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OPTIMIZING THE STAGING OF MELANOMA PATIENTS FOR THEIR BEST SURGICAL MANAGEMENT

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ABSTRACT

Interval nodes (IN) are defined as lymph nodes that lie along the course of lymphatic collecting vessels between a primary tumor site and a draining node field. Sometimes INs contain metastases and a consensus on their surgical management is needed. Therefore, to optimize the surgical management of melanoma patients with metastatic lymphatic involvement, especially when the sentinel lymph node biopsy identifies an unusual drainage field, we identified patients treated at the Department of Plastic and Reconstruction Surgery of Bari between July 1994 and December 2012 identified with a primary-cutaneous melanoma who underwent lymphoscintigraphy and subsequent positive-IN the lymphadenectomy to evaluate the impact of this procedure on overall survival and disease-free-period. 51 patients presented INs, and lymphadenectomy (LA) of the subsequent lymphatic field was performed in 13 subjects with positive-IN. In 4 cases additional lymphatic metastases were detected in the usual basin beyond the IN+. Recurrence-free period and survival rate at 5 years were higher in patients with positive-IN who underwent LA than in subjects who underwent LA due to positive lymph nodes in the usual field. Immediate lymphadenectomy of the subsequent lymphatic field in patients with positive-INs may afford patients earlier stage treatment of their disease and improved prognosis.

Keywords: melanoma, interval node, lymphatic mapping, sentinel node biopsy, in-transit lymph node, lymphoscintigraphy, prognosis

Melanoma frequently metastasizes to regional lymphatic pathways and the first lymph node receiving direct lymphatic drainage from a primary tumor site is called the sentinel lymph node (SN) (1). Lymphoscintigraphy (LS) is an indispensable tool to identify dispersion into sequential lymph node basins (2,3); sentinel lymph node biopsy (SNB) allows better staging of disease by identifying patients eligible for loco-regional lymphadenectomy. Lymphatic mapping is useful to identify both conventional basins (axillary, inguinal/pelvic, and cervical) and "unusual" sentinel node fields. Variously termed *interval, aberrant, in-transit, ectopic*, or *intercalated nodes* (4-11), these lymph nodes located outside of the conventional nodal basins sometimes contain metastatic disease. The interval nodes (IN) are defined as lymph nodes that lie along the course of lymphatic collecting vessels between a

TABLE 1
Clinical Characteristics of Patient Population and Primary Tumor Sites

Characteristics	Patients without IN	Patients with IN
Total, n (%)	504	51 (9.19)
Gender (M), n (%)	271 (53.8)	26 (51.0)
Age (y)		
Median	53.6	56.5
Range	13.0 – 94.2	30.6 – 79.2
Breslow thickness, n (%)		
≤2 mm	352 (69.8)	28 (54.9)
2-4 mm	91 (18.0)	12 (23.5)
≥4 mm	61 (12.1)	11 (21.6)
Ulceration, n (%)		
Present	121 (24.0)	17 (33.3)
Primary site, n (%)		
Posterior Trunk	165 (32.7)	21 (41.2)
Anterior Trunk	90 (17.9)	9 (17.6)
Head and Neck	48 (9.5)	10 (19.6)*
Upper limb	55 (10.9)	1 (2.0)
Lower limb	146 (29.0)	10 (19.6)*
Histological subtype		
Superficial Spreading	251 (49.8)	27 (52.9)
Nodular	103 (20.4)	13 (25.5)
Others	150 (29.8)	11 (21.6)

*p<0.05

primary tumor site and a draining node field (4). They can occur anywhere along the course of the vessels and are usually found in subcutaneous fat. In the literature, there is not a consensus on interval classification although the frequency of these lymph nodes is different, representing 2% in some studies and rising to 22% in others (4,5,12-14). These differences in prevalence are related to difficulty in their detection and to the absence of a consensus in their classification. However, although the presence of occult metastases in IN indicates a worse prognosis (15), there are no guidelines for surgical treatment when interval nodes contain metastases (10,16,17).

