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ORIGINAL ARTICLE

Lymph node ratio has impact on relapse and outcome in patients with stage III melanoma

Faruk Tas[1] · **Kayhan Erturk**[1]

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Abstract

Background Even though both the involvement of regional lymph nodes and the number of metastatic lymph nodes are regarded as major determinants of survival in cutaneous melanoma, the extent of node dissection has been analyzed as an independent prognostic indicator in only a few studies. This study aims to determine how the lymph node ratio (NR) (ratio of positive nodes to total nodes removed) might predict the disease relapse and survival in node-positive melanoma.

Materials and methods A total of 317 patients with stage III primary melanoma were included in the study and reviewed retrospectively. All patients had nodal staging (*N*) by radical lymph node dissection. Patients were divided into three groups based on NR1 ≤ 10%, NR2 10–25%, and NR3 > 25%.

Results The median age was 50 years (range 16–86) and men were predominant (59.3%). The majority of the patients had thicker Breslow depth (> 2 mm) (83.3%), higher mitotic rate (> 2/mm^2) (64.1%) and ulcerated lesions (69.4%). The median number of positive nodes was 1 (range 1–32). The largest group was N1 (52.4%), which was followed by N2 (29.6%) and N3 (18%). The ratios of patients were 37.5%, 35.3%, and 27.1% in NR1, NR2, and NR3, respectively. The median number of excised lymph nodes was 13 (range 1–73). For all patients the estimated 5-and 10-year relapse-free survival (RFS) rates were 41% and 39%, respectively; and the estimated 5-and 10-year overall survival (OS) rates were 51% and 42%, respectively. Nodular histopathology, ulcerated lesions, higher mitotic rates, and higher node substages were the independent variables that were inversely correlated with survival for all patients; and NR was one of the significant prognostic factors and strongest predictors of relapse and survival ($p = 0.03$ and $p = 0.01$, respectively).

Conclusion Our results suggest that, apart from the conventional nodal status, NR is an independent prognostic factor-regarding both RFS and OS in stage III cutaneous melanoma.

Keywords Melanoma stage III · *N*-ratio · Prognostic factor · Survival

Introduction

Stage III melanoma constitutes 9% of newly diagnosed melanomas, and 5-year relative survival rate will be expected as 62% in the US for 2017 [1]. In node-positive disease; along with others, such as tumor thickness and ulceration, the number of metastatic lymph nodes is one of the most prominent independent prognostic factors [2, 3]. A marked diversity in the natural history of pathologic stage III melanoma was demonstrated by fivefold differences in 5-year survival rates for defined subgroups, ranging from 69% to as low as 13% [2] and from 70% for patients with T1-4N1a to 39% for those with T1-4N3 [3].

The standard approach to node-positive disease is radical lymph node dissection (RLND) [4] and the increasing number of involved lymph nodes has been reported as having a significant impact on survival [5–10]. To determine the prognostic significance of the extent of RLND, investigators used two parameters; the total number of lymph nodes removed [5] and the lymph node ratio [6]. Lymph node ratio (NR), defined as the ratio of the positive lymph node number to the total number of lymph nodes excised, was demonstrated as an important prognostic factor in patients with stage III melanoma [7–10].

In this retrospective study, we aimed to determine the prognostic importance of NR in stage III melanoma patients from a single tertiary referral institution.

✉ Faruk Tas
faruktas2002@yahoo.com

[1] Department of Medical Oncology, Institute of Oncology, University of Istanbul, 34390 Istanbul, Capa, Turkey

Materials and methods

The data of 1255 adult cutaneous melanoma patients who had been admitted, treated and followed-up in Istanbul University, Institute of Oncology between the years 1993 and 2017 were analyzed retrospectively. A total of 317 patients with pathological stage III primary melanoma were included in the study.

