

Surgical management of tumor-positive interval node in melanoma patients

An observational study

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Abstract

The presence of interval nodes (IN) in melanoma is testified in several studies and sometimes these lymph nodes can contain metastatic disease. Currently there are no guidelines about the management of patients with tumor-positive INs.

We enrolled all patients affected by melanoma who underwent sentinel lymph node biopsy (SLNB) in a single institution. All patients with tumor-positive IN underwent the lymphadenectomy of the subsequent draining lymphatic field. Prognosis of IN+-patients was compared with subjects with positive SLNB in usual field through Kaplan-Meier and multivariate Cox regression analysis.

Overall 596 subjects underwent lymphoscintigraphy and one or more INs were identified in 94 (15.8%) patients. The mean number of sentinel lymph nodes (SNs) identified per patient was significantly higher in patients with INs. Macrometastasis were more common in patients with INs. Matched pair analysis testified a statistically significant better prognosis in patients with positive-INs when compared with patients with positive SNs in usual side with the same demographic and clinical characteristics. These findings were confirmed both in analysis of 10-year recurrence-free period, then in 10-years overall survival analysis.

Lymphadenectomy of the lymphatic draining field beyond positive-IN testify has proved to be a safe procedure that may improve prognosis in melanoma patients with tumor-positive INs. The better prognosis of patients with tumor-positive INs undergoing lymphadenectomy may be justified by the earlier treatment of lymphatic metastases. Further multicentric comparative studies are needed to evaluate possible impact of this procedure on prognosis of melanoma patients.

Abbreviations: IN = interval nodes, LA = lymphadenectomy, LFBI = lymphatic field beyond the positive-IN, SLNB = sentinel lymph node biopsy, SNs = sentinel lymph nodes, SPECT/CT = single photon emission computerized tomography/computerized tomography.

Keywords: interval lymph node, melanoma, metastasis, sentinel lymph node biopsy, tumor progression

KEY POINTS

- The presence of interval nodes (IN) in melanoma is testified in several studies.
- Lymphadenectomy of the lymphatic draining field beyond positive-IN has proved to be a safe procedure that may improve prognosis in melanoma patients with tumor-positive INs.
- Lymphadenectomy should be recommended in melanoma patients with positive interval nodes.

1. Introduction

Lymphatic metastatic progression in melanoma is characterized by the development of a rich lymphovascular network.^[1] Lymphoscintigraphy is indicated to identify the lymphatic draining pathways and to guide the sentinel lymph node biopsy (SLNB).^[2,3] SLNB allows a better staging of disease and an early detection of melanoma lymphatic metastasis, identifying patients eligible to locoregional lymphadenectomy (LA).^[4] The sentinel lymph node (SN) is the first lymph node receiving direct lymphatic drainage from a primary cancer site.^[5] SNs is usually located in axillary, inguinal, and cervical basins, but SNs may be located outside from these conventional basins because of anatomical differences in lymphatic pathway. This is even more true in melanomas arising in specific surgical sites (such as the head and neck), because the presence of the high complexity and variability of lymphatic drainage.^[6] Sentinel lymph nodes (SLNs) arising outside of conventional basins were called in different ways (*aberrant, in-transit, ectopic, or intercalated*) during years,^[7–10] but nowadays literature termed them as interval sentinel lymph nodes (INs).^[11–13] INs lie in subcutaneous fat along the course of lymphatic collecting vessels between a primary tumor site and a draining node field.^[14] INs can contain metastatic disease and the presence of tumor-positive IN (IN⁺) worsens the prognosis of patients affected by melanoma.^[10] Nevertheless, currently there are no guidelines about the surgical management of these patients.^[15–18]

Editor: Jianxun Ding.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2018) 97:18(e0584)

Received: 6 November 2017 / Accepted: 5 April 2018

<http://dx.doi.org/10.1097/MD.00000000000010584>

2. Materials and methods

2.1. Population in study

All patients who underwent SLNB for primary cutaneous melanoma were retrospectively identified from a single-institution (Plastic and Reconstructive Department of Policlinico di Bari) electronic medical records, including data of patients treated from July 1994 to December 2016. Patients with stage IV melanoma or affected by other carcinomas were excluded.

