

## Original Article

# IMPACT OF INGUINAL SENTINEL LYMPH NODE BIOPSY (SLNB) ON LONG TERM SURVIVAL OF PATIENTS WITH LOWER EXTREMITY MALIGNANT MELANOMA: A RETROSPECTIVE REVIEW

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### ABSTRACT

**Background:** Sentinel lymph node biopsy (SLNB) is widely accepted as the standard of care for correct lymphatic basin staging for patients with clinically localized malignant melanoma. Herein, our experience of determining the impact of inguinal SLNB on node-negative, primary cutaneous melanoma of lower extremity in terms of long-term survival will be presented.

**Methods:** In this study, we retrospectively reviewed data of patients having lower extremity melanoma with Breslow thickness < 4 mm, who underwent inguinal SLNB (ISLNB) from January 2013 to January 2015 with follow up till January 2020, retrieved from hospital database software (EX-07-02-19-01). We collected demographic, primary disease data, surgery data, histological data, and outcome data during a 5-year follow-up.

**Results:** Of the 22 patients who underwent SLNB from 2013 to 2015, 13 (59.1%) patients had positive inguinal SLNB. The mean age of patients was 40 years, with more chances of positive SLNB (8 out of 13) in patients of age  $\leq 45$  ( $p$  value 0.019). Mean  $\pm$ SD tumor Breslow thickness was  $2.57 \pm 0.86$  ( $p$  value 0.0034). The mean follow-up period after surgery was 72.3 months (6.02 years). The mean  $\pm$ SD number of days of hospital admission at the time of surgery was  $3.7 \pm 1.2$  days ( $p$  value 0.037). The total number of OPD visits during the first year follow up were less in Inguinal SLNB negative patients ( $p$  value 0.097).

**Conclusion:** SLNB can be used as a routine procedure in node-negative malignant melanoma of the lower extremity for better survival and quality of life with fewer complications.

**Key Words:** Sentinel lymph node biopsy, Melanoma, Lower extremity

## INTRODUCTION

Malignant melanoma is one of the most fatal cutaneous malignancies and is the most common malignant skin tumor of the foot. It is thought that lower extremity melanoma may be associated with poorer prognosis as its diagnosis is delayed due to its similarity with certain common ulcerative conditions, painlessness, and difficult position for every patient to visualize.<sup>1</sup> It can arise from any melanin-containing cell of the body and spreads primarily by the lymphatic system.

Therefore, regional lymph node metastasis is the most important outcome parameter in melanoma patients. It determines the risk of recurrence and mortality after surgical excision of melanoma.

Currently, wide local excision (WLE) and sentinel lymph node biopsy (SLNB) is widely accepted as the standard of care for correct lymphatic basin staging for patients with clinically localized malignant melanoma.<sup>2</sup> Because the sentinel lymph node (SLN) is the first site of regional metastasis, its tumor status accurately predicts the tumor status of other nodes in the lymphatic basin.<sup>3</sup> The effectiveness of SLNB is directly related to both patient and tumor characteristics including age, sex, site of the tumor, depth of invasion, ulceration, and vascular invasion. It is done as routine management in patients with melanoma  $\geq 1$  mm depth of invasion and may be considered for thin lesions with high-risk characteristics (e.g. ulceration,

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lymphovascular invasion, high mitotic rate).<sup>4</sup> Having shown both the staging accuracy and pathological specificity of the SLNB technique, Morton et al. postulated that this minimally invasive alternative to radical regional lymphadenectomy could not only reliably identify patients with clinically occult nodal metastasis, but would also favorably affect the oncological outcomes.<sup>5</sup> However, the impact of SLNB on the long-term survival of patients with melanoma in terms of clinical and histopathological characteristics has yet to be established. Also, there is a scarcity of studies on lower extremity melanoma and its outcome after surgery specifically in our population. This study aims to determine the impact of inguinal SLNB on clinically localized, node-negative, primary cutaneous melanoma of the lower extremity in terms of long-term survival.

## MATERIAL AND METHODS

This retrospective cohort study was conducted in the Surgical Oncology Department of Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMCH & RC), Lahore, Pakistan. After approval from the Institutional Review Board (EX-07-02-19-01), data of patients who underwent inguinal sentinel lymph node biopsy for lower extremity melanoma from January 2013 to January 2015 with follow-up till January 2020 was retrieved from the hospital database software. Patients, age 15-75 years having biopsy-proven <4mm deep melanoma of lower extremity with no palpable inguinal lymphadenopathy on presentation, were included in the study. Patients, with age <15 years, having Breslow thickness >4mm, microscopic satellite lesions, distant metastasis, or recurrent disease were excluded from the study. Patients who had melanoma excision outside our hospital were also excluded.