MATERIAL AND METHODS

Study Population

All patients with a primary cutaneous melanoma treated in the Department of Plastic and Reconstructive Surgery of Bari are included in an electronic clinical medical registry after giving informed consent. Patients with another occult primary carcinoma were excluded from the study. The 555 patients (M 53.5%, mean age 54.2 ± 16.5 years) who underwent a lympho-scintigram from 01/07/1994 to 31/12/2012 were enrolled. The clinical-pathological features and the location of the primary cutaneous melanoma are reported in *Table 1*. Within the 90th day of excision of the primary lesion, patients with a primary melanoma ≥ 0.75 mm in thickness or with Clark level IV or V invasion, or with a thinner tumor associated with adverse prognostic features (regression, ulceration, high mitosis rate) underwent lymphoscintigraphy to identify SN draining fields. The follow-up period is defined as the time between the melanoma diagnosis date until the last visit occurred by

the end of June 2013, so that the hypothetical shorter-term follow-up is fixed at 6 months.

Mapping, Surgical, and Histological Techniques Used for Lymphatic Metastasis Diagnosis

Lymphoscintigraphy was performed using technetium 99m nanocolloid HSA (human serum albumin) (18-20) with a dosage of 18-37 MBq injected in 4 sites closely around the scar of the primary lesion biopsy (18,19). Ultrahigh resolution collimators were used to ensure that all the territory between the primary melanoma site and the recognized draining node field or fields was imaged and to reduce artifacts. Dynamic and planar images (anterior, posterior and lateral) were acquired using a large field of view dual-headed digital gamma camera both immediately after the radio-labelled colloid injection and then after every lymph node visualization to ascertain all drainage basins and the total node number. A 25-min dynamic image at 1 frame/min in 64x64 matrix in word mode was used to determine where the lymphatic collectors were headed. Further 5-10 min static images in word mode 128x128 were acquired over the node field to identify the collectors as they reach the actual SNs. Static images were performed to ensure that all SNs were marked. A static imaging node that appears in a separate field only in a subsequent image was considered as a different SN, unless it was on the same path in the dynamic scans. A handheld gamma probe was used during surgery to guide SN detection. Multiple sections of each SN were examined by conventional hematoxylin and eosin (H&E) and by immunohistochemical stains at both S100 and HMB-45 (21). A positive SN was defined as a lymph node containing melanoma cells detected by either H&E or immunohistochemistry. All histo-pathologic slides of the interval SNs containing metastatic disease were reevaluated for this study to document the deposit size, the tumor penetrative depth, and the intranodal tumor volume. The histological presence of metastasis was categorized into micrometastasis (with deposits $\leq$ 2mm) and macrometastasis (with deposits >2mm) affecting the peripheral sinus of a lymph node (20,22). Complete lymph node dissection was performed in all cases with a diagnosis of lymph node metastasis. All patients underwent a clinical and imaging follow-up every six months for the first five years and yearly thereafter.

Sentinel Lymph Node Assessment

Axillary, inguinal, and cervical (levels I-V) regions are considered as usual (or major) lymph node drainage fields. Supraclavicular, preauricular/parotid, and chin lymph nodes were included in the cervical basin; iliac and pelvic nodes in the inguinal field; all the lymph nodes between the anterior and posterior axillary line and the 6th intercostal space were considered to be in the axillary drainage basin. In some studies, popliteal and epitrochlear nodes are classified as IN (4,5,14), while – in accordance with other authors (24,25) – we considered these sites as a functional extension respectively of the inguinal and axillary fields. The lymph nodes that lie along the course of lymphatic collecting vessels between a primary tumor site and a draining node field (4), recognized as being outside anatomical lymph node basins (5,14), are defined IN.

Statistical Analysis

Patients' baseline characteristics were reported as the frequency (percentage) and mean ± standard deviation (SD) or median and interquartile ranges. Categorical variables were assessed by the chi-squared test to compare the results for specific subgroups with those of the rest of the patient population. Recurrence-free survival was defined as the time between the definitive surgical treatment of the primary melanoma and clinical detection of the first recurrence.

