LR, patients fall into 4 categories as follows: SLNB negative and all known extremity disease excised (n = 12), SLNB negative and extremity disease not excised (n = 8 plus n = 1 no SLN found), SLNB positive and all known extremity disease excised (n = 4), and SLNB positive and extremity disease not excised (n = 6). Two of 12 patients in category 1 had extremity recurrences develop at 6 and 8 months, respectively, and subsequently underwent ILI. Eight patients in category 2 underwent ILI with melphalan; 3 patients were complete responders, 1 was a partial responder, 3 patients had progressive extremity disease, and 1 patient had progressive extremity disease after ILI with melphalan, but has complete response to ILI with temozolomide (Douglas Tyler, unpublished data).

All 4 patients in category 3 (SLNB positive, extremity disease excised) underwent completion nodal dissections of the basin with the positive SLN. Two patients in category 3 underwent inguinal node dissections with 0 of 7 and 0 of 3 lymph nodes positive for malignancy. One of these patients had a recurrence in the extremity at 6 months, underwent ILI with no response, then underwent HILP, during which 0 of 3 external iliac and 0 of 9 obturator nodes were found to be positive for malignancy. Two other patients in category 3 had 0 of 32 and 0 of 24 lymph nodes positive for malignancy at the time of axillary dissection. Finally, 6 patients were in category 4 (SLNB positive, extremity disease not resected). Two patients subsequently had HILP, during which 2 of 15 pelvic lymph nodes were found to be positive for melanoma and 0 of 13 nodes were found to be positive for melanoma in the other patient. Three patients underwent completion node dissection (1 of 7, 3 of 15, and 3 of 8 lymph nodes positive for metastatic disease) plus ILI. One patient (positive iliac SLN) had metastatic cutaneous disease develop outside the extremity and received systemic therapy with no additional surgery. In total, 9 of 10 patients with a positive SLN underwent completion dissection and 56% (4 of 9) had evidence of additional lymph node involvement.

DISCUSSION

The role of SLNB in the management of LR or IT cutaneous melanoma is currently not well established. Here, we report a 33% (10 of 30) rate of SLN positivity in patients with IT/LR melanoma. Interestingly, patients (n = 2) who had positive SLNB at the time of their primary melanoma also had positive SLNB at time of presentation with IT disease, and 5 patients who were SLNB negative at the time of primary excision were SLNB positive at presentation with IT/LR. Whether these 5 represent initial false negatives or subsequent metastasis from the recurrent disease is unknown. The status of the SLN had important prognostic implications and helped guide optimal treatment strategies for all patients in this study.

Repeat SLN biopsy for recurrent breast cancer has been well studied.[13] The false-negative rate was 0.2%.[13] The status of the repeat SLN biopsy results for these breast cancer patients (n = 692) led to sparing an axillary dissection in 213 patients and, in 17.9% of patients, the

information led to a change in therapy.[13] The status of the SLN in our melanoma population in this study was prognostic for development of distant metastatic disease. We chose to compare time to development of distant metastatic disease instead of survival because long-term follow-up is not yet available. Time to distant metastatic disease is important, as the 5-year survival rate for stage IIIC melanoma is around 40%, and 5-year survival rate for stage IV is 15% to 20%.[14] In addition to prognostic information, the status of the SLN also served to help guide treatment strategies in patients who were candidates for regional chemotherapy treatments. Isolated limb infusion alone does not treat the regional nodal basin, and patients with a positive SLN underwent ILI plus lymph node dissection or HILP. Our data from >200 regional chemotherapy treatments suggests a survival benefit for those obtaining complete response to regional chemotherapy; for ILI median survival was 39 months for complete responders, and for HILP, patients with complete response had median survival of 100 months.[5,6] Although treatments are generally well tolerated, there is a small risk (3% to 4%) of serious toxic limb side effects. Appropriate patient selection is critical. Given the likelihood for development of distant metastatic disease, patients with a positive SLN when the IT/LR is mapped should also be highly considered for systemic therapy. Memorial Sloan-Kettering Cancer Center is currently conducting a trial of systemic ipilimumab after ILI with melphalan, and our group will be initiating a trial of neoadjuvant ipilimumab before ILI, both of which would be highly appropriate for patients with a positive SLN (personal communication, Mary S. Brady, February 2011).