All patients had nodal staging by sentinel lymph node biopsy (SLNB) or elective lymph node dissection. Patients with pathologically positive SLNB had undergone a completion lymphadenectomy. After lymph node status was determined by radical lymph node dissection (RLND) the disease was staged according to AJCC (8th edition) staging system [3]. Patients were treated and followed-up according to standard international guidelines including National Comprehensive Cancer Network guidelines [4]. The records were retrieved from the cancer registry. The study was reviewed and approved by our local ethical committee.

The numbers of positive lymph nodes was categorized into three different groups: N1 for only 1, N2 for both 2 and 3, and N3 for 4 or more involved lymph nodes [3]. Furthermore, the NRs, numbers of involved lymph nodes divided by the total number of lymph nodes removed, were divided into three different groups (based on the study by Rossi et al. [7]): NR1 ($\leq$10%), NR2 (10–25%), and NR3 (>25%).

Kaplan–Meier and Cox methods were used to analyze the survival. Relapse-free survival (RFS) was calculated from the date of pathologic diagnosis to the date of the clinical recurrence which was defined as detected by imaging studies or by clinical examination. Overall survival (OS) was determined from the date of pathologic diagnosis to death resulting from any cause. A p value $\leq$0.05 was considered significant. Statistical analysis was carried out using SPSS 21.0 software (SPSS Inc., Chicago, Illinois, USA).

Results

Patients

A total of 317 melanoma patients with stage III disease were included in our study. Patient and disease characteristics are listed in Table 1. The median age was 50 years (range 16–86) and men were predominant in number (59.3%). The majority of the patients had thicker Breslow depth (>2 mm) (83.3%), higher mitotic rate (>2/mm^2) (64.1%) and ulcerated lesions (69.4%).

Table 1 Patient and disease characteristics

Characteristics	*n* (%)
No. of patients	317 (100)
Age, year	
≤ 50/> 50	153 (48.3)/164 (51.7)
Sex	
Female/male	129 (40.7)/188 (59.3)
Site of lesion	
Axial/extremity	159 (51.8)/148 (48.2)
Histopathology	
Non-nodular/nodular	154 (62.3)/93 (37.7)
Clark invasion	
I–III/1V–V	39 (14.6)/228 (85.4)
Breslow thickness, (mm)	
≤ 2/> 2	44 (16.7)/220 (83.3)
Ulceration	
No/yes	74 (30.6)/168 (69.4)
Mitotic rate, (/mm^2)	
≤ 2/> 2	84 (35.9)/150 (64.1)
Lymphovascular invasion	
No/yes	167 (79.5)/43 (20.5)
Neurotropism	
No/yes	140 (92.1)/12 (7.9)
Tumor-infiltrating lymphocytes	
No/yes	148 (64.3)/82 (35.7)
Regression	
No/yes	157 (75.5)/51 (24.5)
Association with a preexisting melanocytic nevus	
No/yes	125 (70.2)/53 (29.8)
BRAF (V600E) mutation	
No/yes	27 (55.1)/22 (44.9)
Adjuvant treatment	
No/yes	96 (30.3)/221 (69.7)
Lymph node involvement, AJCC	
N1/N2/N3	166 (52.4)/94 (29.6)/57 (18.0)
Relapse in follow-up	
No/yes	178 (56.2)/139 (43.8)
Last status	
Died/alive	111 (35.0)/206 (65.0)

Positive node (*N*) status

The median number of the dissected lymph nodes was 13 (range 1–73) and majority of the patients (68.1%) had more than ten excised lymph nodes. The median number of positive nodes was one (range 1–32). The largest group was N1 (n=166, 52.4%); followed by N2 (n=94, 29.6%) and N3 (n=57, 18%).

N-ratio status (NR)

The patients were grouped into NR1 (37.5%), NR2 (35.3%), and NR3 (27.1%) (Fig. 1). The majority of the patients in N1 group had NR1 (61.6%) followed by 29.9% of the patients having NR2 and 8.5% having NR3 (Fig. 1). Only 17.5% of the patients in N2 group had NR1, but 32% had NR3, and

50.5% had NR2. Finally, N3 group patients had NR3 with the greatest percentage (74.5%) which was followed by NR2 (25.5%). No patients in N3 group had NR1.