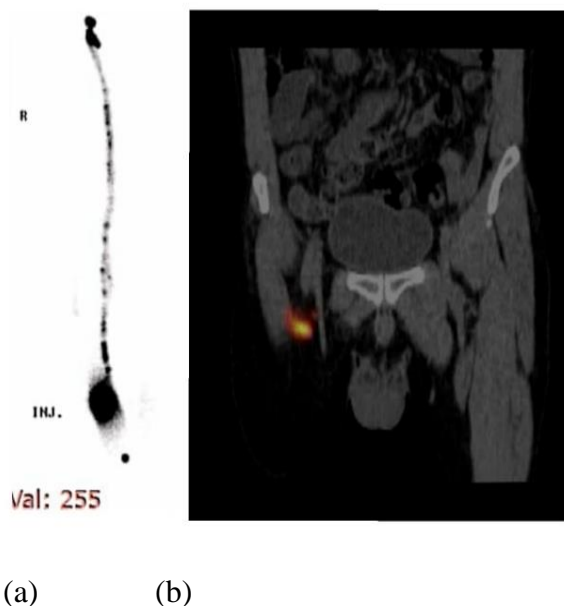
It was found all the study patients were admitted to the hospital one day before surgery and had a subcutaneous injection of

technetium-99m (<sup>99m</sup>Tc) labeled filtered sulphur colloid in four quadrants near the tumor, on the morning of surgery. Dynamic imaging of drainage pattern from the primary lesion was made using scintillation camera in 1-30 min after injection followed by delayed whole-body imaging. During surgery, a handheld gamma probe (Neoprobe™ GDS, Gamma detection system) was used to identify sentinel lymph nodes [Figure-1]. The sample lymph nodes were sent for frozen section and the decision of complete inguinal lymph node dissection was made in patients with sentinel lymph nodes positive for micrometastasis.



**Figure-1:** Gamma detection system with a handheld probe

We collected demographic, primary disease data (duration of the tumor, site of the tumor, tumor size, Breslow thickness, and presence of ulceration), surgical data (Tumor excision margin, thickness, and post-operative complications), histological data (tumor margin clearance achieved, histological subtype, number of SLN and number of positive lymph nodes), and outcome data (recurrence, metastasis, and mortality) during 5-year follow-up. To assess morbidity, the number of days of hospital stay and number of hospital visits during the first-year post-operative was also recorded.



**Figure-2:** Inguinal sentinel lymph node identification using lymphoscintigraphy and SPECT/CT in a patient with melanoma right foot

- (a) Lower extremity image showing tracer drainage from injection site with visualization of lymphatic ducts towards the inguinal lymph nodes.
- (b) Further localization of sentinel lymph nodes on SPECT/CT scan with volume rendering.

Descriptive variables were presented by proportions, mean or median values, and percentage as appropriate by data distribution. Age (15-45 or 46-75 years) and Breslow thickness ( $\leq 2.0$  or 2.1-4.0 mm) were dichotomized. In SLNB positive and negative patients, categorical variables like age, gender, Breslow thickness, ulceration, and outcome measures like recurrence were compared using the chi-square test. Data of variables like duration of melanoma, anatomical site of melanoma, histological subtype, complications, metastasis, number of days of hospital stay, and number of hospital visits during 1<sup>st</sup> year after surgery were compared in SLNB positive and negative patient by t-test. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 21.0 statistical

software. Statistical significance was defined as p value  $< 0.05$ .

## RESULTS

There were 22 patients who presented with biopsy-proven, node-negative lower extremity malignant melanoma and underwent excision and inguinal SLNB from January 2013 to January 2015. Among them, 13 (59.1%) patients had positive inguinal SLNB and 9 (40.9%) patients had a negative inguinal SLNB. The mean follow-up period after surgery was 72.3 months (6.02 years) with a range of 62.7-83.7 months (5.2-6.98 years).

The mean (SD) age of patients at the time of presentation was  $40 \pm 9.3$  years, of which 12 (54.5%) were males. The median patient age was 40 years in ISLNB positive group and 44 years in ISLNB negative group. Patients with age  $\leq 45$  years were more likely to have a tumor with positive ISLNB (8 out of 13) and it was found to be statistically significant ( $p=0.019$ ). Mean (SD) total duration of melanoma at the time of presentation was  $12 \pm 7$  months.

