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Failure to identify sentinel lymph nodes for malignant melanoma – Outcome after over 10 years median follow up

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ABSTRACT

Background: Sentinel lymph node biopsy (SLNB) is routinely performed during surgery for malignant melanoma, using double mapping. Still, in some cases, a sentinel lymph node identified pre-operatively by lymphoscintigraphy is not identified during surgery. We hypothesized that disease specific survival would not be significantly impacted by intra-operative lymph node mapping (IOLM) failure.
Methods: The patient population study included 1300 malignant melanomas operated on by a single surgical oncologist (H.G.) after sentinel lymph node scintigraphy. Patients were included in the analysis if intra-operative lymph node (IOLM) mapping failed.
Results: Among 1300 patients who underwent surgery for malignant melanoma during the study period and after median follow up of >10 years, 33/36 lymphatic drainage basins with failed sentinel node identification were free of disease. Disease specific survival for the entire group of 33 patients with IOLM failure was 91.0%, which is comparable to previously published disease specific survival for all melanoma patients.
Conclusion: We conclude that failure to identify a pre-operatively marked sentinel lymph node by an experienced melanoma surgeon has, generally, no impact on disease specific survival, as demonstrated in this review of a series of surgical melanoma patients.

Background

Sentinel lymph node biopsy (SLNB) is routinely performed during surgery for malignant melanoma. Involvement of sentinel lymph node with malignant tumor cells was shown to be the most important prognostic factor for staging and determining disease free survival [1]. More than 85% of patients with primary cutaneous melanoma have localized melanoma that can be cured with wide local excision alone [2]. Sentinel lymph nodes are commonly identified by the double mapping technique, using both Tc99 labeled colloidal tracer preoperatively and intraoperative injection of specified lymphatic tracer blue dye [3], and a hand held gamma detector. Identification of sentinel LN using this technique has a 99% success rate [4]. Occasionally, sentinel lymph nodes identified pre-operatively by lymphoscintigraphy are not identified during surgery. However, no studies discussing such cases were found in the literature. This situation creates a clinical dilemma for surgeons – how extensive a dissection is needed in order to find the pre-operatively identified sentinel lymph node, and what is the potential impact of non-retrieval of a node at risk [5]. We reviewed the clinical outcome of patients in whom sentinel lymph nodes were not identified during surgery with special reference to the risk of failure at the site of missed sentinel node and rate of melanoma recurrence. We hypothesized that disease specific survival would not be significantly impacted by IOLM failure.

Methods

Study design

This study is an observational retrospective study based on a prospectively collected, institution registered data base. This data base included 1300 malignant melanoma patients operated on by a

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single surgical oncologist (H.G.). Patients were included in the analysis if intra-operative lymph node (IOLM) mapping failed. Failure was declared when (1) IOLM failed to recognize any sentinel node in a lymphatic basin marked pre-operatively, or (2) preoperative mapping and IOLM failed to demonstrate any sentinel lymph nodes. All pre-operative lymphoscintigraphy results were revised by a single nuclear medicine imaging specialist (H.B). All patient's files, operative notes, pathology reports and status at end of follow up were reviewed for this study. The study was approved by the institutional review committee of the Rabin Medical Center (RMC-16-0296)

Patients and methods

This study included 1300 patients who underwent melanoma surgery at Beilinson Hospital between 1994 and 2015. All lymphatic drainage basins at risk were preliminarily evaluated clinically, by ultrasound or PET CT according to the risk assessed based on the revised pathology of the primary melanoma. Pathologic revision referred mainly to thickness, mitotic rate, lymphocytic infiltration, presence and extent of regression, ulceration, pleomorphism, cellularity, and margins of primary biopsy.

Since 1994, all patients with vertical growth phase melanoma and negative regional and systemic workup have been offered sentinel node biopsy with preoperative lymphoscintigraphy.

Briefly, 2–3 mCi of Technetium 99m–labeled nano-colloid (Nanocoll; Nycomed Amersham Sorin Srl, Milan, Italy) were injected intra-dermally at 4–6 sites around the biopsy scar or the primary lesion (0.1–0.3 mL). Day before surgery, gamma cameras equipped with a high-resolution collimator were used to obtain static images. The projected location of the sentinel node was marked on the patients' skin. Both imaging and skin markings were performed with the patient lying in the position planned for their future surgery. All patients underwent IOLM during the operation with injection of Patent Blue V dye (Laboratoire Guerbet, Aulnay-Sous-Bois, France). A handheld gamma probe (Neoprobe 1000 or 2000; Neoprobe Corporation, Dublin, Ohio) has been used for this procedure at our hospital since 1997. Sentinel nodes were serially sectioned, stained with standard hematoxylin-eosin, and, if negative, stained with S100 and HMB-45, or with Melanoma Cocktail. Patients found to have an involved sentinel node or a clinically apparent metastatic lymph node, without evidence of systemic disease, underwent completion lymphatic basin dissection. Upon the initiation of this technique during 1994-5, three patients with intermediate thickness melanoma still underwent prophylactic lymphatic basin dissection concurrent with IOLM. Those patients were excluded from this study.