Relapse and RFS

A total of 139 (43.8%) node-positive patients relapsed during follow-up (Table 1). For all node-positive patients the median RFS time was 18.95 months and estimated 5-and 10-year RFS rates were 41% and 39%, respectively (Table 2). The patients with nodular histopathology ($p=0.013$), ulcerated lesions ($p=0.03$), higher mitotic rates (more than 2/mm^2) ($p=0.006$), and advanced node involvements had worse RFSs (Table 3). There was a significant association between increasing N-stage and shortening RFS ($p=0.03$) (Table 3; Fig. 2). A similar correlation was also observed between advanced NR and poor RFS ($p=0.03$) (Table 3; Fig. 3).

Death and OS

One hundred and eleven patients (35%) died at the time of the analysis (Table 1). The median OS time for all cases was 24.25 months; 5-and 10-year OS rates were 51% and 42%, respectively (Table 2). Nodular histopathology ($p=0.012$), ulcerated lesions ($p=0.05$), higher mitotic rates (more than 2/mm^2) ($p=0.03$), higher node substages ($p=0.01$) and relapse of disease ($p=0.001$) were independent variables that found to be inversely correlated with overall survival for all node-positive melanoma patients (Table 3). A significant association between increasing N stage and worsening survival was observed ($p=0.01$) (Table 3; Fig. 4). Moreover, we found that NR was a poor prognostic factor for OS, as it was for RFS ($p=0.01$) (Table 3; Fig. 5).

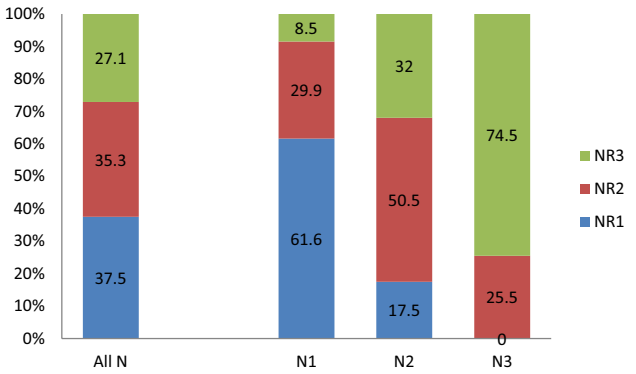

Fig. 1 Distribution of *N*-ratios (NR) on node stages (*N*) for 317 patients with stage III melanoma (%)

Discussion

This study investigated the prognostic significance of the extension of RLND in cutaneous melanoma patients using lymph node ratio (NR) and it concluded that NR was one of the prognostic factors that strongly predicted relapse and survival in melanoma.

A number of studies have already shown that survival is associated with NR for miscellaneous tumors, such as gastric carcinoma [11] and bladder cancer [12] and they concluded that NR (ranging from 0.1 to 0.2) was a significant prognostic factor for these cancers.

Furthermore, NR was also assessed in several trials as an important indicator for the extension of the RLND in melanoma and all of these studies showed that NR was significantly associated with survival [7–10]. In the first study, Rossi et al. investigated NR in 213 melanoma patients who had undergone RNLD and found that NR was significantly associated with clinical outcome, which suggested that this simple pathological indicator added significant prognostic information to tumor thickness and TNM stage ($p<0.0001$) [7]. Likewise, in 168 patients who underwent RLND, Berger et al. showed that NR was an important prognostic factor [8]. Patients with more than 10% NR had decreased survival compared to those with 10% or less NR ($p\leq0.005$). In an analysis of the SEER