Within the 90th day from excision of the primary lesion, patients with a primary melanoma ≥ 0.75 mm in thickness or with adverse prognostic features (high Clark level, regression, ulceration, high mitosis rate) underwent lymphoscintigraphy to identify SN draining fields. Complete lymph node dissection was proposed to all patients with positive SLNB.^[19–22]

Histological reports were reviewed and standardized for all patients included in the study. Pathologists reviewed results of specimens of the SLNB and wide excision for each patient include in this study. All patients underwent a clinical and imaging follow-up—including chest x-ray, abdominal and lymphatic ultrasound, and single photon emission computerized tomography/computerized tomography for difficult areas—every 6 months for the first 5 years and yearly thereafter.

2.2. Lymphatic mapping, sentinel lymph node biopsy, and follow-up

Lymphoscintigraphy was performed using Technetium 99m nanocolloid human serum albumin with a dosage of 18 to 37 MBq (in relationship with procedure time) injected closely around primary lesion. Ultra-high-resolution collimators were used to image all the territories between the primary melanoma site and the recognized draining node fields, reducing artifacts. Dynamic and planar images were acquired using dual-headed digital gamma cameras both immediately after the radiolabeled colloid injection and then after every lymph node visualization. Further static images were acquired to ensure that all SNs were marked. A handheld gamma probe was used during surgery to guide SN detection.^[23,24] Lymph nodes lying outside from usual or minor fields between a primary tumor site and an usual drainage field are considered INs.^[23,24] For each SN, multiple sections of specimens were examined both by conventional hematoxylin and eosin and immunohistochemical stains using European Organization for Research and Treatment of Cancer protocol from 2009^[25–27] and World Health Organization melanoma program protocol before 2009.^[27] A clinically detectable nodal metastasis confirmed by therapeutic LA, or the histological presence of a metastasis exhibiting gross extracapsular extension, was considered as macrometastasis, otherwise it was defined as micrometastasis.^[28] After obtaining informed consent, complete lymph node dissection was performed in all patients with lymphatic metastasis. All patients underwent a clinical and imaging follow-up every 6 months for the first 5 years and yearly thereafter.

2.3. Statistical analysis

Patients' baseline characteristics were reported as the frequency (percentage) and mean \pm standard deviation or median and interquartile ranges. Categorical variables were assessed by the χ^2 test to compare the results for specific subgroups with those of the rest of the patient population, whereas continuous variables were compared among groups using Wilcoxon rank-sum test.

Recurrence-free survival was defined as the time between complete removal of the primary melanoma and clinical or imaging detection of the first recurrence. Follow-up time was defined as the time between complete removal of the primary melanoma and the last contact with patient. A matched pair 1-to-1 analysis was used to allow an unbiased comparison between patients in which the IN was the only positive-SN (Group 1) and those with a positive-SN in usual field (control group).^[29] A logistic regression model including age, sex, ulceration of primary lesion, Breslow thickness, and size of metastasis in SLNB as covariates was used to predict the probability (propensity score) to detect a positive-IN as the only SL. Adequacy of balance for the covariates in the matched sample was assessed via standardized mean difference between the 2 groups, considering differences $< 10\%$ as good balance.^[30]

Overall survival and disease-free period were evaluated through time-to-death analyses performed using survival curves and probabilities according to the Kaplan-Meier method. Multivariate analysis was performed using Cox proportional hazards regression models, with risks reported as hazard ratios along with their 95% confidence interval. The *P* value was considered significant if $P < .05$. All statistical analyses were performed using SAS Software Release 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Patients' characteristics, frequency of interval nodes, and results of sentinel lymph node biopsy

Overall 596 subjects underwent lymphoscintigraphy and one or more INs were identified in 94 (15.8%) patients. The clinical-pathological features and the location of the primary cutaneous melanoma are reported in Table 1. INs were reported significantly more frequently in patients with melanomas on head and neck,^[31,32] whereas the incidence of interval nodes was significantly lower in patients with primary lesion in the limbs ($P < .001$). No further major differences were found in age and sex or primary lesion characteristics between patients with and without INs. The mean number of SNs identified per patient was significantly higher in patients with INs (Table 2). This finding was due to the presence of at least another usual draining

Table 1
Clinical and pathological characteristics of population.