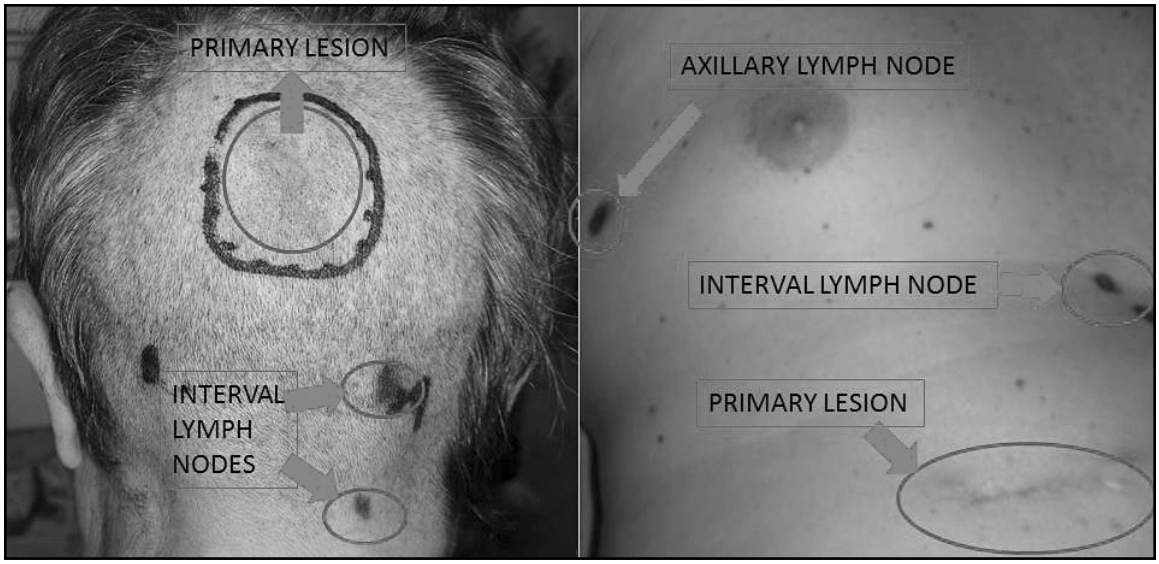

Fig. 1. Interval nodes identified in subcutaneous fat of the nuchal (left) and xiphoid (right) regions.

Follow-up time was defined as the time between definitive surgical treatment of the primary melanoma and the last contact with patients. Time-to-death analyses were performed using multivariate Cox proportional hazards regression models, and risks were reported as hazard ratios (HRs) along with their 95% confidence interval (CI). Survival curves and probabilities were reported according to the Kaplan-Meier method. All statistical analyses were performed using SAS Software Release 9.2 (SAS Institute, Cary, NC).

RESULTS

Frequency of Interval Lymph Node

Among 555 subjects who underwent lymphoscintigraphy, 51 patients (9.19%) had interval SLNs identified. Some examples of interval nodal drainage on lymphoscintigraphy are shown in *Fig. 1*. The majority of interval SNs (58.8%) occurred in cutaneous melanomas arising on the trunk, but INs are reported significantly more frequently in patients with melanomas on head and neck. The incidence of interval nodes in upper and lower limbs was significantly lower ($p<0.001$). No further major differences were found in age and gender or primary tumor characteristics between patients with and without interval SNs. With regard to the location of INs, we classified the following anatomical regions:

- nuchal region, bounded by a horizontal line passing through the occipital prominence and a horizontal line passing through the 7th cervical vertebra;
- mastoid region, laterally to the nuchal region and bounded by auricular-mastoid sulcus;
- anterior thoracic region, bounded at the top by the inferior margin of clavicles, below by the xiphoid process and the lower margin of the 12th rib, and laterally by the anterior axillary lines;
- posterior thoracic region, bounded at the top by a horizontal line passing through the occipital prominence, below by the lower margin of the 12th rib, and laterally by the posterior axillary lines;
- anterior abdominal wall, including