Importantly, the majority of patients in this study (78%) had some previous removal of lymph nodes in the expected drainage location of the IT/LR lesion. This is a reflection of the current era, in which SLNB is performed routinely for appropriate primary melanomas. We found redo SLNB to be technically feasible in most situations. Ideally, redo SLNB is probably best performed at the first recurrence instead of after multiple recurrences and possible excisions. The selective use of blue dye also did not seem to affect our ability to recover the SLN. This is not necessarily surprising, considering that the use of lymphoscintigraphy alone without blue dye has been shown to have a technical success rate of 98%.[15] The few difficulties in this study were mainly in patients with earlier formal lymph node dissections or who had a recurrence in an ambiguous region of drainage, such as the mid back. In the large meta-analysis of breast cancer patients undergoing repeat SLNB for recurrent disease, sentinel node identification was successful in 81% of patients with no previous axillary dissection, with a 52.2% success rate in patients who had axillary dissections previously.[13] For patients with previous lymph node dissections or ambiguous drainage patterns like the mid back, SLNB can still be considered, but might be technically more challenging. We outline the following separate algorithms for patients with truncal melanoma recurrences and recurrent extremity disease in Figure 4. For patients with recurrent truncal melanoma that is not surgically resectable, SLNB is not recommended because of the technical difficulty as well as the need for systemic therapy. Patients with resectable truncal disease can be considered for SLNB; if SLNB is positive, patients should undergo completion lymph node dissection plus systemic therapy, SLNB-negative patients might need observation with or without systemic therapy. For any recurrent extremity disease, SLNB is recommended. Patients with unresectable extremity disease should undergo regional chemotherapy to include treatment of the lymph node basin (HILP or lymph node dissection) when the SLNB is positive. Patients with resectable extremity disease should also undergo SLNB biopsy, and completion dissection with or without systemic therapy should be considered for those who are SLN positive.

Our study is limited by a small number of heterogeneous patients. Certainly larger numbers and more long-term follow-up are needed.

CONCLUSIONS

This is the first study, to our knowledge, to examine the use of SLNB in patients with LR/IT melanoma who also had SLNB at the time of primary melanoma diagnosis. Here we demonstrated technical feasibility and that SLN status is a valuable prognostic factor, and assessed how SLN status can help guide treatment strategies. An SLNB at the time of development of IT/LR should be considered even if SLNB was performed at the time of primary diagnosis, as in this study, 33% (10 of 30) of patients had evidence of metastatic disease in the SLN when the IT/LR was mapped, including 5 patients who had a negative SLN at time of primary diagnosis.

Author Contributions

Study conception and design: Beasley, Tyler
Acquisition of data: Beasley, Speicher, Sharma, Tyler
Analysis and interpretation of data: Beasley, Speicher, Sharma, Seigler, Salama, Mosca, Tyler
Drafting of manuscript: Beasley, Speicher, Sharma, Seigler, Salama, Mosca, Tyler
Critical revision: Beasley, Speicher, Sharma, Seigler, Salama, Mosca, Tyler

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Discussion

DR CRAIG SLINGLUFF (Charlottesville, VA): Dr Beasley and colleagues are to be congratulated for a large body of work addressing the management of regional melanoma metastases, and, in the current setting, they have addressed the fairly common surgical question of the feasibility and value of sentinel node mapping and biopsy for patients with local recurrence or intransient metastases of melanoma.

Because about 20% of patients with extremity melanomas develop local or intransient metastases usually before distant disease, this is a common and clinically significant problem. There's little published experience with lymphatic mapping and sentinel node biopsy in these patients, where the procedure can be complicated, as shown here, both by the multifocality of the recurrences and the fact that most patients have previously had a sentinel node biopsy or a complete dissection, which may alter lymphatic drainage.

The authors demonstrated very well that lymphatic mapping and sentinel node biopsy are feasible in 90% or more of these patients, despite previous sentinel node biopsy or node dissection. They've addressed the challenge of mapping for patients with multiple scattered intransient metastases, and their technique of selecting the most proximal or largest metastasis for mapping is an interesting potential solution.

This report from Beasley and colleagues is particularly valuable because of the detail provided in a wide range of patients. Also, and importantly, their paper is the first to show that a sentinel node biopsy at recurrence has prognostic significance for distant metastasis in these already high-risk patients. I have 4 questions for the authors.

First, what proportion of patients in the study had metastases localized to a small area of skin vs scattered over a wide area? In the latter setting, do you have experimental or clinical data that lymphatic mapping from multiple metastases does not add to mapping from a single metastasis?

Second, was the sentinel node status associated with the number or extent of regional metastases or other evident clinical factors?

Third, among the 10 patients with positive sentinel nodes, were any of the nodal metastases large enough that they might have been detectable by preoperative ultrasound examination? Do you have guidance about the role of ultrasound staging for regional nodes in these patients?

Finally, the authors now know that among patients with local and intransient recurrences, the status of the sentinel node divides them into low vs high risk for distant metastatic disease. Do they recommend changes in regional or systemic management other than completion node dissection based on the sentinel node status?

DR KEITH DELMAN (Atlanta, GA): I have questions from Dr John Zager, who had a family emergency and couldn't be here. I'll first read Dr Zager's questions, and then I have one of my own. Dr Zager asked how many patients are in the denominator to get the cohort identified in the study? In other words, how many had nodal disease seen on examination or PET imaging and did not have a sentinel node biopsy? And how were those patients approached?

You mentioned in your algorithm at the end the management of truncal patients, but I think the study did not actually report on any patients with truncal disease. And so he asks why there are no truncal or head and neck locoregionally recurrent melanomas