Characteristics	Patients with IN	Patients with SNs in usual field	<i>P</i>
Total, n (%)	94 (15.8)	502	/
Sex (M), n (%)	53 (56.4)	272 (54.2)	.69
Age, y	Mean \pm SD Median (range)	54.9 \pm 17.4 52.8 \pm 14.9 57.9 (13.0–88.9)	.22 53.4 (13.9–94.2)
Breslow thickness, n (%)	<1 mm	13 (13.8)	.19
	1–2 mm	47 (50.0)	275 (54.8)
	2–4 mm	19 (20.2)	82 (16.3)
	>4 mm	15 (16.0)	50 (10.0)
Ulceration, n (%)	Present	23 (24.5)	121 (24.1)
High mitotic rate (%)	Present	28 (29.8)	127 (25.3)
Primary site, n (%)	Trunk	43 (45.7)	265 (52.8)
	Head and neck	34 (36.2)	22 (4.4)
	Limbs	17 (18.1)	215 (42.8)
Histological subtype	Superficial spreading	59 (62.8)	329 (65.5)
	Nodular	30 (31.9)	148 (29.5)
	Others	5 (5.3)	25 (5.0)

IN = interval nodes, SD = standard deviation, SN = sentinel lymph node.

Table 2
Results of sentinel lymph node biopsy and lymphadenectomy.

Outcomes	Patients with INs	Patients with SNs in usual field	P
Number of SNs			
Mean ± SD	2.6 ± 1.8	1.6 ± 1.2	<.001
Median (range)	2 (1–9)	1 (0–9)	
Positive-SLNB, n (%)	28 (29.8)	144 (28.7)	.83
Micrometastasis, n (%)	18 (19.1)	121 (24.1)	.30
Macrometastasis, n (%)	10 (10.6)	23 (4.6)	.02
Additional positive lymph nodes after lymphadenectomy, n (%)	7 (7.5)	36 (7.2)	.92
Micrometastasis, n (%)	2 (2.1)	15 (3.0)	.65
Macrometastasis, n (%)	5 (5.3)	21 (4.2)	.62

IN = interval nodes, SD = standard deviation, SLNB = sentinel lymph node biopsy, SN = sentinel lymph node.

Table 3
Follow-up period and outcomes of patients of group 1 and control group.

Outcomes	Group 1	Control group	P
Mean follow-up period, mo (mean ± SD)	67.9 ± 39.8	80.7 ± 56.1	.41
Positive-lymphadenectomy, n (%)	3 (21.4)	40 (28.6)	.57
Micrometastasis, n (%)	2 (14.3)	15 (10.7)	.68
Macrometastasis, n (%)	1 (7.1)	25 (17.9)	.31
No patients with recurrences	3 (21.4%)	71 (50.7%)	<.05
Deaths	2 (14.3%)	57 (40.7%)	.05

SD = standard deviation.

lymphatic field in 54 patients with INs, whereas in 40 cases the interval node was the only SN.

Overall, positive-SLNBs were recognized in 172 (28.9%) subjects: in 144 (28.7%) out of 502 patients with SNs in usual field and in 28 (29.8%) out of 94 subjects with INs. Macrometastasis were more common in patients with INs; in fact, macrometastasis were reported in 10 (10.6%) patients with INs versus 23 (4.6%) subjects with SNs in usual field (*P* < .02). After LA, additional lymph nodes were detected in 7 (7.5%) patients with positive-INs and in 36 (7.2%) patients with positive SLNBs in usual field, without significant differences between the 2 groups.

Among subjects with positive-INs, in 14 cases the IN was the only positive-SN (group 1), whereas in 14 there was another positive-SN in a usual field. Although in patients with both positive-INs and usual site SNs the complete dissection of the

usual basin is recommended, there were no guidelines about the indication to LA in patients of group 1. According with the sequential diffusion of lymphatic metastases, radical dissection of the draining lymphatic field beyond the positive-IN (LFBI) was proposed also to patients of group 1.^[16,19]

3.2. Frequency of lymphatic metastases, survival, and recurrence-free analysis

Follow-up information was available for 154 out 172 patients with tumor-positive SNs. The mean follow-up period in the population with positive-INs amounted to 67.9 ± 39.8 months, whereas the mean follow-up in the cohort with usual site positive-SNs (control group) was 80.7 ± 56.1 months. Additional positive lymph nodes were detected in 3 (21.4%) patients in group 1 and in 40 (28.6%) patients with positive-SNs in usual basin (control group). Among patients of control group, in 2 (1.4%) cases SNs identified in lymphoscintigraphy were not found during surgical resection.