The most common site of melanoma was foot 14 (63.6%), followed by leg 3 (13.6%), thigh 2 (9.1%), knee and popliteal fossa 2 (9.1%), and ankle 1 (4.5%). Mean (SD) size of tumor (Length x width) was  $4 \pm 1.5 \times 3 \pm 1.1$  cm. Mean (SD) tumor Breslow thickness was  $2.57 \pm 0.86$  and 17 (77.3%) tumors had ulceration. Most common melanoma subtype was superficial spreading in 10 (45.4%), nodular in 5 (22.7%), acral lentiginous in 4 (18.2%), lentigo maligna in 2 (9.1%) and desmoplastic melanoma in 1 (4.5%). In 5 (22.7%) of patients, melanoma arisen from pre-existing nevus while 1 (4.5) arisen from post-burn scarring. There was no statistically significant difference in ISLNB positive and negative patients in distribution according to gender, anatomical site, ulceration, and tumor subtype. (Table 1).

**Table-1:** Demographic, clinical, and histopathological data of patients with positive and negative Inguinal sentinel lymph node biopsy (ISLNB).

Demographic, clinical, and histopathological characteristics	Positive ISLNB patients (%)	Negative ISLNB patients (%)	p-value
<b>Age</b> 15-45 years (n=14) 46-75 years (n=8)	8 (36.4) 5 (22.7)	6 (27.3) 3 (13.6)	0.33 0.019
<b>Gender</b> Male (n=12) Female (n=10)	6 (27.3) 7 (31.8)	6 (27.3) 3 (13.6)	0.34 0.61
<b>Anatomical location</b> Thigh (n=2) Knee and popliteal fossa (n=2) Leg (n=3) Ankle (n=1) Foot (n=14)	1 (4.5) 2 (9.1) 3 (13.6) -- 7 (31.8)	1 (4.5) -- -- 1 (4.5) 7 (31.8)	0.45
<b>Melanoma arising from the previous nevus</b>	3 (13.6)	2 (9.1)	
<b>Melanoma arising from post-burn scar</b>	1 (4.5)	---	
<b>Breslow thickness</b> ≤ 2.0 mm (n=9) 2.1 – 4.0 mm (n=13)	2 (9.1) 11 (50)	7 (31.8) 2 (9.1)	0.0034
<b>Ulceration</b> Yes (n=17) No (n=5)	11 (50) 2 (9.1)	6 (27.3) 3 (13.6)	0.32
<b>Melanoma subtype</b> Superficial spreading (n=10) Nodular (n=5) Acral lentiginous (n=4) Lentigo maligna (n=2) Desmoplastic melanoma (n=1)	8 (36.4) 2 (9.1) 2 (9.1) -- 1 (4.5)	2 (9.1) 3 (13.6) 2 (9.1) 2 (9.1) --	0.28

The range of resection margin was 10-20 mm according to proximity to vital structures. Mean margin clearance achieved after tumor resection was 9.2mm (Range 5-15mm). Number of SLN sent for frozen section was 2 in 12 (54.5%) and 1 in 10 (45.5%). Inguinal SLNB was positive for tumor cells in 13 (59.1%) and negative in 9 (40.9%) patients. Completion inguinal lymph node dissection (CILND) with Saphenous sparing and Sartorius muscle transposition was done in SLNB positive patients after confirmation by frozen section during the same surgery. To

reduce the risk of lymphedema, all patients undergoing CILND, were advised to use compression garments for at least 6 months postoperatively.

ISLNB negative patients had a few complications as compared to ISLNB positive patients. No complication was seen in 14 (63.6%) patients with partial graft loss in 4 (18.2%), wound dehiscence in 2 (9.1%), seroma formation after complete inguinal lymph node dissection (CILND) in 2 (9.1%), and flap tip necrosis in 2(9.1%). Lymphedema did not develop in our study patients. (Table 2).

**Table-2:** Distribution according to complications in Inguinal SLNB positive and negative patients.

Complications (n=9)	ISLNB positive patients (%)	ISLNB negative patients (%)
Partial graft loss (n=4)	3 (13.6)	1 (4.5)
Infection and wound dehiscence (n=2)	2 (9.1)	--
Seroma formation (n=2)	2(9.1)	--
Skin flap tip necrosis (n=2)	2(9.1)	--
No complications (n=14)	6 (27.3)	8 (36.4)