Results

Among 1300 patients who underwent surgery for malignant melanoma during the study period, 33 patients had IOLM failure. IOLM failure occurred in 36 of 63 lymphatic drainage basins at risk demonstrated by preoperative lymphoscintigraphy. These patients/basins form the cohort investigated in this study. Disease recurrence after IOLM failure occurred in 4 patients. The lymphatic drainage basins' locations, IOLM failure rate, and recurrence rates are depicted in Table 1. Recurrence rates, death rates, and disease specific survival rates/patient are depicted in Table 2. Lymphoscintigraphy and operative findings of patients with axillary IOLM failures are specifically depicted in Table 3, as they are relatively uncommon.

Sentinel nodes were not retrieved in 36/63 lymphatic drainage basins. After a median follow up of >10 years, 33/36 lymphatic drainage basins with failed sentinel node identification were free of disease.

Table 1
Basins locations, IOLM failure rate, and recurrence rate.

Basin location	Number of pre-operatively mapped basins	Number of basins with IOLM failure	Number of basins with melanoma recurrence
Axilla	20	7	0
Neck	14	10	1
Superficial Inguinal	5	1	0
Supra Clavicular	4	2	0
Submandibular	2	0	0
Scapular	4	2	0
Femoral	2	0	0
Iliac	2	2	1
Labial fold	2	0	0
Forearm	2	1	0
Others: Parotis, Peri-Nuchal	2	1	0
Infra Clavicular	1	1	0
Deep Inguinal	1	0	0
Popliteal	2	1	1
Total	63	36	3

IOLM-intra operative lymph node mapping.

Over all four patients with melanoma recurrences were noted in this patient series.

Patient #1 who presented with scalp melanoma (Breslow 1.6 mm, Clark level 4, no ulceration) with only blue channels identified during an attempted right neck sentinel lymph nodes biopsy, had a massive neck recurrence two years later, subsequently dying of melanoma.

Patient #2 presented with scalp melanoma (Breslow 10 mm, Clark level 5, satellites, ulceration, and 6 mitosis/mm). Lymphoscintigraphy indicated drainage to the right anterior neck. Four sentinel nodes free of metastases were removed from the anterior neck (triangles 2–3). One month post-surgery the patient presented with a necrotic, metastatic lymph node in his right posterior neck (Triangle 5), which had not been identified during preoperative ultrasound, lymphoscintigraphy or IOLM, and thus was considered an IOLM failure. This patient died of metastatic melanoma 6 months following surgery.

Patient #3 had a wide local excision of a melanoma of the right forearm (Breslow 2 mm, clark level 4, no ulceration), with negative axillary SLNB of the right axilla. Four years later this patient presented with synchronous left shoulder (Breslow 1.9 mm, Clark level 4, no ulceration) and right foot (Breslow 2 mm, Clark level 4, no ulceration) melanomas. He had a femoral microscopically metastatic sentinel lymph node, and IOLM failed to identify an external iliac sentinel node. The patient then underwent a completion radical superficial groin dissection that was negative for metastatic melanoma in the remaining 12 nodes. Five years after the superficial groin dissection, this patient had local recurrence on his foot with concurrent metastasis in his right calf (in transit), right iliac nodes, and left groin. Due to this regional-in transit - systemic failure he was treated by IL2 based chemo-biotherapy, achieved full remission and is currently alive with no evidence of disease, seven years after melanoma recurrence.

Patient #4 had a primary melanoma of the left foot (Breslow 1.95 mm, Clark level 4, with ulceration). Pre-operative lymphoscintigraphy demonstrated linear uptake of TC-99 along his entire left leg and focal uptakes in his left calf, knee, groin, and left pelvis. During surgery five popliteal, groin, and mid left thigh nodes were retrieved, with residual gamma radiation detected in the popliteal region/upper calf. Attempts at discovering additional lymph nodes failed. Micro-metastases was found in one sentinel mid-thigh in-transit lymph node. Completion lymph node dissection was not

Table 2
Disease specific survival and melanoma recurrence rate.

	Thin melanoma	Intermediate thickness melanoma	Thick melanoma	All
Disease specific survival	100%	91.00%	75%	91%
Basins with melanoma recurrence/basins with IOLM failure	0/7	3/22	1/4	33
Melanoma related death rate	n = 0	n = 2	n = 1	n = 3
Median follow up period	9.85 years (range 6.53–15.28)	11.31 years (range 1.47–21.78)	10.55 years (range 0.2–20.34)*	11.16 years (range 0.2–21.78)

IOLM- Intra operative lymph node mapping failure.
* Patients with very short follow-up periods (1.47 in intermediate thickness group and 0.2 in thick melanoma group) are patients who died a short time after surgery.

Table 3
Axillary intra-operative lymph node mapping failures.