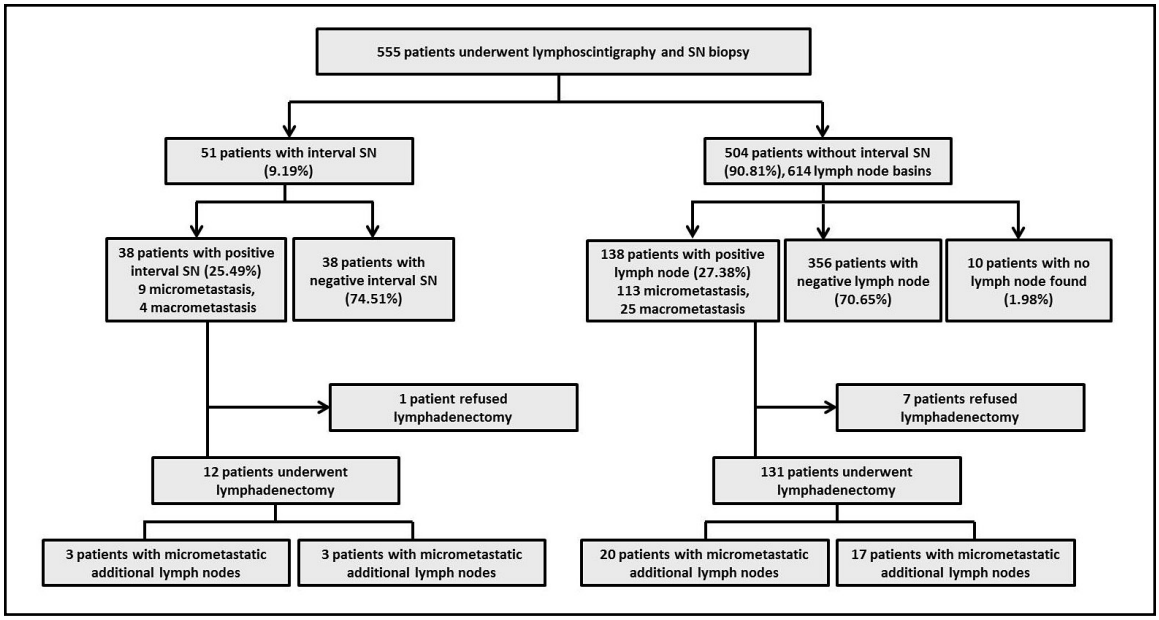

Fig. 2. Schematic flowchart and findings of the 555 patients studied.

lymph nodes located above the inguinal ligament but not classifiable as iliac-obturator basins, because these lymph nodes are in the thickness of the abdominal wall up to the transversalis fascia;

- lumbar region, bounded at the top by the lower margin of the 12th rib and below by the iliac crest.

In our experience, the lymph nodes were distributed as follows: 17 cases (33.3%) in posterior thoracic region, 14 (27.4%) in anterior abdominal wall, 7 (13.75%) in anterior thoracic region, 6 (11.8%) in nuchal region, 6 (11.8%) in mastoid region, and 1 (2.0%) in lumbar region. No INs have been reported in arm, forearm, and thigh. In 21 patients the interval node is the only sentinel node found, while in 30 cases there is at least another draining lymph node field.

Frequency of Occult Lymphatic Metastasis

In the 504 patients without IN who underwent biopsy, a total of 614 lymph node fields were detected. Overall SNs positive for metastases were reported in 138 (27.38%) subjects, 356 patients (70.65%) were negative, and in 10 cases no lymph node was found (*Fig. 2*). Within the group of 51 patients with IN, 13 subjects (25.49%) had a tumor-positive interval SN biopsy (*Table 2*). In accordance with the sequential dissemination of lymphatic metastases (25), we proposed a radical dissection of the subsequent lymphatic basin to each patient with a positive IN (12): 1 subject refused any further surgical treatment, while in 12 cases, lymphadenectomy was performed. We divided IN+ patients into 3 groups:

- Group A: 3 patients with a positive IN and without any usual lymphatic drainage field;
- Group B: 6 patients with a positive IN and with a negative-SLN detected in usual field;
- Group C: 3 subjects with both IN and usual basin SLN positive for metastasis.

Complete lymphadenectomy of the cervical field was carried out in the 2 patients with mastoid region positive IN. Total axillary

TABLE 2
Demographic and Clinical Characteristics of Patient with Metastatic INs

Age	Gender	Histological subtype	Breslow thickness	Primary site	Interval SN	Metastasis deposit type	BLNS+ in other field	Subsequent basic lymphadenectomy result	Distant metastasis	Survival at the end of followup
63	M	Superficial spreading	2.1	Posterior Thorax	Anterior Abdominal wall	MICRO	No	Negative	No	Yes
78	M	Superficial spreading	5.5	Posterior Thorax	Posterior Thoracic Region	MICRO	MICRO	Negative	No	Yes
49	F	Superficial spreading	0.7	Anterior Thorax	Anterior Thoracic Region	MICRO	No	Negative	No	Yes
48	F	Superficial spreading	4	Thigh	Anterior Abdominal wall	MACRO	No	1/14 lymph node with intracapsular metastasis	Yes	Yes
42	M	Nodular	2.5	Deep back	Anterior Abdominal wall	MICRO	MICRO	Negative	No	Yes
48	M	Nodular	3.5	Thigh	Anterior Abdominal wall	MICRO	No	Negative	Yes	No
50	F	Superficial spreading	1.9	Thigh	Anterior Abdominal wall	MACRO	No	Negative	No	Yes
56	F	Superficial spreading	1.9	Thigh	Anterior Abdominal wall	MICRO	No	Negative	No	Yes
32	F	Nodular	8.5	Anterior Thorax	Anterior Thoracic Region	MACRO	MACRO	4/27 lymph nodes with extracapsular metastasis	No	Yes
70	M	Superficial spreading	1	Posterior Thorax	Posterior Thoracic Region	MICRO	No	Negative	No	Yes
44	F	Superficial spreading	5	Head	Mastoid region	MICRO	No	1/23 lymph node with intracapsular metastasis	No	Yes
49	M	Superficial spreading	1.6	Anterior Thorax	Anterior Thoracic Region	MICRO	No	NO LYMPHADENECTOMY	Yes	Yes
47	F	Superficial spreading	5	Head	Mastoid region	MACRO	No	1/16 lymph node with intracapsular metastasis	No	Yes