Table 2 RFS and OS values by node (*N*) stage and *N*-ratio

Variables	RFS			OS		
	Median (months)	5-year (%)	10-year (%)	Median (months)	5-year (%)	10-year (%)
Node (*N*)						
All	18.95	41	39	24.25	51	42
1	20.70	48	48	25.40	61	48
2	16.20	40	31	22.80	50	33
3	13.40	33	33	22.50	38	38
N-ratio (NR)						
1	19.20	53	53	23.00	63	63
2	17.00	43	43	25.60	56	40
3	19.30	25	15	25.60	43	20

Table 3 Univariate analyses of variables associated with relapse-free survival (RFS) and overall survival (OS)

Variables	RFS			OS		
	HR	(95% CI)	*p*	HR	(95% CI)	*p*
Age	1.151	0.824–1.606	0.40	1.119	0.771–1.626	0.55
Sex	1.205	0.856–1.698	0.28	1.263	0.858–1.857	0.23
Site of lesion	1.029	0.734–1.442	0.87	0.972	0.668–1.414	0.88
Histopathology	**1.644**	**1.111–2.430**	**0.013**	**1.750**	**1.132–2.703**	**0.012**
Clark invasion	1.275	0.728–2.233	0.39	1.106	0.603–2.030	0.75
Breslow thickness	1.280	0.753–2.176	0.36	1.269	0.691–2.333	0.44
Ulceration	**1.631**	**1.046–2.546**	**0.03**	**1.790**	**1.110–2.867**	**0.05**
Mitotic rate	**1.831**	**1.189–2.818**	**0.006**	**1.671**	**1.043–2.667**	**0.03**
Lymhpovascular invasion	1.150	0.683–1.937	0.60	1.497	0.850–2.635	0.16
Neurotropism	0.657	0.239–1.808	0.41	0.903	0.326–2.504	0.84
Tumor-infiltrating lymphocytes	0.971	0.643–1.465	0.88	0.850	0.530–1.365	0.50
Regression	0.677	0.393–1.166	0.16	0.935	0.535–1.634	0.81
Association with a preexisting melanocytic nevus	0.675	0.390–1.168	0.16	0.765	0.424–1.381	0.37
BRAF (V600E) mutation	**0.524**	**0.265–0.935**	**0.05**	0.755	0.348–1.639	0.48
Adjuvant therapy	0.927	0.647–1.329	0.68	0.949	0.633–1.422	0.80
Relapse of disease	–	–	–	**10.02**	**5.709–17.599**	**0.001**
Node stage (*N*)	**1.261**	**1.018–1.562**	**0.03**	**1.359**	**1.075–1.718**	**0.01**
1 vs 2	1.373	0.941–2.003	0.09	**1.518**	**1.005–2.322**	**0.05**
1 vs 3	**1.241**	**1.012–1.589**	**0.05**	**1.342**	**1.051–1.712**	**0.02**
2 vs 3	1.132	0.703–1.823	0.60	1.203	0.727–1.992	0.47
N-ratio (NR)	**1.233**	**1.014–1.500**	**0.03**	**1.345**	**1.072–1.688**	**0.01**
1 vs 2	1.098	0.881–1.370	0.40	1.227	0.952–1.580	0.11
1 vs 3	**1.526**	**1.031–2.259**	**0.03**	**1.803**	**1.133–2.869**	**0.012**
2 vs 3	0.756	0.497–1.150	0.19	0.755	0.482–1.183	0.21

Bold values show statistical significant ($p \leq 0.05$)