It was observed that patients with negative SLNB had a better outcome. Local recurrence in the form of the nodule/non-healing ulcer near or under the previous tumor resection site was seen in 6 (27.3%) patients within mean (SD) time of 3.16 ± 1.5 months. Out of the 5 (22.7%) patients were SLNB positive while only 1 (4.5%) was SLNB negative. Recurrence in the regional lymph nodes (Inguinal) occurred in 2 (9.1%) patients who were SLNB negative. Distant metastasis occurred in 11 (50%) patients (not significant, *p* value 0.19). The mean (SD) number of days of hospital admission at the time of surgery was 3.7 ± 1.2 days (significant, *p* value 0.037). Out of 22 patients, 11 (50%) required additional hospital admission for 14 ± 5.4 days (range

6-25 days) for management of surgery or outcome (recurrence and metastasis) related complications (not significant, *p* value 0.46). The total number of OPD visits during the first-year follow-up was less in Inguinal SLNB negative patients i.e,  $7.7 \pm 3.7$  compared to  $10 \pm 4.14$  in Inguinal SLNB positive patients (significant, *p* value 0.097). It was also observed that 11 (50%) remained alive and disease-free even after a mean follow-up period of 72.3 months (6.02 years) after surgery, with additional 4 (18.2%) patients alive after chemotherapy for recurrence or metastasis. Mortality of 7 (31.8%) SLNB positive patients occurred after a mean time period of  $8.4 \pm 3.4$  months during treatment. No death occurred in SLNB negative patients. (Table 3).

**DISCUSSION**

SLNB is a minimally invasive technique for the detection of metastatic melanoma in a targeted fashion using radioisotopes. It was first described by Morton and colleagues in 1992.<sup>6</sup> With the refinement of the technique, its reliability and acceptance have increased worldwide. In this observational study, the

impact of SLNB on survival outcome of lower extremity melanoma patients was studied in relation to clinicopathological characteristics. It was noticed that in patients with age 45 years and younger, the risk of lymph node involvement became higher which was comparable with the results of other studies.<sup>7</sup> In our patients, it was most likely associated with a longer duration of melanoma and delay in seeking treatment. After the diagnosis of melanoma by incisional biopsy, the single most important factor that determines further management course is the thickness of the melanoma.<sup>8</sup> Various studies have shown that Clarks levels are only prognostic for <1mm thick melanoma.<sup>9</sup> In most of our cases melanoma thickness was >1mm at the time of presentation due to delayed presentation and diagnosis. Therefore, in this study, Breslow thickness was considered.

There are no defined criteria to identify these lower extremity melanoma patients who have more chances to have positive SLNB results. Most guidelines suggest considering SLNB for melanomas with pathologic stage T1b and above, as well as T1a melanomas with high-risk features.<sup>10</sup> In the present study, all

**Table-3:** Outcome in both inguinal SLNB positive and negative patients.

Outcome measures (n= number of patients)		ISLNB positive patients (%)	ISLNB negative patients (%)	<i>p</i> - value
Recurrence (n=8)	Local nodule (satellite or in transit) (n=6)	5 (22.7)	1 (4.5)	---
	Regional nodal basin (n=2)	--	2(9.1)	
Metastasis (n=11)	Pelvic Lymph nodes (n=8)	7 (31.8)	1 (4.5)	0.19
	Pulmonary (n=9)	7 (31.8)	2 (9.1)	
	Hepatic (n=1)	1 (4.5)	--	
	Peritoneal (n=1)	1 (4.5)	--	
Morbidity and mortality	Mean ± SD number of days of hospital admission after surgery (n=22)	$4 \pm 1.3$ (n=13)	$3 \pm 0.5$ (n=9)	0.037
	Mean ± SD number of additional days of hospital admission during the first year after surgery (n=11)	$14 \pm 6$ (n=8)	$13.7 \pm 3.3$ (n=3)	0.46
	Mean ± SD number of OPD visits during the first year follow up	$10 \pm 4.14$ (n=13)	$8 \pm 3.7$ (n=9)	0.097
	Number of patients alive without disease (n=11)	5 (22.7)	6 (27.3)	0.47
	Number of patients who are alive after receiving chemotherapy (n=4)	1 (4.5)	3 (13.6)	
	Number of patients who died during treatment (n=7)	7 (31.8)	--	



melanoma patients with <4mm thickness and clinically no palpable inguinal lymph nodes were included. It was found that positive SLNB results were directly related to increasing Breslow thickness and ulceration. It was also observed that delayed presentation in seeking medical advice for developing lesion resulted in deeper melanoma with Breslow thickness ranging from 2.1-4.0 mm in 13 (59.1%) patients. Sladden et. al. reported equivocal results for wider versus narrower margins of melanoma excision in their systematic review.<sup>11</sup> The same finding was implemented by taking a narrow margin (10 mm) near the heel pad and the wider margin (20 mm) elsewhere. Regarding anatomical location, it was seen that the foot was the most common site of presentation in the lower extremity. Some studies showed that up to one-third of total body melanoma presentation occurs in the foot or distal lower extremity.<sup>12</sup> It was also observed that superficial spreading melanoma was the most common primary histological subtype 10 (45.5%) which was consistent with findings of several other studies.<sup>13</sup>