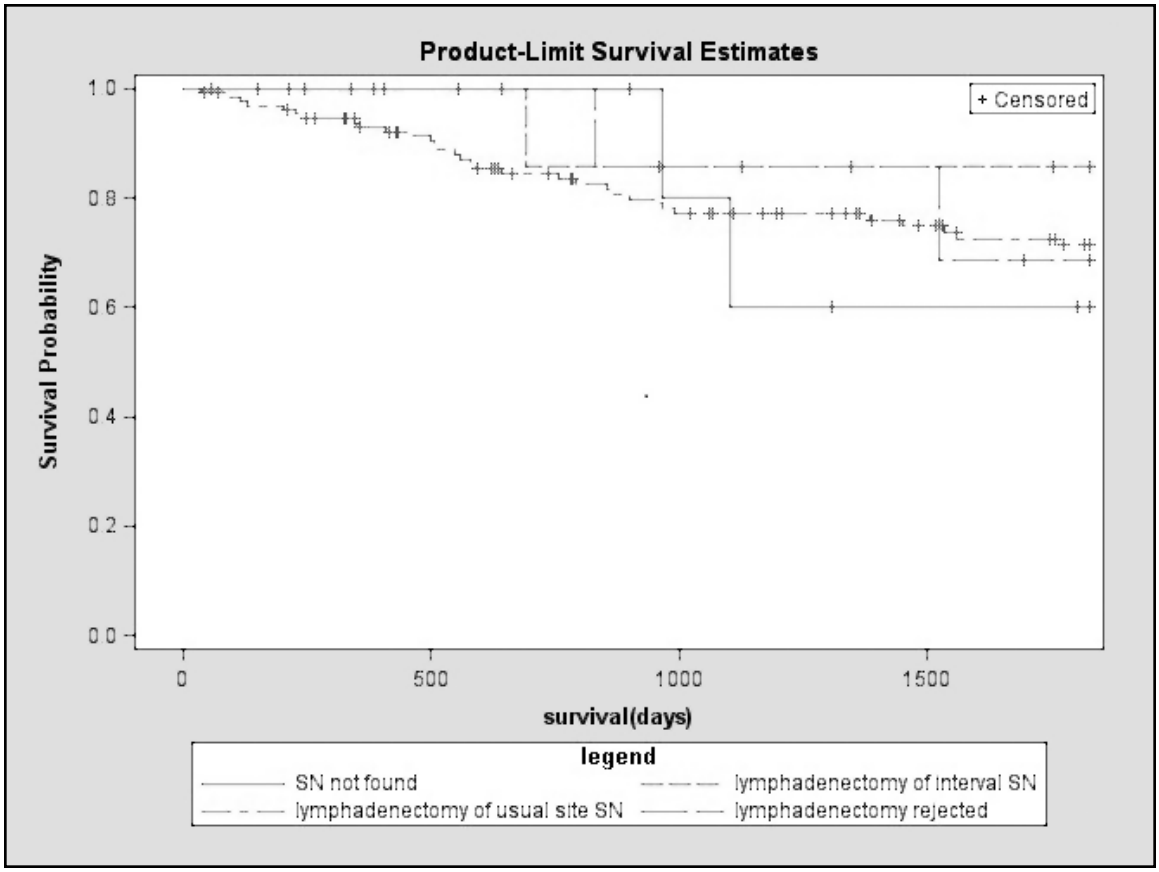

Fig. 3. Kaplan-Meier overall survival curve for subjects in the 4 groups.