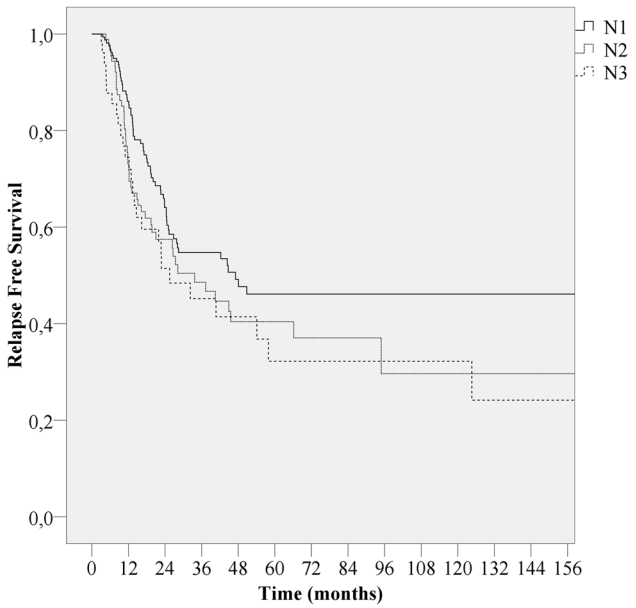

Fig. 2 RFS curves by node-positive (*N*) substages ($p=0.03$ for all substages; $p=0.09$ for N1 vs N2, $p=0.05$ for N1 vs N3; and $p=0.6$ for N2 vs N3)

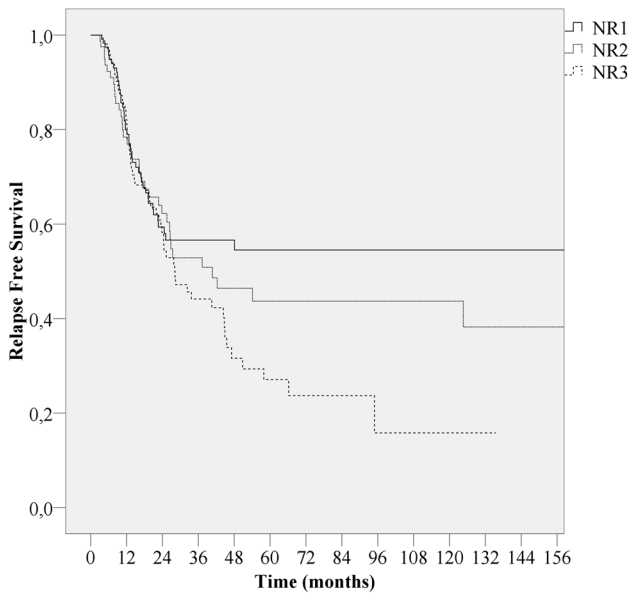

Fig. 3 RFS curves by *N*-ratio (NR) subtypes ($p=0.03$ for all substages; $p=0.4$ for NR1 vs NR2, $p=0.03$ for NR1 vs NR3; and $p=0.19$ for NR2 vs NR3)

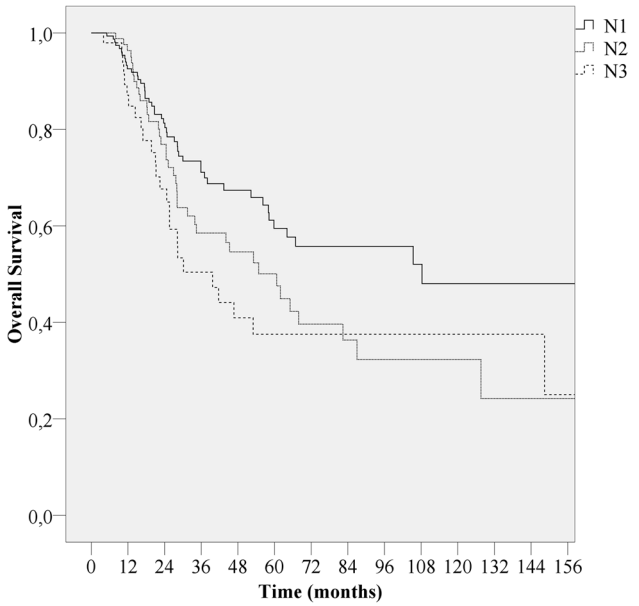

Fig. 4 OS curves by node-positive substages (*N*) ($p=0.01$ for all substages; $p=0.05$ for N1 vs N2, $p=0.02$ for N1 vs N3; and $p=0.47$ for N2 vs N3)