Overall, 74 (46.9%) of 154 patients with positive SNs developed a local, in-transit, regional, or distant recurrence: 3 (21.4%) out of 14 patients of group 1 after a median period of 33.2 ± 25.9 months and 71 (50.7%) out of 140 patients of control group after a mean period of 33.4 ± 36.6 months. Instead, 2 (14.3%) deaths were recorded in group 1 after a mean period of 40.6 ± 15.9 months and 57 (40.7%) in control group after a mean period of 41.1 ± 35.4 months (Table 3). Although frequencies of recurrences and deaths were significantly lower in patients in group 1, recurrence-free period (*P* = .13) and overall survival (*P* = .14) did not significantly differ between the 2 groups when compared in a Kaplan-Meier survival analysis.

3.3. Matched pair analysis

From the initial cohort of 14 subjects of group 1, 11 were selected using propensity score matching. Prematching characteristics widely differ between patients of group 1 and those of control group, but matched pair analysis let to a satisfactory balance for all the characteristics considered (Table 4). Postmatching cohort with positive-IN include patients with a mean age of 51.3 ± 18.4 years who showed a thick melanoma at diagnosis in 27.3% of cases; ulceration of primary lesion was present in 5 (45.5%) subjects and a macrometastatic-SN 3 (27.3%) cases. After LA, additional positive lymph nodes were detected in 3 (27.3%) patient in group 1 and in 4 (36.4%) patients of control group. Ten years recurrence-free period and survival rate were compared between the 2 postmatching cohorts. Kaplan-Meier analysis

Table 4
Clinical and pathological characteristics of patients of group 1 and control group before and after matching.

Characteristics	Prematching			Postmatching		
	Group 1	Controls	P	Group 1	Controls	P
Total, n	14	140	/	11	11	/
Sex (M), n (%)	6 (42.9)	88 (62.9)	0.14	6 (54.5)	6 (54.5)	.66
Age, y (mean ± SD)	53.4 ± 17.5	52.5 ± 15.5	0.84	51.3 ± 18.4	50.1 ± 17.7	.47
Breslow thickness, n (%)						
<1 mm	1 (7.1)	13 (9.3)	0.12	0	0	.86
1–2 mm	4 (28.6)	76 (54.3)		4 (36.4)	4 (36.4)	
2–4 mm	4 (28.8)	32 (22.9)		4 (36.4)	4 (36.4)	
>4 mm	5 (35.7)	19 (13.6)		3 (27.3)	3 (27.3)	
Ulceration, n (%)	7 (50.0)	40 (28.6)	0.10	5 (45.5)	5 (45.5)	.66
Macrometastatic SNs	5 (35.7)	23 (16.4)	0.07	3 (27.3)	3 (27.3)	.68

SD = standard deviation, SNs = sentinel lymph nodes.

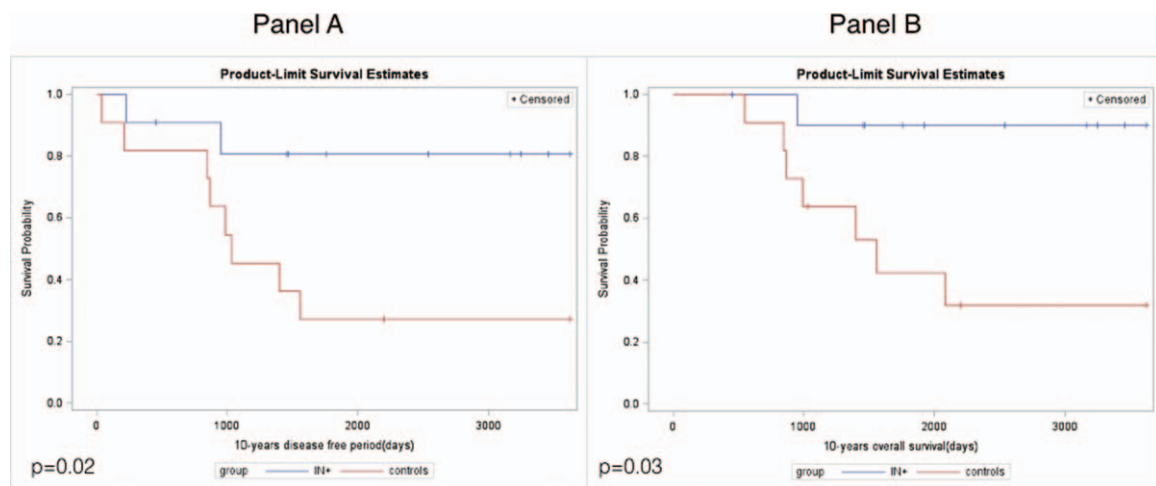


Figure 1. Kaplan-Meier curves. A, Overall survival. B, Recurrence-free period. Results of matched pair analysis.