lymph node dissection was performed in the 2 cases with posterior thoracic region IN+ and in the 2 cases with anterior thoracic region IN+. A complete lymphadenectomy of the inguinal basin was carried out in the 6 subjects with positive-IN in anterior abdominal wall. Overall metastases were detected in the usual basin subsequent to IN+ site in 4/12 cases: 1 in Group A, 2 in Group B and 1 in Group C. In our experience, there was a higher frequency of metastatic findings in the lymphadenectomy of IN+ patients (33.3%) than in patients with usual side positive-SN (28.2%). Additional nodes were found in all the groups, suggesting the possible presence of lymphatic metastasis beyond the site of INs also in patients in whom the IN is the only positive lymph node or the only draining field. The presence of additional lymphatic metastasis in lymphadenectomy was evident in 3 of 4 patients (75%) with macrometastatic INs, while the frequency of further positive lymph nodes was lower in subjects with micrometastasis in INs (12.5%).

Survival and Recurrence-Free Analysis

Follow-up information was available for 153 of 161 patients with positive or unfound SN; the other 8 patients were lost to follow-up. The mean follow-up period in the population with positive or unfound SN amounted to 56.5 months (median duration 46.4, range 1.2-179.6), while the mean follow-up in the cohort with positive INs was 35.1

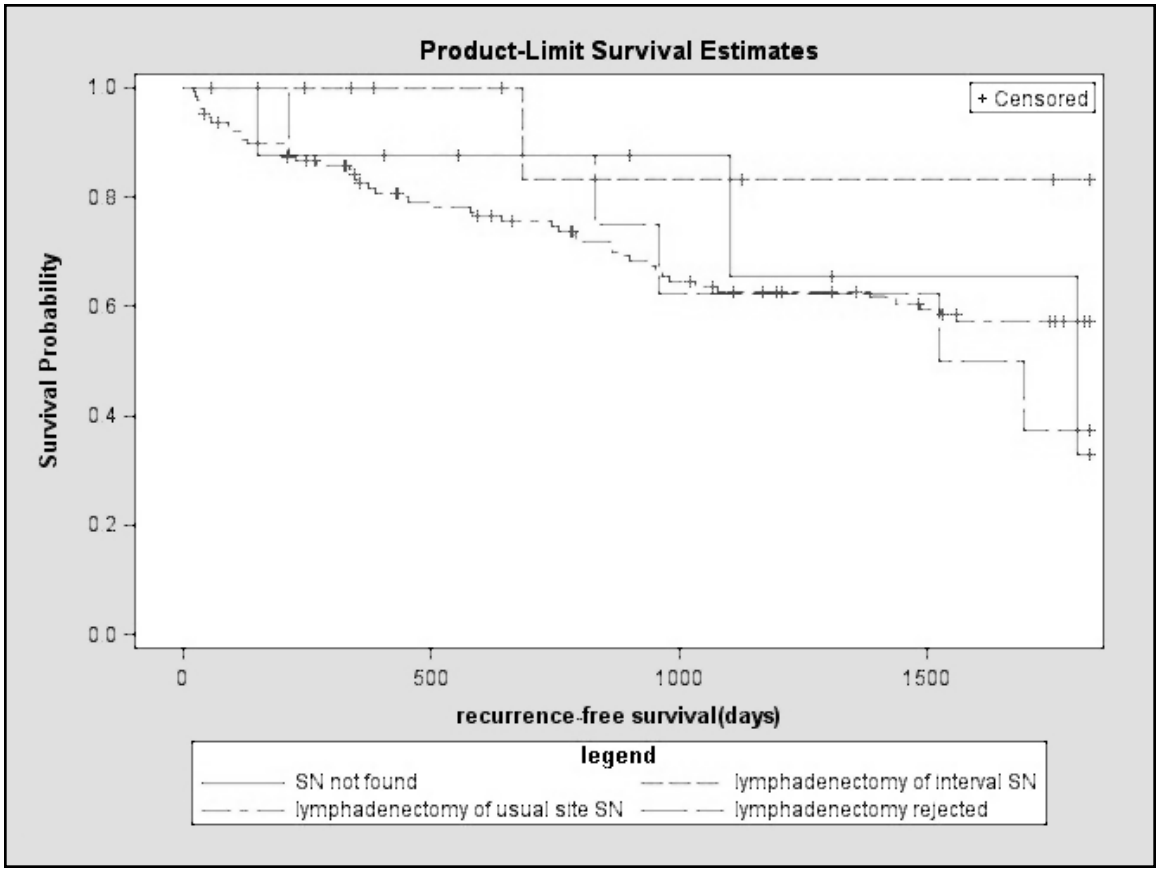

Fig. 4. Kaplan-Meier disease-free survival curve for subjects in the 4 groups.