Patient number	Age	Primary Melanoma	Lymphoscintigraphy findings	Operative Findings
1	71	Right trapezius muscle area	Lymphoscintigraphy report was vague, sentinel lymph nodes were possibly supraclavicular rather than axillary	No Sentinel lymph nodes were detected. only a supraclavicular lymph channel with blue dye was identified.
2	38	Right upper back	Right Axillary lymph node and Right Scapular in transit uptake was reported. Uptake from the primary might have been identified as sentinels.	Sentinel nodes were not identified, one axillary non-sentinel node was biopsied.
3	59	Left arm	Left axilla	Only a blue channel was found during surgery.
4	57	Upper back	Both Axillae	No radioactivity and no blue dye in both axillae during surgery. Obese patient with large amounts of fatty tissue in both axillary regions.
5	50	Left upper back	Left Axilla	No blue dye or radioactive uptake.
6*	64	Subxyphoid	A repeated lymphoscintigraphy after 24 h did not demonstrate uptake outside the primary melanoma site.	On the left side 11 left axillary non sentinel lymph nodes were biopsied, All negative for malignancy. Right axillary sentinel nodes was not identified, blue tissue was biopsied but no lymph nodes were identified by the pathologist.

*patient number 6 was counted as two axillary failures.

performed. One year later he had a recurrence in-transit along the entire left leg, and subsequently died of metastatic melanoma.

In summary, four melanoma recurrences in association with IOLM failure were detected in this cohort; three were in lymphatic drainage basins missed by IOLM (patients # 1,3,4). In two of these three cases the recurrence was in the context of in-transit and systemic disease recurrence (patients # 3,4), where patient #3 was salvaged by chemo-biotherapy. Patient #2 failed in the neck (Triangle 5) one month after negative 4 sentinel nodes were retrieved from the ipsilateral neck Triangles 2–3. Drainage to Triangle 5 had not been noted on preoperative lymphoscintigraphy. The metastatic node was also missed by preoperative US that seems to have screened only the anterior neck.

Disease specific survival for the entire group of patients with IOLM failure was 91.0% (3/33 patients died of melanoma). Median disease-free survival was 11 years (range 0.2–21. years). Rate of melanoma recurrence was 12.0% (n = 4) during a median follow up period of 11 years (range 0.64–22 years).

Discussion

In this cohort with a median follow up of >10 years, melanoma specific survival was 91% and 75% for intermediate thickness and thick melanoma respectfully (81.4% and 58.9% in MSLT1) [6]. The non-inferiority of this cohort compared to MSLT1 supports our hypothesis, that IOLM failure does not significantly affect disease-free and over-all survival.

While failed IOLM is not very frequent as reflected in this cohort (33 lymphatic drainage basins of approximately 1442 lymphatic drainage basins operated on), this is still an under-reported and under investigated event. IOLM failure could result from several technical reasons; a vague description of sentinel lymph nodes location, a decay of radioactive substance, low lymphoscintigraphy marking threshold, difficult anatomic location (e.g. neck, mammary chain, subcostal/paraspinal), surgeon's technical failure, and discordance between gamma camera and hand-held probe sensitivities. Upper back melanomas might be more prone to IOLM failure, as they were associated with most cases of axillary IOLM failure in this cohort. These cases are described Table 3.

However, some biological factors were also important in the cohort, as in those patients with concurrent in-transit/satellite failures (patients #2, 3, 4), sentinel node massively replaced by metastases (patient #2), and scalp and foot locations (patients #1,2 and 3,4 correspondingly). The neck area has long been associated with higher IOLM failure rates [7,8]. The need to retrieve external iliac/obturator sentinel nodes is still debatable [9,10].

Our hypothesis that IOLM failure is not associated with failures in these specific lymphatic drainage basins can be supported by our data. Nevertheless, it is noticeable that patients #1 and #3 could have had a higher probability for cure had their sentinel nodes (neck, external iliac) been identified at first surgical attempt followed by completion dissection (neck and ilio-inguinal correspondingly).

Patients #2 and #4 had melanomas with very aggressive biological behavior. Both could not have been salvaged by a “better” IOLM.

Patient #2 was evaluated preoperatively by CT head, chest and abdomino-pelvis + US of the neck (PET unavailable at that time). We presume that the posterior (Triangle 5) metastatic node was missed by those tests, and by-passed by the radioactive tracer due to the massive necrotic metastatic replacement of the Triangle 5 node that became clinically apparent one month post-surgery.

This study has some limitations. The number of lymphatic drainage basins is small although we reviewed a large data base of 1300 patients. As an immediate outcome, we identified only four recurrences. The size of the cohort limits the validity of our

conclusions, specifically regarding the disease specific survival data.

Conclusion

Failure to identify a pre-operatively marked sentinel lymph node by an experienced melanoma surgeon had low impact on disease specific survival as demonstrated in this series of surgical melanoma patients. However, such a failure regarding formal lymphatic (as opposed to in-transit) basins may become significant for some patients. Our results suggest that ultrasound for head and neck melanomas should include the posterior neck as well. External iliac sentinel nodes' retrieval should be individually considered, and PET CT is recommended for better evaluation of very-high-risk lesions preoperatively.

Postoperative (clinical, ultrasound) follow up is well deserved for these missed basins.

Competing interests

We have no competing interests to declare.

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