It is proven now that surgical morbidity of SLNB is very low as it is minimally invasive compared to complete inguinal lymph node dissection (CILND). All the patients with positive SLNB results (13 (59%) in our study) underwent CILND to achieve regional control. It does not reduce the risk of further spread of tumor but reduces disease burden. To reduce the risk of lymphedema, saphenous vein sparing inguinal lymph node dissection with sartorius muscle transposition was done in all patients.<sup>14,15</sup> In the postoperative period, all patients who underwent complete inguinal lymph node dissection were advised compression garments and lymphatic drainage massage for at least 6 months to reduce the risk of lymphedema<sup>16</sup>. Various studies show complications rate of up to 71-77% after CILND with seroma formation in 46%.<sup>17</sup> Overall complication rate in our patients was 41%, including partial graft loss, infection and wound dehiscence, seroma formation,

and skin flap tip necrosis. Most of these complications were seen in SLNB positive patients (36.4%) and were associated with CILND. One of the SLNB negative patients 4.5% patient had partial graft loss which healed by conservative management.

In literature, it is described that the chance of recurrence in SLNB negative patients ranges from 9-24%<sup>18,19</sup> which was found to be 4.5% in our study. It is thought to be associated with primary hematogenous dissemination instead of lymphatic spread.<sup>20</sup> Certain prognostic factors such as increasing age, thicker primary tumor, ulceration, nodular subtype<sup>21</sup>, and the location at foot<sup>22</sup> were found to be associated with a high risk of recurrence. Recurrence at the primary tumor site was mostly seen in SLNB positive patients (22.7%) and was associated with deep, ulcerated melanoma (Mean Breslow thickness 3mm).

In our study, 9.1% of SLNB negative patients later on developed regional lymph nodal metastasis which was consistent with the range of 3-11% given by various studies.<sup>23</sup> It was also seen that 13.6% of our SLNB negative patients developed pelvic lymph node and distant metastasis after ILND which was diagnosed at 6 months follow up with CT chest, abdomen, and pelvis. Also, distant metastasis developed in 36.4% of SLNB positive patients who underwent CILND at the time of tumor extirpation. It can be explained by the concept of primary hematogenous spread as described earlier.<sup>24</sup> With respect to morbidity, the low rate of surgery-related complications and metastasis in 31.8% of SLNB negative patients resulted in a reduced need for the hospital stay and OPD visits. Those SLNB negative and positive patients (18.2%) who had chemotherapy for distant metastasis and were alive even after five years of follow-up, had to visit the hospital more frequently for the treatment of surgery and chemotherapy-related complications leading to prolonged morbidity. It was also observed that the disease-free survival rate markedly reduced with the presence of positive sentinel lymph node and increased thickness of the primary

tumor. A high mortality rate was seen in SLNB positive patients (31.8 %). In our study, 5-year survival was 68.2% which was comparable with the range 51-87% of various studies.<sup>25</sup>

Our study has certain strengths and limitations. The main strength of our study is that it gives a detailed analysis of demographical, clinical, histopathological, and follow-up data with respect to SLNB negative and positive results. It also gives thorough information about the surgical approach for the excision of melanoma and regional lymph node management in our patients. Also, high-quality follow-up data in terms of recurrence, overall morbidity, and mortality is measured in detail.

### Limitation of study

The main limitation of our study is that it is a retrospective cohort from a single-center leading to more chances of selection bias. The patient number was also small and results were based on a relatively short follow-up period (5 years instead of 10 years). There are different imaging and lymphoscintigraphy protocols to identify sentinel lymph nodes therefore, our study results cannot be generalized.

### CONCLUSION

SLNB is a minimally invasive technique that can help early detection of lymphatic spread of lower extremity melanoma. By making it a routine procedure in node-negative malignant melanoma of the lower extremity, a better outcome can be achieved in terms of survival and quality of life with fewer complications, a smaller number of hospital admission days, and OPD visits.

### AUTHOR'S CONTRIBUTION

SM: Main researcher

AFB: Supervisor of the research work

SU: Helped in data collection and writing

ST: Data analysis and performed analytical calculations

EAK: Data collection and performed computation

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