months (median 29.8, range 1.8-78.8). Overall, 73 (47.7%) of 153 patients with positive or not found SN developed a local, in-transit, regional, or distant recurrence, after a median follow-up of 28.6 months. Two of 12 patients who underwent lymphadenectomy of the usual field subsequent to positive IN developed distant metastatic disease at a median time of 31.5 months and 1 of them died of melanoma. Recurrence-free period and survival rate at 5 years were analyzed in the cohort with positive INs who underwent lymphadenectomy, in subjects who refused lymphadenectomy, in patients who underwent lymphadenectomy after usual field positive SN, and in the cohort without SN biopsy taken (*Figs. 3-4*). Recurrence-free period and survival rate at 5 years were analyzed in a multivariate Cox proportional hazards regression model corrected for age, gender, Breslow thickness, presence of ulceration, lymphatic metastatic deposit type, and mitotic rate factors (*Table 3*). There was a trend toward a better prognosis in patients who underwent a lymphadenectomy after a positive IN, when compared to the patients undergoing lymphadenectomy for usual SN+ and with patients without SN taken or who refused lymphadenectomy, but the results did not reach statistical significance.

DISCUSSION

In our experience, INs were identified in 51 (9.19%) of 555 patients who underwent

TABLE 3
Cox Hazard Ratio on 5-year Mortality and Recurrence Corrected for Clinical Characteristics and Melanoma Prognostic Factors

	5 years survival		5 years recurrence-free	
	HR	***IC 95%***	***HR***	***IC 95%***
Lymphadenectomy after interval SN+	1.000		1.000	
Lymphadenectomy after usual SN+	2.138	*0.287 15.910*	2.173	*0.516 9.158*
Rejection of lymphadenectomy	1.266	*0.112 14.365*	3.323	*0.668 16.519*
No SN biopsy taken	3.403	*0.301 38.424*	2.438	*0.394 15.077*
High mitotic rate	0.939	*0.376 2.345*	1.173	*0.611 2.250*
Macrometastasis	1.751	*0.839 3.656*	1.969	*1.106 3.506*
Ulceration	2.228	*1.019 4.872*	1.125	*0.611 2.074*
Breslow ≥ 2mm	1.612	*0.789 3.292*	1.263	*0.728 2.190*
Age	1.003	*0.982 1.024*	1.012	*0.996 1.028*
Gender (M)	2.127	*1.040 4.350*	1.050	*0.631 1.750*

SN biopsy. The reported incidence of INs is similar to that of others recent studies (16-28) but higher than the rate of 2.1-7.2% reported in previous studies (4,5,10,12,14,17-26). This finding can be explained by the better definition of lymphatic drainage provided by the small particle radiocolloid (technetium 99m nanocolloid HSA) combined with the use of ultrahigh resolution collimators currently routinely utilized for lymphoscintigraphy. The majority of INs in our study were collected in patients with primary melanoma on the trunk, and there were significantly more interval SNs in subjects with cutaneous melanomas on head and neck than in those with primary tumors on limbs. In this study, the lower frequency of INs in melanomas located on the upper and lower limbs, reported also by other authors (4-16), can be explained by the exclusion of popliteal and epitrochlear lymph nodes from the fields defined as "interval," as they are considered to be a functional extension of the inguinal (24) and axillary (24) basins respectively. In our experience, anterior abdominal wall and dorsum are reported as the more frequent location of Ins (5), while none were found in limbs. Furthermore, for the first time, an IN is reported in the xiphoid region.

The rate of metastatic INs (25.49%) in our study is similar to that shown in other studies (5,14,17,27). Some authors report lower tumor-positive rates (*Table 4*), but these differences may be explained by the following:

1) Some authors (4-16) reported a low rate of patients with positive INs, but in their studies patients with clinically evident metastases were treated by a direct complete dissection without any preliminary scintigraphy (16) resulting in the exclusion of patients with clinically evident or more infiltrative metastasis in INs, leading to an evident selection bias;

2) Some studies (8,12,27,28) included epitrochlear and popliteal lymph nodes in the