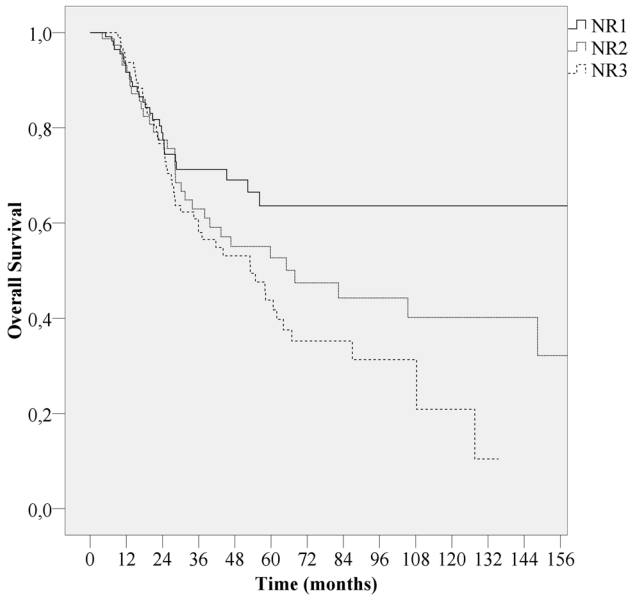

Fig. 5 OS curves by *N*-ratio (NR) subtypes ($p=0.01$ for all group, $p=0.11$ for NR1 vs NR2; $p=0.012$ for NR1 vs NR3; $p=0.21$ for NR2 vs NR3)

database, Xing et al. concluded that among other prognostic factors NR was the best indicator for the extent of lymph node dissection, regardless of anatomic nodal regions [10]. A large study on 1514 melanoma patients showed that the NR groups had similar survival outcomes with AJCC N-stage groups, so NR was concluded as a useful independent prognostic factor that might substage melanoma patients [9]. We concur that NR is a significant independent prognostic factor on both recurrence and outcome for stage III melanoma patients who had undergone RLND (Table 4).

We observed that NR is independently associated with clinical survivals, suggesting that it adds significant prognostic information to survival analysis similar to TNM stage. The N-stage and NR are not overlapping classification systems which were determined by this study (Fig. 1) and others [7, 8]; a significant number of patients were staged differently. Therefore, N-stage and NR regulate each other's prognostic value, the potential misclassifications due to the actual limitations of each system [7]. For example, when we look at overall survival curves based on N-stage and NR category, we see that there are differences between patients using NR and N-stage (Table 2). Likewise, similar even much discrimination was also observed in these cases when we assess them for relapse-free survival (Table 2).

To the best of our knowledge, this is the first work that shows NR's strength to predict relapse in node-positive melanoma patients, even though its association with survival had already been concluded in previous studies. In conclusion, we suggest that the prognostic potential of NR be considered equivalent to TNM-staging in melanoma and serve as important stratification for patients undergoing adjuvant therapy for node-positive melanoma.

Table 4 Comparisons of the published trials regarding *N*-ratio (NR)

	Rossi et al. [7]	Berger et al. [8]	Spillane et al. [9]	Tas et al. [this study]
No. of patients	213	168	1243	317
Node status (*N*) (%)				
N1	44	47	50	52
N2	45	25	30	30
N3	11	28	20	18
N-ratio (NR) (%)				
NR1	44	55	49	38
NR2	45	27	21	35
NR3	11	18	12	27
OS (5-year, %)	52			
N1	–	48	65[a]	48
N2	–	44	47[a]	40
N3	–	13	30[a]	33
NR1	76[a]	52	63[a]	53
NR2	47[a]	24	45[a]	43
NR3	25[a]	0	24[a]	25

[a]Approximate rate provided from survival curves because of nonexistence of exact value

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Informed consent Informed consent was obtained from all individual participants included in the study. The study was reviewed and approved by our local ethical committee.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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