testified a statistically significant better prognosis in patients with positive-INs when compared with patients with positive SNs in usual side with the same demographic and clinical characteristics. These findings were confirmed both in analysis of 10-year recurrence-free period ($P=.02$) then in 10-years overall survival analysis ($P=.03$) (Fig. 1).

4. Discussion

In our study, INs were reported in 15.8% of patients who underwent SLNB. This evidence was in accord with previous studies, in which the reported frequency of INs ranged among 3% and 22%.^[7-18,26] The variability in frequency of INs could be explained by technical improvement in lymphoscintigraphy. Nowadays, routine use of small particle radiocolloid combined with ultrahigh resolution collimators allow a better definition of lymphatic pathways, ensuring an accurate imaging of minor/unusual lymphatic fields.^[33] The high accuracy of the lymphatic mapping in our study was testified by the low rate of SNs identified in lymphoscintigraphy but not found during surgical remotion. This high reliability could explain also the increasing rates of INs reported in more recent studies.

We found a similar frequency of positive-SLNBs in INs and usual site SNs. Currently, there are no guidelines about the management of patients with positive-IN and in literature several approaches are described:

1. some authors recommended only clinical and imaging follow-up of the lymphatic fields^[9];
2. others proposed the LA of the usual LFBI in all patients with positive-IN^[13,16];
3. more recently Verwer et al^[18] recommended LA of the LFBI in patients with both positive-INs and positive-SNs in the LFBI, defining useless any further treatment in patients in which the positive-IN was the only positive SN.

Our and previous studies findings have testified the presence of additional lymph nodes after LA of the lymphatic pathways beyond a positive-IN.^[13,16] Moreover, some authors reported a higher risk of recurrence and death from melanoma in patients with positive-INs during a period of 10 years of follow-up.^[25] For these reasons a conservative approach with a clinical and imaging follow-up seems inadequate. Furthermore, a significant difference

between positive and negative INs in the percentage of Ki67 positive nuclei and mean vessel number was already established, suggesting an increased cellular proliferation and angiogenesis in positive INs.^[26] The presence of a high angiogenesis in melanomas and its correlation with poor prognosis and increased rates of relapse is well know.^[33] This increased angiogenesis could be responsible of developing of pathways of drainage between the IN site and the LFBI, justifying the presence of lymphatic metastasis beyond the site of positive-IN also in patients in which the interval is the only metastatic-SN. Therefore, the LA appears recommendable not only in patients with metastasis in INs and in LFBI—as suggested by Verwer^[18]—but also in patients in which the IN is the only metastatic lymph node.

For these reasons—in accordance with the pathophysiological mechanism of sequential diffusion of lymphatic metastases—we propose the radical dissection of the LFBI in all patients with a positive-IN. This surgical approach was already proposed by Sumner et al,^[16] without meaningful conclusions on prognosis due to the limited number of patients and events. The greater numerical sample of this study and the use of a matched pair analysis has allowed to evaluate the possible impact of the proposed procedure on overall survival and disease-free period. In fact—although we cannot directly compare the prognosis of patients with IN+ undergoing or not undergoing LA of the LFBI—we were able to compare prognosis of patients in whom the IN was the only positive_SN with a control group with positive-SNs in usual field. Ten-year free recurrence and survival were significantly better in patients of group 1 than in subjects of control group with same clinic-demographic characteristics. This result suggests that the immediate dissection of the LFBI could allow to treat patients in earlier stages of disease, before the dissemination of the lymph nodes in the usual basins.

5. Conclusion

The increased cellular proliferation and angiogenesis and the detection of additional tumor-positive lymph node beyond positive-INs suggest the possible dissemination across the lymphatic pathways, even in case of detection of metastasis after SLNB of INs. The good prognosis of patients who underwent complete dissection of the lymphatic field beyond

the metastatic IN can be explained by an early treatment of the lymphatic metastatic spread.

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