TABLE 4
Frequency and Positivity Rate of Interval SNs Reported in the Literature

Study	Year	Patients	Patients with INs	Tumor-positive interval SNBs
Lieber et al (10)	1998	32	7 (22.0%)	Not reported
Uren et al (4)	2000	2045	148 (7.2%)	3/21 (14.0%)
Roozentaal et al (14)	2001	379	22 (5.8%)	4/18 (22.2%)
McMaster et al (5)	2002	2332	62 (3.1%)	13/62 (21.0%)
Sumner et al (12)	2002	1117	59 (5.3%)	7/54 (13.05%)
Vidal-Sicart et al (8)	2004	599	59 (9.8%)	10/59 (16.9%)
Carling et al (17)	2007	374	8 (2.1%)	3/8 (37.5%)
Matter et al (27)	2007	402	18 (4.5%)	2/18 (11.1%)
Ortin-Perez et al (28)	2008	900	80 (8.9%)	15/80 (19.5%)
Chekera et al (15)	2008	554	34 (6.1%)	Not reported
Verwer et al (16)	2011	4845	442 (9.0%)	16/197 (8.1%)
Caracò et al (26)	2014	1045	32 (3.0%)	4/32 (12.5%)
Present Study	**2014**	**555**	**51 (9.19%)**	**13/51 (25.49%)**

IN group, lowering in this way the frequency of tumor-positive IN (29,30);

3) The frequency (1.98%) of lymph nodes identified in lymphoscintigraphy but surgically not found was low; in fact, the failure to find a SN could result from the failure in searching for an INs.

There are no current guidelines for the management of positive interval SNs. In literature several proposals to manage these patient are described:

1) Some authors recommend only clinical and imaging follow-up of the lymphatic fields (4-14); but some studies demonstrated the simultaneous presence of occult metastases both in INs and in the subsequent lymphatic fields (5-17), suggesting the existence of pathways of drainage. For this reason, if the positive INs were not removed, the lymphatic metastatic spread cannot be properly treated;

2) Sumner et al proposed the completion lymph node dissection of both the unusual site and one regional lymphatic basin upstream from the unusual site for all patients with metastatic INs, but the small patient population and the limited number of events make it premature to draw meaningful conclusions from any analysis of recurrence and survival data (12);

3) Recently Viewer et al recommended lymphadenectomy in patients with both positive IN and positive usual field SN, defining as useless any treatment in patients in whom the only positive node was the interval (16);

4) McMasters et al advised that re-excision of the IN site should be performed when there is evidence of extracapsular nodal extension or contamination of the surgical wound (5).

In our experience, INs were always completely removed during SNB procedure and no patient developed local recurrence or in-transit metastasis. In 1 patient there was extracapsular nodal spread in IN and also in this case no further dissection was necessary.

In accordance with the sequential

diffusion of lymphatic metastasis (25), radical dissection of the subsequent lymphatic basin was proposed for all patients with a positive IN. It is important to note that an additional metastatic lymph node was found in patients with positive INs and positive recognized field SNs (Group C), in subjects with positive IN and negative usual site SN (Group B), and above all in patients with positive IN and without any other drainage field (Group A) (*Table 3*). The patient with macrometastatic INs showed a higher probability of additional lymphatic metastases in lymphadenectomy, but the involvement of the lymphatic field beyond the micrometastatic IN was reported only in 1 subject. In our experience, the metastatic involvement of the subsequent lymphatic field after positive interval node in melanoma patients confirms the indication for the complete dissection of the subsequent lymphatic basin. Even in the case of positive INs, however, a higher frequency of occurrence of additional lymph nodes is demonstrated in case of detection of macrometastases in INs.

Overall, the 5-year survival rate was 73.6%, in accordance with results of larger multicenter trials (31). Patients with positive IN show a good prognosis; in fact, only 2 patients presented local or distant recurrences. Five year disease-free and overall survival of this cohort is higher than the population who underwent total dissection after usual field positive SN, confirming the utility of immediate lymphadenectomy after a tumor-positive IN. This result suggests that the immediate dissection of the lymphatic field beyond the positive IN could allow patients to be treated in earlier stages of disease before the dissemination of the lymph nodes in the usual basins.

CONCLUSION

INs were found in 9.19% of patients and 25.49% of them contained metastatic melanoma. The failure to adequately investigate interval SN sites may result in under-staging of disease, increasing the number of false negatives and not-found sentinel nodes, and increasing the finding of occult metastasis. Furthermore, our data suggest that the complete dissection of the subsequent lymphatic field can avoid metastatic dissemination across the lymphatic pathways, making it possible to treat patients in earlier stages of disease. For this reason, a prospective trial is ongoing with the Italian Melanoma Intergroup in order to define classification, prognosis, and impact of differing surgical management in melanoma patients with interval nodes.

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